Prospective experimental single-cohort study:
- Icatibant, an inhibitor of bradykinin receptor 2, for hereditary angioedema attacks

Quantitative cross-sectional study:
- Relationship between lower-limb muscle strength and functional independence among elderly people according to frailty criteria

Retrospective cohort study:
- Natural history and surgical treatment of chordoma: a retrospective analysis on 42 patients treated in a single institution

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DIR. M.F. PAES E ALCANTARA - DIR. MÉDICO - CRM-SP 10223
Editorial
259 Smartphones and health promotion
Alessandro Wasum Mariani, Paulo Manuel Pêgo-Fernandes

Original article
261 Icatibant, an inhibitor of bradykinin receptor 2, for hereditary angioedema attacks: prospective experimental single-cohort study
Regis Albuquerque Campos, Solange Oliveira Rodrigues Valle, Alceu Tavares França, Elisabete Cordeiro, Faradiba Sarquis Serpa, Yara Ferreira Mello, Eliana Toledo, Elie Mansour, Gustavo Fusaro, Anete Sevciovic Grunach

266 Audiometric thresholds and auditory processing in children with early malnutrition: a retrospective cohort study
Patricia Aparecida Zuanetti, Maria Fernanda Laus, Adriana Ribeiro Tavares Anastasio, Sebastião de Sousa Almeida, Marisa Tomoe Hibiha Fukuoka

273 Relationship between birth weight and overweight/obesity among students in Florianópolis, Santa Catarina, Brazil: a retrospective cohort study
Camila Elizandra Rossi, Francisco de Assis Guedes de Vasconcelos

282 Relationship between lower-limb muscle strength and functional independence among elderly people according to frailty criteria: a cross-sectional study
Fernanda Sotello Batista, Grace Angelica de Oliveira Gomes, Maria Jose D’Elboux, Fernanda Aparecida Cintra, Anita Liberaisso Neri, Maria Elena Guariantto, Maria da Luz Rossário de Souza

290 Nebivolol reduces central blood pressure in stage I hypertensive patients: experimental single cohort study
Renan Oliveira Vaz-de-Melo, Luiz Tadeu Girolio-Junior, Débora Duda Martinelli, Heitor Moreno-Junior, Marco António Mota-Gomes, José Paulo Cipullo, Juan Carlos Yugar-Toledo, José Fernando Vilela-Martín

297 Natural history and surgical treatment of chordoma: a retrospective cohort study
Samuel Aguiar Junior, Wesley Pereira Andrade, Glauco Baiocchi, Gustavo Cardoso Guimarães, Isabela Werneck Cunha, Daniel Alvarez Estrada, Sergio Hideki Suzuki, Luiz Paulo Kowalski, Ademar Lopes

303 Leadership, management and teamwork learning through an extra-curricular project for medical students: descriptive study
Maria Lucia da Silva Germano Jorge, Izabel Cristina Meister Coelho, Mariana Martins Paraizo, Ester Fogel Piacornik

Case report
307 Renal autotransplantation to treat renal artery aneurysm: case report
Tercio Genzini, Huda Maria Noujaim, Leonardo Toledo Mota, Luiz Estevam Ianhez, Rodrigo Azevedo de Oliveira, Erica Takako Muramoto Shiroma, Fernando Tawata, Marcelo Perosa de Miranda

311 Comorbidity between Klinefelter syndrome and diaphragmatic hernia. A case report
Carolina Melendez Valdez, Stephan Philip Leonhardt Allmayer, Adyr Eduaro Virmond Faria, Aline Weiss, Jorge Alberto Bianchi Telles, Paulo Renato Krall Feli, Luciano Vieira Targa, Paulo Ricardo Gazzola Zen, Rafael Fabiano Machado Rosa

Cochrane highlights
314 HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis
Comments: Gianna Mastroianni Kirsztajn

316 Perioperative corticosteroids for preventing complications following facial plastic surgery
Edina Mariko Koga da Silva, Bernardo Hochman, Lydia Masako Ferreira
Comments: Rolf Gemperli and Alexandre Mendonça Munhoz

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• One-year subscription for the year 2014: individual US$ 165; institutional US$ 230.
There is no doubt that technological development has made major contributions towards improvement of health worldwide. There are countless examples: diagnostic tools like computed tomography and magnetic resonance imaging, and therapeutic measures like minimally invasive surgery and radiotherapy, among many others. Since both hardware and software are constantly under development, day by day, it can be expected not only that improvements will be made to current devices but also that brand new devices will appear.

In the general field of technology, the market for so-called smartphones is the cutting-edge segment. Use of smartphones or similar devices, like the now-superseded personal digital assistant (PDA) and the recently introduced tablets, as instruments for delivering care is not new. These devices can carry instantly needed information such as pharmaceutical specialty compendiums, emergency books and medical calculators, along with many other medical applications.1 However, this year, some of the main technology companies around the world have turned to a new focus of technology usage to promote health through direct use by patients. New devices and special software applications (frequently called apps) are being created for a myriad of health promotion purposes focusing on patients.2 One of the first of these “mobile health monitoring device initiatives” was the integration of smartphones with the heart rate monitors frequently used by professional and amateur athletes. In the beginning, there was only one application, which gave heart rate information in real time. However, the new devices go further: they can measure distances through integration with GPS, estimate calorie consumption, record the type and intensity of exercise and, ultimately, organize all these data and present them in a simpler form for interpretation.

Other examples of mobile health monitoring devices available on the market that have already been integrated with smartphones include personal sleep monitors, blood glucose monitors and blood pressure cuffs.2 One shared characteristic among these devices is the possibility of recording the information and creating structured ways to interpret it, like graphics and spreadsheets. Another important characteristic that makes the mix of smartphone and personal health monitoring devices so interesting is their internet capability, which opens up a great range of applications, like warnings that can be sent if blood glucose levels are too low.

This industry trend seems to be confirmed by some rumors over the internet that one of the major smartphone companies will include a host of health-tracking features on its next generation smartphones, including “the ability to help users track weight, pulse, blood pressure, hydration and blood glucose levels”.3 In addition, the software could track common parameters like the number of steps taken, quantity of calories burned and distance travelled. These rumors clearly indicate the direction that other companies are likely to follow.

There are few studies measuring the possible impact of these devices on public health. Nonetheless, use of the terms mobile and health monitors has been increasing over the years in the PubMed database. This trend probably demonstrates medical researchers’ interest in this emerging field located between technology for consumer use and medical science. One example of this is a meta-analysis on mobile devices and physical activity behavior that has been published. The authors concluded that research using mobile devices is gaining in popularity, and suggested that this platform is an effective means for influencing physical activity behavior.4
Another expected impact is better self-control among patients in relation to chronic conditions such as diabetes or hypertension, guided by mobile health monitoring devices. However, there are no definitive studies on this subject.

In conclusion, a flood of new mobile devices directed towards personal healthcare can be expected. In particular, these will integrate existing devices like blood glucose monitors and heart rate monitors with smartphones, using mobile phone internet connection capability to its fullest extent. The real impact of this commercial and technological trend will only become fully understood over the years to come.

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Sources of funding: None
Conflict of interest: None

Date of first submission: July 15, 2014
Last received: July 15, 2014
Accepted: July 29, 2014

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Icatibant, an inhibitor of bradykinin receptor 2, for hereditary angioedema attacks: prospective experimental single-cohort study

Icatibanto, um inibidor de receptor 2 de bradicinina, para ataques de angioedema hereditário: estudo experimental prospectivo de coorte sem grupo controle

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ABSTRACT

CONTEXT AND OBJECTIVE: Hereditary angioedema (HAE) with C1 inhibitor deficiency manifests as recurrent episodes of edema involving the skin, upper respiratory tract and gastrointestinal tract. It can be lethal due to asphyxia. The aim here was to evaluate the response to therapy for these attacks using icatibant, an inhibitor of the bradykinin receptor, which was recently introduced into Brazil.

DESIGN AND SETTING: Prospective experimental single-cohort study on the efficacy and safety of icatibant for HAE patients.

METHODS: Patients with a confirmed HAE diagnosis were enrolled according to symptoms and regardless of the time since onset of the attack. Icatibant was administered in accordance with the protocol that has been approved in Brazil. Symptom severity was assessed continuously and adverse events were monitored.

RESULTS: 24 attacks in 20 HAE patients were treated (female/male 19:1; 19-55 years; median 29 years of age). The symptoms were: subcutaneous edema (22/24); abdominal pain (15/24); and upper airway obstruction (10/24). The time taken until onset of relief was: 5-10 minutes (5/24; 20.8%); 10-20 (5/24; 20.8%); 20-30 (8/24; 33.4%); 30-60 (5/24; 20.8%); and 2 hours (1/24; 4.3%). The time taken for complete resolution of symptoms ranged from 4.3 to 33.4 hours. Adverse effects were only reported at injection sites. Mild to moderate erythema and/or feelings of burning were reported by 15/24 patients, itching by 3 and no adverse effects in 6.

CONCLUSION: HAE type I patients who received icatibant responded promptly; most achieved improved symptom severity within 30 minutes. Local adverse events occurred in 75% of the patients.

RESUMO

CONTEXTO E OBJETIVO: O angioedema hereditário (AEH) com deficiência de inibidor de C1 manifesta-se por episódios recorrentes de edema envolvendo pele, trato respiratório superior e gastrointestinal. Pode ser letal devido à asfixia. O objetivo foi avaliar a resposta à terapia para esses ataques com icatibanto, inibidor do receptor de bradicinina, recentemente introduzido no Brasil.

TIPO DE ESTUDO E LOCAL: Estudo experimental prospectivo de coorte, sem grupo controle, da eficácia e segurança do icatibanto em paciente com AEH.

MÉTODOS: Pacientes com diagnóstico confirmado de AEH foram incluídos de acordo com os sintomas, independentemente do tempo de início do ataque. Icatibanto foi administrado segundo protocolo aprovado no Brasil. A gravidade do sintoma foi estabelecida continuamente e os eventos adversos foram monitorados.

RESULTADOS: 24 ataques em 20 pacientes com AEH foram tratados (19 F:1 M; 19-55 anos; mediana 29 anos). Os sintomas foram: edema subcutâneo (22/24); dor abdominal (15/24) e obstrução de vias aéreas superiores (10/24). O tempo para o início do alívio foi: 5-10 minutos, 5/24 (20,8%); 10-20, 5/24 (20,8%); 20-30, 8/24 (33,4%); 30-60, 5/24 (20,8%) e 2 horas, 1/24 (4,3%). O tempo para a resolução completa variou de 4,3 a 33,4 horas. Somente efeitos adversos nos locais das injeções foram relatados. Eritema leve a moderado e/o sensação de ardor foram relatados em 15/24 pacientes, prurido em 3 e não houve efeitos adversos.

CONCLUSÃO: Pacientes com AEH tipo I receberam icatibanto com pronta resposta; a maioria teve melhora na gravidade dos sintomas em 30 minutos. Eventos adversos locais ocorreram em 75% dos pacientes.
INTRODUCTION
Hereditary angioedema (HAE) with C1 inhibitor (C1-INH) deficiency is a rare disease that manifests as recurrent episodes of subcutaneous edema, most commonly involving the skin, upper respiratory tract, oropharynx and gastrointestinal tract. Two forms of HAE have been described: type I HAE with low C1-INH antigenic protein and functional activity (85% of the cases); and type II HAE with normal or elevated protein but low C1-INH function (15% of the cases). The disease is disabling and can be lethal. No official data exists concerning complications and deaths due to asphyxia among Brazilian HAE patients, but these outcomes have been registered by the Brazilian Association of HAE Patients (ABRANGHE) over recent years (personal communication).

The pathogenesis of edema attacks due to HAE remains elusive. In several reports, bradykinin was found to mediate swelling. Its plasma levels increased during attacks and mice that were deficient in both C1-INH and the bradykinin receptor 2 (BR-2) gene showed diminished vascular permeability, thus confirming the previous evidence. Considering the importance of bradykinin binding and activation of BR-2 in angioedema formation in HAE patients, it would be possible for acute attacks to be treated with the BR-2 antagonist, icatibant.

Effective management of HAE targets either prevention or treatment of attacks. Drugs for both approaches have been available since the late 1970s, but not uniformly registered. In Brazil, until icatibant was approved recently, fresh frozen plasma was the only available therapy for acute HAE attacks.

OBJECTIVE
The aim of this study was to describe the clinical response of HAE patients to therapy for HAE attacks using icatibant, an inhibitor of the bradykinin receptor, and the possible side effects. This was the first report on the use of this new drug in a real-life setting.

METHODS
We conducted a prospective experimental single-cohort study on 20 patients who were treated using icatibant. In order to be eligible for treatment in accordance with the Brazilian approval, adult patients needed to have a documented diagnosis of hereditary angioedema (including a low C4 level, a normal C1q level and a low antigenic or functional C1 inhibitor level) and to have a well-documented history at outpatient clinics, as stipulated in the Brazilian guidelines. The exclusion criteria for treatment were other differential diagnoses of HAE (drugs such as hormones and angiotensin converser enzyme (ACE) inhibitors), pregnancy and age greater than 65 years. Subjects were not required to change any of their regular medications, including androgens or antifibrinolytic drugs. Icatibant was administered during an attack of moderate or severe intensity, involving the abdomen, face or external genitalia, with symptoms of upper airway obstruction such as a change in voice tone and difficulty in swallowing, regardless of the time that had elapsed since the onset of symptoms. The severity of the attacks was established in accordance with Giavina-Bianchi et al. and Bowen et al. One syringe (30 mg) of icatibant was slowly administered subcutaneously in the abdominal wall. Brazilian legislation also stipulates that a second injection of the same drug could be administered if necessary, six hours after the first administration.

Prior to icatibant administration, all participants were informed about its effects and potential adverse reactions and gave their consent to treatment. Self-administration is not allowed, according to Brazilian legislation; therefore, all injections were administered under medical supervision, as established by the Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, ANVISA), with access to medical emergency facilities.

The physicians and the patients were asked to describe the symptoms at each site affected (extremities, throat, abdomen, face and external genitalia). Symptom severity was assessed continuously until the subject reported achieving relief. The patients were allowed to leave the hospital facilities after improvement, but were subsequently contacted to confirm that complete resolution of symptoms had occurred. Safety was evaluated by assessing adverse events, changes in physical findings and vital signs before and after the injection.

RESULTS
From August 2011 to February 2012, 24 attacks were treated using icatibant, in 20 HAE type 1 patients (19 females and one male). One patient was treated four times and another, twice, in different attacks. The median age at the initial appearance of HAE symptoms was 5 years old (range 1-28 years), with median age at diagnosis of 23 years (range 5-54 years). The youngest patient treated with icatibant was 19 years old and the oldest, 55 years old (median 29 years) (Figure 1).

The following involvement was observed during the attacks: subcutaneous edema (22/24); gastrointestinal pain (16/24); upper airway obstruction (12/24), reported as changes in voice tone and swallowing difficulty; and laryngeal edema (2/24) (Figure 2). Facial edema was observed in 16/24 and in nine cases was also associated with abdominal pain. Gastrointestinal pain alone was present in 1/24 patients only. In 18 patients, the HAE attack was classified as severe and in six as moderate. At the time of the treatment for the HAE attack, fifteen patients were taking androgen prophylaxis (4/15 using oxandrolone and 11/15 using danazol), one patient was being treated with antifibrinolytics and eight patients were not undergoing any specific therapy.
Administration of icatibant was started at an average of 6.3 hours (median = 6 hours; range 2-12 hours) after the onset of symptoms. The estimated time taken for relief to begin after the injection was: 5-10 minutes (5/24; 20.8%); 10-20 (5/24; 20.8%); 20-30 (8/24; 33.4%); 30-60 (5/24; 20.8%); and two hours (1/24; 4.3%) (Figure 3). The upper airway obstruction improved first, followed by the abdominal pain, whereas the skin swelling took a longer time to resolve. The time taken to achieve complete resolution of symptoms was variable, from 4.3 to 33.4 hours. None of the patients required more than one injection for the same episode; however, two patients presented recurrence within 24 hours but with no medical intervention, and spontaneous regression occurred. Mild to moderate erythema and/or feelings of burning were reported in the cases of 15/24 applications; itching was described after injections in 3 cases; and 6 treatments had no adverse effect. The patient who was treated for four different attacks showed a good clinical response in each instance, and the time from treatment to the resolution of symptoms remained constant.

**DISCUSSION**

In this study, we reported on treatment using icatibant during 24 episodes of acute swellings in HAE type I patients in a real-life setting in Brazil. All the patients showed good clinical responses to this treatment and most of them reported clinical relief even before any change was observed in cutaneous swelling. The initial onset of relief was earlier for upper airway obstruction symptoms. Subcutaneous edema was the clinical manifestation that persisted the longest. Most of the patients showed an improvement in respiratory and gastrointestinal symptoms within 30 minutes following the injection. Importantly, total regression of the complaints occurred within 24 hours (median), in comparison with attacks in which there was no specific drug therapy, which lasted three to five days, as previously reported.8,9

Evaluation of icatibant was performed in three controlled trials: FAST-1, FAST-2 and FAST-3. In the FAST-1 trial, statistical significance between the drug and placebo regarding the time taken to achieve symptom relief was not found, although the patients receiving icatibant reported the first endpoint improvement after 2.5 hours and those with the placebo, after 4.6 hours. The analysis parameters used in this trial and the time taken for the treatment to be introduced probably influenced the results.8,10 In the second study, the efficacy of icatibant was compared with tranexamic acid and a significant reduction in symptoms was observed (2.0 hours versus 12.0 hours). FAST-3, which was a randomized placebo-controlled study, demonstrated that icatibant was effective in treating HAE attacks in adults (88 subjects; 43 with icatibant and 45 with placebo).10
In our series of patients, the upper airway obstruction symptoms were the first to resolve. Greve et al. found the same results after reporting on administration of icatibant in 141 attacks in a single patient.\textsuperscript{11} During the FAST studies, most of the laryngeal attacks were treated as an open-label phase and the median time taken to achieve relief was longer than one hour.\textsuperscript{8,10} The discrepancy between the findings from those studies and our results may be due to the different analysis parameters used in those studies. The quick response may have been associated with anatomical issues in the upper airways, in which even a small amount of edema can lead to significant clinical repercussions. Also, this observation points to the importance of mediation of this symptom through bradykinin binding to B2 receptors, which is a leading cause of death in HAE patients.

Icatibant is approved in Brazil for use under medical supervision only, i.e. patients are not allowed to inject themselves. This resulted in a delay in the therapy with a median elapsed time of 6 hours until application, and a maximum of 12 hours. However, this did not influence the efficacy of the therapy, since our patients who received therapy more than 10 hours after the attack started achieved improvement within the same length of time as shown by those who had early access to medical assistance, as has previously been reported.\textsuperscript{12} Development of home treatment strategies for patients with HAE is an important step towards improving the management of this debilitating condition, which would lead to a better response and, consequently, better quality of life.\textsuperscript{12,13} Approval for self-administration is under analysis by the Brazilian authorities.

The attack was classified as severe in approximately 60\% of the patients studied (14/24), and suggestive clinical manifestations associated with laryngeal edema were the indication for icatibant use in 50\% of the situations in our report. The patients reported that voice changes and facial edema were the sensations that preceded airway obstruction. Although no official classification of severity is available, the Brazilian guidelines was used for therapy indication.\textsuperscript{1} Therefore, the severity of the disease may explain some of the delays in achieving complete improvement that were seen in some individuals in this subgroup of patients. However, patients could choose to have even mild attacks of HAE treated, if the therapy was available. In addition, combination of preventive and on-demand therapy with reduction of the androgen dose and treatment of breakthrough attacks using C1 inhibitor or icatibant has been proposed.\textsuperscript{14,15} Such observations are limited by the type of study developed, with no control group.

Two patients who received icatibant more than once did not observe any reduction in the efficacy of the therapy and did not present any increase in adverse events. Greve et al. reported that icatibant was used 141 times in one patient without any loss of efficacy.\textsuperscript{11} There were no adverse events in one third of our cases and the complaints reported consisted of local burning, hyperemia and mild itching. These symptoms were self-limited and related to local release of histamine induced by subcutaneous injection of icatibant, a development that may be attenuated by H1-antihistamines.\textsuperscript{16}

Sixty percent (12/20) of the patients who received icatibant were undergoing prophylactic treatment with androgens. In fact, the approved therapy for HAE within the public healthcare system in Brazil only includes danazol. It has been estimated that about 25\% and 50\% of the HAE patients in Switzerland and Austria, respectively, receive long-term therapy with androgens, with variable indications.\textsuperscript{13} Long-term prophylaxis with attenuated androgens is effective in many patients, but side effects such as virilization in females, weight gain and other factors result in restrictions on their use. It is possible that restricted access to therapy probably leads physicians to introduce prolonged use of drugs as well as higher androgen doses in HAE patients.

Brazil was the only South American country with access to icatibant at the time of reporting this experience. The health authorities in Colombia and Argentina have approved icatibant, but the drug is not available yet.\textsuperscript{17} Regarding diagnosis and therapy of HAE in Latin America, we are at the forefront of a process that is just beginning,\textsuperscript{18} except in Argentina, where the first reports were published almost 30 years ago and plasma-derived C1 inhibitor is available.\textsuperscript{17} Icatibant was launched three years ago in Brazil and the use of this drug is not financially supported by the government, although some health insurance companies reimburse its use on demand.

Most of the patients (65\%) reported their first symptoms when they were five years old; only four of them presented after adolescence. The median age for diagnosis was 23 years, thus suggesting that there is a delay in identifying HAE patients. One patient was 55 years old by the time that the disease was recognized, but its symptoms first presented when she was 15 years old; her case is a testament to how restricted knowledge about HAE is. If we consider the fact that there is almost no registration of cases in other Latin American countries, it becomes obvious that many opportunities to treat HAE patients have been lost. Gastrointestinal complaints were reported by 62.5\% of our patients and were not associated with facial edema in 21\% of the cases treated in our experience.

Marqués et al. reported that one potential future use for icatibant would be for short-term prophylactic HAE treatment, and they reported on its use for a patient with previous severe attacks during some procedures.\textsuperscript{19} The patients who may benefit from switching to on-demand therapy, or from combining preventive and on-demand therapy, include women, children and adolescents, as well as patients with various risk factors for androgens such as organ toxicity, cardiovascular disease or possible drug interactions.\textsuperscript{20} Use of icatibant has been restricted for patients under 18 years of age and for patients with cardiac diseases.\textsuperscript{21}
Medication cost is a major concern for both patients and physicians. The US Hereditary Angioedema Association has estimated that hospital stays and emergency department visits during acute attacks comprise 68% of the cost of a severe attack. As understanding of HAE physiopathology and management improves, decisions regarding continuous or on-demand therapy should become easier, and studies evaluating pharmacoeconomics will certainly help.

