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Thyroid disorders in Brazil: time for action

Distúrbios da tireoide no Brasil: hora de agir

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Chronic diseases are the leading cause of death and hospitalization in Brazil. In this regard, attention has been drawn to cardiovascular, neoplastic, respiratory, digestive and mental diseases, but not to thyroid disorders.[1,2] There is certainly a contradiction between the epidemiological profile and the fact that thyroid conditions are one of the most prominent points of interest for clinicians. This discrepancy between the collective and individual approach probably arises because diagnosis, treatment, screening and prevention of thyroid diseases have been outstanding actions of both public health and medicine over the last two centuries. Nowadays, occurrences of patients with myxedematous facies and Graves's disorder are less frequent because of the combination of awareness among physicians of the symptoms and signs of thyroid dysfunction, availability of thyroid tests and use of inexpensive medicines for thyroid replacement or for blocking hyperfunction of the thyroid gland.

One successful public health action that is rarely mentioned by epidemiologists is the iodine supplementation that was proposed 170 years ago, which may have been one of the first examples of "translational medicine." Goiter has been treated in China with marine sponges and seaweeds since 1900 BC and in Europe with burnt and dried marine sponges, cuttlefish and starfish since the 13th century. In 1812, Gay-Lussac isolated the chemical element iodine from seaweed. Very soon thereafter, in 1813, physicians in Switzerland and England hypothesized that iodine should be the first-choice treatment for people with goiter, and iodine has been widely prescribed since then for people with goiter. In Colombia in 1825, J. Baptiste Boussingault recommended goiter prophylaxis with iodized salt.[3]

It may be that iodine deficiency after the postnatal period is a cause of goiter: in fact, a compensatory disease. Furthermore, iodine deficiency in utero can impair brain development, with marked effects on the psychoneural evolution of newborns, children and adolescents, thus leading to adults with an intellectual handicap called cretinism. Screening for hypothyroidism was applied worldwide subsequent to the results from the New England Congenital Hypothyroidism collaborative study, in which newborns with hypothyroidism received treatment from the 5th to the 40th day of life, i.e. before the appearance of any recognizable clinical manifestations, which led to good intelligence quotients.[4]

Today, there is serious concern about how effective the neonatal screening and iodine supplementation polices implemented in Brazil have been. This is due not only to the impact on children's intellectual development caused by lack of access to screening, but also to the effects of under or oversupplementation of iodine. High levels of salt iodination can possibly be correlated with outcomes such as thyroid cancer and imbalance of thyroid hormone distribution in the population, thereby elevating the proportion of people with subclinical hypothyroidism or hyperthyroidism. Unfortunately, two initiatives funded by the Ministry of Health, named the National Program for Neonatal Screening (NPNS) and the National Survey for Evaluation of the Impact of Salt Iodation (Pesquisa Nacional para Avaliação do Impacto da Iodação do Sal, PNAISAL), have not released updated data coming from the results from these surveys.

NEONATAL SCREENING FOR HYPOTHYROIDISM

In Brazil, neonatal screening for congenital hypothyroidism began in 1976, through voluntary work by Dr. Benjamin Schmidt, a professor of Pediatrics, at APAE-SP (a non-governmental organization of parents and friends of disabled children in the state of São Paulo). Only in 2001

was the formal NPNS established, organized in all states. To the best of our knowledge, no recent data evaluating this program is available, except for one paper authored by Nascimento, who analyzed data from the NPNS and found that there were huge differences in screening performance among the Brazilian states. The coverage of the NPNS system was 82% among newborns, but blood samples were only collected within the first seven days of life for 57% of them. Moreover, a delay between arrival of the blood at the laboratory and release of the results was observed.[5]

In conclusion, to the best of our knowledge, there is no recent national data on the status of neonatal screening for hypothyroidism, and the old news is not exactly good news.

SALT IODINATION

In Brazil, salt iodination was established in the 1950s, but the amount of iodine added to salt has varied since then. Over the last 30 years, addition of different amounts of iodine (in milligrams) per kilogram of salt has been stipulated: 10-30 (1984); 40-60 (1994); 40-100 (1999); 20-60 (2003); and 15-45 (2013). Before this apparent mess of state-driven guidelines, three national surveys among schoolchildren showed a downward trend of goiter prevalence rates: 25% (1955), 15% (1975) and a median of 1.3% (1996).[6]

Today, the data on iodine supplementation in Brazil are divergent. A national survey called PNAISAL on 19,600 children aged 6 to 14 years began in 2008 and ended in 2011.[7] However, the results have so far not been made available. Meanwhile, there have been other surveys in several locations indicating lower or higher levels of urinary iodine and differences in the prevalence of goiter.[8-10]

In conclusion, to the best of our knowledge, no recent national data on the prevalence of goiter or on urinary iodine levels is available to enable rational actions towards thyroid health.

THYROID CANCER

In 2013, the incidence of thyroid cancer for both sexes ranked 19th worldwide and 9th in Brazil, among types of cancer. In contrast, the death rates relating to thyroid cancer were similar worldwide and in Brazil, respectively the 25th and 23rd most lethal malignant neoplasm.[11] The initial conclusion from these data could be that overdiagnosis is occurring in Brazil. Nevertheless, comparison between the cancer registry of Sao Paulo and the United States (US) National Cancer Institute's Surveillance Epidemiology End Results (SEER) revealed that there was higher incidence of thyroid cancer in São Paulo than in the US. The higher rate of thyroid cancer was differential, such that there were more cases of the papillary type than of the follicular type. The higher papillary-to-follicular ratio observed in São Paulo than in the US weakens the medical surveillance hypothesis and strengthens another hypothesis relating to excess iodination, which is a risk factor for papillary but not for follicular thyroid cancer.[12]

In conclusion, differences in iodine nutrition status between São Paulo and the US SEER population may have affected the incidence patterns observed.

SUBCLINICAL THYROID DISORDERS

The concept of subclinical disorders is familiar, but it is in fact weird. To understand the meaning of "subclinical disorders," we must look back to a historical debate on the definition of hypertension that was conducted in the 1950s. There were two sides. On one side, led by Richard Platt, hypertension was defined as a disease that could be present or absent. In opposition to this, George Pickering stated the view that now prevails: hypertension is only an arbitrary point on a continuous curve of blood pressure risk.[13]

During the 1980s, myxedema coma and thyroid storm were still being diagnosed in Brazil. However, because of improvements in laboratory tests and medical access, clinical cases of hypo and hyperthyroidism are diagnosed very early in the clinical phase of the disease. Individuals with subclinical disorders of the thyroid have a condition without a clinical picture but with a higher risk of evolving into overt disease than what is seen among individuals who have healthy thyroid function. There are data on the Brazilian population from two studies.

The first is the "São Paulo Ageing & Health Study (SPAH)", which studied a population-based sample of low-income elderly people greater than or equal to 65 years of age and revealed that presence of subclinical hyperthyroidism showed a fourfold greater association with the presence of any dementia or vascular dementia.[14,15] The other is the "Brazilian Longitudinal Study of Adult Health" (ELSA-Brasil), a multicenter cohort study on 15,105 public employees (35-74 years of age) in six Brazilian cities.[16] ELSA-Brasil showed that participants with subclinical hyperthyroidism had a 2.5 times greater chance of presenting panic disorder, while those who had subclinical hypothyroidism had a 25% lower frequency of generalized anxiety disorder.[17] Moreover, ELSA-Brasil showed that thyrotropin levels had associations with insulin resistance and subclinical atherosclerosis.[18,19]

In conclusion, the effect of thyroid hormones should be analyzed as a risk factor for adverse outcomes regarding cardiovascular and mental functions.

FINAL REMARKS

This editorial presents many more questions than answers about thyroid epidemiology in Brazil. It recognizes the important role that thyroidologists, dietitians and public health specialists working under harsh conditions have played over many decades, in creating and maintaining programs relating to neonatal screening and salt iodination. However, it is undeniable that these programs deserve a place within the continuous processes of research policy. Continuing collaboration among all individuals

with an interest in this fascinating chapter of the biological and health sciences needs to be invigorated by the Ministry of Health. Lastly, this Journal is opening its pages for new insights on thyroid diseases in Brazil.

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Post-thoracotomy pain relief with subpleural analgesia or thoracic epidural analgesia: randomized clinical trial

Alívio da dor pós-toracotomia com analgesia subpleural ou analgesia epidural torácica: ensaio clínico randomizado

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KEY WORDS:
Pain, postoperative.
Analgesia, epidural.
Pleura.
Thoracotomy.
Analgesia, patient-controlled.

PALAVRAS-CHAVE:
Dor pós-operatória.
Analgesia epidural.
Pleura.
Toracotomia.
Analgesia controlada pelo paciente.

ABSTRACT

CONTEXT AND OBJECTIVE: Post-thoracotomy pain is a severe and intense pain caused by trauma to ribs, muscles and peripheral nerves. The current study aimed to compare subpleural analgesia (SPA) with thoracic epidural analgesia (TEA) in patients undergoing thoracotomy.

DESIGN AND SETTING: Randomized study at Ankara Numune Education and Research Hospital, in Turkey.

METHODS: Thirty patients presenting American Society of Anesthesiologists physical status I-III were scheduled for elective diagnostic thoracotomy. The patients were randomized to receive either patient-controlled SPA or patient-controlled TEA for post-thoracotomy pain control over a 24-hour period. The two groups received a mixture of 3 µg/ml fentanyl along with 0.05% bupivacaine solution through a patient-controlled analgesia pump. Rescue analgesia was administered intravenously, consisting of 100 mg tramadol in both groups. A visual analogue scale was used to assess pain at rest and during coughing over the course of 24 hours postoperatively.

RESULTS: In the SPA group, all the patients required rescue analgesia, and five patients (33%) required rescue analgesia in the TEA group ($P < 0.05$). Patients who received subpleural analgesia exhibited higher visual analogue scores at rest and on coughing than patients who received thoracic epidural analgesia. None of the patients had any side-effects postoperatively, such as hypotension or respiratory depression.

CONCLUSION: Thoracic epidural analgesia is superior to subpleural analgesia for relieving post-thoracotomy pain. We suggest that studies on effective drug dosages for providing subpleural analgesia are necessary.

RESUMO

CONTEXTO E OBJETIVO: Dor pós-toracotomia é severa e intensa, causada por trauma de nervos periféricos, músculos e costelas. O objetivo foi comparar analgesia subpleural (SPA) com analgesia epidural torácica (TEA) em pacientes submetidos à toracotomia.

TIPO DE ESTUDO E LOCAL: Estudo randomizado no Hospital Educação e Pesquisa de Numune, em Ancara, Turquia.

MÉTODOS: Trinta pacientes com o estado físico I-III da Sociedade Americana de Anestesiologistas foram agendados para toracotomia diagnóstica eletiva e escolhidos aleatoriamente para receber, num período de 24 horas, SPA ou TEA, ambas controladas pelo próprio paciente, para controle da dor pós-toracotomia. Os dois grupos receberam mistura de 3 ug/ml de fentanil com solução de 0,05% de bupivacaína por meio de bomba de analgesia controlada pelo paciente. Foi administrada analgesia de resgate por via intravenosa, com 100 mg de tramadol, nos dois grupos. No pós-operatório, a escala visual analógica foi utilizada para medir presença de dor durante a tosse ou em repouso, ao longo de 24 horas.

RESULTADOS: No grupo SPA, todos os pacientes necessitaram de analgesia de resgate. Cinco pacientes (33%) necessitaram de analgesia de resgate no grupo TEA ($P < 0,05$). Os pacientes com SPA exibiram pontuações superiores na escala visual analógica, em repouso e ao tossir, em comparação aos que receberam TEA. Nenhum dos pacientes teve quaisquer efeitos secundários no pós-operatório, como hipotensão ou depressão respiratória.

CONCLUSÃO: A analgesia peridural torácica é superior à analgesia subpleural no alívio da dor pós-toracotomia. Consideramos que estudos sobre a dosagem de drogas eficazes para proporcionar analgesia subpleural são necessários.

INTRODUCTION

Post-thoracotomy pain is a severe and intense pain caused by trauma to ribs, muscles and peripheral nerves. Effective postoperative analgesia helps to reduce postoperative morbidity through early mobilization and rehabilitation and also reduces the development of chronic post-thoracotomy syndrome.[1,2] Various analgesic techniques have been developed to treat postoperative thoracotomy pain.[1-6] Thoracic epidural analgesia is the gold standard not only for pain relief after thoracotomy, but also because of its many beneficial effects, such as reduction of intraoperative opioid requirements, improvement of postoperative cardiopulmonary function and suppression of stress response.[1-6] Thoracic epidural block is usually performed percutaneously, with considerable failure rates. Unfortunately, it is contraindicated in patients who are using anticoagulant or antiplatelet drugs.[7] Intercostal nerve block, intrathecal administration of opioids and interpleural analgesia have also been developed as alternative regional techniques for post-thoracotomy pain management.[5] Many of these techniques are claimed to provide good pain control, but studies to ascertain the ideal technique are still ongoing.[5] There have not been enough studies on the subject of subpleural catheters for patient-controlled subpleural analgesia.

OBJECTIVE

The current study aimed to compare subpleural analgesia (SPA) with thoracic epidural analgesia (TEA) in patient-controlled analgesia devices for patients undergoing thoracotomy.

METHODS

This randomized clinical study included 30 patients with American Society of Anesthesiologists (ASA) physical status I-III, ranging in age from 20 to 70 years, for whom thoracotomy was planned. Approval for the study was granted by the institutional ethics board and written informed consent was obtained from all patients. Any patients with ASA status IV or greater, previous history of thoracotomy, use of chronic pain medication or contraindication against receiving local anesthetics or thoracic epidural block were excluded from the study. All the surgical procedures were performed by the same surgeons.

The patients were instructed how to use a patient-controlled analgesia (PCA) pump (Abbot Pain Management Provider, Abbott Laboratories, North Chicago, IL 60064, USA) and how to assess pain on a visual analogue scale (VAS), before their surgery. All the patients were pre-medicated with 1-2 mg of midazolam intravenously before surgery. The intraoperative monitoring included ECG, invasive arterial blood pressure, pulse oximetry, end-tidal carbon dioxide ($EtCO_2$), end-tidal sevoflurane concentration and serial arterial blood gas (ABG) analysis.

Patients were randomly assigned by means of the sealed envelope technique to either the thoracic epidural group (TEA group; n = 15) or the subpleural group (SPA group; n = 15). The patient inclusion and exclusion flowchart is described in **Figure 1**. Allocation was organized by a member of the medical staff who was not included in the study.

Anesthesia comprising fentanyl (2 μg/kg) and propofol (2-2.5 mg/kg) was induced and tracheal intubation was facilitated using 0.6 mg/kg of rocuronium. To maintain anesthesia, the patients received sevoflurane at 2% to 4% end-tidal concentration and 1 mcg/kg/h of remifentanil infusion, intravenously. All the patients were ventilated with a 50% oxygen and 50% air mixture. Muscle relaxation was obtained by means of a 0.1 mg/kg rocuronium bolus. After surgery, the neuromuscular blockade was reversed and the trachea was extubated in the operating room. All the patients were then transferred to the post-anesthesia care unit, where they were observed for 24 hours. All patients in this unit received O_2 via a face mask at 0.4 FiO_2 and were nursed in a 30° head-up position.

In the thoracic epidural anesthesia group (TEA group; n = 15), before induction of anesthesia, an epidural catheter was inserted in the thoracic region between T4 and T6 by an anesthesiologist, to a depth of 3-5 cm into the epidural space. The catheter placement was confirmed using 3 ml of 2% lidocaine with 1:200,000 adrenaline. Heparin and low molecular weight heparin therapies were stopped at least 6 or 12 hours, respectively, before the catheter insertion.

In the subpleural analgesia group (SPA group; n = 15), before the surgical wound was closed, the parietal pleura was removed bluntly from the posterior chest wall towards the vertebral body through three intercostal spaces above the thoracotomy incision. An 18-gauge epidural catheter was advanced into the space at the level of the neck of the ribs and laid on the endothoracic fascia under direct viewing. The catheter was secured with 4-0 prolene sutures to maintain its position during lung expansion and it extruded through the chest wall.

The TEA group received 10 ml of 0.125% bupivacaine and the SPA group received a loading dose of 20 ml of 0.25% bupivacaine via the catheter. In our department's routine, PCA infusion is used postoperatively for all suitable patients, in order to achieve better analgesia outcomes. The two groups (SPA and TEA) received a mixture of 3 μg/ml of fentanyl with 0.05% bupivacaine solution through a PCA pump. The PCA pump was programmed to deliver at an infusion rate of 6 ml/h, and a bolus dose of 6 ml/h, with a locked-out interval of 15 minutes, and 60 ml within a 4-hour limit. In addition, all the patients received 75 mg of diclofenac sodium intramuscularly and 1 g of paracetamol intravenously every 12 hours. If required, 10 mg of metoclopramide was administered intravenously for nausea or vomiting. Rescue analgesia was administered consisting of 100 mg tramadol intravenously in both groups whenever the VAS score was > 4 at rest despite three consecutive PCA boluses. Absence of improvement in the VAS (VAS > 5) despite rescue analgesics was defined as analgesic failure. Pain intensity was measured at rest (VASr) and on coughing (VASc) using a visual analogue scale (0 = no pain; 10 = intolerable pain). The total tramadol doses were recorded over a 24-hour period postoperatively.

Preoperative baseline variables (heart rate, mean arterial blood pressure (MAP), PaO_2, $PaCO_2$ and respiratory rate) were recorded for each patient. These parameters together with analgesia and side effects (nausea/vomiting, pruritus, hypotension, respiratory depression and desaturation) were recorded in the post-anesthesia care unit at 0, 2, 8, 12 and 24 hours. Hypotension was defined as a drop in blood pressure of more than 25% of the baseline value. Respiratory depression was defined as respiratory rate of < 10/min. All the postoperative clinical outcome assessors and statistical analysis assessors were blinded. The member of the medical staff who monitored the PCA consumption, VAS scores and rescue analgesia requirements was blinded to the study.

Statistics

To detect a difference from 80% to 30% in the incidence of analgesic failure, with a one-tailed significance level of 5% ($\alpha = 0.05$) and β of 0.2 (power 80%), a sample size of 15 patients was required in each group.

Demographic variables (age, weight and height) and duration of surgery were compared using Student's t test. Categorical variables were compared using the χ^2 test. Pain scores, heart rate, mean arterial blood pressure (MAP), PaO_2 and $PaCO_2$ at different time intervals were compared using the Mann-Whitney U test. SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. P values < 0.05 were considered statistically significant.

RESULTS

The demographic data from the two groups were similar with regard to age, height, weight, sex ratio and duration of surgery (**Tables 1** and **2**). The patients with patient-controlled subpleural analgesia (SPA group) had higher visual analogue scale scores (VAS) at rest (**Table 3**) and on coughing scores (**Table 4**) at all measurement times than the patients with patient-controlled thoracic epidural analgesia (TEA group).

In the SPA group, all the patients required rescue analgesia using tramadol (100%). Five patients (33%) required rescue analgesia in the TEA group (P < 0.05). The mean dose of tramadol consumed as rescue analgesia postoperatively in the SPA group was 380 mg, compared with 120 mg in the TEA group (P = 0.002; Mann-Whitney U test).

The mean number of PCA boluses used was significantly lower in the TEA group: 7 in the TEA group versus 28 in the SPA group (P < 0.002; Mann-Whitney U test). The respiratory rate, heart rate, MAP, PaO_2 and $PaCO_2$ values were comparable

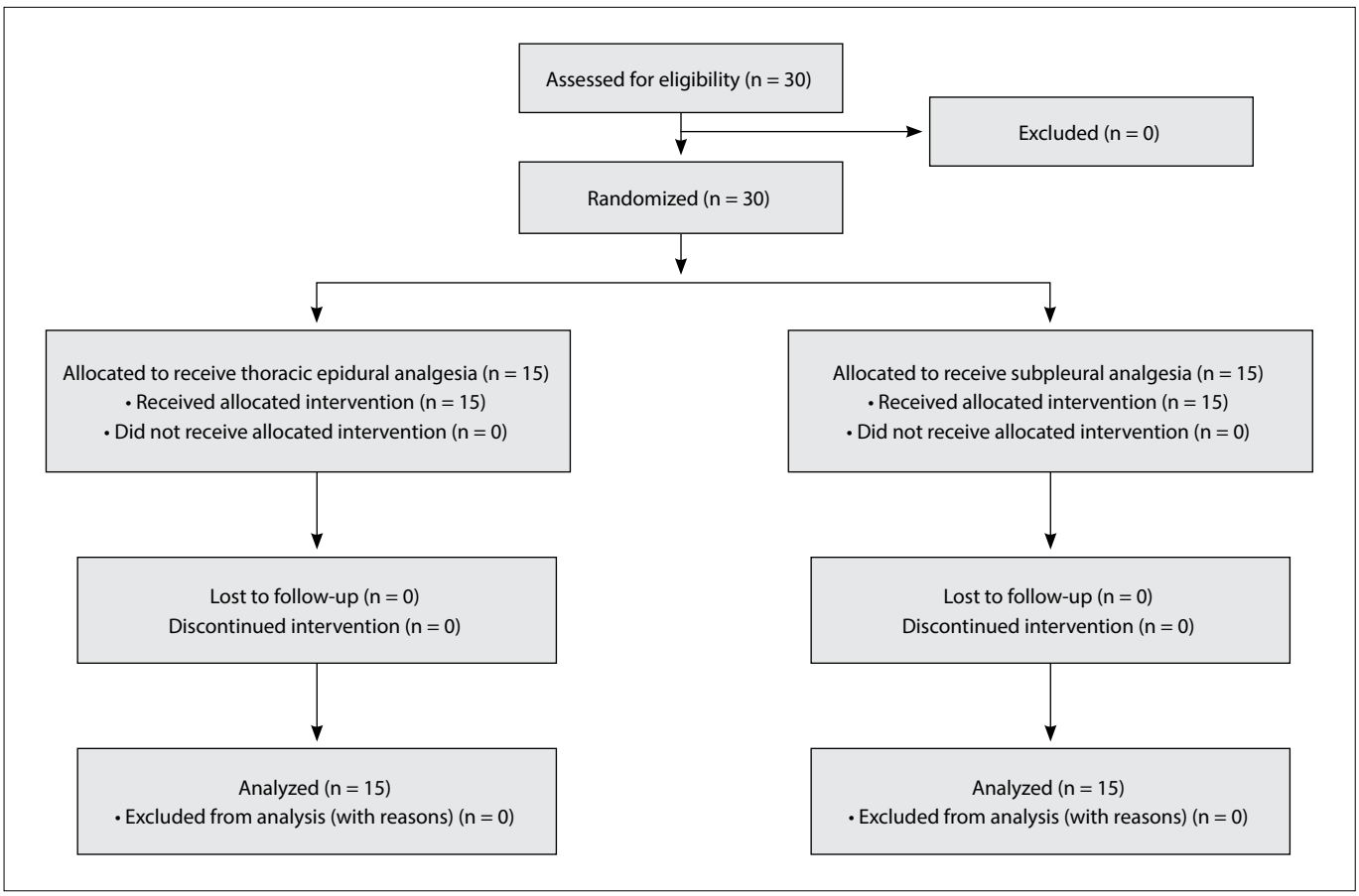

Figure 1. Patient inclusion and exclusion flowchart.

Table 1. Demographic data and preoperative variables

	SPA (n = 15)	TEA (n = 15)
Age	49.65 ± 14.12	49.60 ± 13.70
M/F	8/7	9/6
Weight (kg)	63 ± 15 (58.8-72.9)	61 ± 11 (56.8-69.1)
Height (cm)	160 ± 11 (155.1-166.3)	162 ± 8 (159.2-168.0)
ASA II-III	6/9	5/10

Values are mean ± standard deviation (95% confidence interval) or number (P > 0.05). SPA = subpleural analgesia; TEA = thoracic epidural analgesia; M = male; F = female; ASA = American Society of Anesthesiologists.

Table 2. Postoperative variables

	SPA (n = 15)	TEA (n = 15)
HR (per minute)	91 ± 7 (89.8-96.2)	88 ± 8 (82.5-93.7)
MAP (mmHg)	95.3 ± 10 (85.3-98.5)	90.1 ± 7(83.2-94.3)
Duration of surgery (h)	3.55 ± 0.93 (3.30-4.10)	3.95 ± 0.96 (3.28-4.15)
PaO_2 (mmHg)	105 ± 10 (98.6-105.2)	108 ± 15 (98.7-104.8)
$PaCO_2$ (mmHg)	37 ± 4 (35.9-40)	37 ± 4 (36.8-39.4)
RR (per minute)	18 ± 2 (16.5-19.5)	18 ± 2 (16.3-19.5)

Values are mean ± standard deviation (95% confidence interval) or number. SPA = subpleural analgesia; TEA = thoracic epidural analgesia; MAP = mean arterial pressure, H = heart rate, RR = respiratory rate; P > 0.05.

Table 3. Visual analogue scale for pain at rest

Time (hour)	SPA	TEA	P
0	7 (9-4)	3 (4-1)	0.001
2	6 (8-4)	3 (4-1)	0.001
8	4 (7-3)	2 (3-1)	0.001
12	4 (7-3)	2 (3-1)	0.001
24	4 (6-3)	2 (3-1)	0.001

Values are medians. SPA = subpleural analgesia; TEA = thoracic epidural analgesia.

Table 4. Visual analogue scale for pain during coughing

Time (hour)	SPA	TEA	P
0	8 (10-5)	6 (7-3)	0.001
2	7 (10-5)	5 (6-2)	0.001
8	6 (9-4)	4 (6-2)	0.001
12	6 (9-4)	4 (6-2)	0.001
24	6 (9-4)	4 (6-2)	0.001

Values are medians. SPA = subpleural analgesia; TEA = thoracic epidural analgesia.

between the groups during the study period. None of the patients had hypotension or side effects. Oxygenation was satisfactory (PaO_2 > 90 mmHg) in all the patients. None of the patients in either group showed respiratory depression (**Table 2**).

DISCUSSION

The present study showed that SPA was not sufficiently effective for post-thoracotomy pain management. The patients using TEA with fentanyl and bupivacaine following thoracic surgery, even at low doses, had better analgesia both at rest and on coughing (**Tables 3** and **4**).

The mechanism of subpleural analgesia might be explained by the spread of local anesthetic to the posterior wall of the thorax, i.e. towards the vertebral column, and its diffusion to the paravertebral space, which contains the thoracic spinal nerves.[4,8]

Kanai et al. reported that subpleural analgesia provided successfully adequate pain control in two-thirds of their patients, through continuous infusion of 0.125% bupivacaine at 8 ml/h. However, in the current study, in the SPA group, all the patients required rescue analgesia. The failure to provide adequate post-thoracotomy pain relief could be attributed to dislodgement of the subpleural catheter or inadequate and limited diffusion of local anesthetic to the paravertebral space. The subpleural space is separated from the paravertebral space by the endothoracic or extrapleural fascia,[4,9] and this barrier may prevent adequate diffusion of local anesthetic to the nerve endings.[4,10] The deficiency of this study might be the low doses of local anesthetic usage, but there were not enough data about the ideal local anesthetic dosage for this kind of subpleural block, especially using bupivacaine, which has a long elimination time and cardiac side effects. Because of the unpredictable cardiac side effects, the concentration of bupivacaine used in this study was limited and fentanyl was added to the infusion solution to improve the analgesic quality.[11-13]

The most important advantages of patient-controlled epidural analgesia were the reduction of prolonged ventilation, reduction of re-intubation, improvements of pulmonary functions and early mobilization of the patient. The disadvantages of this technique were hypotension, urinary retention, pruritus and possible technical failure.[2] Local anesthetic plus an opioid combination in PCA is believed to provide synergistic analgesia, thus requiring smaller doses and fewer side effects.[5] Epidurally administered opioids produce segmental analgesia and improve the quality and duration of the sensory block produced by local anesthetics,[14,15] which may explain the better pain relief in the TEA group. In our clinical practice, we usually use an opioid and local anesthetic mixture for TEA solutions and, even at low concentrations, adequate analgesia levels are obtained. As mentioned in relation to this current study, in clinical practice low doses of bupivacaine with TEA are sufficiently efficient to deal with post-thoracotomy pain.

Kanazi et al.[4] determined that the pain scores when coughing were higher than at rest in all their patients and at all times, whether using TEA or SPA, and that VAS scores when coughing were always lower in the TEA group than in the SPA group. In that study, VAS scores at rest in the presence of thoracic epidural analgesia ranged from 1 cm to 6 cm. Those findings are similar to the findings of the current study (**Tables 3** and **4**).

There was no difference between the two groups of the current study in relation to the incidence of hypotension. However, Kanazi et al.[4] reported that the incidence of hypotension was

higher with thoracic epidural analgesia than with subpleural analgesia. This difference might be attributable to low concentrations of local anesthetic.

The strong point of the present study was that it showed that minimal bupivacaine doses were needed for effective thoracic epidural analgesia. The most important limitation of the study was the small sample size.

There are no published data identifying equipotent doses of bupivacaine for use in thoracic epidural and subpleural analgesia. Previous studies have suggested that local anesthetic doses for TEA should be half those of subpleural analgesia.[4,5] In the current study, the starting bolus doses were given at a ratio of 1:2, but the PCA doses were lower than the doses used in the study by Kanazi et al. For supplemental therapy, paracetamol and diclofenac sodium were used in the current study. These bupivacaine doses in the TEA group were sufficient for analgesia, and reduced the rate of complications. However, they were not sufficient in the SPA group.

CONCLUSION

In conclusion, TEA is better than SPA for providing post-thoracotomy pain relief. In order to avoid cardiac side effects of bupivacaine; the doses of the drug in the SPA group were limited and set as twice those of the TEA group. The local anesthetics and opioid doses in the TEA group in this study were safe and effective, but were insufficient in the SPA group even with parenteral supportive analgesic therapy. Subpleural analgesia with this dose regimen is not recommended for clinical practice. Further studies to determine local anesthetic doses and concentrations for this kind of subpleural analgesia are needed in order to achieve better analgesia for thoracic surgery.

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Effect of preoperative gabapentin on pain intensity and development of chronic pain after carpal tunnel syndrome surgical treatment in women: randomized, double-blind, placebo-controlled study

Efeito da gabapentina pré-operatória na intensidade da dor e desenvolvimento de dor crônica após o tratamento cirúrgico da síndrome do túnel do carpo em mulheres: estudo randomizado duplo-cego controlado com placebo

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KEY WORDS:
Pain, postoperative.
Chronic pain.
Carpal tunnel syndrome.
Neuralgia.
Anesthesia, conduction.

PALAVRAS-CHAVE:
Dor pós-operatória.
Dor crônica.
Síndrome do túnel carpal.
Neuralgia.
Anestesia por condução.

ABSTRACT

CONTEXT AND OBJECTIVES: Effective postoperative analgesia is important for reducing the incidence of chronic pain. This study evaluated the effect of preoperative gabapentin on postoperative analgesia and the incidence of chronic pain among patients undergoing carpal tunnel syndrome surgical treatment.

DESIGN AND SETTINGS: Randomized, double-blind controlled trial, Federal University of São Paulo Pain Clinic.

METHODS: Forty patients aged 18 years or over were randomized into two groups: Gabapentin Group received 600 mg of gabapentin preoperatively, one hour prior to surgery, and Control Group received placebo. All the patients received intravenous regional anesthesia comprising 1% lidocaine. Midazolam was used for sedation if needed. Paracetamol was administered for postoperative analgesia as needed. Codeine was used additionally if the paracetamol was insufficient. The following were evaluated: postoperative pain intensity (over a six-month period), incidence of postoperative neuropathic pain (over a six-month period), need for intraoperative sedation, and use of postoperative paracetamol and codeine. The presence of neuropathic pain was established using the DN4 (Douleur Neuropathique 4) questionnaire. Complex regional pain syndrome was diagnosed using the Budapest questionnaire.

RESULTS: No differences in the need for sedation, control over postoperative pain or incidence of chronic pain syndromes (neuropathic or complex regional pain syndrome) were observed. No differences in postoperative paracetamol and codeine consumption were observed.

CONCLUSIONS: Preoperative gabapentin (600 mg) did not improve postoperative pain control, and did not reduce the incidence of chronic pain among patients undergoing carpal tunnel syndrome surgery.

RESUMO

CONTEXTO E OBJETIVOS: Analgesia pós-operatória eficaz é importante para reduzir a incidência de dor crônica. Este estudo avaliou o efeito da gabapentina pré-operatória na analgesia pós-operatória e na incidência de dor crônica em pacientes submetidos à cirurgia para tratamento da síndrome do túnel do carpo.

DESENHO E LOCAL: Randomizado, duplo cego, Universidade Federal de São Paulo.

MÉTODOS: Os 40 pacientes com 18 anos ou mais de idade foram distribuídos aleatoriamente em dois grupos: o Grupo Gabapentina recebeu 600 mg de gabapentina no pré-operatório uma hora antes da cirurgia, e o Grupo Controle recebeu placebo. Todos os pacientes receberam anestesia regional intravenosa com lidocaína a 1%. Midazolam foi utilizado para sedação, se necessário. Paracetamol foi administrado para analgesia pós-operatória, conforme necessário, e codeína, se o paracetamol fosse insuficiente. Foram avaliados: a intensidade da dor pós-operatória (durante seis meses), a incidência de dor neuropática pós-operatória (durante seis meses), a necessidade de sedação intra-operatória e o uso de paracetamol e codeína no pós-operatório. A presença de dor neuropática foi estabelecida utilizando-se o questionário DN4 (dor neuropática 4). Síndrome de dor regional complexa foi diagnosticada através do questionário Budapeste.

RESULTADOS: Não foram observadas diferenças na necessidade de sedação, no controle da dor pós-operatória e na incidência de síndromes dolorosas crônicas (neuropáticas ou síndrome de dor regional complexa). Não foram observadas diferenças no consumo de paracetamol e codeína.

CONCLUSÕES: Gabapentina pré-operatória (600 mg) não melhorou o controle da dor pós-operatória e não reduziu a incidência de dor crônica em pacientes submetidos à cirurgia para tratamento da síndrome do túnel do carpo.

