RAMB
Journal of the Brazilian Medical Association

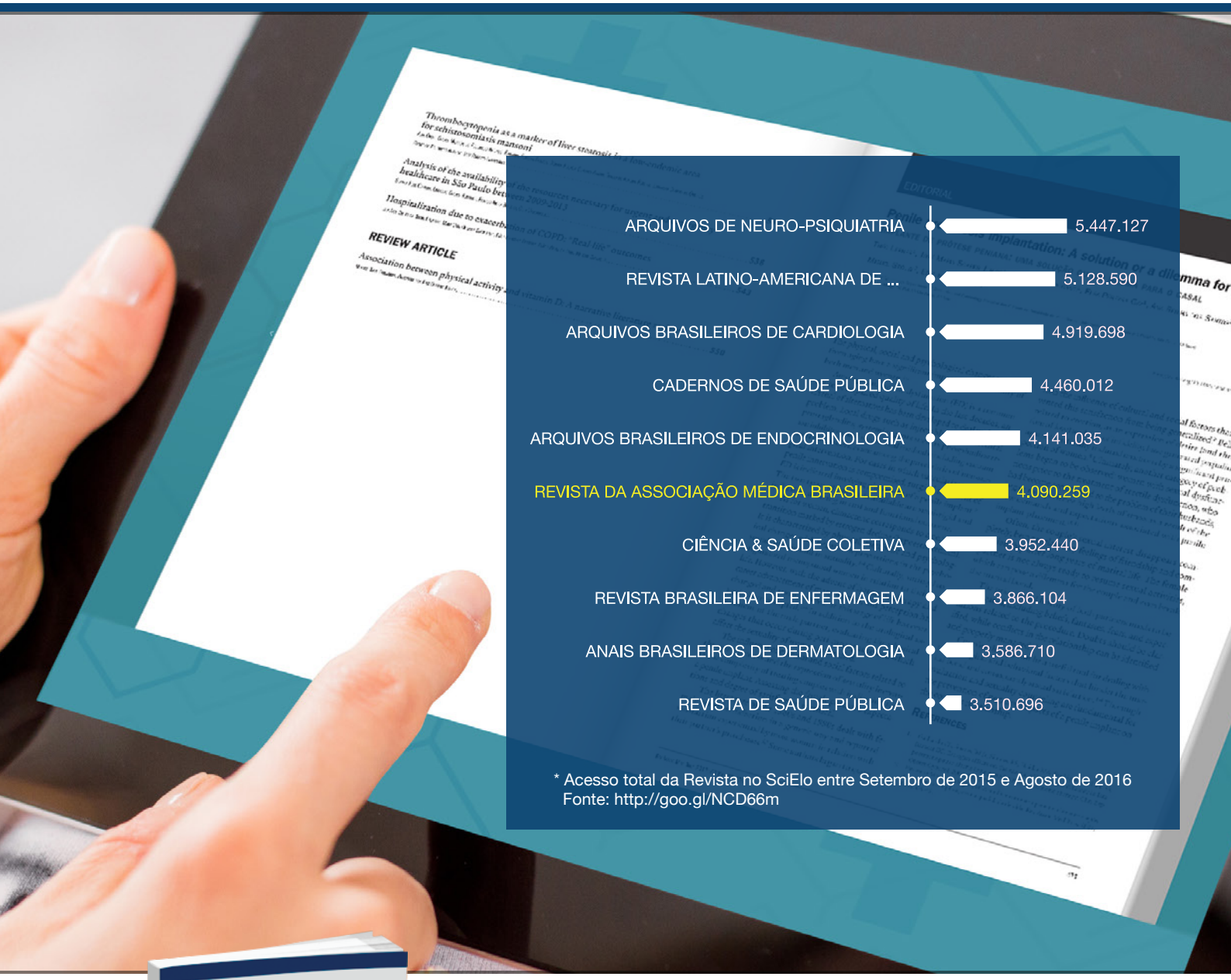
AMB
Brazilian Medical Association

Volume 63
Number 11
November 2017
ISSN 0104-4230
ISSN 1806-9282 (*On-line*)

SECTIONS

ARTICLES

RAMB ESTÁ NOVAMENTE ENTRE AS REVISTAS MAIS ACESSADAS NO SCIELO



Acesse agora os artigos gratuitamente:
http://ramb.amb.org.br/

AMB
Associação Médica Brasileira

RAMB

REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA

JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

AMB Associação Médica Brasileira

www.ramb.org.br

Associação Médica Brasileira

Address: Rua São Carlos do Pinhal, 324
Bela Vista – São Paulo
Postal code: 01333-903
Phone: (+55 11) 3178-6800

Editor-in-chief: Carlos V. Serrano Jr.
Managing editor: César Teixeira
E-mail: ramb@amb.org.br
Website: www.ramb.org.br

The norms for publication are available on the website www.ramb.org.br

The Journal of the Brazilian Medical Association is affiliated to the ANATEC and indexed in Medline, SciELO, Science Citation Index Expanded, Journal Citation Reports, Index Copernicus, Lilacs, and Qualis B2 Capes databases, and licensed by Creative Commons®. Registered in the 1st Office of Registration of Deeds and Documents of São Paulo under n. 1.083, Book B, n. 2.

The Journal of the Brazilian Medical Association is an official publication of the Associação Médica Brasileira (AMB), distributed exclusively to the medical community in Brazil and Latin America.

Publisher: Editora Manole

Authorizing editor: Sônia Midori Fujiyoshi
Editor: Cristiana Gonzaga S. Corrêa
Editorial producer: Quinta Edições
English translation of articles: Graziella Risolia Gallo ME
Proofreading: Graziella Risolia Gallo ME and Folgueira Comunicação
Reference reviewer: Lia Fugita Editorações
Cover: Rafael Zemantauskas
Graphic design: Sopros Design
Layout: Lira Editorial

SUMMARY

Volume 63 – Number 11 – November 2017
ISSN 0104-4230 – ISSN 1806-9282 (*On-line*)

SECTIONS

ORIGINAL ARTICLES

REVIEW ARTICLES

Animal experimentation: A look into ethics, welfare and alternative methods

Experimentação animal: um olhar sobre ética, bem-estar e métodos alternativos

Marcos Rassi Fernandes[1]*, Aline Ribeiro Pedroso[2]

[1]MD. PhD in Health Sciences, Department of Orthopedics and Traumatology, Faculty of Medicine, Universidade Federal de Goiás (FMUFG), Goiânia, GO, Brazil
[2]MSc Student of the Graduate Program in Health Sciences, FMUFG, Goiânia, GO, Brazil

Study performed by the Graduate Program in Health Sciences, Faculty of Medicine, Universidade Federal de Goiás, Goiânia, GO, Brazil

*Correspondence:
Address: Av. Azaléias, Qd. 10 Lt. 20
Aparecida de Goiânia, GO – Brazil
Postal code: 74935-187
marcosombro@ig.com.br

http://dx.doi.org/10.1590/1806-9282.63.11.923

Introduction

Since the fifth century BC, there have been reports of scientific experiments involving animals, but their use has become more frequent since the nineteenth century. Animal welfare would then comprise only stress reduction, animal suffering not being taken into account for many years.[1] In 1824, the first animal protection society, the Society for the Preservation of Cruelty to Animals, was established in England to promote animal comfort, thereby helping to prevent cases of cruelty.[2]

In 1959, Russell and Burch described the principle of the "3 Rs" – Replace, Reduce, Refine – for research using animals. This principle recommended substituting conscious living vertebrates with phylogenetically more primitive life forms, such as the more degenerate metazoan microorganisms and endoparasites, or with computerized simulations. The reduction principle advised that research and procedures should be carried out with as few animals as possible, while the refinement principle suggested that the techniques used should decrease their pain and distress at all stages of the study.[2,3]

In Brazil, Law No. 11,794/08, also known as the Arouca Law, regulates the use of animals in scientific experiments. Chapter IV of the Arouca Law describes the conditions for breeding and using these animals in teaching and scientific research, such as the use of sedation, analgesia or anesthesia in any experiment that may cause pain or distress. It also recommends performing euthanasia whenever the experiment is terminated or at any of its phases when there is intense suffering of the animal.[4]

The Arouca Law created Brazil's National Council for the Control of Animal Experimentation (Concea, Portuguese acronym for Conselho Nacional de Controle de Experimentação Animal), assigned to draw up the guidelines and enforce compliance with them regarding the humane use of animals in scientific research. It also set up the Ethics Commissions on the Use of Animals (CEUAs, Portuguese acronym for Comissões de Ética no Uso de Animais) as an indispensable condition for the accreditation of teaching and research institutions that use animals in scientific experiments.[4]

The purpose of using animals in teaching is to illustrate or carry out procedures that are already known, unlike their use in research, which is aimed at contributing to developing new drugs or treatments, in addition to clarifying certain biological phenomena.[5]

Many advances in health sciences were possible thanks to scientific experiments conducted on animals. However, actions from non-governmental organizations (NGOs) towards protecting and preserving animals are still frequent. Some scientists argue that the predictive value of this type of research is often low and may lead to biased or imprecise results, which would result in unnecessary suffering to the animals and clinically irrelevant data.[6]

It can therefore be stated that the practice of animal experimentation is considered a widespread activity in the scientific environment. Nevertheless, it has provoked public reactions, and this practice has been intensely debated both in society and academic institutions.[5,6]

Our study was aimed at undertaking a narrative review on ethics and welfare in animal experimentation, as well as discussing alternative methods to its use.

Choosing the animal model

Meticulous research should be undertaken for project planning prior to initiating any experiment in order to avoid unnecessary use of living animals.[3] There are reasons for their use in several studies, such as those investigating

human diseases and in toxicity tests. In addition, animals are used as an asset to teaching health professionals and training their surgical skills.[7]

Investigators should know the particular traits of the species they intend to use, such as its physiology, developmental stages, reproductive characteristics, specific behaviors and nutritional needs. In practice, when actually conducting experiments, choosing the appropriate animal model is done based on how easy the husbandry practices and handling of the animal species are, rather than experimental design or animal biological relevance.[8]

Rodents, especially rats and mice, are among the most commonly used animals in scientific research.[3] In the United States alone, 26 million mice and rats are used per year, which makes up to 96 to 98% of all animal testing.[9]

Rats are most appropriate for work involving shock, sepsis, obesity, peritonitis, cancer, gastric ulcers, intestinal operations, the mononuclear phagocytic system, spleen, wound healing and organ transplantations (Figure 1). Mice, in turn, are more suited to studying megacolon and burns, as well as shock, sepsis, obesity and cancer, as previously mentioned.[3]

Pigs are used in liver, stomach and transplantation studies (Figure 2), whereas rabbits are suited for studies on immunology, shock, inflammation, colitis, vascular operations and transplantations. Dogs fell into disuse, mainly due to the activity of NGOs engaged in protecting the species. However, their use was common in teaching surgical technique and studying shock, malabsorption, colitis, pancreatitis, hepatic and splenic operations, as well as transplantations.[3]

FIGURE 1 Healing test using rats as an animal model.

FIGURE 2 Operative technique using pigs as an animal model.

Thus, choosing an animal for laboratory use depends on the scientific research. There are some animals whose genetic lineage makes them prone to certain diseases, such as diabetes mellitus or high blood pressure, and therefore are ideal choices for testing drugs and/or procedures when studying such conditions.[9]

It is of utmost importance to know the microbiological standard of laboratory animals, given that it not only affects people, but can also influence the results of the experiments. Studies have been using an increasing number of specific pathogen-free (SPF) animals, that is, animals which are free of specific microorganisms and parasites. In order to obtain this type of sanitary status, it is essential that animals be husbanded and kept in settings that are protected by strict sanitary barriers and frequently monitored, since many rodent infections are subclinical.[10]

Housing and environmental enrichment

Several aspects relative to the husbandry and housing of species are neglected. Group housing is important, but can give rise to aggression, hence causing pain, injury or death. Also, animals that are stressed or injured may compromise the scientific validity of the study.[11]

Investigators should be concerned about the circumstances in which animals are kept during the study, as well as familiarize themselves with the metabolism of the species kept in vivaria, which can be altered by factors such as confinement, stress, pain, lack of sunlight and more.[8,12]

Housing conditions not only affect the behavior of the animals but also interfere with the results of the experiments. Environmental enrichment and enhancement procedures help reduce stress and positively affect performance.[6]

Accordingly, knowledge of the specific behavior and physiology of the species is extremely important, so that

experiments can be conducted while aiming at reducing pain, suffering and stress inside the enclosure, thereby promoting animal welfare and consequently increasing reliability of research data.[13]

Factors causing agony and distress in animals should be eliminated or controlled so that there is no interference in data collection and interpretation of results. The need for more animals, reduced reliability, increased variability in results and unnecessary use of lives all stem from impaired welfare.[14]

Animals should be kept in a safe and appropriate place in order to reduce experiment data variation arising from the environment. It is essential to keep variables such as temperature, humidity and airflow at levels that are appropriate for each species, since abrupt variations can cause stress, decreased resistance and greater susceptibility to infections.[6,13]

The space allocated to animals must permit free movement, sleep and contact with other animals of the same species.[4] Rats and mice are very sociable animals and, therefore, should be housed in groups so that they can develop normal behavior. Laboratory cages are usually not suitable for the animals' behavioral needs. Hence, environmental enrichment is an important feature for them to express their natural behavior, which will affect their physiology and defense mechanisms.[13]

The enrichment features should satisfy their curiosity, provide them with fun activities, and allow for the fulfillment of their physiological and behavioral needs, such as building nests, exploring, gnawing and hiding. The use of igloos, cardboard/PVC tubes, cotton, paper towel, paper strips and disposable masks favors this objective.[13]

When a new animal is placed into the experiment's settings, they should go through a period of acclimatization (quarantine), as abrupt changes in their living conditions can elicit a pressure response, which, albeit temporary, can lead to distress.[14]

The environment to be used for animal housing must be constantly controlled by hygiene, disinfection, sanitation and sterilization processes. Several infectious agents found in vivaria, such as *Sendai* virus, *Mycoplasma pulmonis* and cestoda, are currently becoming increasingly rarer. However, the mouse hepatitis virus still remains a threat.[10]

Euthanasia

The term euthanasia is derived from Greek and means death without suffering. The Arouca Law (Article 14, Chapter IV, Paragraphs 1 and 2) states that an animal shall be subjected to euthanasia, in strict obedience to the requirements pertaining to each species, whenever the experiment is terminated or at any of its phases, where such a procedure is recommended, as well as whenever severe suffering occurs. If the animal should not be submitted to euthanasia, it may exceptionally leave the vivarium after intervention and be assigned to suitable persons or animal protection entities, duly legalized.[4]

Such a procedure is also indicated where the animal's welfare is irreversibly impaired and neither pain nor suffering can be controlled with analgesics or sedatives, or in those cases where the animal constitutes a threat to public health and a risk to the native fauna or to the environment.[4,13,15]

Euthanasia techniques should result in a rapid loss of consciousness followed by cardiac or respiratory arrest and definite impairment of brain function. It is important to handle the animal calmly and out of its enclosure, seeking to reduce distress, fear and anxiety.[13]

Prior to choosing the most appropriate method, one must take into consideration the animal species involved, the animal's age and physiological status, as well as the safety of the person euthanizing the animal. Every research project should contain the description of appropriate endpoints for the animal species and the procedures that will be used.[13,15]

There are both chemical and physical methods. The chemical methods available include injectable agents (barbiturates, propofol, potassium chloride); inhalable agents (carbon dioxide, nitrogen, argon); and anesthetics (halothane, isoflurane and sevoflurane). Physical ones comprise: compressed air gun (non-penetrating) and captive dart (penetrating); fire gun; decapitation; exsanguination; electrocution; maceration and cervical dislocation.[15]

The physical methods may be classified as either restricted or unacceptable. Therefore, it is important to search for the appropriate method for the species being used. After completion of the procedure, death should be confirmed before the animals' bodies are discarded.[13-15]

Alternative methods

The authorized use of animals in teaching activities raises very controversial issues, especially considering that it often involves invasive procedures. This is quite questionable in veterinary educational programs, where its ethical justification is to foster the progress of medical knowledge.[16]

Continuing medical education is increasingly changing, and the search for alternative methods in surgical training has been increasing, so as to avoid the overuse of animals, thereby reinforcing ethical principles and animal rights. Accordingly, educational institutions seek ways to teach surgical practice without compromising the quality of teaching.[17]

Some authors argue that animal experimentation, in addition to being detrimental to maintaining life and bodily integrity, avoiding pain and frustration, is also non-consensual, given that it is conducted on living beings that did not voluntarily agree to participate in the research. Despite technological advances in alternative methods, it is estimated that scientific research uses around 100 million animals every year worldwide.[17-19]

The use of animals in several studies remains unacceptable to some people, even to some researchers, due to their constant concern for animal welfare. However, some important pieces of information are not always externalized, such as animal care during the investigation and the role of the veterinarian in this process, ensuring that it is possible to balance scientific goals and animal welfare.[20,21]

Most scientists and some members of the general public, nevertheless, agree that animal testing should be allowed where there are no other viable alternatives and provided that it is carried out under strict regulations. They believe it is useful to investigate disease mechanisms, validate new drugs, and to provide information on drug toxicity and interactions.[7]

The search for alternatives to animal experimentation, including its educational aspect, is experiencing intense evolution. These methods can be any given choice that can replace, reduce or refine the use of animals in biomedical research, testing or teaching. In the latter, animal experimentation can practically be replaced altogether without major impairment to learning.[14,22]

Some authors suggest the use of alternative techniques to animal testing, since they consider it an immoral and ineffective practice. These methods include in vitro tests (tissues and cells); the use of vegetables; non-invasive clinical studies in human volunteers; conducting studies with corpses instead; the use of lower organisms that are not classified as protected animals (shrimp and water flea larvae); physicochemical techniques; computer simulations; educational software; films; mathematical models; nanotechnology; and test dummies.[22]

Computer models run on specialized software and lower organisms (Figure 3) are the alternatives of choice for assessing the biological effectiveness of active drugs and molecular/genetic studies,[23] respectively.

The use of porcine small intestine and pork belly skin has proved useful in teaching suturing, grafting and surgical knotting techniques. Still, the absence of bleeding restricts the training for hemostasis, which is thus a limiting factor.[17-19]

The embryo of zebra fish (Danio-rerio) is considered a promising model for predicting toxicity in vertebrates, including humans. Its rapid development and transparency facilitate the evaluation of phenotypic effects, making it an effective model for the study of human diseases.[24]

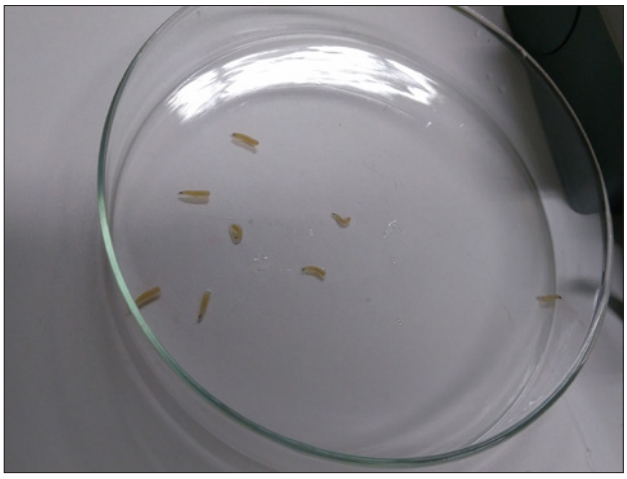


FIGURE 3 Use of inferior organisms as an alternative method to the use of vertebrate animals.

Still, these alternative methods are at different stages of development and validation. This is a difficult and slow process, since it entails collaborative studies, which are in turn carried out in several places, and the analysis of inter- and intra-laboratory variations.[22] They must undergo a series of evaluations, such as effectiveness, safety, toxicity, specificity, sensitivity and predictive value, before they can eventually be validated as alternative methods.[8]

Animal experimentation is still necessary for certain teaching and research practices, since there is still no sufficient technology to replace it altogether,[2] but there has been a clear reduction in the number of studies involving animals over the last decades.[25]

It is undeniable that in vivo animal experimentation has contributed to biological development and biomedical research, yet it is also associated with high production costs and strict ethical considerations. These limitations led to the development of a cost-effective ex vivo model that can effectively replace in vivo and in vitro models, thus contributing to animal welfare.[26]

Ex vivo models can be used to develop new therapies in which the disease can be identified at an earlier stage and treated with very advanced techniques. In dentistry, with the development of an ex vivo culture model, the investigation of inflammatory cell behavior and metabolism in different types of periodontal disease has become easy.[23,26]

Investigators' ethics

The behavior of investigators and professionals who use animals in research has been changing based on the latest

technology and science advances pertaining to laboratory animals. Currently, animal sensitivity is known to be similar to that of humans in regards to pain, memory, anguish and survival instinct.[13] For this reason, it is the investigator's responsibility to monitor the animals operated on and recognize the signs of distress. There is no justification for the absence of analgesia in those animals undergoing invasive experimental surgery.[27]

Scientists are accountable for providing high-quality care to laboratory animals, such as easy access to water and a nutritious diet; prevention of and relief from pain, injury and disease; and appropriate housing for the species.[28] Conducting research is not permitted in cases where the damage to the animal is greater than the gain in knowledge, since no scientific advance can be justified based on the suffering of other living beings.[29] In addition to ensuring animal welfare, researchers must comply with the relevant legislation. Also, it is their responsibility to inquire about the subject.[12]

A clear legislation is mandatory, as well as conducting well-delineated research.[2] Whenever animal experimentation is involved, it is necessary to invest time in appropriately designing the project in order to justify the ethical argument for carrying out the scientific investigation, especially when determining the number of animals needed for ensuring reproducible results.[6]

One should perform all experiments ethically and with a justification, not abusing one's human right over animals and in such a manner as to avoid their suffering.[13] It is important that the use of animal testing be discussed especially in universities, from where future researchers will emerge.[29]

Scientists should make the best of their knowledge and experience so they can share with the general public the reasons why animal studies are important for scientific breakthroughs. All institutions engaged in animal research also have a moral obligation to play a more active role than they are currently doing in fostering education and maintaining a dialog with the general public. They should not only promote the evidence, but also share how they conduct their research and provide care to the animals involved.[7,9,12]

Final considerations

It is evident that the use of animals in both research and teaching has offered great contributions, especially to health sciences as they allowed for many important discoveries, such as the development of new drugs and treatments, as well as the understanding of certain biological phenomena. However, activists fighting against this type of activity are still present, always emphasizing animal welfare and preventing cases of cruelty from against them.[5,6]

The principle of the 3Rs (Replace, Reduce, Refine) represents great progress in favor of the animals.[30] In spite of that, it is necessary to think in an integrative manner, since reducing the number of animals would be pointless if the tests being carried out are of little significance, thereby invalidating the experiment as a whole. Similarly, there would be no use in reducing the number of animals without considering their suffering. This theory seeks full replacement of animal experimentation with alternative models. Nevertheless, it is still hard to imagine certain scientific research projects that involve more complex systems without using this resource.[2,3]

Before beginning any experiment, the researcher should be familiar with the particularities of the species, as well as thoroughly plan the research project in order to avoid unnecessary use of living animals. It is also the researcher's responsibility to provide the animals with adequate housing conditions so as to ensure their welfare and avoid any kind of pain, suffering and stress. Environmental enrichment is a way towards achieving this goal. Stress, in addition to affecting the behavior and physiology of the species, ends up interfering with the reliability of the research.[6,8,12,13]

The experiments must be performed in an ethical manner and be justified, in such a way so as to avoid causing pain, suffering and stress to the animals during the research.[13] Whenever possible, alternative methods to using living animals should be chosen, such as in vitro testing, cadaveric studies, and computer simulations.[2]

Conclusion

The use of animals, both in teaching and research, still raises many controversies. Still, it cannot be denied that various substances that are essential to human health, such as medicines and vaccines, have been and will continue to be developed thanks to these experiments.

One must take into consideration the cost-benefit ratio of this type of scientific study, since animals are sentient beings and should not be used unnecessarily. Investigators are accountable for watching over the welfare of these laboratory animals, avoiding any kind of pain and suffering. Additionally, alternative methods should be used whenever possible.

Whenever necessary, either following the termination of experiments or during any of their stages, painless euthanasia of the animals is recommended, with a rapid loss of consciousness and followed by cardiorespiratory arrest and damage to the brain function.

References

1. Franco AL, Nogueira MNM, Sousa NGK, Frota MF, Fernandes CMSF, Serra MC. Pesquisa em animais: uma reflexão bioética. Acta Bioeth. 2014; 20(2):247-53.
2. Miziara ID, Magalhães ATM, Santos MA, Gomes EF, Oliveira RA. Research ethics in animal models. Braz J Otorhinolaryngol. 2012; 78(2):128-31.
3. Petroianu A. Aspectos éticos na pesquisa em animais. Acta Cir Bras. 1996 MES; 11(3):157-64.
4. BRASIL. Lei nº 11.794 de 8 de outubro de 2008. Procedimentos para o uso científico de animais. Diário Oficial da União; 196; Seção 1.
5. Tréz TA. Caracterização do uso de animais no ensino a partir da percepção de estudantes de ciências biológicas e da saúde. Hist Cienc Saude. 2015; 22(3):863-80.
6. Singh VP, Pratap K, Sinha J, Desiraju K, Bahal D, Kukreti R. Critical evaluation of challenges and future use of animals in experimentation for biomedical research. Int J Immunopathol Pharmacol. 2016; 29(4):551-61.
7. Kehind EO. They see a rat, we seek a cure for diseases: the current status of animal experimentation in medical practice. Med Princ Pract. 2013; 22(Suppl 1):52-61.
8. Knop LB, Maria DA. Métodos substitutivos e a experimentação animal: um enfoque inovador. RESBCAL. 2016; 4(2):101-14.
9. Batalha E. Uso de animais em pesquisa abrange desafios éticos e compromisso com novas tecnologias. Radis. 2017; 174.
10. Muller CA, Ramos S, Saisse AO, Almosny NRP. Videocâmeras em biotérios de experimentação: importante ferramenta no controle da contaminação ambiental na microbiota de camundongos. Arq Bras Med Vet Zootec. 2015; 67(3):689-97.
11. Weber EM, Dallaire JA, Gaskill BN, Pritchett-Corning KR, Garner JP. Aggression in group-housed laboratory mice: why can't we solve the problem? LabAnimal. 2017; 46(4):157-61.
12. Guidelines for the Use of Animals. Guidelines for the treatment of animals in behavioural research and teaching. Anim Behav. 2017; 123:1-9.
13. Neves SMP, Prates FM, Rodrigues LD, Santos RA, Fontes RS, Santana RO. Manual de cuidados e procedimentos com animais de laboratório do Biotério de Produção e Experimentação da FCF-IQ/USP. São Paulo: FCF-IQ/USP; 2013.
14. Iki Y, Ito T, Kudo K, Noda M, Kanehira M, Sueta T, et al. Animal ethics and welfare education in wet-lab training can foster residents' ethical values toward life. Exp Anim. 2017. doi: 10.1538/expanim.17-0026. [Epub ahead of print]
15. Conselho Federal de Medicina Veterinária. Guia Brasileiro de Boas Práticas para Eutanásia em Animais. Brasília: Comissão de Ética, Bioética e Bem-Estar Animal/CFMV; 2013.
16. Baldelli I, Massaro A, Penco S, Bassi AM, Patuzzo S, Ciliberti R. Conscientious objection to animal experimentation in Italian universities. Animals. 2017; 7(24):1-8.
17. Andrade GM, Lopes HDP, Felício SJO, Carmo VM, Matos EP. Experience report on teaching surgical technique without animal use. Acta Cir Bras. 2015; 30(5):371-5.
18. Joffe AR, Bara M, Anton N, Nobis N. The ethics of animal research: a survey of the public and scientists in North America. BMC Medical Ethics. 2016; 17:17.
19. Mayir B, Doğan U, Bilecik T, Yardımcı EC, Çakır T, Aslaner A, et al. Why scientists perform animal experiments, scientific or personal aim? Ulus Cerrahi Derg. 2016; 32(4):256-60.
20. Kehinde EO. They see a rat, we seek a cure for diseases: the current status of animal experimentation in medical practice. Med Princ Pract. 2013; 22(Suppl 1):52-61.
21. Bennett AJ, Ringach DL. Animal research in neuroscience: a duty to engage. Neuron. 2016; 92(3):653-7.
22. Balls M, Combes R. Animal experimentation and alternatives: revealed preferences. Altern Lab Anim. 2017; 45(1):1-3.
23. Pasupuleti MK, Molahally SS, Salwaji S. Ethical guidelines, animal profile, various animal models used in periodontal research with alternatives and future perspectives. J Indian Soc Periodontol. 2016; 20(4):360-8.
24. Zoupa M, Machera K. Zebrafish as an alternative vertebrate model for investigating developmental toxicity—The Triadimefon Example. Int J Mol Sci. 2017; 18(4):817.
25. Ramalli Jr EL, Ho W, Alves M, Rocha EM. Progress in animal experimentation ethics: a case study from a Brazilian medical school and from the international medical literature. Acta Cir Bras. 2012; 27(9):659-63.
26. Abubakar AA, Noordin MM, Azmi TI, Kaka U, Loqman MY. The use of rats and mice as animal models in ex vivo bone growth and development studies. Bone Joint Res. 2016; 5(12):610-8.
27. Brito CVB, Soares RHFC, Botelho NM. Analgesia de animais de laboratório: responsabilidade dos comitês de ética e obrigação dos pesquisadores. Rev Bioet. 2016; 24(3):528-31.
28. Yang NB, Pan XJ, Cheng JJ, Lin JQ, Zhu JY. Ethical Inspection about laboratory animals. Zhongguo Ying Yong Sheng Li Xue Za Zhi. 2015; 31(6):504-7.
29. Singh VP, Pratap K, Sinha J, Desiraju K, Bahal D, Kukreti R. Critical evaluation of challenges and future use of animals in experimentation for biomedical research. Int J Immunopathol Pharmacol. 2016; 29(4):551-61.
30. Tanner R, McShane H. Replacing, reducing and refining the use of animals in tuberculosis vaccine research. ALTEX. 2017; 34(1):157-66.

Benign prostatic hyperplasia: laser prostatectomy (PVP)

Hiperplasia prostática benigna: prostatectomia por vaporização a laser (PVP)

Authorship: Brazilian Society of Urology

Participants: Nunes RLV[1], Oliveira RRM[1], Carneiro A[1], Neto AM[1], Antunes AA[1], Wanderley Marques Bernardo[2], Antônio Silvinato[2]

Final draft: September 3rd, 2016

[1]Sociedade Brasileira de Urologia (SBU)
[2]Associação Médica Brasileira (AMB)

http://dx.doi.org/10.1590/1806-9282.63.11.929

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

Grades of recommendation and levels of evidence

- A: Experimental or observational studies of higher consistency.
- B: Experimental or observational studies of lower consistency.
- C: Cases reports (non-controlled studies).
- D: Opinion without critical evaluation, based on consensus, physiological studies or animal models.

Objective

The objective of this guideline is to present the main available evidence comparing transurethral resection of the prostate with laser prostatectomy (PVP) in patients with benign prostatic hyperplasia (BPH) in relation to the main peri- or postoperative outcomes, allowing the formalization of recommendations directly supported by such evidence.

Description of evidence collection method

This guideline followed the standard of a systematic review with evidence retrieval based on the EBM (evidence-based medicine), so that clinical experience is integrated with the ability to critically analyze and apply scientific information rationally, thus improving the quality of medical care. EBM uses existing and currently available scientific evidence, with good internal and external validity for the application of its results in clinical practice.[1,2]

Systematic reviews are currently considered the level I of evidence for any clinical question by systematically summarizing information on a particular topic through primary studies (clinical trials, cohort studies, case-control or cross-sectional studies) using a reproducible methodology, in addition to integrating information on effectiveness, efficiency, efficacy and safety.[1,2]

We use the structured mode of formulating the question synthesized by the acronym PICO, where P stands for patient or population presenting prostatic hyperplasia, I stands for intervention with laser prostatectomy (PVP), C stands for comparison with transurethral resection of the prostate and O stands for the outcome of efficacy and harm. Based on the structured question, we identified the descriptors that formed the basis of the search for evidence in the following databases: Medline, Embase, Central Cochrane, Cochrane Library. Thus, 367 studies were retrieved, and, after applying the eligibility criteria (inclusion and exclusion), 11 were selected to answer the clinical question (Annex I).

Clinical question

What is the effectiveness of laser prostatectomy (PVP) in patients with benign prostatic hyperplasia?

Introduction

Benign prostatic hyperplasia (BPH) is a common disease with high morbidity in the elderly. Patients with urinary symptoms, mainly obstructive, may require surgical treatment, which is usually performed through transurethral resection of the prostate (conventional TURP). Complications of the procedure include bleeding, TURP syndrome (water intoxication), urinary incontinence,

urinary retention and sexual dysfunction, especially regarding ejaculation function.

In an attempt to reduce morbidity, the development of new alternative surgical procedures has been encouraged, including photoselective vaporization of the prostate (PVP) using laser.

The laser emits light at a wavelength of 532 nm, which will be absorbed by hemoglobin, leading to heating of the prostatic tissue. In the beginning, PVP was performed with potassium-titanyl-phosphate (KTP) laser at 60 W and later at 80 W. Then, laser prostatectomy (PVP) using a high-performance system (HPS) 120 W laser or XPS 180 W laser was introduced, aiming at reducing the limitations of KTP, as well as improving results compared with conventional TURP.

The goal is to reduce hospitalization time, bleeding, and other complications, but there is some doubt as to the effectiveness of laser treatment with regard to the replacement of conventional TURP as a first-line treatment.

Selected evidence results

Patients (> 50 years) with urinary flow (UF) ≤ 15 mL/s; prostate symptoms score (IPSS) ≥ 12; prostatic volume (PV): 15-85 cm^3 (USG); obstruction (AG nomogram) (N: 76), were treated with PVP using KTP 80 W laser and star pulse quasicontinuous wave laser (laserscope) emitting green light at a wavelength of 532 nm (N: 38) compared with transurethral resection of the prostate (conventional TURP) (N: 38), with the following outcomes being assessed: urinary flow, international prostate symptoms score (IPSS), quality of life score (QoL), bother score, postvoid residual volume (PVRV), surgical time, PO Hb, length of catheterization and length of hospitalization after 6 weeks and at 3, 6 and 12-month follow-up. The use of laser leads to significant increase in UF (mL/s), decline in IPSS, increase in quality of life (QoL), increase in bother score, increase in postvoid residual volume (PVRV) (mL), shorter bladder irrigation time (min) and shorter length of hospitalization (days), and less decrease in hemoglobin levels (g/dL). There is no difference in surgical time (min).[3] (**B**)

In patients aged 68 years, BPH; PV: 70 to 100 mL; UF < 15 mL/s; PVRV > 150 mL; IPSS > 7 (N: 76), PVP with KTP/532 high-power laser emitting green light (80W) (N: 39) was compared with transurethral resection of the prostate (conventional TURP) (N: 37), and the following outcomes were assessed: IPSS and IIEF-5 scores; PV; PVRV; UF; urinary retention; transfusion; re-intervention after 6 months. There was a significant benefit with the use of PVP laser in relation to all analyzed outcomes; however, there was an increased risk of urinary retention (NNH: 8) and re-intervention (NNH: 6).[4] (**B**)

Patients with BPH; IPSS > 16; UF < 15 mL/s; PV < 100 mL; PVRV < 100 mL (N: 120) treated with HPS 120-W laser using lithium triborate (LBO) crystal, producing 532-nm waves (N: 60) or transurethral resection of the prostate (conventional TURP) (N: 60) were assessed regarding surgical time; Hb; transfusion; length of catheterization; length of hospitalization; complications; IPSS; PVRV; PV; UF at 1, 3, 6, 12, 24 and 36 months. The use of laser compared with conventional TURP significantly increased the outcome of surgical time, but reduced the outcomes of bleeding, length of catheterization and length of hospitalization. There is a decline in the risk of transfusions (NNT: 6) and intraoperative complications (NNT: 5), but also an increase in the number of early (NNH: 2) and late (NNH: 8) complications.[5] (**B**)

PVP treatment using HPS 120-W laser in 50 patients was compared with transurethral resection of the prostate (conventional TURP) in other 50 patients, the following inclusion criteria being adopted: BPH; IPSS > 15; PV < 80 cm^3; urinary flow < 15 mL/s. At 1, 3, 6, 12 and 24 months, the following outcomes were assessed: IPSS; urinary flow; surgical time; Hb; transfusion; complications; length of hospitalization; length of catheterization. The results of laser intervention reduced blood loss, length of catheterization and length of hospitalization compared with conventional TURP. Nevertheless, they increased surgical time. Regarding catheterization with a probe < 20 Fr, intraoperative and late complications, there is a benefit to using laser with NNT = 1, 10 and 6, respectively.[6] (**B**)

In patients with BPH; > 50 years; IPSS ≥ 12 and bother score ≥ 3; Qmax < 12 mL/s; prostatic volume between 25 mL and 80 mL; PVRV < 300 mL (N: 139), two treatment modalities were compared: PVP HPS 120-W laser (N: 69) and transurethral resection of the prostate (conventional TURP) (N: 70) based on IPSS; length of hospitalization; Qmax; PVRV; complications; sexual symptoms; quality of life at 12 months. Only surgical time was shorter using laser treatment, while none of the other outcomes presented significant differences, although length of hospitalization was shorter with conventional TURP.[7] (**B**)

Bleeding (measured by Hb) and length of catheterization were less noticeable in 64 patients with BPH (age > 50 years; IPSS > 7; prostatic volume > 20 and < 80 cc; urinary flow (Q max) < 15 mL/s) treated with PVP (laser emitting green light at a wavelength of 532 nm, 30 to 80W) compared with 64 patients treated with conventional TURP, at 12-month follow-up. Nevertheless, surgical time was longer in the group treated with PVP.[8] (**B**)

In patients with lower urinary tract symptoms due to BPH (N: 20) treated with PVP HPS 120-W laser) or transurethral resection of the prostate (conventional

TURP), there is no difference between the two treatment modalities regarding outcomes expressed by IPSS, IIEF-5 and ICIQ-SF scores, or the following measures: PVRV and Qmax, at 12-month follow-up.[9] (**B**)

In patients with BPH, IPSS > 15, treatment failure, Qmax < 15 mL/s and prostatic volume < 100 mL (N: 200), comparison between PVP (HPS with 80-W KTP laser) (N: 100) and transurethral resection of the prostate (conventional TURP) (N: 100) made it possible to assess the outcomes of length of catheterization, length of hospitalization, peri- and postoperative complications, IPSS and QoL, Qmax, PVRV and prostatic volume, at 1, 3, 6, 12, 24 and 36-month follow-up. The outcomes measured at 24 months did not present significant difference between the two treatment modalities in relation to the scores: quality of life (QoL), IPSS, urinary flow, PVRV and PO Hb. But there was significant benefit in favor of the laser in the following outcomes: prostatic volume, length of catheterization and length of hospitalization. Conventional TURP yielded a shorter surgical time. Regarding complications, there was a decline in the rate of transfusion and perforation of the prostatic capsule with the use of the laser.[10] (**B**)

Patients with BPH and moderate or severe lower urinary tract symptoms (IPSS >16), therapeutic failure, maximum flow rate (Qmax) < 15 mL/s, PVRV > 100 mL and prostatic volume < 100 mL (N: 62) were treated comparatively with PVP (HPS 180-W laser) (N: 31) and transurethral resection of the prostate (conventional TURP) (N: 31). At the 12-month follow-up, surgical time was longer using laser, but the lengths of hospitalization and catheterization were shorter, with lower rates of transfusion (NNT: 5) and perforation (NNT: 6). The other outcomes did not differ: hemoglobin and transfusion, other peri- and postoperative complications, IPSS, QoL, Qmax, PVRV and prostatic volume.[11] (**B**)

Except for a shorter length of hospitalization, the treatment of patients with symptoms of BPH obstruction; 64 years; IPSS > 7; Qmax < 15 mL/s; prostatic volume < 80 mL; PVRV > 150 mL (N: 124) with PVP 120-W laser (N: 60), compared with transurethral resection of the prostate (conventional TURP) (N: 64), failed to demonstrate superiority or inferiority when analyzed in relation to the following outcomes: IPSS; length of hospitalization; Qmax; PVRV; complications; sexual symptoms; re-intervention or transfusion at 24 months.[12] (**B**)

In patients with lower urinary tract symptoms due to BPH with obstruction; aged 40 to 80 years; IPSS ≥ 12; Qmax < 15 mL/s; prostatic volume ≤ 100 mL (N: 281), there was no difference between treatment with transurethral resection of the prostate (conventional TURP) (N: 142) and PVP with 180-W XPS laser vaporization (N: 139), at 24 months, regarding the following outcomes: quality of life (QoL); IPSS; urinary flow (mL/s); PVRV; prostatic volume; re-treatment and complications.[13] (**B**)

Evidence summary

There is evidence, with high risk of bias, of the benefit of laser prostatectomy (PVP) in patients with BPH compared to conventional TURP regarding UF, IPSS, QoL, bother score, IIEF-5 score, postvoid residual volume (PVRV), bladder irrigation/length of catheterization, length of hospitalization (days), Hb decline, prostatic volume, urinary retention, transfusion (NNT: 6), re-intervention (?), intraoperative complications (NNT: 5), early (NNT: 10) and late (NNT: 6) complications at different times, from 6 to 24 months.

There is evidence, with the same high risk of bias, of lower PVP benefit compared to conventional TURP regarding risk of urinary retention (NNH: 8), re-intervention (NNH: 6), surgical time, number of early (NNH: 2) and late (NNH: 8) complications, as well as length of hospitalization.

There is no difference between the two treatment modalities in relation to the outcomes expressed by the scores: IPSS, IIEF-5 and ICIQ-SF, or the following measurements: urinary flow, PVRV, prostatic volume and Qmax, length of hospitalization, complications, sexual symptoms, re-intervention, need for transfusion or re-treatment at 12 to 24 months of follow-up.

Recommendation

Due to controversies regarding the superiority or inferiority of treatment of benign prostatic hyperplasia using laser PVP compared to transurethral resection, it is not possible to recommend treatment with PVP instead of conventional TURP. (**C**)

Conflict of interest

The authors declare no conflict of interest.

References

1. Nobre MR, Bernardo WM, Jatene FB. A prática clínica baseada em evidências. Parte I – Questões clínicas bem construídas. Rev Assoc Med Bras. 2003; 49(4):445-9.
2. Bernardo WM, Nobre MR, Jatene FB. A prática clínica baseada em evidências. Parte II – Questões clínicas bem construídas. Rev Assoc Med Bras. 2004; 50(1):104-8.
3. Bouchier-Hayes DM, Anderson P, Van Appledorn S, Bugeja P, Costello AJ. KTP laser versus transurethral resection: early results of a randomized trial. J Endourol. 2006; 20(8):580-5.
4. Horasanli K, Silay MS, Altay B, Tanriverdi O, Sarica K, Miroglu C. Photoselective potassium titanyl phosphate (KTP) laser vaporization versus transurethral resection of the prostate for prostates larger than 70 mL: a short-term prospective randomized trial. Urology. 2008; 71(2):247-51.
5. Al-Ansari A, Younes N, Sampige VP, Al-Rumaihi K, Ghafouri A, Gul T, et al. GreenLight HPS 120-W laser vaporization versus transurethral resection of the prostate for treatment of benign prostatic hyperplasia: a randomized clinical trial with midterm follow-up. Eur Urol. 2010; 58(3):349-55.

6. Capitán C, Blázquez C, Martin MD, Hernández V, de la Peña E, Llorente C. GreenLight HPS 120-W laser vaporization versus transurethral resection of the prostate for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia: a randomized clinical trial with 2-year follow-up. Eur Urol. 2011; 60(4):734-9.
7. Lukacs B, Loeffler J, Bruyère F, Blanchet P, Gelet A, Coloby P, et al. ; REVAPRO Study Group. Photoselective vaporization of the prostate with GreenLight 120-W laser compared with monopolar transurethral resection of the prostate: a multicenter randomized controlled trial. Eur Urol. 2012; 61(6):1165-73.
8. Mohanty NK, Vasudeva P, Kumar A, Prakash S, Jain M, Arora RP. Photoselective vaporization of prostate vs. transurethral resection of prostate: a prospective, randomized study with one year follow-up. Indian J Urol. 2012; 28(3):307-12.
9. Pereira-Correia JA, de Moraes Sousa KD, Santos JB, de Morais Perpétuo D, Lopes-da-Silva LF, Krambeck RL, et al. GreenLight HPS™ 120-W laser vaporization vs transurethral resection of the prostate (<60 mL): a 2-year randomized double-blind prospective urodynamic investigation. BJU Int. 2012; 110(8):1184-9.
10. Xue B, Zang Y, Zhang Y, Yang D, Gao J, Sun C, et al. GreenLight HPS 120-W laser vaporization versus transurethral resection of the prostate for treatment of benign prostatic hyperplasia: a prospective randomized trial. J Xray Sci Technol. 2013; 21(1):125-32.
11. Jovanović M, Džamić Z, Aćimović M, Kajmaković B, Pejčić T. Usage of GreenLight HPS 180-W laser vaporisation for treatment of benign prostatic hyperplasia. Acta Chir Iugosl. 2014; 61(1):57-61.
12. Telli O, Okutucu TM, Suer E, Burgu B, Gulpinar O, Yaman O, et al. A prospective, randomized comparative study of monopolar transurethral resection of the prostate versus photoselective vaporization of the prostate with GreenLight 120-W laser, in prostates less than 80 cc. Ther Adv Urol. 2015; 7(1):3-8.
13. Thomas JA, Tubaro A, Barber N, d'Ancona F, Muir G, Witzsch U, et al. A multicenter randomized noninferiority trial comparing GreenLight-XPS laser vaporization of the prostate and transurethral resection of the prostate for the treatment of benign prostatic obstruction: two-yr outcomes of the GOLIATH Study. Eur Urol. 2016; 69(1):94-102.
14. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996; 17(1):1-12.
15. Goldet G, Howick J. Understanding GRADE: an introduction. J Evid Based Med. 2013; 6(1):50-4.
16. Wells G, Shea B, O'Connell D, Robertson J, Peterson J, Welch V, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Eur J Epidemiol. 2011; 25:603-5.
17. Levels of Evidence and Grades of Recommendations – Oxford Centre for Evidence Based Medicine. Available from: http://cebm.jr2.ox.ac.uk/docs/old_levels.htm.

Annex I

Clinical question

What is the effectiveness of laser prostatectomy (PVP) in patients with benign prostatic hyperplasia?

Structured question

- P: Prostatic hyperplasia
- I: Laser prostatectomy (photoselective vaporization of the prostate [PVP])
- C: Transurethral resection of the prostate
- O: Effectiveness and harm

Search strategy

- #1 – (Prostatic Hyperplasia OR Prostatic Hypertrophy OR Prostatic Adenoma)
- #2 – (Laser Therapy OR Laser OR Lasers OR Greenlight)
- #3 – Random*
- #4 – Systematic[sb]

1st RETRIEVAL = (#1 AND #2 AND #3) OR (#1 AND #2 AND #4) = 367

((Prostatic Hyperplasia OR Prostatic Hypertrophy OR Prostatic Adenoma) AND (Laser Therapy OR Laser OR Lasers OR Greenlight) AND Random*)) OR ((Prostatic Hyperplasia OR Prostatic Hypertrophy OR Prostatic Adenoma) AND (Laser Therapy OR Laser OR Lasers OR Greenlight) AND Systematic[sb]))

Articles retrieved

The obtaining of evidence to be used to analyze the clinical question followed the steps of: elaboration of the clinical question, structuring of the question, search for evidence, critical evaluation and selection of evidence, presentation of results and recommendations.

The bases of scientific information consulted were: Medline via Pubmed, Embase, Central Cochrane and Cochrane Library.

A total of 367 articles were retrieved, of which 22 were selected after reading the title and abstract; of these 11 had the full text accessed to answer the proposed clinical question (Table 1).[3-13]

Inclusion and exclusion criteria

Phase III randomized controlled clinical trials, systematic reviews (with or without meta-analyzes), comparative (or non-comparative) studies were included, and, in their absence, the best evidence available to answer the clinical question within the limits of PICO.

According to study design

Narrative reviews, case reports, case series, studies presenting preliminary results only were, in principle, excluded from the selection. Systematic reviews and meta-analyzes were used with the principle of retrieving references that may have been lost since the initial search strategy. Controlled clinical trials were assessed based on the Jadad[14] and GRADE[15] scores.

Language

We included studies available in Portuguese, English or Spanish.

According to type of publication

Only full-text studies were considered for critical assessment.

TABLE 1 Description of characteristics of the selected studies.