CONCLUSIONS
The HAE type I patients who received icatibant responded promptly; most of them achieved improved symptom severity within 30 minutes. Mild local adverse events were reported in 75% of the patients. The introduction of this new drug has opened up new perspectives for HAE patients regarding therapies for attacks.

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Sources of funding: None
Conflict of interest: None

Date of first submission: January 4, 2013
Last received: September 19, 2013
Accepted: September 25, 2013

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Audiometric thresholds and auditory processing in children with early malnutrition: a retrospective cohort study

Límiar audiométricos e processamento auditivo em crianças com subnutrição precoce: um estudo retrospectivo de coorte

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ABSTRACT

CONTEXT AND OBJECTIVE: Malnutrition is one of the causes of changes in cell metabolism. The inner ear has few energy reserves and high metabolism. The aim of this study was to analyze whether malnutrition at an early age is related to impairment of auditory processing abilities and hearing abnormalities.

DESIGN AND SETTING: Retrospective cohort study conducted in a tertiary public hospital.

METHODS: 45 children participated, divided as follows: G1, children diagnosed with malnutrition in their first two years of life; G2, children without history of malnutrition but with learning difficulties; G3, children without history of malnutrition and without learning difficulties. Tympanometry, pure-tone audiometry and the Staggered Spondaic Word (SSW) test (auditory processing) were performed. Statistical inferences were made using the Kruskal-Wallis (α = 5%) and the test of equality of proportions between two samples (α = 1.7%).

RESULTS: None of the 45 children participating in this study presented hearing deficiencies. However, at six of the eight frequencies analyzed, the children in G1 presented hearing thresholds lower than those of the other groups. In the auditory processing evaluation test, it was observed that 100% of the children in G1 presented abnormal auditory processing, and that G1 and G2 had similar proportions of abnormalities (P-values: G1/G2 = 0.1; G1/G3 > 0.001; G2/G3 = 0.008).

CONCLUSIONS: Malnutrition at an early age caused lowering of the hearing levels, although this impairment could not be considered to be a hearing deficiency. Every child in this group presented abnormalities in auditory processing abilities.


INTRODUCTION
The first years of life are considered to be the most important ones for the development of hearing and language skills. Rapid brain growth occurs from the second trimester of gestation to the second year of life, together with accelerated neurogenesis, gliogenesis, neuronal migration and myelination processes. Thus, in order to prevent impairment of the auditory pathways or of other skills relating to language during this period, the child must be exposed to appropriate stimulation. Moreover, no type of intercurrence should occur, since these events may often lead to irreversible cognitive damage at a later time.

In this respect, malnutrition may play an important role, since although its relationship with hearing changes has been little explored at either the peripheral or the central level, it may interfere with the metabolism of the inner ear, thus causing hearing loss. Malnutrition is characterized as a lack of nutrients that are necessary for the physiological metabolism of the organism (chemical reactions that occur in the cells of the body), due to energy expenditure that is greater than the ingested energy. The damage caused by malnutrition to the growth and development of the organism depends on the type of malnutrition, the duration of this disease, its severity and other aggravating factors such as infections and genetic factors, in addition to the individual’s age at the time of onset of this condition.

Studies investigating the interference of malnutrition with the development of the auditory pathways have used brainstem auditory evoked potential (BAEP) as an evaluation instrument. Such studies have observed that malnutrition causes delayed maturation of the auditory pathways, as represented by elevated absolute and interpeak latencies. The set of auditory skills on which individuals depend in order to interpret what they hear (skills such as sound localization, auditory discrimination, recognition of time patterns, temporal resolution, temporal integration and organization) is defined as auditory processing and involves central structures ranging from the cochlear nuclei to areas of the cortex. Children with a history of middle ear abnormalities or some type of hearing deficiency, and those who have been diagnosed as presenting abnormalities of auditory processing are at risk of presenting difficulties with oral and written language.

There is evidence that malnutrition has an effect on peripheral and central hearing and on the development of auditory pathways. Furthermore, integrity of the auditory system is important for the development of oral and written language. However, in both the Brazilian and the worldwide literature, there are only a few studies on how malnutrition affects the peripheral and central auditory system. Nonetheless, this subject is very important in relation to the development of children’s language, and detailed study on the relationship between malnutrition and the auditory system is needed, using other evaluation methods.

OBJECTIVE
To analyze whether malnutrition at an early age is related to damage to auditory processing skills and to changes in hearing thresholds.

METHODS
Ethical issues
The study was approved by our institution’s Research Ethics Committee, under protocol number 1924/2009.

Study design and sample selection
This was a retrospective cohort study carried out at a tertiary-level public hospital. The participants were 45 children (21 girls and 24 boys) aged 7 to 10 years (mean ± SD: 8.2 ± 0.7) divided into three groups: G1 (n = 15), consisting of children with a history of malnutrition at an early age; G2 (n = 15), consisting of children without any history of malnutrition and with learning difficulties; and G3 (n = 15) consisting of children with no history of malnutrition and no learning difficulties. The children in the three groups were matched according to the variables of age and type of school institution in the proportions of 1:1:1, in which G1 children were considered to be the reference category.

The exclusion criteria for all three groups were as follows: not attending school regularly; presence of syndromes that impaired cognitive function; no type A tympanometric curve on the day of the audiological examination; conductive or mixed hearing loss, taking into consideration frequencies from 500 to 4000 Hz; and presence of primary neurological abnormalities due to malnutrition for G1 or a history of malnutrition or altered nutritional status on the date of the evaluation for G2 and G3.

The inclusion criteria for G1 were as follows: a diagnosis of moderate or severe malnutrition during the first two years of life (diagnosed by the medical team of the hospital and described in the subjects’ medical records); and a history of nutritional rehabilitation after malnutrition, regardless of current nutritional status.

Sample selection and characterization
To select the G1 subjects, we analyzed 548 medical records at Hospital das Clínicas (HC), Faculdade de Medicina de Ribeirão Preto (FMRP), of children who had spent some time hospitalized during their two first years of life with a diagnosis of malnutrition. Only 79 children fulfilled the inclusion and exclusion criteria of the study and only 15 came for evaluation. The following data in the medical records were analyzed: date of the medical diagnosis of malnutrition; anthropometric data obtained at the time of diagnosis; child’s age at the time of diagnosis; degree of malnutrition at the time of diagnosis; and time elapsed between...
the diagnosis of malnutrition and the diagnosis of eutrophy or of no remaining evidence of malnutrition.

The School Performance Test was used to assess the school performance of students regularly enrolled in the public elementary school network, in order to form G2 and G3. These students were selected at random for evaluation in the reading, writing and arithmetic tests of the SPT.

The three groups underwent anamnesis consisting of questions about the children’s development and medical history. Their nutritional status was also evaluated, for which the following anthropometric measurements were used: Weight (W): body weight, in kg, was measured by means of a Bal-Isopa TecLine digital scale with 0.1 kg resolution. This procedure was performed in the morning under fasting conditions, with each subject wearing light clothing, barefoot and having voided his/her bladder. Height (H): the subjects stood up in an erect position with their head in the vertical plane, barefoot and with their feet close together, and supporting their back, buttocks and heels against the wall, on which a mark was made and the value in cm was measured with a metric tape with 1 cm graduations.

The Z-score for weight/age (W/A) was used for diagnosing the previous nutritional status of G1 children and the Z-score for body mass index (BMI)/age (BMI/A) was used for the current anthropometric evaluation of all children (G1 and G2). A Z-score of less than -2 was taken to demonstrate malnutrition. A professional nutritionist calculated and analyzed the indicators using the Epi Info software.

Peripheral and central auditory assessment

All the children underwent audiological assessment, which consisted of the procedures listed below.

Tonal threshold audiometry

The Midimate 622 instrument (Madsen Electronics) was used for this procedure. Tonal threshold audiometry consisted of detection of thresholds by means of the air route (frequencies of 250 to 8000 Hz) and the bone route (frequencies of 500 to 4000 Hz), when necessary. The technique used was sound-to-silence, and the threshold was considered to be the lowest intensity at which the child responded 50% of the times to the presence of sound. To classify the degree, we used the mean tonal thresholds per earway at the frequencies of 500 to 2000 Hz and the value proposed by Northern and Downs for children (mean frequency: normal, up to 15 dB; discrete loss, 16 to 25 dB; mild loss, 26 to 40 dB; moderate loss, 41 to 70 dB; severe loss, 71 to 90 dB; profound loss, more than 91 dB). Since all the children had symmetrical hearing between their ears, as confirmed by the Student t test for paired samples (significance level of 0.05), a single numerical value was used for each frequency evaluated (mean of the values obtained at that frequency for each ear).

Tympanometry

A Zodiac 901 tympanometer (Madsen Electronics) was used to assess the condition of the middle ear. In the present study, the tympanometric curve was only used for exclusion purposes. Children with type As, Ad, B or C curves on the day of the audiological examination were excluded.

Staggered Spondaic Word Test (SSW)

We used the Midimate 622 instrument (Madsen Electronics) and band 6 of the volume 2 CD of the Manual of Auditory Processing Assessment, placed in a Discman Panasonic SL-SV590W CD player with an adaptor cable for output to an audiometer. This test assesses the auditory skills of auditory memory, figure-fundus, binaural integration and auditory closure. For application to the Brazilian population, Katz’s SSW test was adapted by Borges, Rejtaman and Schneider under supervision by Katz, in accordance with the basic assumptions of the test, with the same application and analysis. The test was applied at an intensity of 50 dBNS and consisted of presentation of 40 sequences of four words recorded on a CD. All of these words were paroxytone, i.e. the stress was on the penultimate syllable. The presentation of the sequence of words sometimes started with the right ear and at other times with the left ear. Two of these words (second syllable of the second word and first syllable of the third word) were presented simultaneously to the two ears (competitive condition), with partial superimposition. The individual was supposed to repeat the sequence of four words in the order presented. The analysis conducted was both quantitative and qualitative. In the present study, we followed the analysis proposed by the authors of the test adapted to the Portuguese language (analysis of the competitive conditions, auditory effect, order effect, type A effect and inversions).

Statistical analysis

Descriptive statistical methods were used to characterize the sample. The Kruskal-Wallis test was applied to assess possible differences in audiometric threshold values and in the number of correct responses, under the condition of competitive listening in the SSW test between the three groups (G1, G2 and G3), with the significance level set at 5%. When the null hypothesis was rejected (P-value < 0.05), a post-test was applied in order to determine where the difference was located. This was the Kruskal-Wallis multiple comparisons post-test, which defined the points between which there was a difference among the groups. The test of equality of proportions between two samples was used in order to analyze the variables of effect of order, hearing effect, inversions, type A response and presence/absence of altered auditory processing between the three groups, and to compare some variables relating to the children’s medical histories between the groups. Since this test compares two groups at a time (test of equality of proportions
between two samples), and since three groups were present, the significance level was reduced based on the formula \( \alpha/\text{number of tests} \), and was set at 1.7% (\( \alpha = 0.05 \); number of groups = 3; new significance level = 0.05/3 = 0.017) for this test.

**RESULTS**

Table 1 presents the data regarding the children's medical histories, such as prematurity and whether the child was small for gestational age or had a history of repeated otitis or delayed speech development. There was no difference between the groups, thus demonstrating that the groups were similar in these regards.

Table 2 presents the data on assessment of nutritional status for G1 at the time of diagnosis of malnutrition. The degree of malnutrition, demonstrated by the W/A Z-score, was quite variable (-2.26 to -43.15). The duration of malnutrition ranged from less than one month up to one year and five months of age, thus demonstrating that this group consisted of children with a history of acute or chronic malnutrition.

**Table 1. Data regarding the children's medical histories**

<table>
<thead>
<tr>
<th></th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>P-value ( (G1 \times G2) )</th>
<th>P-value ( (G1 \times G3) )</th>
<th>P-value ( (G2 \times G3) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>46%</td>
<td>7%</td>
<td>13%</td>
<td>0.018</td>
<td>0.04</td>
<td>0.5</td>
</tr>
<tr>
<td>Small for gestational age (SGA)</td>
<td>20%</td>
<td>13%</td>
<td>13%</td>
<td>0.6</td>
<td>0.06</td>
<td>0.1</td>
</tr>
<tr>
<td>History of repeated otitis</td>
<td>26%</td>
<td>40%</td>
<td>46%</td>
<td>0.4</td>
<td>0.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Delayed speech development</td>
<td>26%</td>
<td>0%</td>
<td>0%</td>
<td>0.03</td>
<td>0.03</td>
<td>1</td>
</tr>
</tbody>
</table>

Test of equality of proportions between two samples: \( \alpha = 0.017 \);
G1 = children diagnosed with malnutrition in their first two years of life; G2 = children without history of malnutrition but with learning difficulties; G3 = children without history of malnutrition and without learning difficulties.

**Figure 1. Data on current nutritional status according to the Z-score body mass index (BMI) for each group (G1, G2 and G3).**

**Figure 2. Mean hearing threshold values (Kruskal-Wallis; \( \alpha = 0.05 \)) for each group (G1, G2 and G3).**
It can be seen that the G1 and G2 children had larger numbers of inversions and, at the end of the SSW tests, all the G1 children were classified as presenting altered processing of some auditory skills. A similar proportion of abnormalities was detected in G2. The results from statistical analyses on the groups in the SSW test are listed in Tables 4 and 5.

**DISCUSSION**

The results from the present study demonstrate that malnutrition may not be the cause of a large proportion of occurrences of otitis media, but may have a negative effect on the hearing of these children, affecting both the structures of the inner ear and the pathways involved in sound processing.

**Table 3. Data obtained from the statistical test on hearing threshold**

<table>
<thead>
<tr>
<th></th>
<th>Mean values</th>
<th>P-value</th>
<th>Post-test results</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 Hz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>19.1</td>
<td>0.03</td>
<td>G1 ≠ G2</td>
</tr>
<tr>
<td>G2</td>
<td>13.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>14.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 Hz</td>
<td></td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>15.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>12.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>12.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000 Hz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>5.2</td>
<td>0.03</td>
<td>G1 ≠ G2</td>
</tr>
<tr>
<td>G3</td>
<td>7.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000 Hz</td>
<td></td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3000 Hz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>9.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>3.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4000 Hz</td>
<td></td>
<td>0.4</td>
<td>G1 ≠ G2</td>
</tr>
<tr>
<td>G1</td>
<td>11.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>5.7</td>
<td></td>
<td>G1 ≠ G3</td>
</tr>
<tr>
<td>G3</td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6000 Hz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>18.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>14.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8000 Hz</td>
<td></td>
<td>0.007</td>
<td>G1 ≠ G2</td>
</tr>
<tr>
<td>G1</td>
<td>20.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>10.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>12.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kruskal-Wallis test: α = 0.05; G1 = children diagnosed with malnutrition in their first two years of life; G2 = children without history of malnutrition but with learning difficulties; G3 = children without history of malnutrition and without learning difficulties.

**Table 4. Staggered Spondaic Word (SSW) test results for quantitative variables**

<table>
<thead>
<tr>
<th></th>
<th>Mean score</th>
<th>P-value</th>
<th>Post-hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Competitive right</td>
<td>G1 = 64.5%</td>
<td>&gt; 0.001</td>
<td>G1 ≠ G3</td>
</tr>
<tr>
<td></td>
<td>G2 = 71.8%</td>
<td></td>
<td>G2 ≠ G3</td>
</tr>
<tr>
<td></td>
<td>G3 = 83.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Competitive left</td>
<td>G1 = 57.8%</td>
<td>&gt; 0.001</td>
<td>G1 ≠ G3</td>
</tr>
<tr>
<td></td>
<td>G2 = 68.1%</td>
<td></td>
<td>G2 ≠ G3</td>
</tr>
<tr>
<td></td>
<td>G3 = 80.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kruskal-Wallis test: α = 0.05; G1 = children diagnosed with malnutrition in their first two years of life; G2 = children without history of malnutrition but with learning difficulties; G3 = children without history of malnutrition and without learning difficulties.

**Figure 3. Mean values for each group (G1, G2 and G3) in the Staggered Spondaic Word (SSW) test in the situation of competitive listening.**

**Table 5. Staggered Spondaic Word (SSW) test results for qualitative variables**

<table>
<thead>
<tr>
<th></th>
<th>Dyad analyzed</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Order effect</td>
<td>G1 x G2</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>G2 x G3</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>G1 x G3</td>
<td>0.1</td>
</tr>
<tr>
<td>Auditory effect</td>
<td>G1 x G2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>G2 x G3</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>G1 x G3</td>
<td>0.6</td>
</tr>
<tr>
<td>Response type A</td>
<td>G1 x G2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>G2 x G3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>G1 x G3</td>
<td>1</td>
</tr>
<tr>
<td>Inversions</td>
<td>G1 x G2</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>G2 x G3</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>G1 x G3</td>
<td>0.005</td>
</tr>
<tr>
<td>Auditory processing disorder (SSW classification)</td>
<td>G1 x G2</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>G2 x G3</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>G1 x G3</td>
<td>&gt; 0.001</td>
</tr>
</tbody>
</table>

Comparison test for proportions between two samples: α = 0.017; G1 = children diagnosed with malnutrition in their first two years of life; G2 = children without history of malnutrition but with learning difficulties; G3 = children without history of malnutrition and without learning difficulties.

**Figure 4. Data from evaluation of the qualitative aspects of Staggered Spondaic Word (SSW) test in each group (G1, G2 and G3).**
Although all the G1 children were classified as having audition within normal patterns, this group presented reduced auditory thresholds, compared with the other groups, and an inverted U-shaped audiometric curve. It is important to note that at the time of the evaluation, the children in group G1 had an appropriate nutritional status (except for three who had returned to a state of malnutrition), did not have any damage to the inner ear and presented the same clinical conditions as the other children. This result suggests that malnutrition altered the functioning of the inner ear and caused lasting damage, since 12 of the 15 children in G1 had presented malnutrition only during a single period of life, before reaching two years of age.

One possible explanation for this finding is that the homeostasis of the inner ear is highly susceptible to various adverse conditions, particularly those of a nutritional nature. The metabolism of the inner ear is greatly dependent on glucose and oxygen and is intensely active, especially at the level of the vascular stria. However, this organ is practically devoid of energy reserves. Thus, alterations of blood metabolites or lack of proteins, minerals and calories, even in an acute manner, may impair the normal functioning of the inner ear, with negative consequences for the auditory system. The physiological change caused by malnutrition in the inner ear is also suggested by the type of audiometric configuration detected in G1. The inverted “U” curve is only detected in cases of metabolic alterations.

To describe in detail the changes that occur in the inner ear is a complex task that is often only barely possible because of the difficulty of access for histological evaluation, especially in humans. Thus, it is quite difficult to determine in a precise manner what is affected in the inner ear by malnutrition.

Regarding sound processing, 100% of the G1 children showed alterations in the SSW test. Friederici reported that the first two years of life are the critical period for development of hearing skills and that development of these skills depends on brain development, which is also at its critical period during this phase. Magalhães et al. reported that malnourished babies are at risk of developing altered auditory processing, which was confirmed in the present study. These authors observed that malnourished babies showed abnormalities regarding sound location at the age of 12 months.

Sound location is one of the first auditory processing skills that can be measured, and this skill is affected by maturational delay. Neuron. 2006;52(6):941-52. Delayed development of this hearing skill suggests that there is a delay in the maturation of the auditory pathways. On this basis, all babies that show this alteration should be monitored in relation to hearing and language, and should undergo a stimulation process when necessary.

Less than 10% of the children included in this study had undergone audiological examination at the time when malnutrition occurred, and therefore it was not possible to determine whether these children already demonstrated abnormalities of auditory skills when they were less than two years old. This result also demonstrates a lack of awareness among health professionals regarding the damage caused to the auditory system by malnutrition, over the short and long terms. Delayed maturation of the auditory pathways, which is one of the causes of auditory processing disorders, was also reported by Odabas et al. and Vandana and Tandon in BAEP performed on malnourished children.

Lastly, the relationship between the audiometric threshold and auditory processing needs to be discussed. In the present study, it was observed that the children with worse audiometric thresholds were not necessarily the only ones who developed altered auditory processing, given that G2 children with a high incidence of altered auditory processing, along with G1 children, had audiometric thresholds similar to those of G3. This result suggests that the development of auditory skills involves various factors and not simply fluctuating hearing possibly caused by a history of otitis or lower audiometric thresholds. The maturation of auditory processing skills, especially the more complex ones such as those of figure-ground and binaural fusion, and others, depends on development of other cognitive skills such as working memory.

During this study, we tried to control for several variables such as socioeconomic level (all the children were from public schools), age, absence of speech stimulation and absence of abnormalities in the inner ear. However, several sources of bias were present, such as the small sample size and the fact that the G1 children had spent time hospitalized during their two first years of life, which may have hampered their initial stimulation and social interaction.

CONCLUSION

The present findings suggest that malnutrition during the first year of life is a factor involved in a reduction in the audiometric thresholds, even though this does not characterize hearing loss. In the analysis on auditory processing, every child in this group also presented abnormalities of auditory processing abilities.

REFERENCES

Relationship between birth weight and overweight/obesity among students in Florianópolis, Santa Catarina, Brazil: a retrospective cohort study

Relação entre peso ao nascer e sobrepeso/obesidade em estudantes de Florianópolis, Santa Catarina, Brasil: estudo de coorte retrospectivo

Camila Elizandra Rossi1, Francisco de Assis Guedes de Vasconcelos2

Universidade Federal de Santa Catarina (UFSC), Florianópolis, Santa Catarina, Brazil

ABSTRACT

CONTEXT AND OBJECTIVE: Being born heavier than 4 kg is associated with current overweight and obesity over the long term. The objective here was to ascertain whether birth weight was related to overweight or obese status, among 7 to 14-year-old schoolchildren, taking into consideration the possible interactions between socioeconomic factors and other biological variables.

DESIGN AND SETTING: Retrospective cohort study on a probabilistic sample of 2,696 children and adolescents living in Florianópolis, Santa Catarina, Brazil.