INTRODUCTION

Carpal tunnel syndrome surgery is usually a short outpatient procedure performed under intravenous regional anesthesia (IVRA). However, this type of anesthesia is unable to maintain postoperative analgesia.[1,2]

Many patients will develop chronic pain after hand surgery, especially complex regional pain syndrome, which is associated with neuropathic, inflammatory and sympathetic dysfunction mechanisms.[3,4] Postoperative chronic pain (POCP) has been observed in more than 20% of patients after carpal tunnel release.[1,5]

The occurrence of postoperative acute pain is an important predictor for the development of chronic pain. Adequate analgesia in the acute postoperative phase reduces the risk of chronic pain. Effective postoperative analgesia is of major importance for preventing POCP.[6,7]

Gabapentin is known to reduce dorsal horn neuron excitability and central sensitization through various mechanisms.[8-10] A review of the literature suggested that the incidence of postoperative chronic pain was reduced through using gabapentin perioperatively.[11] However, a study on a single preoperative 300 or 600 mg dose of gabapentin prior to caesarean section did not show any improvement in pain control.[12] Therefore, the role of preoperative gabapentin for postoperative pain control remains a matter of controversy.

This study evaluated the effect of preoperative gabapentin on postoperative pain control and chronic pain incidence among patients undergoing carpal tunnel syndrome surgery under IVRA. The primary objective was to evaluate the effect of preoperative gabapentin on postoperative pain control. The secondary objectives were to investigate the incidence of chronic pain, and the adverse event profile of gabapentin and lidocaine.

METHODS

Ethics approval for this study was provided by the Ethics Committee of the Federal University of São Paulo under the number 0223/09. The trial was registered at ClinicalTrials.gov (NCT01632215).

Study design

This was a prospective, randomized, double-blind study.

Place and setting

All patients underwent surgery performed using the same technique (open carpal tunnel release surgery), by the same medical team at the hospital of the Federal University of São Paulo between 2009 and 2011.

Participants

The inclusion criteria were that the patients needed to be 18 years of age or older, of either gender, and presenting American Society of Anesthesia (ASA) physical status I or II, before open carpal tunnel release surgery. Carpal tunnel syndrome needed to have been diagnosed by means of clinical examinations (Phalen and Tinel tests) and electromyography (grade ≥ 2). The electromyography scale was graded as follows: normal (grade 0); very mild (grade 1), carpal tunnel syndrome demonstrable only with the most sensitive tests; mild (grade 2), sensory nerve conduction velocity slow on finger/wrist measurement, and normal terminal motor latency; moderate (grade 3), sensory potential preserved with motor slowing, and distal motor latency to abductor pollicis brevis (APB) < 6.5 ms; severe (grade 4), sensory potential absent but motor response preserved, and distal motor latency to APB < 6.5 ms; very severe (grade 5), terminal latency to APB > 6.5 ms; and extremely severe (grade 6), sensory and motor potentials effectively unrecordable (surface motor potential from APB < 0.2 mV in amplitude).[13]

Patients presenting arrhythmia, myocardial ischemia, cognitive impairment, psychiatric disorders, drug abuse, pregnancy, sensitiveness to anesthetics or opioid, anticonvulsant or antidepressant use were excluded.

The sample size was calculated using SPSS 17 for Windows. A reduction of approximately two points or 30% in the numerical rating scale[14] for pain intensity represented a clinically important difference in chronic pain.[15] To optimize the relevance of the study findings, a three-point difference in a numerical pain intensity score was chosen to be a clinically meaningful endpoint. For a power of 95% (beta), an alpha level of 5% and an estimated standard deviation of the population of 2.44, based on a preliminary evaluation,[16] the calculated sample size was 18 patients per group to demonstrate a three-point difference in the scores.

Randomization, allocation concealment and blinding

The patients were randomly assigned to one of two parallel groups in a 1:1 ratio, through using the computer program Randomizer. Opaque envelopes were prepared in accordance with the computer randomization and were numbered and sealed by a researcher who was not involved in patient assessment. Each envelope contained either a gabapentin or a placebo tablet and was stored at the research hospital, to be given to the research physician prior to each surgery. The gabapentin and placebo tablets were identical in order to maintain patients and researchers blinded to the randomization group. None of the participating physicians or the researchers involved in data collection were aware of the patient study-group randomization. Patients randomized to the Gabapentin Group received 600 mg of gabapentin 1 hour prior to surgery. Patients randomized to the Control Group received placebo.

All patients were asked about dizziness symptoms prior to the onset of anesthesia, and were subsequently assessed for behavioral changes.

Preoperative and operative procedures

Anesthesia, surgical procedure and patient follow-up were performed by the same research physicians for all patients. Routine monitoring by means of electrocardiogram (ECG), pulse oximetry and noninvasive blood pressure (NIBP) was conducted throughout the duration of patient anesthesia. IVRA was performed with 20 ml of 1% lidocaine, using two tourniquets, in accordance with the technique described by Bier.[2] In cases of persistent pain after IVRA, local infiltration of 1% lidocaine was performed and the total dose used was recorded. Midazolam was administered for sedation if needed, e.g. if the patient became agitated, and the total dose was recorded.

Paracetamol (maximum of 4 g/24 h) was given if postsurgical analgesia was required, for up to 6 months post-surgery, e.g. if patients reported moderate or severe pain, defined as a numerical scale score ≥ 4 (on a scale ranging from 1 to 10). Codeine (30 mg) was given if paracetamol was insufficient for pain control. The use of other drugs was not allowed for pain control during the follow-up period. The use of specific orthosis was not allowed prior to or after the procedure.

Outcomes (primary and secondary)

The primary outcome was pain intensity according to a numerical scale (0 = no pain, 10 = worst pain possible) prior to procedure (T-preoperative), at time 0 min (T0 = time of tourniquet release), 30 min, 1 h, 2 h, 2 weeks, 1 month, 3 months and 6 months after the procedure. Secondary outcomes included: total dose of lidocaine supplementation; need for and dose of midazolam; postoperative need for and total dose of paracetamol and/or codeine; development of neuropathic pain and/or complex regional pain syndrome. The DN4 (Douleur Neuropathique 4) questionnaire,[6] which evaluates seven sensory symptoms and three signs on physical exam, indicated neuropathic pain for patients with a score ≥ 4, measured at different assessment points (before anesthesia and at 2 weeks, 1 month, 3 months and 6 months after surgery). Complex regional pain syndrome was diagnosed using the Budapest questionnaire[15] on scheduled assessment dates (2 weeks, 1 month, 3 months and 6 months after surgery). Possible side effects were recorded.

Statistical analysis

SPSS 17 for Windows was used for the statistical analysis. Parametric variables were expressed as means ± standard deviation (SD). Nonparametric variables were described as median, 25th and 75th percentile values. The Mann-Whitney test was used to analyze age, weight, height and body mass index (BMI). The Chi-square test was applied to gender and pain scores. For pain intensity analysis, patients were grouped according to pain intensity score at the different assessment points: mild (score < 4) or moderate/severe pain intensity (score ≥ 4). Proportion tests were used to assess pain intensity score groups between the assessment times (T-preoperative compared with other study points). The McNemar test was used for comparisons within the same study groups. The Mantel-Haenszel test was used for comparisons between study groups. Student's t test was used to analyze total paracetamol and midazolam doses, anesthesia and surgery duration, and occurrences of complex regional pain syndrome. Fisher's test was used to evaluate occurrences of neuropathic pain and adverse effects, and the patients' baseline characteristics (diabetes and prior treatment for carpal tunnel disease). The likelihood test was used to evaluate the electromyography grade of the carpal tunnel syndrome. Missing data were excluded from the analysis.

RESULTS

The patients' recruitment and allocation flowchart, according to the CONSORT guideline, is shown in **Figure 1**. Twenty patients were excluded from the study: two due to arrhythmia, four due to myocardial ischemia and 14 due to opioid, anticonvulsant or antidepressant use. A total of 40 patients were included in the study, i.e. 20 in each group.

There were no differences in patient demographics, duration of surgery and anesthesia, need for midazolam use, carpal tunnel syndrome grade or previous diabetic status between the study groups (**Table 1**). Lidocaine supplementation was not required for any patient. All the patients were ASA I or II, with no difference between the groups (P = 0.642). All the patients were female.

Table 1. Demographic data of patients with carpal tunnel syndrome

	Gabapentin (n = 20)	Control (n = 20)	P
Age (years)	51.5 (48.5-54)	52.1 (46-56.7)	0.583*
Weight (kg)	65.7 (59.2-73)	68.7 (60-75)	0.383*
Height (cm)	158 (155-161.5)	157 (154-162)	0.939*
BMI (kg/m^2)	26.2 (23.6-28.7)	27.5 (23.9-31.4)	0.659*
Duration of surgery	33.06 ± 10.86 min	33.06 ± 16.90 min	0.894†
Duration of anesthesia	55.00 ± 11.50 min	54.21 ± 11.33 min	0.835†
Need for midazolam	7/18	5/19	0.823†
Grade of carpal syndrome			
Grade 2	1	2	0.93‡
Grade 3	7	8	
Grade 4	10	10	
Grade 5	1	1	
Diabetes	2/18	1/19	1.00§
Treatment naive	18/18	19/19	1.00§

BMI = body mass index. *Mann-Whitney test [median (25th and 75th percentiles)]; †Student's t test (mean ± SD); ‡likelihood test; §Fisher test.

The postoperative assessments showed lower pain intensity scores in comparison with the preoperative baseline pain intensity within the same study groups, except for the T30 min assessment (McNemar's test, **Table 2**). However, there was no statistically significant difference in pain intensity scores over time in comparisons across study groups (Mantel-Haenszel test, **Table 2**). There was no statistically significant difference in the incidence of chronic neuropathic pain (**Table 3**) or complex regional pain syndrome between the study groups (**Table 4**).

There was no difference in the use of paracetamol (Gabapentin Group: 24.6 ± 30.1 doses; 95% CI: 13.1 ± 48.1; and Control Group: 30.9 ± 36.9 doses; 95% CI: 9.6 - 39.5; P = 0.572; Student's t test) or codeine supplementation (Gabapentin Group: 0; Control Group: 1) over the six-month observation period between the study groups.

The adverse effects were similar at the preoperative assessment (beginning of surgery): metallic taste: 4 versus 2 (P = 0.660); oral paresthesia: 2 versus 1 (P = 1.0); dizziness: 4 versus 4 (P = 1.0); somnolence: 4 versus 3 (P = 1.0); and tinnitus 2 versus 4 (P = 0.660); for the Gabapentin and Control groups, respectively. No differences in adverse effects at the end of surgery were noted: metallic taste: 0 versus 1 (P = 1.0); oral paresthesia: 0 versus 0; dizziness: 3 versus 1 (P = 0.605); drowsiness: 2 versus 0 (P = 0.487); and tinnitus: 2 versus 0 (P = 0.486); for the Gabapentin and Control groups, respectively.

DISCUSSION

The current study did not demonstrate any difference in pain intensity scores, incidence of postoperative chronic pain (POCP) or complex regional pain syndrome (CRPS), need for additional postoperative analgesia or incidence of adverse effects, through using preoperative gabapentin for open carpal tunnel release surgery.

The demographic data were similar between the study groups. Interestingly, only female patients were included, despite no exclusion of male patients. This could be explained by the known higher prevalence of carpal tunnel syndrome in women.[5]

Previous studies have shown that there is a reduced risk of POCP after other types of surgery with the use of gabapentin preoperatively.[17-19] In the current report, the observed incidence of POCP and CRPS was lower for the gabapentin group, but it did not reach statistical significance, despite a numerical difference.

Gabapentin was administered one hour prior to surgery to allow for drug absorption.[20] The use of a single 600 mg dose of gabapentin could explain the lack of efficacy observed. Pre and postoperative gabapentin administration could have prevented central sensitization from previous pain stimulus, surgical trauma and postoperative inflammation, and may have influenced the outcomes.

However, the use of 600 mg of gabapentin preoperatively followed by two-day maintenance had no beneficial effect after total knee arthroplasty.[21] Also, two study reviews were unable to demonstrate that preoperative gabapentin was effective for prevention of postoperative chronic pain,[22] even at a higher dose (1200 mg).[23] However, it should be noted that there was a difference in surgical trauma between those studies and the current report.

A study by Pandey et al.[24] demonstrated that there was lower opioid consumption and reduced pain scores through using a single

Table 2. Intensity of pain (pain ≥ 4/pain < 4) among patients operated for carpal tunnel syndrome

Time points	Gabapentin (n = 18)	McNemar's test (Gabapentin Group)*	Control (n = 19)	McNemar's test (Control Group)*	Chi-square	Mantel-Haenszel test*
Preoperative	**17/1**		**18/1**		0.969	
T0	**1/17**	0.000	**1/18**	0.000	0.969	0.221
30 minutes	**15/3**	0.625	**18/1**	1.00	0.264	0.518
1 hour	**4/14**	0.01	**8/11**	0.02	0.197	0.824
2 hours	**0/18**	n/a	**0/19**	n/a	n/a	n/a
2 weeks	**9/9**	0.012	**12/7**	0.05	0.634	0.596
1 month	**8/10**	0.012	**11/8**	0.039	0.413	0.496
3 months	**4/14**	0.001	**4/15**	0.001	0.931	0.067
6 months	**3/15**	0.000	**2/17**	0.000	0.948	0.637

T0 = time of tourniquet release; n/a = not applicable; * = P-values.

Table 3. Neuropathic pain (DN4 questionnaire) in patients operated for carpal tunnel syndrome: n (%)

Time points	Gabapentin (n = 18)	Control (n = 19)	P*
Preoperative	18 (100)	19 (100)	1.000
2 weeks	6 (33.3)	8 (42.1)	0.737
1 month	5 (27.8)	8 (42.1)	0.495
3 months	5 (27.8)	7 (36.8)	0.728
6 months	4 (22.2)	5 (26.3)	1.000

DN4 (Douleur Neuropathique 4) questionnaire; *Fisher's test.

Table 4. Complex regional pain syndrome according to the Budapest questionnaire among patients operated for carpal tunnel syndrome: n (%)

Time points	Gabapentin (n = 18)	Control (n = 19)	P*
2 weeks	5 (27.7)	9 (47.3)	0.231
1 month	6 (33.3)	10 (52.6)	0.131
3 months	4 (22.2)	6 (31.6)	0.535
6 months	3 (16.7)	3 (15.8)	0.944

*Student's t test.

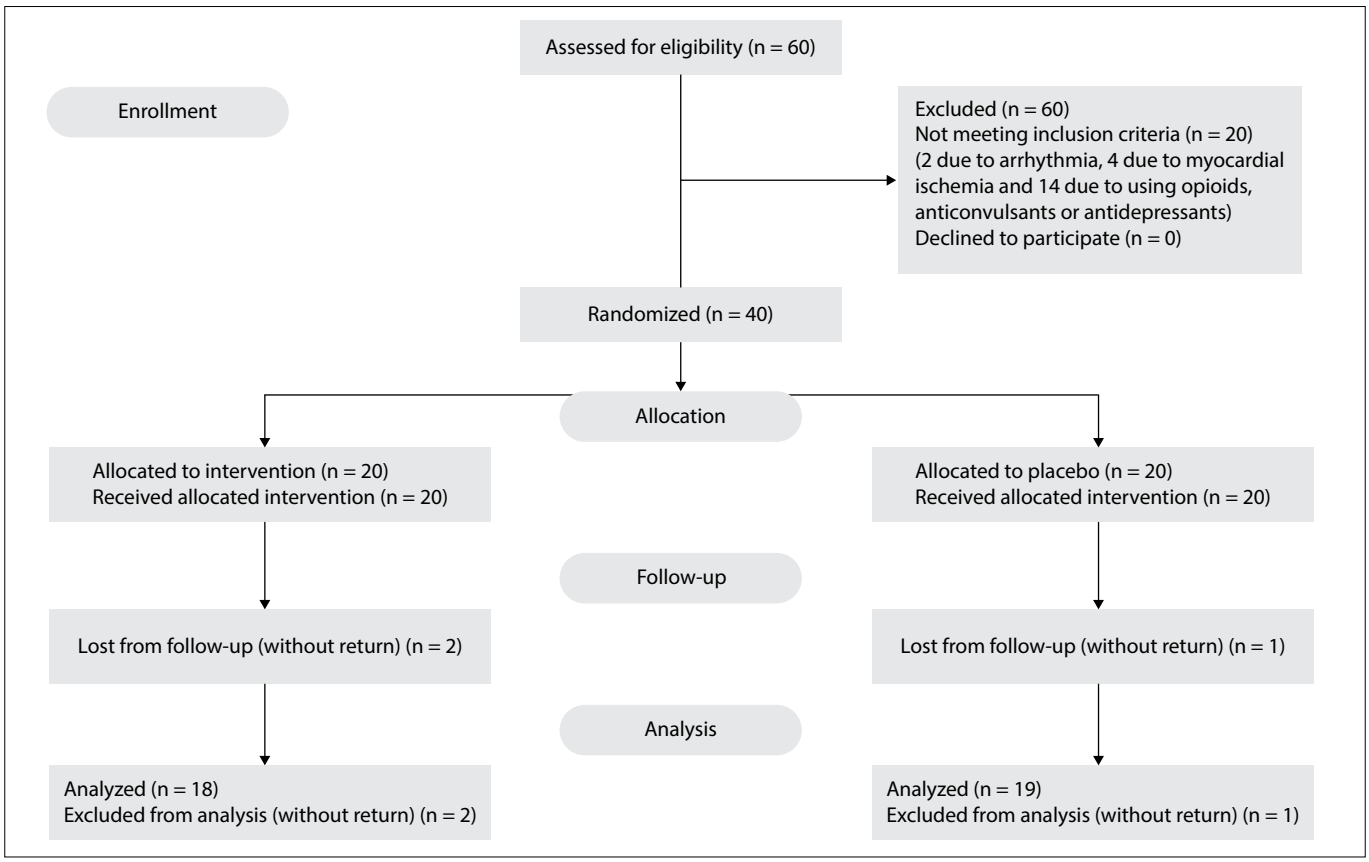

Figure 1. Patients' recruitment and allocation flowchart.

pre or postoperative gabapentin dose after open-door nephrectomy, compared with placebo, but no difference between pre or postoperative gabapentin. Further studies are still required, in order to better evaluate the effect of gabapentin on POCP prevention.[25,26]

The duration of the surgical procedure is known to have an impact on the development of POCP. Procedures that last longer than three hours have been correlated with an increased risk of POCP.[27] However, the total duration of the surgical procedure in the current study was shorter than three hours, which may have contributed towards reduced incidence of POCP.

Brogly et al.[17] demonstrated that there was lower incidence of POCP through using preoperative gabapentin prior to thyroidectomy.[17] The current report only assessed patients until six months of follow-up. However, evaluation after six months would most likely not find any differences in POCP, given that the pain intensity was already mild in both groups at six months.

Surgical procedures that may cause nerve injury have also been correlated with POCP.[1] Previous studies have reported a wide range of POCP (5 to 80%), which may be related to different definitions in the various studies.[28,29] Study design, POCP assessment and interpretation of results may also contribute towards this variability.[28]

The incidence of POCP found in this report was higher than what was previously described.[1] The observed incidence of POCP was 27.8% and 36.8% at three months, and 22.2% and 26.3% at six months, for G1 and G2, respectively, compared with 21% and 12% at three and six months reported by Yung et al.[1] One possible explanation might be the difference in surgical techniques: a limited open carpal tunnel release procedure was used in the above mentioned study. This could result in different efficacy, scar tissue compression of the median nerve and surgery-associated nerve injury, thus leading to POCP.[1]

IVRA is a simple anesthetic technique commonly used for carpal tunnel syndrome release. This type of surgery can usually be performed without intraoperative anesthetic supplementation because IVRA is sufficient for local anesthesia. As expected, there was no need for additional anesthesia in this study. Also, no sedation was required since it is a fast procedure associated with low levels of patient distress.

However, its analgesic effect is limited to the duration of tourniquet use. Additional medication is usually necessary in order to maintain postoperative analgesia,[2] and this was implemented through using paracetamol and codeine. The use of preoperative gabapentin did not affect postoperative analgesic consumption.

Also, there was no difference in the reported side effects between the groups, as demonstrated by others.[9,30] Common lidocaine-related side effects (e.g. metallic taste, oral paresthesia and tinnitus) were also not increased through using gabapentin.

LIMITATIONS OF THE STUDY

Gabapentin was given as a single preoperative dose, which may have been insufficient to reduce central sensitization and development of POCP. Use of gabapentin and other neuromodulatory drugs was not allowed for treating POCP, which may have contributed towards higher incidence of chronic pain. Additionally, this was a single-center study, which may limit the applicability of our results.

CONCLUSION

In conclusion, there was no difference in postoperative pain intensity through using a single 600 mg gabapentin dose after open carpal tunnel release surgery.

Further studies are needed in order to determine the best perioperative gabapentin regimen for postoperative pain control and prevention of postoperative chronic pain syndrome after carpal tunnel surgery.

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Stress, coping and adherence to immunosuppressive medications in kidney transplantation: a comparative study

Estresse, *coping* e aderência a medicamentos imunossupressores em transplante renal: um estudo comparativo

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KEY WORDS:
Stress, psychological.
Adaptation, psychological.
Medication adherence.
Patient compliance.
Kidney transplantation.

PALAVRAS-CHAVE:
Estresse psicológico.
Adaptação psicológica.
Adesão à medicação.
Cooperação do paciente.
Transplante de rim.

ABSTRACT

CONTEXT AND OBJECTIVE: Adherence to medication is a key issue relating to outcomes from transplantation and it is influenced by several factors, such as stress and coping strategies. However, these factors have been poorly explored. We aimed to compare stress and coping strategies between adherent and nonadherent renal transplant recipients who were receiving immunosuppression.

DESIGN AND SETTING: We conducted a comparative, cross-sectional and observational study at a university-based transplantation clinic in Juiz de Fora, Brazil.

METHODS: Fifty patients were recruited and classified as adherent or nonadherent following administration of the Basel Assessment of Adherence to Immunosuppressive Medications Scale. Stress was evaluated using the Lipp Stress Symptom Inventory for Adults and coping strategies were assessed using the Ways of Coping Scale.

RESULTS: The study included 25 nonadherent patients and 25 controls with a mean age of 44.1 ± 12.8 years and median post-transplantation time of 71.8 months. Stress was present in 50% of the patients. Through simple logistic regression, nonadherence was correlated with palliative coping (OR 3.4; CI: 1.02-11.47; P < 0.05) and had a marginal trend toward significance with more advanced phases of stress (OR 4.7; CI: 0.99-22.51; P = 0.053).

CONCLUSION: Stress and coping strategies may have implications for understanding and managing nonadherent behavior among transplantation patients and should be considered among the strategies for reducing nonadherence.

RESUMO

CONTEXTO E OBJETIVO: Aderência à medicação é uma questão chave para o resultado do transplante e é influenciada por diversos fatores, tais como o estresse e estratégias de enfrentamento ou *coping*. Entretanto, esses aspectos têm sido pouco explorados. Compararmos o estresse e as estratégias de *coping* em paciente transplantados renais, aderentes e não aderentes, em uso de imunossupressores.

TIPO DE ESTUDO E LOCAL: Realizamos estudo comparativo, transversal e observacional em uma clínica universitária de transplantes em Juiz de Fora, Brasil.

MÉTODO: Cinquenta pacientes foram selecionados e classificados como aderentes e não aderentes a partir da escala Basel Assessment of Adherence to Immunosuppressive Medications Scale. O estresse foi avaliado pelo Inventário de Sintomas de Estresse para Adulto de Lipp e as estratégias de *coping* foram avaliadas pela escala Escala de Modos de Enfrentamento de Problemas.

RESULTADOS: O estudo inclui 25 pacientes não aderentes e 25 controles com idade média de 44,1 ± 12,8 anos e mediana de tempo de transplante de 71,8 meses. Estresse esteve presente em 50% dos pacientes. Por regressão linear simples, a não aderência foi associada com o *coping* paliativo (OR 3,4, CI: 1,02-11,47; P < 0,05) e teve uma tendência marginal a significância com as fases mais avançadas do estresse (OR 4,7, CI: 0,99-22,51; P = 0,053).

CONCLUSÃO: Estresse e estratégias de *coping* podem trazer implicações na compreensão e manejo do comportamento de não aderência dos pacientes transplantados e deveriam ser considerados nas estratégias na redução da não aderência.

INTRODUCTION

Kidney transplantation is associated with higher survival rates, better quality of life and fewer public health costs than those of dialysis programs.[1,2] These outcomes have been achieved mainly because of the use of immunosuppressive therapy.[3] Nonetheless, long-term survival has not improved to the same degree, and this has therefore become a great challenge for healthcare providers.[4]

According to several studies, strict adherence to the drug regimen is one of the main goals of efficient treatment, and this reduces the frequency of complications, such as late acute rejection episodes and late graft loss.[5,6] Adherence is defined as "the degree to which a person's behavior corresponds to the recommendations from a healthcare provider".[7] This concept is influenced by several factors.[5,7-9] One potential theory that could lead to attainment of this multilevel interaction is the Ecological Model. This model maintains that behavior that interferes with adherence is a result of interaction between factors at multiple levels. These different levels can be divided into "the patient" and the "micro", "meso" and "macro" levels. Specific characteristics of the individual, like psychiatric disorders, stress and coping strategies, are included at the patient level.[10,11]

On the other hand, nonadherence in the field of transplantation, defined as any deviation from the drug regimen prescribed that negatively affects the results,[12] represents risky behavior and is associated with reduced kidney allograft survival, lower quality of life and increased public spending.[5,6,13,14] Unfortunately, nonadherence to immunosuppressants is common among kidney transplantation patients and some reports have shown that kidney recipients are the most nonadherent among all transplantation patients.[6,15,16]

Within this context, since adherence is multifactorial and is related to socioeconomic, individual, clinical and healthcare system variables,[7,11] exploration of which individual factors can have an influence on nonadherence is needed. Although many psychological dimensions contribute towards nonadherence, only a few of them have been extensively studied.[17] Among all of these factors, particular attention should be given to mental health (depression and anxiety), stress and coping patterns.[17,18]

Stress, as was first described by Seyle,[19] can be defined as an organism's response to challenging events. It may also be understood as the relationship between the individual and the environment. There is a clear association between high and persistent levels of stress and the onset or worsening of several chronic pathological conditions.[20,21] Despite the well-established benefits of kidney transplantation, it does not eliminate all health-related stress.[22-28] Many challenges are faced after kidney transplantation, such as following a complex medication regimen, dealing with its side effects, living constantly under the influence of feelings of uncertainty or fear relating to graft survival, and the social pressure to return to the previous routine.[22-28]

Another important aspect in this complex interaction is how patients cope with their condition. Coping refers to a set of cognitive and behavioral efforts aimed at controlling, reducing or eliminating stress.[29] These strategies may be classified according to function: coping focused on the problem (trying to modify the stressor); and coping focused on emotion (trying to regulate the emotional response to stress).[29] Coping patterns contribute towards management of kidney transplantation-related stressors and maintenance of quality of life.[17] However, certain strategies may lead to ineffective adaptation to the demands of the illness and the treatment. Emotion-focused strategies have been correlated with more frequent recognition of stressors and less perception of stress control among kidney transplantation patients.[30]

Therefore, identification of potentially modifiable variables, like stress and coping patterns, could improve adherence behavior relating to medications, and consequently, the clinical outcomes from kidney transplantation.[8]

OBJECTIVE

The present study aimed to compare coping strategies and stress between adherent and nonadherent kidney transplantation patients receiving immunosuppression.

METHODS

Design

We conducted a single-center comparative, cross-sectional and observational study at a university-based transplantation clinic located in the city of Juiz de Fora, Brazil (Núcleo Interdisciplinar de Estudos, Pesquisas e Tratamento em Nefrologia, NIEPEN) between August and December 2010.

Sample and setting

The study sample was recruited from a previous study dealing with validation of the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS) for use in Portuguese.[31] Patients were included based on the following criteria: age of at least 18 years, more than one year after transplantation, and willing to participate in the study; which resulted in a convenience sample of the first 100 kidney transplantation patients who were being followed up at our outpatient facility.

All the patients answered the BAASIS questionnaire, which is a transculturally adapted self-reporting instrument developed by the Leuven-Basel Adherence Research Group, in Basel, Switzerland,[32,33] and which has been validated by our research team.[31] BAASIS was administered during the patients'

regular consultation visits, by transplantation nurses who had been trained as interviewers. However, the patients did not receive any specific feedback about their adherence status during their responses to the questionnaire.

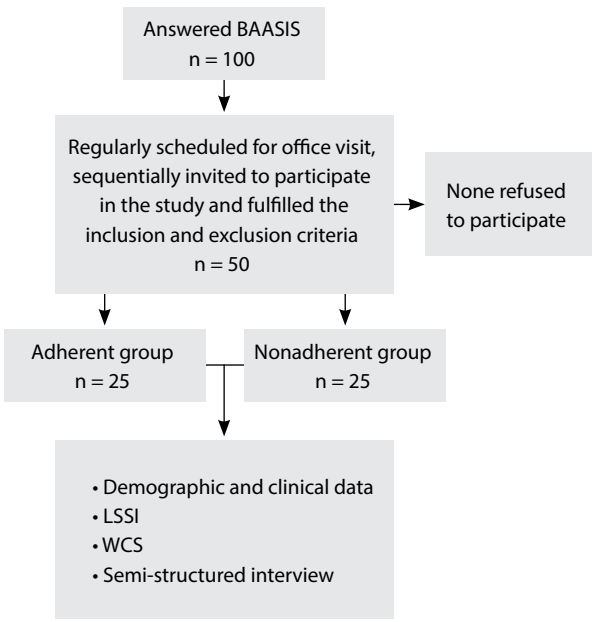
Then, from August to December 2010, all patients routinely scheduled for medical consultations and included in our previous validation study[31] were consequently invited to participate in this new study. Patients were included if they had received their transplant more than one year earlier (thus denoting that stable graft function had been achieved) and were at least 18 years old. No patients with retransplantation or who were unable to understand the objectives of the study or had difficulties in filling out the questionnaire were included.

The first 25 adherent patients (adherent group) and the first 25 nonadherent patients (nonadherent group) were selected, totaling 50 patients (**Figure 1**). None of the first 50 invited patients who fulfilled the inclusion and exclusion criteria declined to participate.

Variables and measurements

General data

Demographic and clinical data were collected through retrieving the following information from the medical records: gender, age, marital status, years of formal education, city of origin, type of donor, time of kidney transplantation, serum creatinine and comorbidities.



BAASIS = Basel Assessment of Adherence to Immunosuppressive Medication Scale; LSSI = Lipp Stress Symptom Inventory for Adults; WCS = Ways of Coping Scale.

Figure 1. Study design.

Adherence

The definition of nonadherence that was used was based on the medication regimen as recommended by the transplantation community.[12] As previously mentioned, to evaluate adherence to immunosuppressive drugs, we applied BAASIS,[32-34] as validated for use in Portuguese.[31] BAASIS assesses relevant dimensions of immunosuppressive drug use (i.e. adherence to taking the drug, adherence to the times for taking the drug, drug holidays and dose reduction) over a fixed time period consisting of the last four weeks. Responses are given on a six-point scale: never (0), once per month (1), every second week (2), every week (3), more than once per week (4) and every day (5). Any deviation, namely an answer differing from "never," among any of the items, is considered to be nonadherence. Cronbach's alpha for the validated translation into Portuguese was 0.70, thus indicating moderate internal consistency.[31]

Stress

The presence and level of stress were evaluated using the Lipp Stress Symptoms Inventory (LSSI) for adults.[35] The LSSI comprises a questionnaire that detects the presence of stress and classifies patients in accordance with Lipp's four-phase model (alert, resistance, quasi-exhaustion and exhaustion). We opted to use LSSI because it was developed and validated in Portuguese (Cronbach's alpha of 0.91).[35] We first evaluated the presence of stress, then used the original stress phases and finally used a composite classification that included an initial stress phase (patients in the alert and resistance phases) (initial phase) and a more advanced phase (patients in the quasi-exhaustion and exhaustion phases) (more advanced phase).[35]

Coping

Coping was assessed using the WCS, a 45-item scale developed by Vitaliano et al.[36] and validated for use in Portuguese.[37] The items on this self-reporting instrument are rated on a five-point Likert scale: I never do this (1); I do this a little bit (2); I sometimes do this (3); I do this a lot (4); and I always do this (5). Four patterns of coping were evaluated: coping focused on the problem (18 items; Cronbach's alpha: 0.84); coping focused on emotion (15 items; Cronbach's alpha: 0.81); searching for/turning to religion/fantasy thoughts (7 items; Cronbach's alpha: 0.74); and seeking social support (5 items; Cronbach's alpha: 0.70).[37] Higher scores indicate greater use of each coping strategy. A further analysis was also performed, in which these original four categories were grouped into two others: **active coping**, focused on the problem and seeking social support; and **palliative coping**, focused on emotion and searching for/ turning to religion/fantasy thoughts.

This categorization was based on the general goal of the coping response, which may be directed towards the situation (active coping) or towards emotional management (palliative coping).[29]

Data collection

First, we invited outpatients who fulfilled the study inclusion and exclusion criteria. As mentioned previously, BAASIS had been administered to these patients during their previous regular consultation visit by trained transplantation nurse interviewers. Then, participants were given written and oral information before signing the informed consent form. Finally, the LSSI and the WCS were applied by a psychologist from outside the kidney transplantation team. The time interval between applying BAASIS and applying LSSI and WCS was about a month, and the data were gathered from all of these questionnaires between August and December 2010. Complementary data were gathered from the medical records.

Ethical considerations

This study was approved by the local research ethics committee (approval number 0028/2010). Patients agreed to participate in the study through signing an informed consent form.

Statistical procedures

Descriptive statistical analyses were conducted using frequencies to evaluate categorical variables and means and standard deviations to evaluate continuous variables. The t test, Mann-Whitney test and chi-square or Fisher's test were used to compare variables between the adherent and nonadherent groups (**Tables 1** and **2**). Odds ratios were then estimated by means of simple logistic regression on stress and coping relating to nonadherence. We analyzed stress in three categories: no stress, initial stress phase and more advanced stress phase. For coping, we considered two grouped categories for the analysis: palliative coping and active coping. A multivariate approach was not feasible due to the small sample size and homogeneity of the adherent and nonadherent groups, as shown in the results section. We presented odds ratio point estimates and their respective 95% confidence intervals.[38,39] The significance level was set at 0.05. The analyses were performed using the SPSS 15.0 statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

Descriptive data

The patients' mean age was 44.1 ± 12.8 years, and 62% were male. Ninety-four percent received their graft from a living donor. The median post-transplantation time was 71.8 months (range: 12-230), and the creatinine level was 1.6 ± 0.74 mg/dl. Fifty-two percent of the patients had finished primary school, 20% secondary school and 28% higher education. Most of the individuals (70%) reported having a steady partner, and only 26% lived in the city of the transplantation center. No significant differences were found in the descriptive data between the adherent and nonadherent groups (**Table 1**).