Study	Population	Intervention	Comparison	Outcome	Follow-up time
Bouchier-Hayes DM 2006	Age > 50 years; Urinary flow (UF) ≤ 15 mL/s; IPSS ≥ 12; Prostatic volume (PV): 15–85 cm^3 (USG); Obstruction (AG nomogram) N: 76	PVP: Laser KTP 80 W with PVP (StarPulse quasicontinuous wave laser (Laserscope) emitting green light at a wavelength of 532 nm) system N: 38	Transurethral resection of the prostate (conventional TURP) N: 38	Urinary flow; IPSS; QoL; bother score; postvoid residual volume (PVRV); surgical time; PO Hb; length of catheterization; length of hospitalization	6 weeks 3, 6 and 12 months
Horasanli K 2008	Age: 68 years; Benign Prostatic Hyperplasia (BPH); PV: 70 a 100 mL; UF < 15 mL/s; PVRV > 150 mL; IPSS > 7 N: 76	PVP: KTP/532 using high-power laser emitting green light (80 W) N: 39	Transurethral resection of the prostate (conventional TURP) N: 37	IPSS and IIEF-5 scores PV; PVRV; UF; urinary retention; transfusion; re-intervention	3 and 6 months
Al-Ansari A 2010	BPH; IPSS > 16; UF < 15 mL; PV < 100 mL; PVRV < 100 mL N: 120	HPS 120-W laser using lithium triborate (LBO) crystal, producing 532-nm waves N: 60	Transurethral resection of the prostate (conventional TURP) N: 60	Surgical time; Hb; transfusion; length of catheterization; length of hospitalization; complications; IPSS; PVRV; PV; UF	1, 3, 6, 12, 24 and 36 months
Capitán C 2011	BPH; IPSS > 15; PV < 80 cm^3; urinary flow < 15 mL/s N: 100	HPS 120-W laser PVP N: 50	Transurethral resection of the prostate (conventional TURP) N: 50	IPSS, urinary flow; surgical time; Hb; transfusion; complications; length of hospitalization; length of catheterization	1, 3, 6, 12 and 24 months
Mohanty NK 2012	BPH; age > 50 years; IPSS > 7; prostatic volume > 20 and < 80 cc; urinary flow (Q max) < 15 mL/s N: 128	PVP: Laser emitting green light at a wavelength of 532 nm (30 W to 80 W) N: 64	Transurethral resection of the prostate (conventional TURP) N: 64	IPSS, QOL, IIEF5; prostatic volume, PVRV and Qmax; surgical time and catheterization; hemoglobin and complications	1, 3, 6 and 12 months
Lukacs B 2012	BPH; > 50 years; IPSS ≥ 12 and bother score ≥ 3; Qmax < 12 mL/s; prostatic volume between 25 mL and 80 mL; PVRV < 300 mL N: 139	PVP (HPS 120-W laser) N: 69	Transurethral resection of the prostate (conventional TURP) N: 70	IPSS; length of hospitalization; Qmax; PVRV; complications; sexual symptoms; quality of life	12 months
Pereira-Correia JA 2012	Lower urinary tract symptoms due to BPH N: 20	PVP (HPS 120-W laser) N: 10	Transurethral resection of the prostate (conventional TURP) N: 10	IPSS; IIEF-5; ICIQ-SF; PVRV; Qmax	1, 3, 6, 9, 12 and 24 months

(*continues*)

TABLE 1 (Cont.) Description of characteristics of the selected studies.

Study	Population	Intervention	Comparison	Outcome	Follow-up time
Xue B 2013	BPH, IPSS > 15; treatment failure; Qmax < 15 mL/s; prostatic volume < 100 mL N: 200	PVP (HPS with 80-W KTP laser) N: 100	Transurethral resection of the prostate (conventional TURP) N: 100	Length of catheterization; length of hospitalization and peri- and postoperative complications; IPSS; QoL; Qmax; PVRV; prostatic volume	1, 3, 6, 12, 24 and 36 months
Jovanović M 2014	Moderate or severe lower urinary tract symptoms (International Prostate Symptom Score IPSS > 16), treatment failure, maximum flow rate (Qmax) < 15 mL/s, PVRV > 100 mL, prostatic volume < 100 mL N: 62	PVP (HPS 180-W laser) N: 31	Transurethral resection of the prostate (conventional TURP) N: 31	Surgical time; hemoglobin and transfusion. Length of catheterization and length of hospitalization; peri- and postoperative complications; IPSS; QoL; Qmax; PVRV; prostatic volume	1, 3, 6 and 12 months
Telli O 2015	Symptoms of obstruction due to BPH; 64 years; IPSS > 7; Qmax < 15 mL/s; prostatic volume < 80 mL; PVRV > 150 mL. N: 124	PVP with 120-W laser N: 60	Transurethral resection of the prostate (conventional TURP) N: 64	IPSS; length of hospitalization; Qmax; PVRV; complications; sexual symptoms; re-intervention; transfusion	6, 12 and 24 months
Thomas JA 2016	Lower urinary tract symptoms due to BPH with an obstruction; 40 to 80 years; IPSS ≥ 12; Qmax < 15 mL/s; prostatic volume ≤ 100 mL N: 281	180-W XPS laser vaporization N: 139	Transurethral resection of the prostate (conventional TURP) N: 142	QoL; IPSS; urinary flow (mL/s); PVRV; prostatic volume; re-treatment; complication-free	6, 12 and 24 months

Critical appraisal method

After applying the inclusion and exclusion criteria, whenever the selected evidence was defined as a randomized controlled trial (RCT), an appropriate Critical Assessment Checklist was applied (Table 2). The critical evaluation of the RCT allows classification according to the Jadad score,[14] so that Jadad < three (3) trials are considered inconsistent (grade B), while those scoring ≥ three (3) are found consistent (grade A), and according to the GRADE classification[15] (strong or moderate evidence).

If the selected evidence was defined as a comparative study (observational cohorts or non-randomized clinical trial), an appropriate critical evaluation check-list was applied (Table 3), allowing the classification of the study according to the New Castle Otawa Scale,[16] so that cohort studies presenting a score ≥ 6 would be consistent, while those scoring < 6 would be inconsistent.

TABLE 2 Script for critical evaluation of randomized controlled clinical trials.

Study data	**Sample calculation**
References, study design, Jadad, strength of evidence	Estimated differences, power, level of significance, total of patients
Patient selection	**Patients**
Inclusion and exclusion criteria	Recruited, randomized, prognostic differences
Randomization	**Patient follow-up**
Description and blinded allocation	Time, losses, migration
Treatment protocol	**Analysis**
Intervention, control and blinding	Intention to treat, analyzed, intervention and control
Outcomes considered	**Result**
Primary, secondary, outcome measurement instrument	Benefit or harm in absolute data, mean benefit or mean harm

TABLE 3 Script for critical appraisal of cohort studies.

Representativeness of exposed studies and selection of non-exposed studies (max. 2 points)	Definition of the exposure (max. 1 point)	Demonstration that the outcome of interest was not present at the beginning of the study (max. 1 point)	Comparability based on design or analysis (max. 2 points)	Outcome assessment (max. 1 point)	Appropriate follow-up time (max. 2 points)	Score and level of evidence

TABLE 4 Description of biases in the selected studies.

Study	Question	Randomization	Allocation	Blinding	Losses	Prognosis	Outcomes	ITT analysis
Bouchier-Hayes DM 2006	Yes	No	No	No	Yes (< 20%)	Yes	Yes	No
Horasanli K 2008	Yes	No	No	No	No	Yes	Yes	No
Al-Ansari A 2010	Yes	Yes	No	No	Yes (< 20%)	Yes	Yes	Yes
Capitán C 2011	Yes	Yes	Yes	No	Yes (< 20%)	Yes	Yes	No
Mohanty NK 2012	Yes	No	No	No	Yes (< 20%)	Yes	Yes	No
Lukacs B 2012	Yes	Yes	Yes	No	Yes (< 20%)	Yes	Yes	Yes
Pereira-Correia JA 2012	Yes	Yes	No	No	No	Yes	Yes	No
Xue B 2013	Yes	Yes	No	No	No	Yes	Yes	No
Jovanović M 2014	Yes	Yes	No	No	No	Yes	Yes	No
Telli O 2015	Yes	Yes	Yes	No	Yes (< 20%)	Yes	Yes	No
Thomas JA 2016	Yes	Yes	Yes	No	Yes (< 20%)	Yes	Yes	No

Exposure of results

For results with available evidence, the population, intervention, outcomes, presence or absence of benefit and/or harm, and controversies will be defined in a specific manner, whenever possible (Table 5).

The results will be preferably expressed in absolute data, absolute risk, number needed to treat (NNT), or number needed to harm (NNH), and occasionally using mean and standard deviation (Tables 6-16).

Recommendation

The recommendations will be elaborated by the authors of the review, with the initial characteristic of synthesis of the evidence, and later validated by all the authors who participate in the elaboration of this guideline.

The grade of recommendation stems directly from the available strength of included studies, according to the Oxford scale[17] and the GRADE system.[15]

TABLE 5 Worksheet used to describe and present the results of each study.

Evidence included
Study design
Population selected
Follow-up time
Outcomes considered
Expression of results: percentages, risk, odds, hazard ratio, mean

TABLE 6 Results of the selected study.

Bouchier-Hayes DM 2006[3]

Outcomes	Mean (SD) of the intervention (38)	Mean (SD) of the comparison (38)	Significance
Increase in flow (mL/s)	11.96±8.23	8.56±9.08	p<0.05
Decline in IPSS	14.0±9.8	12.9±10.6	p<0.05
Decline in QoL	2.65±2.1	2.91±2.04	p<0.05
Decline in bother score	1.91±1.29	1.61±1.22	p<0.05
Post-void residual volume (mL)	125±198	86±124.38	p<0.05
Surgical time (min)	30.24 (9-70)	31.33 (5-70)	NS
Time of irrigation (min)	12.2±8.6	44.52±30.23	p<0.05
Time of hospitalization (days)	1.08±0.28	3.39±1.17	p<0.05
Decline in hemoglobin levels (g/dL)	0.45±0.7	1.5±0.15	p<0.05

TABLE 7 Results of the selected study.

Horasanli K 2008[4]

Outcomes (6 months)	Mean (SD) of the intervention (39)		Mean (SD) of the comparison (37)		Significance		
Urinary flow (mL/s)	13.3±7.9		20.7±11.3		p<0.05		
IPSS	13.1±5.8		6.4±7.9		p<0.05		
IIEF-5	19±5.2		21±6.8		p<0.05		
Post-void residual volume (mL)	78.9±62.1		22.9±18.7		p<0.05		
Surgical time (min)	87±18.3		51±17.2		p<0.05		
Length of catheterization (days)	1.7±0.8		3.9±1.2		p<0.05		
Length of hospitalization (days)	2±0.7		4.8±1.2		p<0.05		
Outcome	**No. of events intervention (39)**	**No. of events control (37)**	**Risk intervention %**	**Risk control %**	**Reduction increase %**	**95CI**	**NNT/ NNH**
Urinary retention	6	1	15.3	2.7	12.6 (ARI)	0.21 to 25.15	8 (NNH)
Transfusion	0	3	0	8.1	8.1 (ARR)	NS	NS
Re-intervention	7	0	17.9	0	17.9 (ARI)	5.90 to 29.99	6 (NNH)

TABLE 8 Results of the selected study.

Al-Ansari A 2010[5]

Outcomes	Mean (SD) of the intervention (60)	Mean (SD) of the comparison (60)	Significance
Urinary flow (mL/s)	NS	NS	NS
IPSS	NS	NS	NS
Hemoglobin (intraoperative)	13.1±1.5	11.3±1.9	p<0.05
Post-void residual volume (mL)	NS	NS	NS
Prostatic volume	NS	NS	NS
Surgical time (min)	89±18	80±13	p<0.05
Length of catheterization (days)	1.4±0.6	2.7±0.9	p<0.05
Length of hospitalization (days)	2.3±1.2	4.1±0.6	p<0.05

Outcome	No. of events intervention (60)	No. of events control (60)	Risk intervention %	Risk control %	Reduction increase %	95CI	NNT/ NNH
Transfusion	0	12	0	17.95	17.95 (ARR)	5.90 to 29.99	6 (NNT)
Intraoperative complications	0	13	0	20	20 (ARR)	9.87 to 30.12	5 (NNT)
Early complications	56	19	93.33	31.67	61.67 (ARI)	48.31 to 75.02	2 (NNH)
Late complications	10	3	16.67	5	11.67 (ARI)	0.74 to 22.59	8 (NNH)

TABLE 9 Results of the selected study.

Capitán C 2011[6]

Outcomes	Mean (SD) of the intervention (50)	Mean (SD) of the comparison (50)	Significance
Urinary flow (mL/s)	22.56	21.98	NS
IPSS	8	8.57	NS
Decline in hemoglobin levels (g/dL)	0.65±1.31	2.30±4.36	p<0.05
Prostatic volume	27.17	23.8	NS
Surgical time (min)	54.13±14.40	48.15±14.71	p<0.05
Length of catheterization (h)	23±22	72±48	p<0.05
Length of hospitalization (days)	1.6 (1-5)	3.6±2.1	p<0.05

Outcome	No. of events intervention (50)	No. of events control (50)	Risk intervention %	Risk control %	Reduction increase %	95CI	NNT/ NNH
Cateter < 20F	50	8	100	16	84 (ARR)	73.94 to 94.16	1 (NNT)
Intraoperative complications	0	5	0	10	10 (ARR)	1.68 to 18.31	10 (NNT)
Early complications	14	8	28	16	NS	NS	NS
Late complications	7	16	14	32	18 (ARR)	1.8 to 34.11	6 (NNT)

TABLE 10 Results of the selected study.

Lukacs B 2012[7]							
Outcomes – 12 months	**Mean (SD) of the intervention (69)**			**Mean (SD) of the comparison (70)**		**Significance**	
QoL	75 (60-85)			77 (69.5-87.5)		NS	
IPSS	6.26 (3.23-9.30)			7.94 (4.9-10.97)		NS	
Urinary flow (mL/s)	16.7 (12-22.7)			16.8 (12.1-24.9)		NS	
PVRV	7 (0-32)			0 (0-43)		NS	
Prostatic volume	30 (22-40)			24.7 (18.5-35)		NS	
Sexual satisfaction	2 (1-4)			2 (1-4)		NS	
Surgical time (min)	55 (45-65)			71 (55-95)		p<0.05	
Length of hospitalization (days)	2.5 (2-3.5)			1 (1-2)		p<0.05	
Outcome	**No. of events intervention (69)**	**No. of events control (70)**	**Risk intervention %**	**Risk control %**	**Reduction increase %**	**95CI**	**NNT/ NNH**
Complications	18	27	26.5	39.7	NS	NS	NS

TABLE 11 Results of the selected study.

Mohanty NK 2012[8]							
Outcomes – 12 months	**Mean (SD) of the intervention (52)**			**Mean (SD) of the comparison (50)**		**Significance**	
QoL	1.52±0.50			1.48±0.50		NS	
IPSS	5.96±1.98			6.00±1.95		NS	
Urinary flow (mL/s)	20.12±3.99			19.77±3.12		NS	
PVRV	23.94±13.26			20.40±12.73		NS	
Prostatic volume	26.27±7.35			26.0±8.88		NS	
Hemoglobin (g/dL)	12.42±1.32			11.16±1.31		p<0.05	
Surgical time (min)	53.72±10.23			42.77±12.93		p<0.05	
Length of catheterization (h)	24.65±2.98			49.23±14.17		p<0.05	
Outcome	**No. of events intervention (60)**	**No. of events control (57)**	**Risk intervention %**	**Risk control %**	**Reduction increase %**	**95CI**	**NNT/ NNH**
Complications	26	28	43.33	49.12	NS	NS	NS

TABLE 12 Results of the selected study.

Pereira-Correia JA 2012[9]			
Outcomes – 12 months	**Mean (SD) of the intervention (10)**	**Mean (SD) of the comparison (10)**	**Significance**
ICIQ-SF	0 (0)	0 (0)	NS
IIEF-5	23 (22-24)	23 (22-24)	NS
IPSS	6 (2-10)	6 (1-12)	NS
Urinary flow (mL/s)	22.2 (12-38)	18 (10-28)	NS
PVRV	2 (0-10)	2.5 (0-20)	NS
BOOI	-12 (-4 to -68)	-1.2 (-4 to -14)	p<0.05

TABLE 13 Results of the selected study.

Xue B 2013[10]							
Outcomes – 24 months	**Mean (SD) of the intervention (100)**		**Mean (SD) of the comparison (100)**			**Significance**	
QoL	1		1.2			NS	
IPSS	10.4		9.1			NS	
Urinary flow (mL/s)	19.6		20.9			NS	
PVRV (mL)	14.4		15.7			NS	
Prostatic volume	33.8		23.8			p<0.05	
Hemoglobin	13.9±1.8		12.1±1.6			NS	
Surgical time	52.3±15.4		47.6±14.2			p<0.05	
Length of catheterization	1.9±0.8		3.6±1.7			p<0.05	
Length of hospitalization	4.3±1.5		6.8±2.1			p<0.05	
Outcome	**No. of events intervention (100)**	**No. of events control (100)**	**Risk intervention %**	**Risk control %**	**Reduction increase %**	**95CI**	**NNT/ NNH**
Transfusion	0	4	0	4	4 (ARR)	0.15 to 7.8	25
TURP syndrome	0	0	0	0	NS	NS	NS
Perforation	0	5	0	5	5 (ARR)	0.7 to 9.2	20
Infection	4	5	0	5	NS	NS	NS
Dysuria	9	8	9	8	NS	NS	NS
Incontinence	3	4	3	4	NS	NS	NS
Urethral stricture	5	2	5	2	NS	NS	NS
Re-intervention	4	1	4	1	NS	NS	NS

TABLE 14 Results of the selected study.

Jovanović M 2014[11]							
Outcomes – 12 months	**Mean (SD) of the intervention (31)**		**Mean (SD) of the comparison (31)**			**Significance**	
IPSS	5.2		4.8			NS	
Urinary flow (mL/s)	18.7		18.5			NS	
Surgical time	92±18		82±13			p<0.05	
Length of hospitalization	1.9±0.8		4.4±0.6			p<0.05	
Hemoglobin	13.2±1.5		11.7±1.9			NS	
Length of catheterization	1.1±0.6		2.9±0.9			p<0.05	
Outcome	**No. of events ntervention (31)**	**No. of events control (31)**	**Risk intervention %**	**Risk control %**	**Reduction increase %**	**95CI**	**NNT/ NNH**
Transfusion	0	6	0	19.4	19.4 (ARR)	5.4 to 33.2	5
Clot retention	0	2	0	6.4	NS	NS	NS
Urethral stricture	1	4	3.2	12.9	NS	NS	NS
Perforation	0	5	0	16.1	16.1 (ARR)	3.1 to 29.0	6
Dysuria/urgency	9	10	29	32.2	NS	NS	NS
TURP syndrome	0	1	0	3.1	NS	NS	NS

TABLE 15 Results of the selected study.

Telli O 2015[12]

Outcomes – 24 months	Mean (SD) of the intervention (39)		Mean (SD) of the comparison (62)			Significance	
IPSS	75 (30-92)		60 (37-91)			NS	
Urinary flow (mL/s)	22.6±0.9		24.5±1.2			NS	
PVRV (mL)	60 (13-88)		58 (95-100)			NS	
Sexual activity (SHIM score)	32 (27-41)		34 (25-46)			NS	
Prostatic volume	23.9±13		22.4±13.3			NS	
Length of hospitalization	2 (1-4)		5 (3-9)			p<0.05	
Outcome	**No. of events intervention (60)**	**No. of events control (64)**	**Risk intervention %**	**Risk control %**	**Reduction increase %**	**95CI**	**NNT/ NNH**
Transfusion	2	2	3.33	3.12	NS	NS	NS
Urinary retention	3	4	4.68	6.66	NS	NS	NS
Urethral stricture	5	12	8.33	18.75	NS	NS	NS
Re-intervention	2	4	3.33	6.25	NS	NS	NS
Infection	4	6	6.66	9.37	NS	NS	NS

TABLE 16 Results of the selected study.

Thomas JA 2016[13]

Outcomes – 24 months	Mean (SD) of the intervention (128)		Mean (SD) of the comparison (121)			Significance	
QoL	1.3±1.2		1.2±1.3			NS	
IIEF-5	12.9±7.5		13.9±8.2			NS	
IPSS	9.5±3.0		9.9±3.5			NS	
Urinary flow (mL/s)	21.6±10.7		22.9±9.3			NS	
PVRV (mL)	45.6±65.5		34.9±47.1			NS	
Prostatic volume	23.9±13		22.4±13.3			NS	
Outcome	**No. Of events intervention (139)**	**No. Of events control (142)**	**Risk intervention %**	**Risk control %**	**Reduction increase %**	**95CI**	**NNT/ NNH**
Re-treatment	78	73	56.12	51.41	NS	NS	NS
Complication-free	116	112	83.45	78.87	NS	NS	NS

Fulminant myocarditis in children. Continuous renal replacement therapy to the rescue?

Patrick M. Honore[1]*, Herbert D. Spapen[2]

[1]MD, PhD, FCCM, Professor of Intensive Care Medicine and Co-director of Research, ICU Department, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium
[2]MD, PhD, FCCM, Professor of Intensive Care Medicine, Head of Unit and Director of Research, ICU Department , Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium

*Correspondence:
ICU Department
UZ Brussel – VUB University
Address: 101, Laarbeeklaan
Jette (Brussels) – Belgium
Postal code: 1090
patrick.honore@az.vub.ac.be

http://dx.doi.org/10.1590/1806-9282.63.11.941

Fulminant myocarditis (FM) is a devastating disease. Patients typically present with flu-like symptoms and then rapidly develop severe heart failure, cardiogenic shock and potentially fatal arrhythmias.[1] In children, FM corresponds to 30-40% of cases of myocarditis with a mortality rate of up to 48%.[2] Treatment is supportive, aiming to bridge the period of severe cardiac distress.[1] In a recent issue of *Revista da Associação Médica Brasileira*, a novel and provocative treatment of FM is proposed based upon the intrinsic involvement of cardiac myosin.[3] Extensive release of cardiac myosin is indeed thought to play a key role in the pathogenesis of FM, in particular by propagating autoimmune-induced myocardial inflammation and subsequent cardiac injury.[4-6] Cardiac myosin is an hexamer consisting of two myosin heavy chains, each associated with two myosin light chains, i.c. an essential light chain (MLC-1) and a regulatory light chain (RLC).[7] The 23-kD MLC-1 isoform has been identified as a sensitive biomarker of cardiac injury.[8-10] Not surprisingly, the authors observed highly elevated MLC-1 levels in their patient cohort.[4]

More importantly, the authors focused on the removal of MLC-1 from the bloodstream in an attempt to attenuate or suppress the noxious action of this molecule on the heart. This is supported by in vitro experience showing that RLC depletion reduced unloaded actin filament velocity and enhanced myosin-based isometric force approximately 2-fold.[8] Its relatively medium molecular weight makes MLC-1 particularly suitable for removal by convective continuous renal replacement therapy (CRRT).[11] Accordingly, a significant decrease of MLC-1 concentrations was noticed when continuous venovenous hemo(dia)filtration (CVVHDF) was applied. This brings to mind the seminal studies of Grootendorst et al., who observed a significant improvement in right ventricular ejection fraction and cardiac performance in endotoxemic pigs subjected to high-volume hemofiltration (HVHF).[12] Infusion of ultrafiltrate from endotoxemic animals in healthy pigs caused a decrease in blood pressure and cardiac output suggesting that HVHF removed one or more vasoactive mediators responsible for sepsis-induced myocardial depression.[13] However, a clinical benefit of HVHF on clinical course or outcome of human sepsis and septic shock has not been demonstrated. The current study also offers insufficient proof that lowering MLC-1 levels are associated with favourable clinical outcome. The reduction in MLC-1 after a 48h CRRT session is certainly significant but CRRT alone cannot account for the observed 23% decrease. The "natural" metabolization rate of MLC-1 is unknown because a control group not receiving CRRT is lacking. An objective evaluation of left ventricular systolic function during treatment (e.g. with echocardiography) is missing. Moreover, the lower mortality rate in this small patient cohort should be weighed against baseline severity of disease and timing of the intervention. The CRRT approach also needs more in-depth evaluation before it can be recommended as a safe and effective adjunctive treatment for FM. Several factors may indeed determine substance removal during CRRT. CRRT-related issues comprise mode, volume, and dialysis membrane type and characteristics. Continuous venovenous hemofiltration (CVVH) and CVVHDF are also different techniques.[11] It is not clear to what proportion these epuration modes were used in the studied patients. Also, no information is provided regarding volume, intercurrent dialysis interruptions or on-off decisions, adverse events, and complications. Finally, it remains to

be determined whether and to what extent MLC-1 is adsorbed on different membranes. Substance-related factors comprise volume of distribution, hydro- or lipophilic nature and protein binding. MLC-1 is a hydrophilic molecule with a distribution volume of approximately 0.7 L/kg and thus easily eliminated by convection.[14] However, the light chain component of myosin expresses high affinity for ionized calcium which suggests a rather strong protein binding.[15] The exact degree of protein binding is not known but may not exceed 80% to allow adequate CRRT removal.[15] Elimination of MLC-1 by CRRT is essentially determined by its molecular weight. Medium cut-off (50 kD) membranes may therefore enhance MLC-1 removal without unwarranted loss of albumin.[11] High cut-off (60 kD) membranes may even perform better, but at the expense of more albumin depletion.[16] Plasmafiltration which uses membranes with a cut-off value of approximately 1,000 kD may be the most efficient option for adequate and swift MLC-1 removal.[11,17]

In conclusion, the authors presented a novel and provocative approach of FM in children. They identified MLC-1 as a prominent culprit of severe myocardial damage in FM and demonstrated substantial elimination of this molecule by CRRT. However, a potential link between lowering MLC-1 levels and improvement of myocardial inflammation or clinical outcome is poorly documented and speculative at the most. Nevertheless, further studies on the role of CRRT as adjuvant therapy for a disease with such grim prognosis must be encouraged. From a technical viewpoint, the use of CVVH with higher cut-off filters or plasmafiltration should be explored in more detail.

Authors' contributions

PMH & HDS designed the paper, participated in drafting the manuscript; and approved the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

References

1. Ginsberg F, Parrillo JE. Fulminant myocarditis. Crit Care Clin. 2013; 29(3):465-83.
2. Saji T, Matsuura H, Hasegawa K, Nishikawa T, Yamamoto E, Ohki H, et al. Comparison of the clinical presentation, treatment, and outcome of fulminant and acute myocarditis in children. Circ J. 2012; 76(5):1222-8.
3. Sheng C, Zhang Z, Jia Y, Li Y. Changes in serum cardiac myosin light chain 1 levels in children with fulminant myocarditis during continuous blood purification. Rev Assoc Med Bras. 2017; 63(10):904-9.
4. Wang ZH, Liao YH, Dong JH, Li SL, Wang JP. Experimental study of autoimmune diseases, cardiac myosin-induced. Chinese J Cardiol. 2003; 31:937-40.
5. Cai G, Zhang J, Liu L, Shen Q. Successful treatment of experimental autoimmune myocarditis by adenovirus-mediated genetransfer of antisense CIITA. J Mol Cell Cardiol. 2005; 38(4):593-605.
6. Reddy J, Massilamany C, Buskiewicz I, Huber SA. Autoimmunity in viral myocarditis. Curr Opin Rheumatol. 2013 ; 25(4):502-8.
7. Yamashita H, Sugiura S, Fujita H, Yasuda Si, Nagai R, Saeki Y, et al. Myosin light chain isoforms modify force-generating ability of cardiac myosin by changing the kinetics of actin-myosin interaction. Cardiovasc Res. 2003; 60:580-8.
8. Pant K, Watt J, Greenberg M, Jones M, Szczesna-Cordary D, Moore JR. Removal of the cardiac myosin regulatory light chain increases isometric force production. FASEB J. 2009; 23(10):3571-80.
9. Celes MR, Malvestio LM, Suadicani SO, Prado CM, Figueiredo MJ, Campos EC, et al. Disruption of calcium homeostasis in cardiomyocytes underlies cardiac structural and functional changes in severe sepsis. PLoS One. 2013; 8(7):e68809.
10. Katus HA, Diederich KW, Ueller M, Remppis A, Schuler G, Kübler W. Myosin light chains release in acute myocardial infarction: non-invasive estimation of infarct size. Cardiovasc Res. 1988; 22(7):456-63.
11. Honore PM,Jacobs R, Joannes-Boyau O, De Regt J, De Waele E, van Gorp V, et al. Newly designed CRRT membranes for sepsis and SIRS--a pragmatic approach for bedside intensivists summarizing the more recent advances: a systematic structured review. ASAIO J. 2013; 59(2):99-106.
12. Grootendorst AF, van Bommel EF, van der Hoven B, van Leengoed LA, van Osta AL. High volume hemofiltration improves right ventricular function in endotoxin-induced shock in the pig. Intensive Care Med. 1992; 18(4):235-40.
13. Grootendorst AF, van Bommel EF, van Leengoed LA, van Zanten AR, Huipen HJ, Groeneveld AB. Infusion of ultrafiltrate from endotoxemic pigs depresses myocardial performance in normal pigs. J Crit Care. 1993; 8(3):161-9.
14. Reetze-Bonorden P, Böhler J, Keller E. Drug dosage in patients during continuous renal replacement therapy. Pharmacokinetic and therapeutic considerations. Clin Pharmacokinet. 1993; 24(5):362-79.
15. Holroyde MJ, Potter JD, Solaro RJ. The calcium binding properties of phosphorylated and unphosphorylated cardiac and skeletal myosins. J Biol Chem. 1979; 254(14):6478-82.
16. Honoré PM, Jacobs R, Boer W, Joannes-Boyau O, De Regt J, De Waele E, et al. New insights regarding rationale, therapeutic target and dose of hemofiltration and hybrid therapies in septic acute kidney injury. Blood Purif. 2012; 33(1-3):44-51.
17. Cerdá J, Baldwin I, Honore PM, Villa G, Kellum JA, Ronco C; ADQI Consensus Group. Role of technology for the management of AKI in critically ill patients: from adoptive technology to precision continuous renal replacement therapy. Blood Purif. 2016; 42(3):248-65.

Human polyomavirus infection: Cytological and molecular diagnosis

Patricia Gioia de Assis[1]*, Maria da Glória da Costa Carvalho[1]

[1]Faculdade de Medicina da Universidade Federal do Rio de Janeiro (FM-UFRJ), Rio de Janeiro, RJ, Brazil

Study conducted at Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Anatomic Pathology Service, Rio de Janeiro, RJ, Brazil

Article received: 4/6/2017
Accepted for publication: 5/7/2017

***Correspondence:**
Cidade Universitária – Ilha do Fundão
Address: Rua Prof. Rodolpho Paulo Rocco, 255
Rio de Janeiro, RJ – Brazil
Postal code: 21941-913
paty.assis@uol.com.br

http://dx.doi.org/10.1590/1806-9282.63.11.943

Summary

Few studies directly compare urinary cytology with molecular methods for detecting BK and JC polyomaviruses. Reactivation of BKV infection is the main risk factor for the development of nephropathy in immunocompromised individuals. The limitation of the cytological method can be attributed to the stage where the infected cell does not have specific and sufficient morphological characteristics for a conclusive diagnosis and can be easily interpreted as degenerative alteration. Moreover, morphologically, it is not possible to differentiate the two types of viruses. Polymerase chain reaction (PCR), not only is a sensitive method, but also allows differentiation of viral types without quantification, and therefore is not indicative of nephropathy. According to the American Society of Nephrology, real-time PCR would be the gold standard to indicate nephropathy because it allows quantifying the number of viral copies.

Keywords: polyomavirus, BK virus, JC virus, kidney transplantation.

Introduction

In the 1950s, cytotechnologist Andrew Ricci observed cells with large, homogeneous nuclei in the urinary sediment, mimicking neoplastic cells but not associated with urothelial neoplasia, and called them decoy cells.[1] The so-called decoy cells have been erroneously diagnosed as cancer cells in the past. It was only in 1968 that it was speculated that these cells could be related to some type of virus, identified as polyomavirus in 1971.[2]

It is believed that they originate in the urothelium of healthy and asymptomatic patients. This hypothesis is based on the fact that it is in the urothelium that the BK virus (BKV) is often latent. Replication of the polyomavirus occurs mainly in the superficial layer of the transitional epithelium, that is, in the umbrella cells that shed easily without causing symptoms or altered renal function. Infected cells are not seen in the kidneys of immunocompetent patients whereas, in immunocompromised patients, nephropathy is characterized by intra-renal replication of BKV with consequent renal dysfunction. The morphological changes caused by viral replication in renal tubular epithelial cells are similar to those observed in transitional cells. Therefore, in BKV nephropathy, decoy cells also originate, probably in the renal parenchyma.[3-5] It is speculated that BKV nephropathy is caused by an ascending transmission pathway with dissemination of the polyomavirus originating from the transitional cells to the collecting ducts and proximal tubular epithelial cells in patients with some immunodepression condition.[6]

Diagnosis

Few studies directly compare urinary cytology with molecular methods for detecting polyomaviruses.

Decoy cells can be easily detected on Papanicolaou stained cytology smears, and its negative predictive value (NPV) is close to 100%. Conversely, the positive predictive value (PPV) of the decoy cell analysis to predict BKV nephropathy (BKVN) ranges from only 25 to 30%.[7] The persistence of decoy cells in repeated urine samples identifies patients with potential risk for BKVN. On the other hand, according to the "patient screening algorithm and monitoring protocols," a patient with a monolayer-treated urine cytology with more than ten decoy cells is indicated for renal biopsy, with no need for confirmation by PCR.[8] Although it is relatively easy to detect the presence of decoy cells in urine, it is not possible to distinguish between BKV and JCV.

Classification of decoy cells[6]

- Type 1. The most common are the classic forms characterized by large, homogeneous and amorphous inclusions, with a ground-glass appearance, and a peripheral halo of condensed chromatin.

- Type 2. They are granular intranuclear inclusions surrounded by a clear halo, so they are called cytomegalovirus-like inclusions.
- Type 3. These are multinucleated decoy cells with granular chromatin.
- Type 4. When infected cells exhibit vesicular nuclei, often with clumped chromatin and evident nucleoli. This is what Koss called the post-inclusion (empty) stage.

The main differential diagnosis of polyomavirus infection in urine is urothelial neoplasms, mainly types 3 and 4. Unfortunately, viral infection can occur in patients with urothelial neoplasia, especially if they are using cytotoxic drugs and infected and neoplastic cells are mixed in the smear. Some details can be analyzed in this differentiation, but, in practice, this is not always possible: decoy cells are seen alone, whereas neoplastic cells can form groups with overlapping nuclei; the nuclei of decoy cells are rounded, in contrast to those of tumor cells, which have irregular nuclei. And if the two conditions (cancer and polyomavirus infection) are associated it may be even more complicated to distinguish one from the other. The search for decoy cells in urine is a marker with a positive predictive value of about 27%, which requires confirmation with more specific techniques, such as polymerase chain reaction.[9,10]

Polymerase chain reaction

As the gold standard for the detection and identification of BK and JC viruses, since it can differentiate them by analyzing the generated DNA fragments,[9,11,12] it revealed the prevalence of BK and JC viruses in the urine of immunocompromised and immunocompetent patients through the technique of polymerase chain reaction (PCR). Even immunocompetent patients excreted BK and JC viruses in the urine, showing that the final diagnosis always depends on a combination of laboratory and clinical data.

Clinical significance of polyomavirus infection

Humans are the natural hosts of two major members of the Polyomaviridae family that are able to develop persistent subclinical infection in the kidneys and peripheral blood. BKV was isolated from the urine of a patient 4 months after renal transplantation. JCV was isolated from the brain of a patient with Hodgkin's disease with progressive multifocal leukoencephalopathy (PML). Both viruses are excreted in the urine of infected patients, suggesting that the kidney is infected in early stages of contact with this pathogen. In the case of JCV, lymphoid tissues and bone marrow also appear to be involved as early or latent infection sites.[13]

Depending on the degree of reactivity, i.e. the intensity of viral replication, the virus can be eliminated in urine without entering the bloodstream, persist in the urine, or progress to viremia.

It is estimated that more than 70% of the general population has been exposed to BKV, showing serological evidence of such contact. Asymptomatic reactivation and a low level of replication are observed in 5% of the healthy population. Reactivation with clinical manifestations is rare in immunocompetent individuals, even though asymptomatic intermittent replication with elimination through urine may occur. Thus, symptoms develop more commonly in immunocompromised individuals, transplant recipients, HIV-infected patients, pregnant women and patients with neoplasms undergoing chemotherapy. BKV is the agent that causes nephropathy in 1-10% of kidney transplant recipients, which can result in graft loss in about 45% of cases. There is a correlation between the degree of immunosuppression performed in renal transplant patients and the reactivation of BKV infection, which is the main risk factor for the development of polyomavirus nephropathy.

Conclusion

The limitation of the cytological method can be attributed to the stage at which the infected cell does not have specific and sufficient morphological characteristics for a conclusive diagnosis and can be easily interpreted as a degenerative alteration. In 2007 Domingues et al.[14] described a semi-nested PCR technique capable of differentiating BK and JC viruses from stored clinical samples. However, this method did not allow quantification of viral particles. Real-time PCR has revolutionized the process of quantification of DNA fragments. According to the American Society of Nephrology (2006), this technique would be the gold standard to indicate nephropathy whenever the number of BKV copies is greater than or equal to 104.

Resumo

Infecção pelo poliomavírus humano: diagnóstico citológico e molecular

Poucos estudos comparam diretamente a citologia urinária com métodos moleculares para detecção de poliomavírus BK e JC. A reativação da infecção por BKV é o principal fator de risco para o desenvolvimento de nefropatia em indivíduos imunocomprometidos. A limitação do método citológico pode ser atribuída ao estágio em que a célula infectada não possui características morfológicas específicas e suficientes para um diagnóstico con-

clusivo, podendo ser facilmente interpretada como alteração degenerativa. Além do mais, morfologicamente, não é possível diferenciar os dois tipos virais. A reação em cadeia pela polimerase (PCR), além de ser um método sensível, permite diferenciar os tipos virais sem quantificá-los, não sendo, portanto, indicativa de nefropatia. Segundo a American Society of Nephrology, a PCR em tempo real seria o padrão-ouro para indicar nefropatia, pois permite quantificar o número de cópias virais.

Palavras-chave: poliomavírus, vírus BK, vírus JC, transplante de rim.

References

1. Koss LG, Melamed MR. Koss' diagnostic cytology and its histopathologic bases. 5. ed. Philadelphia: Lippincott Williams & Wilkins; 2006. 1752 p.
2. Gardner SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet. 1971; 1(7712):1253-7.
3. Nickeleit V, Hirsch HH, Binet IF, Gudat F, Prince O, Dalquen P, et al. Polyomavirus infection of renal allograft recipients: from latent infection to manifest disease. J Am Soc Nephrol. 1999; 10(5):1080-9.
4. Nickeleit, V, Klimkait T, Binet IF, Dalquen P, Del Zenero V, Thiel G, et al. Testing for polyomavirus type BK DNA in plasma to identify renal-allograft recipients with virus nephropathy. N Engl J Med. 2000; 342(18):1309-15.
5. Nickeleit V, Steiger J, Mihatsch MJ. BK virus infection after kidney transplantation. Graft. 2002; 5(Dec Suppl):S46-57.
6. Singh HK, Bubendorf L, Mihatsch MJ, Drachenberg C, Nickeleit V. Urine cytology findings of polyomavirus infections. In: Ahsan N, editor. Polyomaviruses and human diseases. Advances in experimental Medicine and Biology. New York: Springer; 2006. p. 201-12.
7. Varella RB, Almeida JR, Lopes PF, Matos JPS, Menezes P, Lugon JR. BK polyomavirus in kidney transplant recipients: screening, monitoring and clinical management. J Bras Nefrol. 2014; 36(4):529-34.
8. Merlino C, Bergallo M, Gribaudo G, Gregori G, Paolo Segoloni G, Giacchino F, et al. Polyomavirus BK DNA quantification assay to evaluate viral load in renal transplant recipients. J Clin Virol. 2003; 28(3):265-74.
9. Behzad-Behbahani A, Klapper PE, Vallely PJ, Cleator GM, Khoo SH. Detection of BK virus and JC virus DNA in urine samples from immunocompromised (HIV-infected) and immunocompetent (HIV-non-infected) patients using polymerase chain reaction and microplate hybridisation. J Clin Virol. 2004; 29(4):224-9.
10. Fogazzi GB, Cantú M, Saglimbeni L. 'Decoy cells' in the urine due to polyomavirus BK infection: easily seen by phase-contrast microscopy. Nephrol Dial Transplant. 2001; 16(7):1496-8.
11. Randhawa PS, Demetris AJ. Nephropathy due to polyomavirus type BK. N Engl J Med. 2000; 342(18):1361-3.
12. Whiley DM, Mackay IM, Sloots TP. Detection and differentiation of human polyomaviruses JC and BK by LightCycler PCR. J Clin Microbiol. 2001; 39(12):4357-61.
13. Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH. Manual of clinical microbiology. 7. ed. Washington: American Society for Microbiology; 1999.
14. Domingues JT, Paris F, Schmitt VM. Proposta de reação em cadeia da polimerase (PCR) semi-nested para pesquisa e diferenciação dos vírus BK e JC. Scientia Medica. 2007; 17(2):72-8.

Posterior fossa decompression with duraplasty in Chiari surgery: A technical note

Marcelo Ferreira Sabba[1], Beatriz Souza Renor[1], Enrico Ghizoni[2], Helder Tedeschi[2], Andrei Fernandes Joaquim[3]*

[1]MD. Neurosurgery Resident, Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brazil
[2]MD, PhD. Professor of Neurosurgery, Unicamp, Campinas, SP, Brazil
[3]MD, PhD. Neurosurgeon, Unicamp, Campinas, SP, Brazil

Study conducted at Universidade Estadual de Campinas (Unicamp), Campinas, SP, Brazil

Article received: 4/2/2017
Accepted for publication: 4/3/2017

***Correspondence:**
Departamento de Neurologia
Hospital das Clínicas da Faculdade de Medicina da Universidade de Campinas
Cidade Universitária Zeferino Vaz
Campinas, SP – Brazil
Postal code: 13083-888
andjoaquim@yahoo.com

http://dx.doi.org/10.1590/1806-9282.63.11.946

Summary

Chiari malformation (CM) is the most common and prevalent symptomatic congenital craniocervical malformation. Radiological diagnosis is established when the cerebellar tonsils are located 5 mm or more below the level of the foramen magnum on magnetic resonance imaging (MRI). Surgical treatment is indicated whenever there is symptomatic tonsillar herniation or syringomyelia/hydrocephalus. The main surgical treatment for CM without craniocervical instability (such as atlantoaxial luxation) is posterior fossa decompression, with or without duraplasty. The authors describe in details and in a stepwise fashion the surgical approach of patients with CM as performed at the State University of Campinas, emphasizing technical nuances for minimizing the risks of the procedure and potentially improving patient outcome.

Keywords: Arnold-Chiari malformation/surgery, cerebellum/pathology, neural tube defects.

Introduction

Chiari malformation (CM) was described in 1891 by Hans Chiari as a caudal displacement of the cerebellar tonsils through the foramen magnum.[1] The prevalence of patients with CM in the US is estimated at about 215,000 individuals,[2] being the most common and prevalent symptomatic congenital craniocervical malformation.[2-4] Type 1 CM, diagnosed when the cerebellar tonsils are located 5 mm or more below the level of the foramen magnum on magnetic resonance imaging (MRI), is the commonest form and is discussed in the present article.[5] This radiological diagnosis is questioned by many authors, once the amount of herniation needed to be considered as "abnormal" and to produce clinical symptoms is extremely variable (some patients may present with symptoms with less herniation and others may even be asymptomatic).[6] Tonsillar herniation, associated with a small posterior fossa volume, may result in cerebrospinal fluid (CSF) flow abnormalities and in upper cervical spine and brainstem compression, leading to a constellation of clinical symptoms.[7,8]

Surgical treatment is indicated whenever there is symptomatic tonsillar herniation or syringomyelia/hydrocephalus. The main surgical treatment for CM without craniocervical instability (such as atlantoaxial luxation) is posterior fossa decompression, with or without duraplasty. The benefits of posterior fossa decompression in patient outcome are well established in many case series.[9-13]

The present technical note describes in details and in a stepwise fashion the surgical approach of patients with CM as it is done at our institution (State University of Campinas). The rationale of each step is discussed along with a review of the pertinent literature.

Surgical technique

Patient position

After general anesthesia, the patient is positioned prone on the operating table and cushioned with chest rolls. Central venous access is usually not necessary. The neck is flexed in order to expose the posterior fossa, and the foramen magnum and the head are fixed with a head holder. In order to facilitate venous return and avoid excessive bleeding we generally flex the neck only up to a point where we are sure there is no compression of the jugular veins (Figure 1A).

It is of paramount importance to exclude atlantoaxial instability or cranial settling and basilar invagination prior to positioning, once flexion in these patients may result in ventral brainstem or upper cervical spinal cord compres-

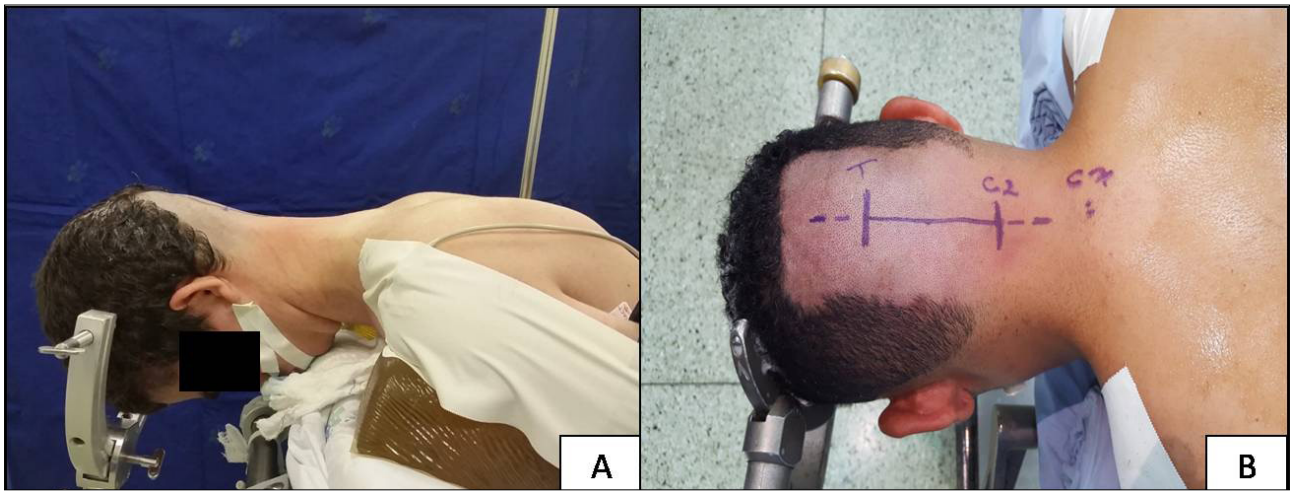


FIGURE 1 A. Lateral view of the patient position. The neck is flexed but not too much, as to avoid jugular compression. B. The incision goes from 3 cm above the inion (T-torcula) to the C2 prominence in the skin.

sion.[14-16] A dynamic CT scan or MRI is recommended to exclude instability. In such cases, we recommend neurophysiologic monitoring with motor and somatosensory evoked potentials. A neutral position is preferred in such cases and mandatory if craniocervical fixation is planned.

Skin incision, dissection and bone exposure

A midline skin incision is started about 3 cm above the inion down to the skin prominence of the C2 spinous process (Figure 1B). The cranial extension of the skin incision is used for harvesting a pericranial graft for the duroplasty.[17] We favor the use of pericranium instead of artificial grafts because it avoids foreign body reaction and potentially decreases the risks for infection and the chances of further arachnoiditis, which may be the cause of Chiari reoperations.[18] The graft is preferentially harvested before opening the dura in order to avoid bleeding into the subarachnoid space.

The fascia is exposed and then opened in a "T" fashion using monopolar cautery (Figure 2). The transverse portion of the "T"-shaped incision is made about 0.5 to 1 cm below the insertion of the muscles in the superior nuchal line. We preserve the muscle attachment in the superior nuchal line so as to allow for the suture of the paraspinous muscles back in place at the end of the procedure. This may preserve function and avoid CSF leak while providing a tight and hermetic closure. The longitudinal incision is made from the transverse incision down toward the posterior tubercle of the atlas (C1) in the midline. Maintaining the incision in the midline, which is practically avascular, potentially decreases postoperative pain and avoids muscle injury. We open the midline with monopolar cautery and then apply self-retaining retractors to separate the paraspinous musculature. The posterior part of the C1 arch is then exposed about 2 cm laterally on each side of the posterior tubercle of the atlas, generally with gentle blunt dissection. Additional lateral exposure is unnecessary and may increase the risk of vertebral artery injury, which courses on the upper superficial portion of the posterior arch of the atlas.

The occipital bone squama and the posterior arch of C1 are exposed. A laminectomy of the atlas is done using a craniotome or Kerrison's rongeurs. After that, a suboccipital decompression is performed. Our upper limit of the craniectomy is the inferior nuchal line, since this allows for a wide enough craniectomy with enough bone left for the eventual need for future craniocervical stabilization. We prefer to make two burr holes just lateral to the midline at the inferior nuchal line and then perform the craniectomy down to the foramen magnum.