METHODS: The following data were collected: anthropometric (student’s weight, height and age; and parents’ weight and height), socioeconomic (family income, number of people in house and parental schooling level), birth weight and gestational age. Overweight and obesity were classified using percentiles of body mass index and triceps and subscapular skinfolds. The outcome variables were overweight and obesity and the main explanatory variables were birth weight and birth weight according to gestational age. The control variables were the parents’ nutritional status, their schooling level and the per capita family income. Poisson multivariate regressions were carried out.

RESULTS: Higher prevalence of high birth weight was observed among overweight male adolescents (PR = 1.14; 95% CI = 1.02-1.27; P = 0.03), but this was not observed among obese male adolescents. Low birth weight and being born small for gestational age were also not associated with the outcomes. Among overweight and obese children, birth weight was not significantly different from that of normal-weight children.

CONCLUSION: No significant association between birth weight and obesity was observed. However, there was a weak but significant association between high birth weight and overweight, among male adolescents.

INTRODUCTION
Among the factors associated with obesity, significant attention has been given to birth weight. High birth weight (HBW), especially greater than or equal to 4 kg, has been correlated with overweight and/or obesity over the long term, in epidemiological studies. Particularly in developed countries, HBW is the main risk factor for obesity among children and adolescents whose mothers were affected by gestational diabetes mellitus, because of the elevated number of adipose cells acquired by the infant.

However, other factors may overlap the association between birth weight and overweight/obesity, such as the mother's body mass index (BMI), both the mother's and the father's BMI, family income, and the type of school attended, with regard to developing countries. These factors may reduce the importance of the birth weight variable in multivariate analysis. Systematic reviews have shown that correlations between birth weight and overweight/obesity among children not only have presented contradictory results, but also have differed regarding the methods used. Thus, these reviews have demonstrated that research on this subject needs to be conducted with the proper methodological rigor, in order to identify factors that might reduce the effect of birth weight on overweight or obesity among children and adolescents.

Because of the contradictions in these studies, it is important to clarify the association between birth weight and overweight/obesity, so as to determine the stage of life at which this relationship first appears. Longitudinal studies have revealed these associations in adulthood.

A study conducted in the city of Florianópolis in the year 2002 by de Assis et al., among children aged 7-9 years, found that the prevalence of overweight (including obesity) was 22.1%, in accordance with the criteria of Cole et al. Data from this city's live births registry, obtained in 2005, showed that the prevalence of low birth weight (LBW) among live births in Florianópolis was 8.3%. These proportions are similar to those found in developed countries, where an increase in HBW has been observed with a simultaneous decrease in LBW. Florianópolis was classified as the fourth highest city in Brazil in terms of human development in 2000 and the third city in 2013. Thus, the importance of the present study lies in the fact that in Florianópolis, elevated HBW prevalence that could be correlated with high rates of overweight and obesity would be expected.

OBJECTIVE
The purpose of this study was to investigate whether overweight and obese children and adolescents aged 7 to 14 years living in Florianópolis, Santa Catarina, southern Brazil, were born with low or high birth weight, taking into consideration the possible interactions between socioeconomic factors and other biological variables.

METHOD
Design, setting and ethics
This study was conducted on a retrospective cohort from the year 2007. An assessment was made on a probabilistic sample of schoolchildren aged 7 to 14 years who were enrolled in public and private elementary schools in Florianópolis, Santa Catarina, southern Brazil. The schoolchildren in this investigation were included after obtaining consent from their parents or legal guardians, who signed a free and informed consent statement. This study had previously been approved by the Ethics Committee for Human Research of the Federal University of Santa Catarina (Universidade Federal de Santa Catarina, UFSC) through project number 028/06.

Sample
The sampling was divided into two stages. Firstly, the 221 schools in Florianópolis were listed according to their geographical location in the city (north, south, east, center or mainland) and their kind of institution (public or private). The number of schools selected in each of the four geographical areas was defined taking into account: the proportion of schools in each area compared to the totality of schools in the city and the proportion of private and public institutions in each geographical area, totaling 17 schools (11 public and 6 private). The selection of the 17 schools was made randomly, by simple draw, but taking into account the previous list (stratified selection by geographical area and kind of school). Subsequently, students in each school were selected taking into consideration the ratios of schoolchildren registered in the 2004 school census in Florianópolis (53,595 individuals) in the following categories: geographical location of the student's home, kind of school, gender and age group.

Sample size was calculated taking the prevalence of overweight (including obesity) among children aged 7 to 9.9 years to be 10%, and 17% for adolescents aged 10 to 14 years, with 95% confidence levels and a two-tailed sampling error of 2%. The design effect was estimated to be 1.3 and the power was taken to be 80%. This calculation resulted in a requirement for a sample size of 1,100 children aged 7 to 9.9 years and 700 adolescents aged 10 to 14.99 years. In addition, all the children who had participated in a previous study conducted in 2002, and who in 2007 were adolescents enrolled in these randomly selected schools were also included. It was possible to locate 30% of all the students who had participated in the previous study in these randomly selected schools.

Considering the error margins for losses in tests, the total sample was estimated to be 1,200 children and 1,900 adolescents (800 new adolescents plus 1,100 adolescents from the previous study). Data on 2,863 students were collected. Those younger than seven years of age (n = 18) and those who were 15 years or...
over \((n = 16)\) were excluded, as were those for whom no valid data for weight \((n = 2)\) or birth weight \((n = 131)\) was available. Thus, the final sample investigated comprised 2,696 students \((857 \text{ children and } 1,839 \text{ adolescents})\), i.e. 94% of the total.

**Data collection**

Biological data (gender, age, birth weight, gestational age, weight, height, and subscapular and triceps skinfolds of the schoolchildren; and age, weight and height of their parents) and socioeconomic data (kind of school, i.e. public or private, family income level and parental educational level) were collected.

Information relating to birth weight, gestational age, age, parents’ weight and height and socioeconomic data were collected by means of a self-administered questionnaire that was sent to the parents and legal guardians of the students.

Anthropometric data on the students were collected by previously trained anthropometry technicians, following a protocol based on the recommendations of Lohman. Weight was assessed using a Marte electronic scale, model PP 180 (Marte Científica, Santa Rita do Sapucaí – MG, Brazil), with a capacity for 180 kg and precision of 100 grams. Height was measured using an AlturExata stadiometer (AlturExata, Belo Horizonte – MG, Brazil) with 1.0 millimeter precision. Skinfolds were measured using a Cescorf caliper (Cescorf Equipamentos Antropométricos, Porto Alegre - RS, Brazil) with 0.1 millimeter precision. The children and adolescents were measured without shoes and wearing light clothes.

A pilot study was conducted among subjects who were not included in the sample and, following the recommendations from the World Health Organization, the intra-rater technical measurement error (TME) for skinfold (SF) measurements was calculated. The intra-rater TME showed a reliability coefficient \((R)\) greater than 0.95, which showed that all of the anthropometry technicians made skinfold measurements properly, thus resulting in low variability in the data.

The data were entered into EpiData 3.2 and were fully checked by the duly trained data entry team, and automatic consistency and amplitude checks were made.

**Statistical variables and analysis**

The outcome variables were overweight and obesity. Overweight was defined as BMI \(\geq 85^{\text{th}}\) percentile, according to age and gender, as proposed by Must et al. and as recommended by the Brazilian Ministry of Health until the year 2008. Obesity was defined as BMI \(\geq 90^{\text{th}}\) percentile, according to age and gender, as proposed by Must et al. along with triceps and subscapular skinfolds in millimeters (mm) \(\geq 90^{\text{th}}\) percentile as proposed by Johnson et al. The criteria of Must et al. were chosen because they are widely used in the literature and have been recommended by the World Health Organization. These were also recommended by the Brazilian Ministry of Health for evaluating nutritional status among children and adolescents until 2008, when this study was conducted.

Birth weight and birth weight according to gestational age were the independent variables (or exposure) and were classified as follows: a) birth weight was classified as a single piece of data, as LBW \((< 3,000 \text{ g})\), appropriate birth weight \((\text{ABW}; \text{between } 3,000 \text{ and } 3,999 \text{ g})\) and HBW \((\geq 4,000 \text{ g})\); and b) birth weight was correlated with gestational age in order to classify schoolchildren as small for gestational age \((\text{SGA})\), i.e. below the 10\(^{\text{th}}\) percentile; appropriate for gestational age \((\text{AGA})\), i.e. between the 10\(^{\text{th}}\) and the 90\(^{\text{th}}\) percentiles; and large for gestational age \((\text{LGA})\), i.e. above the 90\(^{\text{th}}\) percentile. The World Health Organization classifies children as presenting insufficient birth weight if they are born weighing between 1,500 and 2,999 g and as presenting low birth weight if they are born weighing 2,500 g or less.

In our study, these categories were unified because the number of responses was low and this could have hidden an association between the outcome and the independent variables.

The control variables analyzed were the following: age and gender of the students; their parents’ education level classified into three categories \(< 8; 8 \text{ to } 11; \text{ or } \geq 12 \text{ years of education}\), based on the recommendations of the Brazilian Association for Population Studies \((\text{Associação Brasileira de Estudos Populacionais, ABEP})\); per capita family income in quartiles \((\text{in Brazilian money})\); kind of school \((\text{public or private})\); and parental BMI. The socioeconomic variables of parental education, per capita income and kind of school, and the parental BMI, were considered to be control variables.

The BMI of the students and their parents was obtained by dividing the weight measurement \((\text{in kg})\) by the square of their height \((\text{in meters})\). Non-elderly parents were classified as overweight if their BMI was between 25 and 30 kg/m\(^2\) or obese if their BMI was \(\geq 30 \text{ kg/m}^2\), as proposed by the World Health Organization, and elderly parents were classified as overweight if their BMI was \(\geq 27 \text{ kg/m}^2\), as proposed by the American Dietetic Association. Both of these sets of criteria are recommended by the Brazilian Ministry of Health.

An analysis on the consistency of the database was made using the Stata version 9.0 statistical package.

A descriptive analysis was conducted to show the prevalence ratios of overweight and obesity for each independent variable, and the prevalence of LBW, HBW, SGA and LGA.

In an inferential analysis, models divided by age group and gender were used to calculate associations among children aged 7 to 9.9 years and, separately, among adolescents 10 to 14.9 years, because of the possible effect of sexual maturation among the adolescents and the differences between genders.
regarding the prevalences of overweight and obesity. In order to compare the prevalences of overweight and obesity for the different categories within each variable studied, an analysis was performed using Pearson’s modified contingency coefficient, based on chi-square statistics.

Poisson univariate analysis was used to investigate association between birth weight (independent variable) and overweight and obesity (outcomes). Multivariate analysis was performed to ascertain the extent to which the exposure variables influenced the outcomes. Additionally, 95% confidence interval (95% CI) and P-values were estimated. The Poisson analysis model was used because for high-prevalence outcomes in cross-sectional studies (more than 10%), odds ratio estimates are said to either overestimate or underestimate associations with outcomes, in comparison with prevalence ratios.

All the analysis took into consideration the effect of the sampling design, through the svy command in the Stata software, which is used to analyze data from complex samples. Associations among the variables for which the P-value was ≤ 0.05 were considered to be statistically significant.

RESULTS
Data on 2,863 children (aged 7-9 years) and adolescents (aged 10-14 years) were collected. The proportion of the data that comprised refusals or exclusions was 5.8%. Students less than 7 years of age (n = 18) and more than 14.9 years of age (n = 16) were excluded because these ages were outside of the study range. Invalid weight data (less than 10 kg, n = 2) and birth weight (lower than 800 grams, n = 131, and higher than 6 kg) were also excluded. Occurrences of no response or discrepant values were considered to be invalid data. Thus, 2,696 students (857 children and 1,839 adolescents) were studied. In relation to the initial number calculated (3,100), this study presented a data loss rate of 13%. Table 1 describes the data on the population studied.

The LBW prevalences among the children and adolescents were respectively 8.2% and 7.8%. HBW was found in 7.4% and 7.9% of the children and adolescents, respectively. The prevalences of children and adolescents who were born SGA were 14.4% and 13.0%, respectively. Children and adolescents who were born LGA accounted for respectively 10.2% and 12.9%.

The prevalence of overweight among the children was 31.5% and of obesity, 10.9%. Among the adolescents, the prevalence of overweight was 21.0% and of obesity, 6.0%. Table 2 shows the prevalences of overweight and obesity among the children according to gender and the variables investigated. In this table, it can be seen that the prevalence of overweight among children was significantly higher in the following cases: boys born LGA (P = 0.02); children of both genders whose mothers were obese (P = 0.008 for boys and 0.001 for girls); and boys whose fathers were obese (P = 0.02). The prevalence of obesity was higher among girls whose mothers were obese (P < 0.001); and among boys whose fathers were obese (P = 0.05). The other variables investigated did not demonstrate any significant association with overweight or obesity in children (Pearson chi-square test).

Table 3 shows the prevalences of overweight and obesity among the adolescents (10-14 years of age). The prevalence of overweight was higher among the following: boys with HBW (P = 0.01) and LGA (0.01); boys in the top monthly per capita income quartile (P = 0.01); boys whose mothers (P = 0.003) and fathers (P < 0.001) were obese; girls who attended public schools (P = 0.001); and girls whose mothers (P < 0.001) or fathers (P = 0.002) were obese. The prevalence of obesity was higher among the following: adolescents with HBW (P = 0.002); LGA (P = 0.001); and those whose mothers (P < 0.001) or fathers (P = 0.03) were obese (Pearson chi-square test).
Table 2. Prevalence of overweight and obesity according to explanatory variables, by gender, among schoolchildren aged 7-9 years. Florianópolis, Santa Catarina, 2007

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overweight (%)</th>
<th>Obesity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3,000</td>
<td>27.3</td>
<td>27.2</td>
</tr>
<tr>
<td>3,000-3,999</td>
<td>34.3</td>
<td>31.2</td>
</tr>
<tr>
<td>≥ 4,000</td>
<td>41</td>
<td>26.3</td>
</tr>
<tr>
<td>Birth weight according to gestational age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA</td>
<td>19.5</td>
<td>27.7</td>
</tr>
<tr>
<td>AGA</td>
<td>31.2</td>
<td>30.1</td>
</tr>
<tr>
<td>LGA</td>
<td>45.1*</td>
<td>41.4</td>
</tr>
<tr>
<td>Income quartiles (R$/per capita)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>30</td>
<td>31.6</td>
</tr>
<tr>
<td>2nd</td>
<td>34.5</td>
<td>30.9</td>
</tr>
<tr>
<td>3rd</td>
<td>28.1</td>
<td>17.5</td>
</tr>
<tr>
<td>4th</td>
<td>32.9</td>
<td>34.4</td>
</tr>
<tr>
<td>Type of school</td>
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<tr>
<td>Public</td>
<td>32.9</td>
<td>28.6</td>
</tr>
<tr>
<td>Private</td>
<td>34.8</td>
<td>33.3</td>
</tr>
<tr>
<td>Parental nutritional status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese mother</td>
<td>57.1</td>
<td>53.1*</td>
</tr>
<tr>
<td>Obese father</td>
<td>42.5</td>
<td>41.8</td>
</tr>
<tr>
<td>Mother’s schooling level (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 8</td>
<td>37.8</td>
<td>25.5</td>
</tr>
<tr>
<td>8-11</td>
<td>32.9</td>
<td>32.1</td>
</tr>
<tr>
<td>≥ 12</td>
<td>31.8</td>
<td>29.7</td>
</tr>
<tr>
<td>Father’s schooling level (years)</td>
<td></td>
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<tr>
<td>&lt; 8</td>
<td>31.6</td>
<td>27.8</td>
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<td>8-11</td>
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</tr>
<tr>
<td>≥ 12</td>
<td>37.4</td>
<td>28.1</td>
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</table>

*P = 0.02; †P = 0.008; ‡P = 0.001; ††P < 0.001; **P = 0.02; *P = 0.05; χ² test.

These data show that a higher number of variables were associated with overweight and obesity among adolescents (12) than among children (6). Among children, the biological variables (birth weight for boys and parental BMI for both genders) were those that established a positive, proportional and significant association with the prevalences of overweight and obesity. Among adolescents, socioeconomic variables (kind of school and family income) were also associated in addition to the biological variables. The main variable of interest (birth weight) seemed to be associated only among males.

Table 4 shows the prevalence ratios in adjusted analysis on the outcomes of overweight and obesity among children and their associations with the exposure variables. No association between birth weight and overweight or obesity was found among the children in multivariate analysis. Thus, although birth weight according to gestational age was correlated with these outcomes in univariate analysis (Table 2), it ceased to be correlated after controlling for confounding. The father’s and mother’s BMI were probably the variables that were most strongly associated with the outcomes.

Table 5 shows the prevalence ratios for obesity among adolescents and their adjusted associations with birth weight. A significant association was found between birth weight and overweight among male adolescents, for those with HBW (PR = 1.14; 95% CI = 1.02-1.27; P = 0.03). However, it needs to be noted that this association observed between HBW and overweight among male adolescents was weak, because the prevalence of overweight among the male adolescents born with high birth weight was only 1.14 times greater than the prevalence of overweight found among adolescents born with appropriate weight. Hence, birth weight does not seem to be the principal factor that determines overweight in adolescence. Birth weight and birth weight according to gestational age were not significantly associated with
obesity among adolescents. Again, other variables seem to be strongly associated with obesity, and parental BMI may have controlled this association.

**DISCUSSION**

Investigating the influence of birth weight on overweight and obesity among children and adolescents is important, according to public health studies. This study in Florianópolis was justified by the city’s high Human Development Index, which reached the fourth position in Brazil in 2000 and this index is continually increasing. Currently, Florianópolis is the third city in the country in terms of human development. Moreover, the prevalence of newborns who were LGA (10.2% among the children and 12.9% among the adolescents), was similar, in 2000, to that found in developed countries.

The LBW prevalence found in this study (around 8%) is similar to that recorded in the Ministry of Health’s Live Births Registry for the city of Florianópolis, which was 8.3% in 2005, and the same has been found in developing countries such as Argentina and Mexico. However, it must be pointed out that intrauterine growth restriction, which is an indication of poor nutrition during pregnancy, reached 27.4% in this study.

The prevalences of overweight and obesity found in this survey (31.5% and 21% of the children and adolescents, respectively, were overweight and 10.9% and 6% were obese) were similar to those found in other studies on schoolchildren that used the same diagnostic criteria. For example, an assessment made by Dutra et al. in 810 adolescents aged 10 to 19 years in the city of Pelotas found that 19.3% of this population were overweight. Monteiro et al., also in Pelotas, found that 20.5% were overweight and 7.7% were obese, among 1,076 schoolchildren aged 14 to 16 years. Among 2,936 schoolchildren aged 7 to 10 years assessed by de Assis et al. in Florianópolis in the year 2002, 10.6% were obese [BMI/age ≥ 95th percentile of Must et al.]. Elevated proportions of overweight including obesity also were found among preschool children (28.8%) in Taubaté (state of São Paulo) and of obesity among children less than two years of age (10%) in Campinas (state of São Paulo). These findings may indicate that overweight and obese infants also tend to have overweight and obesity during childhood and adolescence.

Regarding the influence of birth weight on the prevalence of overweight in the sample investigated, a significant association was found in the univariate Poisson regression analysis for male adolescents who were born LGA. No association between birth weight and overweight was found among children of both genders, or among female adolescents. In an analysis adjusted for the parental socioeconomic and biological variables, the most significant association found was between HBW and overweight among male adolescents. Additionally, associations with obesity were found in univariate analysis for male adolescents who were born LGA and for those with HBW. However, after inclusion of parental socioeconomic variables and parental BMI in the multivariate analysis, the associations with obesity ceased to be significant.

Gilman et al. conducted a cross-sectional study on a cohort of 7,981 children and adolescents aged 9 to 14 years in the United States and found that the odds ratio for overweight [(BMI ≥ 85th percentile and < 95) was associated with HBW [odds ratio (OR) = 1.2; 95% confidence interval (CI) = 1.1–1.4] in a multivariate model adjusted for socioeconomic, biological and behavioral variables. In Mexico, Moraes et al. conducted a cross-sectional study assessing 700 children and adolescents aged 5 to
13 years and found that birth weight between 2,890 and 3,110 g and birth weight ≥ 3,110 g were associated with overweight according to the cutoff points set by Cole et al.\(^\text{11}\) (OR = 2.85; 95% CI = 1.49-5.47; and OR = 7.03; 95% CI = 3.53-13.99, respectively), in a multivariate analysis.

Monteiro et al.\(^\text{7}\) obtained similar results to those of the present study, in a cross-sectional investigation embedded in a cohort of children born in the city of Pelotas in 1982. Using the same diagnostic criteria for overweight and obesity as used in this study, they also found through a univariate analysis that there was an association between birth weight according to gestational age and obesity (i.e. being born LGA) among adolescents aged 14 to 16 years. However, the association did not remain significant after adjusting for family income and maternal BMI.

The present study showed that being born with high birth weight is a factor associated with overweight among male adolescents. However, this association seemed to be weakened by the variables of obesity in the mother and obesity in the father, in the multivariate analysis. In childhood, this association between birth weight and overweight/obesity was not observed. This seems biologically plausible, since there are reports in the literature showing a strong association between these variables in adulthood.\(^\text{39}\) So, even though it was not so strong, the relationship between overweight in male adolescents and being born with high birth weight indicates that health services should promote nutritional monitoring among adolescents with a focus on lifestyle, in order to reduce the chances of overweight and obesity in adulthood. In addition, it is recommended that epidemiologists and other researchers should investigate whether adolescents with elevated birth weight were born from mothers who presented gestational obesity or gestational diabetes, because the origins of overweight may be found in intrauterine development.

In relation to birth weight and parental weight and height, it should be stressed that this information was reported by the children’s legal guardians through a self-administered questionnaire. This method was chosen in order to make it easier to collect data and administer the data collection instrument. Araújo et al. conducted a validation study on the degree of agreement between reported birth weight information and birth weight measurements made immediately after birth, among eleven-year-old adolescents who were part of a cohort in Pelotas (Rio Grande do Sul) and found a high level of agreement regarding information on low birth weight (kappa = 0.73), with disagreements of the order of -20.0 g (standard deviation = 288.3).\(^\text{40}\) However, when stratifying birth weight information, the authors found that reported information tended to be overestimated in the case of LBW children and underestimated in the case of HBW children.