Stress and adherence

According to the LSSI, 50% of the patients had a diagnosis of stress. However, we found higher frequency of stress in the nonadherent group (64%) than in the adherent group (36%) (P = 0.05) (**Table 2**). On the other hand, neither of the groups showed any differences between the stress phases (P = 0.40) and the composite stress phases (P = 0.68).

Likewise, we did not find any factor independently associated with nonadherence in bivariate analysis (**Tables 1** and **2**), including demographic and clinical data. Because stress and coping variables behaved collinearly, a simple logistic regression model was used to estimate odds ratios and their respective 95% confidence intervals (CI) for stress levels and coping pattern, in relation to adherence. The more advanced level of stress showed a nonsignificant trend towards a positive association

Table 1. Demographic and clinical variables of adherent and nonadherent kidney transplantation patients studied

	Total (n = 50)	Nonadherent (n = 25)	Adherent (n = 25)
Age (years)*	44.1 ± 12.8	47.6 ± 13.6	40.5 ± 11.3
Male gender†	62% (31/50)	56% (14)	68% (17)
Steady partner†	70% (35/50)	76% (19)	64% (16)
Education#			
Less than 8 years	52% (26/50)	52% (13/25)	52% (13/25)
8-11 years	20% (10/50)	12% (3/25)	28% (7/25)
More than 11 years	28% (14/50)	36% (9/25)	20% (5/25)
Living in the city of transplant center†	26% (13/50)	20% (5/25)	32% (8/25)
Time post-transplantation* (months)	71.8 (12-230)	75.0 (23-70)	67.0 (12-204)
Living donor†	94% (47/50)	100% (25/25)	88% (22/25)
Creatinine (mg/dl)*	1.6 ± 0.77	1.7 ± 0.90	1.5 ± 0.54

Continuous variables * were compared using t test or Mann-Whitney test, and frequencies † using chi-square test. No significant differences were found between the groups.

with nonadherence to immunosuppressive medication in this analysis (OR 4.7; 95% CI: 0.99-22.51; P = 0.053) (**Table 2**).

Coping patterns and adherence

There was a difference in the coping patterns relating to searching for religious practices and fantasy thoughts between the groups (52 versus 24%), but the results were not statistically significant (**Table 2**). In contrast, after grouping the coping patterns, adherent patients had more responses associated with active coping directed towards the stressor (76%) than did nonadherent patients (48%) (P = 0.04) (**Table 2**). Moreover, the palliative coping pattern (religion/fantasy thoughts and emotion-focused coping) was associated with nonadherence (OR 3.4; 95% CI: 1.02-11.47) (**Table 3**).

DISCUSSION

In this comparative study, we found that nonadherent patients had high stress (50%) and used more palliative coping strategies than did adherent patients. Although the patients had been previously grouped according to their adherence to immunosuppressive drugs, the demographic and clinical variables were similar between the adherent and nonadherent groups.

Table 2. Bivariate analysis on the presence of stress, stress factors and coping patterns among adherent and non-adherent kidney transplantation patients

Bivariate analysis*			
Variables	**Nonadherent (n = 25)**	**Adherent (n = 25)**	**P**
Presence of stress*	64% (16/25)	36% (9/25)	**0.05**
Stress phase†			
Alert phase	0	4% (1/25)	
Resistance phase	50% (8/16)	20% (5/25)	
Quasi-exhaustion phase	37.5% (6/16)	12% (3/25)	
Exhaustion phase	12.5% (2/16)	0	0.40
Composite stress phase†			
Initial phase (alert and resistance phases)	50% (8/16)	66.7% (6/09)	
More advanced phase (quasi-exhaustion phase and exhaustion phase)	50% (8/16)	33.3% (3/09)	0.68
Stress factor*			
Fear of graft loss	76% (19/25)	56% (14/25)	
Medication issues	84% (21/25)	48% (12/25)	
Excessive need for care	64% (16/25)	60% (15/25)	
Post-transplant treatment	56% (14/25)	32% (8/25)	
Social acceptance/reinsertion	20% (5/25)	28% (7/25)	**0.008**
Coping pattern†			
Focused on problem-solving	40% (10/25)	60% (15/25)	
Seeking social support	8% (2/25)	16% (4/25)	
Emotion-focused	4% (1/25)	0	
Religion/fantasy thoughts	48% (12/25)	24% (6/25)	0.20
Coping according to grouping pattern*			
Active coping	48% (12)	76% (19)	
Palliative coping	52% (13)	24% (6)	0.04

*Variables were analyzed using chi-square * or Fisher test †.

Table 3. Simple logistic regression model for the presence of stress, stress factors and coping patterns among adherent and non-adherent kidney transplantation patients

Simple logistic regression model*				
Variables	**Nonadherent (n = 25)**	**Adherent (n = 25)**	**OR (95% CI)**	**P**
No stress	36% (9)	64.0% (16)	1	-
Initial phase	50% (8)	66.7% (6)	2.4 (0.62-9.02)	0.21
More advanced phase	50% (8)	33.3% (3)	4.7 (0.99-22.51)	0.05
Active coping	48% (12)	76.0% (19)	1	-
Palliative coping	52% (13)	24.0% (6)	3.4 (1.02-11.47)	0.04

*Logistic regression model. We ran two different logistic regression models, one for stress and the other for coping pattern.

These results appear consistent with the conclusions from previous studies, in which kidney transplantation did not eliminate chronic kidney disease-related stressors and those relating to disease treatment, since kidney transplantation is only a form of therapy for chronic kidney disease, and not its cure.[2] Even with a well-functioning graft, these individuals continue to be chronic disease patients who are subject to some level of social, physical and emotional limitations, as is the case with dialysis patients.[9,22-25] However, differently from our study, most other studies failed to directly assess the frequency of stress.

In order to assess stress, we used the LSSI, which is a psychological test that enables diagnosing of stress based on specific symptoms and identification of the stress phase, in accordance with Seyle's theory.[19] This is the only instrument for evaluating stress that has been validated for use among Portuguese-speaking patients and that has characteristics in line with the aims of our study. Nevertheless, previous studies evaluating stress and kidney transplantation have used other instruments such as scales based on subjective measurement of stressful factors or specific life themes, including those relating to the illness.[22-25,28] Those scales probably have limited evaluation capacity because they rely on patient memory and do not consider the coping strategies used by patients, which may alter the stress results.[35]

Additionally, we did not find any studies that have shown any consistent link between the specific phases of stress and nonadaptive behavior of nonadherence in cases of kidney transplantation. Stressed patients, particularly those in the advanced phase, are more likely to develop emotional problems (depression and anxiety), cognitive problems (attention and memory) and affective problems (interpersonal conflicts or social withdrawal).[35] Each of these conditions may potentially contribute towards ineffective coping with health status, thus affecting adherence to medication among kidney transplantation patients.

Concerning coping patterns, nonadherence to immunosuppressants was associated with palliative control in our study, mainly focused on "emotion" and "religion/fantasy thoughts". Coping responses "focused on the problem" or "focused on emotion" are fundamental for attenuating the impact of stressors, given that both of these responses play complementary yet different roles in stress control.[40] However, over a long period of time, active coping strategies tend to be more adaptive, because they attempt to confront the stressor, thereby reducing stress-related symptoms and helping achieve an adjustment to the stressor situation.[41] We have already identified the most frequent stressors in our population.[42] Strategies to help this population deal with the stressors, designed individually or generally, are now the focus of our attention. We have reinforced our educational activities in waiting room and have taken an interdisciplinary approach towards better social support, with psychotherapy for cognitive restructuring and use of motivational interview techniques.

Thus, in the context of adherence to medication among kidney transplantation patients, we expected palliative coping to be related to nonadaptive nonadherence behavior. In fact, Lindqvist et al. observed that patients who used more evasive, fatalistic, palliative and emotional coping strategies were less capable of dealing with the demands of chronic kidney disease and kidney transplantation.[30] Another study on a sample comprising 200 kidney transplantation patients showed that recipients who reported higher stress and more depression, and who coped with stress by using avoidant coping strategies, were less compliant with medication.[41]

There are some limitations to our study. The sample size, similarly to other studies involving psychological factors among kidney transplantation patients,[9,17] was less than 100 patients. We tried to overcome this limitation by applying a sampling design that involved studying the same numbers of adherent and nonadherent subjects, selected from the main study population (BAASIS validation).[31] However, we recognize that this design was underpowered, compared with case-control matched studies. Use of a single self-reporting instrument may have limited the evaluation of immunosuppressive adherence.

We opted for BAASIS as the method for assessing adherence because it was one of the three measurement tools for self-reporting of nonadherence that the Transplant 360 Task Force identified as presenting the potential for effective adaptation for use in transplantation clinical practice.[32,33] Moreover, BAASIS is the only instrument that has been validated for use among Brazilian Portuguese-speaking transplantation patients.[31]

In addition, living donor recipients predominated in our sample. Until recently, this donor profile was the most common type of transplantation performed in Brazil.[43] Future studies should include patients receiving transplants from deceased donors, in order to enable greater understanding of the issues relating to this condition.

The fact that each patient was at a specific post-transplantation time prevented investigation of the potential association between stress and coping over the entire transplantation experience. We also take the view that, because of the design of the present study, it was not possible to evaluated causality and whether stress and coping were the cause or consequence of nonadherence. Moreover, since multivariate analysis was not possible, clinical inferences should be made with caution.

Nevertheless, our results present relevant results, given the paucity of studies in this field and the absence of previous studies among the Brazilian population. A longitudinal follow-up study, including key transplantation periods (i.e. pre, peri and post-transplantation stages), could provide additional evidence with regard to these questions.

CONCLUSIONS

The present study showed that stress occurs frequently, even in cases of well-functioning kidney transplantation. Palliative patterns of coping with transplant-related stressors were independently associated with immunosuppressive nonadherence. These findings support the notion that adherence interventions should integrate behavioral, psychosocial and medical approaches in order to appropriately limit the undesirable consequences of nonadherence in kidney transplantation. Therefore, more studies are needed in this field of research. Healthcare professionals should be prepared to provide whole-person care for their transplantation patients, taking into consideration their bio-psycho-social-spiritual needs and proposing interventions for improving adherence behavior relating to medication and, consequently, the outcomes from kidney transplantation.

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Development of a strategy of physician-patient relationship for improving care for patients with disorders of sex development: a qualitative study

Desenvolvimento de uma estratégia de relacionamento médico-paciente para a melhoria do atendimento aos pacientes com desordens do desenvolvimento do sexo: um estudo qualitativo

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KEY WORDS:
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PALAVRAS-CHAVE:
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Educação médica.
Relações médico-paciente.
Comunicação interdisciplinar.

ABSTRACT

CONTEXT AND OBJECTIVE: Care for patients with disorders of sex development (DSD) should be provided in integrated-care centers by a multidisciplinary team. Implementation of this project within the teaching clinic routine presents several challenges: 1) difficulties in relationships between the medical team and patients and their families; 2) age, ethnic and cultural differences; 3) DSD-related prejudice; and 4) physicians' anxiety. We report on a psychologist's work strategy that focused on creating arrangements that could contribute towards development of the relationship between the medical team and patients and their families, as a way of preparing the clinical staff to manage treatment of adult DSD patients.

DESIGN AND SETTING: Prospective qualitative study.

METHODS: Between February 2010 and April 2015, we conducted a qualitative study in the Adrenal Outpatient Clinic of Escola Paulista de Medicina (São Paulo, Brazil), based on interviews, team discussions and group dynamics with resident physicians, postgraduate students and attending physicians.

RESULTS: Implementation of the project allowed residents to build a story of differentiated care for their patients, thus facilitating dialog between them and making it possible to address taboo topics. Sequential care provided by the same resident led patients to feel that their doctor cared for them, with individuality, continuity and a sense of interest in their story.

CONCLUSION: Presence of a psychologist in the outpatient routine enabled inclusion of subjective factors in the routine of medical consultations, thus broadening the notion of healthcare for patients with DSD, facilitating bonds and providing support for difficulties faced.

RESUMO

CONTEXTO E OBJETIVO: Pacientes com desordens do desenvolvimento do sexo (DDS) e seus familiares devem ser atendidos em centros de atenção integral, por equipe multidisciplinar. A efetivação desse projeto no cotidiano da clínica-escola apresenta vários desafios: 1) dificuldades nas relações entre equipe médica, paciente e família, 2) diferenças etárias, étnicas e culturais, 3) preconceitos relacionados às DDS, e 4) angústia dos médicos. Relatamos o desenvolvimento de uma estratégia de trabalho do psicólogo, que teve como foco a criação de dispositivos que contribuíssem para o aprimoramento da relação entre equipe médica, paciente e família, preparando o *staff* clínico para administrar o tratamento de pacientes adultos com DDS.

DESENHO E LOCAL: Estudo qualitativo prospectivo.

MÉTODOS: De fevereiro de 2010 até abril de 2015, realizamos uma pesquisa qualitativa no Ambulatório de Adrenal da Escola Paulista de Medicina (São Paulo, Brasil), baseada em entrevistas, discussões de equipe e dinâmica de grupo com médicos residentes, pós-graduandos e assistentes.

RESULTADOS: A implementação do projeto possibilitou aos residentes construir uma história de atendimento diferenciado com seus pacientes, facilitando o diálogo entre eles e permitindo que temas-tabus fossem abordados. O fato de ter sido atendido seguidamente pelo mesmo residente possibilitou ao paciente a sensação de cuidado, individualidade, continuidade e a sensação de que havia interesse, por parte do médico, sobre a sua história.

CONCLUSÃO: A presença do psicólogo no cotidiano do ambulatório permitiu que aspectos subjetivos fossem incluídos na rotina das consultas médicas, ampliando a noção de saúde e cuidado aos pacientes com DDS, facilitando o vínculo e dando suporte para as dificuldades encontradas.

INTRODUCTION

The physician-patient relationship and its models still constitute an object of study in several fields of science. The way in which this relationship develops within the medical context defines settings and attitudes, thereby building narratives about patients and their disease, and influencing these subjects' experience.

Disorders of sex development (DSDs) are congenital conditions in which the development of chromosomal, gonadal or anatomical sex is atypical.[1] DSDs are rare diseases that demand handling of hormonal, esthetic/surgical and emotional issues, since they involve matters that are central to the individual's life, such as sex and gender definitions, reconstruction of malformed genitals, gender identity and sexuality. Thus, care for patients with DSDs and their families should be provided in integrated-care centers by a multidisciplinary team, taking into consideration particular issues such as age, religion, culture, socioeconomic status and education, among other factors.[1-3]

The treatment protocol for patients with DSDs has changed over the years,[4] thus influencing the way in which physicians are prepared in order to handle these cases. During the "Money era" (1955-1990), the model for the dynamics between the medical staff and patients and their families was essentially based on policies of discretion and secrecy. This approach aimed to avoid discussion of the patient's condition between the patient and his or her family, and it was justified by the idea that if the prevailing discourse was free from doubt, this would ensure development of a solid and healthy gender identity.[4-6] Accordingly, that model was based on a "functionalist perspective", and it expected the physician to take an active and decisive attitude, while the patient would have passive and submissive behavior.[7]

Today, the foundations for the treatment protocol are those described in the Chicago meeting of 2005.[1] Provision of data on the disease and the treatment has begun to play a central role in handling these cases, thus demanding a new attitude from the physician, in which both sides expect transparency in their exchanges concerning the disease, with sharing of responsibilities between physicians, the families and the patients themselves.[1,4]

However, fragmentation of services (in particular, the disconnection between pediatric and adult clinics), the visits to different specialists that patients with DSDs have to go through and the turnover of professionals who work in the clinics of university hospitals (interns, residents, trainees and postgraduate students) constitute everyday challenges in clinical practice.[8]

One additional challenge intrinsic to any university medical school's practice concerns the training of young doctors. Residents are graduate medical students who decide to follow and master a medical specialty. The in-training residence program is a highly stressful period in which many professionals are likely to develop burnout or depressive syndromes, and to require informative measures and help in caring for their mental status.[9] The particular features of the several medical disciplines involved in attending DSDs patients require a wealth of diverse information and expertise from these in-training residents, as previously mentioned.[4]

In this context, we sensed the need to design a team intervention proposal in our endocrinology outpatient clinic, which specializes in caring for adult patients with DSDs, in an attempt to solve some specific challenges and to improve physician-patient/family relationships.

OBJECTIVE

To report on a psychologist's work strategy that aimed to establish arrangements that could contribute towards development of an effective relationship between the physician team and patients and their families, as a way of preparing the clinical staff to handle treatment of adult DSDs patients. The specific aims were to:

1. facilitate communication between physicians and adult patients; and
2. prepare and qualify young physicians to address and handle matters relating to sexuality, gender identity and sexual orientation.

METHODS

During the period from February 2010 to April 2015, we followed three groups of endocrinology residents as they rotated in the Adrenal Outpatient Clinic of the Division of Endocrinology and Metabolism, Escola Paulista de Medicina, Universidade Federal de São Paulo (AOC-EPM).

During that period, 44 physicians taking part in medical school training and assistance activities provided attendance at the AOC-EPM: 36 in-training residents (third and fourth years of the course; averaging 11 residents/year, who rotated during the period), five postgraduate students and four assistant professors (fixed clinical group). Over the same period, care was provided for 55 patients with DSDs (40 with congenital adrenal hyperplasia due to 21-hydroxylase deficiency, seven due to 17-hydroxylase deficiency, three with total peripheral androgen resistance and five with other DSDs), in quarterly or biannual appointments. This group of patients corresponded to nearly 5% of the total number of patients followed in the clinic, which operates weekly.

In the present study, we assessed questionings, anxieties and doubts among the group of in-training residents who worked at the clinic over that period. We carried out the survey by using suitable psychological techniques:

1. group dynamics (conducted at the beginning and at the end of the in-training program);
2. annotated observations of the daily clinical routine; and
3. several medical school activities.

The latter included class lectures and clinical case discussions focusing on the psychological aspects of experiencing the disease and on matters such as sexuality, identity building, gender roles and ethical issues, among others.

The researcher (MTS) recorded all the activities right after they took place; she analyzed the data gathered by creating categories based on analysis of the transcripts, as per the five steps proposed by Pope[10] (familiarization, identification of a thematic framework, indexing, charting and mapping/interpretation). She also analyzed the effects of patients' discourse on the doctors, and vice-versa, taking psychoanalytical clinical listening as the reference.

Therefore, this report consisted of qualitative research that made use of observations, discussions and institutional interventions. The methodological guideline was research-action/intervention. This methodology was chosen through analysis on the subjective and emotional consequences for those involved in the clinic and interacting with the patients. For this reason, the researcher kept herself emotionally involved with what she intended to study and, in this way, the research field was composed of and through her presence.[10-16]

All the physicians and patients who actively took part in the activities signed a free and informed consent statement allowing the data gathered to be used in this study. The entire research project had gained consent from and was guaranteed by the head of the clinic, who monitored all the phases of development of the work. The project was approved by the Ethics Committee for Human Research of Universidade Federal de São Paulo, São Paulo, SP, Brazil (protocol #1842/10).

Context

From the outset, we noticed that both the requests for psychological care and the participation in the discussion of a clinical case always brought with it some comments relating to aspects of the relationship that was being built between physician and patient. The following are examples:

- *"Do you think that girl wants to be a man or a woman?"*
- *"I don't know how to approach the subject of corrective surgery, nor of relationships… at the same time, the patient tells me she is married. So I guess she does have a sex life…"*
- *"We believe the lack of continuity of the patient indicates that she wants her virilization; do you think that's possible?*
- *"Does this patient like men or women?"*

One of the main problems that we detected, and one that involved the physician-patient relationship, lay in the difficulty in establishing bonds of trust. Since the patient met a different resident physician at every appointment, the physician did not have the opportunity to work through the questions he had raised even if all the staff discussed his questionings thoroughly in the clinical meetings.

The staff turnover and the clinic's routine led to difficulties in the establishment of bonds. The physician could not answer questions that the patient brought, which made it difficult for him/her to build a story. Given the lack of continuity of his/her contact with the patient, the physician was objective and did not interact with the patient's life story; he/she either focused only on the immediate demand, or on the question relating to adherence to treatment. In that model, the only option that remained for the physician was to gather objective data from examinations and compare these with data in the medical records.

Based on these considerations, and as a strategy to create new conditions for establishment of new work bonds, we have devised a clinical approach termed "in-training reference-resident".

This strategy consisted of defining one in-training endocrine resident as the sole reference for caring for a specific DSD patient during a period of at least two years. Other physicians and graduating students could only follow the case together with the "in-training reference-resident" or during a clinical case presentation.

The "in-training reference-resident" was also responsible for scheduling future appointments in accordance with his/her shifts, in order to ensure priority for the patient. In situations of absence, he/she was to request assistance from another colleague within the group, and assemble information on the session afterwards. We explained and shared this procedure with the patient. At the end of the two-year residence, the "in-training reference-resident" would transfer his/her specific cases to a new colleague.

RESULTS

The discourse analysis clearly showed that some categories were repeated:

1. uncertainty as to the patient's adherence (disbelief in the physician's words);
2. uncertainty regarding sexual orientation;
3. adaptation to gender identity;
4. sexuality; and
5. difficulty in handling the patient's and their own subjective issues.

We considered that these comments were expressions of countertransference movements[17,18] on the part of the medical staff, and therefore constituted the background to the patient's clinical care.

Use of the "in-training reference-resident" approach enabled each resident to build a story of individualized care with his/her patients with DSDs. The fact that we directed one resident to each patient made the clinic's functioning easier in many ways, thus allowing new developments for many problems that until then were apparently unsolvable. Consequently, the physicians were better oriented, which resulted in improved provision of care.

Over the course of the process, the psychologist noticed that the residents started to feel more comfortable at every new session, especially when they felt empathy towards the case, or when they understood why a particular patient made them anxious.

During the assessment of the project, we often heard from the residents how impressed they were at the improvement in issues of treatment adherence. Moreover, they could assess how their patients were previously considered to be "protocols", in which the examinations provided measurement and assessment of good or bad adherence. The discussion groups, lectures and group dynamics were crucial for supporting the acquisition of theoretical and subjective terms so that they could withstand the anxiety and tension raised by the situations that the patients brought to the sessions.

From the group dynamics, the residents reported how comforting it was to acknowledge that the difficulties inherent to the DSD clinic were felt by everyone. The exchange of experiences among them, in the various groups, favored building of a network of internal support, as well as maintenance of a common project, as can be inferred from their words:

- *"Wow, it is such a relief to hear what they're saying, because I think I'll have all that support; I think it will be a great learning experience for me. I came with lots of expectations and, by the look of it, there are many nuances; I think what I take from this session today is the importance of listening!"* (R3)
- *" I don't know how to handle a case like this; as a consequence, I don't have doubts or questions; after all, I did not get in contact with that kind of patient; I don't even know where to begin. Listening to the other residents makes me think I will learn a lot, and that the questions and answers will be built in the group!"* (R3)

During implementation of the "in-training reference-resident" project, the residents reported that they could relate the DSD's theoretical-clinical dimension to the singularity of each patient's story. Here are some samples from their words:

- *"I consider the Adrenal Outpatient Clinic one of the most difficult to work at and learn from. Every day, before seeing the patients, I try to prepare and study the pathologies, but when I am studying my patient X, it seems easier to understand the complex mechanisms of the disease"* (R4)
- "*When you see the patients in the project, you think about that particular patient; sometimes we want to get the parameters right and that is not always what the patient want. If I know him, I'll have to consider other aspects, otherwise he will stop taking the medication, and I will blame it on him for being non-adherent!"* (R4)
- *"Our age doesn't matter; there is always some tension in an appointment like that. We're not used to deal with so many different variables. Each patient and each family are unique and they are always the ones who will teach us; it is that closer contact with the patient that will guarantee that we make a difference! Pathology is something we can learn, but relationship is something we have to build".* (Attending physician).

The transition from one resident to another was an important observation to be improved. We noticed that it would be crucial to emphasize this transition, since it could potentially interfere with the progress of the treatments. Some patients established bonds with their doctor (through the mechanism of transference) in such a way that they did not want to leave that relationship, thus missing appointments with the new resident. By observing these behaviors, we were able to draw up measures involving the next resident's turn, thus anticipating problems and sharing the process with the patients. The outcome from this "in-training reference-resident" strategy demonstrated that the organizational work and process influenced the physician-patient relationship and, therefore, the implications of treatment.

From the patients' point of view, we could observe that the project also brought a series of counterparts, such as feelings of care, individuality and continuity, and especially a feeling that the physician was interested in them and their stories. During the follow-up, we no longer heard the patients complain that they did not understand the medical language. Many of them stated that they could not miss their appointments because they did not want to "drop the ball on their doctor".

As a result, we noticed that physicians showing greater commitment had patients who were more engaged in their own treatment. Lastly, over these five years, we achieved effective improvements in medical care and in adherence to treatment.

DISCUSSION

Through organizing the course of treatment of patients with DSDs better over the residence years, these young physicians could testify to concomitant development of a strong therapeutic alliance that was capable of changing behavioral patterns, which had not been considered possible until then. For example, patients had been missing their appointments, not taking their medications and not broaching topics that they initially judged themselves unable to address, etc. The closer contact enabled new ways of assessing patients' suffering, while leaving some prejudice behind.

Implementation of the "in-training reference-resident" project had the aim of reducing fragmentation of the care provided for patients, as well as fostering conditions for the physician to establish a more human and singular form of interaction with the patients. Moreover, according to Campos,[19] the medical project of a reference team has the purpose of creating and stimulating

progressive production of a new standard of responsibility between the two players, thus leading to more responsibility and co-participation.

The residents were able to introduce and discuss taboo topics with the patients, which were not mentioned in the preceding sessions. From one session to the next, the residents had enough time not only to discuss the case with their superiors but also with the psychologist, so as to design a singular project with each patient and decrease the number of requests for psychological intervention, thereby favoring dialog. In other words, the topics that were addressed only by the psychologist could be worked through in the case discussions and could be dealt with directly by the "in-training reference-resident", thus creating a less fragmented relationship and favoring a bond of trust.

Caprara and Franco[7] and Adam and Herzlich,[20] based on the works of Balint,[18] Gadamer[21] and others, stressed the importance of the bond established between physician and patient as a fundamental factor in ensuring greater effectiveness of the therapy established. Caprara's analysis[7] concerns the importance given to the doctor's listening and attention given to the patient as something that can be compared to the healing effect of a medicine ("medicine-doctor", in Balint's expression).[18]

Several reference centers include the subject of Narrative Medicine in their medical programs or courses. This has the guiding principle of teaching physicians to listen and understand the stories of their patients. Narrative medicine has the aim of helping young physician to design listening tools that tell them what to do with patients' stories. According to its founder, Charon,[22] "if physicians do not know how to absorb and act on the stories they listen to, they will miss the opportunity to experience a real and therapeutically meaningful bond with their patients, who will thus be left adrift".[22]

Therefore, creation of work tools that enable broadening of themes and favor development of relationships produces a direct improvement in patient care and decreases the rates of physician burnout, since there will be other people to talk to and share anxieties with.[23]

It is important to take into consideration the fact that, when adult patients start going to the clinic by themselves, without their parents or tutors, they feel pressured by the new questions that the doctor now asks them directly. Without intermediation, and often without previous preparation, we noticed that the diagnosis of anxiety returned, such that it was experienced a second time. In other words, the memories that remained in the patients' bodies added to their present anxiety. When a physician deals with adult patients, this ends up triggering an unconscious association network, which surprises and, at the same time, scares patients. For this reason, treatment measures should cover those issues.

The "in-training reference-resident" project resulted in reorganization of the service, thus making it possible, both for physicians and for patients, to devise a new way of facing issues inherent to this clinic. We can state that there has been a change in quality of the physician-patient relationship, which has made the treatment process easier.

Furthermore, in one of the educational activities, we invited one of the residents who had formed part of the first group to give a class about the case he had worked on and followed up, reporting on the medical record, the challenges and his experience. That activity placed the new resident, who is now a specialist in endocrinology, in a different position, thus serving as a model for those who were arriving.

Finally, our study had one shortcoming: since our outpatient clinic treats patients with adrenal diseases in general and not exclusively DSDs, we were not able to conduct moments of reflection with the staff more often, because that would have taken up the time directed towards other activities in the clinic. In that sense, we believe that there is a need for a new routine in the clinic, centered on the DSD cases, so as to intensify the discussions, explore them in depth and better assess the residents' learning process.

CONCLUSION

The strategy described seemed to be useful for improving care for patients with DSDs, in spite of not being a controlled randomized clinical study. Both among the patients and the physicians, the proposal was highly valued and seems to have had a direct effect with regard to challenging issues, through favoring communication, enhancing bonds and giving greater esteem to these subjects' lives.

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Predictors for choosing the specialty of Family Medicine from undergraduate knowledge and attitudes

Preditores da escolha da especialidade Medicina de Família a partir de competências e atitudes de alunos de graduação

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Medicina de família e comunidade.
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Educação de pós-graduação em medicina.
Atenção primária à saúde.
Estudantes de medicina.

ABSTRACT

CONTEXT AND OBJECTIVE: A cold climate towards primary care (PC) within medical academia could form a barrier against choosing family medicine (FM) as a career option. This study was designed to determine whether medical students' knowledge of and attitudes towards FM predicted their career choice.

DESIGN AND SETTING: Cohort study conducted at two different medical schools.

METHODS: After completing a PC course at the Albacete Medical School in 2005-2006, 81 second-year students were asked to give responses to a questionnaire. In their sixth year (2009-2010), 79 students in Albacete and 42 in Seville (taken as an unexposed cohort) were asked to give responses too. Their choice of specialty was investigated in 2011.

RESULTS: In Albacete, the questionnaire was answered by 79 second-year and 76 sixth-year students; in Seville, it was answered by 26 sixth-year students. After completing the PC course, 69.3% said they would like to become a family doctor. This percentage decreased to 40.3% at the end of the undergraduate course ($P < 0.0001$). In the sixth year, the attitudes towards FM worsened, yet these were significantly more favorable than those in Seville. Only 12 students chose FM; they obtained significantly worse scores in their specialty selection examination than their peers ($P < 0.0001$).

CONCLUSION: In the Albacete Medical School, the students' opinion about FM worsened over the undergraduate course, although it was still better than the Seville students' stance. In any case, FM was seen to be a minority option.

RESUMO

CONTEXTO E OBJETIVO: Um clima frio para a atenção primária na academia médica constitui uma barreira para escolher Medicina de Família (MF) como opção de carreira. Este estudo foi concebido para determinar se o conhecimento e as atitudes dos estudantes de medicina em relação à MF predizem a escolha da carreira.

TIPO DE ESTUDO E LOCAL: Estudo de coorte realizado em duas faculdades de medicina.

MÉTODOS: Depois de terem completado um curso de Cuidados Primários na Faculdade de Medicina de Albacete, em 2005-2006, 81 alunos do segundo ano foram convidados a responder a um questionário. No seu sexto ano (2009-2010), 79 estudantes de Albacete assim como 42 de Sevilha, tomados como coorte não exposta, foram convidados a responder também. Todos eles foram investigados sobre a escolha da especialidade em 2011.

RESULTADOS: Em Albacete, 79 e 76 estudantes responderam no segundo e sexto anos, respectivamente, e 26 em Sevilha. Depois de terem concluído o curso de cuidados primários, 69,3% disseram que gostariam de se tornar médicos de família. Esta percentagem diminuiu para 40,3% no final da graduação ($P < 0,0001$). No sexto ano, as atitudes com relação à MF pioraram, mas estas foram significativamente mais favoráveis do que as de Sevilla. Apenas 12 alunos escolheram a MF; eles obtiveram pontuação significativamente piores no exame do que seus pares ($P < 0,0001$).

CONCLUSÃO: Na Faculdade de Medicina de Albacete, a opinião dos alunos sobre a MF ao longo da graduação piorou; contudo ainda era melhor que as dos estudantes de Sevilha. Em qualquer caso, MF foi opção minoritária.

INTRODUCTION

For many years, a primary care (PC) physician shortage has been highlighted worldwide. This very likely contributes towards fragmented care, inappropriate use of specialists and less emphasis on prevention. The reasons for this are multifold. First of all, the interest in a career in PC has declined over recent years, and the number of medical school graduates selecting a family medicine (FM) career has declined markedly.[1-3] According to the Association of American Medical Colleges (AAMC), these numbers can be explained by an unfavorable practice environment within PC (i.e. poor quality working conditions due to high patient loads, and public and private reimbursement systems that undervalue PC services in comparison with procedures performed by specialists), as well as by perceptions of status and prestige. Also according to the AAMC, medical education and training have a lesser impact on career choices.[4]

However, a cold climate towards PC has traditionally been recognized within medical academia. This could constitute a barrier against choosing this discipline as a career option.[5]

In a previous study, we determined that students at the Albacete Medical School showed a noteworthy initial lack of knowledge and a poor opinion of FM and PC. We also demonstrated that changes in the knowledge of and attitudes towards FM took place after these students completed a course on PC.[6] In short, student's experiences during clinical clerkships or while undertaking specific courses with a field of medicine have a significant impact on their attitudes and interest in a certain specialty afterwards.[7-9] Especially, it has been pointed out that PC training at preclinical stages contributes towards better clinical performance, because it can help medical students to acquire the fundamental cognitive and clinical skills that they will apply during the clinical years of medical training.[10] These clerkships can have a long-term positive effect on approaches towards FM.[11]

FM has existed as a specialty in Spain for more than 30 years. Nevertheless, FM training in Spain has only recently been provided within university courses and its provision around the country remains uneven. Spanish medical schools' offer of FM training ranges from absence from the study program to provision of clinical clerkships alone (either on a mandatory or on an elective basis) or inclusion of FM as a mandatory subject.

Until the European Union higher education reform known as the Bologna Process, the Albacete Medical School (at that time about a decade old) had a mandatory subject on PC for medical students in the second year of a six-year undergraduate program. That used to be the students' first clinical experience. The PC course was four months long and provided five credits (such that one credit represented 10 hours of training). Out of those five credits, 1.5 were theory credits. The rest were practical credits: students were required to complete a one-week clinical clerkship in a PC center within the city of Albacete. During that week, students accompanied a family doctor during all of his or her daily activities. Now, due to the change in the study program, FM is taught in the fifth year. At Seville Medical School, students were taking a mandatory FM subject in their sixth year at the time when this study was conducted.