It is of paramount importance to remove the bone of the foramen magnum as far to the lateral as possible, as we believe that this is the most relevant part of bone decompression (Figure 3A). We do not perform total posterior fossa craniectomy (which would include the bone above the inferior nuchal line to the inion), since we believe decompression of the foramen magnum is the actual goal of the surgery. Large craniectomies may hamper reoperation if craniocervical instability develops after Chiari surgery with associated basilar invagination, as the lack of bone may render craniocervical fixation and arthrodesis extremely difficult. Additionally, large craniectomies are associated with cerebellum ptosis, persistent headache and clinical deterioration, requiring reconstruction of the posterior fossa with titanium plates.[19]

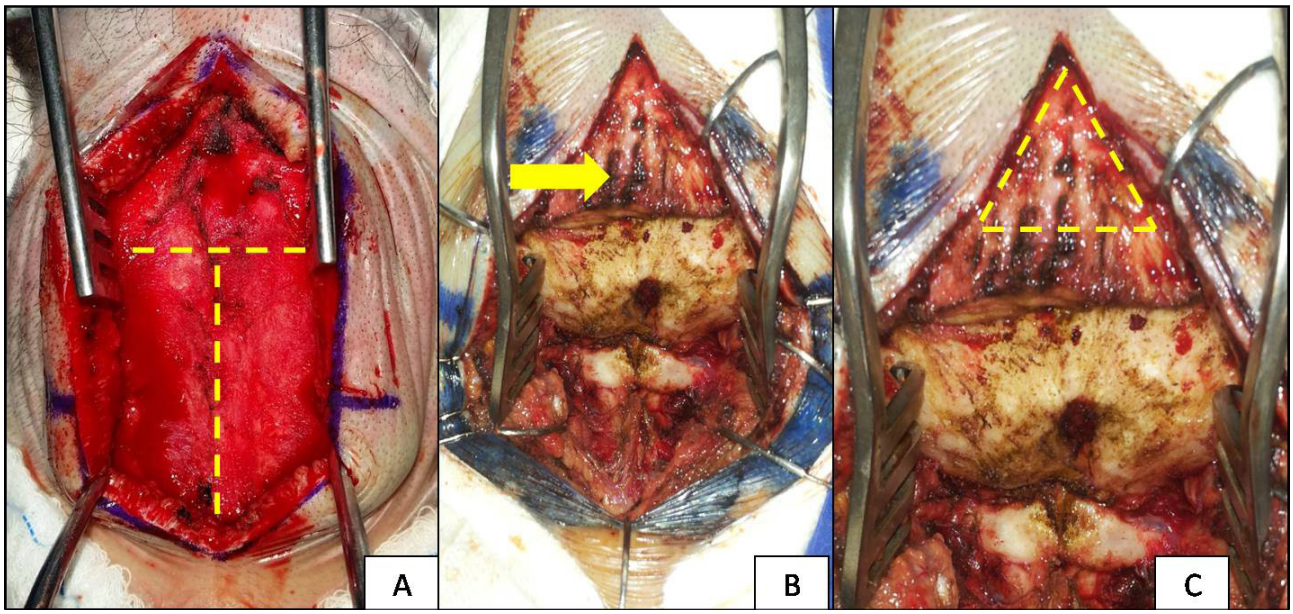


FIGURE 2 A. Exposure of the fascia – the "T" shape illustrates the fascia opening. B. Note the muscle attachment in the superior portion of the incision for suturing the muscles when closuring (yellow arrow). The occipital bone was exposed, as well as the posterior arch of the atlas below. C. The yellow triangle illustrates the site for pericranial harvest for grafting. Note that the muscle inserted in the superior nuchal line is preserved below the grafted area for suturing the paraspinal muscles and the fascia.

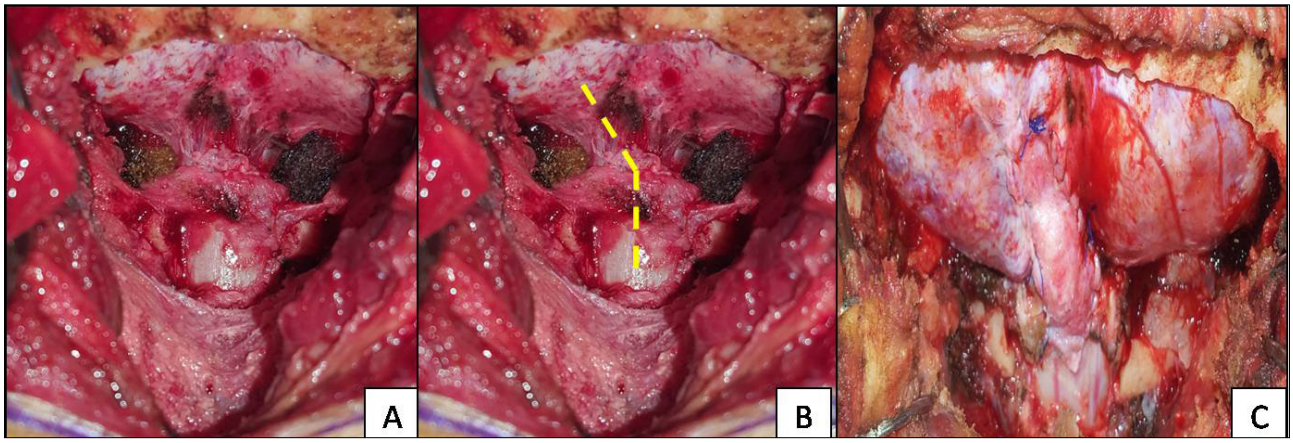


FIGURE 3 A. Posterior fossa craniectomy and removal of the posterior arch of C1. The superior limit of the bone removal is the inferior nuchal line. Laterally, the lateral portions of the foramen magnum were also removed (surgicel was used for bleeding control). Note the muscles still inserted in C2, to preserve their normal function as much as possible. B. We illustrate the dural incision (yellow line). Differently from the "Y" shape traditionally used, this incision allows a more hermetic dural closure after inserting the pericranial graft, decreasing the risks of CSF leak. It starts at the dura mater of the atlas cranially to one of the two sides. C. Final aspect after duraplasty.

Duraplasty and closure

We perform duraplasty in patients with syringomyelia, important tonsillar herniation (up to C2 or more than 10 mm below the level of the foramen magnum) and those with symptoms of neural compression (such as long tract involvement or brainstem compromise). This strategy has also been reported by some authors, such as Gurbuz et al.[20] For patients with only posterior cervical pain, we prefer to perform bone decompression alone. Although both techniques (with or without duraplasty) are acceptable and result in clinical improvement, the outcome of patients who undergo duraplasty seems slightly better despite the higher risks of complications, such as CSF leak.

Of note, some authors recommend the use of intraoperative ultrasound for fluid flow assessment in the posterior fossa after bone decompression in order to help decide when to perform the duraplasty. We do not recommend this, since Bond et al.[21] have reported that, when patients have their necks flexed (positioned for surgery), intraoperative MR demonstrates tremendous improvement in the CSF flow in the foramen magnum dorsal to the tonsils compared to preoperative MRI in prone position. For this reason, we prefer to perform duraplasty using the clinical and radiological criteria previously exposed above.

If we decide to perform duraplasty, instead of the traditional incision in a "Y" shape, we perform a more linear incision as shown in Figure 3B. This type of dural incision allows for a better closure of the dura with the pericranial graft, which decreases the risk of CSF leak. We prefer to use a 5.0 prolene suture, to avoid leak secondary to the other larger needles injury to the dura. We generally do not use any type of glue or dural sealant for primary surgery.

A multilayered closure is then performed. The fascia is sutured in the midline and superiorly to the muscle cushion attached to the superior nuchal line. Simple sutures are preferred to avoid rupture and to maintain a perfect closure. Additional continuous suture may be performed after that. The subcutaneous tissue is then sutured and also fixed to the fascia to avoid the need for postoperative drains and death space. Finally, the skin closure is made with simple sutures.

Conclusion

When treating patients with Chiari malformation, the proper surgical technique with minute attention to details is extremely important for minimizing the risks of the procedure and to improve the patients' final outcome.

Resumo

Descompressão de fossa posterior com duroplastia no tratamento cirúrgico do Chiari: nota técnica

A malformação de Chiari (MC) é a malformação craniocervical congênita sintomática mais comum e prevalente. O diagnóstico radiológico é definido quando as tonsilas cerebelares estão localizadas pelo menos 5 mm abaixo do nível do forame magno na ressonância magnética (RM). Quando há hérnia tonsilar sintomática, siringomielia ou hidrocefalia, o tratamento cirúrgico é indicado. O principal tratamento cirúrgico para MC sem instabilidade craniocervical (como a luxação atlantoaxial) é a descompressão da fossa posterior com ou sem duroplastia. Os autores descrevem detalhadamente a abordagem cirúrgica de pacientes com MC realizada na Universidade Estadual de Campinas, enfatizando nuances técnicas para minimizar os riscos relacionados ao procedimento e melhorar os resultados pós-operatórios.

Palavras-chave: malformação/cirurgia de Arnold-Chiari, cerebelo/patologia, defeitos do tubo neural.

References

1. Chiari H. Uber Veränderungen des Kleinhirns infolge von Hydrocephalie des Grosshirns. Dtsch Med Wochenshr. 1891; 17:1172-5.
2. Speer MC, George TM, Enterline DS, Franklin A, Wolpert CM, Milhorat TH. A genetic hypothesis for Chiari I malformation with or without syringomyelia. Neurosurg Focus. 2000; 8(3):E12.
3. Goel A. Basilar invagination, Chiari malformation, syringomyelia: a review. Neurol India. 2009; 57(3):235-46.
4. Menezes AH, Traynelis VC. Anatomy and biomechanics of normal craniovertebral junction (a) and biomechanics of stabilization (b). Childs Nerv Syst. 2008; 24(10):1091-100.
5. Smith BW, Strahle J, Bapuraj JR, Muraszko KM, Garton HJ, Maher CO. Distribution of cerebellar tonsil position: implications for understanding Chiari malformation. J Neurosurg. 2013; 119(3):812-9.
6. Batista UC, Joaquim AF, Fernandes YB, Mathias RN, Ghizoni E, Tedeschi H. Computed tomography evaluation of the normal craniocervical junction craniometry in 100 asymptomatic patients. Neurosurg Focus. 2015; 38(4):E5.
7. Greitz D. Unraveling the riddle of syringomyelia. Neurosurg Rev. 2006; 29(4):251-63; discussion 264.
8. Oldfield EH, Muraszko K, Shawker TH, Patronas NJ. Pathophysiology of syringomyelia associated with Chiari I malformation of the cerebellar tonsils. Implications for diagnosis and treatment. J Neurosurg. 1994; 80(1):3-15.
9. Zhang Y, Zhang N, Qiu H, Zhou J, Li P, Ren M, et al. An efficacy analysis of posterior fossa decompression techniques in the treatment of Chiari malformation with associated syringomyelia. J Clin Neurosci. 2011; 18(10):1346-9.
10. Bao C, Yang F, Liu L, Wang B, Li D, Gu Y, et al. Surgical treatment of Chiari I malformation complicated with syringomyelia. Exp Ther Med. 2013; 5(1):333-7.
11. Batzdorf U, McArthur DL, Bentson JR. Surgical treatment of Chiari malformation with and without syringomyelia: experience with 177 adult patients. J Neurosurg. 2013; 118(2):232-42.
12. Heiss JD, Suffredini G, Bakhtian KD, Sarntinoranont M, Oldfield EH. Normalization of hindbrain morphology after decompression of Chiari malformation Type I. J Neurosurg. 2012; 117(5):942-6.
13. Logue V, Edwards MR. Syringomyelia and its surgical treatment: an analysis of 75 patients. J Neurol Neurosurg Psychiatry. 1981; 44(4):273-84.
14. Joaquim AF, Ghizoni E, Giacomini LA, Tedeschi H, Patel AA. Basilar invagination: surgical results. J Craniovertebr Junction Spine. 2014; 5(2):78-84.
15. Joaquim AF, Ghizoni E, Almeida JPC, Anderle DV, Tedeschi H. Basilar invagination secondary to hypoplasia of the clivus: is there indication for craniocervical fixation? Coluna/Columna. 2014; 13(1):69-70.
16. Joaquim AF, Fernandes YB, Mathias RN, Batista UC, Ghizoni E, Tedeschi H, et al. Incidence of basilar invagination in patients with tonsillar herniation? A case control craniometrical study. Arq Neuropsiquiatr. 2014; 72(9):706-11.
17. Pritz MB. Surgical treatment of Chiari I malformation: simplified technique and clinical results. Skull Base. 2003; 13(3):173-7.
18. Stevens EA, Powers AK, Sweasey TA, Tatter SB, Ojemann RG. Simplified harvest of autologous pericranium for duraplasty in Chiari malformation Type I. Technical note. J Neurosurg Spine. 2009; 11(1):80-3.
19. Udani V, Holly LT, Chow D, Batzdorf U. Posterior fossa reconstruction using titanium plate for the treatment of cerebellar ptosis after decompression for Chiari malformation. World Neurosurg. 2014; 81(5-6):836-41.
20. Gurbuz MS, Karaaslan N, Caliskan T, Unal E, Berkman MZ. Comparison of the surgical results for foramen magnum decompression with and without duraplasty in Chiari malformation type 1. Turk Neurosurg. 2015; 25(3):419-24.
21. Bond AE, Jane JA Sr, Liu KC, Oldfield EH. Changes in cerebrospinal fluid flow assessed using intraoperative MRI during posterior fossa decompression for Chiari malformation. J Neurosurg. 2015; 122(5):1068-75.

Malignant fibrous histiocytoma in a patient presenting with urinary system symptoms

Mustafa Resorlu[1]*, Ozan Karatag[1], Fatma Uysal[1], Muhsin Ozturk[1]

[1]Canakkale Onsekiz Mart University, Faculty of Medicine, Radiology, Canakkale, Turkey

Study conducted at Canakkale Onsekiz Mart University, Faculty of Medicine, Department of Radiology, Canakkale, Turkey

Article received: 3/15/2017
Accepted for publication: 5/7/2017

***Correspondence:**
Canakkale Onsekiz Mart University,
Terzioglu Yerleskesi
Canakkale – Turkey
Postal code: 17100
mustafaresorlu77@gmail.com

http://dx.doi.org/10.1590/1806-9282.63.11.950

Summary

Malignant fibrous histiocytoma is a rare tumor. It is most commonly seen in individuals between the fifth and seventh decades of life, in extremities, and less frequently in the retroperitoneum. Although its etiology is not clearly known, radiotherapy, chemical agents, previous history of surgery, trauma and fracture, and Hodgkin lymphoma have been blamed. Leiomyosarcoma, liposarcoma and rhabdomyosarcoma should be taken into account in differential diagnosis. It is seen on computed tomography as a mass lesion with irregular borders and density similar to that of the surrounding muscle tissue. Necrotic and hemorrhagic components in the mass are characterized as heterogeneous low density areas. Fluid-fluid levels can be detected by computed tomography and magnetic resonance imaging.

Keywords: histiocytoma, malignant fibrous, tomography, magnetic resonance imaging.

Introduction

Boundaries of the retroperitoneal space are the diaphragm at the top, the levator muscles at the bottom, the parietal peritoneum in anterior aspect, and the vertebral column and psoas muscles at the posterior side. Tumors located in the retroperitoneum might be originated from kidney, pancreas or fatty tissue. Leiomyosarcoma, liposarcoma, fibrosarcoma and malignant fibrous histiocytoma (MFH) are among the retroperitoneal malignant mesenchymal tumors.[1]

MFH, also named malignant fibrous xanthoma or pleomorphic fibrous histiocytoma, has been first reported by O'Brien and Stout in 1964.[2] It is an aggressive and high-grade sarcoma. The most frequent complaints are palpable mass, pressure symptoms on surrounding organs and abdominal pain. Prognosis of these rare tumors originating from connective tissue depends on tumor diameter, number of mitoses and degree of differentiation.[3] We present the case of a patient referred to our hospital who has been diagnosed with MFH following surgery.

Case report

A 61 year-old female who had a history of hypertension and diabetes for 5 years presented to our hospital with abdominal distension and complaints related with the urinary system. Her medical history showed that she had undergone a surgical procedure associated with her uterus and ovaries and that had received no medical treatment after the surgery. Her laboratory tests revealed blood glucose, white blood cell and hemoglobin levels at 165 mg/dL, 15,500/mm^3 and 9.1 g/dL, respectively. No abnormalities were detected in other results of routine complete blood count (CBC) or biochemistry test parameters. A mass lesion with lobulated contours and irregular borders measuring 12 cm in diameter between the kidney and the psoas muscle at the left side was detected by computed tomography (CT) and magnetic resonance imaging (MRI).

CT scan revealed a calcific component measuring 1 cm in diameter at the posteromedial side of the lesion (Figure 1). On MRI, the lesion was isodense on T1 weighted series and slightly hyperdense compared to the muscle on T2 weighted series. Focal areas with low signal indicating fibrous tissue were present in the lesion on T2 weighted series. Intense enhancement was seen in the series after contrast injection (Figure 2). The mass lesion, evaluated as a retroperitoneal sarcoma radiologically, was diagnosed as a malignant fibrous histiocytoma after histopathological examination following surgery.

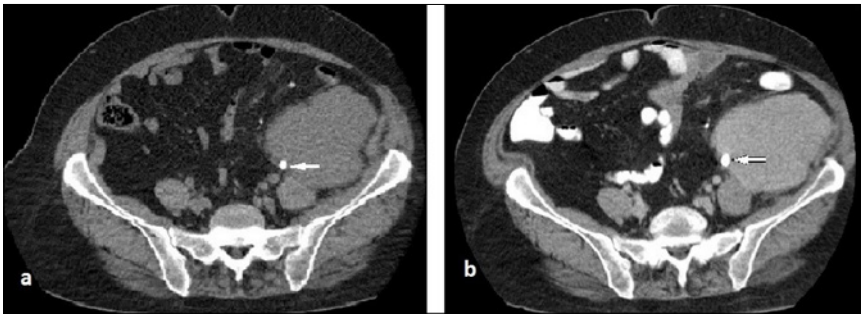


FIGURE 1 A. A mass lesion including a calcific component in close proximity with the psoas muscle in axial pre- (B) and post-contrast CT images.

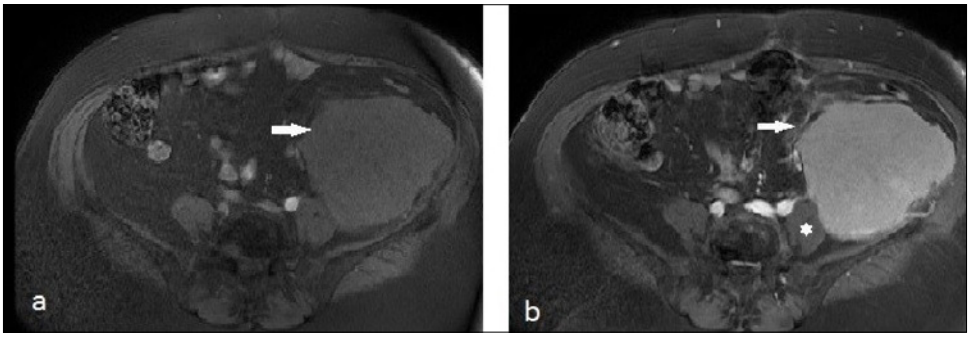


FIGURE 2 A. Intense contrast enhancement is observed in fat-suppressed T1-weighted pre- (B) and post-contrast MRI series.

Discussion

MFH originates from undifferentiated mesenchymal cells and comprises approximately 0.5% of all malignant tumors.[4] They can occur at any age but are more frequent in relatively older individuals, especially in the fifth and seventh decades of life. They are most commonly seen in the extremities but can occur at any localization in the body.[3] Malignant fibrous histiocytoma, which is one of the mesenchymal tumors, includes fibroblasts at different stages and histiocyte-like cells. They are divided into five different subgroups and the ones more commonly seen are pleomorphic and myxoid types, which tend to present higher grades, while the rarer giant cell, inflammatory and angiomatoid subtypes tend to present lower grades.[5]

The etiology of MFH is not completely known; however, it is more common in patients who received radiotherapy, similar to other sarcomas. In addition, sunlight, chemical agents such as phenacetin, previous surgery, trauma and fracture, bone infarct, and tumors such as Hodgkin lymphoma and multiple melanoma are predisposing factors.[4,5] Most of the patients are asymptomatic, since the lesion is located retroperitoneally and deeply, or they have nonspecific symptoms such as flank pain, fever and weight loss. C-reactive protein level and erythrocyte sedimentation rate may be found to be increased in laboratory tests.[6] Palpable mass, compression of surrounding organs and flank pain are the results of the increasing dimensions of the tumor. Also, cases of paraneoplastic syndrome have been reported in the literature.[7]

Differential diagnosis includes leiomyosarcoma, liposarcoma and rhabdomyosarcoma as retroperitoneal tumors. Psoas abscess, hematoma and hydatid cyst should also be considered in differential diagnosis.[6] Radiological findings are nonspecific and the diagnosis is made histopathologically. The dimensions and site of the lesion, presence of hemorrhagic or necrotic components, and mass affecting the surrounding organs might be detected by radiological imaging. Ultrasonographically, the tumor has a hypoechoic mass character and necrotic/hemorrhagic components are seen as hypoechoic or anechoic images with septated formations.[6,8] Typical CT findings include a large infiltrative mass with ill-defined borders and density similar to that of muscle tissue. Hypodense areas secondary to necrotic and hemorrhagic components and hyperdense calcific components cause non-homogeneity. Heterogeneous contrast enhancement might be seen in post-contrast images secondary to necrotic and hemorrhagic components.[5] Fluid-fluid levels may be seen secondary to hemorrhage in CT and MRI. Signal properties of hemorrhagic component in MRI vary according

to the character of the blood products. In addition, fibrous components demonstrate low signal on T1 and T2 weighted sequences. Although radiological findings are nonspecific, some specifications are present and can differentiate MFH from renal carcinoma. Large dimensions at the time of diagnosis, absence of renal vein or vena cava involvement, characteristic signs of fibrous components and necrotic/hemorrhagic or calcific components raise suspicion for MFH.[9]

The prognosis of MFH is generally poor. Determinant prognostic factors are subgroup type and location of the tumor, as well as presence of metastases or paraneoplastic syndrome. Five-year survival rate is 66% when tumor dimension is less than 5 cm, decreasing to 30% if the diameter is greater than 5 cm.[3,10] Similarly, there is a positive correlation between tumor diameter and rate of metastasis. Prognosis is better in tumors located in extremities compared to retroperitoneal or deeply located tumors.[9,10]

Primary treatment of MFH is surgical excision of the mass. Radiotherapy plays an important role in the postsurgical treatment; however, the efficacy of chemotherapy is controversial.[10]

References

1. Gemici K, Buldu İ, Acar T, Alptekin H, Kaynar M, Tekinarslan E, et al. Management of patients with retroperitoneal tumors and a review of the literature. World J Surg Oncol. 2015; 13:143.
2. O'Brien JE, Stout AP. Malignant fibrous xanthomas. Cancer. 1964; 17:1445-55.
3. Hsu HC, Huang EY, Wang CJ. Treatment results and prognostic factors in patients with malignant fibrous histiocytoma. Acta Oncol. 2004; 43(6):530-5.
4. Gutierrez JC, Perez EA, Franceschi D, Moffat FL Jr, Livingstone AS, Koniaris LG. Outcomes for soft-tissue sarcoma in 8249 cases from a large state cancer registry. J Surg Res. 2007; 141(1):105-14.
5. Karki B, Xu YK, Wu YK, Zhang WW. Primary malignant fibrous histiocytoma of the abdominal cavity: CT findings and pathological correlation. World J Radiol. 2012; 4(4):151-8.
6. Gupta MM, Bahri N, Watal P, Rathod K, Thaker S, Bhandari P, et al. Retroperitoneal cystic malignant fibrous histiocytoma mimicking a psoas abscess. Iran J Radiol. 2015; 12(3):e17507.
7. Kageyama K, Moriyama T, Hizuka N, Sakihara S, Takayasu S, Tamasawa N, et al. Hypoglycemia associated with big insulin-like growth factor II produced during development of malignant fibrous histiocytoma. Endocr J. 2003; 50(6):753-8.
8. Rajiah P, Sinha R, Cuevas C, Dubinsky TJ, Bush WH Jr, Kolokythas O. Imaging of uncommon retroperitoneal masses. Radiographics. 2011; 31(4):949-76.
9. Nishino M, Hayakawa K, Minami M, Yamamoto A, Ueda H, Takasu K. Primary retroperitoneal neoplasms: CT and MR imaging findings with anatomic and pathologic diagnostic clues. Radiographics. 2003; 23(1):45-57.
10. Kearney MM, Soule EH, Ivins JC. Malignant fibrous histiocytoma: a retrospective study of 167 cases. Cancer. 1980; 45(1):167-78.

Clinical correlation of biopsy results in patients with temporal arteritis

Volkan Yuksel[1]*, Orkut Guclu[2], Ebru Tastekin[3], Umit Halici[4], Serhat Huseyin[2], Volkan Inal[5], Suat Canbaz[6]

[1]Associate Professor of Cardiovascular Surgery, Trakya University, Edirne, Turkey
[2]Assistant Professor of Cardiovascular Surgery, Trakya University, Edirne, Turkey
[3]Assistant Professor of Pathology, Trakya University, Edirne, Turkey
[4]Cardiovascular Surgery, Education and Research Hospital, Samsun, Turkey
[5]Associate Professor of Internal Medicine, Trakya University, Edirne, Turkey
[6]Professor of Cardiovascular Surgery, Trakya University, Edirne, Turkey

Summary

Objective: Temporal arteritis is systemic vasculitis of medium and large sized vessels. The lowest incidence rates were reported in Turkey, Japan and Israel. We aimed to investigate the results of patients with biopsy-proven temporal arteritis and those classified according to the American College of Rheumatology criteria from a low-incidence region for temporal arteritis. The results of our study are noteworthy, since there is limited data on pathologic diagnosis of temporal arteritis in Turkey.

Method: We studied the medical records, laboratory findings such as erythrocyte sedimentation rate and C-reactive protein levels, biopsy results, and postoperative complications of all the patients operated for temporal artery biopsy at our clinic. We used the computerized laboratory registry that keeps all records of 42 consecutive temporal artery biopsy results from January 2011 to December 2016.

Results: The mean age was 66±12.5 years. The most common manifestations on admission were temporal headache, optic neuritis and jaw claudication, respectively. Temporal artery biopsy results confirmed tempoal arteritis in eight out of 42 (19%) patients. There was no statistically significant difference between biopsy-positive and biopsy-negative groups in terms of sex, age, erythrocyte sedimentation rate, C-reactive protein and biopsy length.

Conclusion: We were not able to find a correlation between the analysis of biopsy results and clinical evaluation of patients with temporal arteritis. We suggest that diagnosis of temporal arteritis depends on clinical suspicion. Laboratory examination results may not be helpful in accurate diagnosis of tempoal arteritis.

Keywords: giant cell arteritis, biopsy, C reactive protein, blood sedimentation.

Study conducted at Trakya University Faculty of Medicine, Edirne, Turkey

Article received: 4/5/2017
Accepted for publication: 5/7/2017

***Correspondence:**
Trakya University Hospitals
Cardiovascular Surgery Department
Edirne – Turkey
Postal code: 22100
drvyuksel@yahoo.com

http://dx.doi.org/10.1590/1806-9282.63.11.953

Introduction

Temporal arteritis (TA) is defined as the systemic vasculitis of medium- and large-sized vessels and affects mainly women above 50 years of age.[1] It is an arterial inflammatory disease mostly affecting temporal arteries and is histologically characterized by arterial infiltration of giant cells.[2] Patients can present with visual disturbances, jaw claudication, scalp tenderness, headache and myalgia. Clinical evaluation and suspicion are important in diagnosis. Other than clinical evaluation and laboratory assessment, duplex ultrasonography, magnetic resonance imaging and positron emission tomography can also be used for evaluation. Temporal artery biopsy (TAB) is a low-sensitivity but gold standard method in the diagnosis of TA.

The highest incidence rates of TA are reported in Scandinavian countries and northern United States. The lowest incidence rates were reported from Turkey, Japan, Israel and among native Alaskans.[3,4] A lower frequency of TA in our center in northwestern Turkey was shown compared to European data.[5]

In this study, we aimed to investigate and discuss the clinical correlation of patients with temporal artery biopsy-proven TA and those classified according to the Amer-

ican College of Rheumatology (ACR) criteria from a low incidence region for TA.[6] The results of our study are noteworthy, since there is limited data on pathologic diagnosis of TA in that region.

Method

We performed a retrospective study to evaluate Turkish patients who fulfilled the ACR criteria for TA and were under regular follow-up in our tertiary university hospital.[6] Detailed clinical history and physical examination were routinely performed in all patients. We studied the medical records, laboratory findings such as erythrocyte sedimentation rate (ESR) and C-reactive protein levels (CRP), biopsy results and postoperative complications of all the patients operated for temporal artery biopsy at our clinic. We used the computerized laboratory registry that keeps all records of 42 consecutive TAB results from January 2011 to December 2016.

All biopsies were performed using samples taken from the symptomatic side and based on high clinical suspicion bilaterally. Biopsy was performed from superficial temporal artery segment, which is a branch of external carotid artery. Location of the artery was determined prior to operation. Operations were performed under local anesthesia. A careful incision was made to explore the frontal branch of the superficial temporal artery at the temples and maximum care was taken in order not to injure the temporal branch of the facial nerve. The superficial temporal artery must be ligated proximally and distally after deciding the necessary length of biopsy. The skin incision is closed subcutaneously after controlling the bleeding of the side branches. Inflammation (red arrow), especially affecting the intima and medial layers of the arterial wall and causing degeneration of internal elastic lamina with characteristic multinuclear giant cells (blue arrow), lymphocytes, neutrophils and histiocytes, is helpful in pathologic diagnosis for TA (Figure 1). We collected and compared the results of patients with biopsy-proven TA and those classified according to ACR criteria. Ethical approval was obtained from the local ethics committee for this retrospective study.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) software version 22.0 (SPSS Inc., Chicago, Illinois, USA) and GraphPad prisma 6 (GraphPad software, La Jolla, CA, USA) were used to carry out the statistical analysis. Categorical data are presented as numbers and percentages, while numerical data are presented as means and standard deviations. Differences between patients were analyzed using the Mann-Whitney U test for continuous variables and Chi-square test for categorical variables. $p<0.05$ was considered significant.

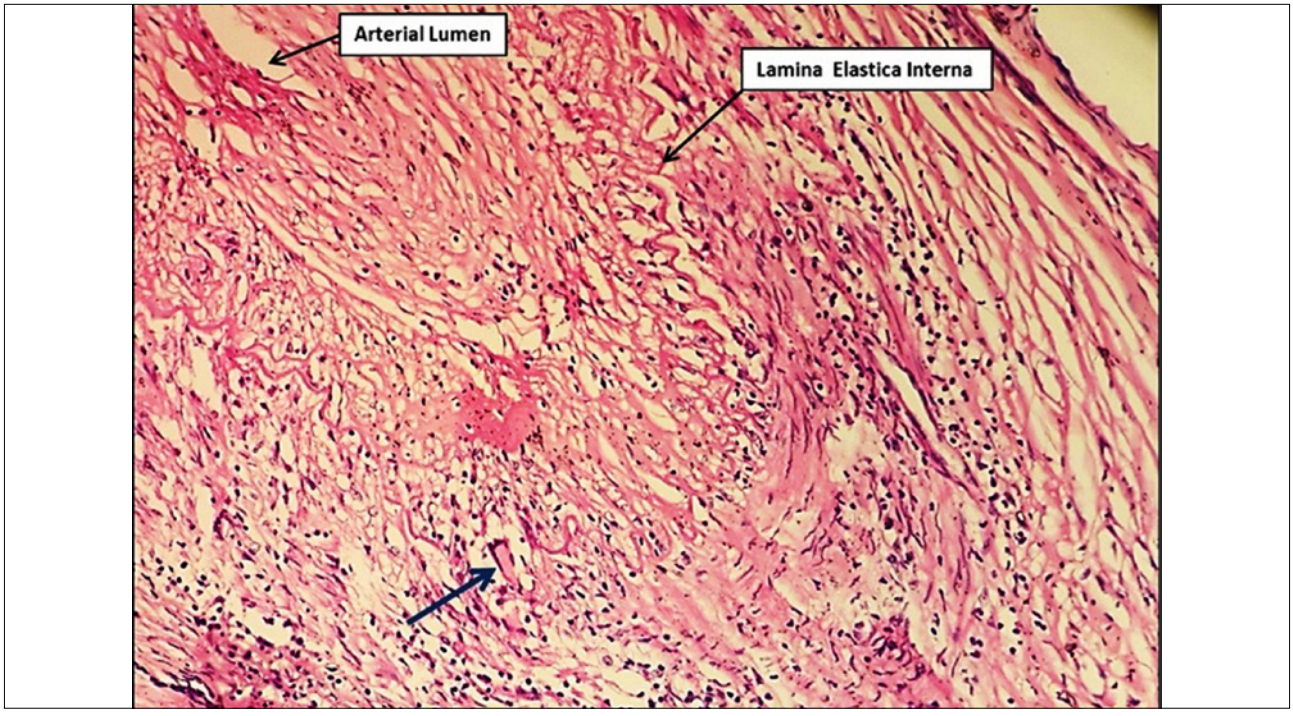


FIGURE 1 Histologic specimen of temporal arteritis.

Results

The results and medical records of 42 patients were studied. There were 22 male and 20 female patients and the mean age was 66±12.5 years (25-85). The most common manifestations on admission were temporal headache, optic neuritis and jaw claudication, respectively. The clinical symptoms of the patients in the study group are summarized in Table 1.

TABLE 1 Clinical symptoms of patients with temporal arteritis.

Symptom	n (%)
Temporal headache	37 (88.1)
Optic neuritis	28 (66.7)
Jaw claudication	26 (61.9)
Weight loss	18 (42.9)
Visual alteration	15 (35.7)
Polymyalgia rheumatica	12 (28.6)
Fever	10 (23.8)

TAB was performed from the left temporal artery in 17 patients and from the right temporal artery in 23 patients and bilateral in two patients. The mean biopsy length was 14.2±4.4 mm (5-20 mm). TAB results confirmed TA in eight (19%) patients. Of the eight biopsy-proven patients, four (50%) were male and four (50%), female. TAB was diagnosed in two cases that were operated bilaterally. No complications were observed postoperatively.

We compared the results of patients with biopsy-proven TA and those classified according to ACR criteria in terms of sex, age, ESR, CRP and biopsy length. There was no statistically significant difference between TAB-positive and TAB-negative groups. The details are summarized in Table 2.

TABLE 2 Comparison between patients with biopsy-proven temporal arteritis and those classified according to ACR criteria.

	TAB-negative	TAB-positive	p
Female / Male	16/18	4/4	1.000
Age (Mean,range)	66.4±11.2	64.1±18.1	0.847
ESR (mm/hr)	54.3±31.4	55±36.2	0.949
CRP (mg/dL)	1.68±2.82	4.29±4.78	0.461
Biopsy length (mm)	14.3±4.6	14.0±3.7	0.935

ACR: American College of Rheumatology; CRP: C-reactive protein levels; ESR: erythrocyte sedimentation rate; TAB: temporal artery biopsy.

Discussion

TA is the most common systemic vasculitis in patients over 50 years of age. The presence of three out of five criteria defined by the American College of Rheumatology may help physicians to establish the diagnosis with 94% sensitivity and 91% specificity: age over 50 years at time of onset, new-onset localized headache, tenderness or decreased pulse of the temporal artery, ESR over 50 mm/h, and positive TAB.[6] Treatment is mainly based on high doses of steroids after clinical diagnosis, especially in patients with visual complaints. The prevalence of TA in our region was found to be lower than that in western populations, including southern Europe.[5]

Although TAB is the gold standard method for diagnosis of TA, biopsy length, presence of skip lesions and steroid treatment prior to biopsy may cause false negative results.[7] Most of the patients have a negative biopsy and this biopsy result does not usually change the management of the patient. For this reason, the role of TAB is not accurately defined. Biopsy results give an idea of disease prognosis and avoid unnecessary treatment.[8-10]

The most common symptom in patients with TA is headache, which is defined as severe, acute and different from previous ones.[11] Visual loss, jaw claudication, tenderness in temporal region and decreased or lack of pulsation of temporal artery may accompany. In our study group, temporal headache, optic neuritis and jaw claudication were the commonest complaints.

TA is characterized histologically by inflammatory infiltration of the arterial wall by lymphocytes, macrophages and giant cells. There is an accumulation of histiocytes, epithelioid cells and giant cells and dissolution of the elastic lamina.[12] The important point is that pathological changes are usually segmental and some patients may have a false negative biopsy, and therefore biopsies can be performed in highly suspected selected cases.[13] Treatment is mainly based on steroids and usually started after confirmation of the diagnosis, and should not be delayed while waiting for TAB results.

Biopsy was performed bilaterally in two patients with bi-temporal headache on admission and both were diagnosed as TA. An additional contralateral biopsy may be beneficial in terms of high clinical suspicion of TA.[14] The mean length of TAB specimen after fixation was 14.2±4.4 mm in the study group. Mahr et al. also recommend a fixed TAB length of at least 5 mm, sufficient to make a histological diagnosis of TA.[15] Another factor affecting positive biopsy results may be that our region presents one of the

lowest incidences of TA.[5] A positive biopsy result is proof of TA, but a negative result does not rule it out.

TAB results confirmed TA in 19% of our study group. Mahr et al.[15] reported a 15% histological evidence of TA in 1,520 patients. Kermani et al.[16] also found 22% accuracy for pathological diagnosis in 1,106 patients. However, Suelves et al.[17] presented 68.4% positive biopsy results in their study. TA is known to affect women more than men. But in our study group, the ratio was found to be equal. Pamuk et al.[5] also reported a male to female ratio of 9:10 from the same region, which can be interpreted as nearly equal. Saedon et al.[18] reported a male-female ratio of 3:2 in a group of 153 patients undergoing TAB. The proportion of the biopsy results may vary in studies from different parts of the world.

We compared the results of patients with biopsy-proven TA and those classified according to ACR criteria in terms of sex, age, ESR, CRP and biopsy length, and there was no significant difference between groups. Also Souza et al.[19] reported no significant difference between groups in terms of age, sex and ESR levels. Due to the postmenopausal onset of TA, sex-based hormonal differences do not play a protective role against autoimmunity anymore.

TAB procedure is a simple and safe procedure, but some complications such as hematoma, scalp necrosis, wound infection, facial nerve injury and stroke may arise.[20,21] In our study group, we did not observe any complications postoperatively.

The limitations of our study are the small sample size due to low incidence of the disease in our region and the fact that the results are not representative of the entire population, including only patients from a tertiary hospital.

Conclusion

In conclusion, we were not able to find a correlation between the analysis of biopsy results and the clinical evaluation of patients with temporal arteritis. We suggest that diagnosis of TA mainly depends on high clinical suspicion. Laboratory examination results may not be helpful for an accurate diagnosis of TA. TAB is still the gold standard technique and can be performed safely. TAB is a simple procedure that can be performed under local anesthesia, and it may help definitive diagnosis of TA with low sensitivity. Results may vary in countries where TA is rare compared to other countries.

Acknowledgments

We thank Fatma Nesrin Turan for her support in statistical analysis.

Conflict of interest

The authors declare no conflict of interest.

References

1. Nordborg E, Nordborg C. Giant cell arteritis: epidemiological clues to its pathogenesis and an update on its treatment. Rheumatology (Oxford). 2003; 42(3):413-21.
2. Alberts M. Temporal arteritis: improving patient evaluation with a new protocol. Perm J. 2013; 17(1):56-62.
3. Borchers AT, Gershwin ME. Giant cell arteritis: a review of classification, pathophysiology, geoepidemiology and treatment. Autoimmun Rev. 2012; 11(6-7):A544-54.
4. Gonzales-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, Miranda-Filloy JA, Gonzalez-Juanatey C, Martin J, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum. 2009; 61(10):1454-61.
5. Pamuk ON, Dönmez S, Karahan B, Pamuk GE, Cakir N. Giant cell arteritis and polymyalgia rheumatica in northwestern Turkey: clinical features and epidemiological data. Clin Exp Rheumatol. 2009; 27(5):830-3.
6. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990; 33(8):1122-8.
7. Bhatti MT, Tabandeh H. Giant cell arteritis: diagnosis and management. Curr Opin Ophthalmol. 2001; 12(6):393-9.
8. Duhaut P, Pinède L, Bornet H, Demolombe-Ragué S, Dumontet C, Ninet J, et al. Biopsy-proven and biopsy negative temporal arteritis: differences in clinical spectrum at the onset of disease. Ann Rheum Dis. 1999; 58(6):335-41.
9. González-Gay MA, Alonso MD, Agüero JJ, Bal M, Fernández-Camblor B, Sánchez-Andrade A. Temporal arteritis in a northwestern area of Spain: study of 57 biopsy proven patients. J Rheumatol. 1992; 19(2):277-80.
10. González-Gay MA, García-Porrúa C. Systemic vasculitis in adults in northwestern Spain, 1988-1997. Clinical and epidemiological aspects. Medicine (Baltimore). 1999; 78(5):292-308.
11. Solomon S, Cappa KG. The headache of temporal arteritis. J Am Geriatr Soc. 1987; 35(2):163-5.
12. Ness T, Bley TA, Schmidt WA, Lamprecht P. The diagnosis and treatment of giant cell arteritis. Dtsch Arztebl Int. 2013; 110(21):376-86.
13. Poller DN, van Wyk Q, Jeffrey MJ. The importance of skip lesions in temporal arteritis. J Clin Pathol. 2000; 53(2):137-9.
14. Davies C, Frost B, Eshan O, McLain AD, Shandall A. Temporal artery biopsy... who needs one? Postgrad Med J. 2006; 82(969):476-8.
15. Mahr A, Saba M, Kambouchner M, Polivka M, Baudrimont M, Brochériou I, et al. Temporal artery biopsy for diagnosing giant cell arteritis: the longer, the better? Ann Rheum Dis. 2006; 65(6):826-8.
16. Kermani TA, Schmidt J, Crowson CS, Ytterberg SR, Hunder GG, Matteson EL, et al. Utility of erythrocyte sedimentation rate and C-reactive protein for the diagnosis of giant cell arteritis. Semin Arthritis Rheum. 2012; 41(6):866-71.
17. Suelves AM, España-Gregori E, Aviñó J, Rohrweck S, Díaz-Llopis M. Analysis of factors that determine the diagnostic yield of temporal artery biopsy. Arch Soc Esp Oftalmol. 2013; 88(4):127-9.
18. Saedon H, Saedon M, Goodyear S, Papettas T, Marshall C. Temporal artery biopsy for giant cell arteritis: retrospective audit. JRSM Short Rep. 2012; 3(10):73.
19. Souza AW, Okamoto KY, Abrantes F, Schau B, Bacchiega AB, Shinjo SK. Giant cell arteritis: a multicenter observational study in Brazil. Clinics (Sao Paulo). 2013; 68(3):317-22.
20. Dummer W, Zillikens D, Schulz A, Bröcker EB, Hamm H. Scalp necrosis in temporal (giant cell) arteritis: implications for the dermatologic surgeon. Clin Exp Dermatol. 1996; 21(2):154-8.
21. Bhatti MT, Goldstein MH. Facial nerve injury following superficial temporal artery biopsy. Dermatol Surg. 2001; 27(1):15-7.

Environmental factors can influence dengue reported cases

Marco Antonio F. Carneiro[1], Beatriz da C. A. Alves[1]*, Flávia de Sousa Gehrke[1], José Nuno Domingues[2], Nelson Sá[2], Susana Paixão[2], João Figueiredo[3], Ana Ferreira[2], Cleonice Almeida[4], Amaury Machi[4], Eriane Savóia[4], Vânia Nascimento[1], Fernando Fonseca[1,5]

[1]Faculdade de Medicina do ABC (FMABC), Santo André, SP, Brazil
[2]Environmental Health – IPC, EsTesC, Coimbra Health School, Coimbra, Portugal
[3]Departamento das Ciências Complementares – IPC, EsTesC, Coimbra Health School, Coimbra, Portugal
[4]Gestão de Saúde Ambiental, FMABC, Santo André, SP, Brazil
[5]Biological Science Department, Universidade Federal de São Paulo (Unifesp), Diadema, SP, Brazil

Summary

Introduction: Global climate changes directly affect the natural environment and contribute to an increase in the transmission of diseases by vectors. Among these diseases, dengue is at the top of the list. The aim of our study was to understand the consequences of temporal variability of air temperature in the occurrence of dengue in an area comprising seven municipalities of the Greater São Paulo.
Method: Characterization of a temporal trend of the disease in the region between 2010 and 2013 was performed through analysis of the notified number of dengue cases over this period. Our analysis was complemented with meteorological (temperature) and pollutant concentration data (PM10).
Results: We observed that the months of January, February, March, April and May (from 2010 to 2013) were the ones with the highest number of notified cases. We also found that there is a statistical association of moisture and PM10 with the reported cases of dengue.
Conclusion: Although the temperature does not statistically display an association with recorded cases of dengue, we were able to verify that temperature peaks coincide with dengue outbreak peaks. Future studies on environmental pollution and its influence on the development of *Aedes aegypti* mosquito during all stages of its life cycle, and the definition of strategies for better monitoring, including campaigns and surveillance, would be compelling.

Keywords: dengue, mosquito vectors, climate, climate change, environmental pollution.

Study conducted at Faculdade de Medicina do ABC (FMABC), Santo André, SP, Brazil

Article received: 2/27/2017
Accepted for publication: 3/1/2017

***Correspondence:**
Address: Av. Príncipe de Gales, 821
Santo André, SP – Brazil
Postal code: 09060-650
bcaalves@uol.com.br

http://dx.doi.org/10.1590/1806-9282.63.11.957

Introduction

Severe climate alterations, a major concern worldwide, have been occurring over the past few centuries. Such changes derive from a global warming effect that leads to ecological imbalance.[1] The World Health Organization (WHO) sees health problems related to climate changes as one of the greatest issues of the 21st century. These alterations directly interfere with the natural environment, and upon relating them with climate and tropical diseases, it can be noted that changes in temperature alter the ecosystem balance, contributing to an increase in the transmission of diseases by vectors, including dengue at the top of the list.[1,2]

Dengue is an infectious disease caused by an RNA virus. Four virus serotypes have been identified so far: DEN-1, DEN-2, DEN-3 and DEN-4. The disease is characterized by variable febrile periods, clinically classified as dengue fever (DF) or classic dengue fever. Acute manifestations of the disease, classified as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) may lead the patient to death.[3]

Aedes aegypti mosquitoes are the main vector for dengue virus. The species is adapted not only to the domestic environment but also to the demographic growth and internal and international processes of migration of people. These factors, along with aspects such as rainfall, humidity and temperature variation, favor the spread of the mosquito and the dissemination of virus serotypes. The existence of suitable sites for the breeding of mosquitoes (water storage) in urban areas completes the scenario.[4]

Dengue transmission peaks may be related to an increase in the survival rate of the adult vector under favorable temperature and humidity conditions in the rainy season. This survival rate enables the infected female the possibility to complete the virus replication cycle, thus becoming an infection vector.[5]

Climate variation among the municipalities, associated with a temporal dimension that allows for the incorporation of isolated phenomena of climate change patterns, are essential elements for the conduction of this study.[6]

The Greater ABC area comprises seven municipalities, namely Santo André, São Caetano do Sul, São Bernardo do Campo, Diadema, Mauá, Ribeirão Pires and Rio Grande da Serra (Table 1). Located in São Paulo's southeast area, it concentrates major industrial complexes and highly urbanized areas, but also plenty of green spaces and nature reserves, intended for environmental preservation, with water reservoirs that supply the whole metropolitan area.

TABLE 1 Approximate population and GDP per capita (BRL)*.

Municipality	Population	GDP per capita (BRL)
Santo André	673,900	21,843.91
São Caetano do Sul	149,295	68,649.65
São Bernardo do Campo	810,203	35,680.05
Diadema	386,039	30,332.87
Mauá	444,136	13,752.84
Rio Grande da Serra	44,084	8,536.14
Ribeirão Pires	113,043	13,347.20

*Brazilian Census Bureau (IBGE), 2010.
GDP: gross domestic product.

Due to the variety of manufacturing industries, these industrialized municipalities attract a great number of people who seek better life conditions. São Caetano do Sul has the highest gross domestic product (GDP) per capita, and General Motors, located in this municipality, directly affects the population's quality of life. Nevertheless, according to a study on the environmental impact caused by the industrial conglomerate, which generates particulate matters (PM10) and may affect climatic conditions, is important. Moreover, our study seeks to relate these impacts to the spread and dissemination of the dengue mosquito.

São Paulo is the industrial and financial center of Brazil, and the ABC area is where most manufacturing plants are located. Therefore, it is important to conduct studies on climate change as well as air pollution rates with the resulting impact on society in general, and more specifically on public health. Investigations such as these may serve as a database for better planning and prevention against vector-borne diseases.

In sum, our study aims to establish a correlation between dengue incidence and environmental-climatic conditions through the analysis of the number of notified dengue cases between the years 2010 and 2013 in the Greater ABC area, in São Paulo, and the following meteorological data: humidity, temperature and particulate matters less than 10 microns in diameter (PM10).

Method

A cross-sectional observational study with an ecological planning model was carried out. Data were collected, and the following variables were used for epidemiological and entomological investigation: space (regions), time (year, month and seasons), meteorology (temperature-humidity index) and the chronological distribution of the disease.

The study covered the period between January 2010 and December 2013 in the Greater ABC area in São Paulo. Data were collected from the National Meteorological Institute, the Environmental Technology and Sanitation Agency (Cetesb, in the Portuguese acronym),[7] the Epidemiological Surveillance Service – Dengue Prevention Department in Santo André and the Epidemiological Surveillance Center (CVE, in the Portuguese acronym).[8]

The data were analyzed in order to verify their relation during the periods of incidence at a certain period of time that allows for the investigation of the resulting phenomena of the interactions with the environment. Pearson correlation was used to analyze the association between humidity, temperature and PM10 regarding the incidence of cases of the disease per year. Statistical significance was reached at $p<0.05$. IBM SPSS Statistics 19 software was used.

Results

According to the numbers obtained from Cetesb and the CVE, the year of highest incidence of dengue was 2010, with 577 cases in total, which corresponds to an incidence of 2.22 cases per 10,000 inhabitants (Table 2). In 2011, this number slightly decreased to 555 cases. In 2012, however, a total of 125 cases were notified (0.48 cases/10,000 population), which represents a sharp drop in relation to the previous year (22.5%). Therefore, it is important to point out that the number of cases reported in 2012 was atypical compared with the previous years, and even 2013, when the number of notified cases rose to 402.

Santo André, São Bernardo do Campo, São Caetano do Sul and Diadema are the most industrialized municipalities in the area, and they are the ones with the highest rate of dengue notifications. The highest incidence

rate per municipality was registered in Diadema, with 14.89 cases per 10,000 inhabitants.

TABLE 2 Number of dengue cases in the Greater ABC area.

Municipality	Year				Incidence rate*
	2010	2011	2012	2013	
Santo André	180	71	40	106	5.45
São Bernardo do Campo	158	136	36	170	6.7
São Caetano do Sul	31	30	9	27	6.49
Diadema	177	295	26	77	14.89
Mauá	21	19	12	16	1.53
Ribeirão Pires	7	1	2	3	1.15
Rio Grande da Serra	3	3	0	3	2.04
Total	577	555	125	402	

Source: CVE (Epidemiological Surveillance Center) – São Paulo.
*Incidence rate per 10,000 inhabitants.