They pointed out that the linear relationship between birth weight and BMI was more consistent when birth weight was measured immediately after birth and not so precise when birth weight was reported. Therefore, validation for birth weight measurements in a subsample is highly recommended, so as to compare the reported variable with data gathered by hospital registries or on health record cards.

In spite of these limitations, the present study had external validity, was probabilistic and had a complex sampling plan. Additionally, the researchers took care to train the anthropometry technicians, which resulted in reliable data. In addition to appropriate data gathering, care was taken in compiling the research data, which were fully entered and checked by a trained team, using software that enables data entry control. Therefore, the results from this study seem not to have been influenced by selection or measurement bias.

CONCLUSION

No significant association was found between high birth weight/being born large for gestational age and obesity after adjusting for the control variables, either among children or among adolescents. The same results were found for low birth weight and being born small for gestational age. Even though the association was not very strong, a relationship between high birth weight and overweight among male adolescents was observed.

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Sources of funding: Research funded by the National Council for Scientific and Technological Development (CNPq) (Procedural no. 402322/2005-3 – Call for bid MCT/CNPq/MS-SCTIE-DECIT/SAS-DAB 51/2005)

Conflict of interest: None

Date of first submission: November 20, 2012
Last received: September 21, 2013
Accepted: October 8, 2013

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Relationship between lower-limb muscle strength and functional independence among elderly people according to frailty criteria: a cross-sectional study

Relação entre força muscular de membros inferiores e independência funcional de idosos segundo critérios de fragilidade: um estudo transversal

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ABSTRACT

CONTEXT AND OBJECTIVE: Muscle strength and functional independence are considered to be determinants of frailty levels among elderly people. The aim here was to compare lower-limb muscle strength (LLMS) with functional independence in relation to sex, age and number of frailty criteria, and to ascertain the influence of these variables on elderly outpatients’ independence.

DESIGN AND SETTING: Quantitative cross-sectional study, in a tertiary hospital.

METHODS: The study was conducted on 150 elderly outpatients of both sexes who were in a cognitive condition allowing oral communication, between October 2005 and October 2007. The following instruments were used: five-times sit-to-stand test (FTSST), Functional Independence Measurement (FIM) and Lawton’s Instrumental Activities of Daily Living Scale (IADL). Descriptive, comparative, multivariate, univariate and Cronbach alpha analyses were performed.

RESULTS: The mean time taken in the FTSST was 21.7 seconds; the mean score for FIM was 82.2 and for IADL was 21.2; 44.7% of the subjects presented 1-2 frailty criteria and 55.3% > 3 criteria. There was a significant association between LLMS and functional independence in relation to the number of frailty criteria, without homogeneity regarding sex and age. Functional independence showed significant influence from sex and LLMS.

CONCLUSION: Elderly individuals with 1 or 2 frailty criteria presented greater independence in all FTSST scores. The subjects with higher LLMS presented better functional independence.


RESUMO

CONTEXTO E OBJETIVO: A força muscular e a independência funcional são consideradas indicadores de níveis de fragilidade em idosos. O objetivo foi comparar a força muscular de membros inferiores (FM de MMII) com a independência funcional em função de sexo, idade e número de critérios de fragilidade e verificar a influência dessas variáveis na independência em idosos ambulatoriais.

TIPO DE ESTUDO E LOCAL: Estudo transversal quantitativo, em hospital terciário.

MÉTODOS: Estudo realizado entre outubro de 2005 e outubro de 2007 com 150 idosos ambulatoriais de ambos os sexos, com condições cognitivas suficientes para comunicação oral, sendo utilizados os seguintes instrumentos: teste de levantar e sentar da cadeira cinco vezes consecutivas, Medida de Independência Funcional (MFM) e Escala de Atividades Instrumentais (AIvDt) de Lawton. Foram realizadas análises descritivas, de comparação, multivariadas, univariadas e de alfa de Cronbach.

RESULTADOS: O tempo médio no teste de levantar e sentar da cadeira foi de 21,7 segundos, a pontuação média da MFM de 82,2 e da AIvDt de 21,2; 44,7% dos sujeitos apresentaram 1-2 critérios de fragilidade e 55,3% > 3 critérios. Houve associação signifi cativa entre FM de MMII e independência funcional em função do número de critérios de fragilidade, sem homogeneidade em relação ao sexo e idade. A independência funcional sofreu influência significativa de sexo e FM de MMII.

CONCLUSÕES: Os idosos com um ou dois critérios de fragilidade apresentaram melhor independência em todos os escores do teste de levantar e sentar da cadeira. Os sujeitos com maior FM de MMII apresentaram melhor independência funcional.
INTRODUCTION

Sarcopenia, which comprises loss of muscle mass associated with aging, derives from a complex process. These changes to muscle composition result from muscle fiber atrophy, reduction in the production of certain hormones (testosterone, adrenal androgens and growth hormone) and inappropriate food intake, among other factors.

The decrease in muscle strength resulting from sarcopenia causes significant functional loss with regard to performing activities of daily living (ADLs), and this is the main etiological factor in the development of functional dependence among elderly individuals. The association between muscle strength and functional independence has been pointed out in the literature, and the study by Janssen et al. deserves special attention. This assessed 504 elderly individuals and identified a significant correlation (P < 0.05) between sarcopenia and high risk of developing dependence for performing ADLs.

Nevertheless, sarcopenia expressively contributes towards development of the frailty syndrome, which was defined by Fried and Walston as a state of physiological vulnerability, with functional dependence. In a study by Woods et al., 19 elderly and that frailty can actually contribute towards development of neuromuscular alterations, deregulation of the neuroendocrine system and dysfunction of the immunological system. Until the 1980s, frailty syndrome was understood as functional incapacity. However, studies have shown that these are distinct conditions, and that frailty can actually contribute towards development of functional dependence. In a study by Woods et al., elderly women who were considered to be pre-frail and frail showed, respectively, 1.64 and 3.15 times greater chances of developing functional dependence, in comparison with non-frail individuals, after a three-year study.

Most studies have shown that women are more likely to present functional incapacity and characteristics of the frailty phenotype, since they are more exposed and live longer than men. Studies on these differences are important for constructing strategies for elderly care. Considering that frailty and decreased muscle strength are associated with elderly people’s functional abilities, the present study had the objectives of investigating the relationship between lower-limb muscle strength (LLMS) and functional independence, taking into consideration gender, age and a number of frailty criteria among elderly outpatients, and of investigating the influence of these variables on functional independence.

OBJECTIVE

The aims of this study were to compare lower-limb muscle strength (LLMS) with functional independence, taking into consideration gender, age and a number of frailty criteria, and to ascertain the influence of these variables on the independence of elderly outpatients.

METHODS

This was a descriptive quantitative cross-sectional study, and data were gathered as part of a major project developed in the Geriatrics Outpatient Clinic of a university hospital in Campinas (Universidade Estadual de Campinas, Unicamp). It was approved by the institution’s Research Ethics Committee, as decision no. 240/2003.

In this study, a non-probabilistic convenience sample of 150 elderly people of both sexes who were followed up as outpatients was assessed between October 2005 and October 2007. The subjects met the following inclusion criteria: agreeing to participate in the study, signing a free and informed consent statement and being in a cognitive condition for oral communication to be established, so that an interview could be conducted and the Mini-Mental State Examination could be applied, as prescribed by Bertolucci et al. The exclusion criteria were: refusal to participate, impaired oral communication, cognitive deficit that could harm comprehension and Mini Mental State Examination (MMSE) score lower than the cutoff score.

As many older adults as possible per day were approached to inquire about their willingness to take part in the study, their availability for an interview and their compatibility with the inclusion criteria. We were able to interview two older adults a day.

The variables for this study were as follows:

Sociodemographic variables: gender and age;

Anthropometry: weight, height, body mass index (BMI) and handgrip strength;

Mobility and flexibility: gait speed test and LLMS, which are part of the short physical performance battery (SPPB) that was proposed by Guralnik et al. and adapted to the Brazilian Portuguese language by Nakano;

Physical activity: practice and weekly frequency;

MMSE: with cutoff score greater than or equal to 13 (for illiterate individuals), 18 (individuals with one to seven years of schooling) and 26 (individuals with eight years of schooling or more);

Depressive status: two questions from the depression tracking scale (Center for Epidemiologic Studies Depression Scale, CES-D), which was developed by Radloff and validated in Brazil for the elderly population by Batistoni et al. To identify frailty, the criteria of Fried et al. were used with some adaptations, as follows:

- Involuntary weight loss: over the last year, over 4.5 kg or 10% of body weight;
- Exhaustion: self-reported fatigue assessed through two questions (“Did you feel that you had to make an effort to accomplish your habitual tasks?” and “Were you unable to do your things?”) taken from the depression tracking scale CES-D.

In the case of an affirmative answer for a period of three or
more days of the previous week, the subject was graded as positive for exhaustion;
- **Decreased walking speed**: the time taken to walk a distance of 4.0 meters one way and 4.0 meters back again was measured using a chronometer, taking the best time for this course, adjusted according to sex and height. For men of heights < 1.73 and > 1.73 meters respectively, times of > 7 seconds and > 6 seconds were considered positive. For women of heights < 1.59 and > 1.59 meters respectively, times of > 7 seconds and > 6 seconds were considered positive;
- **Muscle weakness**: this was evaluated by means of a handgrip dynamometer. The individual under evaluation was positioned standing upright with the arms along the body, except for wheelchair users, who did the test in the seated position. The highest value was taken from three measurements of handgrip strength, with intervals of approximately five minutes between them, adjusted for sex and body mass index. Men were graded positive for muscle weakness when their handgrip strength was < 29.0 kgf for body mass index < 24.0 kgf/m²; < 30.0 kgf for body mass index 24.1 to 26.0; and < 32.0 kgf for body mass index > 28.0. For women, the values were < 17.0 kgf for body mass index < 23.0; < 17.3 kgf for body mass index 23.1 to 26.0; < 18.0 kgf for body mass index 26.1 to 29.0; and < 21.0 kgf for body mass index > 29.0.
- **Low level of physical activity**: this was graded positive for elderly individuals who were inactive or who performed physical activities less than twice a week.

After evaluating the frailty criteria, two groups were obtained: one group with one or two criteria (considered to be pre-frail) and the other with three or more criteria (considered to be frail), as suggested by Fried et al. All of the subjects in this study presented at least one of the criteria.

To evaluate lower-limb muscle strength, the five-times sit-to-stand test (FTSST) was used. This forms part of the Short Physical Performance Battery instrument, which was proposed by Guralnik et al. and was adapted to the Brazilian Portuguese language by Nakano. The test was undertaken using an armless chair that was 46 centimeters high from its seat to the floor. The individual under evaluation sat on the chair with arms folded across the chest. Points were awarded according to the time needed to complete the test. Zero was attributed when the elderly individual was unable to perform the test or required > 60 seconds to complete it; one point if the time needed was > 16.7 seconds; two points if the time was between 13.70 and 16.69 seconds; three points if the time was between 11.20 and 13.69 seconds; and 4 points if the time was < 11.19 seconds. Scores 3 and 4 for the lower-limb muscle strength test were grouped together because of the small number of subjects with each score (n = 8 and n = 6, respectively).

Functional independence was assessed in relation to basic and instrumental activities of daily living (BADL and IADL), and was measured according to the motor score of the functional independence measurement (FIM) and the instrumental activities proposed by Lawton and Brody as adapted by Freitas and Miranda. FIM is an instrument containing 18 items, divided into two subscales: 1- motor FIM (mFIM), concerning self-care, sphincter control and mobility; 2- cognitive-social FIM, concerning communication and social cognition. Each item receives a score ranging from 1 (total dependence) to 7 (complete independence), with a total score ranging from 18 to 126. The motor component score ranges from 13 to 91 points. In assessing the instrumental activities, the following tasks were considered: food preparation; doing the household chores; washing and ironing the clothes; doing manual work; handling medication; using the telephone and handling money; doing the shopping and using means of transportation. If the task is performed "independently" three points are attributed; two points when there is "partial independence" and one point for "total dependence" and the total score ranges from 9 (maximum dependence) to 27 points (maximum independence). In both instruments, the higher the score is, the higher the functional independence is.

The results were subjected to the following analyses. Descriptive analysis was performed to make measurements of position (mean, median, minimum and maximum) and dispersion (standard deviation). Cronbach’s alpha coefficient was used to evaluate the reliability of the instruments, such that high internal consistency was indicated by values greater than or equal to 0.7. The Shapiro-Wilk test was used to point out situations of non-normal distribution of the sample, which would require subsequent use of nonparametric statistical tests. The Kruskal-Wallis test was used to compare the LLMS scores and FIM and IADL, taking into consideration sex, age and frailty criteria, followed by the post-hoc Dunn test.

Univariate analysis of variance (ANOVA) was used to evaluate the impact of each variable of interest (sex, age, LLMS and frailty) on the scores of each functional independence evaluation tool (mFIM and IADL). Multivariate analysis of variance (MANOVA) was used to ascertain the combined influence of the variables of interest on the mFIM and IADL scores (dependent variables). Variables that were not normally distributed were transformed into ranks in these analyses. MANOVA was used to test the significance of the difference between measurements of two or more groups in relation to two or more dependent variables that were taken into account simultaneously. The significance level used was 5% (P < 0.05).

**RESULTS**

Table 1 shows that the mean age of the elderly individuals was 76.4 ± 7.8 years and that women predominated (64.2%).
The mean time taken to perform the LLMS test was 21.7 ± 7.9 seconds; 26 subjects were unable to perform the test; the mean mFIM score was 82.3 ± 9.4 and the mean IADL score was 21.2 ± 4.9.

Regarding the frailty criteria, 67 individuals (44.7%) presented 1 to 2 criteria (and were considered to be pre-frail) and 83 (55.3%) presented 3 or more criteria (and were considered to be frail).

Reliability analysis on the tools was performed through calculating Cronbach alpha coefficient, and this showed high internal consistency, with values of 0.92 for mFIM and 0.86 for IADL.

Table 2 presents the results from comparisons between the median mFIM and IADL scores and the FTSST scores between the sexes. In the LLMS, men with scores of 3 and 4 presented significantly higher median mFIM (P < 0.001) and IADL (P = 0.001) than women with these scores in the LLMS.

Table 3 shows the comparison between FTSST and mFIM and IADL, taking age into consideration. There was a statistically significant difference between FTSST and the median mFIM (P = 0.016) among the elderly subjects aged 60 to 69 years and aged 80 years or over with LLMS score 0, in comparison with the subjects aged 80 years or over with LLMS scores of 3 and 4. Elderly individuals aged 80 years or over with FTSST scores of 3 and 4 showed higher median IADL (P < 0.001) in relation to the elderly individuals in the other age groups with FTSST score 0 and those aged 70 to 79 years with scores of 3 and 4.

Comparative analyses on median mFIM and IADL taking into consideration the number of frailty criteria according to the FTSST scores are presented in Table 4. Significantly higher median mFIM (P < 0.001) was observed for the elderly with LLMS score 1 and one or two frailty criteria, in comparison with the elderly individuals with LLMS scores of 0 and 3 and 4 with three or more frailty criteria. On the other hand, elderly individuals with LLMS score 0 and one or two frailty criteria presented significantly lower median mFIM (P < 0.001), in comparison with the elderly individuals with mFIM score 2 with three or more criteria. Elderly individuals with LLMS scores of 0, 3 and 4 and one or two criteria presented significantly higher median IADL (P < 0.001) than elderly individuals with LLMS scores of 0, 3 and 4 with three or more criteria.

Considering that LLMS is a variable that presents a statistically significant relationship with mFIM and IADL scores, taking into consideration age, sex and frailty criteria, a variance analysis model was created with the aim of identifying the variables that influenced functional independence the most. Thus, by analyzing the impact of each variable on functional independence (Table 5), it was observed that mFIM was significantly influenced by sex (P = 0.004) and LLMS (P = 0.010). IADL was influenced by sex (P = 0.044), age (P = 0.023) and LLMS (P = 0.019). Hence, men and subjects with higher LLMS presented better mFIM and IADL scores; the younger elderly individuals presented better mFIM and IADL scores and the younger elderly individuals also presented better IADL scores. The frailty criteria did not have any influence on functional independence. In the multivariate analysis (MANOVA) presented in Table 5, independence assessed by means of mFIM and IADL scores continued to be significantly influenced by the variables of sex (P = 0.015) and LLMS (P = 0.026).
Table 3. Comparison between lower limb muscle strength (LLMS) scores (five-times sit-to-stand test, FTSST), taking age into consideration, and the median scores for the motor functional independence measurement (mFIM) and instrumental activities of daily living (IADL) among the elderly individuals studied (n = 150)

<table>
<thead>
<tr>
<th>Variable</th>
<th>LLMS 60-69/70-79</th>
<th>LLMS ≥ 80</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>mFIM</td>
<td>68.0/81.0/77.5</td>
<td>88.0/87.0/85.0</td>
<td>85.5/88.0/84.0</td>
</tr>
<tr>
<td>IADL</td>
<td>18.0/19.0/17.0</td>
<td>24.0/24.0/22.0</td>
<td>26.0/26.0/19.0</td>
</tr>
</tbody>
</table>

*Kruskal-Wallis test for comparison of the variables according to muscle strength and age, with Dunn post-hoc test (a) 0/60-69 ≠ 3-4/≥ 80 and 0/80 ≠ 3-4/≥ 80; (b) 0/≥ 80 ≠ 3-4/3-4/80, 3-4/70-79 ≠ 3-4/3-4/80, 0/70-79 ≠ 3-4/3-4/80, 2/80 ≠ 3-4/80 and 0/60-69 ≠ 3-4/80.

Table 4. Comparison between the lower limb muscle strength (LLMS) scores (five-times sit-to-stand test, FTSST), taking the number of frailty criteria into consideration, and the median scores for the motor functional independence measurement (mFIM) and instrumental activities of daily living (IADL) among the elderly individuals studied (n = 150)

<table>
<thead>
<tr>
<th>Variable</th>
<th>LLMS 60-69/70-79</th>
<th>LLMS ≥ 80</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-2/3-4</td>
<td>1-2/3-4</td>
<td>1-2/3-4</td>
</tr>
<tr>
<td>mFIM</td>
<td>76.0/80.0/85.0</td>
<td>89.0/85.0/89.0</td>
<td>88.0/89.0/87.0/80.0</td>
</tr>
<tr>
<td>IADL</td>
<td>20.0/17.0/23.0</td>
<td>24.0/25.0/24.0</td>
<td>25.0/13.0/20.0</td>
</tr>
</tbody>
</table>

*Kruskal-Wallis test for comparison of the variables according to muscle strength and frailty criteria, with Dunn post-hoc test (a) 0/1-2 ≠ 1/2-3, 0/2/3 ≠ 2/2/3, 0/1-2 ≠ 1/2-3, 0/1-2 ≠ 2/2/3, 3-4/3-4/3 ≠ 1/1-2 and 3-4/3-4/3 ≠ 2/2/3; (b) 3-4/3-4/3 ≠ 2/2-1-2, 3-4/3-4/3 ≠ 3-4/1-2, 0/3-4/2/1-2 and 0/3-4/1-2-2.

Table 5. Results from multivariate analysis of variance (MANOVA) and univariate analysis of variance (ANOVA)

<table>
<thead>
<tr>
<th>Variables</th>
<th>MANOVA P-value</th>
<th>mFIM P-value*</th>
<th>IADL P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.015</td>
<td>0.004*</td>
<td>0.044*</td>
</tr>
<tr>
<td>Age</td>
<td>0.063</td>
<td>0.270*</td>
<td>0.023*</td>
</tr>
<tr>
<td>LLMS</td>
<td>0.026</td>
<td>0.010*</td>
<td>0.019*</td>
</tr>
<tr>
<td>Frailty</td>
<td>0.196</td>
<td>0.219*</td>
<td>0.071*</td>
</tr>
</tbody>
</table>

*P-value; mFIM = functional independence measurement; IADL = instrumental activities of daily living; LLMS = lower-limb muscle strength.

DISCUSSION

The main results showed that functional independence was positively related to lower-limb muscle strength at different frailty levels. The sociodemographic characteristics of the elderly individuals attended at the outpatient clinic studied corresponded to the average profile for Brazilian elderly people, i.e. the group was formed mostly by women and was close to the mean age of the elderly Brazilian population (73.1 years). A study using the same sample found that 71.2% of the volunteers had five or more diseases and that 67.1% had five or more comorbidities. Regarding frailty characteristics, a community-based study in the same city showed that females, higher age groups and lower income groups correlated with greater frailty, with more fatigue, less muscle strength and slower gait.

Previous studies that used the FTSST to measure LLMS among elderly individuals showed higher performance than was observed in the present study, in which the mean time taken in the FTSST was 21.7 seconds. It might be possible to explain this discrepancy in terms of the profile of elderly individuals attended at the outpatient clinic studied, which followed certain inclusion criteria, such as advanced age and functional deficit. A study by Aslan et al. on 115 elderly outpatients who were able to walk without help and did not present any neurological disease or visual and/or auditory problems showed that the mean time taken to perform the FTSST was 14.4 ± 6.88 seconds. In a study on 44 elderly individuals of mean age 83.13 ± 3.3 years who were able to walk with or without a device to help them and who presented clinical stability, Ferreira et al. found that the mean time taken to perform the FTSST was 12.72 ± 6.94 seconds. Although these elderly individuals presented advanced age, one of the inclusion criteria of their study was that the subjects needed to be able to walk. On the other hand, this criterion was not taken into consideration in the methodology of the present study.

In comparing LLMS and functional independence in relation to sex, age and number of frailty criteria, it was found that the FTSST distinguished the degree of independence between men and women only at extreme scores, with greater independence among the men. Previous studies on elderly outpatients living in the community did not show any difference in performance in the FTSST between the sexes, except for the study by Barbosa et al. in which the influence of higher numbers of diseases and greater obesity presented by women would explain their worse performance in the test, in comparison with the men. In the present study, the elderly individuals of both sexes probably presented similar performance in the FTSST, thus corroborating the findings in literature, which can explain why there was a difference in independence between the sexes only at the minimum and maximum scores of the test.