That clerkship on PC was our students' first clinical experience and this could, in the words of Miettola et al., have caused a honeymoon effect.[12] Thus, we need to consider how students' opinions on FM and PC will develop over their future academic years. The students' positive perceptions about PC practice may change as realistic perceptions about the professional demands on PC doctors arise during medical school, as Cooter et al. pointed out.[13] However, there is a possibility that this attitude towards FM may become even more positive when medical students end their undergraduate years. This might be partially explained by greater contact with family doctors. Regarding the latter, it should be emphasized that the Albacete Medical School students had, besides the clerkship on PC in the second year (i.e. the one discussed here), another training week within the third year (on Psychology in the Clinical Setting) and another one in their fifth year (within Medicine and Surgery II).

For these reasons, we always stressed that there was a need for our study to continue with a further assessment of senior students who are close to getting their degrees, as well as an investigation of their specialty choice.

OBJECTIVE

Our hypothesis was that taking a course in PC not only would improve students' knowledge of FM and help them to develop a more positive attitude towards it, but also would lead those with more favorable attitudes to be more likely to choose this specialty. Our goal was to determine whether medical students' knowledge of and attitudes towards FM would change between the second and sixth year, and whether these would predict selection of FM as their specialty.

METHODS

We conducted a cohort study among Albacete Medical School students who took a PC subject in their second year and used Seville Medical School students (before they started their school's FM course in their sixth year) as an unexposed cohort.

Study variables

The dependent variable was the result from applying the original version of the Valuation of Attitudes towards and Knowledge of Family Medicine Questionnaire (CAMF, in the Spanish acronym).[14] This is formed by 34 closed-response items (for example: "I would like to become a family doctor in the future"), with five response options on a Likert scale. The questionnaire also

contains items on the sociodemographic and academic characteristics of the students: age, sex, number of inhabitants in the city/town that they come from, social class estimated according to the Domingo and Marcos classification (based on parents' occupation),[15] number of subjects still pending and "grades from medical school entrance examinations (which depend on the university access test and high school average marks).

Study procedures

On the day of the final examination, the Albacete students taking the PC subject in the 2005-2006 school year were asked to give responses to a self-administered, anonymous questionnaire. The students were again invited to answer the same questionnaire at the end of their degree course, i.e. when they were final-year students in 2009-2010. In the same school year, final-year students who had been enrolled in an FM subject at the Seville Medical School (Valme campus), were invited to join in the study as an unexposed group, before they started to attend this course.

We registered the specialty that these students chose after their specialist medical training access examination (MIR, in the Spanish acronym) equivalent to residency in 2011, based on the information provided by the Spanish Ministry of Health on its website.

The data gathered were coded and entered into a computerized database using the SPSS 19.0 statistical software.

Ethical aspects

Ethical approval for this study was granted by the Investigational and Clinical Ethics Committee of the Albacete Health Area.

Student participation in the study was voluntary. In order to compare related samples when needed, the students were asked for a reference number. It was agreed between the students and the research group that the former would sign their answer sheets with the last four digits of their National Identity Card, since this would be easier for them to remember. In any case, we guaranteed the anonymity of their responses.

Statistical analysis

We analyzed the responses to the items and calculated the overall score of the questionnaire, giving the following values: "completely disagree": -2; "disagree": -1; "indifferent": 0; "agree": +1; and "completely agree": +2. In order to make the "-2" value always correspond to the most unfavorable option regarding FM and +2 to the most favorable, we recoded the responses to items 15, 22, 23, 25 and 26 with inverted scales.

The statistical analysis included a description of the different variables, comparing the groups of students. We analyzed the responses to the 34 questionnaire items, thus evaluating Albacete students' level of knowledge and their attitudes at the end of the second and sixth school years. We used the Wilcoxon signed-rank sum test to evaluate the statistical significance of the possible changes in scores for the different items. We also calculated the effect size for each item.[16] The questionnaire responses of the Albacete students were compared with those of the students in Seville using the Mann-Whitney test. Moreover, we calculated the effect size for each item.

A comparative analysis on the responses according to the different sociodemographic and academic variables was made using Pearson's chi-square test to compare proportions in independent groups. Student's t test was applied to compare the means of normally distributed continuous variables, while the nonparametric Mann-Whitney test was used in other situations. The mean score from the questionnaire was compared for different values of the sociodemographic and academic variables, using Student's t test in the case of dichotomous variables and Pearson's linear correlation in the case of continuous variables. Multiple linear regression analysis was also used. Logistic regression was used to determine the association between choosing FM and other conditioning factors, and to avoid possible confounding variables.

RESULTS

In Albacete, the questionnaire was completed by 79 undergraduates at the end of their second year (97.5% of the total number enrolled) and by 76 undergraduates (96.2%) at the end of their sixth year; 62 students completed the questionnaire on both occasions. Meanwhile, at the Seville Medical School, 26 students (61.9% of those enrolled) completed the questionnaire.

Table 1 sets out the sociodemographic and academic characteristics of the students who participated in the study. There were some differences between the groups: the proportion of women was significantly higher in the Seville Medical School (84.6%) and there were more students coming from small towns; the Albacete students had higher grades on entry to the medical school and a higher proportion of them did not have any pending subjects. We did not find any statistically significant differences regarding age or social class.

Table 2 presents the median and the interquartile range for each CAMF item in the second and sixth years for the students at the Albacete Medical School and in the sixth year for the Seville students. **Tables 3** and **4** show items with statistically significant differences: items relating to knowledge of PC and FM and items relating to a positive attitude towards the work of family doctors, respectively. **Table 5** sets out items showing statistically significant differences between sixth-year students in Albacete and Seville.

After completing the PC course, 69.3% of the students said that they would like to become a family doctor in the future. This percentage decreased to 40.3% at the end of the degree course ($P < 0.0001$), without statistical differences in relation to the

students in Seville. Five medical school graduates from Albacete chose FM. One of them had previously showed disagreement when answering the item "I would like to become a family doctor in the future" in the sixth grade. In Albacete, 12.9% of the students considered FM to be their first career choice at the end of the PC course, yet this percentage halved at the end of the degree course.

In the sixth year, a lower level of agreement with statements that could be considered more favorable towards FM and PC was generally observed, in relation to both knowledge and attitudes. Whereas there were higher levels of agreement with "Family doctors have a large work overload", there were also higher levels of disagreement with "Family doctors manage health problems of little importance" and with the statement that these problems were "unlikely to be resolved".

Despite the worsening stance towards PC and FM among Albacete students, their attitudes remained significantly more favorable than those of students in Seville. Nevertheless, the latter had a remarkably higher level of agreement regarding the item "Knowledge of FM is useful although I will choose another specialty".

We compared mean CAMF scores between the second and sixth years among 57 students with full data: 33.8 (standard deviation, SD: 9.2) and 28.5 (SD: 7.1), respectively ($P < 0.0001$). No relationship was found within the mean difference in CAMF scores between the second and sixth years for any of the variables analyzed. The mean CAMF score could be calculated for 72 sixth-year students in Albacete and 24 in Seville: 28.4 (SD: 7.3) and 22.6 (SD: 6.0), respectively ($P = 0.001$).

The graduates' preferred specialty was known in 104 cases: 72 in Albacete and 32 in Seville respectively. Twelve (five in Albacete and seven in Seville) chose FM after the MIR examination. Postgraduates choose their specialty based on the score achieved: the candidate who has the best score is ranked as number 1 and has first choice, and so on. As can be seen in **Table 6**, the students who chose FM obtained significantly

Table 1. Sociodemographic and academic characteristics of the students participating in the study (in brackets: % in relation to total who responded)

	Questionnaire at the end of 2nd year in Albacete	Questionnaire at the end of 6th year in Albacete	Control group (before starting the primary care course in Seville)
Age			
19	61 (79.2)		
20	11 (14.3)		
21	2 (2.6)		
22	1 (1.3)		4 (15.4)
23	1 (1.3)	37 (50.0)	16 (61.5)
24		25 (33.8)	5 (19.2)
25	1 (1.3)	8 (10.8)	0 (0.0)
> 25		4 (5.4)	1 (3.8)
Not stated	2	2	
Gender			
Female	54 (68.4)	48 (63.2)	22 (84.6)†
Male	25 (31.6)	28 (36.8)	4 (15.4)
Number of inhabitants in their town			
< 10,000	20 (29.9)	12 (17.9)	7 (26.9)†
10,000-30,000	17 (25.4)	15 (22.4)	2 (7.7)
30,001-100,000	5 (7.5)	7 (10.4)	8 (30.8)
> 100,000	25 (37.3)	33 (49.3)	9 (34.6)
Not stated	12	9	
Social class based on occupation			
Upper and upper middle	35 (50.0)	33 (47.8)	12 (50.0)
Middle	30 (42.8)	27 (36.9)	9 (37.5)
Lower middle and low	5 (7.2)	9 (11.8)	3 (12.5)
Not stated	9	7	2
Subjects pending			
0	74 (96.1)	70 (92.2)	17 (68.0)‡
1	3 (3.9)	3 (3.9)	3 (12.0)
≥ 2		3 (3.9)	5 (20.0)
Not stated	2		1
Mean grade at entry to medical school (maximum: 10)	8.66 (SD: 0.49)	8.53 (SD: 0.58)*	8.11 (SD: 0.63)§

*P = 0.001; †P = 0.04; ‡P = 0.007; §P = 0.003; SD = standard deviation.

Table 2. Median (with interquartile range) for each of the items of the Valuation of Attitudes towards and Knowledge of Family Medicine Questionnaire (CAMF).

Item	Albacete (2nd)	Albacete (6th)	Seville (6th)
1. I would like to become a family doctor in the future	1 (0 - 1)	0 (-1 - 1)	0 (-1 - 1)
2. Potential of FM to improve the health of the community	2 (1 - 2)	2 (1 - 2)	2 (1 - 2)
3. Better healthcare compared to the previous ambulatory care system	2 (1 - 2)	1 (1 - 2)	1 (0 - 1)
4. High satisfaction of patients with PC	1 (0 - 1)	0.5 (0 - 1)	-1 (-1 - 0)
5. PC is more cost-effective than hospital care	1 (0 - 2)	1 (1 - 2)	1 (0 – 1.5)
6. FM as first career choice	0 (-1 - 0)	-1 (-2 - 0)	-1 (-2 - -0.75)
7. Knowledge is useful although I will choose another specialty	2 (1 - 2)	1 (1 - 2)	2 (1 - 2)
8. Responsibility of the family doctor for the health of the community	2 (1 - 2)	1 (1 - 2)	2 (1 - 2)
9. Team work improves medical care	2 (1 - 2)	2 (1 - 2)	2 (1 - 2)
10. Controlling expenses is more feasible in PC	1 (1 - 2)	1 (0 - 2)	0 (0 - 1)
11. Good knowledge of family doctors' professional tasks	1 (1 - 2)	1 (1 - 1)	1 (0 - 1)
12. PC is the first medical contact with the healthcare system	2 (2 - 2)	2 (1 - 2)	1 (1 - 2)
13. Clinical history is a fundamental tool for the family doctor	2 (2 - 2)	2 (2 - 2)	2 (2 - 2)
14. Diagnostic tests have less certain positive predictive value in FM	1 (0 - 1)	0 (0 - 1)	0 (-1 - 1)
15. Family doctors manage health problems of little importance	1 (1 - 1)	1 (1 - 2)	1 (1 - 2)
16. Steady improving quality of care is a main objective	1 (1 - 2)	1 (1 - 2)	1 (1 - 2)
17. Family doctors manage health problems unlikely to be resolved	0 (-1 - 1)	-1 (-2 - -1)	-1 (-2 - -1)
18. Large responsibility as regards preventive healthcare activities	2 (1 - 2)	2 (1 - 2)	1.5 (1 - 2)
19. Family doctors must have excellent communication skills	1 (1 - 2)	1 (1 - 2)	1 (1 - 2)
20. Family doctors manage chronic health problems	1 (1 - 2)	2 (1 - 2)	1 (1 - 2)
21. FM is highly valued in the medical school	0 (-1 - 1)	0 (-1 - 1)	-1 (-1 - -0.75)
22. It is impossible to be an expert in such a wide field as FM	0 (-1 - 1)	0 (-1 - 1)	0 (-1 - 1)
23. FM is not a very intellectually stimulating specialty	1 (1 - 1)	1 (0 - 1)	1 (1 - 1)
24. Family doctors have a large work overload	1 (1 - 2)	2 (1 - 2)	1 (1 - 2)
25. Family doctors are poorly valued in our society	-1 (-1 - 1)	-1 (-1 - 0)	-1 (-2 - -1)
26. Family doctors are poorly valued by the rest of the medical profession	-1 (-1 - 0)	-1 (-1 - -1)	-1 (-2 - 0)
27. A course in PC in the medical school is appropriate	2 (1 - 2)	2 (1 - 2)	2 (1 - 2)
28. FM should be a cross-sectional course	1 (0 – 1.25)	1 (0 - 1)	1 (-0.25 - 1)
29. Low efficiency of a health system directed exclusively to diagnosis and treatment	1 (1 - 2)	1 (0 - 1)	1 (0 - 1)
30. Family doctors should provide comprehensive and continuing healthcare	2 (1 - 2)	2 (1 - 2)	1 (1 - 2)
31. The family doctor is clinically competent to provide most of the health care an individual may require	1 (1 - 2)	1 (1 - 1)	1 (1 - 1)
32. Family doctors provide health care at their surgeries and at the patient's home	2 (1 - 2)	1 (1 - 2)	1 (0 - 1)
33. Family doctors have little time to spend on their patients	1 (1 - 2)	1 (1 - 2)	1.5 (1 - 2)
34. Family doctors make decisions in highly uncertain circumstances	1 (1 - 2)	1 (1 - 1)	1 (0 - 2)

FM = family medicine; PC = primary care.

Table 3. Albacete 2nd versus 6th year: items relating to knowledge of primary care and family medicine that showed significant differences.

	Completely disagree		Disagree		Indifferent		Agree		Completely agree		P-value
	2nd	6th	2nd	6th	2nd	6th	2nd	6th	2nd	6th	
High satisfaction of patients with primary care	0	0	6	15 (2)	11 (2)	14	42 (3)	32 (3)	3	1	(P = 0.007; ES: 0.51)
Primary care is the first medical contact with the healthcare system	0	0	0	0	0	0	6	20 (2)	56 (5)	42 (3)	(P = 0.003; ES: 0.74)
Diagnostic tests have less certain positive predictive value in family medicine	1	0	10	13 (2)	15 (1)	29 (1)	25 (4)	16 (2)	7	1	(P = 0.031; ES: 0.4)
Family doctors manage health problems unlikely to be resolved	10	18 (3)	18 (1)	39 (2)	10	5	15 (1)	0	9 (3)	0	(P < 0.0001; ES: 0.85)
Family doctors have a large work overload	0	0	2	0	5	0	24 (1)	24 (1)	31(4)	38 (4)	(P = 0.015; ES: 0.34)
Low efficiency of a health system directed exclusively to diagnosis and treatment	0	0	1	2 (1)	8	23	29	29 (2)	24 (5)	8 (2)	(P < 0.0001; ES: 0.74)
Family doctors provide health care at their surgeries and at the patient's home	1	0	0	2	0	4	21 (3)	35 (2)	39 (2)	20 (3)	(P = 0.0001; ES: 0.60)

EF = effect size. In brackets, the number of graduates choosing family medicine in each rank.

Table 4. Albacete 2nd versus 6th items relating to attitudes towards primary care and family medicine that showed significant differences.

	Completely disagree		Disagree		Indifferent		Agree		Completely agree		P-value
	2nd	6th	2nd	6th	2nd	6th	2nd	6th	2nd	6th	
I would like to become a family doctor in the future	1	3	4	13 (1)	14 (1)	21	32 (2)	20 (2)	11 (2)	5 (2)	(P < 0.0001; ES: 0.67)
Better healthcare compared to previous ambulatory system	0	0	0	1	5	9 (1)	20 (3)	32	37 (2)	20 (4)	(P = .002; ES: 0.67)
Family medicine as first career choice	6	14	19 (2)	39 (1)	29 (2)	14 (2)	6	3 (2)	2 (1)	1	(P < 0.0001; ES: 0.56)
Family doctors manage health problems of little importance	13	26 (3)	34 (3)	30 (1)	8	5	5 (1)	1 (1)	2 (1)	0	(P = 0.001; ES: 0.51)
Family doctor is clinically competent to provide most of the health care an individual may require	0	0	1	2	3	7	34 (4)	43 (3)	23 (1)	9 (2)	(P = 0.005; ES: 0.53)

EF = effect size. In brackets, the number of graduates choosing family medicine in each rank.

Table 5. Ranking* obtained, mean of academic qualifications valued as certificated merits and mean score on the specialist medical training access examination (MIR, in the Spanish acronym), for those who chose family medicine and those who chose other specialties

	Family medicine	Other specialty	P
Ranking in the MIR examination: median (interquartile range)	5403 (3961-7160)	1549 (689-2870)	< 0.0001
Academic qualifications: mean (standard deviation)	4.1 (0.5)	5.1 (1.1)	< 0.0001
Score in the MIR examination: mean (standard deviation)	49.5 (12.4)	69.3 (9.4)	< 0.0001

*The MIR candidates are ranked according to their final score and choose their specialty following that order (i.e. the first-placed candidate, with the highest score, will be the first to choose).

Table 6. Albacete (A) 6th versus Seville (S) 6th year items that showed significant differences.

	Completely disagree		Disagree		Indifferent		Agree		Completely agree		P-value
	A	S	A	S	A	S	A	S	A	S	
High satisfaction of patients with primary care	0	0	18 (2)	16 (1)	20	5 (1)	37 (3)	5 (2)	1	0	(P = 0.001; ES: 0.86)
Knowledge is useful although I will choose another specialty	1	0	0	0	1	1	37 (2)	6 (3)	37 (3)	19 (1)	(P = 0.044; ES: 0.47)
Containing expenses is more feasible in primary care	0	0	4 (1)	1	17 (2)	13 (3)	35 (1)	10 (1)	20 (1)	2	(P = 0.012; ES: 0.61)
Good knowledge of family doctors' professional tasks	0	1	0	2	6	6 (1)	59 (3)	13 (3)	11 (2)	4	(P = 0.03; ES: 0.43)
Primary care is the first medical contact with the healthcare system	0	0	1	0	1	1	23 (2)	17 (4)	51 (3)	8	(P = 0.002; ES: 0.67)
Family medicine highly valued in the Medical School	3 (1)	3	28 (2)	17 (4)	24 (1)	5	18 (1)	1	3	0	(P = 0.001; ES: 1.07)
Family doctors should provide comprehensive and continuing health care	0	1	0	1	2	0	30 (2)	15 (4)	44 (3)	9	(P = 0.001; ES: 0.43)
Family doctors provide health care at their surgeries and at the patient's home	0	0	2	5	4	5 (1)	35 (2)	12 (3)	20 (3)	4	(P = 0.002; ES: 0.64)

EF = effect size. In brackets, the number of graduates choosing family medicine in each rank.

worse scores in the examination than those who chose other specialties. There were also statistically significant differences in the means of academic qualifications that were taken into consideration for MIR and in the mean score from MIR. Both the examination scores and the qualifications were significantly higher among those who chose other specialties rather than FM. There were no significant differences relating to access grades for medical school, age, sex, social class, medical school, number of inhabitants in their town of origin or the city where they chose to do their residency.

The logistic regression analysis showed an independent association for the choice of FM only with the ranking in the MIR examination (OR: 1.001; 95% CI: 1.001-1.002).

DISCUSSION

In the Albacete Medical School, the students' opinions about FM and PC declined over the degree course, although they remained higher than those of the students in Seville before the latter started their course on FM. In any case, FM was seen to be a minority option as a specialty, with no significant differences between the two medical schools.

Medical career choice is complex and multifactorial.[17] A well-known theoretical model for medical students' specialty choice that was developed some years ago identified three components: factors associated with students' own features, type of school and students' perceptions of the medical specialty characteristics.[18] As pointed out in our introduction, there is a fairly widespread belief that students' experiences during clinical clerkships or specific courses have a significant impact on their attitudes towards specialties.[7-9,19,20] PC training mostly takes place at the end of the degree course. However, at the Albacete Medical School, the PC subject was taught in the second year. Other medical schools include PC training at preclinical stages, and it has been demonstrated that such training has contributed towards better clinical performance by the students.[10] Early experience could motivate and satisfy undergraduates, help them acclimatize to clinical environments, develop professionally, interact with patients with more confidence and less stress, develop self-reflection and appraisal skills, and develop a professional identity. It could also strengthen their learning and make it more real and relevant to clinical practice.[21] Nevertheless, the present study showed that the students' positive perceptions about PC services at the end of the second year may change, maybe because realistic perceptions about the demands on PC doctors end up being disseminated among undergraduates as they pursue their degrees.[13]

The study by Xu et al. may clarify this issue.[22] They asked general practitioners in the USA whether they had any strong interest in PC before medical school and whether their level of interest changed during medical school, with special regard to their clinical experiences of this type of care. They found that for 7%, the level of interest in PC decreased during their undergraduate training; for 48%, it remained constant; and for 45%; it increased. Increased interest in PC was strongly associated with having taken elective PC courses during medical school. However, clinical experiences of PC had no impact on students' interest in pursuing PC specialties. Therefore, students choosing a curriculum consistent with their expectations and prior inclinations would be the ones who might display increasing interest in a general practice career. Furthermore, those whose interest increased during their undergraduate training, compared with those with declining attention to PC, would be more likely to remain in PC specialties ten years after graduation. This is another indicator of the importance of medical education, not only for increasing interest in PC but also for maintaining it after graduation.

Unlike what is stated in the present paper, Martín Zurro et al. found that interest in FM increased moderately over the years of study.[23,24] These results must be assessed with caution, since the study by Martín Zurro was cross-sectional and therefore lacks the added value achieved in the present study through following a group of classmates from second to sixth year and until choosing their specialty. They collected opinions from first, third and fifth-year students in 22 medical schools in Spain during the first quarter of the 2009-2010 and 2011-2012 academic years. The appeal of FM increased over the years of study (36.7%, 41.7% and 50.2% in years one, three and five respectively; $P < 0.001$), irrespective of student profile or medical school attended. Among third and fifth-year students, 54.6% said that their specialty preferences had changed over their time at medical school.

As these authors stressed elsewhere,[24] although some students generally find FM appealing, it is regarded as a career of low interest and prestige. These authors suggested seven broad themes to explain this situation: the scope and context of practice (the perception that FM is a varied specialty, with broad practice, holistic perspective and flexibility that allows practitioners to have a family); work of lower interest or that is intellectually less challenging (treating common disease, repetitive work and almost an administrative job); influence of role models, either positive or negative, and of society (negative comments from other professionals, peers and family); lower prestige; poor remuneration; medical school influences; and postgraduate training, where conversely the shorter duration and the lower intensity were perceived as positive aspects of FM.[25]

López-Roig et al. agreed with this description of the scope. In their view, FM appears to be largely underestimated as a professional activity among medical undergraduates, perceived as monotonous and non-technological medical practice with no intellectual challenge.[26] Such a negative point of view, which already appears in the early stages of medical training, leads to lack of identification with this medical practice among students.

Although from our previous experience[27] we had considered that female students, especially young female students, would express a more favorable attitude towards FM and PC, the results from this present study do not confirm this statement. Other factors must undoubtedly play a role in choosing a specialty. It has been suggested that the working conditions in FM have a decisive influence on selecting this specialty,[23] and also that the remuneration mechanism has a selection effect on new graduates who would like to become general practitioners.[28]

Lifestyle-related factors are probably equally important for men and women.[29,30] An awareness that general practice is a flexible option may be important; although embracing this as a motivation in choosing FM as a career may occur at the expense of real interest, enthusiasm and vocation, thus risking the sustainability of FM. Other specialties are increasing the availability of flexible training and work, thus contributing towards a continuing trend of women rejecting general practice in favor of other specialties. After removing the influence of lifestyle factors and flexibility, women are probably not more likely to choose general practice than men. This opens up a broad line of research.

Our study has some limitations. The fact that PC teachers handed out the questionnaire to students might have biased the study through having a positive influence on the answers. Another possible limitation of this study is the fact that the questionnaires were applied immediately after the class's examination, which may have led students to respond more positively than they would really have done in other situations. We were aware of this potential limitation, but we took this path because of feasibility issues.

The manner of selecting the unexposed cohort group was a matter of debate. We chose students from a medical school in which the PC course is taught in the sixth year. We could have chosen another school, in which this subject was not taught. However, we preferred the first option for two reasons: first, students at a school in which PC is not taught may show very obvious differences in relation to our students; and secondly, we wanted to test and compare the influence of a PC course in the early and final years.

CONCLUSION

In the Albacete Medical School, students' opinions on FM declined over the degree course, although they remained higher than those of the students in Seville. In any case, FM was seen to be a minority option as a specialty.

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Air pollution and respiratory diseases: ecological time series

Poluição do ar e doenças respiratórias: estudo ecológico de série temporal

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ABSTRACT

CONTEXT AND OBJECTIVE: Exposure to air pollutants is one of the factors responsible for hospitalizations due to respiratory diseases. The objective here was to estimate the effect of exposure to particulate matter (such as $PM_{2.5}$) on hospitalizations due to certain respiratory diseases among residents in Volta Redonda (RJ).

DESIGN AND SETTING: Ecological time series study using data from Volta Redonda (RJ).

METHODS: Data on hospital admissions among residents of Volta Redonda (RJ), between January 1, 2012, and December 31, 2012, due to pneumonia, acute bronchitis, bronchiolitis and asthma, were analyzed. Daily data on $PM_{2.5}$ concentrations were estimated through the CCATT-BRAMS model. The generalized additive Poisson regression model was used, taking the daily number of hospitalizations to be the dependent variable and the $PM_{2.5}$ concentration to be the independent variable, with adjustment for temperature, relative humidity, seasonality and day of the week, and using lags of zero to seven days. Excess hospitalization and its cost were calculated in accordance with increases in $PM_{2.5}$ concentration of 5 μg/m³.

RESULTS: There were 752 hospitalizations in 2012; the average concentration of $PM_{2.5}$ was 17.2 μg/m³; the effects of exposure were significant at lag 2 (RR = 1.017), lag 5 (RR = 1.022) and lag 7 (RR = 1,020). A decrease in $PM_{2.5}$ concentration of 5 μg/m³ could reduce admissions by up to 76 cases, with a decrease in spending of R$ 84,000 a year.

CONCLUSION: The findings from this study provide support for implementing public health policies in this municipality, which is an important steelmaking center.

RESUMO

CONTEXTO E OBJETIVO: A exposição aos poluentes do ar é um dos fatores responsáveis por internações por doenças respiratórias; o objetivo foi estimar o efeito da exposição a material particulado (como $PM_{2,5}$) sobre as hospitalizações devido a certas doenças respiratórias em moradores de Volta Redonda (RJ).

TIPO DE ESTUDO E LOCAL: Estudo ecológico de séries temporais utilizando dados de Volta Redonda (RJ).

MÉTODOS: Foram analisados dados de internação hospitalar, entre 1 de janeiro de 2012 e 31 de dezembro de 2012, devida a pneumonia, bronquite aguda, bronquiolite e asma, em residentes em Volta Redonda (RJ), e dados diários das concentrações de $PM_{2,5}$ obtidos a partir do modelo CCATT-BRAMS. Utilizou-se o modelo aditivo generalizado de regressão de Poisson, sendo o número diário de internações a variável dependente e a concentração $PM_{2,5}$ a variável independente, ajustado para temperatura, umidade relativa, sazonalidade e dia da semana e defasagens entre zero e sete dias. Excesso de internação hospitalar e seu custo, de acordo com o aumento de 5 ug/m³ na concentração de $PM_{2,5}$, foram calculados.

RESULTADOS: Ocorreram 752 internações em 2012; a concentração média de $PM_{2,5}$ foi de 17,2 ug/m³; os efeitos da exposição foram significativos em lag 2 (RR = 1,017), lag 5 (RR = 1,022) e lag 7 (RR = 1,020). A redução em 5 ug/m³ na concentração de $PM_{2,5}$ poderia reduzir até 76 casos as internações com diminuição nos gastos de R$ 84 mil/ano.

CONCLUSÃO: Os achados deste estudo fornecem subsídios para implantar políticas públicas de saúde neste município, que é importante polo siderúrgico.

INTRODUCTION

Hospitalizations due to respiratory diseases may result from acute exposure to air pollutants, among other causes. These pollutants are generated by natural sources or anthropogenic sources, and these sources are classified as stationary sources such as power plants and industries, and mobile sources, represented mainly by the vehicle fleet.

In 2012, 1.3 million hospitalizations due to respiratory diseases (chapter 10 of the International Classification of Diseases, ICD, 10th revision) occurred in Brazil. These gave rise to expenditure of approximately R$ 1.2 billion; of these, 64,000 hospitalizations were in the state of Rio de Janeiro, with an expenditure of R$ 55 million (US$ 1 ≈ R$ 2.00 at that time).[1]

Several factors, such as low birth weight, parental smoking, lack of breastfeeding, in addition to the effects of exposure to air pollutants are known to be associated with pneumonia.[2,3] Studies in Brazil, both in large cities and in medium-sized cities, have shown that respiratory diseases other than pneumonia are noticeably influenced by the effects of exposure to air pollutants, such as particulate matter less than 10 microns in aerodynamic diameter (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3) and carbon monoxide (CO), thereby leading to hospitalizations.[4-8]

These pollutants are usually quantified through monitoring by state environmental control agencies. However, not all places have this monitoring available. Data estimation through mathematical modeling as such as the Chemical Coupled Aerosol and Tracer Transport model for Brazilian developments on the Regional Atmospheric Modeling System (CCATT-BRAMS) can minimize this problem.[9,10]

CCATT-BRAMS is a mathematical model that makes it possible to perform numerical simulations of weather and climate, by solving for large phenomena explicitly on spatial scales and by parameterizing the processes that occur at scales smaller than the spatial resolution of the model. The Center for Weather Forecasting and Climate Research of the National Institute of Space Research (CPTEC-INPE) does this modeling process on a daily basis, producing daily diagnoses and predictions for up to three days, covering all of South America. It takes into consideration transportation of various gases and aerosol particles, which is estimated from the number and locations of outbreaks of fires that are observed through remote sensors, thus generating daily estimates of various pollutants. The horizontal resolution of this operation is 25 km by 25 km, with 38 atmospheric levels, of which the first level is from ground level to 40 meters above the ground, and this method has already been validate.[10] Fine particulate matter ($PM_{2.5}$), which accounts for 60 to 70% of PM_{10},[11] along with carbon monoxide (CO), nitrogen oxides, ozone and volatile organic compounds (VOCs), are the pollutants for which concentrations are estimated through the model. These records are estimated every three hours, daily.

The application of data estimated through this model can be seen in studies developed in Brazil that have correlated exposure to $PM_{2.5}$ with hospitalizations due to pneumonia, other respiratory diseases and cardiovascular diseases.[5,12-14] The importance of studying how exposure to this pollutant can act on human health comes from the fact that, because of its aerodynamic diameter (less than 2.5 microns), it can remain suspended in the air for a longer time and thus be transported over longer distances and also reach deeper portions of the respiratory system.[15]

OBJECTIVE

The aim of this study was to estimate the effects of exposure to $PM_{2.5}$ in hospitalizations due to pneumonia, acute bronchitis, bronchiolitis and asthma in Volta Redonda (RJ), using data estimated through CCATT-BRAMS.

METHOD

This was an ecological time series study with data on hospitalizations due to pneumonia (ICD 10th revision, codes J 12.0 – J 18.9), acute bronchitis and bronchiolitis (ICD 10th revision, codes J 20.0 and J 21.9) and asthma (ICD 10th revision, codes J 45.0 J 45.9), among subjects of both sexes at all ages, living in Volta Redonda (RJ). The study period was between January 1, 2012, and December 31, 2012.

Place of study

Volta Redonda is located at 22° 29 ' S and 44° 06 ' W, in the Paraíba valley, in the state of Rio de Janeiro, Brazil. The total area of the municipality is 182.8 km^2, of which 54 km^2 comprises the main urban area of the municipality. The urban area is located along the banks of the river Paraíba do Sul, and is at an altitude of 350 meters above sea level. Its total population is approximately 260,000 inhabitants with a per-capita income of R$ 27,577.00. It has a vehicle fleet of about 110,000.[16] Volta Redonda has a mesothermal climate and high relative humidity (77%), even in the colder months, when it ranges from 71% to 72%. The mean annual temperature is 21 °C, with a mean minimum of 16.5 °C and mean maximum of 27.8 °C. The economy of Volta Redonda, while still anchored in industry, also focuses on services and trade. The city houses the National Steel Company (Companhia Siderúrgica Nacional, CSN) and other industries such as factories producing cement, oxygen and nitrogen, flat steel and tin products and is an important link between two highways, which have intense traffic of heavy vehicles and buses. The city has nine hospitals. Three of the hospitals are affiliated to the Brazilian National Health System (Sistema Único de Saúde, SUS) and six are private hospitals. All of these hospitals care for pediatric patients.[16]

The data on hospital admissions due to respiratory diseases, according to place of residence, were taken from the database of the Brazilian Ministry of Health, (DATASUS), through authorizations for hospitalization (AIH) within SUS for the study period, day by day. Data on air pollutants, temperature and relative humidity were estimated using the CCATT-BRAMS model. The pollutant analyzed in this study was the fine particulate matter ($PM_{2.5}$), in $\mu g/m^3$.

Pearson's correlation test was used to estimate possible correlations between the concentrations of the pollutants and hospitalizations. The effects of exposure to environmental pollutants may be reflected in admissions on the same day or some days later. Therefore, its effects on hospitalizations were investigated on the same day as the exposure (lag 0) and also on the seven subsequent days (lag 1 up to lag 7), because there is no consensus regarding the size of this window. A generalized additive model (GAM) of Poisson regression was used, because the outcome was a discrete quantitative variable. The model was adjusted for seasonality, using the number of days that had elapsed since the start of the study, and for days of the week by means of indicator variables for the days of the week, because there may have been a decrease in hospital admissions on weekends. Minimum temperature and average relative humidity were included in the model. The statistical software used cubic smoothing spline functions for temperature and relative air humidity in order to account for the non-linearity of meteorological variables.

The exponent of the coefficient value provided by Poisson regression was used to calculate the relative risks (RR) of $PM_{2.5}$ exposure and hospital admission due to some form of respiratory disease.

The average, minimum and maximum values and their standard deviations for the number of hospitalizations, $PM_{2.5}$ concentration, temperature and relative humidity were calculated, along with the Pearson correlation values. The relative risk of hospitalization was calculated with 95% confidence intervals. Increases in the relative risk through increases of 5 $\mu g/m^3$ in $PM_{2.5}$ concentration were calculated as percentage values (pp).