According to the data supplied by the CVE, the months of January, February, March, April and May (from 2010 to 2013) were the ones with the highest number of notified cases. As a result, an analysis of climatic and environmental factors during those months was carried out so that a possible relation between these variables and a higher proliferation and notification of dengue cases could be established.

Figure 1 presents an extremely close relation between temperature values and the notified dengue cases. It can be observed that temperature peaks coincided with epidemic peaks between the months of January and May. Nevertheless, while this relation is quite clear, there was no statistically significant association between them.

There was, however, a statistically significant association of humidity and PM10 with dengue cases (p=0.003 and p=0.001, respectively) (Table 3). As for humidity, this variable had a positive correlation (0.163), i.e., the greater the humidity, the higher the number of dengue cases. In other words, whenever humidity rates reached their highest values, there was an increase in number of registered cases in the area. Interestingly, PM10 had a negative Pearson correlation (-0,213), showing that lower PM10 values coincided with a higher number of dengue cases. Air pollution could therefore be the reason for reported dengue cases.

TABLE 3 Relation of temperature, humidity and PM10 with dengue cases.

		Temperature	Humidity	PM10
Dengue cases	Pearson correlation	0.093	0.163	-0.213
	p-value	0.088	0.003	0.001
	N	336	336	240

Discussion

In scientific terms, there is a relation between temperature and humidity, so that relative humidity can be defined as the ratio of the amount of water vapor in the air at a specific temperature to the maximum amount that the air could hold at that temperature. At higher temperatures the air may contain more water vapor than the same volume of air at lower temperatures.[9]

Our findings show that the months presenting temperature and humidity peaks, namely January, February,

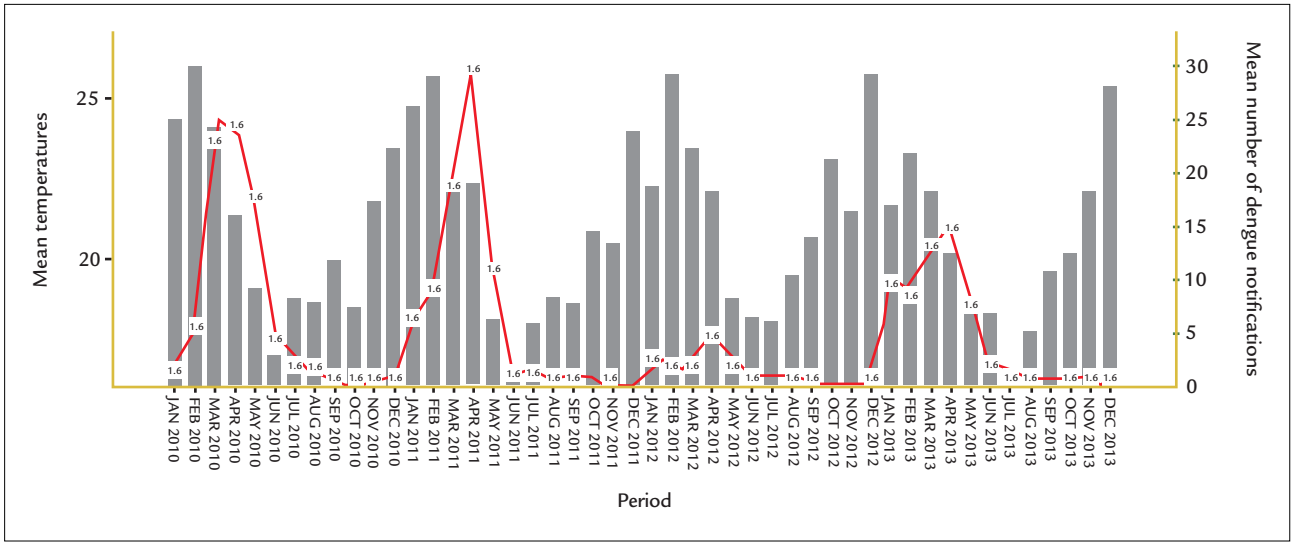


FIGURE 1 Mean temperatures and number of dengue notifications in the Greater ABC area between 2010 and 2013.

March, April and May, also had more notifications of dengue cases.

Another relevant aspect is a significant decline in the number of cases in 2012 compared with the previous year, which, according to Santo André's Health Department, may have occurred as a result of the many awareness campaigns targeting the general population after the 2011 outbreak.

The year 2013 emerges as the year with the highest number of notified cases. One of the possible explanations is that the months in that year were warmer and wetter all over the state of São Paulo according to meteorological data.

This increasingly common scenario, where winter is no longer a cold and dry season, is a climate change resulting from global warming.[10]

The most industrialized municipalities are the ones with the highest rates of notified dengue cases, which can be explained by the possibility of many cases being imported. As a consequence of industrialization, most workers choose to live in other municipalities and commute daily to/from their jobs. Despite the difficulty in identifying whether the disease is autochthonous or imported, one must consider that these individuals may be infected in the municipality where they live but seek assistance in the municipality where they work, if medical care is more convenient or easily accessed in the latter. Therefore, the lower number of cases notified in municipalities such as Ribeirão Pires and Rio Grande da Serra may be justified.

Regardless of other factors, temperature variations and rainfall intensity affect the reproductive cycle and survival of the vector, which cause changes in its distribution and density, since mosquitoes need humidity and temperatures ranging between 15°C and 35°C to survive and reproduce. These climate (abiotic) factors have shown an association with the incidence and prevalence of dengue.[2,3]

Many studies have revealed the important role of rainfall in the renewal and oscillations of puddles, conditions that favor egg hatching and the incubation period of the mosquito.

As for temperature, many authors affirm that it interferes with dengue virus incubation period, which drops from 10 to 7 days whenever temperature rises from 27°C to 37°C.[2] It is thus clear that temperature and rainfall levels in the months of January, February and March throughout the years were favorable for the development of the virus and that these factors may have contributed to a higher incidence of dengue cases. As the mosquito's life span is around 45 days, the generation born in the beginning of January can infect hosts until February 15, whereas the generation born in the second half of January is able to infect people until March 15. Accordingly, dengue cases appear after weeks of peak temperature and rainfall, a time during which the mosquito can develop and contaminate the population.[11]

Another fact to be considered is the time it takes for each individual to show symptoms of the disease, and, as a result, the time that elapses until these individuals search for assistance at a medical care unit. The greatest number of dengue cases is expected to be reported in the months of February, March, April and May. However, there are many difficulties to establish a "key" seasonal pattern of disease incidence and meteorological variables. Concerning particulate matters, a decrease in the concentration of PM10 is observed from January to May, a critical period when cases are registered most often in the region. Although not confirmed by any study to date, the presence of air pollutants apparently interferes with the life cycle of the *Aedes aegypti* mosquito.

The relation between health and environment can be clearly seen through the analysis of epidemiological characteristics in areas close to contamination sources and through the identification of adverse environmental factors that are harmful to health.[12]

Investigations on the special conditions that trigger the occurrence of dengue may contribute to the understanding of the role played by social groups in the complex dynamic chain of disease transmission, considering their own limits and possibilities. They can also shed light on more suitable prevention and control strategies in the construction of new indicators by trying the use of multivariate models that take into consideration the spatial distribution of the events.[13]

Variations in climate patterns may influence some disease cycles, favoring and increasing the number of isolated foci of vector-transmitted diseases. Moreover, these changes stimulate the migration of these vectors, cause an increase in epidemics, reduce productivity, and generate an increase in healthcare-related costs. Although the urgency for action is quite clear, so far, little has been done to reverse this scenario. If actions are not taken, the number of dengue cases will continue to escalate and other diseases will gradually emerge as temperatures rise.[2]

From a scientific point of view, it would be advisable to conduct future studies not only on environmental pollution and its influence on the development of the *Aedes aegypti* mosquito in all of its life cycle phases but also on the definition of strategies for better monitoring of pollutant matters, climate data and dengue cases. The existence of only one climate monitoring station for the entire ABC area was one of the limitations of our study. Therefore,

accessing climate data for the analysis of temperature and humidity in all of the municipalities included in our analysis was very difficult.

Conclusion

We found a statistical association of moisture and PM10 with the reported cases of dengue. There was no statistical correlation between the incidence of dengue and temperature. The presence of air pollutants also interferes with the life cycle of the dengue mosquito, and further studies may reveal important instruments for environmental monitoring and the control of endemic vectors.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Fatores climáticos podem influenciar nos casos de notificação de dengue

Objetivo: As alterações globais que têm ocorrido interferem no ambiente natural, influenciando diretamente no crescimento da transmissão de doenças ocasionadas por vetores, das quais se destaca a dengue. O objetivo deste estudo foi compreender as consequências da variabilidade temporal das condições climáticas em relação à ocorrência de dengue na população da região metropolitana de São Paulo, constituída por sete municípios.
Método: A caracterização da tendência temporal da dengue foi realizada por meio da análise dos números de casos de dengue notificados nos anos de 2010 a 2013, de dados meteorológicos (umidade e temperatura) e dados de concentração de poluentes (PM10).
Resultados: Observou-se que os meses de janeiro a abril (de 2010 a 2013) foram os que apresentaram maior número de casos notificados de dengue, com associação estatística entre a umidade e PM10 com os casos de dengue notificados.
Conclusão: Embora a temperatura não assuma, estatisticamente, uma associação com os casos de dengue registrados, foi possível verificar que os picos de temperatura coincidem com os picos epidêmicos de dengue. Seriam interessantes futuros estudos referentes à poluição ambiental e a sua influência no desenvolvimento do mosquito *Aedes aegypti* em todas as suas fases do ciclo de vida e definição de estratégias para melhor monitoração, campanhas e vigilância.

Palavras-chave: dengue, mosquitos, vetores, clima, mudança climática, poluição ambiental.

References

1. Silva L, Ferreira VF, Santos S, Silva I. Crescimento da dengue em razão do aquecimento global. Proceedings of 61o Congresso Brasileiro de Enfermagem; Fortaleza, CE, Brazil. 2009 [cited 2015 Sept 20]. Available from: http://www.abeneventos.com.br/anais_61cben/files/02214.pdf.
2. Pereda PC, Alves DCO, Rangel MA. Elementos climáticos e incidência de dengue: teoria e evidência para municípios brasileiros. Rio de Janeiro: Sociedade Brasileira de Econometria, 2011 [cited 2015 Oct 28]. Available from: bibliotecadigital.fgv.br/ocs/index.php/sbe/EBE11/paper/download/2938/1333.
3. FUNASA. Fundação Nacional de Saúde, Ministério da Saúde. Programa Nacional de Controle da Dengue – PNCD. Brasília: Ministério da Saúde; 2002 [cited 2015 Oct 28]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/pncd_2002.pdf.
4. Donalísio MR, Glasser CM. Vigilância entomológica e controle de vetores de dengue. Rev Bras Epidemiol. 2002; 5(3):259-79.
5. Glasser CM, Gomes AC. Infestação do estado de São Paulo por Aedes aegypti e Aedes albopictus. Rev Saúde Pública. 2000; 34(6):570-7.
6. Ribeiro AF, Marques GRAM, Voltolini JC, Condino ML. Associação entre incidência de dengue e variáveis climáticas. Rev Saúde Pública. 2006; 40(4):671-6.
7. CETESB - Companhia Ambiental do Estado de São Paulo. Qualidade do ar no Estado de São Paulo. 2014 [cited 2016 Feb 20]. Available from: http://sistemasinter.cetesb.sp.gov.br/Ar/php/ar_resumo_hora.php
8. Centro de Vigilância Epidemiológica "Prof. Alexandre Vranjac"– CVE [cited 2016 Feb 20]. Available from: http://www.cve.saude.sp.gov.br/.
9. Valsson S, Bharat A. Impact of air temperature on relative humidity: a study. Architecture – Time Space and People. 2011; 38-41.
10. Confalonieri UEC, Marinho DP. Mudança climática global e saúde: perspectivas para o Brasil. Rev Multiciência. 2007; 8:48-64.
11. Viana DV, Ignotti E. The ocurrence of dengue and weather changes in Brazil: a systematic review. Rev Bras Epidemiol. 2013; 16(2):240-56.
12. Rocha JRR, Mariano ZF. Aspectos climáticos e ocorrência de casos de dengue em Jataí – GO. Rev Geonorte. 2012 ;3(5):757-69.
13. Flauzino RF, Souza-Santos R, Oliveira RM. Indicadores socioambientais para vigilância da dengue em nível local. Saúde Soc. 2011; 20(1):225-40.

Economic assessment of postoperative pain control strategies for treatment of adult patients with cancer

Rafael Freitas dos Santos[1], Fernando Bliacheriene[2], Flavia Mori Sarti[3]*

[1]Pharmacy degree from Universidade de São Paulo (USP), São Paulo, SP, Brazil
[2]MD, PhD in Medicine from Faculdade de Medicina da USP (FMUSP), São Paulo, SP, Brazil
[3]Economist and Nutritionist, PhD in Applied Human Nutrition from USP, São Paulo, SP, Brazil

Summary

Objective: The authors performed an economic assessment of opioids currently being used for control of postoperative pain relating to the surgical treatment of cancer (fentanyl and sufentanil) within the Brazilian Unified Health System (SUS, in the Portuguese acronym).
Method: The assessment was based on the perspective of the government, in order to collaborate with the promotion of effectiveness in public policies of health, and to optimize the allocation of public resources into health. A cost-effectiveness analysis was performed using data collected from the Brazilian Unified Health System and information from literature review, in order to build a decision tree on the alternatives for control of postoperative pain related to cancer treatment among adult patients. The outcomes considered were: effectiveness of postoperative analgesia and occurrence of nausea and vomit in the 48 hour period after surgery, and additional 24-hour cycles in patient follow-up. A univariate sensitivity analysis was conducted in order to verify robustness of the model estimated.
Results: Literature review showed a limited number of studies directly comparing fentanyl and sufentanil for control of postoperative pain. The adoption of sufentanil (cost = U$ 25.72 / outcome = 1.6 VAS points) was dominant in relation to the use of fentanyl (cost = U$ 32.58 / outcome = 2.6 VAS points). The estimated model showed robustness in relation to changes in the parameters analyzed.
Conclusion: Sufentanil presented higher cost-effectiveness ratio in relation to fentanyl for control of postoperative pain in surgeries related to cancer treatment among adult patients in the Brazilian Unified Health System.

Keywords: health evaluation, analgesia, pain measurement.

Study conducted at Faculdade de Ciências Farmacêuticas e Escola de Artes, Ciências e Humanidades da Universidade de São Paulo (USP), São Paulo, SP, Brazil

Article received: 3/6/2017
Accepted for publication: 4/3/2017

*Correspondence:
Address: Av. Arlindo Béttio, 1.000
São Paulo, SP – Brazil
Postal code: 03828-000
flamori@usp.br

http://dx.doi.org/10.1590/1806-9282.63.11.962

Introduction

The choice of postoperative pain control strategy is a crucial factor to decrease morbidity and increase patients' quality of life.[1] Opioid analgesics are broadly used for management of pain after surgical treatment of cancer, either as single therapy or associated with other drugs to leverage analgesic effect.[2]

Morphine is one of the most studied and commonly used opioids. However, recent evidences show that use of fentanyl and sufentanil present benefits in comparison to the use of morphine, regarding its effectiveness in maintenance of anesthesia and control of post-operative pain, as well as higher liposolubility, resulting in fewer episodes of adverse side effects in comparison to morphine.[3]

The health sector has limited resources to be used for multiple purposes, and within the context of public sector management in the Brazilian health system, the Brazilian Unified Health System (SUS, in the Portuguese acronym) is significantly sensitive to the costs of activities undertaken. Thus, there is need for health economics studies in order to establish cost-effective programs that may benefit a higher number of patients with equal amount of resources.[4]

Therefore, the aim of the paper was to perform an economic assessment of opioids currently being used for control of postoperative pain relating to surgical treatment of cancer (fentanyl and sufentanil) within the Brazilian Unified Health System, in order to collaborate

to the promotion of effectiveness in public health policies, and to enhance the allocation of public resources in health.

Method

Our paper presents a retrospective transversal study on the costs and outcomes of strategies for postoperative pain control strategies for treatment of adult patients with cancer. The study was based on three components: literature review, economic assessment and sensitivity analysis.

Literature review

A literature search was performed on Medline/PubMed and Lilacs databases to identify clinical data available regarding effectiveness and safety of the opioids fentanyl and sufentanil for control of postoperative pain relating to cancer treatment.

The literature review was based on a structured question defining target population, intervention, comparator and outcome (PICO strategy) to perform the economic assessment using the best evidences available according to the methodological guidelines of the National Committee on Technology Incorporation for the Brazilian Unified Health System (Conitec).[5]

PICO represents an acronym for Patient, Intervention, Comparator and Outcome, which are four primary elements in evidence-based medicine for search of relevant information within a certain health context. The appropriate structure of the research question enables the definition of parameters necessary for estimating the model, maximizing data recovery, allowing for research scope definition and avoiding unnecessary search.[6]

The literature search was based on the following question: Is the adoption of sufentanil effective and safe in comparison to the use of fentanyl on postoperative analgesia relating to surgical treatment of cancer among adult patients? The question was structured based on the following parameters applied on PICO strategy:

- Patients: Adult individuals subject to surgical treatment of cancer.
- Intervention: Sufentanil.
- Comparator: Fentanyl.
- Outcomes: Effectiveness of postoperative analgesia (using Visual Analogue Scale points of pain, VAS) and safety in postoperative control of pain (incidence of adverse side effects).

The literature search was performed on Medline/PubMed and Lilacs databases using the following keywords: "oncologic surgery," "cancer surgery," "neoplasm surgery," "cancer," "oncologic," "sufentanil," "fentanyl" and "analgesia" in three to four different quests:

- Medline/PubMed:
  1. ((((((("oncologic surgery") OR "oncologic surgeries") OR "cancer surgeries") OR "cancer surgery") OR "neoplasm* surgery") OR "neoplasm* surgeries")) AND sufentanil) AND analgesia
  2. ((((((("oncologic surgery") OR "oncologic surgeries") OR "cancer surgeries") OR "cancer surgery") OR "neoplasm* surgery") OR "neoplasm* surgeries")) AND sufentanil
  3. (((((((("oncologic surgery") OR "oncologic surgeries") OR "cancer surgeries") OR "cancer surgery") OR "neoplasm* surgery") OR "neoplasm* surgeries")) AND fentanyl)) AND analgesia
- Lilacs:
  1. sufentanil [Palavras] and cancer [Palavras]
  2. sufentanil [Palavras] and oncologica [Palavras]
  3. fentanil [Palavras] and oncologica [Palavras]
  4. fentanil [Palavras] and cancer [Palavras]

The records identified were analyzed, considering the following criteria for inclusion and exclusion:

- Inclusion criteria:
  - Studies based on adult patients sample.
  - Assessment of postoperative analgesia effectiveness using VAS.
  - Main therapy based on fentanyl or sufentanil for postoperative analgesia.
  - Fentanyl or sufentanil administered through intravenous or neuraxial application.
  - Full-text version of the study available for analysis.
- Exclusion criteria:
  - Case studies.
  - Studies without side effects of interest (nausea and vomit).
  - Fentanyl or sufentanil administered through mixed alternative ways (mixed intravenous with nasal or transdermal).

Effectiveness and safety data of fentanyl and sufentanil used for control of postoperative pain were extracted from each study analyzed. Information on use of resources was also collected in the literature, if available.

Parameters of effectiveness and safety data collected in the scientific literature review, an economic assessment model of costs and outcomes was estimated on the po-

tential adoption of fentanyl and sufentanil within the Brazilian Unified Health System.

Economic assessment

The economic assessment was performed using the perspective of the Brazilian Unified Health System, including only direct medical costs covered by the government. A decision tree on the alternatives for control of postoperative pain related to cancer treatment among adult patients was built using effectiveness data from information gathered during literature review.

The decision tree considered two types of outcomes: effectiveness of postoperative analgesia (using VAS points of pain) and safety in postoperative control of pain (incidence of adverse side effects).[7-10] The main adverse side effects identified in the literature review that were associated with use of opioid anesthetics for control of postoperative pain[7-9] were occurrence of nausea and vomit.

Data on incidence of adverse side effects were obtained from direct comparison between fentanyl and sufentanil performed in one of the studies identified in the literature review,[8] considering nausea and vomit in the 48 hour period after surgery, and additional cycles of 24 hour in patient follow-up, in order to reproduce the practice of pain intensity measurement identified in the studies analyzed.[7,8]

The economic assessment was performed using the perspective of the Brazilian Unified Health System, i.e., estimation considered only direct medical costs associated with control of postoperative pain relating to surgical treatment of cancer among adult patients.

Direct medical cost estimation was based on microcosting technique for definition of inputs and costs associated with analgesia and treatment of adverse side effects. The estimation of direct medical costs included: costs of medication used for control of postoperative pain and costs of treatment of adverse side effects. Other costs (costs of surgical procedure, preoperative period and other postoperative procedures) were considered similar and independent of the medication used for postoperative analgesia.

Information on resources required for medical procedures of postoperative analgesia were estimated using the Brazilian Hierarchical Classification of Medical Procedures (Classificação Brasileira Hierarquizada de Procedimentos Médicos).[11] Information on inputs necessary for treatment of adverse side effects of postoperative analgesia (nausea and vomit) was not available in the Brazilian Unified Health System; thus, the microcosting technique was applied based on guidelines for treatment from Hospital Israelita Albert Einstein,[12] one of the main private hospitals in the city of São Paulo.

Information on the cumulative utilization of anesthetic reported in the literature was used to determine the dosage of fentanyl and sufentanil during two days of treatment.[8]

The inputs required for treatment of adverse side effects in the first day were: two clinical assessments, adoption of enteral nutrition, and administration of ondansetron, omeprazole, metoclopramide and bromopride. The inputs required for treatment of adverse side effects in the second day were: two clinical assessments, and administration of ondansetron, omeprazole, metoclopramide and bromopride.[12]

Prices of medication used for control of postoperative pain and treatment of adverse side effects were used to estimate costs, regarding government purchases (named Maximum Price for Sale to Government, PMVG)[13] with additional 18% of Tax on Circulation of Goods and Services (ICMS).

Prices of other inputs used for and treatment of adverse side effects were based on the Brazilian Hierarchical Classification of Medical Procedures[11] and reference prices for medical treatments in the Brazilian Unified Health System.

Prices of inputs for postoperative analgesia and treatment of adverse side effects were collected in Brazilian currency (reais) in August 2014, updated to September 2015 using the National Consumers' Prices Index of the Brazilian Institute for Geography and Statistics (IPCA-IBGE), and converted to U.S. dollars using official exchange rates published by the Brazilian Central Bank.

The global costs of postoperative pain control strategies for treatment of adult patients with cancer using fentanyl and sufentanil were estimated based on the following equation:

$$c_i=\sum_{qi}\times_{pi} + P(ae_{i1})\times\sum q_{1m}\times p_{1m} + P(ae_{i2})\times\sum q_{2n}\times p_{2n} \quad \text{[Eq.1]}$$

Where: c_i = global cost of postoperative pain control strategy *i*; q_i = quantity of anesthetic *i*; p_i = price of anesthetic *i* for government acquisition; $P(ae_{i1})$ = probability of adverse effects using the anesthetic *i* in the first postoperative day; q_{1m} = quantity of *m* inputs necessary for treatment of adverse effects in the first postoperative day; p_{1m} = price of *m* inputs necessary for treatment of adverse effects in the first postoperative day; $P(ae_{i2})$ = probability of adverse effects using the anesthetic *i* in the second postoperative day; q_{2n} = quantity of *n* inputs necessary for treatment of adverse effects in the first second postoperative day; p_{2n} = price of *n* inputs necessary for treatment of adverse effects in the second postoperative day.

The probabilities of occurrence of each outcome were inserted in the software TreeAge Pro 2014, including the costs estimated for each treatment strategy (fentanyl and sufentanil). Each branch of the decision tree included the calculation of cumulative probabilities of outcomes and costs, in order to allow the comparison of global outcomes expected for each treatment strategy and respective costs.

Sensitivity analysis

A univariate sensitivity analysis was conducted in order to verify robustness of the model and to identify the variables that may influence significantly the results obtained in the base case.

An incremental cost-effectiveness ratio (ICER) was estimated using the base case parameters of the economic assessment model and recalculated considering variations in each parameter inserted in the base case scenario, in order to estimate the potential impacts on the decision processes within the Brazilian Unified Health System regarding changes in postoperative pain control strategies for adult patients with cancer.

Patterns of variability in parameters relating to outcomes and medication dosage were based on information of standard deviation obtained from literature review.[8] Other parameters were submitted to a variation of ± 20% in relation to the initial value established, a range of variability considered appropriate to analyze potential changes in the health system scenario that may influence the ICER.

The univariate sensitivity analysis was conducted using the software TreeAge Pro 2014, by estimating the changes occurring in the ICER due to modification of key parameters in outcomes and costs to verify robustness of the model.

Results

Literature review

There were 212 records identified in the Medline/PubMed and Lilacs databases, 21 records were duplicated. Considering the 191 remaining records screened, 178 were excluded due to identification of:

- Studies based on animals models = 3.
- Studies based on other treatments = 74.
- Studies based on alternative administration ways (nasal or transdermal) = 5.
- Studies without outcomes of interest = 53.
- Case studies = 43.

The records selected on the screening (13) were searched for full-text access and analysis; however, five records were found to have full-text unavailable. The full-text of the eight remaining references were obtained and analyzed, in order to evaluate the information available; and four full-texts were excluded due to lack of quantitative measurement of outcomes. Therefore, four full-texts were considered as source of data for decision tree modeling and economic assessment regarding the control of postoperative pain related to cancer surgical treatment.[7-10]

Three studies analyzed intravenous administration of postoperative analgesia, controlled by the patient,[8-10] and the fourth study indicated use of epidural analgesia[7]. Only one study presented analgesia on demand,[9] and the other three presented continuous infusion with bolus, if necessary.[7,8,10] Two studies analyzed intensity of pain during the 48 hour period after surgery,[7,8] one study analyzed it during a period of 24 hours after surgery[9] and one study analyzed it during a period of 96 hours after surgery.[10] Each study analyzed different comparators and different combinations of medication for analgesia. Only one study directly compared fentanyl and sufentanil without associating other medication in the analgesia.[8]

Considering the possibilities of variation in the postoperative analgesia, using different ways of administration, infusion cycles and blocking periods, as well as several associations of medication in the clinical practice and diverse study designs and samples in the studies identified in the literature, the analysis of economic assessment was based on the direct comparison presented between fentanyl and sufentanil without associating any other medication in the analgesia,[8] using information on effectiveness and safety of the medication presented in the study.

Economic assessment

Parameters used to build the decision tree for economic assessment of postoperative pain control strategies using fentanyl and sufentanil for adult patients with cancer within the Brazilian Unified Health System were based on probability of adverse side effects, VAS points for characterization of postoperative pain, medical procedures necessary to perform postoperative analgesia and treatment of adverse side effects of fentanyl and sufentanil use (Table 1).

The economic assessment included two possible health status, occurrence or absence of nausea and vomit, as represented in the decision tree (Figure 1). Values presented for each path of the decision tree represent the probabilities of each health status, and the expected outcomes with respective expected costs are presented at the end of the path.

The use of sufentanil for postoperative analgesia was dominant in relation to the use of fentanyl, based on cost-effectiveness ratios estimated with the parameters defined in the decision tree model; it should be considered that sufentanil presented lower cost (US$25.72) and better outcome (1.6 VAS points of pain) in comparison to the cost (US$32.58) and outcome (2.6 VAS points of pain) obtained with treatment using fentanyl.

Sensitivity analysis

Parameters that presented the highest impact on ICER were the occurrence of adverse side effects (nausea and vomit) in the second day after surgery due to use of sufentanil among patients who did not have adverse side effects in the first day, VAS points of pain due to use of sufentanil and cost of treatment with sufentanil (Table 2).

The variability in VAS points of pain by postoperative analgesia using sufentanil contributed significantly to reinforce the dominance in comparison to fentanyl, in addition to the probability of adverse side effects in the second postoperative day for patients using sufentanil who did not have adverse side effects in the first postoperative day (Figure 2).

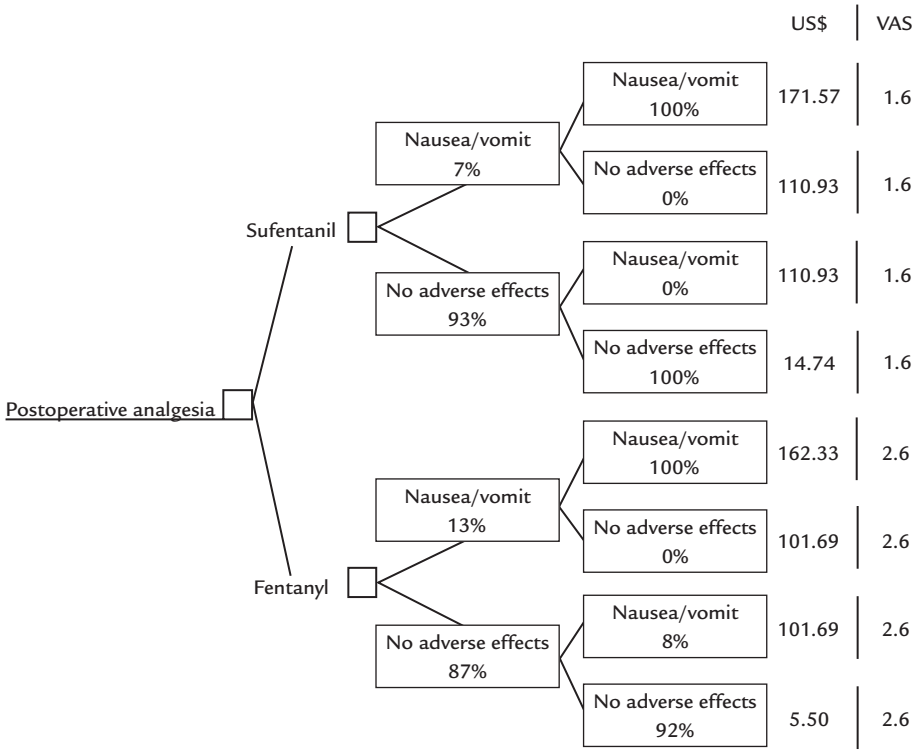
TABLE 1 Characterization of costs for economic assessment of postoperative pain control strategies for adult patients with cancer (fentanyl and sufentanil). Brazil, 2015.

Characterization	Source	Unit	Value
Treatment using fentanyl			
Price of fentanyl (mg)	CMED 2014[13]	US$	0.003
Cost of fentanyl (2 day treatment)	Lin et al. 2006,[8] CMED 2014[13]	US$	5.50
VAS (48h)	Lin et al. 2006[8]	pt.	2.6
Prob. nausea/vomit 24h after surgery	Lin et al. 2006[8]	%	13%
Prob. nausea/vomit 48h after surgery	Lin et al. 2006[8]	%	8%
Treatment using sufentanil			
Price of sufentanil (µg)	CMED 2014[13]	US$	0.093
Cost of sufentanil (2 day treatment)	Lin et al. 2006,[8] CMED 2014[13]	US$	14.74
VAS (48h)	Lin et al. 2006[8]	pt.	1.6
Prob. nausea/vomit 24h after surgery	Lin et al. 2006[8]	%	7%
Prob. nausea/vomit 48h after surgery	Lin et al. 2006[8]	%	0%
Cost of 1st day with nausea/vomit	CBHPM 2014,[11] CMED 2014[13]	US$	96.19
Cost of 2nd day with nausea/vomit	CBHPM 2014,[11] CMED 2014[13]	US$	60.63

TABLE 2 Characterization of costs for economic assessment of postoperative pain control strategies for adult patients with cancer (fentanyl and sufentanil). Brazil, 2015.

Parameter	Variation	$ICER_{min}$	$ICER_{max}$
Prob. AE 2nd day – Patients without AE 1st day (sufentanil)	0.0-0.2	-0.87	10.57
VAS points of pain (sufentanil)	7.5-9.3	-8.68	-0.46
Cost of treatment (sufentanil)	0.0745-0.1117	-3.81	2.07
VAS points of pain (fentanyl)	5.9-8.9	-3.47	1.74
Prob. AE 1st day (fentanyl)	0.104-0.156	-3.27	1.53
Dosage of sufentanil (total)	135.7-180.9	-2.97	1.23
Cost 1st day treatment of AE	76.95-115.43	-2.46	0.73
Prob. AE 1st day (sufentanil)	0.056-0.084	-2.23	0.49
Cost of treatment (fentanyl)	0.0025-0.039	-1.79	0.51
Prob. AE 2nd day – Patients with AE 1st day (sufentanil)	0.8-1.0	-1.37	-0.87
Cost 2nd day treatment of AE	48.51-72.76	-1.30	-0.44
Prob. AE 2nd day – Patients without AE 1st day (fentanyl)	0.064-0.096	-1.72	-0.01
Dosage of fentanyl (total)	1,402.0-1,858.0	-1.64	-0.10
Prob. AE 2nd day – Patients with AE 1st day (fentanyl)	0.8-1.0	-0.87	0.06

AE: adverse side effects of analgesia.



Postoperative pain control strategy using sufentanil during two days		Cumulative probability	Cost (US$)	Total (US$)
Occurrence of adverse effects	**Description of treatment**			
During 2 days	Administration of sufentanil	7.00%	14.74	171.57
	Adverse effects treatment (1st day)		96.19	
	Adverse effects treatment (2nd day)		60.63	
During 1st day	Administration of sufentanil	0.00%	14.74	110.93
	Adverse effects treatment (1st day)		96.19	
During 2nd day	Administration of sufentanil	0.00%	14.74	110.93
	Adverse effects treatment (1st day)		96.19	
No adverse effects	Administration of sufentanil	93.00%	14.74	14.74
Postoperative pain control strategy using fentanyl during two days		**Cumulative probability**	**Cost (US$)**	**Total (US$)**
Occurrence of adverse effects	**Description of treatment**			
During 2 days	Administration of fentanyl	13.00%	5.50	162.33
	Adverse effects treatment (1st day)		96.19	
	Adverse effects treatment (2nd day)		60.63	
During 1st day	Administration of fentanyl	0.00%	5.50	101.69
	Adverse effects treatment (1st day)		96.19	
During 2nd day	Administration of fentanyl	6.96%	5.50	101.69
	Adverse effects treatment (1st day)		96.19	
No adverse effects	Administration of fentanyl	80.04%	5.50	5.50

FIGURE 1 Decision tree for economic assessment of postoperative pain control strategies for adult patients with cancer (fentanyl and sufentanil). Brazil, 2015.

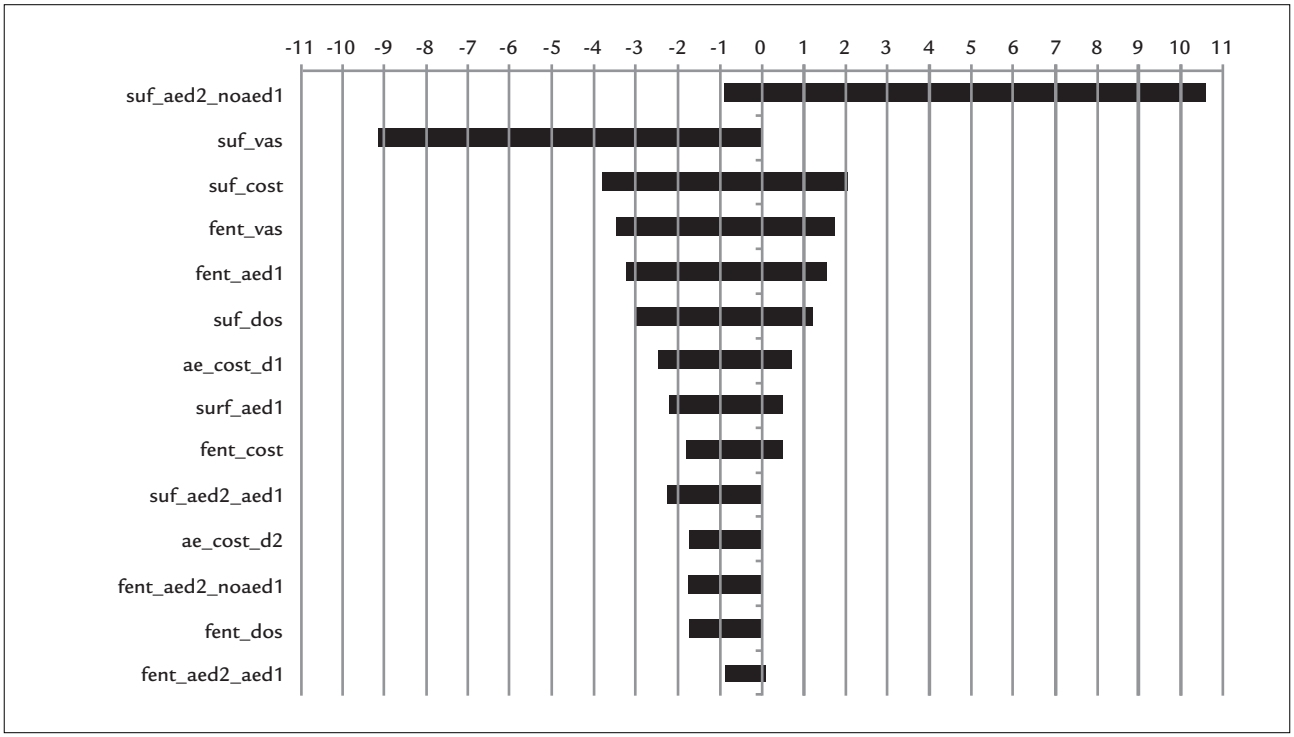


FIGURE 2 Tornado diagram based on sensitivity analysis of economic assessment of postoperative pain control strategies (fentanyl and sufentanil). Brazil, 2015.

Obs.: ae_cost_d1: cost 1st day treatment AE; ae_cost_d2: cost 2nd day treatment AE; fent_aed1: probability AE 1st day using fentanyl; fent_aed2_aed1: probability AE 2nd day for patients using fentanyl with AE 1st day; fent_aed2_noaed1: probability AE 2nd day for patients using fentanyl without AE 1st day; fent_cost: cost of treatment using fentanyl; fent_dos: dosage of fentanyl; fent_vas: VAS points of pain using fentanyl; suf_aed1: probability AE 1st day using sufentanil; suf_aed2_aed1: probability AE 2nd day for patients using sufentanil with AE 1st day; suf_aed2_noaed1: probability AE 2nd day for patients using sufentanil without AE 1st day; suf_cost: cost of treatment using sufentanil; suf_dos: dosage of sufentanil; suf_vas: VAS points of pain using sufentanil. AE: adverse side effects of analgesia.

Discussion

There were no studies assessing cost-effectiveness of adopting fentanyl and sufentanil for postoperative analgesia in the literature review that could allow a comparison with the results obtained in the present study. Furthermore, the literature review conducted in this study showed a lack of other studies regarding effectiveness and safety of treatment using fentanyl and sufentanil for postoperative analgesia on oncologic surgeries, especially economic assessments involving cancer treatment in Brazil.

The structured question used for literature review to search scientific evidences returned only four international studies, and only one of them presented a direct comparison between fentanyl and sufentanil. Considering the wide array of techniques for postoperative analgesia, significant part of the studies was not suitable for comparison of postoperative pain control strategies using fentanyl and sufentanil. Thus, there were a limited number of appropriate parameters to build the decision tree model and proceed to economic assessment of postoperative analgesia.[8]

However, two studies analyzed[7,9] in the literature review showed higher effectiveness of fentanyl and sufentanil in relation to any other medication used as a comparator; except the fourth study,[10] which presented better outcomes of postoperative analgesia based on ropivacaine in relation to fentanyl. However, it is important to point out that the aim of the study was to test the efficacy of ON-Q pain management system;[10] that is, the focus was on the technique for administering postoperative anesthetics.

Both fentanyl and sufentanil presented VAS lower than four, considered the limit for satisfactory analgesia.[7] The costs of treatment with fentanyl was higher than the costs of treatment with sufentanil especially due to the incidence of adverse side effects (nausea and vomit) among patients using fentanyl and due to the higher costs for the treatment of adverse side effects in comparison to the anesthetics prices.

The ICER of sufentanil in comparison to fentanyl may be considered marginal (approximately US$ 6.87 per VAS point of pain), however, there are evidences that the substitution of fentanyl for sufentanil would represent an annual cost reduction of approximately US$ 20,000 to the Brazilian Unified Health System, considering only the number of cancer surgeries in the state of São Paulo.[14]

Sensitivity analysis performed in the study showed that the estimated economic assessment model presented low variation in ICER due to changes in most parameters of the model, indicating robustness to scenario fluctuations. However, it is important to notice that there was high sensitivity to variation in the probability of adverse side effects in the second day among patients who did not have adverse side effects in the first day using sufentanil (variation of up to US$ 10.57 per additional VAS point of pain reduced).

A study conducted with 808 patients in the United States investigated the limits of patients' willingness to pay for reduction of postoperative pain, indicating that patients in pain would be willing to pay up to US$ 35 for perfect analgesia.[15] The study suggests that the use of sufentanil should be considered cost-effective in relation to fentanyl even considering the worst case scenario presented on the sensitivity analysis.

The second parameter influencing ICER was the VAS points of pain in the utilization of sufentanil, reinforcing the dominance of sufentanil in comparison to fentanyl. It is important to notice that the sensitivity analysis showed less ICER variability in relation to the other parameters analyzed, resulting in variations from –US$ 3.81 to up to US$ 2.07 per VAS point of pain reduced.

The main limitations of the study presented include: utilization of data from literature review based on population from other countries due to absence of studies performed in Brazil; significant sensitivity of the model in relation to one key parameter; and lack of observational studies with representativeness at population level, especially involving the Brazilian population, in order to provide additional information on effectiveness and safety of postoperative analgesia relating to cancer treatment.

Conclusion

The economic assessment developed based on the decision tree model for postoperative pain control strategies for adult patients with cancer showed dominance of sufentanil in comparison to fentanyl, due to lower costs of treatment and better outcomes in health status. The sensitivity analysis performed showed robustness of the model, based on parameters derived from literature review and data collection on medical procedures and costs.

The results obtained suggest the need for Brazilian studies on the cost-effectiveness of adoption of fentanyl and sufentanil for postoperative analgesia, in order to validate the premises adopted in the present study and allow for the use of real life data to improve robustness and reliability of economic assessment models designed for comparison of postoperative pain control strategies using fentanyl and sufentanil.

Resumo

Avaliação econômica de estratégias para controle da dor pós-operatória para tratamento de pacientes adultos com câncer

Objetivo: O artigo apresenta uma avaliação econômica de opioides atualmente utilizados no controle de dor pós-operatória relacionada ao tratamento cirúrgico do câncer (fentanil e sufentanil) no contexto do Sistema Único de Saúde.
Método: A avaliação baseou-se na perspectiva do governo, de forma a colaborar na promoção da efetividade das políticas públicas de saúde e melhorar a alocação de recursos públicos em saúde. Uma análise custo-efetividade foi realizada a partir de dados coletados no Sistema Único de Saúde e de informações provenientes de revisão da literatura para construção de uma árvore de decisão contendo alternativas para controle de dor pós-operatória relacionada ao tratamento cirúrgico do câncer entre pacientes adultos. Os desfechos considerados foram: efetividade da analgesia pós-operatória e ocorrência de náusea e vômito no período de 48 horas após cirurgia e em ciclos adicionais de 24 horas de seguimento do paciente. Uma análise de sensibilidade univariada foi conduzida para verificar a robustez do modelo estimado.
Resultados: Na revisão de literatura, um número limitado de estudos efetuou comparação direta entre fentanil e sufentanil no controle de dor pós-operatória. A adoção de sufentanil (custo = U$ 25,72 / desfecho = 1,6 pontos VAS) foi dominante em relação ao uso do fentanil (custo = U$ 32,58 / desfecho = 2,6 pontos VAS). O modelo estimado demonstrou robustez em relação a mudanças nos parâmetros analisados.
Conclusão: O sufentanil apresentou razão custo-efetividade superior em relação ao fentanil no controle de dor pós-operatória em cirurgias relacionadas ao tratamento de câncer entre pacientes adultos no Sistema Único de Saúde.

Palavras-chave: avaliação em saúde, analgesia, medição da dor.

References

1. Tilleul P, Weickmans H, Sean PT, Lienhart A, Beaussier M. Cost analysis applied to postoperative analgesia regimens: a comparison between parecoxib and propacetamol. Pharm World Sci. 2007; 29(4):374-9.
2. Athanasakis K, Petrakis I, Vitsou E, Pimenidou A, Kyriopoulos J. A cost-effectiveness analysis of parecoxib in the management of postoperative pain in the Greek health care setting. Clin Ther. 2013; 35(8):1118-24.

3. Ummenhofer WC, Arends RH, Shen DD, Bernards CM. Comparative spinal distribution and clearance kinetics of intrathecally administered morphine, fentanyl, alfentanil, and sufentanil. Anesthesiology. 2000; 92(3):739-53.
4. Epple J, Kubitz J, Schmidt H, Motsch J, Böttiger BW, Martin E, et al. Comparative analysis of costs of total intravenous anaesthesia with propofol and remifentanil vs. balanced anesthesia with isoflurane and fentanyl. Eur J Anesthesiol. 2001; 18(1):20-8.
5. Ministério da Saúde. Diretrizes metodológicas: diretriz de avaliação econômica. 2. ed. Brasília: Ministério da Saúde; 2014 [cited 2016 Jan 20]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_metodologicas_diretriz_avaliacao_economica.pdf.
6. Nita ME, Nobre MRC, Costa AMN. Busca da evidência a partir do cenário clínico. In: Nita ME, Campino ACC, Secoli SR, Sarti FM, Nobre MRC, Costa AMN, et al., editors. Avaliação de tecnologias em saúde: evidência clínica, análise econômica e análise de decisão. Porto Alegre: Artmed; 2010.
7. Hong JY, Yang SC, Yi J, Kil HK. Epidural ropivacaine and sufentanil and the perioperative stress response after a radical retropubic prostatectomy. Acta Anaesthesiol Scand. 2011; 55(3):282-9.
8. Lin CS, Lu G, Ruan LY, Gu MN. [Patient-controlled intravenous analgesia with sufentanil and fentanyl after thoracotomy: a comparative study]. Nan Fang Yi Ke Da Xue Xue Bao. 2006; 26(2):240-1, 244.
9. Kim HS, Czuczman GJ, Nicholson WK, Pham LD, Richman JM. Pain levels within 24 hours after UFE: a comparison of morphine and fentanyl patient-controlled analgesia. Cardiovasc Intervent Radiol. 2008; 31(6):1100-7.
10. Chung D, Lee YJ, Jo MH, Park HJ, Lim GW, Cho H, et al. The ON-Q pain management system in elective gynecology oncologic surgery: Management of postoperative surgical site pain compared to intravenous patient-controlled analgesia. Obstet Gynecol Sci. 2013; 56(2):93-101.
11. Associação Médica Brasileira. Classificação brasileira hierarquizada de procedimentos médicos. São Paulo: Associação Médica Brasileira; 2014.
12. Cendoroglo Neto M, Hamerschlak N, Ribeiro AAF, Guendelmann RAK, Santos VA. Guia de protocolos e medicamentos para tratamento em oncologia e hematologia. São Paulo: Hospital Israelita Albert Einstein; 2013 [cited 2014 Aug 25]. p. 501-6. Available from: http://medicalsuite.einstein.br/pratica-medica/guias-e-protocolos/Documents/Guia_Oncologia_Einstein_2013.pdf.
13. Câmara de Regulação de Mercado de Medicamentos (CMED). Preços máximos de medicamentos por princípio ativo, para compras públicas preço fábrica (PF) e preço máximo de venda ao governo (PMVG) [cited 2014 Aug 25]. Available from: www.anvisa.org.br.
14. Gomes Junior SCS, Almeida RT. Modelo de simulação para estimar a infraestrutura necessária à assistência oncológica no sistema público de saúde. Rev Panam Salud Publica. 2009; 25(2):113-9.
15. van den Bosch JE, Bonsel GJ, Moons KG, Kalkman CJ. Effect of postoperative experiences on willingness to pay to avoid postoperative pain, nausea, and vomiting. Anesthesiology. 2006; 104(5):1033-9.

Association between the RAGE (receptor for advanced glycation end-products) -374T/A gene polymorphism and diabetic retinopathy in T2DM

Dan Tao[1,2]*, Xuancheng Mai[3], Tiesong Zhang[2], Yan Mei[3,4]

[1]Faculty of Environmental Science and Engineering, Kunming University of Science and Technology, Kunming, China
[2]Kunming Children's Hospital, Kunming, China
[3]The First People's Hospital of Yunnan Province, Kunming, China
[4]Faculty of Medicine, Kunming University of Science and Technology, Kunming, China

Summary

Objective: Interaction between advanced glycation end-products (AGEs) and receptor for AGEs (RAGE) in cells could affect both extracellular and intracellular structure and function, which plays a pivotal role in diabetic microvascular complications. The results from previous epidemiological studies on the association between RAGE gene -374T/A polymorphism and diabetic retinopathy (DR) risk were inconsistent. Thus, we conducted this meta-analysis to summarize the possible association between RAGE -374T/A polymorphism and DR risk.
Method: We searched all relevant articles on the association between RAGE -374T/A polymorphism and DR risk from PubMed, Cochrane Library, ScienceDirect, Wanfang, VIP and Chinese National Knowledge Infrastructure (CNKI) web databases up to August 2016. Odds ratio (OR) with 95% confidence interval (CI) were calculated to assess those associations. All analyses were performed using the Review Manager software.
Results: Nine case-control studies, including 1,705 DR cases and 2,236 controls were enrolled, and the results showed that the A allele of RAGE -374T/A polymorphism was significantly associated with increased DR risk in dominant model (TA/AA vs. TT: OR=1.22, 95CI 1.05-1.41, p=0.006) and heterozygote model (TA vs. TT: OR=1.26, 95CI 1.07-1.47, p=0.005). The subgroup analysis by ethnicity showed that significantly increased DR risk was found in both Asian and Caucasian populations.
Conclusion: This meta-analysis reveals that the A allele of RAGE -374T/A polymorphism probably increase DR risk.