Comparing LLMS and independence among the age groups, there was only a significant difference at the minimum and maximum scores, with greater independence among the subjects aged 80 years or over and with higher LLMS. In the literature, significant associations between FTSST and age conditions.
have been reported, with lower performance in the test among older elderly individuals. It is likely that because of the profile of the elderly individuals attended at the Geriatric Outpatient Clinic studied here, where the outpatients are aged between 60 and 79 years, some degree of functional impairment was presented. All the subjects studied may have presented similar performance in the test, independently of age, and this possibly explains the finding that there was only a difference between the age groups at the extremities of the test scores, and might also explain the better performance of the elderly individuals aged 80 years or over. It was also found that the FTSST significantly distinguished the functional independence of the elderly individuals with one or two frailty criteria from those with three or more criteria, except for the individuals with LLMS score 0 and one or two criteria in relation to those with LLMS score 2 and three or more criteria, in which the latter presented significantly higher mFIM scores. It is possible that the individuals with one or two frailty criteria presented criteria relating to muscle strength (grip strength, gait speed and physical activity) that might have interfered with their BADL performance.

Concerning functional independence, it was found that sex and LLMS influenced BADL and IADL performance: these results are consistent with reports in the literature, except for the absence of the influence of age. Guralnik et al. studied 1,122 elderly individuals and also found that the subjects with higher LLMS evaluated through FTSST presented greater functional independence, a conclusion that was obtained with higher LLMS evaluated through FTSST presented greater functional independence among elderly individuals aged 80 years or over. It was also found that the FTSST significantly distinguished the functional independence of the elderly individuals with one or two frailty criteria from those with three or more criteria, except for the individuals with LLMS score 0 and one or two criteria in relation to those with LLMS score 2 and three or more criteria, in which the latter presented significantly higher mFIM scores. It is possible that the individuals with one or two frailty criteria presented criteria relating to muscle strength (grip strength, gait speed and physical activity) that might have interfered with their BADL performance.

Concerning functional independence, it was found that sex and LLMS influenced BADL and IADL performance: these results are consistent with reports in the literature, except for the absence of the influence of age. Guralnik et al. studied 1,122 elderly individuals and also found that the subjects with higher LLMS evaluated through FTSST presented greater functional independence, a conclusion that was obtained after four years of study. The study by Rosa et al. which investigated the determining factors of functional independence among elderly individuals, identified that females and individuals with advanced age presented greater probability of developing functional independence (P < 0.001). Again, it is likely that the absence of influence of age on independence in the present study was due to the profile of the elderly individuals attended at the Geriatric Outpatient Clinic.

There are some limitations to the present study. Because of the absence of a group of elderly people without frailty criteria, other comparisons were not possible with the non-frail individuals. This is once again possibly due to the profile of the elderly individuals followed up at the Geriatrics Outpatient Clinic. In general, these elderly people seek this health service because they already have some health care needs. In addition, the elderly individuals of this sample present peculiar characteristics; therefore, the results cannot be generalized for the population in general.

Nonetheless, it was possible to identify significant differences in lower-limb muscle strength between the groups with one or two frailty criteria and those with three or more criteria, thus showing that these aspects should be taken into consideration in developing actions aimed towards improving elderly people’s quality of life.

The findings from our study draw attention to the role of decreased muscle strength among elderly people in relation to development of functional dependence, thus suggesting that recovery and rehabilitation programs conducted by qualified professionals need to be created. Further research should evaluate the relationship between frailty and functional performance in settings other than outpatient clinics, especially among women.

**CONCLUSION**

It was observed that male elderly individuals with advanced age (> 80 years), with one or two frailty criteria and higher LLMS presented better functional independence than younger female elderly individuals with lower LLMS and three or more frailty criteria. Separately, men and elderly individuals with higher LLMS presented better functional independence.

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Sources of funding: None
Conflict of interest: None
Date of first submission: February 7, 2013
Last received: October 11, 2013
Accepted: October 15, 2013
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Nebivolol reduces central blood pressure in stage I hypertensive patients: experimental single cohort study

Nebivolol reduz pressão arterial central em pacientes hipertensos estágio I: estudo experimental de coorte única

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ABSTRACT

CONTEXT AND OBJECTIVES: Assessment of central blood pressure (BP) has grown substantially over recent years because evidence has shown that central BP is more relevant to cardiovascular outcomes than peripheral BP. Thus, different classes of antihypertensive drugs have different effects on central BP despite similar reductions in brachial BP. The aim of this study was to investigate the effect of nebivolol, a β-blocker with vasodilator properties, on the biochemical and hemodynamic parameters of hypertensive patients.

DESIGN AND SETTING: Experimental single cohort study conducted in the outpatient clinic of a university hospital.

METHODS: Twenty-six patients were recruited. All of them underwent biochemical and hemodynamic evaluation (BP, heart rate (HR), central BP and augmentation index) before and after 3 months of using nebivolol.

RESULTS: 88.5% of the patients were male; their mean age was 49.7 ± 9.3 years and most of them were overweight (29.6 ± 3.1 kg/m²) with large abdominal waist (102.1 ± 7.2 cm). There were significant decreases in peripheral systolic BP (P = 0.0020), diastolic BP (P = 0.0049), HR (P < 0.0001) and central BP (129.9 ± 12.3 versus 122.3 ± 10.3 mmHg; P = 0.0083) after treatment, in comparison with the baseline values. There was no statistical difference in the augmentation index or in the biochemical parameters, from before to after the treatment.

CONCLUSIONS: Nebivolol use seems to be associated with significant reduction of central BP in stage I hypertensive patients, in addition to reductions in brachial systolic and diastolic BP.
INTRODUCTION

Recent evidence has shown that central blood pressure (BP) is more relevant for predicting cardiovascular (CV) outcomes than peripheral pressure in the brachial artery.1−4 Since the publication of the Conduit Artery Function Evaluation (CAFE) study,1 the importance of assessments of arterial function and central blood pressure (BP) has increased substantially. Although brachial BP is a powerful predictor of CV morbidity and mortality,1,4 this measurement does not reflect the pressure in the central circulation.2 It has been shown that central BP is normally lower than peripheral BP, and many studies have shown a consistent relationship between central systolic BP and cardiovascular mortality. In addition, despite similar reductions in brachial BP, different classes of antihypertensive drugs have different effects on the central BP and arterial stiffness.6 Recent studies have shown that vasodilator antihypertensive drugs,3,7,8 such as renin-angiotensin system (RAS) inhibitors and calcium channel blockers, have a more favorable effect on indices of arterial stiffness than do older β-blockers, and particularly atenolol.9,10 It is conceivable that newer β-blockers with additional vasodilation properties may have favorable effects on arterial stiffness, compared with atenolol.

One such drug is nebivolol, a third-generation beta 1-selective β-blocker, which has favorable effects on carbohydrate and lipid metabolism, as well as on endothelial function and on oxidative stress. In recent studies, nebivolol was shown to improve artery stiffness to a greater extent than older β-blockers. It has been shown to have vasodilation properties in humans and animals.11−14 Among its properties are its ability to increase the bioavailability of nitric oxide (with consequently improvement of endothelial function), its antiproliferative effect and its ability to decrease oxidative stress.15,16 Because endothelial dysfunction and increased arterial stiffness play an important role in the early atherosclerotic processes and are associated with poor outcomes and increased mortality, independently of blood pressure, the ability of nebivolol to enhance the release of endothelium-derived nitric oxide, and consequently improve endothelial function and arterial stiffness,17,18 may have significant clinical implications for the use of this agent in treating hypertension and cardiovascular diseases.

OBJECTIVE

The aim of this study was to analyze the 12-week effect of nebivolol treatment on hemodynamic (BP, heart rate (HR), central BP and augmentation index) and biochemical parameters in stage I hypertensive patients without previous treatment.

METHODS

Study design, setting and sample

A total of 33 patients from our outpatient hypertension clinic who were interested in entering the study were initially screened for eligibility; among these, seven did not satisfy the inclusion/exclusion criteria. Thus, the sample for participation in this single-group prospective cohort study was composed of 26 stage I hypertensive patients. Stage I hypertension was defined as systolic BP ≥ 140 and < 160 mmHg and/or diastolic BP ≥ 90 and < 100 mmHg. Subjects presenting age < 18 years, hypertensive patients treated previously, obesity, alcohol abuse, current corticosteroid treatment, history of asthma, peripheral vascular disease, chronic kidney disease, secondary hypertension, unstable angina or previous myocardial infarction, previous stroke, heart failure, atrioventricular block, bradycardia < 50 bpm, pregnancy, uncontrolled diabetes mellitus or insulin therapy, neoplasia, history of drug abuse or any other clinical conditions associated with poor prognosis were excluded.

Eligible participants visited our clinical research laboratory at 7:00 am after a 12-hour fast, to undertake the protocol procedures. Anthropometric variables were measured and blood was sampled for the lipid profile and routine laboratory parameters (hemoglobin, hematocrit, platelets, leukocytes, glutamic oxaloacetic and pyruvic transaminases, serum creatinine, glucose, urea and total bilirubin). LDL-cholesterol was calculated using the Friedewald formula.17 Furthermore, all patients underwent BP recordings and determination of central aortic BP in the consultation office, and determination of the augmentation index by means of applanation tonometry on peripheral arteries, as described below. All the latter measurements were made in a quiet room with controlled air temperature (approximately 22 °C).

Treatment with nebivolol started after confirmation of the inclusion criteria. The patients received nebivolol at a dose of 5 mg/day. Follow-up visits for BP measurements, physical examination and study medication dispensation were made every month. The study participants’ adherence to the therapy administered was assessed at the follow-up visits by means of tablet counts. At the end of the study (three months), the baseline measurements were repeated for all of the 26 patients evaluated initially.

Assessments

Peripheral BP at the level of the brachial artery was measured in the seated position after a ten-minute rest, using a mercury sphygmomanometer and cuffs with bladder size encircling at least 80% of the upper-arm circumference and covering two-thirds of the upper-arm length.14 Brachial BP was measured in both arms, and if there was a difference in BP levels between the two arms, the measurements in the arm with the higher BP were taken into account. Three BP measurements with at least a one-minute interval between them were obtained, and the mean of the three measurements was recorded. Phase I and V Korotkoff sounds were recorded for systolic BP (SBP) and diastolic BP (DBP), respectively.
Pulse-wave analysis

Central blood pressure and augmentation index
Arterial pulse waveforms from the left radial artery were measured noninvasively by means of an automated tonometry system (HEM-9000 AI; Omron Healthcare Co. Ltd., Kyoto, Japan), after the participants had rested in a seated position for 10 minutes. Pulse-wave analyses were performed at least three times and the mean of the measurements was calculated. The radial arterial waveforms from this device were used to calculate the augmentation index (AIx). The first systolic peak (SBP1) and the late (second) systolic peak (SBP2) were automatically identified using the fourth-derivative wave as the second and third zero crossing points, respectively. The augmentation index (AIx) was defined as the ratio of the height of SBP2 to that of SBP1. The brachial BP and heart rate (HR) were measured simultaneously in the right brachial artery using an oscillometric device incorporated in the HEM-9000 AI device. Late systolic BP in the radial artery, as an index of central BP, was calculated using the following equation: rSBP2 = r-AIx.

Brachial systolic BP was measured noninvasively by means of an automated tonometry system (HEM-9000 AI; Omron Healthcare Co. Ltd., Kyoto, Japan), after the par-ticipants had rested in a seated position for 10 minutes. Pulse-wave analysis was performed at least three times and the mean of the measurements was calculated. The radial arterial waveforms from this device were used to calculate the augmentation index (AIx). The first systolic peak (SBP1) and the late (second) systolic peak (SBP2) were automatically identified using the fourth-derivative wave as the second and third zero crossing points, respectively. The augmentation index (AIx) was defined as the ratio of the height of SBP2 to that of SBP1. The brachial BP and heart rate (HR) were measured simultaneously in the right brachial artery using an oscillometric device incorporated in the HEM-9000 AI device. Late systolic BP in the radial artery, as an index of central BP, was calculated using the following equation: rSBP2 = r-AIx. (brachial systolic BP – brachial diastolic BP) + brachial diastolic BP. The HR-adjusted augmentation index (AIx(75)) was calculated by adjusting AIx at an inverse rate of 4.8% for each ten-beats-per-minute increment in heart rate. All measurements were performed by a single examiner, after the subject had fasted for at least eight hours, both before and after three months of nebivolol use.19,20

Sample-size calculation
A power analysis calculation was conducted using the site http://www.lee.dante.br/pesquisa/amostragem/calcculo_amostra.html. Assuming an error of 0.01 and a study power of 80%, the calculated size of the sample required in order to reject the hypothesis of nullity was 23.

Statistical analysis
Descriptive analysis was performed for qualitative variables, and quantitative results are presented as means ± standard deviations. The Wilcoxon test was used to compare quantitative variables before and after treatment with nebivolol, among these stage I hypertensive patients without previous treatment. All statistical analyses were performed using the Minitab 15.0 statistics software. For all tests, a P-value < 0.05 was considered significant.

Ethical authorization
This study was approved by the Research Ethics Committee of the Medical School and was registered under no. 312/2008. The study protocol was approved by the National Ethics Committee (CONEP-372/2007). Informed consent was obtained from all participants, in relation to both the treatment and the biochemical and hemodynamic evaluation.

RESULTS
The sample was composed of 26 patients (88.5% male) with a mean age of 49.7 ± 9.3 years, who were predominantly overweight (29.6 ± 3.1 kg/m²) and had large abdominal waist circumference (102.1 ± 7.2 cm). Significant decreases in systolic BP (P-value = 0.0020) and diastolic BP (P-value = 0.0049) were observed during the treatment with nebivolol, and these were associated with decreases in heart rate (P-value < 0.0001) and central BP (P-value = 0.0083) (Table 1). There was no difference in the AIx, with or without correction for heart rate, during the treatment period.

Table 1 displays the routine biochemical characteristics and the pulse pressure, heart rate, SBP and DBP levels at brachial artery level and tonometry parameters (AIx, AIx(75) and central BP). Body mass index, abdominal waist measurement, fasting plasma glucose, serum lipids and other biochemical parameters did not differ between before

<table>
<thead>
<tr>
<th>Variable</th>
<th>Initial</th>
<th>After treatment</th>
<th>P-value</th>
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<tr>
<td><strong>Peripheral hemodynamic parameters</strong></td>
<td></td>
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</tr>
<tr>
<td>Brachial systolic blood pressure (mmHg)</td>
<td>137.9 ± 11.5</td>
<td>128.5 ± 7.7</td>
<td>0.0020</td>
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<tr>
<td>Brachial diastolic blood pressure (mmHg)</td>
<td>85.5 ± 9.7</td>
<td>78.0 ± 9.0</td>
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<td>Brachial pulse pressure (mmHg)</td>
<td>52.4 ± 9.6</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>74.1 ± 8.4</td>
<td>64.0 ± 8.3</td>
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<td><strong>Central tonometry parameters</strong></td>
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<td>Augmentation index (%)</td>
<td>86.7 ± 9.8</td>
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<tr>
<td>Augmentation index corrected for heart rate (%)</td>
<td>87.0 ± 8.5</td>
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<tr>
<td>rSBP2 (mmHg)</td>
<td>129.9 ± 12.3</td>
<td>122.3 ± 10.3</td>
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<td><strong>Biochemical parameters</strong></td>
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<td>Hemoglobin (mg/dl)</td>
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<tr>
<td>Hematocrit (%)</td>
<td>46.8 ± 3.6</td>
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<td>Platelets (x10³)</td>
<td>227.4 ± 40.4</td>
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<td>Leukocytes (x10³)</td>
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<td>Glutamic oxaloacetic transaminase (U/l)</td>
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<tr>
<td>Glutamic pyruvic transaminase (U/l)</td>
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<td>Total cholesterol (mg/dl)</td>
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<tr>
<td>HDL-cholesterol (mg/dl)</td>
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<tr>
<td>LDL-cholesterol (mg/dl)</td>
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<td>Triglycerides (mg/dl)</td>
<td>244.4 ± 232.1</td>
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<tr>
<td>Urea (mg/dl)</td>
<td>35.5 ± 9.1</td>
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<td>NS</td>
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<tr>
<td>Total bilirubin (mg/dl)</td>
<td>0.9 ± 0.5</td>
<td>0.8 ± 0.3</td>
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</tbody>
</table>

rSBP2 = Late systolic blood pressure in the radial artery (= central blood pressure); NS = non-significant (P > 0.05).
and after treatment. Figure 1 shows a comparison of hemodynamic parameters (peripheral and central) between the basal and the follow-up evaluations among the patients treated with nebivolol. In this study, nebivolol significantly reduced brachial BP and central BP, even though the AIx and biochemical parameters remaining unchanged.

**DISCUSSION**

In the present study, we examined the 12-week effect of nebivolol on biochemical and tonometry parameters among stage I hypertensive patients without previous treatment. To our knowledge, this is the first study on Brazilian individuals to evaluate the beneficial effects of nebivolol on the hemodynamic profile, and it showed worthwhile reductions in peripheral and central blood pressure.

This study investigated in detail the potential effects of nebivolol, a beta-1 selective beta-blocker, on aortic stiffness, wave reflections and central hemodynamic parameters in patients with mild hypertension that had never been treated. In this study, nebivolol significantly reduced brachial and central BP, even though the AIx remained unchanged.

Brachial BP measurement is considered to be the best method for screening for and diagnosing clinical hypertension. However, over recent years, assessment of CV risk in subjects with hypertension has led to development of more sophisticated methods of BP measurement, such as central BP. Currently, several arguments suggest that central BP is more relevant than peripheral (brachial) BP for determining CV risk assessments. The pressure wave generated by the left ventricle travels down the arterial tree and then is reflected at any discontinuity of the arterial wall, especially multiple-resistance arterioles and their bifurcations. Thus, the pressure waveform recorded at any site of the arterial tree is the sum of a forward travelling waveform generated by left ventricular ejection and a backward travelling wave, reflected at peripheral sites. As a consequence of transmission of the pressure wave and reflections, SBP and pulse pressure (PP) are amplified by as much as 10-15 mmHg when moving from the aorta to the brachial artery. This phenomenon, which is not taken into consideration in published clinical guidelines, has three major consequences,
which relate to CV complications of hypertension, the choice of antihypertensive drugs and HR regulation.

Regarding CV complications, when large-conduit arteries are healthy and compliant (young individuals), the reflected wave merges with the incident wave in the proximal aorta mostly during diastole, thereby augmenting aortic DBP and supporting coronary perfusion. In contrast, when the arteries are stiff (old individuals), wave travel is faster and the reflected wave merges earlier with the incident wave, thus augmenting aortic systolic rather than diastolic pressure. As a result, left ventricular afterload is increased and coronary filling is compromised. This pathophysiological mechanism supports the idea that central BP is superior to peripheral BP for predicting CV risk and that it acts on CV risk independently of atherosclerosis and other traditional CV risk factors.19,21,22

The choice of drug treatment for hypertension is also influenced by wave reflections: both by their amplitude (i.e. the proportion of the incident wave which is reflected) and by their timing. Acutely, vasodilator drugs reduce the amplitude of wave reflections and hence SBP.23 This situation is observed typically with nitrates, but may also occur with SRA inhibitors or calcium channel blockers. With the presence of chronic hypertension, arterial and arteriolar remodeling modifies the baseline characteristics (geometry, distensibility and structure) of reflection sites, particularly at the arteriolar level. Under drug treatment, central SBP will be consistently reduced if vascular remodeling and reflection coefficients are adequately corrected (by means of SRA or calcium channel blockade), but will remain elevated if the structures of the microvasculature and the reflection coefficients remain poorly modified despite drug treatment (β-blockers).21

It is well accepted that calcium channel blockers and drugs acting on the RAS improve endothelial function and arterial stiffness.22–24 On the contrary, β-blockers have failed to show positive effects on vascular function and central hemodynamic parameters.1,25,26 For this reason, recent studies have questioned whether β-blockers are still an appropriate therapy for uncomplicated hypertension.1,25,27 Since β-blockers are a heterogeneous class of drugs with different pharmacological and physiological properties, it may not be possible to extrapolate the results gathered from these studies using atenolol, to other drugs of the same class. It has been well demonstrated that regardless of similar reductions in brachial BP, there are several differences between the currently available β-blockers.

Our results, along with other recent findings, support the conclusion that nebivolol has vascular effects that are more favorable than those of first and second-generation β-blockers. In a double-blind randomized study comparing nebivolol and metoprolol, Kampus et al.6 demonstrated that there was a significant reduction in brachial BP with a significant reduction in central BP only in the nebivolol group. In untreated hypertensive patients randomized to receive nebivolol or atenolol, Mahmud et al. observed a significant reduction in the brachial BP and pulse wave velocity associated with a significant reduction in AIx in the nebivolol group.7 Polónia et al. showed that for similar brachial BP and aortic stiffness, treatment with nebivolol was associated with lower central systolic BP than treatment with atenolol.8 On the other hand, Vitale et al. showed that nebivolol was not inferior to the angiotensin-receptor blocker irbesartan for improving endothelial function, arterial stiffness and central hemodynamic parameters in uncomplicated hypertensive patients.28

Studies on Caucasian and African-American subjects have suggested that the less effective central blood pressure control and consequently lower cardiovascular protection with older β-blockers may be due to an adverse effect from heart rate lowering on arterial wave reflection.29 Because of the vasodilator effect, the reduction in heart rate with nebivolol is lower than with other β-blockers, which leads to decreased wave reflection and improvement in arterial stiffness.30 Peripheral vasodilation also may contribute towards reducing the cardiac afterload, and towards reverting adverse arterial remodeling. Moreover, arterial stiffness is linked to endothelial dysfunction and reduced bioavailability of nitric oxide,11 a phenomenon that can be reduced with drugs that increase nitric oxide production, such as nebivolol. Our findings would support this mechanism and would explain the decrease in central aortic pressure observed in this study.

The present study had several limitations. These included the duration of follow-up, lack of a control group and the study design. If the patients had been followed for a longer time, perhaps we would have observed changes in the AIx. The lack of a comparison group, in our viewpoint, was the main limitation of this study. The randomised, placebo-controlled, and double blind trial represents the gold standard in evidence based medicine. However, this does not invalidate the significant results of central BP reduction after 12 weeks of treatment with nebivolol. Although brachial BP remains the principal tool used for the clinical diagnosis and monitoring of hypertension, there is an increasing body of evidence demonstrating that central BP measurement may be a better prognostic marker for hypertension.

Moreover, recent evidence suggests that some antihypertensive drugs can influence central BP more consistently than peripheral BP. This is especially true for agents acting on the RAS or calcium channel blockade, as well as newer β-blockers. Nevertheless, large prospective studies aiming to compare the predictive value of peripheral and central BP in the general population, as well as studies comparing the effectiveness of hypertension management based on peripheral BP measurements, compared with central BP measurements, are needed before
algorithms based on central BP can be recommended for clinical practice.