The expression IRR = exp (β *Δpol) provides the increase in relative risk (IRR), where β is the coefficient given by the Poisson regression and Δpol is the 5 $\mu g/m^3$ increase in the concentration of the air pollutant $PM_{2.5}$.

The population attributable fraction (PAF) was used to estimate the excess number of hospitalizations according to the increase in $PM_{2.5}$, using the expression

$$PAF = (1- 1/RR) * N$$

RR is the relative risk and N is the total number of hospital admissions in this expression. The financial costs of possible excess hospital admission was calculated using the PAF value multiplied by the average financial cost of each hospital admission due to respiratory disease, which was also obtained through DATASUS.

The Statistica software was used for the analysis and the significance level used in the analysis was alpha = 5%.

RESULTS

There were 1560 admissions due to all respiratory diseases in Volta Redonda (RJ), over the study period, and these cost R$ 1.4 million. Hospital admissions with diagnoses of pneumonia, bronchitis, bronchiolitis and asthma accounted for 752 cases, with costs of around R$ 850,000. The average, minimum and maximum values of the variables, and their respective standard deviations, are shown in **Table 1**.

The average $PM_{2.5}$ concentration was 17.2 $\mu g/m^3$, with a minimum of 11.7 and maximum of 35.2 $\mu g/m^3$. On 22 days, the $PM_{2.5}$ concentration exceeded the values considered acceptable by the World Health Organization (WHO). The Pearson correlation coefficient matrix values are shown in **Table 2**. There was no correlation between the number of hospitalizations and the $PM_{2.5}$ concentrations, but these concentrations were significantly correlated with the temperature and relative humidity values.

The values of the coefficients and their standard errors, obtained through Poisson regression using lags of 0 to 7 days, are shown in **Table 3**. The effects of exposure to $PM_{2.5}$ were seen to be significant two, five and seven days prior to hospitalization, with the following values: lag 2 (RR = 1.017; 95% CI = 1.001-1.034); lag 5 (RR = 1.022; 95% CI = 1.005-1.038); and lag 7 (RR = 1.020; 95% CI = 1.004-1.037). The percentage increases in the relative risks and their 95% confidence intervals, corresponding to lags of zero to seven days for an increase of 5 ug/m^3 are shown in **Figure 1**.

Table 1. Minimums, maximums, means, standard deviations (SD) and quartiles of the study variables. Volta Redonda (RJ), 2012

	Mean (SD)	Minimum-maximum	P-25	P-50	P-75
Particulate matter ($\mu g/m^3$)	17.2 (4.5)	11.7-35.2	13.7	15.9	19.6
Temperature (°C)	21.6 (3.3)	12.6-31.3	19.7	21.8	23.8
Relative humidity (%)	94.8 (8.2)	56.5-100.0	92.9	99.1	99.9
Hospitalization	2.05 (1.67)	0-9			

P-25 = percentile 25; P-50 = percentile 50; P-75 = percentile 75.

Table 2. Matrix of Pearson correlation coefficients. Volta Redonda (RJ), 2012

	$PM_{2.5}$	Temperature	RH	Hospitalizations
$PM_{2.5}$	1			
Temperature	-0,13	1		
RH	0.11	-0.55	1	
Hospitalizations	0.04	-0.09	-0.08	1

RH = relative humidity.

Table 3. Values of the coefficients and standard errors obtained through the generalized additive model of Poisson regression according to lags from zero to seven days. Volta Redonda (RJ), 2012

Lag	Coefficient (standard error)	P-value
Lag 0	0.00496 (0.00814)	0.27
Lag 1	0.01234 (0.00848)	0.07
Lag 2	0.01731 (0.00822)	0.02
Lag 3	-0.00341 (0.00938)	0.36
Lag 4	0.008a25 (0.00846)	0.17
Lag 5	0.02137 (0.00824)	0.01
Lag 6	0.00468 (0.00857)	0.29
Lag 7	0.02010 (0.00827)	0.01

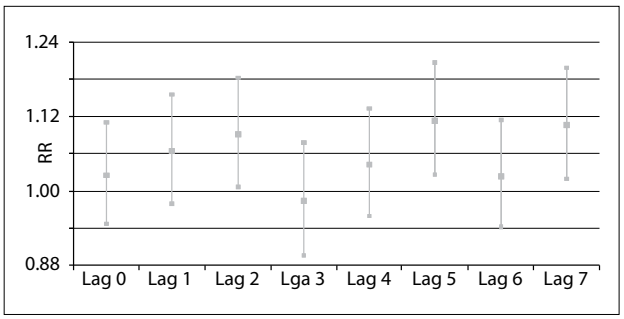

Figure 1. Increase in relative risk according to increment of 5 μg/m³ in the concentrations of fine particulate matter. Volta Redonda, 2012.

This increase in $PM_{2.5}$ concentration was found to result in a significant increase of up to 9 percentage points in the risk of hospitalization due to pneumonia, acute bronchitis, bronchiolitis and asthma. The relative risks according this increase were RR = 1.09 for lag 2 and RR = 1.11 for lag 5 and lag 7, and all of these were statistically significant (P-value < 0.05).

A decrease in $PM_{2.5}$ concentration of 5 μg/m³ would, according to the calculation of the population attributable fraction, entail a decrease of 76 hospitalizations. This would lead to savings of around R$ 84,000 per annum, given that the average cost of hospitalization due to these diseases was R$ 1100.00. It should be noted that this reduction in costs related only to hospitalization due to pneumonia, acute bronchitis, bronchiolitis and asthma.

DISCUSSION

This study, even though it only comprised a one-year time series, showed the relevance of exposure to fine particulate matter, i.e. $PM_{2.5}$, in hospitalizations due to pneumonia, acute bronchitis, bronchiolitis and asthma among people living in Volta Redonda (RJ), which is an important national steelmaking center. Furthermore, it showed that a reduction in the concentration of this pollutant could lead to decreased numbers of hospitalizations and costs to the health system.

Most Brazilian studies have investigated exposure to PM_{10} among hospitalizations due to respiratory diseases, especially pneumonia and asthma.[4-8] Unlike in other Brazilian studies, we used data estimated by means of a mathematical model developed by national researchers. We emphasize that this model has been used in other studies developed in Brazil,[5,12] but even so, few Brazilian studies have been conducted on $PM_{2.5}$ because there are few instrument stations for monitoring this pollutant.

Fine particulate matter ($PM_{2.5}$) originates from the combustion process of diesel and gasoline-powered vehicles, burning of biomass and burning of coal to generate power. Its composition may vary depending on the place of study and whether its surface composition includes nitrates, sulfates, chlorides, metals such as Na, Al, P, S, Ca or Fe, among others, or polycyclic aromatic hydrocarbons. This composition may vary depending on the place of study.[17] This pollutant is generated mainly by stationary sources in the case of Volta Redonda, but the vehicular fleet also provides a contribution, given that this city has intense traffic of heavy vehicles crossing the city, because it is an important link between two major highways.

The findings from our study show the deleterious effect of exposure to $PM_{2.5}$ through hospitalizations due to pneumonia, acute bronchitis, bronchiolitis and asthma, in all age groups. The effect was statistically significant on the second, fifth and seventh days after exposure, with relative risks of between 1.017 and 1.022. The relative risk increased to 1.113 (95% CI: 1.026-1.206) with an elevation of 5 μg/m³ in the concentration of this pollutant.

In a study using similar methodology, with data estimated through CCATT-BRAMS, in which the study population consisted of children and the average $PM_{2.5}$ concentrations were of the order of 28.6 μg/m³, the relative risk was 1.009 (95% CI: 1.001-1.017).[5] Another study used data from CCATT-BRAMS but included all diseases in chapter 10 of the ICD 10th revision (codes J 00-J 99) and included children under the age of 5 years and elderly people aged over 65 years who were admitted to hospitals affiliated to the Brazilian National Health System in Cuiabá, state of Mato Grosso. This study showed that exposure to $PM_{2.5}$ had an influence on hospitalizations due to respiratory disease among children under 5 years of age.[18]

Another study on exposure to $PM_{2.5}$ generated by biomass burning and hospitalizations due to respiratory diseases among children and the elderly, which was conducted in two regions of the state of Mato Grosso, presented values of the order of 45 μg/m³ in the dry season, with a maximum $PM_{2.5}$ concentration of 260 μg/m³. This study showed that an increase in $PM_{2.5}$ concentration of 10 ug/m³ resulted in increases in admissions after lags of 3 and 4 days that were of the order of 6% in the dry season. The data accumulated relating to lags of 3 to 5 days showed that the risk increased by 8%.[12] The CCATT-BRAMS model was also

used to estimate the $PM_{2.5}$ concentration in this study. Likewise, a study in Taubaté, SP, which has a population similar to that of Volta Redonda, also found an association between exposure to $PM_{2.5}$, at concentrations similar to those of Volta Redonda, and hospitalizations due to pneumonia and asthma among children.[13]

Chronic and sub-chronic exposure to fine particulate matter, among other pollutants, was shown to be a risk factor for hospitalization due to acute bronchiolitis among children in California.[19] Using logistic regression, those authors showed that there was an association between exposure to $PM_{2.5}$ and the outcome of hospitalization due to acute bronchiolitis; and that an increase in $PM_{2.5}$ concentration of 10 μg/m^3 increased the odds of hospitalization by 9% (95% CI: 1.04-1.14). This allowed the authors to suggest that bronchiolitis was one of the adverse effects of exposure to $PM_{2.5}$. Hertz-Picciotto et al.[20] also identified the adverse effect of exposure to $PM_{2.5}$ and polycyclic aromatic hydrocarbons (PAH) in cohorts of children in two cities in the Czech Republic that had high concentrations of these pollutants. The risk that children under the age of two years would be affected by lower respiratory tract infections due to exposure to $PM_{2.5}$ was higher (RR = 1.30; 95% CI: 1.08-1.58) when the $PM_{2.5}$ concentrations increased by 25 μg/m^3 and PAH by 100 μg/m^3.

Sheffield et al.[21] in the United States found that a 7% decrease in $PM_{2.5}$ levels could result in savings of $ 15 million a year. These authors worked with information from the Nationwide Inpatient Sample relating to the period between 1999 and 2007. There were more than 70 million hospitalizations and 160,000 children under one year of age with a diagnosis of bronchiolitis.

Recently, a study on the role of air pollutants carried out in Volta Redonda found that exposure to these pollutants was responsible for 6% of 5,000 hospitalizations due to diseases in chapter 10 of the ICD-10 between 2005 and 2007, at a cost of $ 170,000 to SUS.[22]

Using the disability adjusted life years (DALY) methodology in relation to reduction of financial cost, exposure to particulate matter was correlated with costs associated with mortality amounting to US$ 1.7 billion annually in 29 metropolitan areas in Brazil.[23] Ostro and Chestnut[24] calculated that there would be savings of approximately US$ 70 billion if the average $PM_{2.5}$ concentration were 12 μg/m^3. It was demonstrated in a study conducted in 211 counties of 51 US metropolitan areas that a decrease in the concentration of this pollutant of 10 ug/m^3 would increase average life expectancy.[25]

Although the number of hospitalizations in the present study was small, it has to be borne in mind that these related only to hospitalization due to pneumonia, acute bronchitis, bronchiolitis and asthma in all age groups, in a city with around 260,000 inhabitants that was served by SUS hospitals. The damaging effects from exposure in the adult population that led to hospitalization caused by other diseases of the circulatory system, such as hypertension, myocardial infarction and stroke, also has to be taken into consideration.

The mechanisms that lead to pulmonary illnesses are so far poorly understood. Pulmonary and systemic oxidative stress seem to be plausible hypotheses.[26] Studies have shown that these illnesses involve release of inflammatory mediators, spinal cord stimulation that releases leukocytes and platelets and increased levels of C-reactive protein. Exposure to particulate matter when forest fires occur leads to release of neutrophils and monocytes in addition to production of cytokines by alveolar macrophages. Particulate matter can impair superoxide production by alveolar macrophages, thereby compromising the ability of the lungs to eliminate some of the respiratory tree pathogens.[26,27]

Riva et al. showed that impairment of pulmonary function occurred in rats after instillation of $PM_{2.5}$. which was translated as lung inflammation, shown by increased activity of myeloperoxidase (MPO), increased influx of neutrophils into the lung parenchyma and increased expression of cytokines like pro-inflammatory TNF-α and IL-6, in addition to oxidative damage.[28]

Limitations and positive aspects of the study

This study may have limitations; among these, the nature of ecological studies can be highlighted. It was not possible to show the causality between exposure and outcome, but associations between exposures and outcomes could be pointed out. It was not possible to identify whether individuals who were hospitalized had been exposed or whether exposed individuals were admitted. Mistakes in the diagnoses recorded in DATASUS may have led to underreporting or over-notification of cases of pneumonia, asthma, bronchitis and bronchiolitis. Individuals served by private health plans and those treated on an outpatient basis were not included. Another factor that may be considered to be a limitation was that the subjects were not distinguished according to age groups, e.g. as children or elderly people, as done in other studies. Nonetheless, among the total number of hospitalizations shown in our study, 84% were among individuals aged 0 to 10 and over 50 years.

It needs to be pointed out that DATASUS does not provide information about factors associated with the diseases studied here, or about comorbidities. The concentrations were found to be homogeneous throughout the city, and thus exposure to pollutants was assumed to be homogeneous. The pollutant levels were obtained by means of mathematical modeling and good correlation between these data and real data has been identified,[10] but there may have been some degree of uncertainty concerning the estimation of these data. Nonetheless, it needs to be remembered that use of these data has been recorded in several recent articles[5,12-14] and was very adequate, with few gaps in quantifying the values.

One positive aspect of the present study was that it identified the contribution of exposure to $PM_{2.5}$, which has been little studied in Brazil, towards the number of hospitalizations. The study showed that decreasing the concentration of this pollutant may lead to reduction of the financial cost. DATASUS is an official source of information that has been widely used in studies on the effects of exposure to air pollutants and consequent illnesses and is a trusted source.

CONCLUSION

This study has shown that a decrease in $PM_{2.5}$ concentration of 5 $\mu g/m^3$ could reduce admissions by up to 76 cases, with a decrease in spending of R$ 84,000 a year. Thus, the results presented here provide support for the city's healthcare administration towards implementing policies for reducing the levels of air pollution, especially fine particulate material. Such actions would have consequent positive reflections with regard to the number of hospitalizations and expenditure on care provided through these admissions.

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Economic evaluation of the new oral anticoagulants for the prevention of thromboembolic events: a cost-minimization analysis

Avaliação econômica dos novos anticoagulantes para a prevenção de eventos tromboembólicos: análise de custo-minimização

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KEY WORDS:
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PALAVRAS-CHAVE:
Anticoagulantes.
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Saúde pública.

ABSTRACT

CONTEXT AND OBJECTIVE: Randomized clinical trials have shown that the new oral anticoagulants have at least similar impact regarding reduction of thromboembolic events, compared with warfarin, with similar or improved safety profiles. There is little data on real costs within clinical practice. Our aim here was to perform economic analysis on these strategies from the perspective of Brazilian society and the public healthcare system.

DESIGN AND SETTING: Cost-minimization analysis; anticoagulation clinic of Hospital Municipal Odilon Behrens, Belo Horizonte, MG, Brazil.

METHODS: Patients at the anticoagulation clinic were recruited between August and October 2011, with minimum follow-up of four weeks. Operational and non-operational costs were calculated and corrected to 2015.

RESULTS: This study included 633 patients (59% women) of median age 62 years (interquartile range 49-73). The mean length of follow-up was 64 ± 28 days. The average cost per patient per month was $ 54.26 (US dollars). Direct costs accounted for 32.5% of the total cost. Of these, 69.5% were related to healthcare professionals. With regards to indirect costs, 52.4% were related to absence from work and 47.6% to transportation. Apixaban, dabigatran and rivaroxaban were being sold to Brazilian public institutions, on average, for $ 49.87, $ 51.40 and $ 52.16 per patient per month, respectively, which was lower than the costs relating to warfarin treatment.

CONCLUSION: In the Brazilian context, from the perspective of society and the public healthcare system, the cumulative costs per patient using warfarin with follow-up in anticoagulation clinics is currently higher than the strategy of prescribing the new oral anticoagulants.

RESUMO

CONTEXTO E OBJETIVO: Estudos clínicos randomizados demonstraram que novos anticoagulantes orais têm pelo menos impacto semelhante em reduzir eventos tromboembólicos quando comparados à varfarina, com perfil de segurança similar ou superior. Há pouca evidência acerca de custos reais na prática clínica. Nosso objetivo é realizar análise econômica dessas estratégias, na perspectiva do sistema de saúde pública e da sociedade brasileiros.

TIPO DE ESTUDO E LOCAL: Análise de custo-minimização; Clínica de Anticoagulação do Hospital Municipal Odilon Behrens, Belo Horizonte, MG, Brasil.

MÉTODOS: Os pacientes da clínica de anticoagulação foram recrutados de agosto a outubro de 2011, com tempo mínimo de acompanhamento de quatro semanas. Custos operacionais e não operacionais foram computados e corrigidos para 2015.

RESULTADOS: Este estudo incluiu 633 pacientes, com idade mediana de 62 (intervalo interquartil 49-73) anos, sendo 59% mulheres. O tempo médio de acompanhamento foi de 64 ± 28 dias. O custo médio por paciente por mês foi de $ 54.26 (dólares). Custos diretos foram responsáveis por 32,5% do custo total. Destes, 69,5% foram relacionados aos profissionais de saúde. Em relação aos custos indiretos, 52,4% estavam relacionados ao absenteísmo ao trabalho e 47,6% ao transporte. Apixaban, dabigatran e rivaroxaban são vendidos a órgãos públicos brasileiros, respectivamente, a um preço médio mensal de $ 49.87, $ 51.40 e $ 52.26 por paciente por mês, valores inferiores aos custos relacionados ao tratamento com varfarina.

CONCLUSÃO: No contexto brasileiro, na perspectiva do sistema de saúde pública e da sociedade, os custos cumulativos por paciente em uso de varfarina acompanhados em clínica de anticoagulação são atualmente superiores à estratégia de prescrever novos anticoagulantes orais.

INTRODUCTION

Atrial fibrillation is the most common sustained arrhythmia in clinical practice. It is associated with increased risk of stroke, systemic embolism, heart failure and mortality.[1,2] Occurrences of stroke relating to atrial fibrillation are usually more severe, with a more extensive affected area, greater mortality and poorer functional outcome, in comparison with patients without atrial fibrillation.[3] The current treatment for atrial fibrillation focuses on estimating the risk of cardioembolic events, in order to assess the need for anticoagulation, rate control, rhythm control in some symptomatic individuals and aggressive modification of cardiovascular risk.[1] Use of anticoagulant therapy is effective in reducing the incidence of stroke, systemic embolism and mortality.[4]

A recent study that enrolled approximately 300,000 Brazilian primary care patients showed a prevalence of atrial fibrillation similar to that observed in developed countries, with a very low proportion of patients taking anticoagulants.[5] The possible explanations for this underutilization are the lack of doctors in primary care with experience of managing patients with atrial fibrillation and making risk assessments on cardioembolic events; fear of the risk of bleeding complications such as intracranial hemorrhage; and limitations associated with the use of vitamin K inhibitors, such as the need for frequent dose control and adjustment in accordance with the prothrombin time and the international normalized ratio (INR), as well as the interactions of these inhibitors with drugs and food. Anticoagulation clinics are specialized clinics with multidisciplinary composition, which have a dual mission: to ensure patient education and information in accordance with a structured program that is adapted to each case; and to promote anticoagulation control.[6,7]

Clinical trials have shown that the new oral anticoagulants, also known as target-specific anticoagulants, have at least similar impact on the reduction of thromboembolic events, compared with warfarin, with better safety profiles.[8-12] Important additional advantages include convenience, since there is no need to monitor the INR and thus no further consultations except for the routine medical follow-up; and fewer interactions: they present lack of susceptibility to dietary interactions and reduced susceptibility to drug interactions.[8-12]

There are few data comparing the cost of these drugs with actual costs of patients in clinical practice in Brazil.

OBJECTIVE

The objective of this study was to perform an economic analysis comparing new oral anticoagulants versus warfarin, from the perspectives of Brazilian society and the public healthcare system, using real data from an anticoagulation clinic.

METHODS

This was a cost-minimization analysis, using data from a cohort of patients of an anticoagulation clinic of Hospital Municipal Odilon Behrens, a public hospital in Belo Horizonte. This study was approved by the Research Ethics Committee of Hospital Municipal Odilon Behrens, and was conducted in accordance with the Helsinki Declaration. All patients provided written informed consent for their participation in the study.

Patients and setting

All patients registered at this anticoagulation clinic between August and October 2011 were recruited for this study. The service provided by this clinic operates exclusively through the Brazilian public healthcare system (Sistema Único de Saúde, SUS), and its clientele consists mostly of patients of low socioeconomic status and low educational level.[13]

This anticoagulation clinic was established in 2001. Patients from the emergency department and hospital inpatient units with indications for oral anticoagulation are referred to this clinic for follow-up. On the day of the consultation, patients arrive at the hospital earlier, for blood collection for measurement of prothrombin time, which is expressed as the international normalized ratio (INR), using the calibration standardized by the World Health Organization (WHO) in 1982.[14]

While awaiting the test result and consultation, they participate in group educational activities, where they receive guidance on indications, risks and benefits of anticoagulation, and on interactions with food and diet. These educational activities are additional to the personalized educational activities that take place during the consultation. Although group educational activities are not formally recommended through guidelines for patient care in cases of anticoagulant use, this strategy is used in this anticoagulation clinic, because it has been shown to improve the time in therapeutic range (TTR).[15]

At the time of this study, the anticoagulation clinic was operating in four shifts per week, with the participation of one physician with overall responsibility, two or three residents, one pharmacist and one nurse. In addition, the clinic also had a secretary, who organized the records and service.

At each visit, the INR was assessed, the factors that interfere with anticoagulation control were identified and any dose adjustments needed were made, in accordance with a protocol based on guidelines for patient care in cases of anticoagulant use.[14] Patient counseling was reinforced and the next visit was scheduled. The interval between consultations varied from less than one week to up to four weeks, depending on the INR result and whether there were any hemorrhagic complications, in accordance with the guidelines at that time.[14] When the INR was within the therapeutic range, the next visit was scheduled for one week later and,

successively, periods of one week were added to this interval, as long as the INR was still within the therapeutic range, up to four weeks. Thus, the consultation was exclusively for the purpose of anticoagulation control and there was no action towards underlying disease control or comorbidities, which were at the discretion of the attending physician (primary care physician, internal medicine physician, cardiologist, hematologist, etc.).

Data collection and follow-up

Upon enrollment, patients were interviewed using a standardized questionnaire, and their records were reviewed, in order to obtain clinical, demographic and cost data: age, anticoagulation indication, risk factors and comorbidities, disability, occupation, salary, means of transportation to the anticoagulation clinic, home address, need to attend the clinic with a companion, companion's occupation and salary. The categories of employment status used were: employee (defined as a person working for an employer, person or entity, receiving in return a cash compensation, including domestic workers),[16] self-employed (defined as a person who was the owner of his business),[16] unpaid worker or unemployed.

All patients were followed up for a minimum period of four weeks (maximum interval between the consultations, in accordance with the protocol), with assessment of INR tests, warfarin dosage, thromboembolic or hemorrhagic complications and hospitalizations. The data-gathering for this study did not affect the frequency of consultations or warfarin dosage, which were both at the attending physician's discretion.

The quality of anticoagulation control was assessed by calculating the length of TTR, using the linear interpolation method of Rosendaal.[17] The CHADS2-Vasc score, which is a clinical prediction rule for estimating the risk of stroke in patients with nonvalvular atrial fibrillation, was used too.

Assessment of costs

Cost assessment was performed by accounting for all the expenses involved in anticoagulation for the patients of the cohort. The costs were classified into two categories: direct and indirect (**Table 1**). Direct costs included operating costs relating to maintenance of the anticoagulation clinic: salaries of professionals working at the clinic (according to the hours devoted to this activity), cost of INR examination and cost of the drug (warfarin), according to the dose used. Indirect costs were those that were unrelated to the operation of the clinic, and included: patient transportation costs to the clinic, companion's transportation expenses (in the case of patients who attended the consultation with a companion) and opportunity cost.

In order to calculate the transportation cost, the means of transport used by each patient to attend the consultations was taken into account. For those who needed public transportation, we used the price of the bus ticket and the number of tickets used per day. For patients who used their own car, the distance from their home to the anticoagulation clinic was calculated (using Google Maps, available at www.google.com.br/maps) and, considering an average fuel consumption of 10 km per liter of gasoline and the average cost of gasoline (checked at the website www.mercadomineiro.com.br), the transportation cost was calculated. For patients who used the city's patient transportation service, funded by the city government, the cost of fuel was taken into consideration, using the same calculation as above, and the cost of the driver's salary. The cost of car rental was not calculated, since cities generally have their own cars for providing this type of service. Patients who needed taxi services were asked about their exact expenditure for their journey. To calculate the driver's earnings per hour, data from the National Household Sampling Survey were used (Pesquisa Nacional de Amostra de Domicílios, PNAD).[16,18] Through PNAD, we obtained the amount of the average hourly wage, which formed the reference value for the parameter. The range of salary was constructed by taking into consideration a range of one to four minimum wages as the monthly remuneration and assuming a working week of 40 hours.[18]

The opportunity cost refers to the amount of income from work that the individual failed to earn,[18] or the cost to the individual of absence from work, through attending the consultation at the anticoagulation clinic.

The costs were calculated as the prices of July 2013, and were inflated in accordance with the Consumer Price Index (Índice de Preços ao Consumidor Amplo, IPCA) and converted to US dollars (USD) on August 19, 2015 (1 USD = R$ 3.486). In this study, all costs are expressed in US dollars.

Cost-minimization analysis

Since apixaban, dabigatran and rivaroxaban have been shown to be not inferior to warfarin in randomized clinical trials among patients with atrial fibrillation and patients with venous thromboembolism,[6,7,9,19,20] the present study used cost-minimization analysis. This method is a type of cost-effectiveness analysis that only compares two or more medical intervention costs, since the health outcomes resulting from the medical interventions compared are similar.[21]

In Brazil, apixaban, dabigatran and rivaroxaban are authorized by the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, Anvisa) for use in patients with atrial fibrillation for prevention of cardioembolic events. Only dabigatran and rivaroxaban are authorized for use among patients with deep venous thrombosis and/or pulmonary embolism. To calculate the average cost of apixaban, dabigatran and rivaroxaban, we used the average price data for the period from

January 1 to August 19, 2015, from the federal government's drug purchasing website, which lists the prices of drugs for public institutions.[22] Edoxaban was not included, because it has not yet been approved by Anvisa for use in Brazil.

RESULTS

During the study period, 645 patients were registered in the anticoagulation clinic. Of these, 12 refused to participate. Thus, this study included 633 patients with a median age of 62 years (interquartile range 49-73), among whom 53.9% were elderly patients (≥ 60 years) and 59% were women. **Table 2** illustrates the indications for anticoagulation among the patients included.

Among the patients with non-valvular atrial fibrillation (n = 246), the CHADS2-Vase score was 1 for 1.2% of them, 2 for 8.9%, 3 for 20.3%, 4 for 27.2%, 5 for 22.0%, 6 for 15.4%, 7 for 3.3% and 8 for 0.8%. In two cases, we could not obtain all the information needed to calculate the CHADS2-Vasc score.

The mean follow-up period was 64 ± 28 days. The average proportion of the time in therapeutic range was 69.2% ± 25.0% (median 71.2%, interquartile range 52.8 to 92.4%), and 65.7% of the patients were within the therapeutic range for greater than or equal to 60% of the time. During the follow-up, 2.7% of the patients required administration of vitamin K and 1.6% had an episode of minor bleeding (hematoma, epistaxis, gingival bleeding or increased menstrual flow, without the need for hospitalization and/or transfusion of blood components). Two patients had gastrointestinal bleeding and one patient had hematuria. One patient (75 years old, male) presented an embolic event (ischemic stroke) during the follow-up, with INR at admission of 1.94.

Table 1. Description of the costs included in the cost-minimization analysis

Direct costs			
Category	**Variable**	**Description**	**Source**
Clinical maintenance cost	Cost of professionals	Calculation of the cost of each professional who was working in the clinic, with labor charges proportional to the number of hours worked per week in the activity	Data collection in the human resources sector of the hospital
	Cost of INR exams	Calculation of all the costs involved in the INR examination including material for blood collection, laboratory staff and printing costs.	Data collection at the laboratory and human resources sectors of the hospital
	Cost of medication	Annualized cost of the drug (warfarin), according to dose per patient monitoring period. Furthermore, the annualized cost of vitamin K was calculated when it was necessary during the follow-up.	Data collection
Indirect costs			
Category	**Variable**	**Description**	**Source**
Transportation cost (cost for the city's government)	Driver's salary per hour	Ratio between the individual's income for that job and the number of hours worked	PNAD
	Driver's hours	Number of hours spent by the driver on patient transportation and waiting for appointments in anticoagulation clinic	Calculation of the average duration of transportation from Google, and average waiting time for the consultation
	Number of people transported	Number of people transported to be attended at the anticoagulation clinic in Belo Horizonte	NA
	Gasoline price	Gasoline price for patients' transportation	Website "*Mercado Mineiro*"
	Number of km per liter	Number of kilometers per liter of gasoline	The average consumtion rate of 10 km/liter was used
Transportation cost (cost for the individual)	Ticket price	Cost of the ticket for the bus or metro x number of tickets per day	Data collected from the individual
	Gasoline price	Gasoline price for patients' transportation	Website "*Mercado Mineiro*"
	Number of km per liter	Number of kilometers per liter of gasoline	The average consumption rate of 10 km/liter was used
Patient's opportunity cost	Patient's hours	Number of hours spent on shuttling back and forth, blood collection, waiting for consultations at the clinic and duration of consultation	NA
	Patient's salary per hour	Ratio between the individual's income for that job and the number of hours worked	Data collected from the individual
Companion's opportunity cost	Companion's hours	Number of hours spent by the companion for each consultation, including hours spent on shuttling back and forth, blood collection, waiting for consultations at the clinic and duration of consultation	NA
	Companion's salary per hour	Ratio between the individual's income for that job and the number of hours worked	Data collected from the individual

PNAD = Pesquisa Nacional por Amostra de Domicílios; NA = not applicable.

Table 3 shows the total annualized costs for the 633 patients included. The average cost per patient per month was $ 54.26. Direct costs accounted for 32.5% of the total cost. Of these, 69.5% were costs relating to healthcare professionals, 21.8% to INR tests and 8.7% to warfarin. With regard to indirect costs (67.5% of the total), 52.4% were related to absenteeism from work and 47.6% to transportation to the clinic.

According to data from the federal government's drug purchasing website, the average prices of apixaban, dabigatran and rivaroxaban for the public institutions from January 1st to August 19th, 2015,[20] respectively, were $ 49.87, $ 51.40 and $ 52.16 per month, respectively (**Table 4**). **Figure 1** provides a graphical representation of a projection of this difference for the Brazilian population.

Table 2. Characteristics of patients included (n = 633)

Characteristics	n (%)
Indication for anticoagulation*	
Atrial fibrillation	359 (58.8)
Atrial fibrillation with valvulopathy	58 (9.2)
Atrial fibrillation without valvulopathy	301 (47.6)
Deep vein thrombosis/pulmonary embolism	229 (36.2)
Valvulopathy without atrial fibrillation	30 (4.7)
Chagas disease	28 (4.4)
Chagas disease and atrial fibrillation	19 (3.0)
Left ventricle thrombus	25 (3.9)
Arterial thrombosis	22 (3.5)
Chronic pulmonary hypertension	14 (2.2)
Mesenteric thrombosis	11 (1.7)
Intracranial thrombosis	9 (1.4)
Special needs	**70 (11.1)**
Wheelchair	26
Supplementary oxygen	10
Walking stick	23
Walker equipment	5
Visual impaired	2
Prosthetic orthopedic devices	1
Walks with support	3
Occupation	
Retired	332 (52.4)
Employed	131 (20.7)
Unemployed	89 (14.1)
Government funding due to disease	49 (7.7)
Pensioner	25 (3.9)
Missing data	7 (1.1)
Companion	**299 (47.2)**
Companion's occupation	
Retired	60
Employed	143
Unemployed	90
Government funding due to disease	1
Pensioner	2
Transportation	
On foot	20 (3.2)
Bus	401 (63.3)†
Bus with companion	112 (17.7)
Bus and taxi	12 (1.9)
Own car	112 (17.7)
City's car	17 (2.7)
Taxi	64 (10.1)
Missing data	7 (1.1)

*Patients could have more than one indication for anticoagulation; †Out of the 412 patients who used a bus, 63.6% used two buses, 29.6% used four buses and 4.4% used six buses per day to attend the consultation at the anticoagulation clinic.

Sensitivity analysis

Table 5 illustrates the sensitivity analysis on the cost of anticoagulation using warfarin among elderly versus non-elderly patients, according to origin (Belo Horizonte versus other cities), distance from the home to the anticoagulation clinic (greater or less than 20 kilometers and greater or less than 30 kilometers) and indication (atrial fibrillation versus other indications).

Table 3. Annualized direct and indirect costs relating to patients at the anticoagulation clinic who were using warfarin (n = 633)

Direct costs	Costs for the whole sample (n = 633)	Average costs per patient*
INR examinations†	$ 29,161.73	$ 46.07
Clinical staff	$ 93,065.74	$ 147.02
Warfarin	$ 11,615.18	$ 18.35
Vitamin K	$ 14.76	$ 0.02
Indirect costs		
Work absenteeism	$ 145,772.69	$ 230.29
Transportation cost	$ 132,549.63	$ 209.40
Total	$ 412,179.97	$ 651,15

All costs are in US dollars. INR = international normalized ratio. *The costs over the same period for a patient using the new oral anticoagulants would be: $ 598.44 for apixaban, $ 616.80 for dabigatran and $ 625.92 for rivaroxaban; †When the data from the study follow up is annualized, each patient would undergo 28 INR examinations on average.

Table 4. Average price for the new oral anticoagulants to public institutions

Drug	Number of purchases	Average price per pill	Monthly cost
Apixaban 5 or 2.5 mg	3	$ 0.82	$ 49.87
Dabigatran 110 mg	5	$ 0.81	$ 49.24
Dabigatran 150 mg	2	$ 0.93	$ 56.78
Dabigatran (average price)	7	$ 0.84	$ 51.40
Rivaroxaban 20 mg	5	$ 1.64	$ 50.11
Rivaroxaban 15 mg	6	$ 1.77	$ 53.86
Rivaroxaban (average price)	11	$ 1.71	$ 52.16

Source: federal government's drug purchasing website, from purchases made between January 1 and August 19, 2015.[20] Prices are in US dollars. Number of purchases = number of purchases of each dosage of each oral anticoagulant registered in the website, from the purchases made between January 1 and August 19, 2015.