Keywords: polymorphism, genetic, diabetic retinopathy, meta-analysis.

Study conducted by Kunming Health Planning Commission personnel training program (Project number: 2016-sw (backup) -66), Yunnan Science and Technology Planning Project (Kunming Medical Joint Special) (project number: 2017FE468 (-237))

Article received: 4/25/2017
Accepted for publication: 5/7/2017

***Correspondence:**
Kunming University of Science and Technology
Kunming – China
Postal code: 650093
taodan1975@163.com

http://dx.doi.org/10.1590/1806-9282.63.11.971

Introduction

Diabetic retinopathy (DR) is the most common diabetic microvascular complications, affecting approximately 4.8% of diabetes mellitus patients all over the world.[1] DR is one of the most important health threats and the leading cause of blindness in diabetes mellitus patients.[2] The pathophysiology of DR, characterized as basement membrane thickening, pericyte loss, endothelial cell dysfunction, microaneurysms, microvascular infarcts and neovascularization, is complex and multifactorial, and has not yet been clarified.[3-7] DR is a complex disease caused by multiple genetic, environmental, and clinical factors. Previous epidemiological studies have identified several risk factors in the pathogenesis of DR, including duration of diabetes, poor disease control, systemic hypertension and proteinuria.[8] However, these clinical risk factors account only for small portion of the severe forms of DR. Recently, numerous reports have shown that genomics play an important role in the susceptibility and progression of DR.[9-11]

In diabetes mellitus patients, high levels of blood sugar lead to nonenzymatic protein glycation and the formation of advanced glycation end-products (AGE).[12] AGE could bind to a specific receptor known as receptor for advanced glycation end-products (RAGE).[13] Many studies have investigated that AGEs and RAGE were over-expressed in DR.[14,15] The interaction of AGE with

RAGE could lead to a positive feedback loop that enhances the expression of RAGE in the retina, then activates a number of transcription factors, adhesion molecules and tissue factor, and thus induces oxidative stress, cellular dysfunction, increased vascular permeability, adhesion molecule expression and cytokine production.[16-18] All of these effects could promote procoagulant and hypoxic state in the microcapillaries of the retina and leads to the initiation of the angiogenic process in proliferative DR. The RAGE gene is located on chromosome 6p21.3 in MHC Class III region, and the -374T/A polymorphism is the well-characterized genetic variant of this gene.[19,20] Researches have demonstrated that -374T/A polymorphism of the RAGE gene could result in a T-to-A nucleotide substitution, which leads to prevent the binding of a nuclear binding factor and thus increase RAGE gene transcription activity.[20] Therefore, RAGE -374T/A variant may result in susceptibility to and progression of DR.

Numerous case-control studies have observed the association between RAGE -374T/A polymorphism and DR risk.[20-28] However, their results revealed tremendous disparity that may be attributed to possible selection bias or individual small-sized studies. Thus, we carried out the meta-analysis to distinguish the association between the RAGE -374T/A polymorphism and DR risk.

Method

Literature search

Eligible studies were identified using PubMed, Cochrane Library, ScienceDirect, Wanfang, VIP and CNKI web databases with following keywords: "diabetic retinopathy," "RAGE or AGER Receptor for advanced glycation end-products," "-374T/A or -374A" and "polymorphism or mutation or variant" updated up to October17, 2015. Reference lists of relevant articles were reviewed manually to look for additional studies. We did not restrict language of the article in this process.

Inclusion and exclusion criteria

Articles included in this meta-analysis were required to meet the following requisites: a) observe an association between -374T/A polymorphisms in RAGE gene and DR risk; b) apply a case-control or cohort study design; c) have enough genotype frequencies in both case and control groups. The major exclusion criteria were: a) duplicated articles in different databases; b) reviews, comments and editorials; c) low-quality studies, for example case-only studies; d) insufficient data to calculate the effects; e) case groups enrolling type 1 diabetes mellitus (T1DM) patients only. We only included studies presenting good design quality and large sample sizes, in addition to similar patient populations.

Data extraction

Two reviewers independently extracted the following data from the enrolled studies: The data of the enrolled studies, including authors, country, ethnicity, publication year, source of control, sample size, age, gender frequencies, diabetes mellitus (DM) duration, body mass index (BMI) and hemoglobin A1c (HbA1c) levels, and genotype frequencies in both case and control groups. Disagreements regarding the extracted data between the two reviewers were thoroughly discussed in order to reach a final consensus.

Statistical analysis

The χ^2 analysis was used to test Hardy-Weinberg equilibrium (HWE) in control groups and a p-value < 0.05 was considered as departure from HWE.[29] Pooled odds ratio (OR) with 95% confidence intervals (CI) was calculated to assess the strength of the association between RAGE -374T/A polymorphism and DR risk in allelic comparisons (A vs. T), homozygote (AA vs. TT), heterozygote (TA vs. TT), dominant (AA/TA vs. TT) and recessive models (AA vs. TA/TT), respectively. Heterogeneity among studies was evaluated using χ^2 test and I^2. If substantial heterogeneity was present ($p<0.10$ or $I^2>50\%$), the random-effects model was used as the pooling method; otherwise, the fixed-effects model was applied.[30,31] Finally, publication bias was evaluated using egger's linear regression test.[32,33] All statistical analyses of this study were conducted by using Review Manager software version 5.2.11 (RevMan; Cochrane Collaboration).

Results

Characteristics of eligible studies

The flowchart shows the study selection procedures of this meta-analysis (Figure 1). After careful search and selection, nine case-control studies with 1,705 cases and 2,236 controls were enrolled in this meta-analysis. Table 1 shows the main characteristics of each study. Of the nine studies included, five were performed in Caucasian populations and four in Asian populations.

Association of rs1057035 and overall cancer susceptibility

When we pooled all the results of the studies included in our analysis, the results showed that RAGE -374T/A polymorphism was significantly associated with increased DR risk in dominant (TA/AA vs. TT: OR=1.22, 95CI 1.05-

1.41, p=0.006) and heterozygote (TA vs. TT: OR=1.26, 95CI 1.07-1.47, p=0.005) models. However, there was no association between RAGE -374T/A polymorphism and DR risk in allelic comparison, homozygote model, and recessive model. Subgroup analysis by ethnicity showed that significantly increased DR risk was found in Asian populations (TA/AA vs. TT: OR=1.22, 95CI 1.05-1.41, p=0.006; AA vs. TT/TA: OR=2.92, 95CI 1.47-7.48, p=0.030; AA vs. TT: OR=3.17, 95CI 1.23-8.16, p=0.020), and in Caucasian populations (AA vs. TT: OR=1.24, 95CI 1.03-1.50, p=0.030). When stratified by case sample size, significantly increased DR risk was observed in case sample size ≥ 150 group (TA vs. TT: OR=1.22, 95CI 1.02-1.45, p=0.030), but not in case sample size < 150 group in any of the models (Table 2).

Heterogeneity analysis

There was no significant heterogeneity observed in the allelic comparison (A vs. T), heterozygote model (TA vs. TT), and dominant model (AA/TA vs. TT) for overall analysis (P_Q>0.10), thus, fixed effects model was performed to pool the data. However, significant heterogeneity was observed in the homozygote (AA vs. TT) and recessive (AA vs. TA/TT) models for overall analysis (both P_Q<0.10). Because of that, we performed the subgroup analyses to explore the source of heterogeneity. Although the results indicated that heterogeneity was still significant in Caucasian populations (AA vs. TT/TA: P_Q=0.03; AA vs. TT: P_Q=0.03) and in case sample size < 150 group (AA vs. TT/TA: P_Q=0.005; AA vs. TT: P_Q=0.005), it clearly decreased in Asian populations (AA vs. TT/TA: P_Q=0.88; AA vs. TT: P_Q=0.87) and in

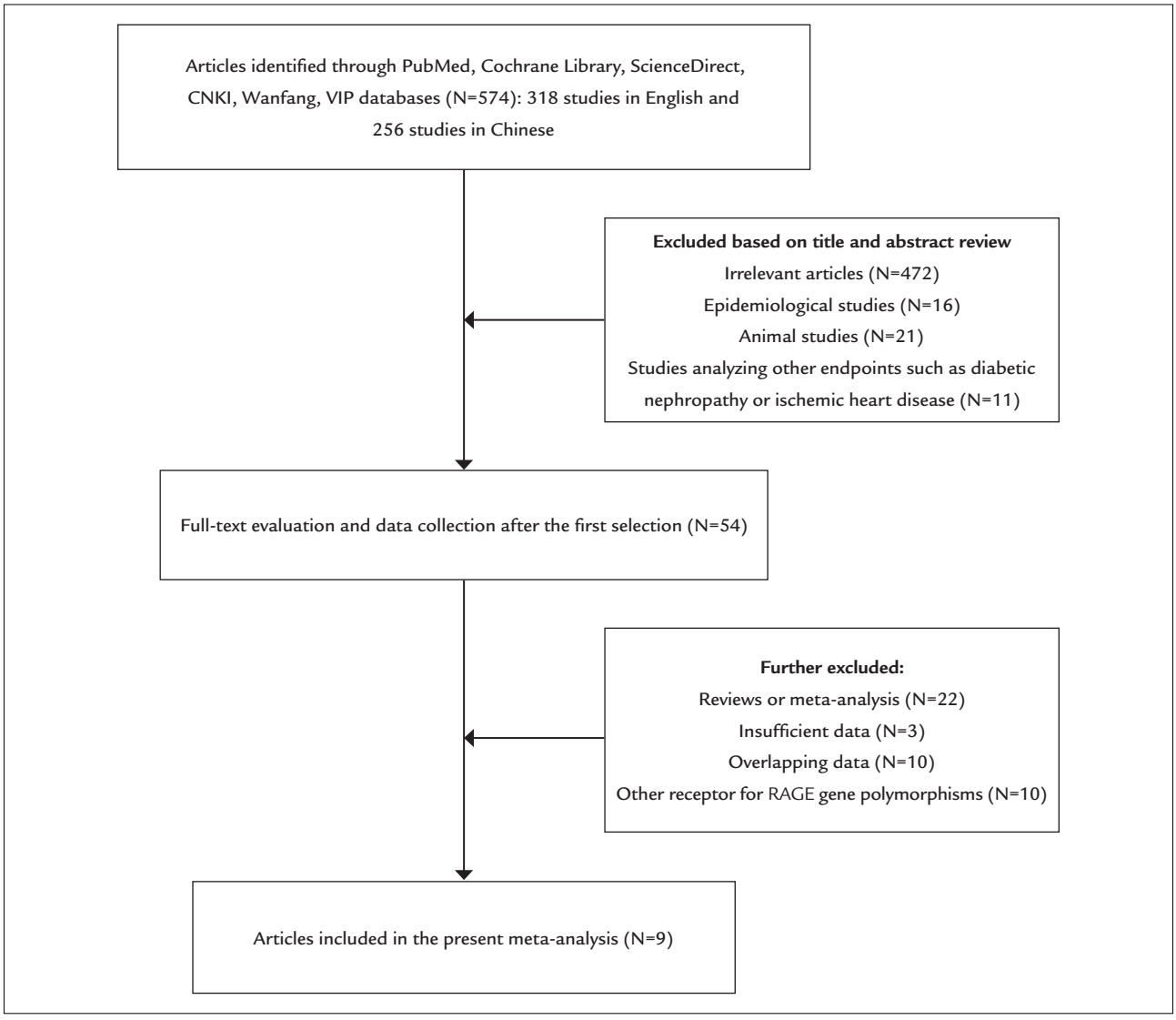


FIGURE 1 Flow diagram of search strategy and study selection.

TABLE 1 Baseline characteristics of the study populations in our meta-analysis.

Study	Country	Ethnicity	Year	Design	Sample source	DM type	Groups	Age, years		Males (%)		DM duration (y)		BMI (kg/m^2)		HbA1c (%)	
								DR	NDR	DR	NDR	DR	NDR	DR	NDR	DR	NDR
Balasubbu 2010	South India	Asian	2010	Case-control	HB	T2DM	PE1:DR=345; NDR=359 PE2:DR=100; NDR=90	PE1: 57±9 PE2: 57±8	PE1: 59±11 PE2: 58±10	PE1: 70.0 PE2: 56.7	PE1: 58.0 PE2: 57.6	PE1: 14±9 PE2: 14±9	PE1: 12±6 PE2: 14±5	NA	NA	PE1: 6.4±1.6 PE2: 7.6±1.7	PE1: 6.4±1.2 PE2: 7.0± 1.7
Globocnik 2003	Slovenia	Caucasian	2003	Case-control	HB	T2DM	DR=116(PDR=76, NPDR=40); NDR=70	66.1± 8.6	70.0±9.2	44	42.9	18.8±8.7	17.2± 6.9	27.8± 4.5	27.7± 4.4	8.3±1.9	8.2± 1.6
Gu 2014	China, Wuxi	Asian	2014	Case-control	PB	T2DM	DR=92;NDR=93; HC=120	63.60 ± 7.23	61.85 ±9.06	48.9	49.5	NA	NA	24.40 ± 2.98	24.93 ± 3.85	8.78 ±2.11	8.38 ±2.35
Hudson 2001	UK, Leeds	Caucasian	2001	Case-control	HB	T2DM	DR=106;NDR=109; HC=113	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lindholm 2006	Sweden	Caucasian	2006	Case-control	HB	T1DM T2DM	T1DM=867(DR=312); T2DM=2467(DR=278); HC =205	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lindholm 2008	Sweden	Caucasian	2008	Case-control	HB	T1DM T2DM	T1DM=742(DR=315); T2DM=2957(DR=298); HC =206	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ramprasad 2007	South India	Asian	2007	Case-control	HB	T2DM	DR=190(PDR=57,NPDR=133);NDR=189; HC=149	NPDR: 59±8; PDR: 59±8	63±9	NPDR: 49 PDR: 70	69	NPDR: 20±6; PDR: 20±8	21±5	NA	NA	NPDR: 8.6±1.9 PDR: 8.9±1.7	8.1± 1.6
Santos 2005	Brazil	Caucasian	2005	Case-control	HB	T2DM	PDR$^+$=46, PDR$^-$=126*	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Z.X.Ng 2012	Malaysia	Asian	2012	Case-control	HB	T2DM	DR=171;NDR=171; HC=235	56.1 ±10.1	59.2 ± 9.6	57.3	58.5	14.8±8.6	10.4± 7.9	26.4± 5.3	27.2± 4.4	9.0±2.1	7.9± 1.8

DM: diabetes mellitus; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; DR: diabetic retinopathy; PDR: proliferative DR; NPDR: non-proliferative DR; HB: hospital-based selection; PB: population-based selection; BMI: body mass index; HbA1C: glycated hemoglobin; PE1: patient enrollment 1; PE2: patient enrollment 2; HC: healthy control; NA: not available.
*PDR-: without DR plus NPDR.

TABLE 2 Overall and subgroup analyses of RAGE gene –374T/A polymorphisms regarding the odds of developing diabetic retinopathy, and exploration of between-study heterogeneity.

Genetic contrast	Population and subgroups under analysis	Studies (cases/controls), n (n/n)	OR (95CI)		p value		Q test p value	I 2 %
			Fixed model (FEM)	Random model (REM)	Fixed model	Random model		
TT vs. TA+AA	All	9(1705/2236)	0.82(0.71-0.94)	0.82(0.70-0.95)	0.006	0.009	0.39	5
	Ethnicity							
	Caucasian	6(907/1424)	0.85(0.71-1.01)	0.84(0.68-1.04)	0.06	0.11	0.27	22
	Asian	4(798/812)	0.74(0.57-0.97)	0.74(0.57-0.97)	0.03	0.03	0.45	0
	Case sample size							
	< 150	4(423/335)	0.70(0.52-0.95)	0.69(0.44-1.07)	0.02	0.10	0.10	52
	≥ 150	5(1282/1901)	0.86(0.72-1.01)	0.86(0.72-1.01)	0.07	0.07	0.92	0
AA vs. TT+TA	All	7(1254/1768)	0.97(0.71-1.33)	1.26(0.65-2.43)	0.86	0.49	0.01	63
	Ethnicity							
	Caucasian	4(801/1315)	0.83(0.59-1.16)	0.85(0.42-1.71)	0.26	0.64	0.03	66
	Asian	3(453/453)	2.92(1.14-7.48)	2.89(1.12-7.44)	0.03	0.03	0.88	0
	Case sample size							
	< 150	3(317/226)	1.73(0.91-3.29)	2.45(0.35-17.28)	0.09	0.37	0.005	81
	≥ 150	4(937/1542)	0.80(0.55-1.15)	0.91(0.50-1.64)	0.22	0.75	0.15	44
TA vs. TT	All	8(1502/1993)	1.26(1.07-1.47)	1.26(1.07-1.47)	0.005	0.005	0.81	0
	Ethnicity							
	Caucasian	4(737/1202)	1.24(1.03-1.50)	1.24(1.03-1.50)	0.03	0.03	0.82	0
	Asian	4(765/791)	1.29(0.96-1.72)	1.29(0.96-1.72)	0.09	0.09	0.43	0
	Case sample size							
	< 150	3(281/212)	1.45(0.98-2.12)	1.44(0.98-2.12)	0.06	0.06	0.47	0
	≥ 150	5(1221/1781)	1.22(1.02-1.45)	1.22(1.02-1.45)	0.03	0.03	0.81	0
AA vs. TT	All	7(784/1164)	1.08(0.79-1.48)	1.39(0.71-2.73)	0.64	0.34	0.01	63
	Ethnicity							
	Caucasian	4(466/828)	0.91(0.64-1.29)	0.93(0.45-1.95)	0.60	0.85	0.03	67
	Asian	3(318/336)	3.17(1.23-8.16)	3.14(1.21-8.13)	0.02	0.02	0.87	0
	Case sample size							
	< 150	3(200/159)	1.98(1.02-3.84)	2.77(0.37-20.95)	0.04	0.32	0.005	81
	≥ 150	4(584/1005)	0.87(0.60-1.27)	0.96(0.55-1.69)	0.48	0.89	0.19	37
A vs. T	All	8(1599/2127)	1.16(0.97-1.38)	1.19(0.96-1.47)	0.1	0.12	0.26	21
	Ethnicity							
	Caucasian	4(801/1315)	1.08(0.88-1.32)	1.11(0.81-1.52)	0.47	0.51	0.12	48
	Asian	4(798/812)	1.43(1.00-2.03)	1.43(1.00-2.03)	0.05	0.05	0.76	0
	Case sample size							
	< 150	3(317/226)	1.50(1.00-2.25)	1.59(0.79-3.21)	0.05	0.20	0.06	64
	≥ 150	5(1282/1901)	1.09(0.89-1.32)	1.09(0.89-1.32)	0.41	0.41	0.81	0

case sample size ≥ 150 group (AA vs. TT/TA: P_Q=0.15; AA vs. TT: P_Q=0.19) (Table 2).

Publication bias

Both the funnel plots and Egger's linear regression test indicated that there was no significant publication bias in any of the above-mentioned inherited models (data not shown).

Discussion

This meta-analysis included nine case-control studies with 1,705 DR cases and 2,236 controls, and the results showed that the A allele of RAGE -374T/A polymorphism was significantly associated with increased DR risk in the dominant and heterozygote models.

The deregulation of AGEs and RAGE is supposed to play a pivotal role in diabetes mellitus development and progression.[34] Many studies have investigated that AGEs and RAGE were overexpressed in the target organ of diabetic microvascular complications.[35] AGEs and RAGE play a complex role in DR through their ability to activate several intracellular cascades, such as NADPH-oxidase/NF-Kb and p21ras/MAP-kinase/AP-1 pathway.[36] The interaction of AGE with RAGE could lead to a positive feedback loop that enhances the expression of RAGE in the retina, then induces oxidative stress, cellular dysfunction, increased vascular permeability, adhesion molecule expression, cytokine production and initiation of coagulation, and thus causes a plethora of deleterious effects.[16-18]

Given the critical function of RAGE in oxidative stress and inflammatory response in DR, it is reasonable to suppose that host genomic polymorphism of RAGE may influence DR risk. -374T/A polymorphism is located in the promoter region of the RAGE gene, which could affect RAGE mRNA and protein expression. Recently, several studies have researched the role of -374T/A polymorphism in the etiology of DR.[20-28] However, their results were not consistent. One meta-analysis was conducted by Lu et al.[37] to assess the association of RAGE -374T/A polymorphism with DR risk. However, there were numerous advantages of our research over that of Lu et al.[37] First, our meta-analysis included a total of nine Chinese populations with 1,705 DR cases and 2,236 controls, which enrolled more studies and subjects than the aforementioned studies. Second, compared with the study by Lu et al., our meta-analysis performed a subgroup analysis that could clarify possible bias from different ethnic populations and sample sizes.[37] Therefore, our meta-analysis could provide additional precision to characterize the association of the RAGE -374T/A polymorphism with DR risk. Third, the study by Lu et al. did not find an association of the RAGE -374T/A polymorphism with DR risk in any genetic models.[37] However, our meta-analysis results showed that the A allele of RAGE -374T/A polymorphism was significantly associated with increased DR risk in both the dominant and heterozygote models. The A allele of RAGE -374T/A polymorphism may prevent the binding of a nuclear binding factor, leading to increased RAGE gene transcription activity, and thus contributes to increase the risk of DR.

In the subgroup analysis by ethnicity, there were different results in Asian and Caucasian populations. One reason may be that the number of studies and number of subjects in Asian and Caucasian populations were relatively small, yielding insufficient statistical power to observe the same association in different populations. The other reason may be that Asian and Caucasian populations have different genetic backgrounds, life-styles, and dietary habits, and therefore produce different degrees of DR susceptibility.

In addition, significant heterogeneity was observed in our meta-analysis. Thus, we performed subgroup analyses stratified by ethnicity and sample size in order to explore the potential sources of heterogeneity, and the results clearly showed less heterogeneity in Asian populations and in case sample size ≥ 150 group, which was still significant in Caucasian populations and in case sample size < 150 group. The reason may be that we were not able to perform an analysis adjusted for the demographic characteristics and clinical features, which were also sources of heterogeneity as the unavailable individual data of the eligible studies.

Despite the meaningful results from our meta-analysis, there were also some limitations. First, although we included nine studies with 3,941 subjects to investigate the association of RAGE -374T/A polymorphism with DR risk, sample size was still not big enough to provide adequate statistical power. Second, there are other important genetic polymorphisms involved in AGE-RAGE interaction and the downstream oxidative stress and inflammatory response pathways that may affect the risk of DR, such as AGEs, endothelin 1, nitric oxide synthase 3, and lymphotoxin-α gene polymorphisms. Nevertheless, we did not research the potential interactions of the RAGE -374T/A polymorphism with them as there were no sufficient data.

In conclusion, our meta-analysis suggests that the A allele of RAGE -374T/A polymorphism might confer a moderately augmented risk for DR. We also conducted a subgroup analysis for ethnicity, the potential confounding of DR, to further clarify this association. Further well-designed studies with larger sample sizes and function researches are warranted to validate our findings.

Conflict of interest

The authors declare no conflict of interest.

References

1. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004; 82(11):844-51.
2. Lin S, Ramulu P, Lamoureux EL, Sabanayagam C. Addressing risk factors, screening, and preventative treatment for diabetic retinopathy in developing countries: a review. Clin Exp Ophthalmol. 2016; 44(4):300-20.
3. Ramsey DJ, Arden GB. Hypoxia and dark adaptation in diabetic retinopathy: interactions, consequences, and therapy. Curr Diab Rep. 2015; 15(12):118.
4. Behl T, Kaur I, Kotwani A. Role of endocannabinoids in the progression of diabetic retinopathy. Diabetes Metab Res Rev. 2016; 32(3):251-9.
5. Roy S, Ha J, Trudeau K, Beglova E. Vascular basement membrane thickening in diabetic retinopathy. Curr Eye Res. 2010; 35(12):1045-56.
6. Beltramo E, Porta M. Pericyte loss in diabetic retinopathy: mechanisms and consequences. Curr Med Chem. 2013; 20(26):3218-25.
7. Behl T, Kotwani A. Exploring the various aspects of the pathological role of vascular endothelial growth factor (VEGF) in diabetic retinopathy. Pharmacol Res. 2015; 99:137-48.
8. Roy MS. Diabetic retinopathy in African Americans with type 1 diabetes: the New Jersey 725: II. Risk factors. Arch Ophthalmol. 2000; 118(1):105-15.
9. Buraczynska M, Zukowski P, Ksiazek K, Wacinski P, Dragan M. The effect of Toll-like receptor 4 gene polymorphism on vascular complications in type 2 diabetes patients. Diabetes Res Clin Pract. 2016; 116:7-13.
10. Kaidonis G, Gillies MC, Abhary S, Liu E, Essex RW, Chang JH, et al. A single-nucleotide polymorphism in the MicroRNA-146a gene is associated with diabetic nephropathy and sight-threatening diabetic retinopathy in Caucasian patients. Acta Diabetol. 2016; 53(4):643-50.
11. Zeng Y, Dai F, Yang K, Tang Y, Xu M, Zhou Y. Association between a vascular endothelial growth factor gene polymorphism (rs2146323) and diabetic retinopathy: a meta-analysis. BMC Ophthalmol. 2015; 15:163.
12. Jahan H, Choudhary MI. Glycation, carbonyl stress and AGEs inhibitors: a patent review. Expert Opin Ther Pat. 2015; 25(11):1267-84.
13. Yamagishi S, Fukami K, Matsui T. Crosstalk between advanced glycation end products (AGEs)-receptor RAGE axis and dipeptidyl peptidase-4-incretin system in diabetic vascular complications. Cardiovasc Diabetol. 2015; 14:2.
14. Chen M, Curtis TM, Stitt AW. Advanced glycation end products and diabetic retinopathy. Curr Med Chem. 2013; 20(26):3234-40.
15. Zong H, Ward M, Stitt AW. AGEs, RAGE, and diabetic retinopathy. Curr Diab Rep. 2011; 11(4):244-52.
16. Glenn JV, Stitt AW. The role of advanced glycation end products in retinal ageing and disease. Biochim Biophys Acta. 2009; 1790(10):1109-16.
17. Yamagishi S, Nakamura K, Imaizumi T. Advanced glycation end products (AGEs) and diabetic vascular complications. Curr Diabetes Ver. 2005; 1(1):93-106.
18. Xie J, Méndez JD, Méndez-Valenzuela V, Aguilar-Hernández MM. Cellular signalling of the receptor for advanced glycation end products (RAGE). Cell Signal. 2013; 25(11):2185-97.
19. Sugaya K, Fukagawa T, Matsumoto K, Mita K, Takahashi E, Ando A, et al. Three genes in the human MHC class III region near the junction with the class II: gene for receptor of advanced glycosylation end products, PBX2 homeobox gene and a notch homolog, human counterpart of mouse mammary tumor gene int-3. Genomics. 1994; 23(2):408-19.
20. Hudson BI, Stickland MH, Futers TS, Grant PJ. Effects of novel polymorphisms in the RAGE gene on transcriptional regulation and their association with diabetic retinopathy. Diabetes. 2001; 50(6):1505-11.
21. Balasubbu S, Sundaresan P, Rajendran A, Ramasamy K, Govindarajan G, Perumalsamy N, et al. Association analysis of nine candidate gene polymorphisms in Indian patients with type 2 diabetic retinopathy. BMC Med Genet. 2010; 11:158.
22. Globocnik Petrovic M, Steblovnik K, Peterlin B, Petrovic D. The - 429 T/C and - 374 T/A gene polymorphisms of the receptor of advanced glycation end products gene are not risk factors for diabetic retinopathy in Caucasians with type 2 diabetes. Klin Monbl Augenheilkd. 2003; 220(12):873-6.
23. Lindholm E, Bakhtadze E, Sjögren M, Cilio CM, Agardh E, Groop L, et al. The -374 T/A polymorphism in the gene encoding RAGE is associated with diabetic nephropathy and retinopathy in type 1 diabetic patients. Diabetologia. 2006; 49(11):2745-55.
24. Lindholm E, Bakhtadze E, Cilio C, Agardh E, Groop L, Agardh CD. Association between LTA, TNF and AGER polymorphisms and late diabetic complications. PLoS One. 2008; 3(6):e2546.
25. Ramprasad S, Radha V, Mathias RA, Majumder PP, Rao MR, Rema M. Rage gene promoter polymorphisms and diabetic retinopathy in a clinic-based population from South India. Eye (Lond). 2007; 21(3):395-401.
26. Santos KG, Canani LH, Gross JL, Tschiedel B, Pires Souto KE, Roisenberg I. The -374A allele of the receptor for advanced glycation end products gene is associated with a decreased risk of ischemic heart disease in African-Brazilians with type 2 diabetes. Mol Genet Metab. 2005; 85(2):149-56.
27. Ng ZX, Kuppusamy UR, Tajunisah I, Fong KC, Chua KH. Association analysis of -429T/C and -374T/A polymorphisms of receptor of advanced glycation end products (RAGE) gene in Malaysian with type 2 diabetic retinopathy. Diabetes Res Clin Pract. 2012; 95(3):372-7.
28. Gu ZY, Yao Y, Xie TH, Cao J, Zou J. Association analysis of advanced glycation end products gene receptor -374T/A polymorphisms in Han people of Wuxi area with type 2 diabetic retinopathy. Rec Adv Opthalmol. 2014; 34(7):655-7.
29. Schaid DJ, Jacobsen SJ. Biased tests of association: comparisons of allele frequencies when departing from Hardy-Weinberg proportions. Am J Epidemiol. 1999; 149(8):706-11.
30. Zintzaras E, Ioannidis JP. HEGESMA: genome search meta-analysis and heterogeneity testing. Bioinformatics. 2005; 21(18):3672-3.
31. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3):177-88.
32. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50(4):1088-101.
33. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109):629-34.
34. Ramasamy R, Yan SF, Schmidt AM. Receptor for AGE (RAGE): signaling mechanisms in the pathogenesis of diabetes and its complications. Ann N Y Acad Sci. 2011; 1243:88-102.
35. Soro-Paavonen A, Forbes JM. Novel therapeutics for diabetic micro- and macrovascular complications. Curr Med Chem. 2006; 13(15):1777-88.
36. Lander HM, Tauras JM, Ogiste JS, Hori O, Moss RA, Schmidt AM. Activation of the receptor for advanced glycation end products triggers a p21(ras)-dependent mitogen-activated protein kinase pathway regulated by oxidant stress. J Biol Chem. 1997; 272(28):17810-4.
37. Lu W, Feng B. The -374A allele of the RAGE gene as a potential protective factor for vascular complications in type 2 diabetes: a meta-analysis. Tohoku J Exp Med. 2010; 220(4):291-7.

What clinical, functional, and psychological factors before treatment are predictors of poor quality of life in cancer patients at the end of chemotherapy?

Ariella Sebastião Mangia[1], Nara Lisiane de Oliveira Coqueiro[2], Fernanda Cabral Azevedo[3], Hiago Tomaz da Silva Araujo[4], Elizandra de Oliveira Amorim[5], Cibelli Navarro Rodrigues Alves[6], Calvino Camargo[7], Allex Jardim da Fonseca[8]*

[1]Physical Educator. MSc in Health Sciences from Universidade Federal de Roraima (UFRR), Boa Vista, RR, Brazil
[2]Psychologist at the Oncology High Complexity Assistance Unit in Roraima. MSc Student, Health Sciences Graduate Program, UFRR, Boa Vista, RR, Brazil
[3]Oncology Physiotherapist at the Oncology High Complexity Assistance Unit, Boa Vista, RR, Brazil
[4]Medical Student, UFRR, Boa Vista, RR, Brazil
[5]Oncology Nurse at the Oncology High Complexity Assistance Unit, Boa Vista, RR, Brazil
[6]MD, Clinical Oncologist at the Oncology High Complexity Assistance Unit. MSc in Health Sciences from UFRR, Boa Vista, RR, Brazil
[7]Psychologist. PhD in Social Psychology from Universidade de São Paulo. Professor in the Health Sciences Graduate Program, UFRR, Boa Vista, RR, Brazil
[8]MD, Clinical Oncologist. PhD in Medicine from Universidade do Estado do Amazonas. Professor in the Health Sciences Graduate Program, UFRR, Boa Vista, RR, Brazil

Summary

Objective: To correlate physical activity level (PAL), functional capacity and psychological state with quality of life (QoL) in cancer patients undergoing chemotherapy (CT).
Method: Observational cohort study. Patients (n=121) with any primary cancer site with indications of chemotherapy with palliative or curative intent were evaluated at three moments: 1) patient admission (week 0), before chemotherapy; 2) week 8; 3) end of CT. Data were collected regarding QoL, PAL, clinical data, functional capacity (short walking distance test, sitting-rising test, isometric manual gripping force), and anxiety and depression tests.
Results: There was significant improvement at the end of CT for: level of physical activity; walk test (> 500 meters); sitting-rising test (> 20x). There was a significant reduction in the prevalence of moderate/severe depression. The prevalence of high QoL showed a significant increase in evaluation 3 (42.4% vs. 40.0% vs. 59.2%, p=0.02). Education up to high school level, low PAL, walking < 300 meters, sitting and rising < 20 times, having depression (moderate to severe) and QoL that was not high at the start of treatment (week 0) all proved to be risk factors for low quality of life at week 16. Conversely, early staging, curative intent chemotherapy and low-grade symptoms were shown to be protective factors.
Conclusion: Performing less than 20 movements in the sitting-rising test and low PAL at the start of chemotherapy represent independent risk factors for low quality of life at the end of chemotherapy.

Keywords: neoplasms, antineoplastic agents, drug therapy, quality of life, exercise, physical and rehabilitation medicine.

Study conducted by Health Science Graduate Program, Universidade Federal de Roraima, Boa Vista, RR, Brazil

Article received: 2/10/2017
Accepted for publication: 3/12/2017

***Correspondence:**
Address: Av. Enê Garces, s/n, Campus de Paricarana
Boa Vista, RR – Brazil
Postal code: 69307-000
allex.jardim@bol.com.br

http://dx.doi.org/10.1590/1806-9282.63.11.978

Introduction

The overall survival of cancer patients has steadily increased over recent decades. Currently, 65% of such patients survive after 5 years of diagnosis.[1,2] Screening strategies and the pursue of early diagnosis of cancer, as well as the development of more effective therapeutic options have resulted in a growing number of cancer survivors in the population, whose function and quality of life have been affected by the disease. This advance in cancer control has also led to the need for new rehabilitation models in order to preserve and promote the patient's functionality before and after cancer treatment.[3,4]

There are many challenges coped by cancer patients, some related to the disease itself and others related to the side effects of cancer treatment, especially chemotherapy. Both impair the physical and psychosocial balance of the

person and, in parallel, quality of life deteriorates. Evidence shows that most cancer patients experience moderate to severe fatigue, in addition to objective muscle weakness. They also demonstrate less tolerance to physical exercise and a decline in functional capacity when performing activities of daily living.[5] Other authors have described how the low level of physical fitness and the reduced functional capacity of cancer patients to perform activities of daily living usually negatively impact the life of the survivors.[6,7] In the medium and long term, the psychosocial and physical problems faced by cancer patients can negatively affect their quality of life.[8] This is more and more concerning given that there is empirical evidence that a reduced quality of life correlates to a shorter survival after cancer treatment.[9]

The type and duration of cancer treatments are individualized and vary, depending on the type, severity and staging of the cancer.[6] Although the primary goal of treatment choice is to cure the cancer and prolong life, there is a need for preservation and/or recovery of the patient's quality of life. The use of complementary therapies to promote well-being and the satisfaction of the patients' holistic and psychosocial needs is important in this context.[5] Physical activity, based on guided physical training, has been studied and indicated in this sense.[3,4,10]

Although there is considerable public awareness about the importance of physical activity for the prevention and control of multiple diseases, its role in the treatment of cancer has been undervalued.[11] Most studies on the correlation between physical activity and cancer are aimed at assessing the role of physical activity in preventing disease. A meta-analysis that re-evaluated 73 studies showed that increased levels of physical activity reduced the risk of breast cancer by 25% over a lifetime.[11] On the other hand, the medical literature is relatively scarce on the role of physical activity in the complementary treatment of cancer patients. There is evidence that high levels of physical activity after the diagnosis of the disease reduce the mortality of patients with breast, colon and prostate cancer.[12] There are also studies demonstrating that cancer patients (especially breast and prostate) undergoing exercise program interventions improve physical fitness, physical function, symptoms and mood.[6,12] Also in this regard, a recent observational study has shown that patients with breast or prostate cancer who participate in higher levels of physical activity significantly reduce the risk of recurrence of the disease, as well as specific cancer mortality.[13]

Cancer is a disease that causes great stress to the patient, family and all those involved in the treatment. Throughout the disease's trajectory, physical and psychological stressors are related to and affect quality of life and the success of patient outcomes.[14] Therefore, studies investigating which factors affect the quality of life of cancer patients undergoing treatment are important and necessary for the development of strategies that minimize the deleterious effects of cancer and cancer therapy. The objective of this study is to correlate the level of physical activity, functional capacity, psychological state (anxiety and depression) and the quality of life of cancer patients undergoing chemotherapy.

Method

Study design

This is an observational descriptive cohort study, including a quantitative analysis, designed to evaluate the correlation between the level of physical activity, functional capacity, psychological status and clinical data and the quality of life (QoL) of patients undergoing chemotherapy in Roraima, in the years 2015 and 2016.

Study setting and population

The study was carried out at the Oncology High Complexity Assistance Unit (Unacon-RR) located in Boa Vista, capital of the state of Roraima. The Unacon-RR has a multiprofessional team and offers clinical oncology and chemotherapy at all levels, among other services.

The target population of the study comprised patients with a cancer diagnosis confirmed by histopathological or cytological tests, registered at the Unacon-RR, with indication for cancer treatment based on adjuvant, curative, palliative or neoadjuvant systemic chemotherapy. Currently, approximately 500 new cases of cancer per year (excluding non-melanoma skin cancers) are estimated for Roraima.[15]

Sample and sampling

For the purposes of sample calculation, an acceptable error of 10%, and 95% confidence interval were considered, yielding a total of 60 patients, considering a prevalence of low quality of life of 30% based on an analogous study.[5] The sampling method was systematic, simple and individual, that is, from the beginning of collection, all patients were invited to participate in the survey, consecutively, without selection, until reaching the sample target. The inclusion period occurred between March 1, 2015 and June 30, 2016.

Research procedures

All patients who attended the Unacon-RR Chemotherapy Center with a medical prescription to begin chemotherapy were approached and invited to participate in the research, daily, through an active search. We included

adult patients of both genders, with a histopathological diagnosis of malignant cancer at any location, with a good or reasonable general condition (defined by an ECOG Performance status between 0 and 3). Patients who had already undergone some form of chemotherapy regimen for the current condition were excluded, as well as patients with significant neurological deficits, oxygen-dependent patients, pregnant women and those who could not understand the purposes of the research.

The cohort consisted of three assessments of each patient. Assessment 1 was performed upon the patient's admission (week 0), before starting treatment. Clinical and sociodemographic data were collected through a face-to-face interview in a confidential doctor's office. For the quality of life analysis, we used the domain "General Health Status and Quality of Life" of the specific questionnaire for cancer patients by the European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire – EORTC QLQ-C 30.[16] The patient's psychological status was analyzed using the Portuguese versions of the Beck Depression Inventory (BDI),[17] for depression, and the Beck Anxiety Inventory (BAI),[18] for anxiety assessment. These tests were conducted by a psychologist.[19] For assessment of the physical activity level, we used the International Physical Activity Questionnaire (IPAQ), an instrument validated to measure physical activity level and effort intensity in the adult population (age range 15-69 years), which generates a metabolic expenditure result called METs.[20] The patients were then submitted to anthropometric measurements and underwent three physical tests for functional capacity: (1) a short walk test of 6 minutes: the patient was motivated to walk as far as possible for 6 minutes under the researcher's supervision. Every 30 seconds the patient was encouraged to continue walking as fast as possible; however, the test would be stopped if requested by the patient. After the time was over, the distance walked by the patient in meters[21] was measured; (2) upper limb strength test: the isometric manual grip strength was measured using a hand dynamometer (Jamar®, USA). The patient was asked to squeeze the dynamometer with as much force as possible. The score obtained was the highest value of three repetitions using the left and right hands;[22] (3) lower limb strength test: the sitting-rising test was performed in 1 minute. After being placed in a chair approximately 43 cm high, the patient was encouraged to perform the greatest number of sitting and rising movements for 1 minute, and the number of movements obtained was recorded.[23]

Assessment 2 was carried out in week 8, during the course of chemotherapy. In this phase, data on quality of life, functional capacity tests, physical activity level, weight, waist circumference and ECOG Status Performance were collected. The last assessment (3) was performed at week 16 (at the end of chemotherapy), and the same data as assessment 1 was analyzed. In order to carry out data collection at all stages, the professionals involved (psychologist, physical educator and physician) were the same, and followed the same methods.

Variables and data analysis

The main outcome was the incidence of poor quality of life at week 16. EORTC-C30 questionnaire score lower than 80 points (according to the author's guidelines) meant a low level of quality of life. Demographic, personal and clinical data, as well as physical activity and psychological status were analyzed as descriptive and/or explanatory variables. The incidence of low quality of life was expressed with a 95% confidence interval using the Newcombe-Wilson method.

A descriptive statistical analysis was performed, including distribution frequency for categorical variables, and means (with standard deviation) and medians (with interquartile deviation) for continuous variables, with normal and non-normal distribution, respectively. For comparison of the sample means, Student's t-test was used for variables with a normal distribution and homogeneity of sample variances. If it was not possible to use Student's t-test, the Mann-Whitney test was used for this purpose.

We used the Chi-squared test to compare differences in the proportions of categorical variables. Relative Risk (RR) and 95% CI were calculated in a bivariate analysis, while the adjusted RR (RRa) derived from a multivariate analysis using the Mantel-Haenszel method. The criterion for selection of explanatory variables for entry into the multivariate analysis was the critical value of $p<0.15$ in the bivariate analysis. The data was analyzed using EpiInfo® software version 7 (CDC, Atlanta, USA).

Ethical aspects

The study was approved by the Research Ethics Committee involving human beings of the Federal University of Roraima (CAAE 42404914.1.0000.5302). The research team ensured the secrecy and confidentiality of the data. The patient's decision not to participate in the research did not result in sanctions of any nature for the research subject.

Results

One hundred and thirty-three (133) patients were invited to participate in the study. Twelve (12) patients refused to participate and the final sample consisted of 121 pa-

tients. Six of these 121 left the study because they died before the final evaluation. At admission, the mean age was 58.7 (±13.1) years. Seventy (70) patients were female (57.8%) and the most common level of education was up to primary school (n=84, 69.4%). The most representative marital status among the patients was married/common law partner (n=72, 59.5%). In relation to current or previous smoking status, 77 patients (63.6%) reported previous or current use of tobacco. Regarding body mass index (BMI), 46 patients (38.0%) were within the normal range (20 to 25 kg/m^2). As for the primary site of cancer, gastrointestinal cancer (n=48, 39.6%) occurred most frequently, followed by breast (n=43, 35.5%) and lung (n=17, 14.0%) cancer. The most common initial staging (TNM) was advanced disease (stage III and IV) compared with early disease, stages I and II (86.7% versus 13.3%); the most prevalent chemotherapy was palliative (n=72, 59.5%).

When evaluating anthropometric measurements over time, there was no significant variation in mean weight or mean BMI. A significant reduction in the proportion of patients with low physical activity level was observed using the IPAQ questionnaire in the three assessments (70.6% vs. 52.2% vs. 51.3%, p=0.01). Also, in the evaluation of the level of physical activity, the mean METs spent in the previous week showed a linear and significant increase (344 vs. 596 vs. 951, respectively, p=0.005). Analyzing the functional capacity tests, in the walk test we observed that the mean number of meters reached in 6 minutes fell in week 8, followed by a significant improvement in week 16, exceeding the baseline values (438 m vs. 371 m vs. 490 m, p=0.002). The same pattern of worsening followed by improvement was observed for the 1-minute sitting-rising test. The mean number of movements performed in the assessments were 18.8 vs. 17.0 vs. 23.7, respectively (p=0.02). The mean values of the palmar grasp test varied slightly in the cohort, with a non-significant trend towards a reduction in both hands. Figure 1 illustrates this data. In the psychological test assessment, there was a significant decline in the prevalence of depression classified as moderate/severe between weeks 0 and 16 (22.0% vs. 10.8%, respectively, p=0.02). There was no significant variation in the prevalence of moderate to severe anxiety (13.5% vs. 6.1%, respectively, p>0.05). The prevalence of high quality of life (score > 80 points) showed a time progression that worsened at week 8 compared with week 0, followed by a significant improvement at week 16, respectively 42.4% vs. 40.0% vs. 59.2% (p=0.02). On the other hand, the data on the functional and symptom scale did not change significantly. Figure 1 illustrates this data.

Considering incidence of low quality of life in the last assessment (week 16) as an outcome, the explanatory variables were correlated in a univariate analysis (Table 1). In this analysis, low level of education (up to high school level) increased the risk of poor quality of life in relation to those with a higher education (58.2% vs. 23.2%, respectively, p 0.02), more than doubling the risk of low QoL (RR=2.27, 95CI 1.15-5.53). On the other hand, early cancer staging and undergoing chemotherapy for curative purposes were protective factors. While patients with early cancer staging had a 10.3% incidence of low QoL, patients with advanced staging presented a 58.8% risk of low QoL (RR=0.21, 95CI 0.08-0.78). Similarly, curative treatment substantially reduced the risk of low QoL compared with palliative chemotherapy (30.6% vs. 65.4%; p=0.01, RR=0.45, 95CI 0.22-0.90). On the other hand, a low level of activity at the start of chemotherapy also correlated unfavorably with QoL at the end of treatment compared to those with moderate/high level of physical activity (62.2% vs. 25.6%, respectively, p=0.008; RR=2.22; 95CI 1.33-6.82). For the walk test, we observed that walking less than 300 meters was also a risk factor for low QoL, which corresponded to a 78.8% incidence of low QoL at the end of CT (p=0.018, RR=1.82; 95CI 1.16-5.88), as opposed to walking more than 500 meters, which provided a lower incidence risk for low QoL (43.2%). Surprisingly, the sitting-rising test was another representative variable to indicate low QoL at the end of chemotherapy. Sitting and rising less than 20 times compared to sitting and rising more than 20 times represented a high risk for developing low QoL (78.8% vs. 30.2%, p<0.001, RR=2.58, 95CI 1.25-4.90).

Regarding the psychological tests, a depressed mood test classified as moderate/severe was shown to be a risk factor for a higher incidence of low QoL compared to patients classified as minimally/mildly depressed (84.8% vs. 34.2%, p=0.005, RR=2.42, 95CI 1.28-4.80). Similarly, having a high quality of life (up to 80 points) at week 0 also increased the incidence of low QoL at the end of chemotherapy (72.2% vs. 20.2%, p=0.0001, RR=3.92, 95CI 1.53-11.21). Functional scale and symptom scale proved to be protective factors, that is, having a high functional scale (> 80 points) reduced the incidence of low QoL to half compared with a low one (up to 80 points) (RR=0.50, 95CI 0.13-0.90). As for the symptom scale, low scores (< 30 points) compared with those not classified as low (30 points or higher) also decreased the risk for incidence of low QoL by half (35.2% vs. 70.6%, p=0.029, RR=0.49, 95CI 0.12-0.89). The other explanatory variables did not correlate with quality of life at the end of chemotherapy (see Table 1).

The variables related to physical activity that correlated with quality of life in the univariate analysis were

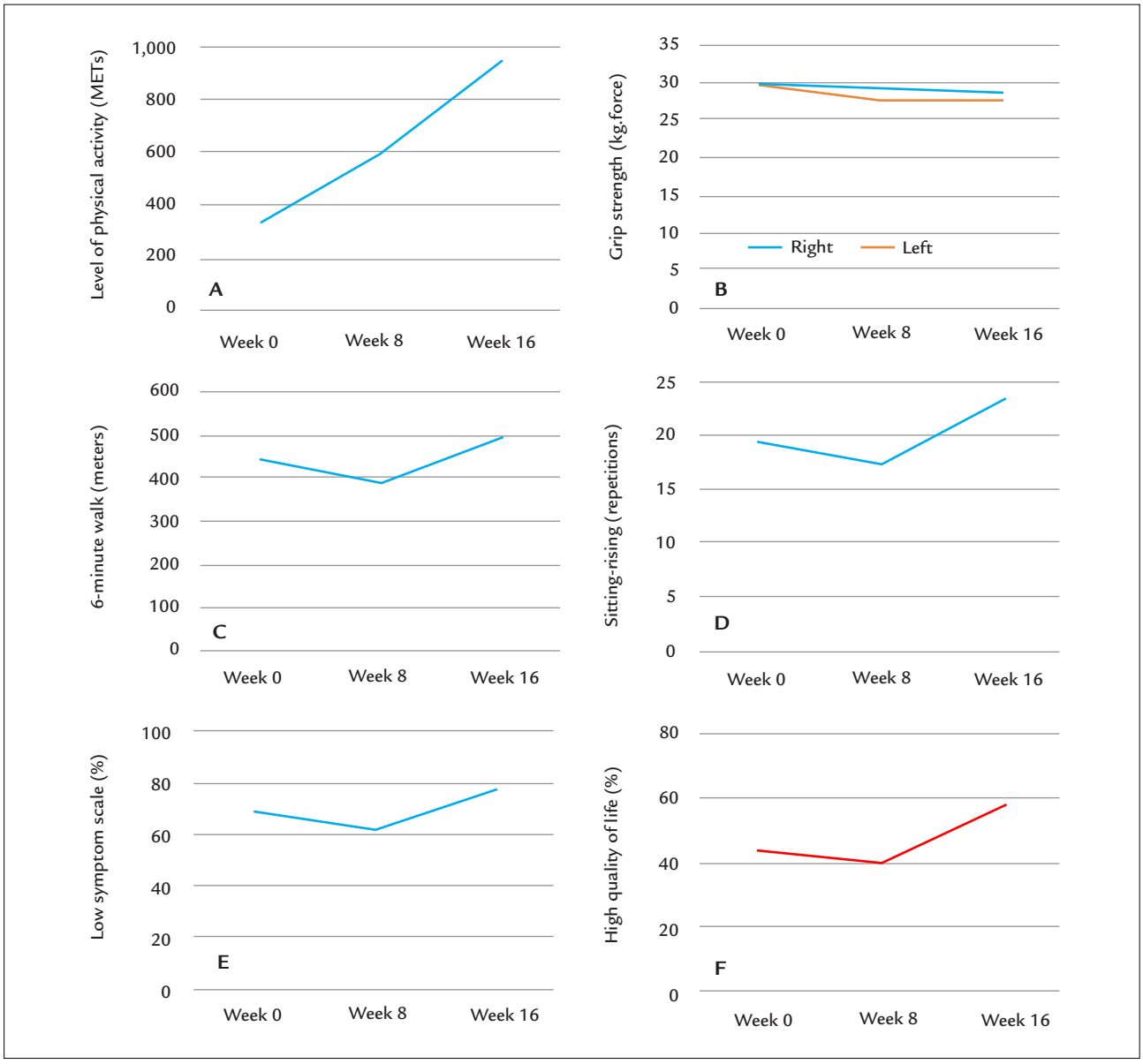


FIGURE 1 Variation of parameters related to physical activity and quality of life at chemotherapy weeks 0, 8 and 16. A. Level of physical activity (METs). B. Grip strength (kg.force). C. 6-minute walk (meters). D. Sitting-rising (repetitions). E. Prevalence of low symptom scale (< 30 points). F. Prevalence of high quality of life (> 80 points).