CONCLUSIONS

In summary, nebivolol presents a favorable effect as an antihypertensive drug with possible additional capacity to improve arterial stiffness by reducing central BP, a characteristic not exhibited by other \( \beta \)-blockers.

REFERENCES


Acknowledgement: The authors wish to thank Torrent-Brazil for financial support.

Source of funding: This study was supported by grants from Torrent-Brazil (Estudo APROVO Protocolo APV-C006)

Conflict of interest: None

Date of first submission: April 23, 2013
Last received: October 14, 2013
Accepted: October 18, 2013

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Natural history and surgical treatment of chordoma: a retrospective cohort study

História natural e tratamento cirúrgico de cordoma: um estudo retrospectivo de coorte

Samuel Aguiar Júnior, Wesley Pereira Andrade, Glauco Baiocchi, Gustavo Cardoso Guimarães, Isabela Werneck Cunha, Daniel Alvarez Estrada, Sergio Hideki Suzuki, Luiz Paulo Kowalski, Ademar Lopes

Hospital A. C. Camargo, São Paulo, Brazil

ABSTRACT

CONTEXT AND OBJECTIVE: Chordoma is a rare tumor with a high risk of locoregional recurrences. The aim of this study was analyze the long-term results from treating this pathological condition.

DESIGN AND SETTING: Cohort study in a single hospital in São Paulo, Brazil.

METHODS: This was a retrospective cohort study on 42 patients with chordoma who were treated at Hospital A. C. Camargo between 1980 and 2006. The hospital records were reviewed and a descriptive analysis was performed on the clinical-pathological variables. Survival curves were estimated using the Kaplan-Meier method and these were compared using the log-rank test.

RESULTS: Nineteen patients were men and 23 were women. Twenty-five tumors (59.5%) were located in the sacrum, eleven (26.2%) in the skull base and six (14.3%) in the mobile spine. Surgery was performed on 28 patients (66.7%). The resection was considered to have negative margins in 14 cases and positive margins in 14 cases. The 5-year overall survival (OS) was 45.4%. For surgical patients, the 5-year OS was 64.3% (82.2% for negative margins and 51.9% for positive margins). In the inoperable group, OS was 37.7% at 24 months and 0% at five years. 

CONCLUSION: Complete resection is related to local control and definitively has a positive impact on long-term survival.


INTRODUCTION
Chordoma is a rare malignant neoplasm that arises from primitive notochord remnants. It occurs exclusively in the axial skeleton and has a predilection for the sacrum (50%), base of the skull (35%) and mobile spine (15%).1-3 Although considered to be a low-grade and slow-growing tumor, a poor long-term prognosis is generally observed due to extensive local recurrences and secondary complications. Metastasis is usually reported as a late event.4
Proximity to neurological and other vital structures is the major challenge in making therapeutic decisions. Surgery is the mainstay of treatment and local control is better achieved with en bloc resection of the tumor with safe margins.1,2,4,5 Because of the poor responsiveness to radiotherapy, this treatment option is generally used only as adjuvant treatment after incomplete surgical resection, or in palliative management.4 Chemotherapy usually results in low response rates. Only a few clinical series have reported the use of chemotherapy for managing chordoma, which is generally used in the latter course of the disease and only as palliative treatment.6,7
Because of the rarity of this disease, only a few retrospective series have been published.

OBJECTIVE
The purpose of this study was to describe a single institution’s experience of treating chordoma.

METHODS
This was a retrospective cohort study on all 42 consecutive patients with chordoma who were treated in the A. C. Camargo Cancer Center between 1980 and 2006. The hospital records were reviewed and a descriptive analysis was performed on the clinical-pathological variables. Survival curves were estimated using the Kaplan-Meier method and the curves were compared using the log-rank test.

The patients were evaluated retrospectively in relation to age, sex, duration of symptoms until diagnosis, chordoma location, symptomatology, biopsy or surgery performed before being admitted into our hospital, treatment and surgical margins, adjuvant treatment, local recurrence, systemic metastasis, complications arising from disease evolution or treatment and mortality. Patients were considered to be asymptomatic if their tumors were discovered accidentally through image examinations conducted for another reason. The surgical resections were considered to have negative margins if they had negative macroscopic or microscopic margins; and positive margins if they had positive macroscopic margins.

Statistical analysis
The database was set up in the Statistical Package for the Social Sciences, version 16.0 for Mac (SPSS, Inc., Chicago, IL, USA). The length of follow-up was considered to be from the date of the patient’s admission to the date of the last objective follow-up information. The survival curves were estimated by means of the Kaplan-Meier method and the curves were compared using the log-rank test. In all the tests, P < 0.05 was taken to be statistically significant.

RESULTS
Nineteen patients were male (45.2%) and 23 were female (54.8%). At the time of diagnosis, the median age was 47 years (range: 5-86). The median follow-up was 28.5 months and the mean was 49.3 months (range: 1-261.6). The patients’ distribution according to their main characteristics is shown in Table 1. Data on the period of time from symptom onset to diagnosis were available for 37 patients (88%) with a median of 19 months (range: 1-48).

Twenty-five tumors (59.5%) were located in the sacrum, eleven (26.2%) in the skull base and six (14.3%) in the mobile spine (three cervical, two thoracic and one lumbar). In relation to the eleven tumors of the clivus (skull base), the main symptoms were pain (six cases), diplopia or strabismus (six cases), paresthesia (two cases), dysarthria (one case) and alteration of the motor function of the tongue (one case).

Regarding the 25 sacrococcygeal tumors, the main symptoms were pain (19 cases), presence of tumor mass in the sacrococcygeal region perceived by the patient (six cases), motor deficit or sensory neuropathy in lower limbs (six cases), constipation/bowel dysfunction (three cases) and bladder dysfunction (one case).

Twenty-eight patients (66.7%) were considered to be in the surgical treatment group and 14 patients (33.3%) were considered to be in the nonsurgical treatment group.

Surgical treatment
Nineteen patients (45.2%) had undergone previous surgical procedures in other institutions before admission. Only one (5.3%) had undergone complete resection previously, while 18 (94.7%) had had incomplete resections. Among the 18 patients who had previously undergone incomplete resections, 12 (66.7%) underwent salvage surgical procedures in our hospital. Five had negative margins and seven had resections with positive margins. The other six patients (33.3%) were considered to present operable disease, based on image analysis. Since these patients showed persistent disease that was measurable on images, they were considered to be in the nonsurgical group.

Twenty-eight patients (66.7%) were included in the surgical group of treatment. The surgical resection was considered to present negative margins in 14 cases (50%) and positive margins in the other 14 cases (50%).

The tumor site influenced the extent of the resection, since neurological structures are more involved when tumors are...
located in the clivus or mobile spine, rather than in the sacral location. Regarding the resection of the 16 sacral tumors, ten (62.5%) were considered to have negative margins and six (37.5%) were considered to have positive margins. Among the eight skull base tumor resections, three (37.5%) were considered to have negative margins and five (62.5%) were considered to have positive margins. Out of the six patients with mobile spine tumors, only four underwent surgical treatment. Just one (25%) had negative margins (cervical spine tumor) and the other three (75%) had positive margins (two cervical and one thoracic spine tumors). When we grouped the patients with mobile spine and clivus tumors, we found that the sacral tumors had higher rates

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Gender</th>
<th>Location</th>
<th>Margins</th>
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M = male; F = female; POS = positive margins; NEG = negative margins; CT = chemotherapy; RT = radiation therapy; Adj. = adjuvant; DOD = died of disease; NED = no evidence of disease; DOC = died of other causes; AWD = alive with disease. *Recurrence with new resection with positive margins.
of negative margins (62.5% versus 33.3%), although this did not reach statistical significance (P = 0.25).

Adjuvant treatment was performed with radiotherapy in nine cases (32.1%), of which four had negative margins (one skull base and three sacral tumors) and five had positive margins (two skull base, one mobile spine and two sacral tumors).

Neurological deficit was the most notable surgical morbidity. Out of the sixteen patients who underwent sacral resections, three (18.8%) had urinary incontinence, three (18.8%) had fecal retention and two (12.5%) had urinary retention. Among the eight skull base resections, one (12.5%) developed strabismus and two (25%) persistent swallowing disorders.

Nonsurgical treatment
Fourteen patients (33.3%) did not undergo surgical treatment in our hospital. Twelve (28.6%) patients had locally advanced tumors that were considered unresectable and the last two (4.7%) received only palliative support because of their poor clinical conditions. Of these, six patients had undergone surgery in another hospital, with incomplete resection. The tumors were considered unresectable based on imaging studies, in which the tumor was seen to involve the S1 sacral level in eight cases, had extensive skull base infiltration in three cases, and involved levels from C3 to T2 in one case. Ten patients (23.8%) were administered palliative radiotherapy and two (4.8%) were administered palliative chemotherapy.

Radiotherapy
Radiotherapy was used for 19 patients of this sample: four patients with negative margins, five patients with positive margins and ten patients with inoperable disease.

The type of radiotherapy currently used in our institution is intensity-modulated radiation therapy (IMRT).

Recurrence
Among the 14 patients who underwent resection with negative margins, six (42.8%) had local recurrence. Five were sacral tumors and one had received adjuvant radiotherapy. The remaining patient had a skull base tumor and did not receive adjuvant radiotherapy.

In the group with positive margins, four patients (28.5%) had stable disease during the follow-up, seven (50%) had only local progression and three developed metastases (21.4%): one with pulmonary disease alone and two with both local progression and distant disease (pulmonary and bone; pulmonary and hepatic). In the group that was considered inoperable, there were three patients (21.4%) that developed systemic metastasis (one skin and one lung).

From analysis on the group with negative margins, the five-year progression-free survival rate was 74%. The primary tumor site also did not influence the risk of recurrence (P = 0.11). Regarding adjuvant radiotherapy, no conclusion could be reached because only four patients (25%) with negative margins received adjuvant radiotherapy.

Overall survival
From the analysis on the whole sample, surgical treatment (Figure 1, P < 0.001) and surgical resection with negative margins (Figure 2, P = 0.021) were the only variables that influenced the risk of death in univariate analysis (Figures 1 and 2). Other variables like sex (P = 0.92), previous tumor manipulation (P = 0.16), tumor location (P = 0.87) and adjuvant radiotherapy (P = 0.845) did not influence overall survival.

![Figure 1. Kaplan-Meier curves for overall survival from surgical and nonsurgical treatment (P < 0.001).](image1)

![Figure 2. Kaplan-Meier curves for overall survival from resection with negative margins and resection with positive margins (P = 0.021).](image2)
Regarding the 14 patients who received nonsurgical/palliative treatment, one patient submitted to palliative support was lost from the follow-up. The median survival in this group was 9.7 months (range: 1.0-50.3). Of these, ten had undergone radiotherapy, two received chemotherapy alone and two received only best supportive care.

The median lengths of survival of the 10 patients who underwent radiotherapy, two patients who underwent chemotherapy and patient with palliative support were respectively 9.76, 13.0 and 7.4 months. There were no difference in survival between radiotherapy and chemotherapy in the nonsurgical group (P = 0.316).

Age did not affect survival. When we divided patients into two groups based on the median age, there was no statistical difference in overall survival between patients over and under the age of 47 years.

The five-year overall survival for all patients was 45.4%. Among the patients who underwent a surgical procedure, the five-year overall survival was 64.3% (82.2% for resections with negative margins and 51.9% for resections with positive margins). In the inoperable group, survival at 24 months was 37.7% and at five years, all patients had died due to the disease.

**DISCUSSION**

Chordoma is a rare malignant bone tumor originating in the axial skeleton, although it is the most common sacral primary neoplasm. The sacrum accounts for 50% of the primary sites for chordoma, followed by the skull base (35%) and mobile spine (15%). Almost the same distribution was also seen in our study (59.5% located in the sacrum, 26.2% in skull base and 14.3% in the mobile spine).

Because of the rarity of this disease, most of the previous clinical reports are based on retrospective series, with a long period of follow-up and with various types of treatment. When patients present with symptoms, they usually have radicular pain and sensory disorders relating to nerve root compression. The nonspecific symptoms often account for the diagnosis delay, with a median time period of 12 to 24 months. Our series corroborated these findings, with a median time period of 12 months before the diagnosis was confirmed.

Surgery is the mainstay of treatment. Wide en bloc resection with adequate bone and soft tissue margins is the primary surgical goal and is the main prognostic factor for local recurrence and an important predictor of mortality. However, sometimes, wide margins are very difficult to attain because these tumors are located at sites that are difficult to access, with high rates of complications and sequelae.

Kaiser et al. reported that local failure correlated with surgical tumor margin violation. They showed a local recurrence rate of 28% for patients who had completed en bloc resection and 64% if the tumor capsule was violated. York et al. reported a statistically significant difference in local failure between patients who underwent radical resection (2.3 years) and those who had incomplete excision (eight months). Bergh et al. demonstrated that local control was highly improved with more aggressive surgery. Only 17% of patients with wide margin resection developed local recurrences. On the other hand, local recurrences occurred in 81% of the patients who underwent intralesional or marginal surgery. The latter authors also showed that local recurrence was significantly associated with an increased risk of metastasis and tumor-related death.

In our report, surgical resection was the only variable that had a positive impact on overall survival. Patients who underwent resections with negative margins showed a better prognosis than those with positive margins. No patient with negative margins developed distant recurrence, even after local recurrence. Surgical resection had a critical value regardless of the primary site of the tumor.

The role of radiotherapy as primary or adjuvant treatment for chordoma has been investigated. Some authors, such as York et al., have reported prolonged progression-free survival with radiotherapy for patients with subtotal resection, whereas others have reported that this had little effect. Because of the small sample that underwent adjuvant radiotherapy in the present study, our report is too limited to formulate any conclusion. In our institution, IMRT is used. Some authors have described potential benefits from carbon ion radiotherapy, but we do not have this technology in our institution.

The quality of primary treatment is reflected in the surgical margins attained in the definitive surgery and seems to be critical for the final outcome. Among the patients who underwent resection with negative margins, 62.5% of them did not develop local recurrences. This factor was correlated with better five-year overall survival (84.4%). Among the 13 patients who had undergone incomplete resections in other institutions, seven (53.8%) had resections with negative margins in our hospital, with an obvious impact on survival for these patients. This finding supports the idea that primary surgery should be performed within a specialized multidisciplinary cancer center.

This study has some limitations because it was conducted retrospectively, but it will certainly help other researchers and surgeons to better understand this rare disease. It also raises some questions about the definitive role of adjuvant radiotherapy after incomplete resection, and inspires investigation about the role of other adjuvant treatments such as tyrosine kinase inhibitors. These issues might need to be addressed by further studies.

**CONCLUSION**

The primary goal in treating chordoma is still adequate surgical resection, and every effort needs to be made towards enabling...
complete removal of sacral, spinal and skull base chordomas. Complete resection is related to local control and definitively has a positive impact on survival.

REFERENCES

Sources of funding: None
Conflict of interest: None

Date of first submission: November 16, 2012
Last received: August 19, 2013
Accepted: October 22, 2013

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Leadership, management and teamwork learning through an extra-curricular project for medical students: descriptive study

Liderança, gestão e aprendizagem de trabalho em equipe através de projeto extracurricular para estudantes de medicina: estudo descritivo

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ABSTRACT

CONTEXT AND OBJECTIVE: Professionalism in medicine requires preparation for the globalized world. Our objective was to describe a project that introduces medical students to the community, hospital and laboratory activities, thereby allowing them to gain experience in people management, leadership and teamwork.

DESIGN AND SETTING: Descriptive study of the process applied at a philanthropic medical school in Curitiba, Paraná.

METHOD: Inclusion of management and leadership practices as part of the medical degree program.

RESULTS: The study groups consisted of fifteen students. After six months, any of the participants could be elected as a subcoordinator, with responsibility for managing tasks and representing the team in hospital departments and the community. The activities required increasing levels of responsibility. In medical schools, students’ involvement in practical activities is often limited to observation. They are not required to take responsibilities or to interact with other students and stakeholders. However, they will become accountable, which thus has an adverse effect on all involved. The learning space described here aims to fill this gap by bringing students closer to the daily lives and experiences of healthcare professionals.

CONCLUSION: Being a physician requires not only management and leadership, but also transferrable competencies, communication and critical thinking. These attributes can be acquired through experience of teamwork, under qualified supervision from teaching staff. Students are thus expected to develop skills to deal with and resolve conflicts, learn to share leadership, prepare others to help and replace them, adopt an approach based on mutual responsibility and discuss their performance.


RESUMO

CONTEXTO E OBJETIVO: Profissionalismo na medicina requer formação para o mundo globalizado. Nosso objetivo é descrever um projeto que introduz os estudantes de medicina em atividades laboratoriais, comunitárias e hospitalares, oferecendo experiência em gestão de pessoas, liderança e trabalho em equipe.

TIPO DE ESTUDO E LOCAL: Estudo descritivo do processo aplicado a uma escola médica filantrópica de Curitiba, Paraná.

MÉTODO: Inclusão de práticas de gestão e liderança como parte do programa de graduação médica.

RESULTADOS: Os grupos de trabalho eram constituídos por 15 estudantes. Após seis meses de participação, o estudante podia ser eleito como subcoordinator, responsável por gerenciar tarefas e representar a equipe junto aos setores do hospital e na comunidade. Na faculdade de medicina, frequentemente, o envolvimento dos alunos em atividades práticas restringe-se à observação, não existem demandas sobre a sua responsabilidade ou sua interação com outros alunos e atores. Entretanto, serão cobrados por isso, resultando em efeito adverso sobre todos os envolvidos. O espaço de aprendizagem aqui descrito visa preencher essa lacuna, trazendo os alunos para mais perto do cotidiano e das experiências dos profissionais de saúde.

CONCLUSÃO: Ser médico exige, ao lado de gestão e liderança, competências transferíveis, comunicação e pensamento crítico. Atributos adquiridos pela experiência do trabalho em equipe sob supervisão qualificada do corpo docente, quando os estudantes devem desenvolver habilidades para lidar e resolver conflitos, aprender a compartilhar a liderança, preparar outras pessoas para ajudar e substituir, adotar uma abordagem baseada na mútua responsabilidade e na análise de desempenho.
INTRODUCTION

In the globalized information age, cultural miscegenation and the ease with which people can travel have given rise to new values and needs. Linked to these changes is the quality of people's health, which is one of the main focuses of attention. Healthcare systems, both public and private, seek to adapt to these changes by dedicating particular attention to disease prevention, constant technological development and scientific discoveries. However, consolidation of healthcare, which is universally sought, is linked to the availability of qualified healthcare professionals.1,2

One important point of reference among healthcare professionals is the physician, whose training must include far more than clinical reasoning and technical skills. Communication skills, responsibility, altruism, humanistic attitudes and other competencies relating to emotions, as well as an understanding of the ethical and legal aspects of medicine and training in dealing with community interests are essential.3,4

Producing professionals with these qualifications requires constant improvements and the development of learning processes that include these competencies. In this context, the Flexner report stressed the need for scientific research to be included in medical training and the importance of teaching scientific principles and methods, evidence-based medicine, critical thinking and the solution of practical problems.5

Nonetheless, after many studies on the application of scientific research as a teaching method and learning process, undergraduate teaching and research continue along separate paths in many institutions.6 While the two areas often share the same physical space in teaching institutions, and in some cases a strategy is adopted in which undergraduate students are introduced to and apply scientific methods, this is done merely to encourage them to go on to postgraduate studies.7,8

To change this situation, the traditional curriculum needs to be reorganized by including technically oriented programs that offer scientific experiences integrating basic, applied and vocational training.

OBJECTIVE

This paper sought to describe an optional curricular activity that was designed to introduce students to the hospital community and provide guidance in practical and management activities in a quality control laboratory.

METHODS

This project was introduced in a private, not-for-profit, philanthropic medical school with a traditional curriculum covering basic scientific subjects and vocational clinical training separately, mainly through guided hospital-based teaching. The findings from the study were applied directly in the community where the study was carried out.

The team, consisting of a member of the teaching staff and students, provided services for the university hospital associated with the institution, and their duties included carrying out legally required quality control tests to control nosocomial infections according to the demand from the hospital's infectious disease control committee (IDCC). The teaching, administrative and laboratory activities were carried out in the university laboratories. The study covers the period 2003 to 2010.

RESULTS

Project organization

The microbiological analysis involved testing the water throughout the hospital as well as products from the food and nutrition department and all pasteurized material in the human milk bank. The activities were divided between three teams of medical students in their 5th to 10th semesters. The selection process for the fifteen students included a test on biological safety, quality control, microbiological diagnostics and infectious diseases followed by examination of candidates' résumés and an interview. Once approved, all the students started by learning how to wash and sterilize material, prepare culture media and carry out maintenance and quality control on equipment (refrigerator, freezer, autoclave and microwave oven).

The next stage involved collecting samples and carrying out laboratory tests. Following this, work protocols were prepared and standard operating procedures updated. Finally, the team members analyzed and recorded the data and discussed their results with their peers and various hospital departments. At this point, sub-coordinators could be elected. The tasks were organized and distributed every month according to the needs of the different hospital departments and students' learning objectives and academic activities. As students’ aptitudes for certain tasks became apparent, they were gradually assigned tasks that were more technically complex and demanded greater responsibility.

The last stage in the training required students to coordinate the team working with human milk. Although this activity was technically easier and less demanding than the previous ones, it involved a high degree of responsibility because the material was released directly for consumption.

Each student spent an average of ten hours on project activities every week. One constant source of concern was the need to ensure that students’ academic performance was not adversely affected. During the study period, project productivity increased significantly: a total of 1380 analyses were carried out in 2003, while in 2009 the corresponding figure was 5100, or 420 samples per month on average.

Management training program

The main reason for organizing the project in this way was to prepare students for team activities and roles requiring them
to exercise leadership. Each group consisted of a subcoordinator and four or five students in different semesters. Every six months, one of the eligible candidates was elected subcoordinator by the team members. Reelection was not allowed.

Four-hour weekly meetings were held to analyze and discuss questions relating to leadership, management, administrative, technical and educational issues, interpersonal relationships, safety procedures, analysis of results, analytical methods and any difficulties that had occurred in the previous week. Students were actively encouraged to correlate their experiences in medical school with their project activities, to examine the data scientifically, to compare the results with the literature and to take part in scientific events.