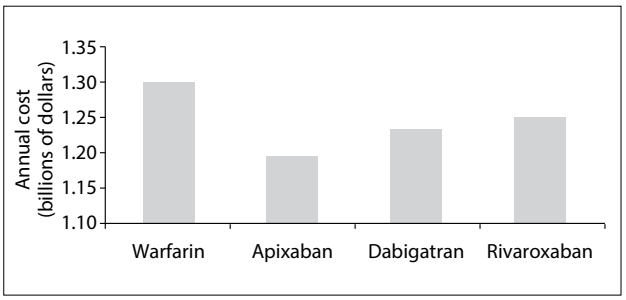

Figure 1. Graphical representation of average monthly cost of the strategy of using warfarin, at a public anticoagulation clinic, versus using apixaban, dabigatran and rivaroxaban, from data available on the federal government's drug purchasing website, projected for the Brazilian population. Considering a population of 200 million inhabitants (according to the Instituto Brasileiro de Geografia e Estatística, at www.ibge.gov.br) and an estimated prevalence of atrial fibrillation of 1%, around 2 million patients need to make use of anticoagulants.

Table 5. Sensitivity analysis on average monthly cost per patient using warfarin, at the anticoagulation clinic

Criteria	Costs
Age	
≥ 60 years	$ 49.78
< 59 years	$ 59.54
Origin	
Belo Horizonte	$ 50.40
Other cities	$ 69.80
Distance from home	
≥ 20 km	$ 63.62
< 20 km	$ 51.80
≥ 30 km	$ 97.39
< 30 km	$ 50.90
Indication	
Atrial fibrillation	$ 51.03
Other indications	$ 57.35

Prices are in US dollars.

DISCUSSION

Population ageing and increasing prevalence of chronic diseases, including hypertension and diabetes, which are factors that raise the risk of stroke among patients with atrial fibrillation, in addition to the higher prevalence of atrial fibrillation in the population,[24] point towards growth in the numbers of patients with indications for anticoagulation. In clinical practice in Brazil, only a small proportion of patients receive anticoagulant therapy and this requires a solution.[5] International guidelines recommend atrial fibrillation screening among patients greater than or equal to 65 years of age.[25] However, within the Brazilian context, patients with recognized atrial fibrillation have not been treated with the recommended therapy for stroke prevention. Therefore, we witness patients being admitted to emergency departments presenting the disastrous consequences of strokes, which are generally more extensive and therefore associated with greater morbidity and mortality than those in patients without atrial fibrillation.[3,26]

The oral anticoagulant therapy currently available in the public healthcare system in Brazil is warfarin. It is recommended that the care for patients using oral anticoagulant therapy with warfarin should be provided in anticoagulation clinics,[14] because these have been shown to be more effective in controlling these patients' coagulation in terms of efficacy and safety. However, given the numbers of patients with indications for anticoagulation, creation of the required number of clinics to attend the Brazilian population is not feasible. Without these clinics, the decision to indicate anticoagulation and monitoring of patients is generally at the discretion of primary care physicians, who often do not have specific training for this and have limited access to continuing education.[27,28] Thus, they feel insecure with regard to making such decisions and do not have enough time to provide the number of consultations that anticoagulation control requires.[14] Additionally, control undertaken at primary care centers may produce results that are inferior to those at anticoagulation clinics,[23] especially considering that performing the blood analysis work in different laboratories with interference from preanalytical factors and/or without adequate standardization of thromboplastin, may lead to problems in measuring INR levels.[14] Consequently, this can generate the need for more consultations and might increase the risk of complications, thereby further increasing the cost.

The present study shows that in the context of Brazilian healthcare, after calculating all the costs involved in controlling anticoagulation at an anticoagulation clinic among patients using warfarin, this strategy has a higher cost than the sale price of the new oral anticoagulants to the public institutions. These results are extremely important, considering the urgent need to act more effectively in primary and secondary prevention of cardioembolic stroke among patients with atrial fibrillation within the Brazilian context.[5]

The costs for consultations relating to the new oral anticoagulants were not calculated, since these drugs do not require further consultations, other than the usual controls among these patients. For both warfarin and the new oral anticoagulants, the patient needs to undergo clinical follow-up with the referral physician, since the anticoagulation clinic only assesses the oral anticoagulant therapy.

It is important to note that the strategy of using the new oral anticoagulants is not appropriate for all patients with indications for oral anticoagulation, since there is lack of evidence regarding the impact of the new oral anticoagulants for some conditions, for example, among patients with rheumatic valve disease and atrial fibrillation,

prosthetic heart valves, Chagas cardiomyopathy and thrombus in the left ventricle. Some patient profiles have been excluded from clinical trials, such as cases of advanced kidney failure or liver failure; or have been underrepresented, such as cases of extremes of weight.

The sensitivity analysis showed that for some patient profiles, the strategy of using the new oral anticoagulants seems to be even more economically attractive. For example, among non-elderly patients, there is a higher cost relating to absenteeism from work than among elderly patients; and among patients living in cities other than where the clinic is located, or living at least 20 kilometers from the clinic, for whom the cost relating to transportation becomes more significant, thus making anticoagulation with warfarin a more expensive strategy. When comparing patients using anticoagulants because of atrial fibrillation with patients with other indications, the costs of taking warfarin were significantly lower among patients with atrial fibrillation ($ 51.03 versus $ 57.35). Thus, for patients with atrial fibrillation, the costs of taking warfarin are comparable to the costs of taking the new oral anticoagulants.

This study has some limitations. Cost-minimization analysis assumes equivalence between interventions. Clinical trials have shown that the new oral anticoagulants are at least as effective as warfarin, with a better safety profile. Thus, there is potential for even greater cost reduction with the new oral anticoagulants. Although this was a single-center study, the protocol used in this anticoagulation clinic is based on international guidelines for patient care with anticoagulant use. Additionally, in these analyses, we assumed that control undertaken at anticoagulation clinics is the recommended strategy for patients taking warfarin.[14] However, control at anticoagulation clinics is not universally available for patients using warfarin, and this comparison may not apply to all settings.

CONCLUSION

This cost-minimization analysis using real data from clinical practice found that in the Brazilian context, from the perspectives of the public healthcare system and of society, the calculated costs relating to warfarin use in anticoagulation clinics seem to be currently higher than those relating to the strategy of using the new oral anticoagulants. These data provide support for the discussion about incorporating these new drugs for patients within the public healthcare system, with the potential to reduce the incidence of systemic embolic events and to bring even greater savings from a financial point of view and in terms of public health.

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Blood pressure levels and body mass index in Brazilian adults with Down syndrome

Níveis de pressão arterial e índice de massa corporal em adultos brasileiros com síndrome de Down

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KEY WORDS:
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PALAVRAS-CHAVE:
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Índice de massa corporal.
Adulto.

ABSTRACT

CONTEXT AND OBJECTIVE: Increased life expectancy among people with Down syndrome (DS) has introduced new environmental factors that may affect blood pressure (BP) and/or lead to obesity in this population. The aim here was to investigate BP levels and body mass index (BMI) in adults with DS, correlating these data with the patients' sex and age.

DESIGN AND SETTING: Analytical cross-sectional observational study conducted in special schools in Curitiba (PR), Brazil.

METHODS: 97 adult patients were included. BP was measured in accordance with the established guidelines. BMI was calculated by dividing the weight by the height squared (kg/m^2).

RESULTS: Sex had no influence on BMI; nor did systolic BP (SBP) or diastolic BP (DBP). The age range was from 18 to 56 years. No correlation was observed between increasing age and greater BMI or BP. Eighty-six individuals (88.7%) presented normal BP, eleven (11.3%) prehypertension and none hypertension. Twenty patients (20.4%) presented BP lower than 90 × 60 mmHg. BMI ranged from 18 to 48 kg/m^2 (mean of 28.8 ± 3.92 kg/m^2): 21.9% had normal weight; 40.7% were overweight; and 25.3% had obesity class I, 9.9% class II and 2.2% class III. Higher BMI was associated with significantly greater SBP and DBP (P = 0.0175 and P = 0.0015).

CONCLUSION: Sex and age did not influence SBP, DBP or BMI in Brazilian adults with DS. Higher BMI was associated with greater BP (both systolic and diastolic).

RESUMO

CONTEXTO E OBJETIVO: O aumento da expectativa de vida das pessoas com síndrome de Down (SD) introduziu novos fatores ambientais que podem afetar a pressão sanguínea e/ou levar a obesidade nessa população. O objetivo foi investigar os níveis de pressão arterial (PA) e o índice de massa corporal (IMC) em adultos com SD, correlacionando estes dados com a idade e o gênero dos pacientes.

DESENHO E LOCAL: Estudo observacional, transversal e analítico, realizado em escolas especiais em Curitiba (PR), Brasil.

MÉTODOS: Foram incluídos 97 pacientes adultos. A aferição da PA foi feita de acordo com as diretrizes estabelecidas. O IMC foi calculado dividindo-se o peso pela altura ao quadrado (kg/m^2).

RESULTADOS: O gênero não influenciou o IMC, a pressão arterial sistólica (PAS) e diastólica (PAD). A idade variou de 18 a 56 anos. Não foi observada correlação entre aumento da idade e maior IMC ou pressão arterial. 86 indivíduos (88,7%) apresentaram PA normal, 11 (11,3%) pré-hipertensão e nenhum hipertensão. Vinte (20,4%) apresentaram PA inferior a 90 × 60 mmHg. O IMC variou entre 18 e 48 kg/m^2 (média de 28,8 ± 3,92), 21,9% tinham peso normal, 40,7% sobrepeso, 25,3% obesidade grau I, 9,9 % grau II e 2,2% obesidade grau III. Aumento significativo da PAS e PAD foi associado com elevação do IMC (P = 0,0175 e P = 0,0015).

CONCLUSÃO: Verificou-se que sexo e idade não influenciaram PAS, PAD e IMC em adultos brasileiros com SD. O aumento significativo da PAS e PAD foi associado com o aumento do IMC.

INTRODUCTION

Over the last five decades, there has been a trend toward longer survival among individuals with Down syndrome (DS).[1-3] In developed countries, recent estimates have indicated that their average age at death is greater than 50 years.[2,3] Reduced institutionalization with increased mobility and integration into society has also played a role.[1,4,5]

DS is a multiorgan disorder, affecting the heart and vascular system both structurally and functionally.[6] Conditions such as obesity, mobility restrictions, depression, hypothyroidism and Alzheimer's disease are known to become increasingly prevalent in later life,[7] including increased blood pressure (BP) and body mass index (BMI). There are a few studies evaluating blood pressure in adults with DS that have reported that their BP is lower than that of the general population and people with other forms of mental handicap. However, some of these studies were conducted many years ago.[8,9] Today, individuals with DS are exposed to different environmental factors such as stress, fast foods, greater social inclusion and new challenges that can affect BP and cause obesity.

Draheim et al.[10] investigated 52 DS patients and reported that systolic and diastolic BP were significantly lower in adults with DS than in a matched control group; and that their body mass index (BMI) was 31.0 ± 6, which was significantly higher than that of the controls (28.0 ± 7). There are no studies on this topic conducted in Brazil.

OBJECTIVE

In the present study, we investigated the levels of diastolic/systolic BP and BMI among noninstitutionalized adults with DS in Curitiba, Brazil, correlating the findings with the patients' sex and age.

METHODS

This study had an observational cross-sectional design and was approved by the local research ethics committee (Positivo University, number 297.349/2013). The parents or guardians of all participants signed informed consent forms.

The study population comprised adults with DS over the age of 18 years who were being followed up at two institutions: Associação de Pais e Amigos dos Excepcionais (APAE-PR) and Associação Reviver, both in Curitiba, Paraná. The parents were sent a letter proposing the study. If they agreed, they signed the consent form and the patient was included in the study. In a brief questionnaire, the participants answered questions about the presence of diagnosed hypertension, smoking and alcohol consumption. The participants received guidance on healthy habits and were encouraged to practice physical activity. The study was conducted over the period from May 2013 to September 2013.

The researchers invited 97 consecutive adults with DS who were attending the schools that collaborated in the study. All agreed in to participate. Thus, a total of 97 DS patients (49 male and 48 female patients) in Curitiba, Paraná, Brazil, were included in the study. None of them were smokers or alcohol consumers or had hypertension diagnosed previously.

BP measurements were made using the auscultatory method with a calibrated mercury sphygmomanometer, performed by an operator trained in the standardized technique. The patients were properly prepared and positioned. They remained seated quietly for at least five minutes on a chair, with feet on the floor and arms supported on armrests at heart level. Caffeine and exercise needed to be avoided for at least 30 minutes prior to the measurements, in accordance with the guidelines established by the American Heart Association in the Seventh Report of the Joint National Committee (JNC-7).[11] The measurements made by the two researchers agreed well when simultaneous recordings were made in the right and left arms of the patients, with appropriate cuff sizes used. For all the patients in this study, three BP measurements were made, done on different days within one week. The mean from these measurements was used in the analyses.

BMI was calculated by dividing the weight in kilograms by the height in meters squared (kg/m^2), in accordance with the World Health Organization (WHO) recommendations.[12] To obtain the patients' body weight and height, we used an electric scale and a tape measure. Patients who presented abnormal BP measurements received a letter from the school, in which their parents were advised to seek the municipal health service for the patients' BP to be measured. The healthcare professional assigned to the special school was also informed about the findings. All the patients received information about proper nutrition and physical exercise for maintaining their health.

The data distribution was analyzed using the Kolmogorov-Smirnov test. The results were expressed as the mean and standard deviation (SD) for parametric data and as the median and interquartile range (IQR) for nonparametric data. The Fisher exact and chi-square tests were used for association studies on nominal data and the unpaired t test and Mann-Whitney test were used for continuous data. Calculations were done with the aid of the GraphPad Prism software, version 4.0, and Medcalc version 12.1.3.0. The significance level used was 5%.

RESULTS

Among the 97 DS patients, 49 (51%) were male. There were no statistically significant differences according to sex with regard to evaluations on BMI (P = 0.84), systolic blood pressure (SBP) (P = 0.64) or diastolic blood pressure (DBP) (P = 0.33), as demonstrated in **Table 1**.

Table 1. Clinical and demographic data and comparison between sexes in the study group

	Men	Women	Total
Demographic data			
Subjects (%)	49 (50.5%)	48 (49.5%)	97
Mean age ± SD (years)	25.1 ± 5.21	27.8 ± 7.8	26.5 ± 6.52
Average weight (kg)	70.6	63.6	67.1
Average height (cm)	157	147	152
Blood pressure (BP)			
Mean systolic BP (mmHg)	102.0 ± 15.73	104.4 ± 14.41	104.1 ± 12.55
Mean diastolic BP (mmHg)	67.2 ± 10.75	69.3 ± 10.94	68.2 ± 8.90
Normal BP	45	41	86 (88.7%)
Prehypertension	4 (8.1%)	7 (17.1%)	11 (11.3%)
Body mass index			
Normal weight	10 (22.2%)	10 (21.7%)	20 (21.9%)
Overweight	18 (40%)	19 (41.3%)	37 (40.7%)
Obese class I	14 (31.1%)	9 (19.6%)	23 (25.3%)
Obese class II	3 (6.7%)	6 (13%)	9 (9.9%)
Obese class III	0	2 (4.3%)	2 (2.2%)

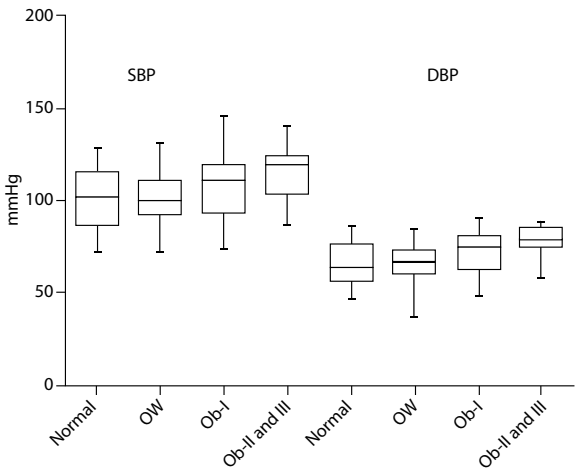
SD = standard deviation.

The population age range was from 18 to 56 years, with a mean age of 26.5 ± 6.52 years; 74.2% were less than or equal to 30 years of age (**Table 1**). The statistical analysis showed that there was no association between increasing age and higher BMI (P = 0.64), or between increasing age and SBP (P = 0.45) or DBP (P = 0.80).

The systemic arterial pressure ratios of the 97 patients evaluated in this study ranged from 72/36 mmHg to 132/88 mmHg. Eighty-six of them (88.7%) presented BP below the "optimal" reference value (120/80 mmHg) for individuals with normal BP, as recommended through JNC-7.[11] Eleven patients (11.3%) were classified as presenting prehypertension and no patient presented hypertension (**Table 1**). Three patients (3.1%) had borderline BP, defined as SBP 130-139 mmHg and another two patients (2.1%) showed DBP between 85 mmHg and 89 mmHg. On the other hand, twenty patients (20.4%) presented BP levels lower than 90 mmHg × 60 mmHg (10 males; mean age of 26.4 years): seven individuals with normal BMI, 10 with obesity class I and three with obesity class II. Four of them had systemic BP of 70 mmHg × 50 mm/Hg.

BMI screening was performed on 91 patients. Six patients did not allow weight and height measurements to be made. The BMI ranged from 18 to 48 kg/m^2, with a mean of 28.8 kg/m^2 ± 3.92 kg/m^2. Among the patients, 21.9% presented weight within normal limits, while 40.7% were classified as overweight, 25.3% as obese class I, 9.9% as obese class II and 2.2% as obese class III, in accordance with the World Health Organization classification system[12] (**Table 1**).

Higher BMI was associated with significant greater SBP and DBP (P = 0.0175 and P = 0.0015, respectively). **Figure 1** shows the SBP and DBP values according to BMI variation. No significant correlation was observed when the patients' ages were compared with either SBP or DBP. Among the patients with normal weight (21.9%), the median BP was 101 mmHg x 65 mmHg. The overweight patients (40.7%) had median BP of 102 mmHg x 66 mmHg and those with obesity class I (25.3%) had median BP of 105 mmHg x 70 mmHg. BP was significantly greater among the patients with obesity classes II and III (12.1%), who showed median BP of 115 mmHg x 80 mmHg (P = 0.0038), in comparison with the patients with normal weight.



SBP = systolic blood pressure; DBP = diastolic blood pressure; OW = overweight; Ob-I = obesity class I; Ob-II and III: obesity classes II and III.

Figure 1. Blood pressure levels in patients with Down syndrome, according to body mass index.

DISCUSSION

In this study, we evaluated the BP and the BMI of adults with DS. We showed that the diastolic and systolic BPs were lower among individuals with DS and that high BMI was associated with increased BP.

In terms of BP, in our study, the majority (88.7%) of the patients had BP below the recommended levels, which is consistent with the findings of other authors.[8,10] Among our patients, none presented hypertension; 11 cases (11.3%) were classified as presenting prehypertension, among which 9 presented obesity class II and III. These patients will be monitored through periodic measurements of their BP and referral for medical care. On the other hand, 20.6% of the patients presented low systemic blood pressure, i.e. below 90 mmHg x 60 mmHg, without any association with sex or age. Some authors have suggested that this low BP may be associated with Alzheimer's disease and premature aging among individuals with DS.[8] On the other hand, the lack of influence of sex and age on BP and BMI may be due to the small sample size or to survival bias, in the case of age.

A sedentary lifestyle and an unhealthy diet are common among individuals with DS, especially among those living in community settings.[13,14] The prevalence of overweight and obesity among patients with DS is significantly higher than among other patients with intellectual disabilities or in the general population. The reported prevalence of obesity among adults with DS is between 31% and 47%.[15-17] In our study, the prevalence of obesity among adults with DS was 37.8%, and 40% of the population was overweight. Only 22.2% presented appropriate weight for age. It is natural to emphasize the importance of consistent exercise, good diet, community involvement and regular health examinations for these individuals. In a study on physical inactivity among adults with intellectual disability, Draheim et al.[18] reported that less than 46% of the men and women participated in the recommended amount of physical activity and that no adults older than 30 years reported participation in vigorous physical activity. However, Fujiura et al.[19] founded that there were no strong links between BMI, diet and exercise among adults with DS. They discovered a significant link between friendships or access to recreation and BMI, concluding that community interactions had a major effect on health. In our view, healthy behavior should be stimulated. It is to be expected that a specific approach is needed to get these people interested and motivated to change their lifestyle. Therefore, development of specific programs for DS patients that may be conducted in schools is necessary.

CONCLUSION

In our study, we found that sex and age did not influence SBP, DBP or BMI among Brazilian adults with DS. We observed that our DS patients presented high BMI. Furthermore, higher BMI was associated with higher systolic and diastolic BP.

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Hematological approaches to multiple myeloma: trends from a Brazilian subset of hematologists. A cross-sectional study

Condutas hematológicas perante o mieloma múltiplo: tendências de um subgrupo de hematologistas brasileiros. Um estudo transversal

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PALAVRAS-CHAVE:
Mieloma múltiplo.
Hematologia.
Condutas na prática dos medicos.
Medicina baseada em evidências.
Prática clínica baseada em evidências.

ABSTRACT

CONTEXT AND OBJECTIVE: For the last nine years, hematologists and oncologists have gathered annually at an educational symposium organized by a Brazilian and an American hospital. During the 2015 Board Review, a survey among the attendees evaluated the differences in management and treatment methods for multiple myeloma (MM).

DESIGN AND SETTING: Cross-sectional study during an educational hematology symposium in São Paulo, Brazil.

METHODS: Hematologists present at the symposium gave responses to an electronic survey by means of mobile phone.

RESULTS: Among the 350 attendees, 217 answered the questionnaire. Most of the participants believed that immunotargeting agents (iTA) might be effective for slowing MM progression in heavily pretreated patients (67%) and that continued exposure to therapy might lead to emergence of resistant clones in patients with MM (76%). Most of the physicians use maintenance therapy after hematopoietic stem cell transplantation (95%) and 45% of them would further restrict it to post-transplantation patients with underlying high-risk disease. The first-line drugs used for transplantation-ineligible patients (TI-MM) were bortezomib-thalidomide-dexamethasone (31%), bortezomib-dexamethasone (28%), lenalidomide-dexamethasone (Rd; 17%) and melphalan-based therapy (10%). Lenalidomide was the drug of choice for post-transplantation maintenance for half of the participants. No significant differences were observed regarding age or length of experience.

CONCLUSION: The treatment choices for TI-MM patients were highly heterogenous and the melphalan-based regimen represented only 10% of the first-line options. Use of maintenance therapy after transplantation was a common choice. Some results from the survey were divergent from the evidence in the literature.

RESUMO

CONTEXTO E OBJETIVOS: Há nove anos, hematologistas e oncologistas se reúnem anualmente em um simpósio educacional organizado por um hospital brasileiro e outro norte-americano. Durante o Board Review 2015, uma pesquisa foi conduzida entre os participantes e avaliou as diferenças na conduta e opções de tratamento para o mieloma múltiplo (MM).

DESENHO E LOCAL: Estudo transversal no simpósio educacional de hematologia em São Paulo.

MÉTODOS: Hematologistas presentes no simpósio responderam a uma pesquisa por celular.

RESULTADOS: Dos 350 inscritos, 217 responderam o questionário. A maioria dos participantes acredita que a terapia-alvo imune (iTA) pode ser efetiva para desacelerar a progressão do MM em pacientes que já foram muito tratados previamente, e que a exposição contínua à terapia pode gerar clones resistentes em pacientes com MM (76%). A maioria usa terapia de manutenção após transplante de células-tronco hematopoiéticas (95%) e 45% dos médicos a restringiriam a pacientes pós-transplante com doença de base de alto risco. As drogas de primeira linha adotada para os pacientes inelegíveis para transplante (PIT) foram bortezomibe-talidomida-dexametasona (31%), bortezomibe-dexametasona (28%), lenalidomina-dexametasona (Rd; 17%) e terapia baseada em melfalan (10%). A lenalidomida foi a droga de escolha para a manutenção pós-transplante para metade dos participantes. Nenhuma diferença significativa foi encontrada para idade ou tempo de experiência.

CONCLUSÃO: As escolhas de tratamento para PIT foram altamente heterogêneas e o regime baseado em melfalan representou somente 10% das opções de primeira linha. Terapia de manutenção após transplante é opção comum. Alguns dos resultados do levantamento foram divergentes das evidências na literatura.

INTRODUCTION

Multiple myeloma (MM) is a plasma cell disease that represents about 10% of hematological malignancies and has an annual incidence of up to 5.6 per 100,000 individuals in the western hemisphere.[1,2] On a worldwide scale, approximately 86,000 new cases of MM occur annually.[3] Regarding Latin American epidemiological datasets, little is known about the incidence and clinical features,[3,4] and the exact incidence of MM in Brazil has not yet been determined,[4,5] but according to the International Myeloma Foundation, there are around 30,000 Brazilian MM patients currently under treatment.[6] The management of MM has been revolutionized over the last few years and this has been based on understanding recent advances in MM pathophysiology, discovery of new target pathways and development of novel therapeutic agents.[7]

Over the last nine years, Albert Einstein Hospital (São Paulo, SP, Brazil), in collaboration with MD Anderson Cancer Center (Houston, TX, USA), developed an annual state-of-the-art hematological symposium that was attended by over 400 hematologists from Latin America (mostly Brazil). In 2015, the symposium was held on June 23-26 and included a hematological review course, which promoted opportunities for physicians (mostly clinical hematologists and oncologists) to update and share their understanding of diseases and to disseminate practical knowledge (including in relation to therapeutic agents) on different topics within hematology. The educational content included both malignant and benign hematology. The majority of the lectures were in Portuguese, and there were four international speakers. In the light of recent advances and controversies, one of the highly appreciated topics discussed was that of MM.

OBJECTIVES

With the aim of assessing Latin American common standards of care, and their distinctions, and also the experience and expectations of hematologists concerning new treatments, a survey was developed and administered among the Brazilian symposium attendees. The objective of the survey was to evaluate the controversies and differences in practical management and treatment methods for MM. We hypothesized that better understanding of Latin American hematologists' treatment choices would allow us to identify and improve physician support and patient care.

METHODS

During the Board Review of the Ninth International Symposium for Updating on Hematological Topics and the Ninth Symposium for Bone Marrow Transplantation (IX Simpósio Internacional de Atualização em Temas de Hematologia/IX Simpósio de Transplante de Medula Óssea), held jointly from June 23 to 26, 2015, 350 participants were invited to answer a survey on MM therapy using a free mobile phone application called MDRing (**Figure 1**). Questions were synchronized with the lecture topics and the participants were encouraged to answer the questionnaire preferably before each presentation. Each electronic questionnaire had multiple closed options for responses and the numbers of options for each question were variable. In addition, pertinent demographic information was collected, including gender, academic practice, age and number of years of professional experience. The survey was composed of 15 questions involving treatment-related topics, including immunotargeting, transplantation, options for multiple myeloma patients who are ineligible for transplantation and maintenance treatment.

We report here the survey results as percentages of respondents, excluding those who did not provide an answer to a particular question. Subgroup analyses were conducted according to gender, age (groups of greater than or equal to 35 years or less than 35 years) and experience (more than 10 years after specialization and less than 10 years). The univariate statistical analysis included the chi-square test. The statistical analyses were performed using the SPSS software (IBM, Chicago, 2013). The significance level was set at a P-value of 0.05.

RESULTS

During the four-day symposium, a total of 217 participants answered the questionnaire completely. The median age of the population studied was 35 years (range: 25-47 years); 59% were male; the median length of time since graduation was 10 years (range: 3-24 years); and 53% had less than 10 years of experience. The survey participants' characteristics and their responses are shown in **Tables 1** to **4** and **Figure 2**. Although some participants

Figure 1. On-screen appearance of MDRing, an application created for surveying the physicians during the symposium.

at the symposium were from other Latin American countries, only Brazilian hematologists answered the questionnaire on this occasion.

In analyzing new drugs, the majority of the participants believed that immunotargeting agents (iTA) might be effective in slowing disease progression in MM patients with multiple lines of prior therapy. Younger physicians (83% versus 58%; P = 0.069) and physicians with less than 10 years of experience (93% versus 60%; P = 0.08) tended to consider that iTA would be effective in this situation, although the difference was not significant. iTA was perceived to be important equally by male and female physicians (73% males versus 64% females; P > 0.175; **Table 1**).

The majority of the physicians (76%) believed that continued exposure to therapy might lead to emergence of resistant clones in patients with MM. No significant differences were observed based on participant's age, gender or years in practice, for this variable (**Table 2**).

With regard to maintenance therapy (MT), the majority (95%) of the physicians declared that they would offer it to patients undergoing treatment for MM. However, the majority (46%) would restrict maintenance therapy to post-transplantation cases that were classified as high-risk, while 29% of the physicians would extend MT to all transplantation patients. No significance difference was found in relation to gender, age or years in practice (**Table 3**).

Side effects were considered to be the main reason (56%) for halting oral therapy for MM beyond complete remission, followed by the practice of saving therapy for future relapses (22%) and the practice of using a fixed drug approach (12%), in which the physician offers two additional cycles beyond complete remission. There was no significant difference in age or years in practice among these respondents (**Table 4**).

The responses to additional questions on transplantation and maintenance pulse therapy for MM patients are shown in the graphs of **Figure 2**. Regarding first-line treatment for transplantation-ineligible MM patients, we observed that 31% of the physicians used bortezomib-thalidomide-dexamethasone, 28% bortezomib-dexamethasone and 17% lenalidomide-dexamethasone (Rd), while only 10% of the participants chose melphalan-based therapy. In relation to the melphalan-based regimen of choice for non-transplantation myeloma cases, 41% of the participants chose a regimen with bortezomib, known as bortezomib-melphalan-prednisone (VMP), followed by melphalan-prednisone-lenalidomide (MPR) (14%). Melphalan-prednisone-thalidomide (MPT) was the option for only 10% of the physicians and melphalan-prednisone (MP) for 7%. About half of all the survey respondents answered that they continued to provide maintenance therapy for MM patients who were not eligible for transplantation until progression, whereas 38% chose maintenance therapy for two years and 12% reported that they were not concerned about this treatment.

Regarding the duration of post-transplantation MT, 50% of the physicians said that they would maintain it until disease progression, 30% would use it for two years, 10% would apply it for six months and the other 10% would not agree with the latter options. Lenalidomide was the drug of choice for post-transplantation maintenance for half of the participants, followed by thalidomide (20%) and bortezomib or prednisone (10%).