TABLE 1 Univariate analysis: correlation between explanatory variables measured at admission (week 0) and incidence of low quality of life (score < 80) at the end of the cohort (week 16), Boa Vista, RR.

Explanatory variable (week 0)	Incidence of low quality of life at week 16	p-value	Relative risk (95CI)
Age over 50 years	52.2%	ns	1.08 (0.74-3.99)
Age up to 50 years	46.8%		1
Age over 60 years	49.2%	ns	0.78 (0.35-1.86)
Age up to 60 years	54.7%		1
Female	48.2%	ns	0.95 (0.50-1.57)
Male	54.4%		1

(*continues*)

TABLE 1 (Cont.) Univariate analysis: correlation between explanatory variables measured at admission (week 0) and incidence of low quality of life (score < 80) at the end of the cohort (week 16), Boa Vista, RR.

Explanatory variable (week 0)	Incidence of low quality of life at week 16	p-value	Relative risk (95CI)
Married/Common-law	52.2%	ns	1.30 (0.59-1.86)
Single/Widow(er)/Divorced	41.7%		1
Education up to high school	58.2%	0.02	2.27 (1.15-5.53)
Higher education	23.2%		1
Early staging	10.3%	0.008	0.21 (0.08-0.78)
Late staging	58,8%		1
Curative chemotherapy	30.6%	0.01	0.45 (0.22-0.90)
Palliative chemotherapy	65.4%		1
ECOG performance status			
0, 1 or 2	40.6%	ns	0.85 (0.25-3.25)
3 or 4	50.2%		1
Body mass index			
Less than 20	52.0%	ns	1.18 (0.25-4.87)
Less than 25	50.2%	ns	1.15 (0.28-3.21)
Less than 30	48.6%	ns	1.04 (0.32-3.22)
Greater than 30	40.6%		1
Manual grip strength, right			
Less than 30 kg.force	55.6%	ns	1.12 (0.35-2.84)
Greater than 30 kg.force	50.2%		1
Manual grip strength, left			
Less than 30 kg.force	47.2%	ns	0.95 (0.52-2.61)
Greater than 30 kg.force	51.4%		1
Baseline level of physical activity			
Low	62.2%	0.008	2.22 (1.33-6.82)
Moderate/High	25.6%		1
Walk test			
Less than 300 m	78.8%	0.018	1.82 (1.16-5.88)
Less than 400 m	48.2%	ns	1.12 (0.62-2.34)
Less than 500 m	47.6%	ns	1.10 (0.60-2.23)
More than 500 m	43.2%		1
Sitting-rising test			
Less than 20 times	78.0%	<0.001	2.58 (1.25-4.90)
More than 20 times	30.2%		1
Anxiety test			
Moderate/Severe	68.2%	ns	1.58 (0.66-3.24)
Minimal/Mild	45.2%		1

reassessed in a multivariate analysis, through stratification from other explanatory variables and adjustment using the Mantel-Haenszel method. Maintaining low quality of life as an outcome, we observed that patients who failed the sitting-rising test (< 20 times) at week 0 were established as an independent risk factor for low QoL at week 16, when adjusted for the explanatory variables (functional scale, symptom scale, depression test and quality of life at week 0). The same can be observed for the level of physical activity classified as low on admission. On the other hand, a walk test less than 300 meters was not confirmed as an independent risk factor. Table 2 describes the adjusted values.

Discussion

In our sample, gastrointestinal cancer was the most common type of cancer, followed by breast and lung disease. According to Inca data, in the North and Northeast regions,

TABLE 2 Multivariate analysis: adjustment of relative risk of variables related to physical activity for low quality of life at week 16. Stratification by selected variables in the univariate analysis (Mantel-Haenszel method).

	Adjusted relative risk (95% confidence interval) for low quality of life (week 16). Stratification based on the variables below (week 0) Mantel-Haenszel method.			
Explanatory variables related to physical activity (week 0)	Depressed mood (moderate/severe vs. mild/mininal)	Baseline quality of life (cut-off = 80)	Functional scale (cut-off = 80)	Symptom scale (cut-off = 30)
Baseline level of physical activity				
Low	2.24 (1.05-6.3)	2.16 (1.12-4.8)	2.40 (1.07-5.9)	2.23 (1.06-6.0)
Moderate/High	1	1	1	1
Adjusted p-value	0.032	0.022	0.030	0.031
Walk test				
Less than 300 m	1.83 (1.11-5.2)	1.20 (0.82-3.2)	1.21 (0.78-3.4)	1.31 (0.68-4.0)
More than 300 m	1	1	1	1
Adjusted p-value	0.024	ns	ns	ns
Sitting-rising test				
Less than 20 times	2.25 (1.15-4.8)	2.01 (1.13-3.0)	2.02 (1.14-3.2)	2.24 (1.16-4.7)
More than 20 times	1	1	1	1
Adjusted p-value	0.002	0.020	0.018	0.002

malignant tumors of the stomach occupy a prominent position compared with other areas in Brazil, where lung cancer has a higher incidence.[15] We observed that the majority (80%) of patients presented advanced disease (stages III and IV) in the initial manifestation of the disease. Our data corroborates the Inca estimates, which indicate that 60% of cancer cases in Brazil are diagnosed at an advanced stage.[15] Therefore, the most common chemotherapy proposal in the present study was the palliative one, with the main objective of soothing symptoms and improving the patients' quality of life.

All patients were evaluated objectively for physical capacity. The results of the walk test and the sitting-rising test behaved similarly: the results were low at week 0, suffered a decline at week 8 and increased significantly at week 16. This "V" shaped curve may also be observed for functional scale assessments, symptom scale and the main outcome. That is, in the first weeks of chemotherapy, patients present a worsening of their overall state, markedly represented by the lowest point in functional capacity and quality of life, and worsening of symptoms in the second evaluation. After week 8, these variables improved as a whole, exceeding the baseline levels (of week 0). This pattern of worsening followed by improvement definitely has a multifactorial etiology. This possibly demonstrates that, upon initiating treatment, patients experience a worsening of overall health due to the appearance of the adverse effects of chemotherapy. This deleterious effect is only compensated later on, after week 8, probably due to the control of symptoms and deleterious effects directly caused by the tumor. Therefore, the sharp and fine correlation of the outcome (quality of life) with the walk test and the sitting-rising test is noticeable. These results have direct implications for the clinical management of cancer patients. First, the physician's anticipation that the patients may experience a worsening of their physical capacity in the initial phase of treatment, and that this phase precedes an overall improvement after week 8 of chemotherapy, can be a tool that helps the patient seek better psychological methods to cope with a difficult initial period. Second, the study helps to define that the first 8 weeks of chemotherapy are the period of greatest need for interventions by the multidisciplinary team, since some studies have already demonstrated the health benefits of psychological interventions and physical exercise programs in cancer patients.[6,7,13,14,24] Backman et al.[25] conducted an interesting interventional study in breast cancer patients in 2014. Patients were advised to take a daily walk for 10 weeks during chemotherapy. Those who increased their levels of physical activity reported a decrease in specific symptoms such as swelling, pain and improved mobility.[25] Concerned for the safety of physical interventions in cancer patients, Schmitz et al.[6] conducted an interventional study with patient-oriented physical training and concluded that physical training is safe during and after chemotherapy and results in improvements in physical functioning, quality of life and cancer-related fatigue.[6] Another study that evaluated the level of physical activity in patients with bone metastasis, and submitted the patients to specific and guided resistance exer-

cises, showed that, even in this population, significant improvements in functional capacity, physical activity level and quality of life were obtained 6 months after the program ended.[13] It is noteworthy that this recent evidence represents a paradigm shift. Historically, cancer patients were advised by their physicians to rest and avoid physical activity. However, it is now evident that physical inactivity is deleterious. The most recommended guidance today is that any physical activity would be better than nothing.

Not all variables, however, presented a "V"-shaped time curve. When analyzing the dynamometer tests, for example, the manual grip strength did not change much. There was a tendency towards a decline in strength throughout the treatment, without statistical significance. In a similar longitudinal study that assessed physical activity and physical fitness in cancer patients before, during and after chemotherapy, results for manual grip strength were similar to those described in our study. Vermaete et al.[10] described a tendency towards a reduction in strength throughout chemotherapy treatment.[10] The behavior of the variable "level of physical activity" in our study was also discrepant in relation to the others, which is noteworthy. The level of physical activity reported went upward from the beginning to the end of the study, with no decline in week 8. However, we did expect a behavior similar to the one seen in the walk and sitting-rising tests. According to Galiano-Castilho et al.,[26] a reduction in the level of physical activity of cancer patients was expected after starting chemotherapy.[26] The level of physical activity was assessed through information on the patient's perception of their movements over the last 7 days prior to the interview, including their leisure, domestic and gardening activities, and physical activity related to work and transportation, that is, the activities involved in their daily lifestyle; unlike the functional capacity tests that were objectively measured during the assessments. This may represent a measurement bias: being engaged in a study protocol that assessed the level of physical activity, patients might have been motivated to report an (unreal) increase in their daily physical activities. However, the data may also be real. The non-correlation between physical activity level and quality of life at week 8 may be true, and perhaps explained by the fact that the physical activity level questionnaire takes into account daily activities, as mentioned above. At this stage of the treatment, an incipient improvement of the patient's physical and psychological conditions (mood, motivation, resilience) may stimulate the patient to resume daily activities early, such as taking care of their home. This positively influences the questionnaire assessing the level of physical activity. However, this type of physical activity may not be enough to increase quality of life. The studies are consensual in affirming that, in order to improve the quality of life of cancer patients, more intense physical activities are necessary. As such, the variable in question (level of physical activity) would not present worsening in week 8 because it is the precursor of the overall improvement in health that was observed at week 16. Further studies are needed in order to better understand the behavior of patients in terms of level of physical activity during chemotherapy.

Regarding psychological state, we observed that the depressive state classified as moderate to severe was more common at the beginning of the study than at the end of chemotherapy. If we compare this with the level of physical activity, we can observe that both variables behaved in a similar manner in the cohort, which leads us to believe that being more physically active during chemotherapy, together with the improvement of symptoms and regression of the disease caused by treatment, may help to decrease the depressive state during chemotherapy. That is, raising the level of physical activity precedes the improvement of mood and possibly contributes to it. Psychological stress is common in patients diagnosed with cancer and is characterized by vulnerability, uncertainties, loss of control and worries.[14] The level of anxiety presented a tendency towards reduction, but without statistical significance.

The main objective of this study was to evaluate the quality of life outcome through correlation with the variables of physical activity level, functional capacity and psychological status. In a univariate statistical analysis, we observed that the variables level of education up to high school, low level of physical activity, walking less than 300 meters, sitting and rising less than 20 times, having moderate to severe depression and lower quality of life at the beginning of treatment (week 0) all proved to be risk factors for the incidence of low quality of life in week 16, corresponding to the end of treatment. Conversely, early staging, curative chemotherapy, high functional scale, and low grade symptoms are shown as protective factors against low quality of life at the end of treatment. The variables were reevaluated in a multivariate analysis in order to refine the risk analysis, discarding confounding factors. This more demanding analysis demonstrated that having a low level of physical activity and sitting and rising less than 20 times at the beginning of chemotherapy are risk factors for low quality of life at week 16, regardless of depressed mood, baseline quality of life, functional scale and symptom scale at the start of treatment. To the extent

of our knowledge, we did not find studies reporting similar results. This is perhaps the main contribution of our study to the clinical practice. The sitting-rising test, particularly, was the explanatory variable with the greatest influence on quality of life at the end of the treatment. The importance of this data lies in its contribution to medical decision-making. This is an objective test, which can be easily carried out in the physician's office, presenting low risk and low cost, and without the need for concomitant action by other health professionals. This test offers another piece of data for the difficult decision-making by oncologists when there is doubt as to whether a patient would benefit from treatment. There are not many difficulties regarding making the decision to carry out chemotherapy in young patients, with the intention of curing the cancer. However, medical practice is fraught with dubious situations, such as the decision to treat elderly or debilitated patients with palliative chemotherapy, whose main purpose is the soothing of symptoms and the improvement of quality of life at the end of treatment. As such, asking the patient to perform the sitting-rising test or applying a questionnaire for the level of physical activity could contribute to this decision-making.

Strassmann et al. determined the reference values for the sitting-rising test in 1 minute for 6,926 healthy adults; the mean of the results found was 50 repetitions/minute (25-75%, 41-57/min) in young men; 47 repetitions/minute (39-55/min) in young women; 30 repetitions/minute (25-37/min) in elderly men and 27 repetitions/minute (22-30/min) in elderly women. Another study evaluating chronic obstructive pulmonary disease (COPD) showed that the mean number of repetitions per minute was 17.[27] Although it is not possible to compare the results of these studies with the data found in our cohort, it were able to notice that the mean values of the sitting-rising test vary from one population to another. Aware of this, we chose to set a sitting-rising cutoff of 20 times for cancer patients, which in fact proved to be a satisfactory indicator of quality of life at the end of chemotherapy. In a study that assessed functional dependence for daily life activities in older adults (without a diagnosis of cancer), the sitting-rising test was also shown to be sensitive to indicating a risk factor for functional dependence in the elderly;[28] highlighting the sensitivity of this test in predicting different outcomes related to different diseases. However, we did not find studies that used the sitting-rising test as a marker for risk of poor quality of life in cancer patients. In view of this, we believe that further studies are needed to confirm these results in the context of a predictor of successful treatment of cancer patients.

Conclusion

The variation in physical activity level, sitting-rising test and walk test in the three assessments in this cohort showed a clear correlation with the quality of life of cancer patients undergoing chemotherapy, presenting a pattern of initial worsening, followed by improvement at the end of treatment. These findings demonstrate the relevance of our study in the scope of the importance of physical activity for this population. Strategies to increase the level of physical activity early during chemotherapy can positively affect the quality of life of these patients. In order for this to become a reality in cancer treatment and care centers, a multidisciplinary team is needed so that physicians and physical educators, together with other health professionals, advise patients on the benefits of practicing physical activity during cancer treatment. In addition, training and discussions on exercises for patients with cancer under treatment are extremely important, since this population requires special care. In the current scenario, in which both the relevance of the practice of physical activity in the prevention and rehabilitation of chronic degenerative diseases, as well as the maintenance of health and quality of life are discussed, we found few interventionist studies in the national databases on activity during cancer treatment, especially chemotherapy. To our understanding, this demonstrates the need for more discussions and research about the optimal level of physical activity prior to chemotherapy treatment, the ideal number of repetitions of the sitting-rising test for elderly patients and those receiving palliative chemotherapy, as well as the best physical activity to perform, its frequency, intensity and duration of the exercises; questions that still need answering.

The level of physical activity and the sitting-rising test were independent predictors of quality of life at the end of chemotherapy. The sitting-rising test, in particular, is simple, easy to perform and inexpensive, and may contribute to medical decision-making, especially for patients undergoing palliative treatment, due to evidence pointing that it is a test predictive of the incidence of high quality of life at the end of chemotherapy.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Que fatores clínicos, funcionais e psíquicos antes do tratamento são preditores de baixa qualidade de vida em pacientes oncológicos ao término da quimioterapia?

Objetivo: Correlacionar nível de atividade física (NAF), capacidade funcional, estado psicológico com qualidade de vida (QdV) de pacientes com câncer em tratamento quimioterápico (QT).

Método: Estudo de coorte observacional. Pacientes (n=121) com qualquer sítio primário de câncer, com indicação de quimioterapia com intuito paliativo ou curativo foram avaliados em three momentos: 1) admissão do paciente (semana 0), antes da quimioterapia; 2) semana 8; 3) ao término da QT. Foram coletados dados sobre QdV, NAF, dados clínicos, testes de capacidade funcional (teste de curta distância de caminhada, teste de sentar/levantar, força de preensão manual isométrica) e testes de ansiedade e depressão.

Resultados: Houve melhora significativa ao término da QT para: nível de atividade física; teste de caminhada (> 500 metros); teste de sentar e levantar (> 20x). Notou-se redução significativa da prevalência de depressão moderada/grave. A prevalência de QdV elevada apresentou aumento significativo na avaliação 3 (42,4% vs. 40,0% vs. 59,2%; p=0,02). Escolaridade até nível médio, baixo NAF, caminhar < 300 metros, sentar e levantar < 20 vezes, ter depressão do humor (moderado a grave) e QdV não elevada no início do tratamento (semana 0) foram fatores de risco para baixa qualidade de vida na semana 16. Inversamente, estadiamento precoce, intuito de quimioterapia curativo, baixa escala de sintomas foram fatores de proteção.

Conclusão: Realizar menos de 20 movimentos no teste de sentar e levantar e possuir baixo NAF no início do tratamento quimioterápico representam fatores de riscos independentes para baixa qualidade de vida ao fim da quimioterapia.

Palavras-chave: neoplasias, antineoplásicos, tratamento farmacológico, qualidade de vida, exercício, medicina física e reabilitação.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136(5):E359-86.
2. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. Lancet Oncol. 2012; 13(8):790-801.
3. Galán S, de la Vega R, Tomé Pires C, Racine M, Solé E, Jensen MP, et al. What are the needs of adolescents and young adults after a cancer treatment? A Delphi study. Eur J Cancer Care (Engl). 2017; 26(2).
4. Tran H, Lin C, Yu F, Frederick A, Mieras M, Baccaglini L. A multicenter study on the relative effectiveness of a 12-week physical training program for adults with an oncologic diagnosis. Support Care Cancer. 2016; 24(9):3705-13.
5. Sancho A, Carrera S, Arietaleanizbeascoa M, Arce V, Gallastegui NM, Giné March A, et al. Supervised physical exercise to improve the quality of life of cancer patients: the EFICANCER randomised controlled trial. BMC Cancer. 2015; 15:40.
6. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvão DA, Pinto BM, et al.; American College of Sports Medicine. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010; 42(7):1409-26.
7. Oechsle K, Aslan Z, Suesse Y, Jensen W, Bokemeyer C, de Wit M. Multimodal exercise training during myeloablative chemotherapy: a prospective randomized pilot trial. Support Care Cancer. 2014; 22(1):63-9.
8. Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee Report, 2008. Washington: U.S. Department of Health and Human Services; 2008.
9. Buffart LM, Thong MS, Schep G, Chinapaw MJ, Brug J, van de Poll-Franse LV. Self-reported physical activity: its correlates and relationship with health-related quality of life in a large cohort of colorectal cancer survivors. PLoS One. 2012; 7(5):e36164.
10. Vermaete N, Wolter P, Verhoef G, Gosselink R. Physical activity and physical fitness in lymphoma patients before, during, and after chemotherapy: a prospective longitudinal study. Ann Hematol. 2014; 93(3):411-24.
11. Courneya KS, Friedenreich CM. Physical activity and cancer: an introduction. Recent Results Cancer Res. 2011; 186:1-10.
12. Granger CL, Parry SM, Edbrooke L, Denehy L. Deterioration in physical activity and function differs according to treatment type in non-small cell lung cancer: future directions for physiotherapy management. Physiotherapy. 2016; 102(3):256-63.
13. Cormie P, Galvão DA, Spry N, Joseph D, Taaffe DR, Newton RU. Functional benefits are sustained after a program of supervised resistance exercise in cancer patients with bone metastases: longitudinal results of a pilot study. Support Care Cancer. 2014; 22(6):1537-48.
14. Knobf MT, Musanti R, Dorward J. Exercise and quality of life outcomes in patients with cancer. Semin Oncol Nurs. 2007; 23(4):285-96.
15. Brasil, Ministério da Saúde. Estimativa 2016: Incidência de câncer no Brasil. Rio de Janeiro: INCA; 2016. Available from: http://www.inca.gov.br/dncc.
16. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993; 85(5):365-76.
17. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 4:561-71.
18. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988; 56(6):893-7.
19. Cunha JA. Manual da versão em português das escalas Beck. São Paulo: Casa do Psicólogo; 2001.
20. Canário AC, Cabral PU, Paiva LC, Florencio GL, Spyrides MH, Gonçalves AK. Physical activity, fatigue and quality of life in breast cancer patients. Rev Assoc Med Bras. 2016; 62(1):38-44.
21. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002; 166(1):111-7.
22. Mathiowetz V, Kashman N, Volland G, Karen W, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil. 1985; 66(2):69-74.
23. Janssen WG, Bussmann HB, Stam HJ. Determinants of the sit-to-stand movement: a review. Phys Ther. 2002; 82(9):866-79.
24. Henke CC, Cabri J, Fricke L, Pankow W, Kandilakis G, Feyer PC, et al. Strength and endurance training in the treatment of lung cancer patients in stages IIIA/IIIB/IV. Support Care Cancer. 2014; 22(1):95-101.
25. Backman M, Wengström Y, Johansson B, Sköldengen I, Börjesson S, Tärnbro S, et al. A randomized pilot study with daily walking during adjuvant chemotherapy for patients with breast and colorectal cancer. Acta Oncol. 2014; 53(4):510-20.
26. Galiano-Castillo N, Ariza-García A, Cantarero-Villanueva I, Fernández-Lao C, Díaz-Rodríguez L, Arroyo-Morales M. Depressed mood in breast cancer survivors: associations with physical activity, cancer-related fatigue, quality of life, and fitness level. Eur J Oncol Nurs. 2014; 18(2):206-10.
27. Puhan MA, Siebeling L, Zoller M, Muggensturm P, ter Riet G. Simple functional performance tests and mortality in COPD. Eur Respir J. 2013; 42(4):956-63.
28. Gill TM, Williams CS, Tinetti ME. Assessing risk for the onset of functional dependence among older adults: the role of physical performance. J Am Geriatr Soc. 1995; 43(6):603-9.

The analysis on the expression of gasotransmitters in early trauma patients

Zhiyong Wang[1], Mignxing Fang[1], Jianying Guo[1], Yong Yang[1], Fengjun Tian[2]*

[1]Department of Critical Care Medicine, The Third Hospital of Hebei Medical University, Shijiazhuang, Hebei, China
[2]Department of Respiratory, The Third Hospital of Hebei Medical University, Shijiazhuang, Hebei, China

Study conducted at The Third Hospital of Hebei Medical University, Shijiazhuang, Hebei, China

Article received: 3/7/2017
Accepted for publication: 3/12/2017

***Correspondence:**
The Third Hospital of Hebei Medical University
Address: No.139 Ziqiang Road, Qiaoxi District
Shijazhuang, Hebei – China
Postal code: 050051
tianfengjun29@126.com

http://dx.doi.org/10.1590/1806-9282.63.11.988

Summary

Objective: Nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) were endogenously-generated molecules gas. They owned important biological activity and participated in many pathophysiological processes. This study aimed to examine the levels of three gasotransmitters in the early phase of trauma patients.
Method: Blood samples were collected from 60 trauma patients and ten healthy volunteers. Concentration of serum iNOS and HO-1 were analyzed by enzyme linked immunosorbent assay and plasma H_2S was determined by colorimetric method. Meanwhile, the occurrence of multiple organ dysfunction syndrome (MODS) was also monitored.
Results: The levels of iNOS, HO-1 and endogenous H_2S in the patients group were significantly different from the healthy control group, and the difference was more obvious with the increase of ISS score. iNOS levels were positively correlated with ISS scores and blood lactic acid values, and HO-1 and endogenous H2S were negatively correlated with ISS scores and blood lactic acid values. Of 60 trauma patients, eight (13.33%) developed MODS. The level of iNOS in the MODS group was higher than that in non-MODS group, while HO-1 and H_2S were significant lower in the MODS group.
Conclusion: The three gasotransmitters participated in systemic inflammatory responses during early trauma and could be used as important indicators for trauma severity. Their measurements were meaningful for evaluating the severity and prognosis of trauma.

Keywords: wounds and injuries, nitric oxide synthase type II, heme oxygenase-1, hydrogen sulfide, multiple organ failure.

Introduction

Recently, severe trauma involving multiple locations and multiple organs has become one of the major causes of deaths. There are three peak incidences of death for the patients with multiple trauma: (i) within several seconds to several minutes after trauma, immediate death is always caused by damage in the brain, heart and large blood vessels, as well as high spinal cord injury; (ii) within several minutes to several hours after trauma, early death is mainly caused by asphyxia, circulatory insufficiency and uncontrolled massive hemorrhage; (iii) within several days to several weeks after trauma, late death is caused by organ failure and infection. In all of the three situations, systemic inflammatory response syndrome (SIRS) exists in different degrees. The excessive release of inflammatory mediator and the over-activation of inflammatory cells would lead to an excessive immune response in severe trauma.[1] In addition to the direct injury, inflammatory mediators also cause a "second injury" to human body. Thus, control of inflammatory mediators is critically important in the inhibition of SIRS in multiple-organ dysfunction syndrome (MODS).

Endogenous gasotransmitters not only play an important role in the regulation of immunological reactions, but also function in the regulation of vascular activity. It was found that gasotransmitters are the important signaling pathways in inflammatory reactions. Among them, nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S), the three gases and their corresponding synthetases compose an interactional system. NO is an endothelium-

-derived relaxing factor, generated from L-arginine under the catalysis of inducible nitric oxide synthase (iNOS). Endogenous NO is activated in the conditions of severe trauma, infection and shock, and abundant NO is produced. Furthermore, endogenous NO also has a negative inotropic effect; it can inhibit cardiac function, and even cause low blood pressure and shock. Meanwhile, it also interacts with the accumulated superoxide anion (O_2^-) and forms peroxynitrite anion ($ONOO^-$), thus more poly polymerase is over-activated and causes cellular injury.

CO has anti-inflammatory, anti-oxidation and cell-protection properties. HO-1 is considered one of the major rate-limiting enzymes for synthesis of endogenous CO. Under the influence of hypoxia, endotoxins and cytokines, it can catalyze the degradation of heme to CO. Studies found that endogenous CO activates guanylate cyclase, and thus leads to increase of cGMP and induces the relaxation of vascular smooth muscle.[2] In addition, it also inhibits the expression of iNOS and decreases the cytotoxicity caused by excessive NO.[3]

Endogenous H_2S was mainly produced from L-cysteine-substrate by cystathionine-β-synthetase (CBS) and cystathionine-lyase (CSE). The former mainly exists in liver, brain and other parenchymal organs, while the latter mainly exists in the cardiovascular system. The distribution of endogenous H_2S in the human body has tissue specificity. However, there is no consensus regarding the anti-inflammatory ability or pro-inflammatory ability of H_2S.[4,5]

The participation of the above three gasotransmitters in inflammatory reactions has been widely investigated. However, their roles in different diseases and during different disease courses still calls for further study. So far, knowledge about the three gasotransmitters in early trauma is inadequate. Our research aimed to examine the changes in NO, CO and H_2S in the early phase of severe trauma, and explore the relationship between incidence of MODS and blood lactic acid.

Method

Subjects

A total of 70 participants were included in the study: 60 patients who were treated at the Department of Emergency of the Third Hospital of Hebei Medical University between October 2012 and November 2013, and ten healthy volunteers. In all, there were 61 males and nine females.

The enrollment of these patients met the following conditions: 1. severe trauma; 2. received treatment within 3 hours after severe trauma; 3. aged ranged between 18 and 60 years. The exclusion criteria of the subjects were as follows: 1. the interval of severe trauma and blood drawing was more than 3 hours; 2. received blood transfusion; 3. received IV transfusion more than 2,000 mL; 4. surgical history; 5. coagulation dysfunction or anti-coagulation medication history; 6. common diseases and simultaneous liver and kidney function damages; 7. severe cardio-cerebral vessel diseases; 8. pregnant and lactating women. Informed consent was obtained from all participants. All the procedures were approved by the ethics committee of the Third Hospital of Hebei Medical University.

Measurement

Severity of the patients' injuries was evaluated using the Abbreviated Injury Scale (AIS) and the Injury Severity Score (ISS). According to the results, the patients were classified into three groups: mild group (score ≤ 16), medium group (score in 16-25) and severe group (score ≥ 25). And based on their prognosis, they were divided into MODS group and non-MODS group.

Cardiograph, blood pressure and finger pulse oxygen saturation were monitored continuously to evaluate the clinical condition of the patients. Routine blood test, liver and kidney function evaluation, blood gas analysis and blood lactic acid monitoring were examined. The diagnosis of MODS was performed according to the modified Fry-MODS diagnosis criteria.[6]

Blood samples were collected within 3 hours of the injury for a routine blood test, measurement of kidney function and procalcitonin. 3 mL of venous blood was collected and centrifuged, the supernatant was stored at -80°C for the analysis of inducible nitric oxide synthase (iNOS), heme oxygenase-1 (HO-1) and plasma H_2S. Concentration of serum iNOS and HO-1 were analyzed by enzyme-linked immunosorbent assay (ELISA) using commercially available ELISA kits (Jiancheng, Nanjing, China) and following the manufacturer's instructions. Plasma H_2S was determined by colorimetric method.

Statistical analysis

SPSS 19.0 was used to perform statistical analyses. The data were presented as mean± standard deviation (SD). Normally distributed continuous data were assessed by independent sample t-test. ANOVA test was performed to compare the differences among the groups. Non-normally distributed parameters were analyzed with nonparametric sum rank test. Correlation analysis was performed by Pearson correlation analysis for normally distributed data and Kendall correlation analysis for non-normally distributed data. A p-value of less than 0.05 is indicated as statistically significant differences.

Results

Table 1 listed the general characteristics and the serum gasotransmitter levels of the study subjects. There were no statistical differences between the groups in terms of age, gender ratio and the time from trauma to treatment ($p<0.05$). The levels of iNOS, HO-1 and endogenous H_2S in the patient group were significantly different from the healthy control group, and the difference was more obvious with the increase of ISS score. The expression of iNOS in the patient group was higher than that found in the healthy control group, and the expression found an upward trend depending on injury severity ($p<0.05$). Meanwhile, the HO-1 and endogenous H_2S contents were significant lower compared with the control group ($p<0.05$) (Figure 1).

TABLE 1 The clinical characteristics and serum gasotransmitter levels of the study subjects.

	Healthy control group	Mild group (ISS ≤ 16)	Medium group (ISS in 16-25)	Severe group (ISS ≥ 25)
n	**10**	**23**	**27**	**10**
Age (years)	34±7	38±9	35±8	32±7
Gender (male/female)	9/1	20/3	24/3	8/2
Time (h)	–	1.6±0.4	1.5±0.5	1.5±0.5
iNOS (U/mL)	474.5±35.9	547.1±52.9*	688.48±74.8*	753.4±92.33*
HO-1 (ng/mL)	3.54±0.42	2.92±0.65*	2.44±0.45*	1.77±0.655*
H_2S (μmol/L)	50.77±2.00	48.64±1.72*	46.40±1.82*	44.15±1.60*

Compared with the healthy control group, *p<0.05.

To clarify whether the changes in serum gasotransmitter levels played a role in the trauma, the relationship between gasotransmitter levels and ISS scores as well as blood lactic acid values were further investigated (Table 2). The results of the analysis demonstrated that iNOS levels were positively correlated with ISS scores ($r^2=0.586$, $p<0.001$) and blood lactic acid ($r^2=0.440$, $p<0.001$) and HO-1 and endogenous H_2S values were negatively correlated with ISS scores ($r^2=0.473$, $p<0.001$; $r^2=0.590$, $p<0.001$) and blood lactic acid values ($r^2=0.525$, $p<0.001$; $r^2=0.515$, $p<0.001$).

TABLE 2 The relation between gasotransmitter levels with ISS scores and blood lactic acid values.

	Association with ISS scores		Association with blood lactic acid values	
	r^2	p	r^2	p
iNOS	0.586	<0.001	0.440	<0.001
HO-1	0.473	<0.001	0.525	<0.001
H_2S	0.590	<0.001	0.515	<0.001

Among the 60 trauma patients, eight (13.33%) developed MODS. There were no statistical differences between the non-MODS and MODS in age, gender ratios and the time from trauma to treatment ($p<0.05$) (Table 3). The level of iNOS in the MODS group was higher than that in the non-MODS group, while HO-1 and H_2S were significant lower in the MODS group ($p<0.05$) (Figure 2).

TABLE 3 The rate of MODS and serum gasotransmitter levels.

	Control group	Non-MODS	MODS
n	**10**	**52**	**8**
Age (years)	34±7	33±9	34±7
Gender (female/male)	9/1	45/7	7/1
Time (h)	–	1.6±0.5	1.5±0.4
iNOS (U/mL)	474.5±3.9	628.9±102.3*	736.5±86.93*#
HO-1 (ng/mL)	3.54±0.42	2.61±0.61*	1.98±0.85*#
H_2S (μmol/L)	50.77±2.00	47.30±2.18*	44.53±1.92*

Compared with the healthy control group, *p<0.05. Compared with the non-MODS group, #p<0.05.

Discussion

NO, CO and H_2S were endogenously-generated gas molecules. They present important biological activity and participated in many pathophysiological processes. Gasotransmitters were freely permeable across cell membranes and served as regulators of a multitude of biochemical pathways and physiological processes. Recently, the roles of gasotransmitters in trauma were recognized, which led to a new broad perspective on inflammatory mediators.

The release of inflammatory factors into the blood causes a "second strike" to the tissues and cells in trauma sites, and is the main reason for the systemic inflammatory response at the early stage of injury. Lactic acid is an important intermediate product in the glycometabolism of the human body in the presence of hypoxia. Thus, it is an important and sensitive indicator of cellular hypoxia. In acute trauma, the effective blood capacity is insufficient and accumulates large amounts of lactic acid. In the process of fluid resuscitation, dynamic observation of the lactic acid values could help understand characteristics of blood perfusion.[7] A decline in lactic acid after fluid resuscitation usually means a better prognosis, while an increase in lactic acid might indicate ischemic reperfusion. In the present study, the level of blood lactic acid was increased, and it was positively correlated with NO content and negatively correlated with CO and H_2S contents. The synthesis of iNOS and endogenous NO was high after being damaged.

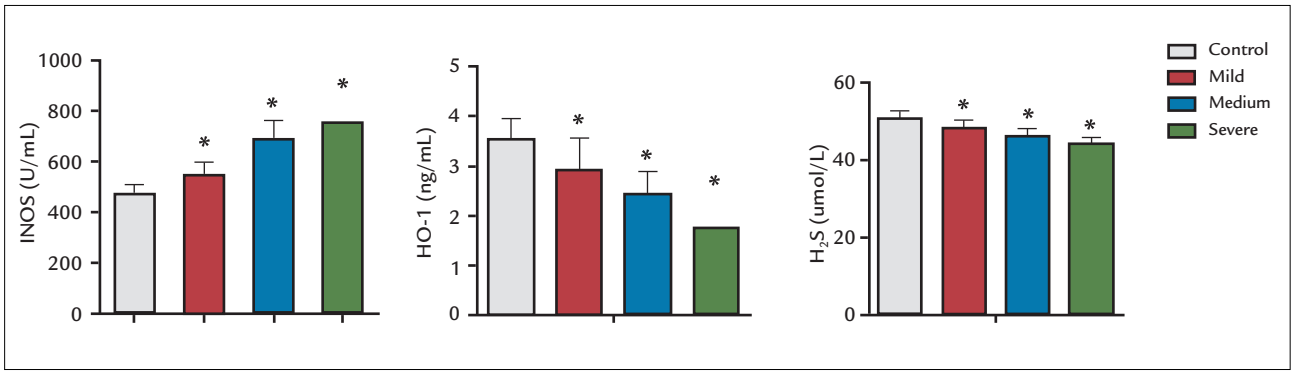


FIGURE 1 Serum gasotransmitters levels of the study subjects in traumatic patients group and healthy control group. *indicates p<0.05 compared with control.

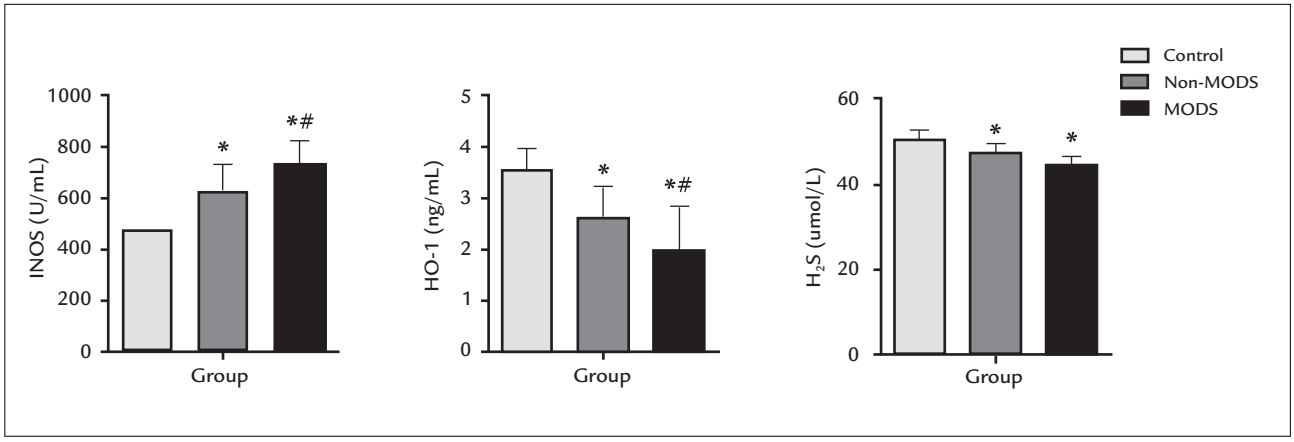


FIGURE 2 Serum gasotransmitters levels of the study subjects in non-MODS and MODS group.
*indicates p<0.05 compared with healthy control, # indicates p<0.05 compared with non-MODS.

Trauma, infection, hypoxia and excessive stress response could both lead to systemic inflammatory response. In normal physiological conditions, a small amount of NO was catalyzed by iNOS. In our study, the generation of iNOS was increased with the ISS score in the early phase of trauma patients. When a large amount of NO was generated, it could react with superoxide anion and lead to the accumulation of peroxynitrite anion, also causing cell damage.[8] Besides, excessive NO led blood vessels to expand and produced hypotension shock. Some studies found that different types of inflammation could lead to image enhancement in animal models. In addition, inhibition of iNOS can reduce the production of NO, and subsequently relieve inflammatory response.[9,10] iNOS is the only rate-limiting enzyme in NO production, decreasing the synthesis of NO could diminish the inflammatory response, septic shock and other symptoms.[9] Hemoglobin plays a vital role in the synthesis of NOS; it can be degraded by HO-1 and thus inhibit NOS. HO-1 can influence the activity of iNOS.[11] Furthermore, H_2S donors inhibited iNOs production by enhancing the expression of HO-1.[12]

HO-1 is the major rate-limiting enzyme for the synthesis of endogenous CO, it can catalyze the degradation of heme into CO, catalytic iron and bilirubin. Catalytic iron and bilirubin have a strong capacity of anti-oxidation.[13,14] CO not only plays an important role in anti-inflammation, anti-apoptosis, improving circulation and anti-thrombosis, but also down-regulates the expression of proinflammatory molecules such as IL-8 and TNF-α.[15] Some studies found that a small amount of inhaled CO enhances the ability of anti-oxidation and anti-apoptosis in the experimental model of LPS-induced lung injury; meanwhile, up-regulations with HO-1 could achieve similar effects.[16] In our study, HO-1 level was significantly lower in the early phase of trauma patients than in the healthy control group, and they were negative correlated with ISS score and blood lactic acid level. The results

demonstrated that the HO-1/CO pathway is activated in severe trauma; CO participated in the inflammatory response as an important gasotransmitter.

Similar with CO and NO, H_2S plays important roles in physiological regulation. Due to the specific distribution of its synthetase, the regulatory functions also exhibited apparent tissue specificity. However, there was no consensus regarding the anti-inflammatory ability or pro-inflammatory ability of H_2S. In some researches, pretreatment of mice with H_2S improved leukocyte rolling/adhesion as well as neutrophil migration, which subsequently contributed to reduce bacteria levels and improve survival rate.[17] This suggested that endogenous H_2S played a protective role in systemic inflammatory responses. The study by Li et al. revealed that the damage of ALI/ARDS mouse was aggravated after NaHS was administered, which suggested the proinflammatory role of H_2S.[4] In the current study, H_2S is significantly lower in patients with ISS ≥ 25 compared with the patients with ISS ≤ 16.

MODS refers to the sequential failure of more than two organs. Any disease can cause inflammatory immune disorders that may induce MODS. Gasotransmitters, such as NO, CO and H_2S, are the important signaling molecules that participate in the inflammatory response, and at the same time they interact with each other. A study found that the iNOS/NO and the HO-1/CO systems were restricted with each other.[18] A possible explanation is that CO is produced by decomposition of hemoglobin after the oxidation of HO-1; meanwhile, hemoglobin was also the main component of prosthetic group of iNOS. Thus, hemoglobin degradation influenced the production of NO. Furthermore, CO also occupied the coordination center of NOS and reduced its activity. CSE mainly exists in vascular smooth muscle; it could be activated by NO and inhibited by the precursors of NO (hydroxyl ammonium). As for the iNOS/NO and CSE/H_2S system, there were no consensus reached. Both synergetic and inhibitive dynamic interplay between iNOS/NO and CSE/H_2S were reported.[19] CSE/H_2S system showed a synergetic effect on HO-1/CO system.

In the current study, iNOS was found to be significantly higher in the MODS group than in the non-MODS group, which indicated that the iNOS/NO system was activated when severe trauma occurred. A large amount of NO was released into the blood and exacerbated the systemic inflammatory response, caused severe damage to body tissues and organs. HO-1 and H_2S were significantly lower in the MODS group than in the non-MODS group. The results suggested that the three gasotransmitters were closely related with the incidence of MODS and severity of trauma.

Conclusion

During the early phase of trauma, it can be suspected that these gasotransmitters not only participate in systemic inflammatory responses, but also facilitate the generation of blood lactic acid. There was a positive correlation between iNOS level and both trauma severity and blood lactic acid value. Meanwhile, a negative correlation was found between HO-1 and H_2S levels, as well as trauma severity and blood lactic acid values. In systemic inflammatory responses, they would not function independently. The interaction between these gas molecules may vary under different conditions. iNOS, HO-1 and endogenous H_2S could be used as important indicators of trauma severity and the onset of post-trauma MODS. Their measurement was meaningful for evaluating the severity and prognosis of trauma.

References

1. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med. 2008; 34(1):17-60.
2. Zhao W, Zhang J, Lu Y, Wang R. The vasorelaxant effect of H(2)S as a novel endogenous gaseous K(ATP) channel opener. EMBO J. 2001; 20(21):6008-16.
3. Sarady JK, Zuckerbraun BS, Bilban M, Wagner O, Usheva A, Liu F, et al. Carbon monoxide protection against endotoxic shock involves reciprocal effects on iNOS in the lung and liver. FASEB J. 2004; 18(7):854-6.
4. Li L, Bhatia M, Zhu YZ, Zhu YC, Ramnath RD, Wang ZJ, et al. Hydrogen sulfide is a novel mediator of lipopolysaccharide-induced inflammation in the mouse. FASEB J. 2005; 19(9):1196-8.
5. Wang P, Zhang JX, Li LF, Zhang QZ, Jin PL, Ding CM. Change of endogenous hydrogen sulfide/cystathionine-γ-lyase system in acute lung injury induced by LPS in rats. Chinese J Pathophysiol. 2008; 24:434-8.
6. Qin HB, Zhou SX. The modern therapy of multiple organ dysfunction syndrome. Beijing: People' s Military Medical Publisher; 2001. p.20-9.
7. Wang CT, Ren HS, Jiang JJ, Zhang JC, Meng M, Yu JB, et al. [Study the effects of high-volume hemofiltration and fluid resuscitation on removing blood lactic acid and pro-inflammatory cytokines in patients with refractory septic shock]. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2009; 21(7):421-4.
8. Chunfu Z. Nitric oxide and parasitization. Foreign Medical Sciences (section of Clinical Biochemistry and Laboratory Medicine). 2000; 21:81-6.
9. Pae HO, Oh GS, Choi BM, Chae SC, Kim YM, Chung KR, et al. Carbon monoxide produced by heme oxygenase-1 suppresses T cell proliferation via inhibition of IL-2 production. J Immunol. 2004; 172(8):4744-51.
10. Suh GY, Jin Y, Yi AK, Wang XM, Choi AM. CCAAT/enhancer-binding protein mediates carbon monoxide-induced suppression of cyclooxygenase-2. Am J Respir Cell Mol Biol. 2006; 35(2):220-6.
11. Zhu XY, Liu SJ, Liu YJ, Wang S, Ni X. Glucocorticoids suppress cystathionine gamma-lyase expression and H2S production in lipopolysaccharide-treated macrophages. Cell Mol Life Sci. 2010; 67(7):1119-32.
12. Chen YH, Wang PP, Wang XM, He YJ, Yao WZ, Qi YF, et al. Involvement of endogenous hydrogen sulfide in cigarette smoke-induced changes in airway responsiveness and inflammation of rat lung. Cytokine. 2011; 53(3):334-41.
13. Foresti R, Bains S, Sulc F, Farmer PJ, Green CJ, Motterlini R. The interaction of nitric oxide with distinct hemoglobins differentially amplifies endothelial heme uptake and heme oxygenase-1 expression. J Pharmacol Exp Ther. 2006; 317(3):1125-33.
14. Takahashi T, Morita K, Akagi R, Sassa S. Heme oxygenase-1: a novel therapeutic target in oxidative tissue injuries. Curr Med Chem. 2004; 11(12):1545-61.
15. Morita T. Heme oxygenase and atherosclerosis. Arterioscler Thromb Vasc Biol. 2005; 25(9):1786-95.

16. Liu SH, Ma K, Xu B, Xu XR. Carbon monoxide inhalation protects lung from lipopolysaccharide-induced injury in rat. Sheng Li Xue Bao. 2006; 58(5):483-9.
17. Bertova A, Cacanyiova S, Kristek F, Krizanova O, Ondrias K, Tomaskova Z. The hypothesis of the main role of H2S in coupled sulphide-nitroso signalling pathway. Gen Physiol Biophys. 2010; 29(4):402-10.
18. Foresti R, Clark JE, Green CJ, Motterlini R. Thiol compounds interact with nitric oxide in regulating heme oxygenase-1 induction in endothelial cells. Involvement of superoxide and peroxynitrite anions. J Biol Chem. 1997; 272(29):18411-7.
19. Taoka S, Banerjee R. Characterization of NO binding to human cystathionine beta-synthase: possible implications of the effects of CO and NO binding to the human enzyme. J Inorg Biochem. 2001; 87(4):245-51.

Update on antiphospholipid antibody syndrome

Michelle Remião Ugolini Lopes[1]*, Adriana Danowski[2], Andreas Funke[3], Jozelia Rêgo[4], Roger Levy[5], Danieli Castro Oliveira de Andrade[6]

[1]MD, Assistant Physician, Antiphospholipid Syndrome and Systemic Lupus Erythematosus Outpatient Clinic, Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, SP, Brazil
[2]PhD, Hospital Federal dos Servidores do Estado (HFSE), Rio de Janeiro, RJ, Brazil
[3]PhD, Head of the APS and Vasculitis Outpatient Clinic, Rheumatology Service, Hospital de Clínicas da Universidade Federal do Paraná (UFPR), Curitiba, PR, Brazil
[4]PhD, Adjunct Professor of Rheumatology, Faculdade de Medicina da Universidade Federal de Goiás (UFG), Goiânia, GO, Brazil
[5]PhD, Associate Professor of Rheumatology, Faculdade de Ciências Médicas da Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil
[6]PhD, Head of the APS Outpatient Clinic, Rheumatology Division, FMUSP, São Paulo, SP, Brazil

Study conducted at Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HC-FMUSP), São Paulo, SP, Brazil

Article received: 3/1/2017
Accepted for publication: 3/12/2017

***Correspondence:**
Address: Rua Francisco Cruz, 287, apto. 144
São Paulo, SP – Brazil
Postal code: 04117-091
michelleugolini@gmail.com

http://dx.doi.org/10.1590/1806-9282.63.11.994

Summary

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by antiphospholipid antibodies (aPL) associated with thrombosis and/or pregnancy morbidity. Most APS events are directly related to thrombotic events, which may affect small, medium or large vessels. Other clinical features like thrombocytopenia, nephropathy, cardiac valve disease, cognitive dysfunction and skin ulcers (called non-criteria manifestations) add significant morbidity to this syndrome and represent clinical situations that are challenging. APS was initially described in patients with systemic lupus erythematosus (SLE) but it can occur in patients without any other autoimmune disease. Despite the autoimmune nature of this syndrome, APS treatment is still based on anticoagulation and antiplatelet therapy.