Minutes of the meetings were recorded and made fully available to students. The information in these served as a database that could be used for decision-making, further studies and assessment of the team’s activities. The students who took part in this project were supervised and worked with the mothers who were contributing to or using the milk bank and with staff from the various departments.

They spent time in the quality control laboratory, learning “hands on” about the legal requirements for controlling hospital infection, and carried out different tasks, from basic technical work to personnel management. Over the course of the study period, one student was asked to leave because of problems adapting to the project, and two left for personal reasons. By 2010, 56 students had taken part in the project, and 26 of these had completed their medical studies.

**DISCUSSION**

This paper describes an enriching experience involving a teaching method and learning space that were used to introduce students to a simple working environment that can easily be set up. The study not only provided an opportunity for students to take part in activities in a hospital setting and in the satellite communities, but also met the needs of the IDCC and the community for the services that the students provided.

The project also stimulated development of leadership and management competencies and skills, teamwork and interpersonal relations among the students, and accountability for the results of their work and the consequences of these results. A learning process like this needs to result in a product for students, so that they can appropriate and share knowledge and recognize other perspectives and possibilities for conceiving, perceiving and explaining reality.

Learning spaces are constructed by articulating learning and work processes and allowing students to participate in the formulation of alternative procedures and interventions.9-11 In a globalized world, it is of particularly importance to produce students who can occupy leadership and management positions and work in teams and, above all, who are ready to take up political and administrative positions in the academic world.12,13 Students in medical school take part in various activities alongside multiprofessional teams, fellow students and patients, but their roles in these are merely observational. No demands are made on them in terms of a requirement for them either to take responsibility for their actions or to interact with fellow students and other stakeholders. Furthermore, students are in general only required to be accountable for the results of their work and the consequences of these results during the final years of their course, a situation that naturally has an adverse effect on all those involved.10

The learning space described here has brought medical school students closer to the daily lives and experiences of healthcare professionals, has required them to be accountable for their professional activities and has stimulated communication and results from the first semesters of their course.14

According to de Souza et al., promoting collaboration between staff who teach basic, applied and vocational subjects and non-teaching healthcare professionals represents a major challenge. It is therefore difficult, in a project that combines basic and applied subjects with vocational practice, to ensure that healthcare measures are effective for the community. However, if teamwork is undertaken based on the needs and work routines of teaching and non-teaching health professionals and lecturers in basic subjects, all those involved will be able to work as they normally do, but together, thereby motivating student-oriented learning.9

Despite the fundamental importance of scientific research in producing critical, reflective professionals, it is considered by medical students to have little relationship to patients and individuals. A qualitative survey of undergraduate medical students’ perceptions of research found that more than a quarter (60/317) of those who took part made negative comments about it.12 This can be explained by the difficulty that medical students have in understanding the concepts involved in scientific research, starting with the professor/researcher situation. Teaching staff do not normally have the necessary background to produce students equipped with a knowledge of scientific methodology.

However, in comparing medical students from two courses with different curricula, Pruskil et al. found that individuals were more confident about their own scientific competencies when they had had more research opportunities. Many medical students identified research as something remote, a misconception that can be explained by the lack of research activities in medical programs.10

Putting students into a position in which they need to apply their acquired knowledge to day-to-day activities, while making reference to scientific articles and comparing results, favors development of critical thinking. Similarly, in a statement about the purpose of scenarios in physicians’ development, Blank proposed a new paradigm for an integrated approach that would allow physicians to intervene in a health-disease process within the overall context of the process, while balancing technical issues with social and behavioral issues.15
The aim of any medical school is to prepare students to practice medicine in an ethical, competent and socially responsible manner. It is very important to produce professionals who have an overall vision and aptitudes that span a variety of processes rather than just knowledge of medical procedures. Likewise, in addition to being able to solve clinical problems, students must work as researchers to enable them to be leaders in the healthcare community. To achieve this goal, a curriculum supported by educational programs that help students develop critical analysis, resolve problems and manage people is fundamental.

CONCLUSION
Nowadays, being a physician requires not only an understanding of management and leadership but also transferrable competencies, such as communication, teamwork, time management and critical thinking. These attributes can be acquired by exposure to teamwork, thus giving students the opportunity to use the knowledge that they have acquired, in real situations in which they are in charge under the supervision of members of the teaching staff. In this way, students can acquire the skills to deal with and solve conflicts, learn to share leadership, prepare others to help and replace them, approach their work with an attitude of mutual responsibility and hold discussions on detailed aspects of their performance. The model described here is notable for its potential, and consideration should be given to its inclusion in curricula in medical schools.

REFERENCES

Acknowledgements: We would like to thank the medical school at Faculdade Evangélica do Paraná for the many years of personal and professional development that it has made possible, the medical students who allowed us to learn with them and the CQM-FEPAR team for making the study happen.

Sources of funding: None
Conflict of interest: None

Date of first submission: March 8, 2013
Last received: October 18, 2013
Accepted: October 22, 2013

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Renal autotransplantation to treat renal artery aneurysm: case report

Autotransplante renal para tratamento de aneurisma de artéria renal: relato de caso

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ABSTRACT

CONTEXT: Renal artery aneurysm (RAA) is uncommon and usually asymptomatic, but complications like rupture or thromboembolism of the aneurysm can occur, with consequent renal infarction. Most of the clinical findings are found incidentally through imaging examinations, in investigating other diseases. Renal autotransplantation (RAT) is an alternative treatment for complex RAA, with satisfactory results described in the literature.

CASE REPORT: The patient was a 48-year-old man with a history of systemic arterial hypertension, thrombocytopenia and advanced hepatosplenic schistosomiasis. He complained of right lumbar pain, which was investigated through imaging examinations (computed tomography and angiotomography). These revealed right RAA of 2.5 cm in diameter. Evaluation by the vascular surgery team found that this was untreatable using endovascular methods. The treatment performed was open right nephrectomy with kidney preservation in solution, followed by aneurysmectomy, suturing of the injured artery and kidney reimplantation in the right iliac fossa with anastomosis of the iliac vessels and ureter. The durations of the surgery and kidney ischemia were 385 and 140 minutes, respectively. The patient was discharged on the 20\textsuperscript{th} postoperative day, with creatinine concentration of 1.4 mg/dL, urea 41 mg/dL, urine volume 1400 mL/24 h and ascites treated with diuretics.

CONCLUSION: RAT is indicated basically in three situations: extracorporeal reconstruction of complex aneurysms of the renal pedicle, extensive ureteral injury, and conservative kidney cancer surgery in patients with a single kidney. This study presents a case of a patient with advanced liver disease and RAA that was untreatable using endovascular methods and was successfully treated using RAT.

KEY WORDS:
Aneurysm.
Renal artery.
Transplantation.
General surgery.
Kidney.

PALAVRAS-CHAVE:
Aneurisma.
Artéria renal.
Transplante.
Cirurgia geral.
Rim.
INTRODUCTION
Renal artery aneurysm (RAA) is unusual and occurs in approximately 0.09% of the population.\(^1\) In general, this condition is asymptomatic, but severe complications such as rupture, embolism or thrombus expansion of the aneurysm with consequent renal infarction may occur. It is often diagnosed accidentally and is done through imaging tests such as computed tomography (CT) and arteriography during investigations of other diseases. Epidemiologically, it more often affects women and the left kidney; it is typically solitary and associated with fibromuscular dysplasia.\(^2,3\) The indications for treatment should take into consideration the patient’s age, sex, blood pressure and renal function, and the size of the aneurysm. Most often, a size of 2 cm has been considered to be the threshold for endovascular repair.\(^4\) Thus, renal autotransplantation (RAT) has emerged as an alternative for treating complex RAA.\(^4,5\)

CASE REPORT
The patient was a 48-year-old man with a previous history of high blood pressure and thrombocytopenia and a diagnosis of advanced hepatosplenic schistosomiasis. He reported having right lumbar pain, and this was found to be caused by an RAA of 2.5 cm in diameter, which was observed on CT and CT arteriography (Figures 1 and 2). The preoperative serum creatinine level was 1.8 mg/dl.

The patient was referred to the department of vascular surgery, but the RAA was considered to be untreatable using an endovascular approach. RAT was performed by the transplantation group. The treatment consisted of right nephrectomy and preservation of the kidney in Euro-Collins solution, followed by aneurysmectomy and artery reconstruction by means of end-to-end anastomosis between the renal artery and the hilar branches using 7/0 Prolene suturing on the back table (Figures 3 and 4).

Figure 1. Computed tomography showing right renal artery aneurysm.

Figure 2. Computed tomography arteriography showing aneurysm of approximately 2.5 cm in the right renal artery.

Figure 3. Renal artery aneurysm of 2.5 cm in diameter.

Figure 4. End-to-end anastomosis for reconstruction of the renal artery.
Kidney reimplantation was performed in the right iliac fossa. A renal vein graft was anastomosed end-to-side with the right external iliac vein using 5/0 Prolene suturing and the reconstructed renal artery graft was anastomosed end-to-end with the hypogastric artery using 7/0 Prolene suturing. Ureter anastomosis was performed using the modified Lich Gregoir technique on the anterolateral side of the bladder. The operation lasted 385 minutes and the time of ischemia renal graft was 140 minutes. The patient was extubated in the operating room and transferred to the intensive care unit, where he stayed for six days due to ascites caused by liver disease decompensation. He was discharged on the 20th postoperative day, with a creatinine level of 1.4 mg/dl, urea of 41 mg/dl, urine volume 1400 ml/24 h and ascites treated with diuretics. Currently, the patient is symptom-free, as seen at the 34th month follow-up with normal renal function (creatinine = 1.0 mg/dl).

DISCUSSION
In most cases, renal artery aneurysm does not cause any clinical symptoms, but some nonspecific signs such as lumbar pain may be present. In suspected cases, imaging tests should be performed and digital subtraction angiography is the best diagnostic test. When an aneurysm is identified, surgery is the best treatment option, in order to avoid hypertension or rupture of the aneurysm, especially in cases in which the aneurysm is larger than 2 cm in diameter and considered to comprise complex RAA.\(^5\)

RAT is mainly indicated in three situations: extracorporeal reconstruction of complex aneurysms of the renal pedicle; extensive ureteral injury; and conservative surgery due to kidney cancer in patients with only one kidney. Furthermore, RAT should be considered for treating renal artery aneurysm that is found to be untreatable by means of endovascular methods. Some reports in the literature have shown that RAT was effective in treating complex renal artery aneurysm\(^2,^4\) (Table 1).

Recently, the laparoscopic approach to nephrectomy has been increasingly used.\(^9\) In our case, we chose to use a surgical and non-endovascular approach towards treating RAA, because in our case it was too close to the bifurcation of the hilar renal artery and, especially, because of the need to preserve the kidney, given that schistosomiasis liver disease and portal hypertension can impair renal function. Anticoagulation was not used because there was thrombocytopenia and liver failure consequent to schistosomiasis.

CONCLUSION
In patients with a clinical risk of renal disorder following nephrectomy, RAT should be considered for treating RAA that is untreatable using endovascular methods.

Table 1. Search strategies performed in February 2012 and results from Pubmed, Embase, Lilacs (Literatura Latino Americana e do Caribe em Ciências da Saúde) and the Cochrane Library regarding the topic of renal autotransplantation in cases of renal aneurysms

<table>
<thead>
<tr>
<th>Database</th>
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<th>Results</th>
<th>Relevant findings</th>
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<td>(Renal) AND (transplantation) AND (aneurysm) with case report filter</td>
<td>382</td>
<td>Use of ex vivo repair or vein graft for arterial reconstruction of the aneurysmectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Laparoscopic nephrectomy with backbench ex vivo repair followed by autotransplantation through a small laparoscopic extraction incision</td>
</tr>
<tr>
<td>Lilacs (via Bireme)</td>
<td>(Renal) AND (transplantation) AND (aneurysm)</td>
<td>40</td>
<td>Renal autotransplantation is indicated in cases of complex aneurysms or ureteral injury</td>
</tr>
<tr>
<td></td>
<td>(Rim) AND (transplante) AND (aneurisma)</td>
<td>11</td>
<td>Vascular reconstruction bypass is indicated when the artery aneurysms cannot be corrected by endovascular treatment or in situ</td>
</tr>
<tr>
<td>Embase (via Elsevier)</td>
<td>(Renal transplantation) AND (aneurysm)</td>
<td>250</td>
<td>Most symptom-free aneurysms &lt; 2.5 cm in diameter can be safely treated expectantly</td>
</tr>
</tbody>
</table>

REFERENCES


Sources of funding: None
Conflict of interest: None

Date of first submission: February 19, 2013
Last received: October 23, 2013
Accepted: October 29, 2013

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Comorbidity between Klinefelter syndrome and diaphragmatic hernia. A case report

Comorbidade entre síndrome de Klinefelter e hérnia diafragmática. Um relato de caso

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ABSTRACT

CONTEXT: Intrathoracic cystic lesions have been diagnosed in a wide variety of age groups, and the increasing use of prenatal imaging studies has allowed detection of these defects even in utero.

CASE REPORT: A 17-year-old pregnant woman in her second gestation, at 23 weeks of pregnancy, presented an ultrasound with evidence of a cystic anechoic image in the fetal left hemithorax. A morphological ultrasound examination performed at the hospital found that this cystic image measured 3.7 cm x 2.1 cm x 1.6 cm. Polyhydramnios was also present. At this time, the hypothesis of cystic adenomatoid malformation was raised. Fetal echocardiography showed only a dextroposed heart. Fetal magnetic resonance imaging produced an image compatible with a left diaphragmatic hernia containing the stomach and at least the first and second portions of the duodenum, left lobe of the liver, spleen, small intestine segments and portions of the colon. The stomach was greatly distended and the heart was shifted to the right. There was severe volume reduction of the left lung. Fetal karyotyping showed the chromosomal constitution of 47,XXY, compatible with Klinefelter syndrome. In our review of the literature, we found only one case of association between Klinefelter syndrome and diaphragmatic hernia.

CONCLUSIONS: We believe that the association observed in this case was merely coincidental, since both conditions are relatively common. The chance of both events occurring simultaneously is estimated to be 1 in 1.5 million births.

RESUMO

CONTEXTO: Lesões císticas intratorácicas são diagnosticadas em ampla variedade de faixas etárias, e o uso aumentado dos estudos de imagem pré-natal tem permitido a detecção desses defeitos ainda intraútero.

RELATO DO CASO: Uma gestante de 17 anos que estava em sua segunda gravidez, com 23 semanas de gestação, apresentou ultrassom com evidência de imagem cística anecoica no hemitórax esquerdo fetal. O ultrassom morfológico realizado no hospital verificou que esta medida 3,7 cm x 2,1 cm x 1,6 cm. Evidenciou-se também a presença de polidrâmnio. Neste momento, levantou-se a hipótese de malformação adenomatoid de cística. A ecocardiografia fetal mostrou apenas coração desviado para a direita. A ressonância magnética fetal revelou imagem compatível com hérnia diafragmática à esquerda, contendo estômago e, pelo menos, primeira e segunda partes do duodeno, lobo esquerdo do fígado, baço, segmentos de intestino delgado e porções do colón. O estômago mostrou-se muito distendido e o coração, deslocado para a direita. Havia redução importante do volume do pulmão esquerdo. O cariótipo fetal mostrou constituição cromossômica 47,XXY, compatível com a síndrome de Klinefelter. Em nossa revisão da literatura, encontramos apenas um caso de associação entre síndrome de Klinefelter e hérnia diafragmática.

CONCLUSÃO: Acreditamos que a associação observada neste caso foi puramente uma coincidência, uma vez que ambas as condições são relativamente comuns. A chance de os dois eventos ocorrerem simultaneamente é estimada em 1 em 1,5 milhões de nascimentos.
INTRODUCTION
Intrathoracic cystic lesions have been diagnosed in a wide variety of age groups, and the increasing use of prenatal imaging studies has allowed detection of these defects even in utero. Diaphragmatic hernias are intrathoracic lesions characterized by a posterolateral defect of the diaphragm that allows passage of the abdominal viscera into the thorax.1

Klinefelter syndrome is considered to be the most common disorder of sex chromosomes. It was first described by Harry F. Klinefelter and colleagues in 1942 and it is clinically characterized by features related especially to gonadal development and fertility. Other findings frequently observed include tall stature, delayed speech development, learning disabilities and behavioral problems.2 However, Klinefelter syndrome may be difficult to diagnose without karyotyping analysis, especially in the fetus during pregnancy and during childhood, because the main features of the syndrome, such as azoospermia and increased gonadotropin levels, are observed only after the puberty period.2,3

Our aim was to report on a rare case of association between Klinefelter syndrome and diaphragmatic hernia, with diagnosis in utero.

CASE REPORT
A 17-year-old pregnant woman in her second gestation, with a prior history of a pregnancy loss, presented a nuchal translucency measurement of 2 mm, at the first-trimester screening. Obstetric ultrasound revealed the presence of a cystic anechoic image in the left hemithorax of the fetus. On average, she smoked five cigarettes per day. She denied using illicit drugs or alcohol. Her husband was a healthy and non-consanguineous 19-year-old man. There was no history of malformations or genetic diseases in the family.

A morphological ultrasound examination performed at the hospital, at 23 weeks and 6 days, confirmed the finding of the fetal cystic image. It measured 3.7 cm x 2.1 cm x 1.6 cm. Polyhydramnios was also present (Figure 1). Cystic adenomatoid malformation was initially considered as a diagnosis for the patient. Fetal echocardiography only showed a dextroposed heart.

Fetal magnetic resonance imaging showed polyhydramnios and findings compatible with left diaphragmatic hernia involving the stomach and at least the first and second portions of the duodenum (distended with fluid), left lobe of the liver, spleen, small intestine segments and portions of the colon. The stomach was greatly distended and the heart was shifted to the right. There was severe volume reduction of the left lung (Figure 2). Fetal karyotyping showed that the chromosomal constitution was 47,XXY, which was compatible with Klinefelter syndrome.

The child was born through cesarean section, at 34 weeks of gestation, with weight of 2,070 g, length of 45 cm, head circumference of 31 cm and Apgar scores of 6 at the first minute and 8 at the fifth minute. No dysmorphic features were seen in the child. He did not present micropenis or cryptorchidism. He underwent surgery on the diaphragmatic hernia on the fifth day of life. Duodenal atresia was also verified. An echocardiography showed the presence of an atrial septal defect of ostium secundum type. The child died a few days later due to complications from pulmonary hypoplasia.

DISCUSSION
In our review of the literature, we found only one case of an association between Klinefelter syndrome and diaphragmatic hernia (Table 1).4 The etiology of the diaphragmatic hernia is largely unknown and most cases are isolated, i.e. not associated with other malformations or conditions. However, it may be a component of some syndromes, such as Pallister Killian, Fryns and Brachman-De Lange.1 We believe that the association observed in the present case was merely coincidental, since both conditions are relatively common. The frequency of diaphragmatic hernia has been postulated to be up to 5 in 10,000 births, and about half of the patients are male.1 The incidence of Klinefelter syndrome is around 1 in 660 among newborn boys, and thus the estimate for occurrences of both events together would be around 1 in 1.5 million births. This chance is similar to that described by Taheri and Kadir4 for a fetus to be affected by both conditions.
Comorbidity between Klinefelter syndrome and diaphragmatic hernia. A case report

Samangaya et al.6 reported that the risk of having a chromosomal abnormality in a case of congenital diaphragmatic hernia after being diagnosed through ultrasound is up to 15.9%, which enhances the importance of fetal karyotyping in this situation.7 The chromosomal abnormalities observed among patients with congenital diaphragmatic hernia include tetrasomy 12p mosaicism and trisomy 18.1,8 Interestingly, cystic adenomatoid malformation was our first hypothesis for the intrathoracic cystic lesion observed in the fetus, and this has been poorly associated with chromosomal abnormalities, especially as an isolated defect.7

The prognosis for diaphragmatic hernia is still very poor.4 Fetuses with Klinefelter syndrome usually do not present associated major malformations and, differently from other chromosomal anomalies, such as Turner syndrome or trisomy 13 and 18, do not show increased rates of intrauterine mortality.2,9 Although the risk of dying due to a variety of diseases, such as malignant neoplasms, diabetes type 2 and respiratory and circulatory system diseases may be greater among Klinefelter patients,10 we believe that the chromosomal anomaly present in our patient did not interfere with the prognosis associated with his diaphragmatic hernia.

CONCLUSIONS
We believe that the association observed in this case was merely coincidental, since both conditions are relatively common. Further reports would be needed in order to conﬁrm a possible association between Klinefelter syndrome and diaphragmatic hernia. Our report also highlights the importance of using magnetic resonance imaging for elucidating fetal intrathoracic cystic lesions.

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Sources of funding: None
Conflict of interests: None
Date of first submission: June 21, 2013
Last received: October 31, 2013
Accepted: November 6, 2013

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Table 1. Results obtained from each database using the descriptors corresponding to the main features presented by the fetus/patient. The search in these databases was conducted on June 26, 2013.

<table>
<thead>
<tr>
<th>Database</th>
<th>Search strategy</th>
<th>Results</th>
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<td>Medline (Medical Literature Analysis and Retrieval System Online; via PubMed)</td>
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<td>SciELO (Scientific Electronic Library Online)</td>
<td>“Klinefelter syndrome” OR “47,XXY” AND “Hernia, Diaphragmatic”</td>
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HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis


The independent commentary was written by Gianna Mastroianni Kirsztajn

ABSTRACT

BACKGROUND: Cardiovascular disease (CVD) is the most frequent cause of death in people with early stages of chronic kidney disease (CKD), for whom the absolute risk of cardiovascular events is similar to people who have existing coronary artery disease. This is an update of a review published in 2009, and includes evidence from 27 new studies (25,068 participants) in addition to the 26 studies (20,324 participants) assessed previously; and excludes three previously included studies (107 participants). This updated review includes 50 studies (45,285 participants); of these 38 (37,274 participants) were meta-analysed.

OBJECTIVE: To evaluate the benefits (such as reductions in all-cause and cardiovascular mortality, major cardiovascular events, MI and stroke, and slow progression of CKD to end-stage kidney disease (ESKD)) and harms (muscle and liver dysfunction, withdrawal, and cancer) of statins compared with placebo, no treatment, standard care or another statin in adults with CKD who were not on dialysis.