DISCUSSION

The data on the responses regarding iTA presented here demonstrated that younger physicians believed more strongly that iTA was the preferred option for decreasing disease progression. Critical new steps in MM management rely on development of

Table 1. Perceptions about the effectiveness of immunotargeting agents according to age, clinical experience and gender of the respondent (%)

Variable	Do you believe immunotargeting agents may be effective for slowing disease progression in cases of heavily pretreated multiple myeloma?			P
	No	We need more data	Yes	
Gender				
Female	0	36	64	0.175
Male	9	18	73	
Experience				
< 10 years	0	7	93	0.080
≥ 10 years	0	40	60	
Age				
< 35 years	0	17	83	0.069
≥ 35 years	0	42	58	

Table 2. Perceptions about resistance caused by continued exposure to therapy, according to age, clinical experience and gender (%)

Variable	Do you believe that continued exposure to therapy can produce resistant myeloma?		P
	No	Yes	
Gender			
Female	24	76	0.702
Male	17	83	
Experience			
< 10 years	20	80	0.999
≥ 10 years	23	77	
Age			
< 35 years	13	87	0.075
≥ 35 years	33	67	

second-generation novel agents and the advent of monoclonal antibodies. Various antigens have been implicated as potential therapeutic targets in MM. CD38 is an important immunotherapy target because of its high level of expression in malignant plasma cells and low expression in other cells, as well as being an important modulator of intracellular signaling.[8] Preliminary results suggest that the use of CD38-targeting antibodies in case of relapsed or refractory MM presents a safe profile and at least a minimal response rate.[9] Furthermore, an ability to overdrive genetic mutations, with prolonging of the durable response, has been reported.[10]

As described above, most respondents believed that continued exposure to therapy might lead to emergence of resistant clones. The literature shows that chemoresistance patterns can indeed be acquired. One study reported that the mechanism consisted of a situation of coexistence of several clones, in which treatment was able to eradicate the major chemosensitive clone, but not the minor chemoresistant clone, which eventually became the dominant clone with continued treatment and subsequently drove the proliferation.[11] Continuous exposure to therapy could contribute to this process and, in cases of adverse cytogenetic abnormalities, maintenance therapy has demonstrated lack of efficacy primarily due to the emergence of tumor-resistant clones in patients with prolonged exposure to thalidomide.[12,13]

We observed that the great majority of respondents would offer MT to their MM patients, and their first-choice drug was lenalidomide. Although a cure for MM is still not possible in many patients, long-term MT can have a positive impact on response duration, progression-free survival and overall survival, assuming controlled minimal toxicity rates, as shown in several studies.[10] There is evidence supporting lenalidomide as the best candidate for use as MT. Two randomized trials evaluating maintenance therapy using lenalidomide versus placebo following autologous stem cell transplantation (ASCT) have been published, and have demonstrated that use of lenalidomide provides significantly prolonged progression-free survival of two to four years.[14,15] The Cancer and Leukemia Group B (CALGB) trial also demonstrated that the group who received induction therapy with lenalidomide obtained an overall survival benefit.[15]

Most participants in the present study reported that high-dose therapy with ASCT was still the standard of care, corresponding to the preferred therapy for patients at their first complete remission, even in the era of novel therapies. The emergence of deep complete remission with novel drugs has led some groups to test new upfront treatments without immediate transplantation.[10] The criteria for defining eligibility for transplantation were heterogeneous in the present study, as shown in

Table 3. Personal experience with maintenance therapy according to age, experience and gender (%)

Variable	Do you offer maintenance therapy for multiple myeloma?				P
	No	Yes, to all patients regardless of transplantation	Yes, only to high-risk post-transplantation patients	Yes, to all post-transplantation patients	
Gender					
Female	4	11	50	35	0.592
Male	0	24	38	38	
Experience					
< 10 years	7	6	60	27	0.955
≥ 10 years	7	7	50	36	
Age					
< 35 years	10	17	40	33	0.202
≥ 35 years	0	23	54	23	

Table 4. Main reason for stopping oral therapy for multiple myeloma beyond complete remission (%)

Variable	What is the main reason for stopping oral therapy for myeloma beyond complete remission?					P
	I give 2 cycles past complete remission	I save drug for relapse	Patient preference	Reimbursement issues	Side effects	
Gender						
Female	11	15	0	7	67	**0.011**
Male	39	23	15	0	23	
Experience						
< 10 years	0	30	7	0	63	0.106
≥ 10 years	23	23	0	8	46	
Age						
< 35 years	4	28	4	4	60	0.200
≥ 35 years	22	13	4	9	52	

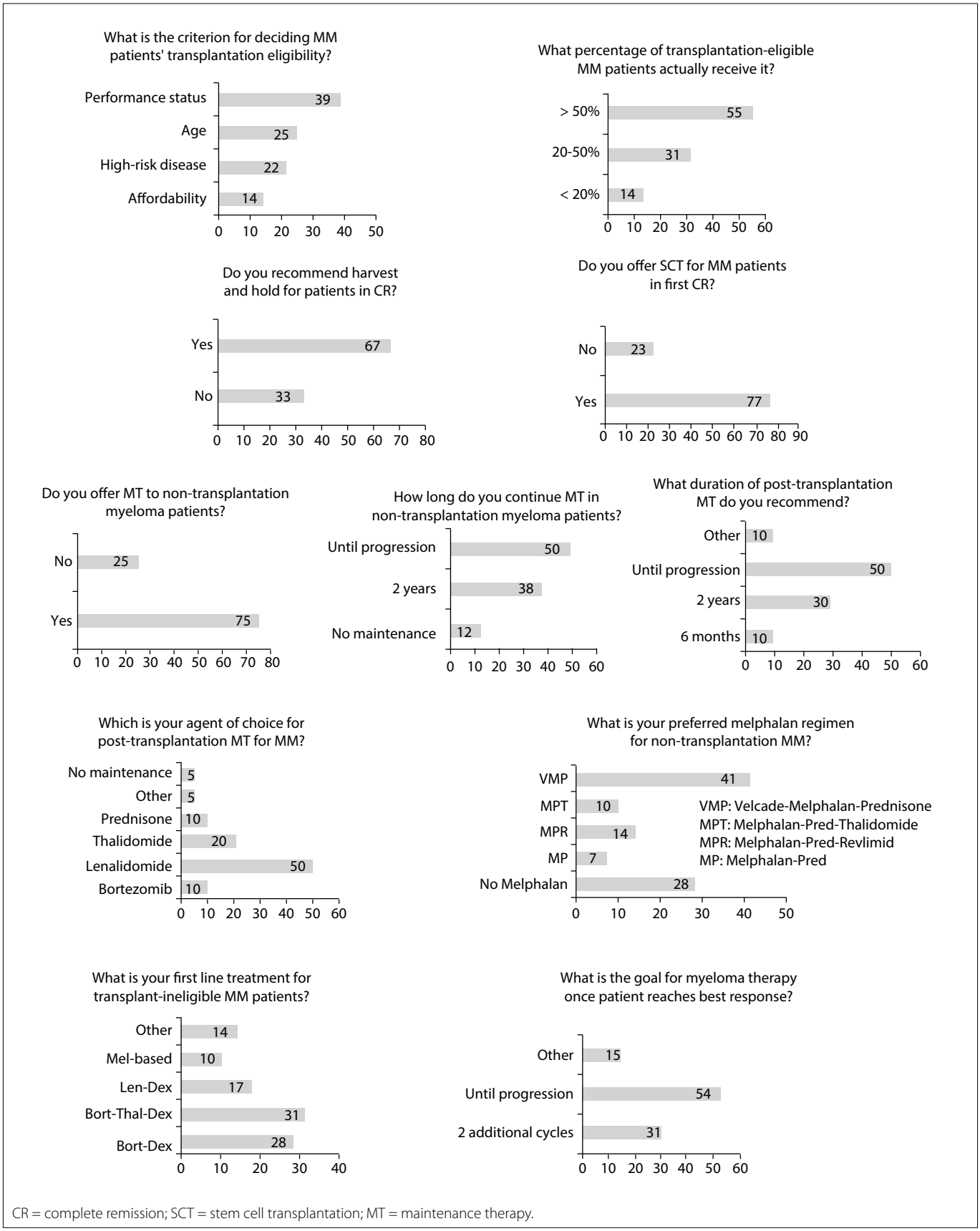

Figure 2. Responses to questions about treatment methods for multiple myeloma (MM) among hematologists attending a symposium in São Paulo, Brazil, in 2015.

Figure 2. Regarding the percentage of transplantation-eligible MM patients who actually receive this therapy, 45% of the respondents declared that less than 50% of the patients really underwent transplantation. However, the reason for this was not investigated. We believe that this is an issue worth exploring in future investigations. Lack of availability of public healthcare services for transplantation may have been the reason for this.

The first-line treatment for transplantation-ineligible patients was found to be heterogeneous in this study. Several randomized trials have shown that the MPT regimen can delay disease progression and improve overall survival, in comparison with MP.[16-18] A meta-analysis on six randomized trials comparing MPT with MP showed that there was an improvement in progression-free survival and overall survival with MPT, but also an increased rate of toxicity.[19] Based on these studies, MPT has been approved as the standard of care. The phase III VISTA trial demonstrated better overall survival with VMP, in comparison with MP, after five years of follow-up, among patients ineligible for transplantation.[20] The European Myeloma Network recommendations indicated that MPT and VMP are the preferred regimen for transplantation-ineligible patients.[21] Indeed, according to a recent review of clinical trials undertaken globally, MPT and VMP are the first-choice regimens for transplantation-ineligible patients.[13] However, the melphalan-based regimen represented only 10% of the options as first-line treatment for transplantation-ineligible multiple myeloma in our study. Use of bortezomib-thalidomide-dexamethasone (VTD), which was the first choice among our participants, and use of a bortezomib-dexamethasone (VD) regimen alone, which was their second choice for patients with transplantation-ineligible multiple myeloma, were evaluated in the UPFRONT trial, published recently in the *Journal of Clinical Oncology*. These options were not inferior to VMP.[22] With a median follow-up of 42.7 months, the median progression-free survival, median overall survival and overall response rates were similar for these three options, with no significant difference. Nevertheless, VTD, which was the first choice in Brazil in our study, was correlated with greater numbers of common adverse events than VMP and VD, based on the UPFRONT trial. The results from a multicenter open-label phase III trial (FIRST) comparing the efficacy and safety of Rd versus MPT among transplantation-ineligible patients demonstrated that Rd significantly improved the primary endpoint of progression-free survival, compared with MPT.[23] Based on these findings, continuous Rd, which was the third treatment option among our physicians, could become a new standard of treatment for these patients.

We believe our survey helps to identify how physicians approach patient care and treatment in multiple myeloma cases and the expectations for the future. We are thus opening a worldwide dialogue about opportunities for improving physician support and patient treatment.

CONCLUSIONS

The physicians surveyed believed that iTA would be an option for decreasing disease progression among MM patients. These Latin American hematologists mostly adopted MT over the long-term, with lenalidomide as the first-choice drug. The criteria for defining eligibility for stem cell transplantation were quite heterogeneous, according to the hematologists' responses, as also were the criteria regarding first-line treatment for patients who were ineligible for transplantation. This last response was divergent from the evidence in the literature. Evidence-based medical education initiatives are therefore necessary.

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Perspectives for treating Alzheimer's disease: a review on promising pharmacological substances

Perspectivas no tratamento da doença de Alzheimer: uma revisão sobre substâncias farmacológicas promissoras

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Tauopathies.

PALAVRAS-CHAVE:
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Mecanismos moleculares de ação farmacológica.
Quimioterapia.
Peptídeos beta-amiloides.
Tauopatias.

ABSTRACT

CONTEXT AND OBJECTIVE: Dementia is a syndrome characterized by functional and cognitive decline. Alzheimer's disease (AD) is one of the most common causes of dementia and has high prevalence among the elderly. It is known that there is no drug capable of interfering with the course of the disease. Research on treatments for AD has been marked by the appearance of new drugs and their abandonment. This study aimed to describe drugs that have been studied with regard to treating AD and which are capable of influencing the course of the disease.

DESIGN AND SETTING: Narrative review on original articles published worldwide.

METHODS: A systematized search was conducted in the PubMed/MEDLINE, Cochrane Library/Cochrane and SciELO/Bireme databases. The descriptors "Molecular Mechanisms of Pharmacological Action" and "Drug Therapy" were each combined with the descriptor "Alzheimer disease". All of these can be found in MeSH and DeCS. These descriptors were used alone or in combination, and a filter specifying publication between January 2009 and October 2015 in English, Spanish or Portuguese was set.

RESULTS: 6,888 articles were found, of which 37 were included in this review; 70.3% of the articles selected were of good quality with low or unclear risk of bias. 86 drugs were considered promising for AD treatment and these were classified into 20 pharmacological categories.

CONCLUSION: There are no drugs capable of influencing the course of AD such that treatments are safe and effective. However, immunomodulators stood out as promising, given their effectiveness and quality in the articles analyzed.

RESUMO

CONTEXTO E OBJETIVO: A demência é uma síndrome caracterizada por declínio funcional e cognitivo, sendo a doença de Alzheimer (DA) uma das causas mais comuns e de alta prevalência em idosos. Sabe-se que não há medicamento capaz de interferir no curso da doença e as pesquisas para o tratamento da DA têm sido marcadas pelo surgimento e abandono de novas drogas. O objetivo deste estudo foi descrever as drogas capazes de influenciar o curso da DA que têm sido estudadas para o tratamento da doença.

TIPO DE ESTUDO E LOCAL: Revisão narrativa de artigos originais publicados mundialmente.

MÉTODOS: Foi realizada uma busca sistematizada nas bases de dados PubMed/MEDLINE, Cochrane Library/Cochrane e SciELO/Bireme. Cada um dos seguintes descritores "Mecanismos Moleculares de Ação Farmacológica" e "Quimioterapia" foram combinados com o descritor "Doença de Alzheimer", todos encontrados no MeSH e DeCS. Os descritores foram usados sozinhos ou em combinação, fixando como filtros as publicações de 2009 a 2015, em língua inglesa, espanhola e portuguesa.

RESULTADOS: Foram encontrados 6.888 artigos, dos quais 37 foram incluídos nesta revisão; 70,3% dos artigos selecionados tiveram boa qualidade com baixo ou indefinido risco de viés. Foram elencadas 86 drogas promissoras ao tratamento da AD. Elas foram classificadas em 20 categorias farmacológicas.

CONCLUSÃO: Não há fármacos capazes de interferir no curso da DA com efetividade e segurança no tratamento. Contudo, os imunomoduladores foram considerados promissores devido ao fato de apresentarem efetividade e qualidade nos artigos analisados.

INTRODUCTION

Dementia is a syndrome characterized by functional and cognitive decline.[1-4] Alzheimer's disease (AD) is one of the several possible causes of dementia, corresponding to 60% to 70% of cases.[4,5] The prevalence of dementia due to AD increases with age, such that AD accounts for 5% of dementia cases in the age group of 65-74 years and 50% in the age group over 85 years.[6] AD is responsible for reduction of life expectancy by 50% from the time of diagnosis in elderly patients.[7]

AD is characterized by destruction of the functional activity of neurons in the cerebral cortex, amygdale, frontal base, limbic system and hippocampus, and also by cortical atrophy, thereby causing impairment of cholinergic synapses in the central nervous system (CNS). This is due to formation of inflammatory plaque or neuritic plaque (NP) and neurofibrillary tangles (NFTs), which are associated with the first onset of disease and secondary development thereafter. The brain regions affected account for memory, learning, emotional reactions and behavior.[8-10]

The mechanisms for formation of NP and NFTs that have been best elucidated relate to amyloid-beta (Aβ) peptide and tau protein. Some studies have indicated possibilities that represent the "start" of NP and NFT formation, such as inflammation, mitochondrial function, oxidative stress, vascular changes, gene expression and functionality of the endocrine system. These may be factors relating to the physiopathology of AD.[4,10]

Aβ peptide is a natural product from the metabolism of the amyloid precursor protein (APP), which is a neuronal transmembrane protein.[8,11] Aggregation of Aβ in the brain and in the walls of cerebral blood vessels gives rise to extracellular lesions that lead to formation of NP, thus causing neurotoxicity. Overproduction of APP or diminished clearance are possible explanations for the occurrence of this process. These situations arise through mutation of both genes that encode APP (chromosome 21) and in the genes encoding presenilin 1 and output 2 (chromosomes 14 and 1, respectively).[10,12,13]

NFT formation can be explained in terms of hyperphosphorylation of tau protein filaments. This protein is important for formation of the neuronal cytoskeleton and for transport through formation of microtubules. Thus, this hyperphosphorylation involves denaturing the protein that takes part in intracellular transport, which culminates in neuronal cell death.[10,12]

Over almost the entire course of the disease, cholinergic activity is most affected and this is correlated with the severity of AD. The reduction in the number of cholinergic neurons through development of AD implies loss of nicotinic receptors in the hippocampus and cortex. These are responsible not only for release of acetylcholine (ACh), but also for release of other important neurotransmitters that are involved in memory and mood, including glutamate, serotonin and norepinephrine.[10]

Noradrenergic and serotonergic systems are also impaired through loss of neurons in the locus coeruleus and raphe nuclei.[14] Glutamate receptors, particularly of the type N-methyl-D-aspartate (NMDA), are continuously activated with lower concentrations of glutamate, thereby resulting in stimulation of uncoordinated neurons and hyperarousal mediated by increased calcium influx.[15] This leads to destruction of neurons, with cortical atrophy, which then leads to ventricular enlargement and impairment of different neurotransmission pathways in key regions responsible for memory, learning, emotional reactions and behavior.[14,16]

In this context, the guidelines established in pharmacological therapies for treating AD can be summarized as inhibition of degradation of ACh or blocking of glutamate receptors, thereby reducing glutamatergic activity. This has the aim of enhancing cholinergic activity and decreasing the hyperactivity of the excitatory neurotransmitter glutamate in the cortex and hippocampus regions.[10]

Accordingly, the drugs commonly used in current clinical practice are acetylcholinesterase inhibitors (IAChEs): donepezil, galantamine and rivastigmine, which can be used alone or in combination with memantine, an antagonist of NMDA receptors that can also be used alone, depending on the stage of the disease. However, the pharmacological agents so far available as drug therapy have not been proven to modify the course of the disease, since they are only effective for symptomatic treatment.[10,17]

In fact, success in this quest has consistently required clarification of the molecular mechanisms relating to the two best pathological pathways elucidated with regard to formation of NP and NFTs in AD cases.[18-21] Some studies have put forward new biomolecular mechanisms linked to the physiopathology of AD, which could become possible therapeutic targets within the treatment for this disease. Many of these are called alternative targets and are justified because they are closely linked to neuroregeneration, reduction of neurotoxicity and promotion of positive effects on neuronal homeostasis.[18,21] However, it has been reported in the literature that only 30% of the compounds studied with a view to treating AD are molecules with mechanisms of action that are directly related to the above pathophysiological pathways, i.e. molecules that are able to modify the course of the disease. Within this percentage, almost 90% do not have a very clear therapeutic target, while about 10% are directed towards alternative targets requiring further elucidation about their association with AD.[18,21,22]

According to evidence in the literature, drug treatments for Alzheimer's disease had not presented any innovations up to the year 2015 and there were no drugs that would be able to combat the pathophysiology of AD. In this context, it is necessary to

elucidate the ways in which the search for new drugs has always been conducted. In this manner, new proposals for drug therapies that have been studied for treating AD can be disseminated, thus strengthening research on new drugs and providing updates for the scientific community with regard to promising drug treatments.

In addition, the development of new drugs for treating AD has been marked by the appearance of new possibilities and their subsequent abandonment. This difficulty encourages the need to search for new treatments that could influence the course of AD, through a review of the literature, given that many clinical trials have shown that some drugs are likely to be promising, yet these studies were inconclusive.[18,22]

OBJECTIVE

The present study had the aim of conducting a review, among publications indexed in scientific databases, of the studies on drug and chemical groups that have been investigated in relation to treating AD over the last five years, highlighting those with promising results in terms of their propensity to modify the course of AD.

METHODS

This study consisted of a narrative review conducted through a qualitative assessment on the articles analyzed. The search was conducted in the PubMed database (MEDLINE) (http://www.ncbi.nlm.nih.gov/pubmed/), Cochrane Library database (Cochrane Collaboration) (http://www.cochranelibrary.com/) and SciELO database (Bireme) (http://www.scielo.br/). MeSH (Medical Subject Headings) and DeCS (Descriptors in Health Sciences) descriptors were used. The descriptors "Alzheimer disease", "Molecular Mechanisms of Pharmacological Action" and "Drug Therapy" were used alone or in combination, as follows: "Alzheimer disease"; "Alzheimer disease" AND "Molecular Mechanisms of Pharmacological Action" AND "Drug Therapy"; "Alzheimer disease" AND "Molecular Mechanisms of Pharmacological Action"; "Alzheimer disease" AND "Drug Therapy". Studies in the English, Spanish and Portuguese languages were taken into consideration. We set a filter to limit the search to articles published from January 2009 to October 2015.

In addition, the review was divided into two stages. In the first stage, only review articles were selected, including narratives, systematic reviews and systematic reviews with meta-analyses. At this stage, we sought to answer the following question: "What new drugs that have been studied in relation to treating AD would be capable of influencing the course of the disease?" The second stage involved a search for articles that discussed laboratory studies, human studies, observational studies and clinical trials on the drugs or chemical groups found in the first stage. The second search was conducted using the same specifications as in the first search, but the descriptors were modified such that they became "Alzheimer disease" and the name of the drugs or chemical groups.

Articles were identified and all duplicate records were excluded. Initially, the title and abstract were read in order to include original articles in which the main objective was to describe the pharmacotherapy of AD. Therefore, original articles relating to AD that did not include drugs, molecules or substances for pharmacological treatment were excluded. To ascertain the eligibility criteria, we used the manual of the Brazilian Academy of Neurology.[23] The Cochrane classification criteria for risk of bias from the Cochrane Bias Methods Group were used to assess the quality of the articles selected.[24] This classification was made by two researchers and, when necessary, a third researcher gave his opinion.

RESULTS

The search identified 6,888 studies, of which 37 were included in this study (**Figure 1**). All the articles that were in accordance with our inclusion criteria were available as full texts.

Among the articles selected for this study, the United States were seen to be the most important source country for publications, with 15 articles (40.5%); followed by Germany, with 4 articles (10.8%), and Canada, with 3 articles (8.1%). Regarding the quality of the articles accessed in the first part of this review, 7 (26.5%) were identified as presenting low risk of bias, 12 (46.1%) were identified as presenting unclear risk of bias and 7 (26.5%) were identified as presenting high risk of bias. In all the articles selected for this study, the percentages were 12 (32.5%), 14 (37.8%) and 11 (29.7%), respectively for the three categories of quality (**Table 1**).

In an attempt to gain better insight into the pharmacological substances found in this review, they were classified using chemical groups as described by the ATC/DDD of the World Health Organization, whenever possible. These groups were classified based on their action on therapeutic targets relating to the course of the disease. There were groups under investigation that effectively act on the course of the disease, on targets relating to physiopathology that have not been well elucidated, and groups with therapeutic targets not clarified for the disease course. There was another group that acts on alternative therapeutic targets that have an association with the newly discovered pathophysiological pathways of AD; this group was classified as an alternative therapeutic target for the course of the disease. There was also the group of substances in which the mechanism of action of the drug is not related to any specific therapeutic target, but associated with pathophysiological mechanisms already accounting for AD; this group has been classified as a group of potential modifiers of the course of the disease without specific therapeutic target (**Table 2**).

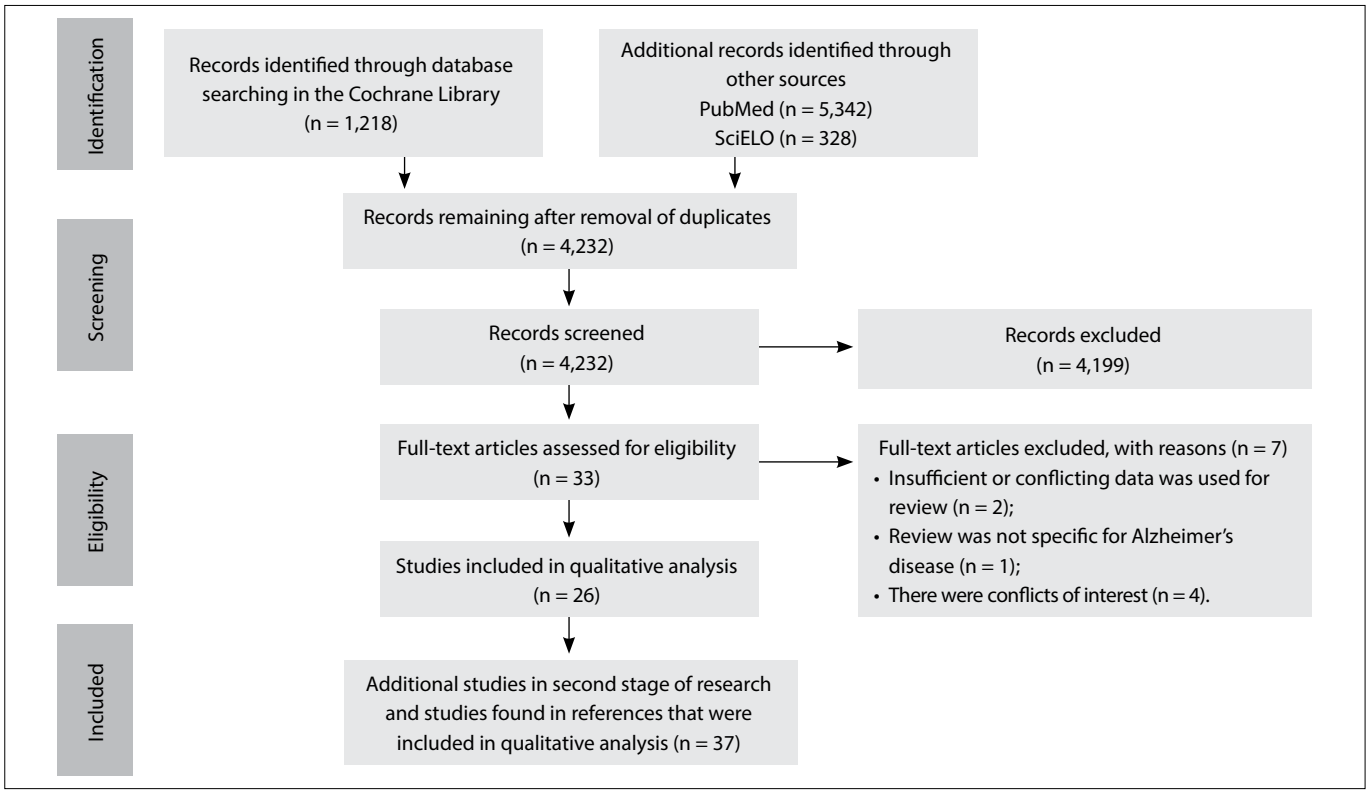

Figure 1. Flowchart of article selection

Table 1. Results from the articles selected for this study

Reference	Authors, year and country	Therapeutic classes	Results basis	Study design	Cochrane risk of bias classification*
18	Léon et al., 2013 (England)	Cholinesterase inhibitors; statins: lipid-modifying agents; antioxidants; chelating agents	Clinical evidence	Narrative review	Unclear
19	Konrath et al., 2013 (Brazil)	Cholinesterase inhibitors; alkaloids	Not specific	Narrative review	High
20	McGuinness et al., 2013 (Ireland)	Statins: lipid-modifying agents	Phase III clinical trial	Systematic review (randomized with meta-analysis)	Low
21	Rubio-Perez and Morrilas-Ruiz, 2012 (Spain)	Anti-inflammatory agents; cytokines	Not specific	Narrative review	High
22	Appleby et al., 2013 (USA)	Agents for treating diabetes mellitus; nicotinic receptor agonists; phosphodiesterase inhibitors	Clinical evidence	Narrative review	Unclear
25	Pettenati et al., 2003 (Italy)	Cholinesterase inhibitors; immunomodulators; anti-inflammatory agents; NMDA receptor antagonists; antioxidants; phospholipase A2 inhibitors; nootropic drugs without elucidated mechanism of action for Alzheimer's disease; hormone therapy agents; chelating agents	Clinical evidence	Narrative review	Unclear
26	Sun et al., 2012 (China)	Cholinesterase inhibitors; muscarinic agonists; immunomodulators; anti-inflammatory agents; statins: lipid modifying agents; antioxidants; chelating agents; antihypertensive agents	Clinical evidence	Narrative review	Unclear
27	Yoo and Park, 2012 (Korea)	Terpenoids; antioxidants	Not specific	Narrative review	High
28	Dodel, 2013 (Germany)	Immunomodulators	Clinical evidence	Narrative review	Unclear
29	Mikulka et al., 2014 (USA)	Immunomodulators; secretase inhibitors; Inhibitors or modulators of beta and gamma-secretase	Phases I, II and III clinical trial	Systematic review (with clinical trial)	Low
30	Shukla et al., 2012 (USA)	Immunomodulators; cyclin kinase-5 dependent modulators	Not specific	Narrative review	High

Table 1. Continues...

Reference	Authors, year and country	Therapeutic classes	Results basis	Study design	Cochrane risk of bias classification*
31	Doody et al., 2014 (Germany)	Immunomodulators	Phase III clinical trial	Randomized clinical trial (double blind)	Low
32	Salloway et al., 2014 (USA)	Immunomodulators	Phase III clinical trial	Randomized clinical trial (double blind)	Low
33	Enciu and Popescu, 2013 (Romania)	Anti-inflammatory agents	Clinical evidence	Narrative review	Unclear
34	Feng and Wang, 2012 (China)	Anti-inflammatory agents; antioxidants; phospholipase A2 inhibitors	Not specific	Systematic review	High risk of bias
35	Wolfe, 2012 (USA)	Anti-inflammatory agents; Inhibitors or modulators of beta and gamma-secretase; chelating agents	Clinical evidence	Narrative review	Unclear
36	Ghosh et al., 2012 (USA)	Inhibitors or modulators of beta and gamma-secretase	Phase II clinical trial	Narrative review	Low
37	Hopkins, 2011 (USA)	Inhibitors or modulators of beta and gamma-secretase	Phase III Clinical trial	Short report	Unclear
38	Piccinni et al., 2013 (Italy)	Inhibitors or modulators of beta and gamma-secretase	Not specific	Narrative review	High
39	Eschecerria et al., 2012 (USA)	Nicotinic receptor agonists	Clinical evidence	Narrative review	Unclear
40	Freiherr et al., 2013 (Germany)	Agents for treating diabetes mellitus	Clinical evidence	Narrative review	Unclear
41	Morris and Burns, 2012 (USA)	Agents for treating diabetes mellitus	Clinical evidence	Narrative review	Unclear
42	Xu et al., 2015 (China)	Agents for treating diabetes mellitus	*In vitro*, in laboratory	Experimental study	High
43	Papadopoulos et al., 2013 (Canada)	Agents for treating diabetes mellitus	*In vivo*, in laboratory	Experimental study	High
44	Fukasawa et al., 2012 (Japan)	Retinoids	*In vivo*, in laboratory	Experimental study	High
45	Wong et al., 2013 (USA)	Statins: lipid-modifying agents	Not specific	Systematic review (randomized with meta-analysis)	Unclear
46	Calcul et al., 2012 (USA)	Polyphenols	Clinical evidence	Narrative review	Unclear
47	García-Osta et al., 2012 (Spain)	Phosphodiesterase inhibitors	Clinical evidence	Narrative review	Unclear
48	Evans et al., 2014 (USA)	Antioxidants; NMDA receptor antagonists	Phase III clinical trial	Randomized controlled clinical trial	Low
49	Revett et al., 2013 (Canada)	Antioxidants; NMDA receptor antagonists	Not specific	Narrative review	High
50	Kellermann et al., 2011 (Germany)	Antioxidants	Phase III clinical trial	Systematic review (randomized with meta-analysis)	Low
51	Freund Levi et al., 2014 (USA)	Antioxidants	Phase II clinical trial	Randomized controlled clinical trial	Low
52	Sun et al., 2012 (USA)	Phospholipase A2 inhibitors	Not specific	Narrative review	High
53	Koliaki et al., 2012 (Greece)	Nootropic drugs without elucidated mechanism of action for Alzheimer's disease	Phase III clinical trial	Randomized controlled clinical trial	Low
54	Maki and Henderson, 2012 (USA)	Hormone therapy agents	Randomized clinical trial	Narrative review	Low
55	Anekonda and Quinn, 2011 (Canada)	Antihypertensive agents	Clinical trials	Narrative review	Low
56	Valenzuela et al., 2012 (Australia)	Antihypertensive agents	Randomized controlled clinical trial	Narrative review	Low

*We used the classification criteria of the Cochrane risk of bias to access the quality of the articles. In the case of review articles, the results from the selected articles were accessed in order to ascertain the evidence that was present in the kind of study that generated the results. Consequently, the Cochrane classification was made based on this evidence.

Table 2. Classification of pharmacological groups that showed the prospect of changing the course of the disease, with regard to action on therapeutic targets

Class	Agent	Characteristics
Groups with therapeutic targets not clarified in relation to the course of the disease	Cholinesterase inhibitors	Investigated the positive relationship of acetylcholinesterase with formation of Aβ peptide and increased density, with subsequent deposition in neurons.
	Terpenoids	Capable of reducing levels of Aβ and promoting its degradation. Investigated the ability to reduce the production of Aβ in the process modulated by the APP.
	Immunomodulators	Showed the ability to restrain deposition and formation of Aβ plaque and also assisting in the clearance of the oligopeptide in the CNS.
	Agents for treating diabetes	Investigated the possible association for reducing the aggregation of Aβ oligomers through cleavage of this peptide.
	Stains: lipid-modifying agents	Promoted reduced formation of Aβ plaque in individuals with the APOE e4 allele. Considered to be multitargeted drugs because they lowered cholesterol levels in the brain, had anti-inflammatory properties and improved the microcirculation, which reduced formation of NFTs.
	Polyphenols	Increased the clearance of tau protein when it was unstructured.
	Muscarinic agonists	Capable of modifying the concentration and aggregation of Aβ in cerebrospinal fluid, thus decreasing formation of NP.
	Nicotinic receptor agonists	Acted on nicotinic acetylcholine receptors, thereby preventing hyperphosphorylation of tau protein.
	Retinoids	Suppressed accumulation of Aβ and decreased brain inflammation process.
	Antagonist of NMDA-receptors	Inhibited the neurotoxicity of the excitation process caused by glutamate and reduced hyperphosphorylation of tau protein.
	Antihypertensives: calcium channel blockers	Capable of inhibiting the influx of calcium ions in Aβ channels, thereby avoiding apoptosis and disproportionate signaling between neurons.
Groups with alternative therapeutic targets within the course of the disease	Inhibitors or modulators of gamma or beta-secretase	Inhibited or modulated enzymatic activity, thereby controlling production of Aβ in the brain and formation of insoluble aggregates.
	Phosphodiesterase inhibitors	Decreased gene expression via cAMP that was involved in production of tau protein and therefore minimized disruption process.
	Cyclin-dependent kinase modulators (CDK 5)	Modulated hyperphosphorylation of tau protein through a cyclin-dependent kinase process.
	Phospholipase A2 inhibitors	Decreased excitotoxicity through inhibition of phospholipase A2, and increased clearance of tau when it was unstructured.
Possible modifiers of the course of the disease without any specific therapeutic target	Anti-inflammatory agents	Possibility of action by this class of drugs through mediation of inflammatory processes caused by pro-inflammatory signals involving cytokines that are characteristic in regions with Aβ plaque.
	Nootropic drugs	Increased cognitive performance in AD.
	Hormone therapy agents: hormones	Provided preventive action against Alzheimer's disease in women undergoing hormone replacement therapy.
	Antioxidants	Reduced reactive oxygen species (ROS), thus giving rise to neuroprotection.
	Chelating agents	Modulated neurotoxicity caused by free radicals.

NP = neuritic plaque; NFT = neurofibrillary tangles; CNS = central nervous system; APP = amyloid precursor protein; Aβ = amyloid-beta; APOE = apolipoprotein E; NMDA = N-methyl-D-aspartate; cAMP = cyclic adenosine monophosphate; CDK5 = cyclin-dependent kinase 5.