Keywords: antiphospholipid syndrome, anticoagulants, thrombosis.

Introduction

Antiphospholipid syndrome (APS) is the most common cause of acquired thrombophilia and accounts for 15 to 20% of all episodes of deep vein thrombosis, one third of new cases of cerebrovascular accident (CVA) occurring in patients aged less than 50 years, and 10 to 15% of recurrent fetal loss. In addition, pregnant women positive for antiphospholipid antibodies (aPL) have an 80% risk of recurrence of gestational events such as miscarriage and/or premature birth.[1,2]

APS can occur alone or in the presence of another autoimmune disease. Association with systemic lupus erythematosus (SLE) is the most frequent, but other diseases such as rheumatoid arthritis, Sjögren's syndrome and inflammatory myopathies may also occur.[2] About 30 to 40% of patients with SLE present circulating antiphospholipid antibodies and 15% will have the complete syndrome.[2,3]

Despite being considered a rare disease (estimated incidence of five cases per 100,000 people per year), this is a disease that affects young adults of reproductive age, and which adds significant morbidity to the affected individuals. In addition to physical sequelae, caused by thrombotic events, there is still considerable emotional repercussion from recurrent gestational losses.[4]

Pathophysiology

It is now recognized that aPL positivity is the most frequent acquired risk factor and is more related to thrombotic events and gestational morbidity. Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-β2-glycoprotein-I) are classificatory antibodies of the disease, used for diagnosis, but also important elements in the pathogenesis of APS. Although the presence of these antibodies is a predisposing factor for thrombotic events, a second trigger, such as infections, prolonged rest or an inflammatory state, is usually necessary for the progression of the syndrome.[5,6]

Antiphospholipid antibodies bind to phospholipids and plasma or membrane proteins expressed in various cells (platelets, endothelial cells, monocytes, fibroblasts and trophoblasts), producing a prothrombotic state. Despite the known thrombophilic action of antiphospholipid antibodies, the exact pathogenesis of the disease is not yet fully elucidated. β2-glycoprotein-I (β2GPI) and prothrombin appear to be the major binding proteins in these antibodies involved in the pathogenesis of the disease.[5,6] There is also a genetic component related to the HLA class II system that needs to be better studied, and which may predispose the individual to the disease.[5,7]

Chart 1 shows the probable thrombotic and obstetric mechanisms proposed in the literature for APS.

CHART 1 Pathogenic mechanisms mediated by antiphospholipid antibodies.

Changes in anticoagulant reactions
Inhibition of β2GPI anticoagulant action
Inhibition of protein C
Inhibition of antithrombin activity
Displacement of annexin 5 from its sites
Endothelial cell-mediated changes
Increased expression of adhesion molecules
Increased expression of tissue factor
Ineffective fibrinolysis
Reduced prostacyclin production
Reduction of the action of nitric oxide synthase
Platelet-mediated changes
Increased production of thromboxane A_2
Increased platelet activation and aggregation
Monocyte-mediated changes:
Increased expression of tissue factor
Increased oxidative stress
Complement system activation

Diagnostic criteria

The classification criteria for APS were developed in 1999 in Sapporo and subsequently revised in 2006 at an international congress held in Sydney. At present, they comprise the requirement of at least one clinical criterion (thrombotic event or gestational morbidity) and at least one laboratory criterion (confirmed positive aPL at two or more separate time points with a 12-week minimum interval), as shown in Figure 1.[8,9]

Clinical aspects

Virtually all clinical manifestations of APS are due to arterial and venous thrombotic events. Theoretically, APS thrombosis can occur in any organ, affecting vessels of different calibers, and determining a great number of clinical manifestations. It is also believed that placental insufficiency, the main reason for late fetal loss, is also related to a loss of uteroplacental circulation derived from thrombotic phenomena.[5]

Thrombotic events

Venous thromboses are more frequent than arterial thromboses.[1] Chart 2 shows the most frequent thrombotic manifestations of APS.

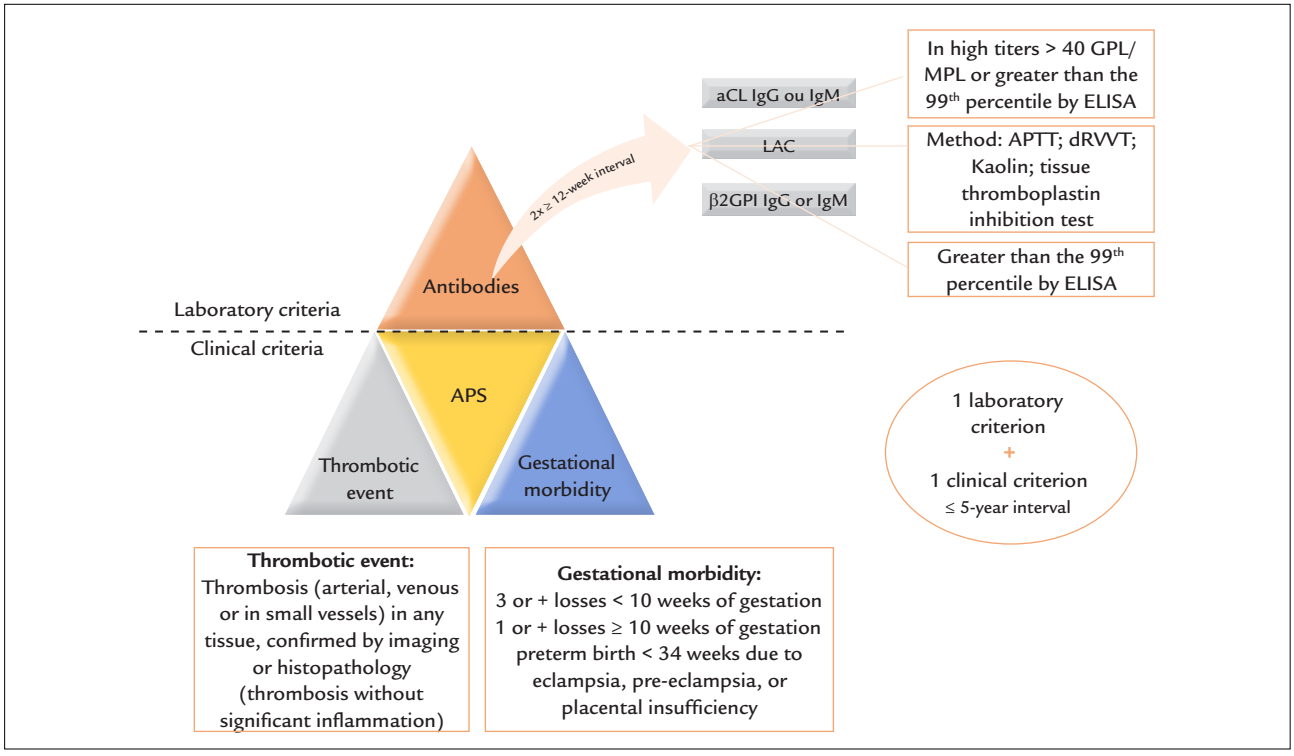


FIGURE 1 APS classification criteria.

APS: antiphospholipid antibody syndrome; aCL: anticardiolipin; LA: lupus anticoagulant; β2GPI: anti-beta-2-glycoprotein I; APTT: activated partial thromboplastin time; dRVVT: dilute Russell's viper venom time.

CHART 2 Thrombotic manifestations of antiphospholipid syndrome.

Extremities	Venous: deep vein thrombosis Arterial: ischemia and gangrene
Liver	Venous: Budd-Chiari syndrome Arterial: liver infarction and nodular regenerative hyperplasia
Central nervous system	Venous: sagittal sinus thrombosis Arterial: cerebrovascular accident and Sneddon's syndrome
Lung	Venous: thromboembolism and pulmonary hypertension
Kidney	Venous: renal vein thrombosis Arterial: renal artery thrombosis and thrombotic microangiopathy
Skin	Venous: ulcers Arterial: livedo, gangrene, ulcers
Eyes	Venous: retinal vein thrombosis Arterial: retinal artery thrombosis

Obstetric events

Another frequent manifestation in women with APS is recurrent fetal loss, which may occur at any stage of pregnancy, but typically happens as of the second trimester. In addition to fetal losses, placental insufficiency with restricted fetal growth, preeclampsia, eclampsia and preterm birth may occur.[10]

Only 10-15% of women with recurrent fetal loss are aPL-positive and the probability of finding aPL in prenatal exams is less than 2%, which is why routine screening is not indicated.[10]

Non-criteria manifestations

There are other less frequent clinical manifestations, but also related to APS, which are not part of the classification criteria of the disease. Migraine, convulsions, superficial venous thrombosis, ulcers, thrombocytopenia, chorea, longitudinal myelitis, renal microangiopathy, cardiac valvulopathies and livedo reticularis are all non-criterion manifestations.[11]

Catastrophic antiphospholipid syndrome

Catastrophic antiphospholipid syndrome (CAPS) is characterized by multiple thromboses (in more than three sites) in a short time interval (1 week). Although rare, this is the most severe spectrum of APS, with a mortality rate of up to 50%.[12]

Laboratory aspects

The diagnosis of APS as proposed by the Sydney criteria includes the laboratory dosage of anticardiolipin (IgG and/or IgM), anti-β2GPI (IgG and/or IgM) and lupus anticoagulant (LA). Two positive antibody measurements, separated by a minimum interval of 12 weeks, should be obtained to rule out the possibility of a transient positivity of antiphospholipid antibodies induced by infections or drugs.[8,9]

Lupus anticoagulant

LA is the most specific test for the diagnosis of APS and should be performed according to the International Society for Thrombosis and Hemostasis. These are functional investigations and comprise three stages. The first is a screening test using at least two of the following tests: APTT, dilute Russell viper venom test or Kaolin clotting time. In this step, phospholipid-dependent tests are used. Prolongation of clotting time in these tests indicates the presence of an inhibitor, or deficiency of coagulation factors. In the next step, the plasma of the patient is mixed in a 1:1 ratio with the plasma of a normal person. In the case of deficiency of coagulation factors, there will be a correction of the tests used in the screening, since the normal plasma contains the necessary factors. In the presence of an inhibitor (LA), clotting time remains prolonged. Then, in the third step, an excess of phospholipids (e.g., platelets) is added, which will compete with the antiphospholipid antibodies, neutralizing their action in vitro and, therefore, correcting the coagulation time. The use of unfractionated heparin alters the result of this assay, generating false-positive results. Therefore, it is necessary to wait a moment when the patient is not using this drug. If the international normalized ratio (INR) is widened because of the use of warfarin, the sample should be normalized before the test – this procedure requires experience and is not routinely performed by laboratories.[2,13,14]

Anticardiolipin

Anticardiolipin (aCL) is the most sensitive test for APS diagnosis. It is performed by a standardized enzyme immunoassay (ELISA) technique containing a source of β2GPI. Internationally used positive controls are used so that this test has less variability and meets international standards. This test is not influenced by warfarin and heparins.[2,13,14] aCL titers are divided into: low (< 40 GPL or MPL), moderate (40 to 80 GPL or MPL) or high (> 80 GPL or MPL).

Anti-β2-glycoprotein-I

Anti-β2GPI antibodies are also used and detected using the ELISA technique and have recently been included in the classification criteria. There is still no standardization for this methodology. [2,13,14]

Chart 3 shows the main indications in which aPL cannot fail to be investigated.[15]

CHART 3 Indications for antiphospholipid antibodies testing.

Presence of DVT or PE in young people without risk factors
Thromboses in atypical sites, or multiple thromboses
CVA or TIA in a patient aged less than 50 years
Any thrombosis in a patient with SLE or other autoimmune disease
Recurrent abortions or associated obstetric complications
Unexplained thrombocytopenia
Presence of livedo reticularis racemosa

DVT: deep venous thrombosis; PE: pulmonary embolism; CVA: cerebrovascular accident; TIA: transient ischemic attack; SLE: systemic lupus erythematosus.

Differential diagnosis

The main differential diagnoses of APS are hereditary or acquired thrombophilias. In hereditary thrombophilias, positive family history helps and guides the request for complementary tests. In this group, the presence of Leiden's factor V or deficiencies of C and S proteins and/or antithrombin III, as well as mutant prothrombin, must be taken into account. In acquired thrombophilia, in addition to APS, hyperhomocysteinemia can cause venous and also arterial events.[2]

Predisposing factors for thrombosis should be investigated, such as: nephrotic syndrome, atrial fibrillation, puerperium, use of estrogens and paraneoplastic syndromes. Other rheumatologic diseases such as systemic vasculitis and Behçet's disease should be considered in the list of differential diagnoses. Diseases that occur with thrombocytopenia should be ruled out, including: autoimmune thrombocytopenic purpura, thrombotic thrombocytopenic purpura (PTT), hemolytic uremic syndrome (HUS), heparin-induced thrombocytopenia and disseminated intravascular coagulation.[2]

Regarding gestational losses, whenever possible, we should investigate anatomical and genetic changes in the mother and malformations in the fetus, as well as serology for infectious diseases (toxoplasmosis, rubella, syphilis, cytomegalovirus, herpes, HIV). Maternal hormonal changes should also be investigated, in addition to the use of alcohol or drugs, which may cause recurrent fetal loss.[16]

Treatment

The treatment of APS mainly involves the treatment of the acute thrombotic event as well as the prevention of new events, whether thrombotic or unfavorable gestational outcomes.

Treatment of acute thrombotic event

Treatment of acute thrombosis is usually based on full anticoagulation, either with unfractionated heparin (UFH) or with low molecular weight heparins (LMWHs), such as enoxaparin.[17,18]

After initiation of full parenteral anticoagulation, an oral anticoagulant may be associated. The most commonly used are vitamin K antagonists (VKA). For VKA dose control, we used prothrombin time (PT) or INR. In the case of the first venous thrombotic event, the INR target should remain between 2.0 and 3.0. In cases of arterial events or venous re-thrombosis, the INR target should be elevated to the range of 2.5-3.5. An alternative to increasing the INR target would be to keep the target between 2.0 and 3.0 and to associate 100 mg of aspirin, but the risk of bleeding is higher.[17,18]

In cases of acute ischemic CVA, the patient should be evaluated by a neurologist to assess the need for thrombolysis or only secondary prophylaxis. It is the neurological team that will determine the best time to start secondary prophylaxis, based on the risks of the event's hemorrhagic transformation.

Secondary prophylaxis

After the acute episode, long-term treatment with oral anticoagulant is the therapy of choice. The recommended INR target for prophylaxis after venous thrombosis is between 2.0 and 3.0 and for arterial phenomena, between 2.5 and 3.5. Recent studies have found that higher INRs, between 3 and 4, added an increased risk of bleeding.[17] In addition to anticoagulant therapy, hydroxychloroquine seems to reduce aPL titers and has a beneficial antithrombotic role for patients with APS. Therefore, it should be added in all patients with APS associated with SLE.[19]

In the specific case of a first episode of atherosclerotic ischemic CVA in low-risk patients, treatment with aspirin 300 mg or double antiplatelet therapy may be attempted before anticoagulation is indicated. In the case of thromboembolic ischemic CVA the treatment of choice is anticoagulation.

It is not yet known whether non-vitamin K antagonist oral anticoagulants (Xa-factor inhibitors and direct thrombin inhibitors) are effective in the treatment of APS.

Clinical trials are being conducted to assess the actual benefit in this subpopulation of patients.[20,21] Nevertheless, several case reports of thrombotic events in APS patients taking this new oral anticoagulants were recently published.[22]

Primary prophylaxis

There is no evidence to support primary prophylaxis of persistently positive aPL patients without thrombotic or gestational events. However, these patients should receive prophylactic heparin in situations of high thrombotic risk such as immobilization, hospitalization or postoperative. These patients should also avoid situations that increase the risk of thrombosis such as smoking or the use of estrogen.[15] LA is the test with the highest predictive value for thrombotic events and unfavorable gestational outcomes, and its positivity should be considered when introducing prophylaxis.[23]

Treatment of obstetric events

Patients with exclusively obstetric APS who are not pregnant should be treated with aspirin alone at a dose of 81-100 mg per day. During pregnancy, aspirin should be associated with prophylactic heparin (UFH or LMWH). It should be maintained for up to 6 weeks after delivery.[16]

Patients with previous thrombotic events should use aspirin 100 mg associated with full dose heparin (enoxaparin 1 mg/kg every 12h). VKA are teratogenic between 6 and 9 weeks of pregnancy, when heparin is a better therapeutic option. If UFH is to be used, the dose should be adjusted in relation to the baseline PTT (before UFH), to maintain the baseline rate of 1.2 to 1.5. In general, doses of UFH increase during pregnancy progression, while the doses of LMWH (calculated by the weight of the mother at conception) remain the same throughout pregnancy. Heparins, VKAs and aspirin are all safe concerning breastfeeding.[16]

Treatment of catastrophic APS

Patients with CAPS, in addition to anticoagulation with heparin, should receive immunosuppression with corticoid (prednisone, 1 mg/kg/day) or pulses of methylprednisolone associated with plasmapheresis or intravenous immunoglobulin. Therefore, they should receive triple therapy: anticoagulation, corticosteroid and plasmapheresis/immunoglobulin. Rituximab can be used in refractory cases.[12] Recent studies have demonstrated benefits from the use of anti-C5 monoclonal antibody (eculizumab) in patients with CAPS, proving the importance of complement activation in cases of thrombotic microangiopathy.[24]

Other considerations

Every patient should be instructed to avoid factors that increase thrombotic risk, in addition to those that the syndrome already involves. Advising the patient to stop smoking, control obesity, properly treat comorbidities such as diabetes, dyslipidemia and hypertension is essential to reduce the risk of thromboses, especially arterial.[25]

The use of oral contraceptives containing estrogen or hormone replacement therapy is contraindicated in aPL-positive women. The most recommended methods of contraception for efficacy and safety are the progestin-releasing intrauterine devices and injectable medroxyprogesterone. Barrier methods or oral progesterone contraceptives may be used, but are less effective.[15]

Patients taking VKA therapy should receive vitamin D supplementation and an adequate supply of dietary calcium in addition to proton pump inhibitors, considering, respectively, the risk of osteoporosis and the risk of digestive bleeding, associated with prolonged use of oral anticoagulants.[15]

Future perspectives

Since this is a rare disease, most of the therapeutic options are based on small studies, and often with a low level of evidence. There is also a need to standardize the antiphospholipid antibody tests in the different centers, since the technique varies greatly.[26] Therefore, the APS-ACTION (Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking) was established as the first international network created to design and conduct large-scale multi-center trials in patients with persistently positive antiphospholipid antibodies.[27] Brazil actively participates in this alliance and believes that better studies will guide better practices in APS.

Conclusion

There is a need to recognize APS in various medical specialties, as well as CAPS in intensive care settings. Initiation of appropriate therapy for a prolonged time may change the prognosis of the individuals affected by this disease.

Resumo

Atualização da síndrome do anticorpo antifosfolípide

A síndrome antifosfolipídide (APS) é uma doença autoimune caracterizada por tromboses e morbidade gestacional associadas à positividade de *antiphospholipid antibodies* (aPL). A maioria das manifestações da APS está diretamente relacionada aos eventos trombóticos, que podem afetar

pequenos, médios ou grandes vasos. Outras manifestações como trombocitopenia, nefropatia, valvulopatia, disfunção cognitiva e úlceras cutâneas (chamadas de manifestações não critérios) agregam significativa morbidade e muitas vezes são refratárias ao tratamento convencional. Embora tenha sido inicialmente descrita em pacientes com lúpus eritematoso sistêmico (LES), a síndrome antifosfolípide também pode ocorrer em pacientes sem outras doenças autoimunes associadas. Apesar do caráter autoimune dessa síndrome, o tratamento da APS ainda é baseado na anticoagulação e na antiagregação plaquetária.

Palavras-chave: síndrome antifosfolipídica, anticoagulantes, trombose.

References

1. Ginsburg KS, Liang MH, Newcomer L, Goldhaber SZ, Schur PH, Hennekens CH, et al. Anticardiolipin antibodies and the risk for ischemic stroke and venous thrombosis. Ann Intern Med. 1992; 117(12):997-1002.
2. Khamashta M, Pierangeli S, Harris EN. Antiphospholipid syndrome: overview of pathogenesis, diagnosis, and management In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. Rheumatology. 5. ed. Philadelphia: Elsevier Mosby; 2011. p. 1445-53.
3. Lockshin MD. Update on antiphospholipid syndrome. Bull NYU Hosp Jt Di. 2006; 64(1-2):57-9.
4. Cervera R, Khamashta MA, Shoenfeld Y, Camps MT, Jacobsen S, Kiss E, et al.; Euro-Phospholipid Project Group (European Forum on Antiphospholipid Antibodies). Morbidity and mortality in the antiphospholipid syndrome during a 5-year period: a multicenter prospective study of 1000 patients. Ann Rheum Dis. 2009; 68(9):1428-32.
5. Giannakopoulos B, Passam F, Rahgozar S, Krilis SA. Current concepts on the pathogenesis of the antiphospholipid syndrome. Blood. 2007; 109(2):422-30.
6. Meroni PL, Borghi MO, Raschi E, Tedesco F. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. Nat Rev Rheumatol. 2011; 7(6):330-9.
7. Kamboh MI, Wang X, Kao AH, Barmada MM, Clarke A, Ramsey-Goldman R, et al. Genome-wide association study of antiphospholipid antibodies. Autoimmune Dis. 2013; 2013:761046.
8. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006; 4(2):295-306.
9. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum. 1999; 42(7):1309-11.
10. Jesus GR, Agmon-Levin N, Andrade CA, Andreoli L, Chighizola CB, Porter TF, et al. 14th International Congress on Antiphospholipid Antibodies Task Force report on obstetric antiphospholipid syndrome. Autoimmun Rev. 2014; 13(8):795-813.
11. Abreu MM, Danowski A, Wahl DG, Amigo MC, Tektonidou M, Pacheco MS, et al. The relevance of "non-criteria" clinical manifestations of antiphospholipid syndrome: 14th International Congress on Antiphospholipid Antibodies Technical Task Force Report on Antiphospholipid Syndrome Clinical Features. Autoimmun Rev. 2015; 14(5):401-14.
12. Cervera R, Rodríguez-Pintó I, Colafrancesco S, Conti F, Valesini G, Rosário C, et al. 14th International Congress on Antiphospholipid Antibodies Task Force Report on Catastrophic Antiphospholipid Syndrome. Autoimmun Rev. 2014; 13(7):699-707.
13. Bertolaccini ML, Amengual O, Andreoli L, Atsumi T, Chighizola CB, Forastiero R, et al. 14th International Congress on Antiphospholipid Antibodies Task Force. Report on antiphospholipid syndrome laboratory diagnostics and trends. Autoimmun Rev. 2014; 13(9):917-30.
14. Wong RC, Adelstein S, Gillis D, Favorolo EJ. Development of consensus guidelines for anticardiolipin and lupus anticoagulant testing. Semin Thromb Hemost. 2005; 31(1):39-48.
15. Keeling D, Mackie I, Moore GW, Greer IA, Greaves M; British Committee for Standards in Haematology. Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haematol. 2012; 157(1):47-58.
16. Petri M, Qazi U. Management of antiphospholipid syndrome in pregnancy. Rheum Dis Clin North Am. 2006; 32(3):591-607.
17. Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. JAMA. 2006; 295(9):1050-7.
18. Pierangeli SS, Chen PP, González EB. Antiphospholipid antibodies and the antiphospholipid syndrome: an update on treatment and pathogenic mechanisms. Curr Opin Hematol. 2006; 13(5):366-75.
19. Belizna C. Hydroxychloroquine as an anti-thrombotic in antiphospholipid syndrome. Autoimmun Rev. 2015; 14(4):358-62.
20. Arachchillage DJ, Cohen H. Use of new oral anticoagulants in antiphospholipid syndrome. Curr Rheumatol Rep. 2013; 15(6):331.
21. Cohen H, Machin SJ. Antithrombotic treatment failures in antiphospholipid syndrome: the new anticoagulants? Lupus. 2010; 19(4):486-91.
22. Signorelli F, Nogueira F, Domingues V, Mariz HA, Levy RA. Thrombotic events in patients with antiphospholipid syndrome treated with rivaroxaban: a series of eight cases. Clin Rheumatol. 2016; 35(3):801-5.
23. Lockshin MD, Kim M, Laskin CA, Guerra M, Branch DW, Merrill J, et al. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. Arthritis Rheum. 2012; 64(7):2311-8.
24. Shapira I, Andrade D, Allen SL, Salmon JE. Brief report: induction of sustained remission in recurrent catastrophic antiphospholipid syndrome via inhibition of terminal complement with eculizumab. Arthritis Rheum. 2012; 64(8):2719-23.
25. Rodrigues CE, Bonfá E, Caleiro MT, Vendramini MB, Bueno C, Lopes JB, et al. Association of arterial events with the coexistence of metabolic syndrome and primary antiphospholipid syndrome. Arthritis Care Res (Hoboken). 2012; 64(10):1576-83.
26. Dusse LM, Silva FD, Freitas LG, Rios DR, Armond SC, Marcolino MS. Antiphospholipid syndrome: a clinical and laboratorial challenge. Rev Assoc Med Bras (1992). 2014; 60(2):181-6.
27. Barbhaiya M, Andrade D, Erkan D; APS ACTION. AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION): 5-year update. Curr Rheumatol Rep. 2016; 18(10):64.

Mirror therapy: A potential intervention for pain management

Priscilla G. Wittkopf[1]*, Mark I. Johnson[2]

[1]MSc. Centre for Pain Research, School of Clinical and Applied Sciences, Leeds Beckett University and Leeds Pallium Research Group, Leeds, United Kingdom
[2]PhD. Centre for Pain Research, School of Clinical and Applied Sciences, Leeds Beckett University and Leeds Pallium Research Group, Leeds, United Kingdom

Study conducted at Leeds Beckett University, United Kingdom

Article received: 4/13/2017
Accepted for publication: 4/15/2017

***Correspondence:**
School of Clinical and Applied Sciences
Leeds Beckett University, City Campus
Leeds – United Kingdom
Postal code: LS1 3HE
p.wittkopf@leedsbeckett.ac.uk

http://dx.doi.org/10.1590/1806-9282.63.11.1000

Funding: The authors are currently delivering a programme of research in this area funded by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), government of Brazil.

Summary

The consequences of chronic pain and associated disabilities to the patient and to the health care system are well known. Medication is often the first treatment of choice for chronic pain, although side effects and high costs restrict long-term use. Inexpensive, safe and easy to self-administer non-pharmacological therapies, such as mirror therapy, are recommended as adjuncts to pain treatment. The purpose of this review is to describe the principles of use of mirror therapy so it can be incorporated into a health care delivery. The physiological rationale of mirror therapy for the management of pain and the evidence of clinical efficacy based on recent systematic reviews are also discussed. Mirror therapy, whereby a mirror is placed in a position so that the patient can view a reflection of a body part, has been used to treat phantom limb pain, complex regional pain syndrome, neuropathy and low back pain. Research evidence suggests that a course of treatment (four weeks) of mirror therapy may reduce chronic pain. Contraindications and side effects are few. The mechanism of action of mirror therapy remains uncertain, with reintegration of motor and sensory systems, restored body image and control over fear-avoidance likely to influence outcome. The evidence for clinical efficacy of mirror therapy is encouraging, but not yet definitive. Nevertheless, mirror therapy is inexpensive, safe and easy for the patient to self-administer.

Keywords: chronic pain, self care, pain/physiopathology/psychology.

Introduction

Chronic pain is a global healthcare problem affecting developed and developing countries. A systematic review estimated that the weighted mean prevalence of chronic pain in the adult population worldwide may be as high as 30.3% (19 studies, 65 surveys, 34 countries, and 182,019 respondents).[1] Data from Brazil suggests that the prevalence of chronic pain in the adult population can be as high as 42%.[2] The economic burden of chronic pain is greater than that of many other illnesses and diseases because of the high cost to health care and to social security services.

Pharmacological interventions are most commonly used as the first-line treatment for chronic pain, although side effects and high costs mitigate long-term use. For example, chronic use of acetaminophen may cause hepatotoxicity; NSAIDs may cause gastrointestinal renal disturbances and a risk of bleeding; and opioids may cause respiratory depression, urinary retention, constipation, nausea and cognitive impairment. Rehabilitation techniques are often used as stand-alone treatments or as adjuncts to pharmacological treatments and include physical activity and exercise, manual therapy, acupuncture, thermal therapy and electrotherapy such as transcutaneous electrical nerve stimulation (TENS).[3] The World Health Organization (WHO) supports the use of rehabilitation techniques that are inexpensive, safe and easy to self-administer in order to reduce healthcare costs and empower individuals to manage their own pain which is known to improve outcome.[3]

A rehabilitation technique that proved promising in recent years is mirror therapy, which involves a mirror being placed in a position that allows the patient to view a reflection of a body part. Mirror therapy is most commonly used to relieve pain in limbs by hiding the painful limb behind the mirror (out of view) whilst the non-painful limb is placed in front of the mirror so that it creates a reflection that can be seen by the patient. Thus, the patient can observe a reflection of the non-painful limb so that it appears to be in the same position as the

painful limb (which is out of view) (Figure 1). In amputees, this creates the illusion of having two intact limbs.[4] In individuals with inflamed limbs that appear swollen and red (e.g. complex regional pain syndrome) it creates the illusion of having a "healthy-looking" limb.[5] Often patients are reluctant to move painful limbs, creating pain behaviors dominated by fear and avoidance of movement. Mirror therapy can be used to create a reflection of a normally moving healthy limb that is located in the same place in space as the painful limb hidden behind the mirror. This gives the illusion that the painful limb can move normally too.

Mirror therapy can be used as a stand-alone therapy or in combination with other pain-relieving techniques. Mirror therapy has been incorporated into therapeutic programs to treat painful conditions resulting from neuropathy complex regional pain syndrome and non-specific mechanical back pain.[6,7] It has also been used to improve functional outcomes after stroke.[8]

Mirror therapy is not frequently used to treat chronic pain in Brazil, although it has been suggested that mirror therapy could be inserted in a continuous rehabilitation program to modify behavior to improve movement and alleviate pain.[5,9,10]

The purpose of this review is to describe the principles of use of mirror therapy so it can be incorporated into a health-care delivery. The physiological rationale of mirror therapy for the management of chronic pain and evidence of clinical efficacy based on recent systematic reviews are also discussed.

FIGURE 1 Positioning for upper limb mirror therapy.

Principles of use

During mirror therapy the patient should be seated comfortably with the mirror positioned between their affected and unaffected limbs. Patients are asked to align the reflection of their unaffected limb with the position of their affected limb, so that the reflection appears as if it is in the same location as the affected limb hidden behind the mirror. The mirror should be sufficiently large to observe the reflected limb whilst it moves without observing the limb behind the mirror.[5] Rehabilitation departments usually have mirrors with stands. In their absence, portable mirrors can be used; they are relatively inexpensive and can be purchased over the counter and via the internet without prescription at a cost of approximately U$10.00. It is important that the mirror is easily accessible, to encourage the patient to use it and that it has a good reflection quality and is not bent, to prevent blurry or distorted reflections. It is advisable to remove jewelry from limbs as much as possible before treatment.

Treatment begins with an adaptive phase, where the patient looks at the reflection without moving the limbs. The reflection of the healthy limb may feel as if it has been perceptually embodied into the patient's body schema so that they get a sense that the reflected limb is their real limb. Perceptual embodiment is the subjective sense of one's body, including a sense of ownership of body parts. Some patients have difficulty experiencing embodiment, and in this situation the therapist can facilitate the process by instructing the patient to imagine that they are looking through a glass instead of a mirror. Another option is to start with a passive sensory stimulus with slow and easy to achieve bilateral movements whilst the patient observes the reflection.[9] Then the therapist encourages the patient to move their affected limb, which is hidden from view, in synchrony with the unaffected limb. For those in whom movement of the affected limb is not possible, or if pain or stiffness limit the duration of movement, the patient should just look at the reflected image of the unaffected limb until the patient feels ready to progress to movements.[5] Patients are told that outcomes improve by regularly repeating the technique over time and they are encouraged to perform mirror therapy daily as part of a self-administered home treatment programme.[9] Mirror therapy should be performed for short periods of time and often, for example, five minute sessions, five to six times per day. A single half hour session once a day or once a week is not encouraged. A diary where the patient documents time using the mirror, types of movements, symptoms and outcomes can be a useful aid to sustain adherence to the treatment regimen.[10]

Side effects to mirror therapy are motor extinction, increased pain, exacerbation of movement disorders, confusion and dizziness.[11] Treatment is discontinued and contraindicated if any of these occur during a course of mirror therapy.

Physiological rationale

Mirror therapy was first described in 1995 by Ramachandran et al.[4] They used a mirror to create the illusion that an amputated limb appeared fully intact when an individual observed a reflection of their intact limb in a mirror (i.e. mirror visual feedback). Generally, reflections of normal-sized limbs are used, although mirrors, lenses, binoculars and virtual reality have been used to magnify and minify the visual appearance of painful body parts.[12]

Mirror therapy is commonly used to decrease anxiety, fear of movement and perceived threat associated with movement of painful body parts. This is achieved by creating a visual illusion of a normally-moving healthy limb located in the same place in space as the painful limb hidden behind the mirror. The visual feedback of a normal moving limb breaks the link between pain and fear of movement.[6,8]

It has been suggested that pain relief associated with mirror therapy results from manipulation of sensory and motor integration within the central nervous system.[4,8] During movement, sensory information is used to compare intention with performance, and motor commands are updated to adjust for discrepancies, ensuring movement matches intention. Motor signals associated with intended movement are sent not only to muscles but also to higher centers within the central nervous system, as an efference copy, to prepare for the consequence of the motor output and to compare with sensory information arising from actual movement (Figure 2). It has been suggested that some painful conditions can be mediated, in part, by incongruence of sensory and motor information. Mirror therapy provides corrective sensory feedback to restore congruence between motor output and sensory input.[4,8]

Mirror therapy has also been used to correct disruptions of body image (body schema) associated with pain when, for example, patients feel as if body parts are large, twisted, heavy and swollen (e.g. complex regional pain syndrome and phantom limb pain) or small and withered (e.g. osteoarthritic hands).[13] Research suggests that painful disruptions in body image are associated with re-organization of neural circuits in the brain due to disrupted somatosensory input from the body part. Mirror therapy is used to provide a corrective visual representation of the affected body part to facilitate reorganization of brain circuits back to their pre-pain state.[8,13]

Mirror therapy can be used to create a sense of a healthy limb. Painful conditions disturb body image and disrupt an individual's sense of ownership of their painful body part.[13] A sense of ownership of body parts has been investigated using the rubber hand illusion whereby an individual observes a rubber hand being stroked with a brush (in view) whilst their real hand is stroked in synchrony but out of view. Eventually, usually within a few minutes, the sensation of stroking feels as if it arises from the rubber hand and the individual experiences a sense that the rubber hand is part of their body (i.e. embodiment of the rubber hand into the body schema). This embodiment of the rubber hand is accompanied by a sense of "loss" (disembodiment) of the real hand and it is accompanied by physiological responses such as local skin cooling, proprioceptive drift and alterations of neural activity in the brain.[13] The use of mirror therapy to induce the embodiment of the healthy reflected limb may help to disembody the painful limb, thereby reducing sensory input and pain.[5]

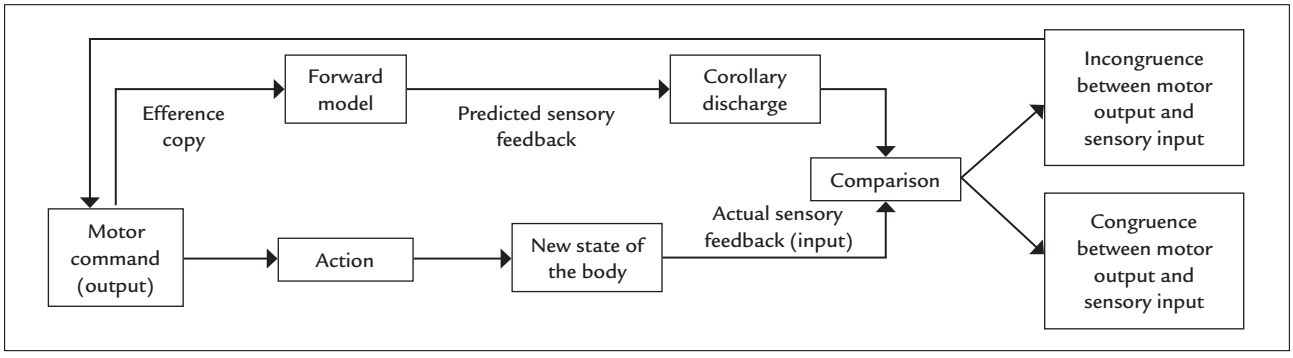


FIGURE 2 Mechanisms involved with motor control. Based on the efference copy of the motor command, a forward model predicts the result of the action. The prediction (corollary discharge) is compared with the information coming from sensory systems, which indicates the new state of the body.

Clinical efficacy

According to Grant and Booth,[14] our review is classified as an overview, which is a summary of the medical literature that attempts to survey the literature and describe its characteristics. Recently, a number of systematic reviews of randomized controlled clinical trials (RCTs) evaluating the effect of mirror therapy on pain have been published. A summary of the studies included in the systematic reviews is provided in Table 1.

The first systematic review to be published was inconclusive due to the heterogeneity and low quality of included studies.[15] Rothgangel et al.[15] included six RCTs evaluating the effect of mirror therapy on phantom limb pain, complex regional pain syndrome and pain after stroke. Four of these RCTs (123 participants) evaluated mirror therapy as a stand-alone treatment and all found pain reduction compared with covered mirror control, mental practice or direct observation of the affected limb.[16-19] Two RCTs (64 participants) used mirror therapy in combination graded motor imagery techniques such as limb laterality recognition and mental practice and both found a reduction of pain intensity compared with usual physiotherapy care.[20,21]

The first meta-analysis of data from RCTs evaluating mirror therapy was conducted as part of a larger review on the effects of graded motor imagery.[22] Bowering et al.[22] concluded that graded motor imagery and mirror therapy alone may be effective for a variety of chronic pain conditions. The meta-analysis consisted of data from three RCTs (86 participants) and found no effect of mirror therapy on pain when used as a stand-alone treatment. Control groups included direct view of both hands[23] and covered mirrors.[16-18] When used in combination with graded motor imagery, mirror therapy was found to produce a large effect size (standardized mean difference = 1.06; 95%CI 0.41-1.71; p=0.001) on pain reduction in comparison to usual physiotherapy care (63 participants).[20,21]

More recently, Thieme et al.[24] published a systematic review with a meta-analysis of data from eight RCTs (224 participants), including five additional RCTs to the previous review.[22] Conditions included complex regional pain syndrome,[25] phantom limb pain[18,26] and pain after stroke.[16,17,19,23,27] Results indicated that mirror therapy reduced pain in the affected limb (standardized mean difference = -1.00; 95%CI -1.77 to -0.24; p=0.01) when compared with covered mirror, direct view of both limbs, no treatment and repetitive transcranial magnetic stimulation.

Boesch et al.[7] meta-analyzed data from one RCT, one non-randomized controlled trial and one within subject comparison study (97 participants) to evaluate the effect of one session of mirror therapy on phantom limb pain[28,29] and complex regional pain syndrome.[30] Boesch et al.[7] did not detect differences from no treatment or covered mirror controls, but their meta-analysis of two RCTs on the effect of a course of mirror therapy lasting four weeks resulted in a large significant reduction (standard mean difference = -1.11; 95%CI -1.66 to -0.56; p<0.0001) in phantom limb and complex regional pain syndrome compared with covered mirror therapy.[16,18] The analgesic effect of mirror therapy was maintained over time ranging from 2 to 6 months.

An RCT of 30 individuals with complex regional pain syndrome has been published after these systematic reviews and the authors concluded that mirror therapy, when used as an adjunct to conventional stroke rehabilitation over the course of four weeks, reduced pain intensity when compared to conventional stroke rehabilitation alone.[31]

There are also RCTs on the efficacy of mirror therapy for back pain, although there are no systematic reviews to date. Wand et al.[6] placed one large mobile mirror in front of the participant and one mirror behind the participant so that there was a clear view of the reflection of their back. They found that pain intensity was reduced immediately post exercise compared with no reflection control during repeated lumbar movements (mean difference = 9.3 mm; 95%CI 2.8-15.7; p=0.007; 25 participants). The duration of low back pain elicited was also shown to be significantly reduced in the mirror condition (mean difference = 49.9 s; 95%CI 19.3-80.6; p=0.003).

Conclusion

Mirror therapy has been used in clinical practice for over two decades but it is still not widely accepted as a treatment option in Brazil. At present, there are no evidence-based treatment protocols for mirror therapy to be used in clinical settings because of a lack of studies investigating clinical indications, treatment duration and frequency, or characteristics of mirror therapy intervention. This means that techniques are likely to vary considerably among practitioners and patients. Evidence for clinical efficacy is encouraging but not yet definitive. Nevertheless, mirror therapy is inexpensive, safe and easy for the patient to self-administer following initial training. Contraindications and side effects are few. These characteristics make mirror therapy a potential treatment option for pain management.

Conflict of interest

The authors declare no conflict of interest.

TABLE 1 Description of studies included in the systematic reviews investigating the effect of mirror therapy on pain.

Study and design	Condition	Total duration	Intervention	Author's conclusion
Cacchio et al.[17] RCT	Complex regional pain syndrome	4 weeks 7 days a week 30 minutes	Patients performed all of the cardinal (proximal to distal) movements of the affected arm	Evidence of effect
Cacchio et al.[16] RCT	Complex regional pain syndrome	First 2 weeks 5 days a week 30 minutes Last 2 weeks 5 days a week 1 hour	Flexion and extension of the shoulder, elbow and wrist, and pronosupination of the forearm	Evidence of effect and effect maintained after 6 months
Chan et al.[18] RCT	Phantom limb pain	4 weeks 7 days a week 15 minutes	Not specified	Evidence of effect
Brodie et al.[28] RCT	Phantom limb pain	1 session	Patients attempted to perform the following movements: straighten and bend the legs at the same time, and alternately. Point feet upwards, and downwards. Turn soles in towards and away from each other. Move feet in a circle. Lift feet off the ground in a walking movement. Point toes upwards and downwards keeping ankle and foot still. Clench, unclench, spread out and relax toes. Point up big toe and point down the other toes, then reverse	Evidence of no effect
Michielsen et al.[23] RCT	Chronic pain post stroke	6 weeks 5 days a week 1 hour	Participants performed bimanual exercises, with the difficulty of the exercises depending on the patients' individual levels of functioning	Evidence of no effect
Dohle et al.[19] RCT	Severe hemiparesis	6 weeks 5 days a week 30 minutes	Arm, hand and finger postures in response to verbal instructions, protocol scaled according to the patients' level of performance	Not reported
Moseley[21] RCT	Complex regional pain syndrome type 1	2 weeks 7 days a week 10 minutes for each waking hour	Patients were instructed to conduct smooth and pain-free movements in accordance to pictures randomly presented	Evidence of effect in combination with GMI
Moseley[20] RCT	Complex regional pain syndrome type 1	2 weeks 7 days a week 10 minutes for each waking hour	Patients were instructed to conduct smooth and pain-free movements in accordance to pictures randomly presented	Evidence of effect in combination with GMI
Flinn et al.[29] Non-randomized controlled trial	Phantom limb pain	Not specified	Not specified	Evidence of no effect
McCabe et al.[30] RCT	Complex regional pain syndrome	1 session 5 minutes	Flexion-extension cycles of both limbs with the range of movement and speed dictated by the patients' pain	Evidence of effect
Michenthaler[30] RCT	Complex regional pain syndrome	6 weeks 2 days a week 30 minutes	Motor activities in 5 positions (not specified)	Not reported
Stein[26] RCT	Phantom limb pain	5 days 45 minutes	Motor and sensory tasks (not specified)	Not reported
Acerra et al.[27] RCT	Stroke	2 weeks 7days a week 20 to 30 minutes	Functional motor tasks (i.e. with objects); motor coordination tasks; sensory discrimination tasks; grip strength; active range of motion	Not reported

RCT: randomized controlled trial; GMI: graded motor imagery.

References

1. Elzahaf RA, Tashani OA, Unsworth BA, Johnson MI. The prevalence of chronic pain with an analysis of countries with a Human Development Index less than 0.9: a systematic review without meta-analysis. Curr Med Res Opin. 2012; 28(7):1221-9.
2. Cabral DM, Bracher ES, Depintor JD, Eluf-Neto J. Chronic pain prevalence and associated factors in a segment of the population of São Paulo City. J Pain. 2014; 15(11):1081-91.
3. Boyers D, McNamee P, Clarke A, Jones D, Martin D, Schofield P, et al. Cost-effectiveness of self-management methods for the treatment of chronic pain in an aging adult population: a systematic review of the literature. Clin J Pain. 2013; 29(4):366-75.
4. Ramachandran VS, Rogers-Ramachandran D, Cobb S. Touching the phantom limb. Nature. 1995; 377(6549):489-90.
5. McCabe C. Mirror visual feedback therapy. A practical approach. J Hand Ther. 2011; 24(2):170-8.
6. Wand BM, Tulloch VM, George PJ, Smith AJ, Goucke R, O'Connell NE, et al. Seeing it helps: movement-related back pain is reduced by visualization of the back during movement. Clin J Pain. 2012; 28(7):602-8.
7. Boesch E, Bellan V, Moseley GL, Stanton TR. The effect of bodily illusions on clinical pain: a systematic review and meta-analysis. Pain. 2016; 157(3):516-29.
8. Ramachandran VS, Altschuler EL. The use of visual feedback, in particular mirror visual feedback, in restoring brain function. Brain. 2009; 132(Pt 7):1693-710.
9. Rothgangel A, Braun S, de Witte L, Beurskens A, Smeets R. Development of a clinical framework for mirror therapy in patients with phantom limb pain: an evidence-based practice approach. Pain Pract. 2016; 16(4):422-34.
10. Grünert-Plüss N, Hufschmid U, Santschi L, Grünert J. Mirror therapy in hand rehabilitation: a review of the literature, the St Gallen protocol for mirror therapy and evaluation of a case series of 52 patients. Hand Therapy. 2008; 13(1):4-11.
11. Casale R, Damiani C, Rosati V. Mirror therapy in the rehabilitation of lower-limb amputation: are there any contraindications? Am J Phys Med Rehabil. 2009; 88(10):837-42.
12. Wittkopf PG, Johnson MI. Managing pain by visually distorting the size of painful body parts: is there any therapeutic value? Pain Manag. 2016; 6(3):201-4.
13. Moseley GL, Gallace A, Spence C. Bodily illusions in health and disease: physiological and clinical perspectives and the concept of a cortical 'body matrix'. Neurosci Biobehav Rev. 2012; 36(1):34-46.
14. Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. Health Info Libr J. 2009; 26(2):91-108.
15. Rothgangel AS, Braun SM, Beurskens AJ, Seitz RJ, Wade DT. The clinical aspects of mirror therapy in rehabilitation: a systematic review of the literature. Int J Rehabil Res. 2011; 34(1):1-13.
16. Cacchio A, De Blasis E, De Blasis V, Santilli V, Spacca G. Mirror therapy in complex regional pain syndrome type 1 of the upper limb in stroke patients. Neurorehabil Neural Repair. 2009; 23(8):792-9.
17. Cacchio A, Blasis E, Necozione S, Orio F, Santilli V. Mirror therapy for chronic complex regional pain syndrome type 1 and stroke. N Engl J Med. 2009; 361(6):634-6.
18. Chan BL, Witt R, Charrow AP, Magee A, Howard R, Pasquina PF, et al. Mirror therapy for phantom limb pain. N Engl J Med. 2007; 357(21):2206-7.
19. Dohle C, Püllen J, Nakaten A, Küst J, Rietz C, Karbe H. Mirror therapy promotes recovery from severe hemiparesis: a randomized controlled trial. Neurorehabil Neural Repair. 2009; 23(3):209-17.
20. Moseley GL. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. Pain. 2004; 108(1-2):192-8.
21. Moseley GL. Graded motor imagery for pathologic pain: a randomized controlled trial. Neurology. 2006; 67(12):2129-34.
22. Bowering KJ, O'Connell NE, Tabor A, Catley MJ, Leake HB, Moseley GL, et al. The effects of graded motor imagery and its components on chronic pain: a systematic review and meta-analysis. J Pain. 2013; 14(1):3-13.
23. Michielsen ME, Selles RW, van der Geest JN, Eckhardt M, Yavuzer G, Stam HJ, et al. Motor recovery and cortical reorganization after mirror therapy in chronic stroke patients: a phase II randomized controlled trial. Neurorehabil Neural Repair. 2011; 25(3):223-33.
24. Thieme H, Morkisch N, Rietz C, Dohle C, Borgetto B. The efficacy of movement representation techniques for treatment of limb pain: a systematic review and meta-analysis. J Pain. 2016; 17(2):167-80.
25. Michenthaler M. Effectiveness of mirror therapy in complex regional pain syndrome (CRPS): a functional magnetic resonance imaging (fMRI) supported, double blinded RCT to the clinic-psychological status of affected patients before and after therapy [thesis]. Klagenfurt: Alpen-Adria-Universität Klagenfurt; 2013.
26. Stein R. Influence of non-pharmacological interventions (repetitive transcranial magnetic stimulation or mirror therapy) on pain intensity and pain associated central nervous plasticity in patients with phantom limb pain. Bochum: Ruhr-Universität Bochum; 2012.
27. Acerra NE. Is early post-stroke upper limb mirror therapy associated with improved sensation and motor recovery? A randomised-controlled trial. Sensorimotor dysfunction in CRPS1 and stroke: characteristics, prediction and intervention. Australia: University of Queensland; 2007.
28. Brodie EE, Whyte A, Niven CA. Analgesia through the looking-glass? A randomized controlled trial investigating the effect of viewing a 'virtual' limb upon phantom limb pain, sensation and movement. Eur J Pain. 2007; 11(4):428-36.
29. Flinn SR, Hotle AC. A case series report on amputees with pro digit hand prostheses receiving mirror therapy. J Hand Ther. 2011; 24(4):390-1.
30. McCabe CS, Haigh RC, Ring EF, Halligan PW, Wall PD, Blake DR. A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). Rheumatology (Oxford). 2003; 42(1):97-101.
31. Pervane Vural SP, Nakipoglu Yuzer GF, Sezgin Ozcan D, Demir Ozbudak S, Ozgirgin N. Effects of mirror therapy in stroke patients with complex regional pain syndrome type 1: a randomized controlled study. Arch Phys Med Rehabil. 2016; 97(4):575-81.