METHODS:
Search methods: We searched the Cochrane Renal Group’s Specialised Register to 5 June 2012 through contact with the Trials’ Search Co-ordinator using search terms relevant to this review.
Selection criteria: Randomised controlled trials (RCTs) and quasi-RCTs that compared the effects of statins with placebo, no treatment, standard care, or another statins, on mortality, cardiovascular events, kidney function, toxicity, and lipid levels in adults with CKD who were not on dialysis were the focus of our literature searches.
Data collection and analysis: Two or more authors independently extracted data and assessed study risk of bias. Treatment effects were expressed as mean difference (MD) for continuous outcomes (lipids, creatinine clearance and proteinuria) and risk ratio (RR) for dichotomous outcomes (major cardiovascular events, all-cause mortality, cardiovascular mortality, fatal or non-fatal myocardial infarction (MI), fatal or non-fatal stroke, ESKD, elevated liver enzymes, rhabdomyolysis, cancer and withdrawal rates) with 95% confidence intervals (CI).

MAIN RESULTS: We included 50 studies (45,285 participants); 47 studies (39,820 participants) compared statins with placebo or no treatment and three studies (5547 participants) compared two different statin regimens in adults with CKD who were not yet on dialysis. We were able to meta-analyse 38 studies (37,274 participants). The risk of bias in the included studies was high. Seven studies comparing statins with placebo or no treatment had lower risk of bias overall, and were conducted according to published protocols, outcomes were adjudicated by a committee, specified outcomes were reported, and analyses were conducted using intention-to-treat methods. In placebo or no treatment controlled studies, adverse events were reported in 32 studies (68%) and systematically evaluated in 16 studies (34%). Compared with placebo, statin therapy consistently prevented major cardiovascular events (13 studies, 36,033 participants; RR 0.72, 95% CI 0.66 to 0.79), all-cause mortality (10 studies, 28,276 participants; RR 0.79, 95% CI 0.69 to 0.91), cardiovascular death (7 studies, 19,059 participants; RR 0.77, 95% CI 0.69 to 0.87); and MI (8 studies, 9018 participants; RR 0.55, 95% CI 0.42 to 0.72). Statins had uncertain effects on stroke (5 studies, 8658 participants; RR 0.62, 95% CI 0.35 to 1.12). Potential harms from statin therapy were limited by lack of systematic reporting and were uncertain in analyses that had few events: elevated creatine kinase (7 studies, 4514 participants; RR 0.84, 95% CI 0.20 to 3.48), liver function abnormalities (7 studies, RR 0.76, 95% CI 0.39 to 1.50), withdrawal due to adverse events (13 studies, 4219 participants; RR 1.16, 95% CI 0.84 to 1.60), and cancer (2 studies, 5581 participants; RR 1.03, 95% CI 0.82 to 1.30).

Statins had uncertain effects on progression of CKD. Data for relative effects of intensive cholesterol lowering in people with early stages of kidney disease were sparse. Statins clearly reduced risks of death, major cardiovascular events, and MI in people with CKD who did not have CVD at baseline (primary prevention).

AUTHORS’ CONCLUSIONS: Statins consistently lower death and major cardiovascular events by 20% in people with CKD not requiring dialysis. Statin-related effects on stroke and kidney function were found to be uncertain and adverse effects of treatment are incompletely understood. Statins have an important role in primary prevention of cardiovascular events and mortality in people who have CKD.

This is the abstract of a Cochrane Review published in the Cochrane Database of Systematic Reviews 2014, issue 5, Art. No.: CD007784. DOI: 10.1002/14651858.CD007784.pub2 (http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007784.pub2/abstract). For full citation and authors’ details, see reference 1.

REFERENCE

COMMENTS

Statins improve cardiovascular outcomes in cases of chronic kidney disease

For some time now, clinicians who deal with chronic kidney disease (CKD) have been awaiting data of greater consistency regarding the real contribution of statins towards treating patients with CKD at the different stages that precede the need for kidney replacement therapy. Given the strong association between CKD and cardiovascular outcomes, as well as between dyslipidemia and such outcomes, defining whether therapeutic interventions (like statin administration) aimed at dyslipidemia in stages 1 to 4 of CKD have a positive influence on CKD progression and cardiovascular outcomes is an important goal from a clinical point of view.
The study by Palmer et al. certainly approaches these questions comprehensively, bringing a large number of individuals together through meta-analysis. This analysis sought especially to include randomized controlled trials comparing statin therapies versus placebo or no treatment, and evaluated the cardiovascular and renal benefits, along with adverse effects. This study has unquestionable relevance to medical practice, through giving clinicians the information that statins in fact reduce death and major cardiovascular events by 20% in patients with CKD who are not at the point of needing kidney renal replacement therapy. On the other hand, these findings have not yet been confirmed in dialysis patients. It should be noted that even after analyzing data on more than 37,000 patients with CKD, it was not possible to establish what the role of dyslipidemia correction is in relation to CKD progression, or what the real contribution of hyperlipidemia is in this process. This is still a controversial topic, with implications for the decision to treat dyslipidemia, the time at which this should be done and its intensity. Lastly, the impact of statin administration on CKD progression, particularly in the earlier stages of the disease, is still a relevant motive for further investigations.

Gianna Mastroianni Kirsztajn, MD, MSc, PhD. Nephrologist, Full Professor, Adjunct Professor and Head of the Division of Nephrology, Department of Medicine, Universidade Federal de São Paulo (Unifesp), São Paulo, Brazil.
Perioperative corticosteroids for preventing complications following facial plastic surgery

Edina Mariko Koga da Silva, Bernardo Hochman, Lydia Masako Ferreira

The independent commentary was written by Rolf Gemperli and Alexandre Mendonça Munhoz

ABSTRACT

BACKGROUND: Early recovery is an important factor for people undergoing facial plastic. However, the normal inflammatory processes that are a consequence of surgery commonly cause oedema (swelling) and ecchymosis (bruising), which are undesirable complications. Severe oedema and ecchymosis delay full recovery, and may make patients dissatisfied with procedures. Perioperative corticosteroids have been used in facial plastic surgery with the aim of preventing oedema and ecchymosis.

OBJECTIVES: To determine the effects, including safety, of perioperative administration of corticosteroids for preventing complications following facial plastic surgery in adults.

METHODS:

Search strategy: In January 2014, we searched the following electronic databases: the Cochrane Wounds Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library), Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid Embase; EBSCO CINAHL; and Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS). There were no restrictions on the basis of date or language of publication.

Selection criteria: We included RCTs that compared the administration of perioperative systemic corticosteroids with another intervention, no intervention or placebo in facial plastic surgery.

Data collection and analysis: Two review authors independently screened the trials for inclusion in the review, appraised trial quality and extracted data.

MAIN RESULTS: We included 10 trials, with a total of 422 participants, that addressed two of the outcomes of interest to this review: swelling (oedema) and bruising (ecchymosis). Nine studies on rhinoplasty used a variety of different types, and doses, of corticosteroids. Overall, the results of the included studies showed that there is some evidence that perioperative administration of corticosteroids decreases formation of oedema over the first two postoperative days. Meta-analysis was only possible for two studies, with a total of 60 participants, and showed that a single perioperative dose of 10 mg dexamethasone decreased oedema formation in the first two days after surgery (SMD = -1.16, 95% CI: -1.71 to -0.61, low quality evidence). The evidence for ecchymosis was less consistent across the studies, with some contradictory results, but overall there was some evidence that perioperatively administered corticosteroids decreased ecchymosis formation over the first two days after surgery (SMD = -1.06, 95% CI: -1.47 to -0.65, two studies, 60 participants, low quality evidence). The difference was not maintained after this initial period. One study, with 40 participants, showed that high doses of methylprednisolone (over 250 mg) decreased both ecchymosis and oedema between the first and seventh postoperative days. The only study that assessed facelift surgery identified no positive effect on oedema with preoperative administration of corticosteroids. Five trials did not report on harmful (adverse) effects; four trials reported that there were no adverse effects, and one trial reported adverse effects in two participants treated with corticosteroids as well as in four participants treated with placebo. None of the studies reported recovery time, patient satisfaction or quality of life. The studies included were all at an unclear risk of selection bias and at low risk of bias for other domains.

AUTHORS’ CONCLUSIONS: There is limited evidence for rhinoplasty that a single perioperative dose of corticosteroids decreases oedema and ecchymosis formation over the first two postoperative days, but the difference is not maintained after this period. There is also limited evidence that high doses of corticosteroids decrease both ecchymosis and oedema between the first and seventh postoperative days. The clinical significance of this decrease is unknown and there is little evidence available regarding the safety of this intervention. More studies are needed because at present the available evidence does not support the use of corticosteroids for prevention of complications following facial plastic surgery.


REFERENCE


COMMENTS

Most patients seeking facial rejuvenescence surgery desire less extensive procedures and a faster return to social and work activities. In this type of plastic surgery, rhytidectomy and rhinoplasty are the procedures most performed worldwide and all attempts to improve the outcome and minimize discomfort are relevant. Thus, the authors of this systematic review should be congratulated, given that they have provided important data concerning the results and complications in facial plastic surgery and the role of corticosteroids. Corticosteroids are used in facial esthetic surgery to reduce postoperative edema and improve the postoperative recovery. In a randomized, double-blind study, Rapaport et al. evaluated 50 consecutive patients who underwent facial plastic surgery procedures with randomization into groups with steroids (6 mg of betamethasone preoperatively) and without steroids. It was concluded that there were no significant differences between the two groups at any postoperative interval. On the other hand, Youssef et al. evaluated the use of steroids to decrease postoperative edema following rhinoplasty. Their results indicated that steroids should be given to patients undergoing rhinoplasty in order to de-
crease postoperative periorbital edema, especially during the first three days. However, steroids had little effect after the third day. Similarly, in a recent systematic review of the literature, Pulikkotil et al. did not observe any statistically significant long-term reduction in postoperative edema or ecchymosis after rhinoplasty, although significant reductions were noted over the short term (less than two days).³

Thus, based on the present data, we believe that corticosteroids are not indicated for the postoperative period following facial plastic surgery. Moreover, it is unclear whether there are any significant benefits from steroid use after rhytidectomy, and this is a matter of controversy. In the future, the results need to be evaluated more critically in an attempt to establish safe and effective practice guidelines, so as to maximize surgical safety as well as the esthetic result. Therefore, the requirements for information based on scientific data and informed consent make it necessary to discuss the impact of surgery and likely complications. We believe that the present review provides a new contribution to the facial plastic surgery literature.

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REFERENCES
Indexing and scope

The São Paulo Medical Journal/Evidence for Health Care was founded in 1932. Its articles are indexed in Medline, Lilacs, SciELO, Science Citation Index Expanded, Journal Citation Reports/Science Edition (ISI) and EBSCO Publishing.

Published bimonthly by the Associação Paulista de Medicina, the journal accepts articles in the fields of clinical health science (internal medicine, gynecology and obstetrics, mental health, surgery, pediatrics and public health). Articles will be accepted in the form of original articles (clinical trials, cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies and systematic reviews with or without meta-analysis), narrative reviews of the literature, case reports, short communications and letters to the editor. Papers with a commercial objective will not be accepted.

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The manuscript must be submitted in English. Nonetheless, it must also include a summary and five key words both in Portuguese and in English. The key words must be selected from the DeCS and MeSH lists only, as explained in detail below (no other key words will be accepted).

Papers submitted must be original and therefore all the authors need to declare that the text has not been and will not be submitted for publication in any other journal. Papers involving human beings (individually or collectively, directly or indirectly, totally or partially, including the management of information and materials) must be accompanied by a copy of the authorization from the Research Ethics Committee of the institution in which the experiment was performed.

All articles submitted must comply with the editorial standards established in the Vancouver Convention (Uniform Requirements for Manuscripts Submitted to Biomedical Journals) and the specific quality guidelines for papers reporting on clinical trials (CONSORT), systematic reviews and meta-analyses (PRISMA), observational studies (STROBE) and accuracy studies on diagnostic tests (STARD).

The style known as the “Vancouver Style” is to be used not only for the format of the references, but also for the whole text. The Editors recommend that authors should familiarize themselves with this style by accessing http://www.icmje.org.

Abbreviations must not be used, even those in common use. Drugs or medications must be referred to using their generic names, avoiding unnecessary mention of commercial or brand names, and should be followed by the dosage and posology. Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, prostheses, orthoses and intraoperative devices must be described together with the manufacturer’s name and place (city and country) of manufacture in parentheses.

Grants, bursaries and any other financial support for studies must be mentioned separately after the references, in a section named “Acknowledgements”, along with any other acknowledgements to individuals or professionals who have helped in producing the study but whose contribution does not constitute authorship (we recommend that the item “Authorship” at http://www.icmje.org should be read to obtain clarifications regarding the criteria for authorship).

For any type of study, all statements in the text that are not results from the study presented for publication in the São Paulo Medical Journal/Evidence for Health Care, but are data from other studies already published elsewhere must be accompanied by citations of the pertinent literature. Thus, statements about the incidence or
prevalence of diseases, costs, frequency of use of certain therapies and epidemiological data in general should be followed by the references for the surveys that generated this information, even if the data come from government institutions or databases, given that these are data from other studies.

Format

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The first page must contain:

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3) the full name of each author (the editorial policy of the São Paulo Medical Journal is that abbreviations for authors’ names must not be used; thus, names should either be sent complete or with middle names omitted, for example: an author whose full name is John Richard Smith can be presented as John Smith or John Richard Smith, but not as John R. Smith; likewise, use Christopher Smith and not Chris Smith, or William Smith and not Bill Smith, and so on)), his/her academic titles (abbreviated in English), in the order obtained (for example: MD for medical doctor, MSc for holders of a master’s title, PhD for holders of a doctorate or BSc for bachelor of science, such as in biology), and the positions currently held (for example, Doctoral Student, Attending Physician, Adjunct Professor, Associate Professor, Head of Department, etc.), in the department and institution where he/she works, and the city and country;
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5) the complete address (name of street or avenue, building number, city) of the corresponding author, telephone and e-mail that can be published together with the article.

Second page: abstract (English and Portuguese) and key words
The second page must include the title and an abstract (English and Portuguese, maximum of 250 words each), structured in five items:

1) context and objective;
2) design (type of study) and setting (place where the study was developed);
3) methods (described in detail);
4) results; and
5) conclusions.

The abstract (both in English and in Portuguese) should contain five key words. The English terms must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which are available on the internet (http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh).10 The Portuguese terms must be chosen from the Descritores em Ciências da Saúde (DeCS), developed by Bireme, which are available on the internet (http://decs.bvs.br/).11

References
The list of references (in the “Vancouver style”, as indicated by the International Committee of Medical Journal Editors, ICME) should be laid out in the final part of the article, after the conclusions and before the tables and figures. In the text, the references must be numbered according to the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences (see examples in the preceding section), and must be in superscript form (without using parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references cited in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression “et al.” For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into their computer internet browsers, the journal’s readers will be taken to the exact document cited, and not to a general website. The following are some examples of the most common types of references:

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The last page must contain:

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2) sources of support in the forms of finance for the project, study bursaries or funding for purchasing equipment or drugs. The protocol number for the funding must be presented;
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be prepared in Microsoft Excel (do not send them in image formats) and must be accompanied by the tables of data from which they have been generated. The number of illustrations must not exceed the total number of pages minus one.

All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The legend or title sentence should be short but comprehensible without depending on reading the article.

All the figures and tables should be cited in the text.

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Clinical trials, cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies, and systematic reviews with or without meta-analysis, are considered to be original articles.

The São Paulo Medical Journal/Evidence for Health Care supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, from 2008 onwards, manuscripts on clinical trials have been accepted for publication only if they have received an identification number from one of the clinical trial registers that have been validated in accordance with the criteria established by WHO and ICMJE. Authors of randomized clinical trials must thus register their studies before submitting them for publication in the São Paulo Medical Journal/Evidence for Health Care. The addresses for these registers are available from the ICMJE website (http://www.icmje.org). The identification number should be declared at the end of the abstract.

Authors will be required to comply with the guidelines for writing each type of original article, as follows:

1. Observational articles: STROBE Statement;5,6
2. Clinical trials: CONSORT Statement;2
3. Accuracy studies on diagnostic tests: STARD Statement;5,6
4. Systematic reviews of the literature and meta-analyses: PRISMA4

The São Paulo Medical Journal takes the view that these guidelines not only aid in writing and organizing the content of articles in a standardized manner, thereby improving their quality and facilitating reading and assessment, but also these guidelines help to avoid situations in which important information on the methodology of studies remains outside of the manuscript.

As a partner institution of the Cochrane Collaboration and the Brazilian Cochrane Center, the Associação Paulista de Medicina considers that production of articles in accordance with these guidelines also aids in future production of systematic reviews of the literature and meta-analyses. Thus, articles submitted for publication that are not in accordance with these norms may be returned to their authors for adjustment before the peer review process begins.

Original articles must be structured so as to contain the following parts: Introduction, Objective, Methods, Results, Discussion and Conclusion. The text must not exceed 5,000 words (excluding tables, figures and references), from the introduction to the end of the conclusion, and must include a structured abstract with a maximum of 250 words.9 “Structured abstract” means that the abstract must contain the following items: Context and objective, Design and setting, Method, Results and Conclusion.

The structure of the document should follow the format laid out below:

1) Title and abstract: the study design and/or the way participants were allocated to interventions, for example “randomized” or “retrospective” study, should be mentioned in the title and in the abstract. The abstract should provide a summary of what was done and what was found.

2) Introduction: specify the reasons for carrying out the study, describing the present state of knowledge of the topic. Describe the scientific background and “the state of the art”. Do not include here any results or conclusions from the study. Use the last paragraph to specify the principal question of the study, and the principal hypothesis tested, if there is one. Do not include discussions about the literature in the introduction; the introduction section should be short.

3) Objective: describe briefly what the main objective or question of the study was. Clearly describe the pre-specified hypotheses.

4) Methods

4.1) Type of study: describe the design of the study and specify, if appropriate, the type of randomization (the way in which draws were conducted), the blinding (how this was ensured), the diagnostic test standards (gold standard or range of normal values) and the time direction (retrospective or prospective). For example: “randomized clinical trial”, “double-blind placebo-controlled clinical trial”, “cross-sectional accuracy study”, “retrospective cohort study”, “cross-sectional prevalence study” or “systematic review of clinical trials”.

4.2) Sample, participants or patients: describe the eligibility criteria for participants (inclusion and exclusion criteria) and the sources and procedures for selection or recruitment. In case-control studies, describe the rationale for distributing the subjects as cases and controls, and the matching criteria. The numbers of patients at the beginning and end of the study (after exclusions) must be made clear. A flow diagram showing the initial recruitment, the exclusions and the
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4.3) Setting: indicate the place where the study was carried out, including the type of healthcare provided (i.e. whether primary or tertiary; and whether in a private or in a public hospital). Avoid stating the name of the institution where the study was developed (for blinding purposes in the peer review). Only the type of institution should be made clear, for example: “public university hospital” or “private clinic”.

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4.5) Main measurements, variables and outcome: state what the primary and secondary outcomes analyzed in the study are. Describe the method of measuring the primary result, in the way in which it was planned before data collection. For each variable of interest, detail the assessment methods. If the hypothesis of the study was formulated during or after data collection (and not before), this needs to be declared. Describe the methods used to enhance the quality of measurements (for example, multiple observers, training, etc.) and to avoid bias. Explain how quantitative variables were handled in the analyses.

4.6) Sample size and statistical analysis: describe the sample size calculation method, or the study period in the event that patients were consecutively admitted over a period. Readers need to understand why a given number of patients was used. The planned statistical analysis, the statistical tests used and their significance levels, along with any post hoc analyses, should be presented in this section. Describe the methods used to control for confounding factors and variables, and explain how missing data and cases lost from the follow-up were dealt with.

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5) Results: describe the main findings. If possible, these should be accompanied by their 95% confidence intervals and the exact level of statistical significance (it is not enough to write “P < 0.05”: the exact P value should be supplied). For comparative studies, the confidence interval must be stated for the differences between the groups.

5.1) Participant flow diagram: describe the flow of participants through each stage of the study (inclusions and exclusions) and the follow-up period, and the number of participants completing the study (or lost from the follow-up). Use a flow diagram to demonstrate the numbers of patients, from the initial recruitment to the end of the study, and the reasons for exclusions. If there was any “intention-to-treat” analysis, describe it.

5.2) Deviations: if there was any deviation from the protocol, away from what was initially planned, describe it and the reasons for it.

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6) Discussion: provide an interpretation of the results, taking into account the study hypotheses and conclusions. Emphasize the new and important factors encountered in the study, which will form part of the conclusion. Do not repeat data presented in the introduction or results in detail. Mention any limitations of the findings that should be noted and any possible implications for future research. Describe any potential bias. Report any relevant findings from other studies: it is important to review the recent literature to seek new evidence that may have been published, which needs to be discussed. State whether the findings can be generalized to populations (i.e. whether the findings have external validity). It is recommended that the last two paragraphs should contain implications for practice and for future research.

7) Conclusions: specify only the conclusions that can be sustained by the results, together with their clinical significance (avoiding excessive generalization). Draw conclusions based on the objectives and hypotheses of the study. The same emphasis should be placed on studies with positive and negative results.

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Short communications and case reports must be limited to 3,000 words (from the introduction to the end of the conclusion). Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured thus: Introduction, Objective, Methods, Results, Discussion and Conclusion, like in original articles. Individual case reports should contain: Introduction, Case Report, Discussion and Conclusion. Reports on case series constitute...
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Both short communications and case reports must be submitted with abstracts and key words. The abstracts in short communications should be structured with: Context and objective, Design and setting, Methods, Results and Conclusion, like in original articles. The abstracts in case reports and case series should contain: Context, Case Report (with a description of the case and a pertinent discussion) and Conclusion.

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Narrative reviews may be accepted by the São Paulo Medical Journal/Evidence for Health Care and should be structured with: Introduction, Objectives, Methods, Results, Discussion and Conclusions. The abstract must be structured with: Context and objective, Design and setting, Methods, Results and Conclusions, like in original articles. The manuscript must comply with the norms of the Vancouver style and must include a systematic search in the main databases: Medline, Embase, Lilacs and Cochrane Library. The search strategy for each database and the number of articles obtained from each database should be presented in a table. The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bioreme). For the search strategies, MeSH terms must be used for Medline, LILACS and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, search strategy must be performed, at the same time, with English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, AND NOT).

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Letters to the editor may address articles published in the São Paulo Medical Journal/Evidence for Health Care or may deal with health issues of interest. Case reports must not be submitted as letters. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

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