Pilates for breast cancer: A systematic review and meta-analysis

Roberta Costa Espíndula[1], Gabriella Barbosa Nadas[1], Maria Inês da Rosa[1], Charlie Foster[2], Florentino Cardoso de Araújo[3], Antonio Jose Grande[1,4]*

[1]Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil
[2]Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom
[3]President of the Associação Médica Brasileira, São Paulo, SP, Brazil
[4]Universidade Estadual de Mato Grosso do Sul, Dourados, MS, Brazil

Summary

Introduction: Breast cancer is the leading type of cancer causing death in women worldwide. The incidence of the disease is expected to grow worldwide due to the aging of the population and risk factors related to lifestyle behaviors. Considering the lifestyle of women with breast cancer before or after surgery, pilates exercise may be a complementary intervention additionally to standard treatment.
Objective: To analyze the efficacy of pilates compared to other exercises and to no exercise for women with breast cancer diagnosis.
Method: We searched Medline via Pubmed, Embase via Ovid, Amed via EBSCO, Biosis via Ovid, Lilacs and the Cochrane Library for relevant publications until March 2017. The keywords used were pilates and "breast cancer," and only randomized controlled trials were included. Critical appraisal was done using Risk of Bias Tool and GRADE score for assessing the quality of evidence.
Results: A total of five studies were included in our review. Our results demonstrate that pilates or home-based exercises are better than no exercise in each individual study. We observed significant improvements in the pilates groups compared to home-based exercises. Additionally, in the individual studies, we observed improvements in range of motion, pain and fatigue.
Conclusion: The evidence shows that pilates or home-based exercise should be encouraged to women with breast cancer.

Keywords: motor activity, exercise movement techniques, breast neoplasms, delivery of health care.

Study conducted at Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil

Article received: 4/1/2017
Accepted for publication: 4/3/2017

***Correspondence:**
Address: Av. Universitária, 1.105
Criciúma, SC – Brazil
Postal code: 88806-000
grandeto@gmail.com

http://dx.doi.org/10.1590/1806-9282.63.11.1006

Introduction

Breast cancer is the leading type of cancer causing death in women worldwide, affecting 1,2 million new cases/year.[1] The incidence of the disease is expected to grow worldwide due to the aging of the population, risk factors related to lifestyle behaviors such as smoking, poor diet and physical inactivity.[2-5] Data from the GLOBOCAN 2012, produced by the International Agency for Research on Cancer (IARC), estimate that breast cancer incidence was as high as 1,676,600 new cases in that year.[6] The prognosis is good when early treatment is started, reaching 88% of cure rate in five years.[1]

Breast cancer diagnosis can lead a woman's life to consternation, translated into psychophysical suffering, and to an invasive surgery to remove an organ that is symbolic for women and has a negative impact on their quality of life. Physically, women may have their functional capacity compromised by losing muscular strength, reducing the range of motion and increasing pain.[7,8] Socially, women may feel isolation, since breast is a symbol of femininity, sexuality and maternity.[9-12] With the evolution of better diagnostic methods, early detection was improved, leading to favorable prognosis and, thus, a longer survival rate to the patients.[13,14]

Breast cancer usually occurs in women over 40 years of age but it has recently been more and more diagnosed in younger individuals.[15] With this in mind, the social aspects of surgery and chemotherapy are more relevant in younger populations. Women being treated for breast cancer experience many complex situations that require adaptations for the improvement of her physical and emotional structure.[16]

Despite providing longer survival with early diagnosis of breast cancer, treatment leaves sequelae with adverse effects such as: influence on functional capacity, fatigue, depression, neuropathic lymphoedema, low immunity and loss of flexibility. All of these effects end up affecting the quality of life.[1]

From the previously described weaknesses that post-treatment for breast cancer provides to patients, the pilates method aims to aid in symptom relief by helping patients regain functionality, improve performance in daily life activities and help reduce fatigue and improve quality of life.[8] Lastly, pilates exercise may be a complementary intervention, additionally to standard treatment. It is based on the main movements of the body, encouraging the performance of a mind-body connection, using principles such as: breathing, concentration, body alignment, precision, control, rhythm and endurance.[17,18]

The evidence to support the recommendation and widespread use of pilates in women with breast cancer or after surgery has not been well reported yet. Some studies compared the efficacy of pilates compared to other types of exercises on functional capacity, pain and muscular strength showing the benefits of any type of exercise, especially with pilates. Thus, the aim of our study was to analyze the efficacy of pilates compared to other exercises and to no exercise for women with breast cancer diagnosis.

Method

Data sources and searches

The protocol for this systematic review was registered at PROSPERO (international prospective register of systemic reviews, http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016050360). We searched Medical Literature databases Analysis and Retrieval System Online (Medline) via Pubmed, Excerpta Medical Database (Embase) via Ovid, Allied and Complementary Medicine Database (Amed) via EBSCO, Global health, Biological Abstracts/Reports, Reviews, Meetings (Biosis) via Ovid, as well as the Latin American and Caribbean Health Sciences (Lilacs) and the Cochrane Library for relevant publications until March 2017. All searches were run individually. Additionally, we searched the WHO ICTRP (International Clinical Trials Registry Platform) and ClinicalTrials.gov for completed and ongoing studies.

The search, Cochrane Highly Sensitive Search Strategy, used the following keywords: Pilates AND "Breast Neoplasms" [Mesh] OR "breast cancer." The search was sensitive and did not use study filters. We checked the reference lists of all primary studies included for additional references. We applied no language or publication restrictions.

We included only randomized controlled trials about women with breast cancer or women after breast cancer surgery undergoing treatment and doing pilates exercises in one arm of the study comparing to no exercise or a different type of exercise in the control group.

Study selection

Two review authors (AJG, GBN) independently assessed all studies identified from the database searches by screening titles and abstracts using the Review Management website Covidence (http://www.covidence.org). We separated potential studies for full-text reading. A third review author (ET) resolved any disagreements. We described the reasons for including and excluding trials.

Data extraction and quality assessment

Two review authors (AJG, GBN) independently extracted data from the included studies using a standard data extraction form. In this form we extracted information regarding study design, participant description, pilates exercises, control description, each outcomes explored in the studies.

All included studies were assessed for their methodological quality using the Risk of Bias tool from Cochrane Collaboration. The tool is composed of six categories of bias (selection, performance, detection, attrition, reporting and other biases). Items were scored as positive (low risk of bias), negative (high risk of bias) or insufficient information (unclear risk of bias). A figure described the assessment for each study in the results section.

Data synthesis and statistical analysis

All included studies were organized in Table 1, which summarizes all of the participants' data, all interventions and characteristics of the control group participants, as well as all published outcomes.

A meta-analysis was possible only for the functional capacity outcome. All the tables were organized using Microsoft Excel 2016 and the review was performed using RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

The search led to the identification of 34 studies and two additional studies were found by manual search, four of which were excluded as duplicates (Figure 1). A total of 32 studies were assessed based on title and abstract, of which 21 were excluded because they did not fulfill inclusion criteria. Full-text studies were retrieved for 11 titles, of which seven were excluded.

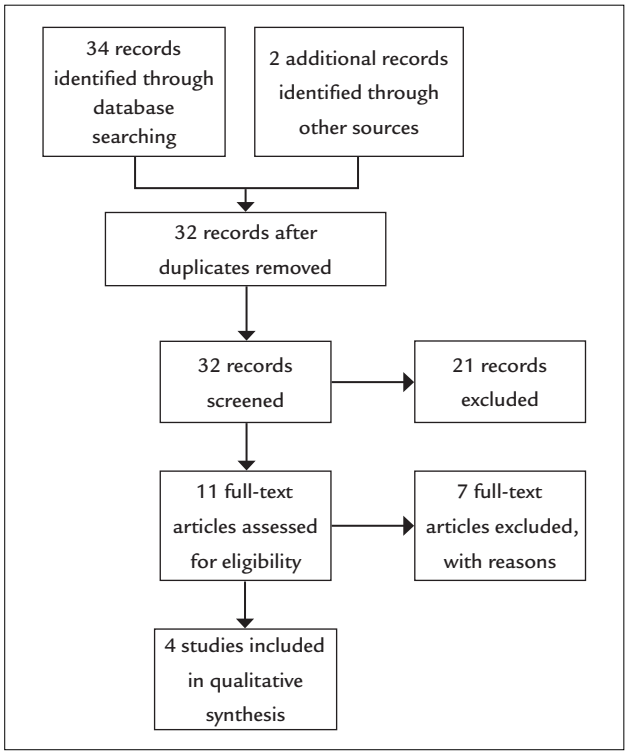


FIGURE 1 Flow chart of systematic review process.

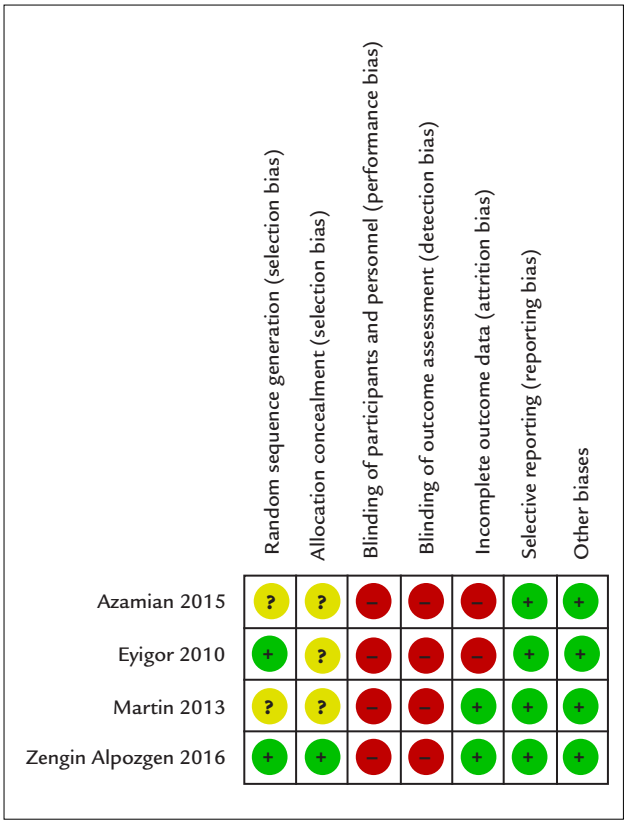


FIGURE 2 Results of the evaluation of each study according to the Risk of Bias tool.

A total of four studies[1,8,19,20] were included in the review. The number of participants in each study ranged from 26 to 57. Two studies were from Turkey, one from Iran and one from the USA. The mean age of participants in each study ranged from 44.11±6.19 to 56.50±12.97 years. Most studies included women diagnosed with stage I, II or III breast cancer. Most of the studies prescribed pilates three times per week during 8 weeks and each session lasted 45-60 minutes. All studies had supervision of a physiotherapist.

Methodological quality of included studies

We used the Risk of Bias tool adopted in Cochrane reviews to analyze the risk of bias in randomized controlled trials. Figure 2 describes each category of bias assessed as low risk, unclear risk and high risk. Random sequence generation was properly described only in two studies;[1,20] other two studies[8,19] did not provide enough information about how randomization was conducted and were randomized according to baseline values.

Allocation concealment was unclear in three studies,[1,8,19] which did not provide information on how it was done. Alpozgen et al.[20] properly described allocation concealment and did not conceal allocation. Blinding of participants, personnel and outcome assessment presented high risk in all studies due to the characteristics of participants; nevertheless, the outcome assessor could have been blinded.

Two studies[1,19] had high loss of follow-up and did not properly adjust the statistics for the missing participants, while other two studies[8,19] did properly adjust the statistical analysis. All studies reported what they proposed in the methods; however, most of them did not present a trial registration number and thus we judged all studies as low risk of bias for selective reporting. In the category Other bias, one study was considered High risk, since the study design was not adequate to answer the research question.

Pilates x home-based exercise

Only one comparison was possible in this study. After extracting all data from the primary studies, we observed that two studies[1,20] compared pilates x home-based exercises for the outcome functional capacity. Both studies used different scales to measure functional capacity, thus we used standardized mean difference to pool the results. Using random effects meta-analysis we found significant difference between pilates x home-based exercise (two studies, 79 participants; standardized mean difference

TABLE 1 Characteristics of the included studies.

Study name/ location	Participants/ Loss	Mean age	Participants included	Pilates frequency	Intensity	Duration	Supervision	Experimental group	Control group	Outcomes	Main results
Eyigor 2010/ Turkey	52/10	48.52±7.62 years	Female, with breast cancer with no evidence of recurrent or progressive disease, completion of treatment with surgery, radiotherapy and/or chemotherapy with or without current hormone treatment, consent to participate in the study, and cognitive functions good enough to understand the questionnaires	3 sessions per week for 8 weeks	Not informed	One hour	Physiotherapist	Pilates + home exercises + 30-minute information	Home exercise	All the patients were evaluated for functional capacity with the 6-min walk test (6MWT), flexibility (modified sit and reach test), fatigue with the Brief Fatigue Inventory (BFI), depression with the Beck Depression Index (BDI), quality of life (EORTC-QLQ-C30 and EORTC QLQ BR23) and complications before the treatment and 8 weeks after the exercise by the same physician	Both groups improved significantly in the 6MWT; Only pilates group significantly improved BDI; Only pilates group significantly improved EORTC-QLQ-C30 and EORTC QLQ BR23 functional
Azamian 2015/Iran	34/7	44.11±6.19 years	Women diagnosed with breast cancer	3 sessions per week for 12 weeks	Not informed	Not informed	Physiotherapist	Pilates	No exercise	BMI, fat percent, WHR, VO_2max, FBS level, insulin, HOMA, adiponectin	Serum adiponectin level and VO_2max significantly increased in the pilates group. Insulin level, insulin resistance and body fat percentage significantly decreased and the FBS level had no significant change after selected pilates exercise training ($P<0.05$)
Martin 2013/USA	26/0	44.6	Women diagnosed with stage I, II or III breast cancer that had completed all treatments within 6 months, had consent from their oncologist to participate	3 sessions per week for 8 weeks	The two protocols matched in volume of work and sequence of muscles exercised. Perceived Exertion (RPE) scale from 6 to 20	50 minutes	Bachelors or Masters of Exercise and Sport Science	Group 1 - Pilates Group 2- Resistance exercise	No exercise	Muscular endurance and adherence to exercise programs	Pilates and traditional resistance training may be equally effective at improving muscular endurance as significant improvements in muscular endurance were observed
Zengin Alpozgen 2016/ Turkey	57/2	51.94±8.05	"Stages I–III" with a diagnosis of breast cancer and development of shoulder ROM limitation (limitation of 20 ≥ ROM in shoulder flexion, abduction, external or internal rotation) secondary due to breast cancer treatment	3 sessions per week for 8 weeks	Not reported	45 minutes	Physiotherapist	Group 1 - Pilates Group 2- Combined exercises	Home exercises	Body mass index; Pain, Range of motion; Handgrip strength; functional status of the affected limb	Levels of pain decreased significantly in the three groups analyzed. Range of motion and functional status improved in all three groups, but pilates and combined exercises showed better results

[SMD] 0.99 [95CI 0.51-1.47]; Chi² test 0.71; df=1; p<0.001; I² statistic 0% for functional capacity). Figure 3 presents the forest plot with comparison of pilates x home-based exercise for functional capacity.

Discussion

Breast cancer is a chronic degenerative disease with significant global public health importance for women.[6] The risk factors are well known and improving lifestyle may be a protective factor and reduce the risk of developing the disease.[4,5,10,21] This is the first systematic review and meta-analysis to specifically investigate and compare the practice of pilates with no exercise and with other exercises for women with breast cancer.

Overall, our results demonstrate that pilates or home-based exercises are better than no-exercise in each individual study. Considering the pooled data for two studies, a meta-analysis was conducted only for the outcome of functional capacity, thus we observed significant improvements in the pilates group compared to home-based exercises. This result was expected: since pilates had a professional monitoring the performance of every exercise, the women had an extra motivation to take pilates training, and had company to exercise. Additionally, in the individual studies we observed improvements in range of motion, pain and fatigue.

There is a systematic review about the methods used in pilates for women's health published in 2015.[17] Considering pilates and breast cancer, the authors included only two studies. In our systematic review, we found three more RCTs in the literature, and so we can consider it an update of the evidence. We were also able to conduct a meta-analysis on functional capacity. There is growing interest in the topic and new studies are being conducted.

Considering the quality of the studies, improvements are necessary, to perform randomization and allocation concealment, not only in the conduction of the study, but also better described in the study. Due to the type of intervention, blinding was not possible; however, outcome assessors could have been blinded in the studies. Incomplete outcome data was another problem found, with some studies presenting high loss at follow-up.

As for risk of bias assessment, imprecision, inconsistency, indirectness and publication bias, we were able to categorize the evidence based on the GRADE score as low quality. This means that the evidence organized is this systematic review is "very likely that further research would change our estimate of effect or our confidence in it."

The limitations of our research rely on the fact that different protocols of pilates exercises and home-based exercises were used across studies. Heterogeneity was tested but not found across studies. A strong factor is that our review considered all studies around the world. Note that one study was Persian and we had a collaborator translating it.

Conclusion

The individual studies show that pilates is better than home-based exercises and no-exercise. The studies also showed that home-based exercise or pilates are better than no exercise on fatigue, range of motion, mood and it does not bring risks.

The evidence shows that pilates or home-based exercise should be encouraged for women with breast cancer, and we believe that future studies will succeed in presenting the evidence in a stronger and more reliable manner.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Pilates para mulheres com câncer de mama: revisão sistemática e metanálise

Introdução: O câncer de mama é o principal tipo de câncer que causa morte em mulheres em todo o mundo.

Study or subgroup	Pilates Mean	SD	Total	Home-based exercises Mean	SD	Total	Weight	Standard mean difference IV, random, 95CI
Eyigor 2010	84.39	10.47	27	75.83	10.59	15	53.8%	0.80 [0.14, 1.46]
Zengin	72.17	6.66	18	60.05	11.97	19	46.2%	1.22 [0.51, 1.92]
Alpozgen 2016								
Total (95CI)			45			34	100%	0.99 [0.51, 1.47]

Heterogeneity Tau²=0.00; Chi²=0.71, df=1 (p=0.40); I²=0%

Test for overall effect Z=4.04 (p<0.0001)

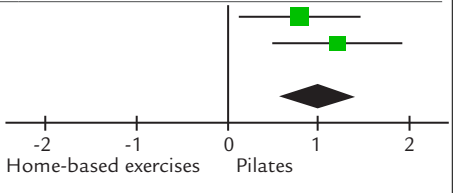


FIGURE 3 Forest plot comparing pilates versus home-based exercises for functional capacity.

Estima-se que a doença cresça em razão do envelhecimento da população e dos fatores de risco relacionados ao comportamento e estilo de vida. Considerando o estilo de vida das mulheres com câncer de mama antes ou após a cirurgia, o exercício de pilates pode ser uma intervenção complementar, além do tratamento padrão.

Objetivo: Analisar a eficácia do pilates em relação a outros exercícios e a nenhum exercício para mulheres com diagnóstico de câncer de mama.

Método: Buscamos em Medline via Pubmed, Embase via Ovid, Amed via EBSCO, Biosis via Ovid, Lilacs e Cochrane Library publicações relevantes até março de 2017. As palavras-chave utilizadas foram pilates e "câncer de mama"; apenas ensaios clínicos randomizados foram incluídos. A avaliação crítica foi feita com a ferramenta Risk of Bias e escore GRADE para avaliar a qualidade da evidência.

Resultados: Um total de cinco estudos foi incluído nesta revisão. Nossos resultados demonstram que pilates ou exercícios feitos em casa são melhores do que a ausência de exercícios em cada estudo individual. Observamos melhorias significativas no grupo de pilates em comparação com exercícios em casa. Adicionalmente, nos estudos individuais observamos melhorias na amplitude de movimento, dor e fadiga.

Conclusão: A evidência mostra que pilates ou exercícios em casa devem ser encorajados a mulheres com câncer de mama.

Palavras-chave: atividade motora, técnicas de exercício e de movimento, neoplasia de mama, assistência à saúde.

References

1. Eyigor S, Karapolat H, Yesil H, Uslu R, Durmaz B. Effects of pilates exercises on functional capacity, flexibility, fatigue, depression and quality of life in female breast cancer patients: a randomized controlled study. Eur J Phys Rehabil Med. 2010; 46(4):481-7.
2. Bernardo LM, Abt KL, Ren D, Bender C. Self-reported exercise during breast cancer treatment: results of a national survey. Cancer Nurs. 2010; 33(4):304-9.
3. Metsker J. A healthy lifestyle program for breast cancer survivors: women embracing and loving life. Am J Clin Oncol. 2011; 34(5):552.
4. Schmitz K. Physical activity and breast cancer survivorship. Recent Results Cancer. 2011; 186:189-215.
5. Stan DL, Rausch SM, Sundt K, Cheville AL, Youdas JW, Krause DA, et al. Pilates for breast cancer survivors. Clin J Oncol Nurs. 2012; 16(2):131-41.
6. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136(5):E359-86.
7. Magrani do Rosario P, Naumann F, Martin E. The effects of an individual versus a group delivered exercise and counselling intervention on fatigue in breast cancer survivors. J Sci Med Sport. 2011; 14(Suppl. 1):e116-7.
8. Martin E, Battaglini C, Groff D, Naumann F. Improving muscular endurance with the MVe Fitness Chair™ in breast cancer survivors: a feasibility and efficacy study. J Sci Med Sport. 2013; 16(4):372-6.
9. Finestone S. Meeting the changing emotional and educational needs of breast cancer patients. Psycho-Oncology. 2011; 1:1-2.
10. Aaronson N, Turo AM. Pilates for breast cancer survivors: a guide to recovery, healing, and wellness. New York: Demos Health; 2014.
11. Furzer BJ, Wright KE, Petterson AS, Wallman KE, Ackland TR, Joske DJ. Characteristics and quality of life of patients presenting to cancer support centres: patient rated outcomes and use of complementary therapies. BMC Complement Altern Med. 2013; 13:169.
12. Stan DL, Collins NM, Olsen MM, Croghan I, Pruthi S. The evolution of mindfulness-based physical interventions in breast cancer survivors. Evid Based Complement Alternat Med. 2012; 2012:758641.
13. Luz ND, Lima ACG. Recursos fisioterapêuticos em linfedema pós-mastectomia: uma revisão de literatura. Fisioter Mov. 2011; 24(1):191-200.
14. Panati S, Shahid K, Watson KS, Adair L, Juneja S, Nguyen K, et al. Socioeconomic factors and the use of complimentary and alternative therapies in patients with early stage breast cancer. Cancer Research Conference: 37th Annual CTRC AACR San Antonio Breast Cancer Symposium San Antonio, TX United States Conference Start. 2014; 75(9 Suppl. 1):P2-12-11.
15. Carneiro Neto JD, Barreto JBP, Freitas NS, Queiroz MA. Câncer colorretal: características clínicas e anatomopatológicas em pacientes com idade inferior a 40 anos. Rev Bras Coloproctol. 2006; 26(4):430-5.
16. Eramo A, Lotti F, Sette G, Pilozzi E, Biffoni M, Di Virgilio A, et al. Identification and expansion of the tumorigenic lung cancer stem cell population. Cell Death Differ. 2008; 15(3):504-14.
17. Mazzarino M, Kerr D, Wajswelner H, Morris ME. Pilates method for women's health: systematic review of randomized controlled trials. Arch Phys Med Rehabil. 2015; 96(12):2231-42.
18. Wells C, Kolt GS, Bialocerkowski A. Defining Pilates exercise: a systematic review. Complement Ther Med. 2012; 20(4):253-62.
19. Jazi AA, Mobarekeh BG, Vismeh Z, Gohar NP. Effect of 12 weeks of selected Pilates exercise training on serum adiponectin level and insulin resistance in female survivors of breast cancer and its role in prevention of recurrence. Scientific J Kurdistan University of Medical Sciences. 2015; 20(5):61-73.
20. Alpozgen AZ, Ozdincler AR, Karanlik H, Agaoglu FY, Narin AN. Effectiveness of Pilates-based exercises on upper extremity disorders related with breast cancer treatment. Eur J Cancer Care (Engl). 2016. [Epub ahead of print]
21. Fong TC, Hoffmann B. Images in clinical medicine. Disappearance of a breast prosthesis during Pilates. N Engl J Med. 2011; 365(24):2305.

Approach to concurrent coronary and carotid artery disease: Epidemiology, screening and treatment

Patrícia Feitosa Frota dos Reis[1], Pedro Vieira Linhares[1], Fábio Grunspun Pitta[1], Eduardo Gomes Lima[1]*

[1]Department of Atherosclerosis, Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da USP (InCor-HCFMUSP), São Paulo, SP, Brazil

Study conducted at Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da USP (InCor-HCFMUSP), São Paulo, SP, Brazil

Article received: 4/13/2017
Accepted for publication: 4/15/2017

***Correspondence:**
Address: Av. Dr. Enéas de Carvalho Aguiar 44, 2º andar, sala 2
São Paulo, SP – Brazil
Postal code: 05403-000.
eduglima@yahoo.com.br

http://dx.doi.org/10.1590/1806-9282.63.11.1012

Summary

The concomitance between coronary artery disease and carotid artery disease is known and well documented. However, it is a fact that, despite the screening methods for these conditions and the advances in surgical treatment, little has been achieved in terms of reducing the risk of complications in the perioperative period. Publications are scarce, being mostly composed of reports or case series. There is little agreement on the best initial therapeutic approach (myocardial versus carotid revascularization) or the best technique to be used (surgery with or without extracorporeal circulation, hybrid treatments, etc.). The authors performed a review of the evidence in this clinical scenario, raising pragmatic questions that help in the therapeutic decision.

Keywords: coronary disease, carotid artery diseases, myocardial revascularization.

Introduction

Cerebrovascular accident (CVA), or stroke, is a perioperative complication that occurs in about 2% of myocardial revascularization (CABG) surgeries.[1] Evidence suggests that the main etiology is the macroembolization of atherothrombotic debris derived from the aortic arch.[2]

An important subgroup of risk for such complication is that of patients with significant carotid stenosis (> 70%). However, it has been demonstrated in some studies that this is also a predictor of severe atherosclerotic disease in the aortic arch.[3] Therefore, the presence of significant carotid stenosis seems to serve more as a marker of risk for aortic arterial disease than as a causal relationship for CVA in the perioperative period of CABG.[4]

Although carotid Doppler ultrasound (USG) screening is routinely performed for preoperative CABG assessment in many institutions, the benefit of carotid revascularization surgery (CAR) in asymptomatic patients is questioned.[5]

Therapeutic choice in patients with coronary artery disease (CAD) and concomitant carotid disease is also controversial, based on few studies and the experience of institutions. Therapeutic strategies include: 1. combined surgery (CABG and CAR in the same procedure); 2. staged surgeries (CABG with subsequent CAR x CAR with subsequent CABG); 3. hybrid procedure (CABG with percutaneous carotid intervention – PCI). The strategies can be simultaneous or staged, being performed in one or two surgical times, respectively.[6,7]

Carotid artery disease screening in the preoperative period of myocardial revascularization

Currently, there is a strong tendency to request USG carotid Doppler as part of preoperative assessment of CABG. In patients undergoing CABG, the prevalence of major carotid disease is known to range from 2.8 to 22%. On the other hand, among patients undergoing endarterectomy, the prevalence of coronary artery disease is between 28 and 40%.[8] Despite the strong association between diseases, the incidence of CVA in patients submitted to CABG is low, varying from 1.3 to 2.0%.[5]

The etiology of perioperative CVA is multifactorial, the most common being embolism calcified plaques. According to a meta-analysis by Naylor and Bown,[9] the incidence of ipsilateral CVA combined with important asymptomatic ipsilateral carotid stenosis is low, only 2%. Note that the main etiologies are related to the procedure per se, such as pressure control, diastolic pulmonary hypertension, atherothrombotic macroembolization during aortic clamping and cannulation, and microembolization of platelet aggregates caused by a swirling flow in cardiopulmonary bypass.[10]

Risk factors for perioperative CVA are: previous CVA or transient ischemic attacks (TIA), peripheral arterial

disease, systemic arterial hypertension, advanced age (> 65 years), left ventricular dysfunction, obstructive carotid disease and atrial fibrillation.[5] Although risk factors help in the stratification of patients undergoing surgery, Durand et al.[11] created an algorithm based on the characteristics of the patients in an attempt to predict the occurrence of carotid disease, finding a high false-positive rate and low specificity.

Doppler USG has proved to be a very accurate test in the quantification and definition of carotid disease, and it is useful to define patients with a high risk of atherothrombotic events ranging from 3%, in the case of asymptomatic patients with unilateral stenosis from 70 to 99%, to 7-11% in carotid occlusion. Although this is a cost-effective screening test, there is no study to justify its routine large-scale use in an attempt to reduce morbidity and mortality, so it should be used in selected patients as directed by the Society of Thoracic Surgeons and the American College of Cardiology.[12] According to the 2014 European directive on myocardial revascularization, Doppler USG is indicated in the preoperative context for patients with a history of CVA or TIA, in addition to carotid bruit. Its utility should also be considered in patients with peripheral obstructive arterial disease, elderly individuals (> 70 years), and in multi-vessel coronary disease.[13]

Screening of coronary artery disease in the preoperative workup of carotid artery revascularization

While prevalence of significant carotid disease among CABG candidates is low, this seems to be different in a reverse context. The association between carotid and coronary atherosclerosis is very prevalent, consisting of 46 to 71% in patients undergoing elective vascular surgery.[14,15] Despite the high prevalence, there is little consensus among cardiologists regarding the stratification of coronary disease in patients with no evidence of angina or anginal equivalent. Illuminati et al.[14] randomized two groups of patients, asymptomatic from a cardiovascular standpoint, either with indication of endarterectomy for coronary angiography (CINE) or not, with further treatment using percutaneous angioplasty or surgical revascularization. All patients were maintained with dual-antiplatelet therapy (ASA 100 mg + clopidogrel 75 mg) and high-potency statin. In the comparison of the group of patients undergoing CINE with those that did not receive this treatment, a substantial difference was found in the prevalence of acute myocardial infarction (AMI), respectively 1.4 and 15.7%. Despite the optimistic data, the severity of the patients in this study was low, being mostly uniarterial or biarterial, asymptomatic and without ventricular dysfunction, with only two indications of surgical revascularization. It is also important to note the excess of interventions in patients with chronic coronary artery disease, who would probably have a good long-term prognosis in optimized clinical treatment.

According to the II Guideline for Perioperative Evaluation of the Brazilian Society of Cardiology,[16] patients with intermediate risk for CAD according to the Lee criteria, with an indication for vascular surgery, should undergo noninvasive tests for diagnosis of CAD: stress myocardial perfusion imaging (scintigraphy), exercise stress test or pharmacologic stress echocardiography. The indication of CINE should be reserved for patients with non-invasive tests suggestive of high risk or patients with acute coronary syndrome.[16]

Management of dual-antiplatelet therapy

According to the current literature, there is no consensus on the management of antiplatelets in this setting. ASA dosage is 100-325 mg/day and clopidogrel dosage is 75 mg/day,[9] with some reports of clopidogrel loading dose of 600 mg approximately 4 hours before endarterectomy or carotid angioplasty. When choosing between staged procedures, if patient is using DAPT there is a tendency to maintain ASA and to suspend clopidogrel at least 5 days prior to CABG, but it is important to assure the mandatory period of 3-4 weeks of DAPT after carotid stenting, which can delay CABG.[17] In some patients with limiting CCSIII-IV angina, Lopes et al.[18] chose to maintain double antiaggregation and perform CABG soon after clinical stabilization after carotid angioplasty.

According to the protocol for update and focus on arterial vascular surgery of the II Guideline for Perioperative Evaluation of the Brazilian Society of Cardiology,[16] ASA should be maintained at a dosage of 75 to 100 mg/day. Regarding the use of clopidogrel, the risk of bleeding inherent to the procedure should be considered. When the risk is moderate or high, clopidogrel should be discontinued five days prior (recommendation grade I, level of evidence C), and when the risk of bleeding is low, the antiaggregant should be maintained in the perioperative period.

Combined coronary and carotid surgical revascularization versus staged surgical revascularization

There is great divergence of opinion as to the best way to approach simultaneous carotid and coronary disease. According to a meta-analysis by Fareed et al.,[10] the safest and lowest mortality rates for CVA and AMI would be to

perform endarterectomy synchronously to CABG without extracorporeal circulation (ECC).

On the other hand, when evaluating data by Naylor and Bown[9] regarding studies from 1972 to 2002, results opposite those of Fareed et al. are observed.[10] The worst outcomes, including overall mortality, composite endpoint of death + CVA and death + CVA + AMI were higher in patients submitted to synchronized surgery, respectively 4.6, 7.4, 8.7 and 11.5% compared with staged procedures. However, the incidence of CVA alone, both ipsilateral in major carotid disease and CVA in any territory, was higher in CABG prior to CAR; and the rate of AMI alone was higher in patients submitted to CAR preceding CABG. It is important to mention that the majority of patients were asymptomatic from a neurological point of view, and there was no standardized way to diagnose perioperative AMI, which was therefore underdiagnosed.

Despite the divergence among studies, much can be asked about the actual prevalence of CVA combined with carotid disease. The fact is that most CVAs were diagnosed after 24 hours of surgery, regardless of the territory of carotid disease, and many of the patients did not have significant carotid atherosclerosis.

According to recommendations by Masabni et al.,[5] when choosing a carotid approach prior to CABG, both procedures should be avoided at the same anesthetic time due to the risk associated with hyperperfusion syndrome after carotid revascularization, making it imperative to observe level of consciousness and neurological parameters shortly after the procedure. Another logical approach is that performed by the team of Seyed Ebrahim,[19] at the Tehran Heart Center, which advocates prioritizing the treatment of the most severe entity: in patients with symptoms of unstable angina or asymptomatic carotid disease, only CABG is performed; while in patients with stable coronary disease and symptomatic carotid stenosis, the approach advocated is that of carotid artery simultaneously with CABG. The common sense is that the CAR option is based on patient comorbidities, CABG urgency, supra-aortic vessel anatomy and medical center experience.[13]

Such heterogeneity in the results of studies comparing surgical techniques to approach these two entities reflects the limited evidence in this scenario: the studies are mostly single-center studies composed of series of cases with selection bias, so that the experience of the surgeon and the service seems to have direct interference in the results.

Hybrid treatment

An alternative strategy for the management of patients with CABG indication and those with significant carotid stenosis is the hybrid procedure. It consists of PCI (angioplasty and stent placement) combined with CABG. It may be synchronous (performed at the same surgical time) or staged (performed at two different times), and associated with CABG with or without ECC. It is another therapeutic alternative based on the experience of certain services, in series of cases, single-center studies and retrospective analyzes. Although there are no multicenter and prospective studies that evaluate the superiority and safety of this therapeutic approach to the detriment of others, it is another alternative for the treatment of patients with coronary artery disease and carotid stenosis in institutions with structure and experience to carry out hybrid procedures.[20]

The synchronic approach, using percutaneous treatment with stent implantation in carotid lesions (≥ 60% symptomatic or ≥ 70% asymptomatic) followed immediately by CABG, showed an incidence of 2.2% of CVA/death after 30 days and absence of neurological complications related to the percutaneous procedure and AMI. In this single-center, prospective and nonrandomized study (n=90), synchronic hybrid treatment was a reasonable option for the selected group of patients.[21]

The prospective/multicenter SHARP trial (n=101) evaluated PCI associated with CABG at the same surgical time in high-risk patients (EuroESCORE ≥ 5).[22] Simultaneous hybrid technique demonstrated 98% success in the procedure and 2% cumulative incidence of AMI/CVA/death within 30 days. It thus demonstrated a feasible and promising approach for this group of patients.[22]

Retrospective evaluation of the CARE[23] (Carotid Artery Revascularization) registry evaluated the clinical characteristics of patients undergoing carotid endarterectomy and percutaneous intervention of carotid lesions immediately before CABG. Despite regional variations, patients undergoing percutaneous intervention had more advanced vascular disease, but less pre-surgical risk.[23]

Patients with symptomatic carotid stenosis are four times more likely to develop neurological complications during CABG perioperative period. The hybrid treatment was also evaluated in this group of patients (previous TIA/CVA) in a prospective/single-center study (n=57). The hybrid procedure was shown to be a viable alternative for the treatment of this high-risk group, although the strategy also lacks studies with a higher level of evidence for recommendation to the detriment of other therapeutic options in this context.[24]

A prospective cohort compared the staged hybrid treatment (prophylactic PCI followed by CABG) with CABG (non-ECC) in 112 patients with significant carotid stenosis and CABG indication. Prophylactic percu-

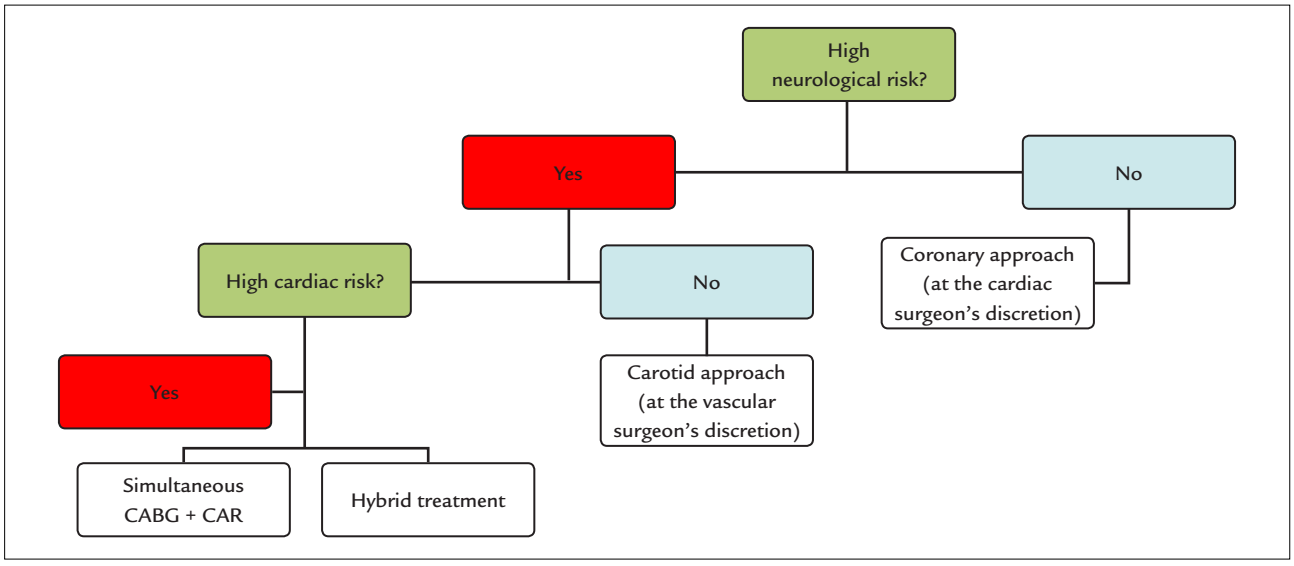


FIGURE 1 Suggested algorithm for therapeutic management of concurrent carotid and coronary artery disease.

CABG: surgical myocardial revascularization; CAR: carotid artery revascularization surgery.
High neurological risk: Clinical variables: symptomatic patient (previous stroke or TIA, amaurosis fugax, ischemic or infarction areas in CNS images, even without previous neurological symptoms). Angiographic variables: bilateral carotid stenosis 70-99%, unilateral carotid stenosis 70-99% + contralateral occlusion.
High cardiac risk, clinical variables: unstable angina, CCS III-IV angina, acute coronary syndrome (AMI, STEMI or non-STEMI). Angiographic variables: left coronary artery lesion greater than 70%, or proximal anterior descending (AD) artery greater than 90%, or AD and proximal circumflex (CX) > 70%, one of them greater than 90%.

taneous carotid stenosis did not reduce the risk of CVA in patients undergoing CABG, except for the subgroup of symptomatic patients (CVA/TIA) with bilateral carotid obstruction, in whom hybrid staged treatment could present a better neurological outcome in centers experienced and qualified for such procedure.[19]

Comparing CABG alone versus PCI + CABG (11) performed within a mean interval of 5-6 weeks, there is a trend in absolute numbers of higher risk of death, CVA and AMI with combined surgery, respectively 0.9, 3.6 and 1.8% vs. 3.2, 6.4 and 6.4%, but without statistical significance. We emphasize that this study was performed by a medical center with extensive experience in carotid angioplasty and should be taken into account when observing the results.

The lack of standardization of current studies, for instance the surgical technique (percutaneous intervention versus endarterectomy with or without a filter basket), demographic and symptomatic profile of patients, and a small number of patients, often without randomization, make comparisons and broad definition of the best approach difficult. A feasible percentage, which would function as a treatment target, would be < 3% in the rate of complications following carotid angioplasty in asymptomatic patients, and < 6% in symptomatic patients.[10,25]

Conclusion

As already mentioned, the association of carotid and coronary atherosclerosis is very prevalent, with no consensus to date on which sequence of surgical approaches is the safest. In fact, greater importance should be given to intraoperative care, focusing on strict control of systemic blood pressure, avoiding extreme BP levels and including careful evaluation of the aorta during clamping and cannulation, as well as monitoring of cerebral oxygenation.[2] The risks inherent to the procedure should be considered (higher CVA rate in revascularization surgeries in the presence of carotid disease and higher rate of AMI in carotid surgeries concomitant with significant CAD) in the therapeutic decision (Figure 1). Individualization of treatment, use of less invasive techniques (PCI whenever possible or endovascular treatment of carotid arteries), and shared decisions with the Heart Team should be encouraged. Surely the maxim that advocates treatment of the most severe entity in the first place has a place in this scenario.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Abordagem da doença coronariana e carotídea concomitante: epidemiologia, rastreamento e tratamento

A concomitância entre doença arterial coronária e doença carotídea é conhecida e já bem documentada. Fato é, porém, que, a despeito dos métodos de rastreio dessas condições

e da evolução do tratamento cirúrgico, pouco se tem conseguido em termos de redução de risco de complicações no perioperatório. As publicações são escassas, sendo em sua maior parte compostas por relatos ou séries de caso. Há pouco consenso sobre qual a melhor abordagem terapêutica inicial (revascularização miocárdica *versus* carotídea), bem como sobre a melhor técnica a ser empregada (cirurgia com ou sem uso de circulação extracorpórea, tratamentos híbridos, etc.). Os autores realizaram uma revisão da evidência nesse cenário clínico, pontuando questões pragmáticas que ajudem na decisão terapêutica.

Palavras-chave: doença das coronárias, doenças das artérias carótidas, revascularização miocárdica.

References

1. Naylor AR, Mehta Z, Rothwell PM, Bell PR. Carotid artery disease and stroke during coronary artery bypass: a critical review of the literature. Eur J Vasc Endovasc Surg. 2002; 23(4):283-94.
2. Djaiani GN. Aortic arch atheroma: stroke reduction in cardiac surgical patients. Semin Cardiothoracic Vasc Anesth. 2006; 10(2):143-57.
3. Sen S, Wu K, McNamara R, Lima J, Piantadosi S, Oppenheimer SM. Distribution, severity and risk factors for aortic atherosclerosis in cerebral ischaemia. Cerebrovasc Dis. 2000; 10(2):102-9.
4. Balsam LB, DeAnda A Jr. To screen or not to screen, that is the question. Or is it? J Thorac Cardiovasc Surg. 2015; 149(6):1485-6.
5. Masabni K, Raza S, Blackstone EH, Gornik HL, Sabik JF 3rd. Does preoperative carotid stenosis screening reduce perioperative stroke in patients undergoing coronary artery bypass grafting? J Thorac Cardiovasc Surg. 2015; 149(5):1253-60.
6. Akins CW, Moncure AC, Daggett WM, Cambria RP, Hilgenberg AD, Torchiana DF, et al. Safety and efficacy of concomitant carotid and coronary artery operations. Ann Thorac Surg. 1995; 60(2):311-8.
7. Antunes PE, Anacleto G, Oliveira JM, Eugénio L, Antunes MJ. Staged carotid and coronary surgery for concomitant carotid and coronary artery disease. Eur J Cardiothorac Surg. 2002; 21(2):181-6.
8. Ogutu P, Werner R, Oertel F, Beyer M. Should patients with asymptomatic significant carotid stenosis undergo simultaneous carotid and cardiac surgery? Interact Cardiovasc Thorac Surg. 2014; 18(4):511-8.
9. Naylor AR, Bown MJ. Stroke after cardiac surgery and its association with asymptomatic carotid disease: an updated systematic review and meta-analysis. Eur J Vasc Endovasc Surg. 2011; 41(5):607-24.
10. Fareed KR, Rothwell PM, Mehta Z, Naylor AR. Synchronous carotid endarterectomy and off-pump coronary bypass: an updated, systematic review of early outcomes. Eur J Vasc Endovasc Surg. 2009; 37(4):375-8.
11. Durand DJ, Perler BA, Roseborough GS, Grega MA, Borowicz LM Jr, Baumgartner WA, et al. Mandatory versus selective preoperative carotid screening: a retrospective analysis. Ann Thorac Surg. 2004; 78(1):159-66.
12. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011; 58(24):e123-210.
13. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014; 35(37):2541-619.
14. Illuminati G, Schneider F, Greco C, Mangieri E, Schiariti M, Tanzilli G, et al. Long-term results of a randomized controlled trail analyzing the role of systematic pre-operative coronary angiography before elective carotid endarterectomy in patients with asymptomatic coronary artery disease. Eur J Vasc Endovasc Surg. 2015; 49(4):366-74.
15. Dieter RS, Tomasson J, Gudjonsson T, Brown RL, Vitcenda M, Einerson J, et al. Lower extremity peripheral arterial disease in hospitalized patients with coronary artery disease. Vasc Med. 2003; 8(4):233-6.
16. Gualandro DM, Yu PC, Calderaro D, Marques AC, Pinho C, Caramelli B, et al. II diretriz de avaliação perioperatória da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol. 2011; 96(3 suppl.1):1-68.
17. Shishehbor MH, Venkatachalam S, Sun Z, Rajeswaran J, Kapadia SR, Bajzer C et al. A direct comparison of early and late outcomes with three approaches to carotid revascularization and open heart surgery. J Am Coll Cardiol 2013; 62(21):1948-56.
18. Lopes DK, Mericle RA, Lanzino G, Wakhloo AK, Guterman LR, Hopkins LN. Stent placement for the treatment of occlusive atherosclerotic carotid artery disease in patients with concomitant coronary artery disease. J Neurosurg. 2002; 96(3):490-6.
19. Kassaian SE, Abbasi K, Hakki Kazazi E, Soltanzadeh A, Alidoosti M, Karimi A, et al. Staged carotid artery stenting and coronary artery bypass surgery versus isolated coronary artery bypass surgery in concomitant coronary and carotid disease. J Invasive Cardiol. 2013; 25(1):8-12.
20. Gray WA. Carotid artery stenting before cardiac surgery: a promising path down a muddy road? JACC Cardiovasc Interv. 2011; 4(11):1197-9.
21. Velissaris I, Kiskinis D, Anastasiadis K. Synchronous carotid artery stenting and open heart surgery. J Vasc Surg. 2011; 53(5):1237-41.
22. Versaci F, Reimers B, Del Giudice C, Schofer J, Giacomin A, Saccà S, et al. Simultaneous hybrid revascularization by carotid stenting and coronary artery bypass grafting: the SHARP study. JACC Cardiovasc Interv. 2009; 2(5): 393-401.
23. Don CW, House J, White C, Kiernan T, Weideman M, Ruggiero N, et al. Carotid revascularization immediately before urgent cardiac surgery. practice patterns associated with the choice of carotid artery stenting or endarterectomy: a report from the CARE (Carotid Artery Revascularization and Endarterectomy) registry. JACC Cardiovasc Interv. 2011; 4(11):1200-8.
24. Van der Heyden J, Van Neerven D, Sonker U, Bal ET, Kelder JC, Plokker HW, et al. Carotid artery senting and cardiac surgery in symptomatic patients. JACC Cardiovasc Interv. 2011; 4(11):1190-6.
25. Naylor AR, Cuffe RL, Rothwell PM, Bell PR. A systematic review of outcomes following staged and synchronous carotid endarterectomy and coronary artery bypass. Eur J Vasc Endovasc Surg. 2003; 25(5):380-9.

Para mais informações:
(11) 3178-6800 - diretrizes@amb.org.br

AMB
Associação Médica Brasileira

CBHPM

ASSOCIADOS RECEBEM A CBHPM GRATUITAMENTE*

CBHPM 2016 BROCHURA (LIVRO)

NÃO SÓCIO	PESSOA JURÍDICA
R$ 250,00	R$ 400,00

CBHPM 2016 CD (DADOS TABULADOS)

NÃO SÓCIO / PESSOA JURÍDICA

R$ 650,00

*Para associados serão cobrados apenas valores de manuseio e envio: R$ 35,00 para versão impressa e R$ 70,00 para versão digital. Restrição de uma compra por CPF. Para demais aquisições será cobrado o valor de médico não sócio.

Para adquirir e mais informações, consulte nosso site:
amb.org.br/cbhpm

AMB
Associação Médica Brasileira