DISCUSSION

Cholinesterase inhibitors

Alkaloids: huperzine, aporphyrin, lycorine and quaternary beta-carboline

Although this is a chemical group used for symptomatic treatment of AD in the clinical phase of the disease, its possible mechanism of action with regard to changing the course of the disease has been investigated. This source is based on the positive relationship of the enzyme cholinesterase (ChE) with formation of Aβ oligomers and increased density, with subsequent deposition in neurons.[25]

Cholinesterase inhibitors (ICHE) appear to be promising drugs for treating AD, based on the action of some compounds of this enzyme. Inhibiting alkaloids such as physostigmine and galantamine are used in conventional treatment. Thus, some natural alkaloids have been investigated in an attempt to highlight changes to the course of AD. Among these compounds are the steroidal alkaloid triterpene, which promotes non-competitive inhibition; quinolizidine and lycopodium alkaloids such as huperzine, which promotes competitive inhibition; isoquinolines such as aporphyrin and benzylisoquinoline, which are non-competitive compounds, and galantamine and lycorine, which are competitive; and indole alkaloids, which are divided into indole alkaloids, monoterpenes and physostigmine, which are competitive, and quaternary beta-carbolines, which are non-competitive.[18,19,25]

Out of all of these, we highlight huperzine as a potent, selective and reversible inhibitor of AChE. This is used in cases of myasthenia

gravis, organophosphate poisoning and schizophrenia. Clinical trials on huperzine have shown that its use improves short-term memory, but there is need for more robust studies in order to prove its effectiveness and minimal toxic effects, which are due to its high selectivity and its ability to cross the blood-brain barrier (BBB).[19,26]

Muscarinic agonists

Xanomeline and milameline

These substances are capable of modifying the CSF concentration of Aβ aggregation and decreasing formation of amyloid plaque.[25] Xanomeline and milameline have the ability to cross the BBB and have important effects relating to cognitive improvement, but they also have significant side effects on the cardiovascular and gastrointestinal tracts.[26]

Terpenoids

Ginseng

Ginsenosides are natural compounds extracted from the plant *Panax ginseng*. They have been the subject of *in vitro* clinical trials aimed at reducing the levels of Aβ and promoting its degradation. They have the ability to suppress production of Aβ, in a process modulated by APP. The results from animal studies have shown that ginsenosides are effective in relation to attenuating some neuroinflammation markers, improving spatial perception and increasing synaptic density.[27]

Immunomodulators

Gammagard Liquid, bapineuzumab, solanezumab, crenezumab, gantenerumab and Affitope

Passive immunization has been shown to reduce the brain levels of Aβ oligomers, increase their clearance and redistribute them through the circulatory system, to other brain areas and tissues that favor their elimination.[25] One immunoglobulin with important effects in relation to AD, which effectively binds to Aβ oligomers and increases their clearance is Gammagard Liquid. The monoclonal antibodies bapineuzumab, solanezumab, crenezumab and gantenerumab have also been tested for the same purpose.[25,28-32]

Active immunization with synthetic peptides has been tested with the aim of reducing Aβ aggregation caused by the pro-inflammatory signals involved in AD. However, some vaccines that have been tested in relation to AD have presented certain difficulties relating to side effects such as encephalitis and inflammation in the CNS.[25,28] One example is Affitope, a patented drug consisting of synthetic peptides with a mechanism of action on AD that so far remains not very well understood.[29]

Many vaccines and drugs relating to monoclonal antibodies have been tested and are protected by patents. These are very effective with regard to active immunization for treating AD. However, the big challenge is to ascertain how safe these interventions are, because some promising forms of immunotherapy have shown serious toxic effects.[26,29]

Anti-inflammatory drugs

Prednisone, prednisolone, ibuprofen, rofecoxib, naproxen, flavonoids, sulindac sulfide and indomethacin

The inflammation caused by proinflammatory signals that are highlighted by cytokines during the process are characteristic of regions of Aβ plaque mediated by astrocytes and microglia cells. This process promotes continual deposition of Aβ, and therefore some anti-inflammatory drugs have been tested.[21,25,26,33,34]

It is noteworthy that prednisone and its active metabolite prednisolone are effective in reducing formation of Aβ oligomers *in vitro*, but their effectiveness has not been proven in phase II and III clinical trials. Evidence has emerged from studies on animals that selective inhibitors of cyclooxygenase (ICOX2) are effective, but they are not recommended for chronic treatment.[21,25]

Ibuprofen, rofecoxib and naproxen have been shown to be able to reduce Aβ levels in animals but not cognitive decline in human trials. However, the possibility that these might help reduce the incidence of the disease rather than its course has recently been investigated.[21,25,26,33] It is important to highlight natural compounds with anti-inflammatory activity, such as flavonoids. There is evidence from experimental studies on animals that flavonoids prevent cognitive impairment. However, this has been contradicted in some observational studies.[4]

This drug class can be considered to have multiple targets for AD, because some anti-inflammatory drugs have presented activity modulating gamma-secretase, an enzyme involved in formation of NP and NFTs. Ibuprofen, sulindac sulfide and indomethacin were the first non-steroidal anti-inflammatory drugs (NSAIDs) to be reported to decrease Aβ through this mechanism. A Phase III clinical study on r-flurbiprofen in 2009 showed that this agent had good capacity for reducing Aβ, thereby changing the course of AD.[35]

Inhibitors or modulators of beta and gamma-secretase

Pirezenpine, pseudopeptides based on beta-secretase inhibitor, hydroxyethylene, hydroxyethylamine base, carbinamine base, non-peptidomimetics, macrocyclic inhibitors, acylguanidine base, aminoimidazole base, aminohidantoin, aminoquinozoline base, molecules with diversification of non-peptide substrates, semagacestat, avagacestat and malonamide

The preponderant factors in the physiopathology of AD via amyloids involve outflow of Aβ from the brain and formation of insoluble aggregates. The enzymes beta and gamma-secretase are heavily involved in this process. Some drugs that

have been studied are able to interfere with the functionality of these enzymes, thereby controlling these pathogenic factors. Although it has been questioned whether enzymes are an important therapeutic target in relation to AD, some molecules that are protected by patents have been studied with regard to such treatments.[29,36-38]

Pirezenpine, a muscarinic receptor antagonist for acetylcholine, has shown evidence of capacity for regulating the activity of beta-secretase. In studies conducted in Japan, another molecule called CTS-21166 (which is an analog of pirezenpine) has been shown to decrease formation of Aβ plaque *in vivo*.[39] Pseudopeptides that inhibit beta-secretase enzymatic activity are noteworthy: replacement of a leucine-alanine statin derivative has led to a variety of potent inhibitors. These include hydroxyethylene, hydroxyethylamine base, carbinamine base; non-peptidomimetics, macrocyclic inhibitors (molecules modified for stability of bioactivity), acylguanidine base, aminoimidazole, aminohidantoin base, aminoquinozoline molecule-based diversifications and non-peptide substrates.[36]

Some compounds such as gamma-secretase inhibitors are currently being studied. Among these are semagacestat, avagacestat and benzodiazepine (under patent), and malonamide. The drug-modulating activity of this enzyme comprises several perspectives because it has lower toxicity than that of inhibitors.[35]

The biggest challenge is to put greater amounts of selective gamma-secretase into the neurons affected by AD.[29,35] It is also important to emphasize the challenge of achieving effectiveness with regard to inhibiting or reducing cognitive decline coupled with absence of toxicity, in phase II and III studies. It is possible that structural modifications to these molecules will improve their effectiveness.[36,37]

Agents for treating diabetes mellitus

Intranasal insulin, rosiglitazone and pioglitazone

Some drugs in this class have been emphasized for treating AD because they have shown evidence of effectiveness in decreasing the accumulation of Aβ oligomers in *in vitro* brain studies. There is also evidence that they decrease the neuronal inflammatory processes that lead to cell death. Intranasal insulin may be an effective way to prevent or treat this disease, since it has significant action in the hippocampus (a region with a large concentration of insulin receptors), thereby improving memory.[40,41]

Some glitazones have been studied as important drugs for AD, and rosiglitazone and pioglitazone are among these. However, no precise conclusions regarding the evidence for their effectiveness have been reached, and some researchers have condemned them as unpromising drugs.[22,42,43]

Retinoids

Tamibarotene

Retinoids have been attributed with great prospects because of the ability of the oligomers to suppress accumulation of Aβ and to decrease some brain inflammation. One example of these drugs is tamibarotene, which has presented promising results. These results showed its effectiveness in stimulating emotional function, through regeneration of cholinergic and glutaminergic nodes. In addition, treatment with this drug has shown improved cognition and orientation with regard to timelines. The expectations for this drug have been strengthened through its good tolerability with prolonged use.[44]

Statins: lipid-modifying agents

Simvastatin and lovastatin

Action by the apolipoprotein E subtype APOE4, which is expressed by the allele APOE Ɛ4, can lead to greater propensity for binding between Aβ oligomers to form NPs. It can also increase the activity of glycogen synthase kinase 3beta (GSK 3beta), thereby causing hyperphosphorylation of tau proteins and formation of NFTs. In some epidemiological studies, statins have shown significant reduction of formation of Aβ plaque in individuals with this protein subtype.[20,26]

Additionally, one form of action that is already well known for this drug class and which makes it a multitarget drug for AD is its lipid-lowering action. This association is based on scientific evidence linking reduction of systemic cholesterol to neuron preservation in some cases of dementia. There is also evidence of a mechanism for reduction of cholesterol levels in the brain that leads to reduction of NFTs and some pleiotropic effects attributed to anti-inflammatory properties.[20,45]

Use of statins may be an important adjunct in treating AD. Some physicians have advocated their use as a preventive measure for patients who have a dementia risk profile mediated by cerebral vasculature. However, this class of drugs (such as simvastatin and lovastatin) has great ability to cross the BBB. Therefore, the priority in using these drugs is to promote improvement of circulation loci in the CNS. On the other hand, there is insufficient evidence to recommend their use as a preventive measure or for modifying the course of AD. Furthermore, it needs to be borne in mind that statins have a risky safety profile and there may be hepatic impairment and risk of rhabdomyolysis at doses that would be effective for continuous treatment of AD.[18,20]

In a meta-analysis on separately evaluated cross-sectional and longitudinal observational studies (total of 19), the cross-sectional studies showed that statins had a protective effect, and it was noted that use of statins was associated with a reduced risk

of developing AD and other forms of dementia. However, progress in such studies is still restricted by bias in some of them.[45]

Nicotinic receptor agonists

Nicotine and cotinine

Cotinine is a metabolite of nicotine and it has pharmacological effects similar to those of nicotine. It acts on nicotinic acetylcholine receptors but with lower side effects. Its pharmacodynamic properties have been investigated with regard to treating AD because of its neuroprotective capacity over the course of the disease. Cotinine is able to prevent hyperphosphorylation of tau protein denaturation and thus has been shown to reduce neuronal death *in vitro*. Use of this substance has shown evidence of memory improvement, along with a certain degree of safety profile, in phase II clinical trials.[22,46]

Polyphenols

Curcumin

Some polyphenols have been tested on the basis of the hypothesis that they increase tau protein clearance when they are destructured, as in AD. Thus, their effectiveness has been highlighted in terms of reductions of NFT formation and neuronal death. Curcumin is noteworthy: it is classified as anti-tau, given that it increases production of the anti-inflammatory cytokine IL-4 and reduces tau Aβ levels *in vivo*. It can be highlighted that many molecules in this class of natural products are being studied and some synthesis routes have been patented.[39]

Phosphodiesterase inhibitors

Vinpocetine, rolipram, roflumilast, vardenafil, sildenafil, tadalafil and papaverine

Phosphodiesterase inhibitors have been tested in relation to AD because they act by decreasing gene expression in the cAMP pathway for production of tau and thereby minimize the disintegration process. This leads to a possible reduction in formation of NFTs. These drugs have shown effectiveness in animal testing, in which they have restored cognitive impairment and memory. Among the most effective drugs are vinpocetine, rolipram, roflumilast, vardenafil, sildenafil, tadalafil, papaverine and other molecules under patent.[22,47]

NMDA receptor antagonists

D-cycloserine and nitromemantine

In the literature, there are studies that have justified increases in hyperphosphorylated tau protein levels and increases in production of βA oligomers through the hypothesis of loss of neuronal homeostasis. This hypothesis is explained by increased glutamatergic activity, i.e. there is an increase in the action of glutamate at NMDA receptors, which leads to excitotoxicity and cell death. Thus, some drugs have been tested in an attempt to modulate NMDA receptors so that they can decrease the formation of amyloid-β plaque and NFTs in AD.[25,48,49]

D-cycloserine is an antibiotic capable of modulating the activity of NMDA receptors. It is capable of improving memory and cognitive processes. However, no evidence for its clinical effectiveness has been shown in randomized trials. This means that in studies on AD, this drug has not presented extensive activity. However, it was argued in a recent study that making changes to its molecule would be instrumental for continuing with new tests towards achieving better results.[25] Nitromemantine is another drug that has shown good results in animals, through high specificity for NMDA receptors, in addition to having fewer side effects.[49]

Cyclin-dependent kinase modulators: CDK 5

Aminothiazole and roscovitine

The subtype of cyclin-dependent kinase known as CDK 5 is an enzyme that has the function of regulating higher neuron life cycles. However, it is also fundamental to the process of hyperphosphorylation of tau proteins. Drugs that show the prospect of capacity for modulation of their activity in order to treat AD now exist. While most of the drugs tested have not shown effectiveness that would justify their use in AD therapy, aminothiazole and roscovitine have shown promise in this regard. These alternatives have shown good efficacy *in vitro*, but they binds to the CDK 5 site without much specificity, thereby leading to side effects that would be serious *in vivo*.[30]

Antioxidants

Vitamin E, selegiline, Ginkgo biloba*, resveratrol, vitamin B12, carotenoids, ascorbic acid, catalase, glutathione peroxidase, caffeine, selenium, melatonin, omega-3, silibinin, palmatine, berberine and ubiquinone*

Some studies have shown that cellular oxidative stress is a major aggravating factor in the course of AD. Before the pathophysiological process takes place, some protein, lipid and glicidic oxidation may contribute towards the inflammatory processes and result in emergence or progression of NP and NFTs. Therefore, some compounds with antioxidant activity have been tested with a view to prevention and treatment of AD. These have the capacity to reduce reactive oxygen species (ROS) and interfere with the pathophysiological course of the disease.[18,34]

One example of this pharmacological subgroup that has been a major subject of study is the vitamin E substance known as α-tocopherol. Clinical trials have shown the ability of this compound to reduce the chance of developing AD over a four-year follow-up period by about 2.5 to 4.0-fold. Although there is sufficient evidence to show that this substance can influence the course of AD, there are few studies that have measured its great potential as an adjunct to treatment.[25,26,34,48]

Another drug that has shown promise in studies on AD is selegiline. Eight clinical trials on this drug involving twelve evaluators have shown evidence of improvement in mood and behavior. Additionally, significant benefit for memory has been shown in a meta-analysis. Although the results relating to this drug have been good, there is not enough evidence to include it in treatments for AD.[25,26,34]

Ginkgo biloba produces a substance belonging to the class of cyclic diterpenes that is a nootropic drug that has significant effects as a multitargeted drug for treating AD. It is effective in this treatment because of its ability to increase blood flow in the microcirculation and its antioxidant properties, which prevent reduction of synapses and increase the production of neurotrophic factors relating to neuronal apoptosis in AD. Therefore, it is capable of causing behavioral improvements regarding the damage induced by Aβ and positive effects on perception and memory. This substance has significant side effects that have been investigated. These include bleeding when anticoagulation therapy or drugs likely to cause bleeding are used concomitantly. However, no side effects have been seen when it is used alone.[25,27,34,50]

Other drugs with antioxidant action in relation to AD include resveratrol (a compound from grapes), vitamin B12, carotenoids, ascorbic acid (vitamin C), catalase, glutathione peroxidase, caffeine, selenium, melatonin, omega 3, silibinin flavonoids, palmatine alkaloids, berberine and ubiquinone terpenoids.[26,34,51]

Phospholipase A2 inhibitors

Methyl arachidonoyl fluorophosphate, arachidonoyl trifluoromethyl ketone, Ginkgo biloba*, curcumin and epigallocatechin gallate*

Some studies have shown that abnormal phospholipase A2 (PLPA2) activity implies the existence of some neurodegenerative pathogens, including AD. Although this association is currently not well understood, it is believed that prolonged neuron exposure to Aβ may gradually give rise to mitochondrial dysfunction and stimulate activation of PLPA2 through increasing ROS and excitotoxicity.[25,34]

Two compounds that have shown effective results *in vitro* with regard to this mechanism are methyl arachidonoyl fluorophosphate and arachidonoyl trifluoromethyl ketone. These have shown good ability for modulating the properties of neuronal membranes and increasing protection against the neuronal impairment caused by Aβ plaque. Studies have shown a correlation between neuroexcitatory PLPA2 glutamate receptors and NMDA capability in relation to stimulating production of ROS through NADPH oxidase. *Ginkgo biloba*, curcumin and epigallocatechin gallate (polyphenols) are substances capable of protecting against the pathological course of AD through this mechanism.[34,52]

Nootropic drugs without an elucidated mechanism of action for Alzheimer's disease

Nicergoline, piracetam and aniracetam

This pharmacological class covers drugs that enhance cognitive performance and, as such, are targets for evaluation with a view to treating psychobehavioral symptoms relating to dementia. In addition, they have the significance of being drugs that have passed through phase IV clinical studies, have been on the market for a while and have some degree of safety profile.[25,53]

Nicergoline, a derivative of ergot, has positive effects on behavior and cognition in AD. Piracetam is a derivative of gamma-aminobutyric acid (GABA) that binds to the neuronal membrane, thus promoting formation of active phospholipid complexes. This increases lamellar restoration, thereby improving perception and memory. *In vivo* studies have shown evidence that this improves memory retention. However, some reviews on this drug have not shown any evidence for its applicability in treatments for AD.[25]

Aniracetam is a drug that has shown good tolerability in relation to treating AD. Experimental data have suggested that this medication presents interactions with multiple neurotransmitter systems. In monotherapy, it has shown clinical results that are more effective than those from conjugated cognition therapy and ICHE monotherapy for starting the treatment. Over the long term, it has shown improved functional capacity in relation to depression and improvement in the physiopathology of dementia only when combined with ICHE. However, it has been found to present some adverse events that counter its supposed effectiveness and which do not corroborate its indication for treating AD.[53]

Agents for hormone therapy: hormones

Estrogen, conjugated estrogens and medroxyprogesterone

It has been hypothesized that hormone levels in the postmenopausal period provide physiological mechanisms that trigger AD. Thus, some research has been developed in order to investigate this idea. Based on the notion that decreased estrogen levels

combine with an increased chance of developing AD, studies have attempted to evaluate therapy using raloxifene. However, this issue remains controversial. A study on postmenopausal women on estrogen replacement therapy and without this therapy revealed that in the first group, 4% of the women had AD, and that in the second group, 10% had AD. However, reviews and meta-analyses indexed in the Cochrane Library have not found any evidence to show that estrogen replacement therapy is effective for preventing and treating AD.[25,54]

Some studies have shown that therapy consisting of a combination of estrogen and progesterone before the menopause was able to reduce the risk of AD, although, this association may increase the risk of developing AD after the age of 65 years. It is noteworthy that conjugated estrogen therapy in association with medroxyprogesterone showed a clear clinical response in terms of memory and aphasia among both young women and postmenopausal women.[54]

Chelating agents

Desferrioxamine and copper and zinc chelating agents

Chelating agents exhibit efficacy through removal of excess ferric ions and other ions such as copper, aluminum and zinc, which may be related to neurotoxicity through formation of free radicals that bind to Aβ peptides. One drug that has been studied for this purpose in relation to treating AD is desferrioxamine. However, it has shown retinoid toxicity.[35] Copper and zinc chelating agents have also shown the ability to mediate aggregation of Aβ peptides. However, many of these drugs present concerns regarding their safety profile, given that they are responsible for causing optic neuritis.[18,25,26]

Antihypertensive agents: calcium channel blockers

Isradipine

Antihypertensive drugs that are calcium channel blockers reduce the influx of Ca^{2+} ions into Aβ channels, thereby minimizing and reducing the neurotoxicity of Aβ formation *in vitro*. Isradipine has been tested in clinical trials as monotherapy and has already shown positive effects in relation to treating AD based on this mechanism.[55]

Six broad experimental studies that were double-blind, randomized and placebo-controlled investigated about 50 antihypertensive medications for treating dementia and cognitive decline. These studies suggest that treatment with antihypertensive drugs may play an important role in preventing dementia, thereby producing notable cognitive improvement. The important effect of calcium channel blockers on this line of treatment was emphasized.[56]

The effectiveness of this alternative drug treatment for AD becomes more pronounced when antihypertensive agents are used in association with other classes of drugs. A combination of calcium channel blocker, angiotensin-converting enzyme (ACE) inhibitor and diuretic was found to have reduced the incidence of dementia in AD cases after two and four years of follow-up by 50% and 55% respectively.[56] A combination consisting only of ACE inhibitor and diuretic reduced the occurrence of dementia by 31%. Thus, this suggested that treatment with calcium channel blockers helped in preventing dementia.

Nonetheless, the evidence from studies remains insufficient to be able to state that this class of medication should be used for treating AD. Therefore, it is essential to conduct clinical studies with greater robustness regarding use of antihypertensive treatment, since the evidence suggests that the effectiveness of this class of drugs with regard to prevention of AD relates to specific cases such as dementia of microcirculatory origin.[26,56]

CONCLUSION

From the studies analyzed, it could be seen that there is a current trend among researchers towards separating out the dementia phase from the preclinical phase at which AD usually usually starts. This trend has influenced the search for new drugs. In addition, we can conclude from the results of this study that there are no promising drugs capable of providing effectiveness and safety. In this context, immunomodulators are more likely to become drugs capable of influencing the course of AD, because the studies selected showed better quality and the results were promising. However, the toxicity of these drugs for treating AD constitutes a major obstacle. This was also observed in relation to new drugs that can interfere with alternative targets, such as inhibitors or modulators of gamma or beta-secretase, phosphodiesterase inhibitors, cyclin-dependent kinase modulators (CDK 5) and phospholipase A2 inhibitors. However, the evidence relating to these drugs is weak, as shown by the quality of the articles accessed in this review. No robust studies have yet been conducted, and this is due to the high toxicity of these drugs in relation to treating AD.

One alternative for conducting successful searches relating to the safety and effectiveness profiles of drugs for treating AD would be to use molecular modeling investigations or combination therapies such as statins and antihypertensive drugs. However, even though the articles accessed in relation to these therapeutic groups were of good quality, these are drugs without any clear mechanism of action. These drugs would probably be effective for some types of AD, such as disease of vascular origin in the preclinical phase, and they might not interrupt the course of the disease.

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Intrauterine thrombosis of umbilical artery – case report

Trombose intrauterina de artéria umbilical – relato de caso

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KEY WORDS:
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PALAVRAS-CHAVE:
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Retardo do crescimento fetal.
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Desenvolvimento embrionário e fetal.

ABSTRACT

CONTEXT: Umbilical cord thrombosis is related to greater fetal and perinatal morbidity and mortality. It is usually associated with umbilical cord abnormalities that lead to mechanical compression with consequent vascular ectasia. Its correct diagnosis and clinical management remains a challenge that has not yet been resolved.

CASE REPORT: This study reports a case of umbilical artery thrombosis that occurred in the second half of a pregnancy. The umbilical cord was long, thin and overly twisted and the fetus presented severe intrauterine growth restriction. The clinical and histopathological findings from this case are described.

CONCLUSIONS: This case report emphasizes the difficulty in diagnosing and clinically managing abnormalities of intrauterine life with a high chance of perinatal complications.

RESUMO

CONTEXTO: A trombose do cordão umbilical está relacionada com o aumento da morbimortalidade fetal e perinatal. É geralmente associada a alterações do cordão umbilical que levam à compressão mecânica com consequente ectasia vascular. Seu correto diagnóstico e manejo clínico é um desafio que não está ainda bem esclarecido.

RELATO DE CASO: Neste relato se descreve caso de trombose da artéria umbilical de ocorrência na segunda metade da gravidez associada a cordão umbilical longo, fino, excessivamente retorcido, associado a feto com restrição de crescimento intrauterino grave. São descritos seus achados clínicos e histopatológicos correlacionados.

CONCLUSÃO: Este relato de caso reforça a dificuldade diagnóstica e de manejo clínico em alteração da vida intrauterina com grande possibilidade de complicações perinatais.

INTRODUCTION

Vascular thrombosis of the umbilical cord has been described as an abnormality that increases fetal morbidity and mortality during intrauterine life and the perinatal period. Its incidence is estimated to be one case in every 1300 gestations and up to one in every 250 deliveries when only high-risk pregnancies are taken into consideration.[1] The main causes of this phenomenon are abnormalities of the umbilical cord, such as: excessive twisting, presence of a true knot, very long or very short cord, loops around the body or cervical region, marginal or velamentous placental insertion and very thin cord with little Wharton jelly. Such situations may lead to vascular ectasia followed by thrombosis with a high risk of impairment of fetal wellbeing.[2,3] In this article, we report a case of umbilical artery thrombosis that was diagnosed during the prenatal period with development of significant intrauterine growth restriction.

CASE REPORT

The patient was 30 years of age, in her second pregnancy, without any relevant personal or family history, and had been attending prenatal care for low-risk pregnancies. Her previous pregnancy had run its course without any complications, with a neonate born at term with adequate weight.

At 32 weeks of gestation in the second pregnancy, the uterine height was observed in a routine consultation to be less than what would be expected for the gestational age. The patient was referred for ultrasonography, from which the fetal weight was diagnosed as below the 5th percentile for the gestational age, with a single umbilical artery and presence of a cervical umbilical cord loop. Doppler flow analysis did not show any abnormalities in this examination.

Retrospective analysis on ultrasound imaging on the patient that had been produced during this pregnancy showed that there were no abnormalities of growth, fetal structure or umbilical cord up to the 22nd week (**Figures 1A, B** and **C**). The hypothesis of spontaneous intrauterine umbilical artery thrombosis was raised. Weekly serial ultrasound imaging was started and fetal pulmonary maturation treatment was instituted using corticosteroids.

At 34 weeks of gestation, cessation of fetal growth was observed and also a slight decrease in amniotic fluid volume. Doppler velocimetry on the umbilical artery showed that the pulsatility index value was close to the 90th percentile for the gestational age, with adequate venous flows. It was decided to implement early delivery by means of caesarean section. It was observed during the procedure that the amniotic fluid had the appearance of meconium and that the umbilical cord was thin and approximately 80 cm in length, with excessive twisting (**Figure 2**) and two tight cervical loops.

The newborn was male, with first-minute Apgar of 9 and fifth-minute Apgar of 10, weighing 1080 g. His gestational age from the somatic Capurro method was 34 weeks. He was referred to the neonate intensive care unit only because of low weight. He presented good postnatal evolution and was discharged from hospital on the 37th day of life. The histological analysis showed massive thrombosis in one of the umbilical arteries.

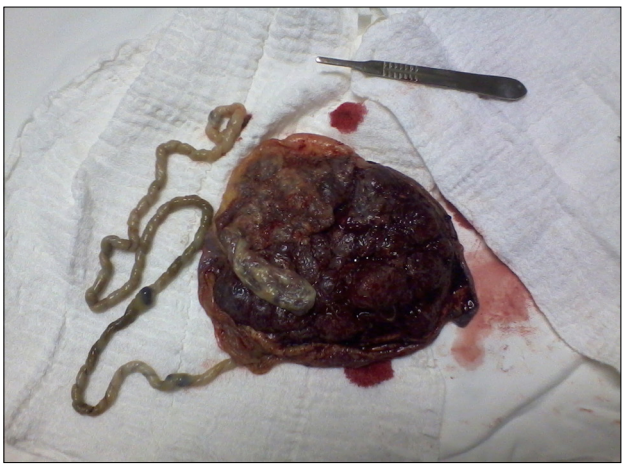

Figure 2. Imaging in which the long, thin, excessively twisted umbilical cord was identified.

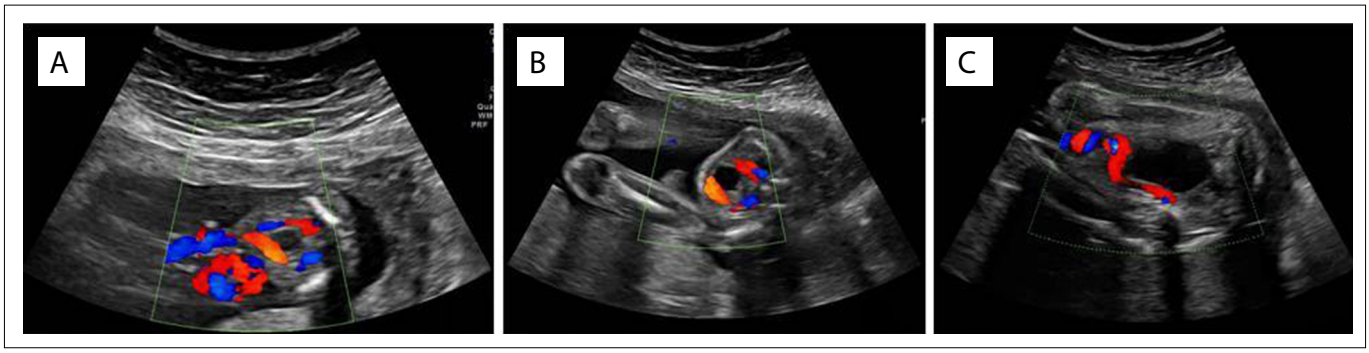

Figure 1. Imaging of the case at 18 weeks (1a) and 22 weeks (1b), and then at 32 weeks (1c), when the "disappearance" of one of the umbilical arteries was noticed.

DISCUSSION

Over recent decades, there have been great advances in prenatal care, especially through the evolution of ultrasound imaging and better understanding of embryology and fetal life. Concomitantly, pregnant women have become more demanding, such that they require their obstetrician and prenatal doctor (who are often faced with threats and lawsuits) to provide safe and precise follow-up.[4] However, situations without any precise diagnosis or clear management are frequently encountered. It is known that umbilical cord thrombosis is associated with adverse fetal and perinatal outcomes, but its diagnosis and follow-up constitutes a clinical challenge.

Umbilical cord abnormalities such as an overly long cord (more than 70 cm) or short cord (less than 35 cm), excessive twisting (more than 0.3 cm/loop, reduced diameter (less than 8.0 mm), anomalous placental insertions and presence of true knots and loops are well-established risk factors for gestational complications and impairment of fetal wellbeing. These abnormalities lead to mechanical compression or blood ectasia in the fetal vascular path.[5-10] Moreover, such abnormalities are related to the etiology of umbilical cord thrombosis, and the risk of their occurrence is generally three times higher in the presence of cord thrombosis.[11] In a study on autopsies conducted on 139 fetuses after spontaneous intrauterine death, vascular thrombosis of the umbilical cord was identified in 20% of the cases, mainly when there was excessive twisting of the umbilical cord and reduction of its diameter.[6] In situations of presence of umbilical cord abnormalities, intensive fetal monitoring during delivery and histological analysis on the umbilical cord are recommended, especially in cases of intrauterine death.[12]

A few studies on umbilical cord thrombosis have already been conducted. The systematized results from the main database in the literature are presented in **Table 1**. There seems to be slight male predominance. Venous thrombosis alone is the most common occurrence, found in approximately 70% of the cases, followed by concomitant arterial and venous thrombosis in 20% of the cases and arterial thrombosis alone in 10% of the cases.[1] It is believed that the incidence of umbilical artery thrombosis alone is very small, ranging from 0.0025% to 0.045% of gestations.[1,3] Although venous thrombosis is more frequent, it is believed that adverse outcomes are more common in arterial thrombosis.[1] In the main published papers on this subject, associations with growth restriction, fetal death, meconium in the amniotic fluid, acute fetal distress during labor and higher rates of emergency caesarian sections have been noted.[2,3,6,13] The most common abnormalities of the umbilical cord associated with umbilical artery thrombosis are: short or long cord, excessive twisting and anomalous placental insertions.[3,11]

Table 1. Search of the literature in medical databases, for cases of vascular thrombosis of the umbilical cord and prenatal diagnosis

Database	Search strategies	Papers found
Medline (via PubMed)	(umbilical cord abnormalities) and (fetal thrombotic vasculopathy) and (intrauterine)	8*
Medline (via PubMed)	(umbilical artery thrombosis)	7*
Lilacs (via Bireme)	(umbilical artery thrombosis)	0
Cochrane Library	(umbilical artery thrombosis) or (umbilical cord abnormalities) or (fetal thrombotic vasculopathy)	0

*Two studies were available through both the first and the second database searches.

CONCLUSIONS

In the case presented here, which occurred in a low-risk pregnancy in which up to the 22nd week there had been no suspicion of abnormality, spontaneous intrauterine umbilical artery thrombosis was detected in the third trimester of pregnancy and was associated with a thin and long umbilical cord, with excessive twisting and cervical loops. Severe intrauterine growth restriction and deterioration of fetal wellbeing were also observed. The diagnosis only became possible through making comparisons with the patient's initial ultrasound screenings, in which both umbilical arteries were clearly identified, with subsequent confirmation through histological analysis. Unfortunately, findings such as cord length abnormality and cord twisting are not commonly identified. In the presence of umbilical cord abnormalities, the risk of complications during intrauterine life, at the time of delivery and during the perinatal period, needs to be taken into consideration. Although the procedure in such cases is not well established, regular monitoring of fetal wellbeing, implementation of pulmonary maturation and early delivery in the event of fetal deterioration are recommended. Fetal monitoring is important because of the risk of adverse outcomes.

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Splenic diffuse red-pulp small B-cell lymphoma associated with hepatitis B virus: a report of two cases

Linfoma esplênico difuso da polpa vermelha, de linfócitos B pequenos, associado ao vírus da hepatite B: relato de dois casos

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KEY WORDS:
Lymphoma.
Lymphoma, non-Hodgkin.
Lymphoma, B-cell.
Hepatitis B.
Hepatitis B virus.

PALAVRAS-CHAVE:
Linfoma.
Linfoma não Hodgkin.
Linfoma de células B.
Hepatite B.
Vírus da hepatite B.

ABSTRACT

CONTEXT: Splenic diffuse red-pulp small B-cell lymphoma is a rare disease, representing less than 1% of all non-Hodgkin lymphomas (NHL). This entity is characterized by involvement of bone marrow sinusoids and peripheral blood. The majority of cases are at an advanced stage when diagnosed. Its pathogenesis is still poorly understood.

CASE REPORTS: We report on two patients with chronic non-replicating hepatitis B virus (HBV) who developed splenic diffuse red-pulp small B-cell lymphoma. Both of them were in stage IV at diagnosis and evolved with aggressive disease. Both of them achieved a complete response through chemotherapy, but one of them died due to infectious complications during bone marrow transplantation. The other decided not to undergo transplantation and continues not to show any evidence of disease today (three years after treatment). Some studies have shown a possible association between B-cell NHL and HBV. Nonetheless, the mechanism through which this oncogenic virus interacts with B-cell NHL is still poorly understood. HBV is lymphotropic and may insert into the host's genome, thus causing overexpression of oncogenes and downregulation of tumor suppressor genes. Therefore, chronic stimulation by HBV can increase B-cell proliferation, which promotes monoclonal expansion of these cells and results in malignancy.

CONCLUSION: HBV may be implicated in the pathogenesis of this lymphoma, although no direct association between these two entities could be proved in the present study. Further investigations are necessary.

RESUMO

CONTEXTO: Linfoma esplênico difuso da polpa vermelha, de linfócitos B pequenos, é uma doença rara, representando menos do que 1% de todos os linfomas não Hodgkin. Essa entidade é caracterizada por envolvimento de sinusoides da medula óssea e sangue periférico. A maioria dos casos está em estádio avançado ao diagnóstico. Sua patogênese ainda é pouco compreendida.

RELATOS DE CASOS: Reportamos dois pacientes com vírus da hepatite B (HBV) crônica não replicante que desenvolveram linfoma esplênico difuso da polpa vermelha, de linfócitos B pequenos. Ambos estavam em estádio IV ao diagnóstico e evoluíram com doença agressiva. Ambos alcançaram resposta completa com a quimioterapia, porém um deles evoluiu a óbito por intercorrências infecciosas durante o transplante de medula óssea e o outro optou por não realizar o transplante e encontra-se sem evidência de doença até os dias atuais (três anos após tratamento). Alguns estudos demonstraram a possível associação entre linfomas não Hodgkin B e HBV. Entretanto, o mecanismo pelo qual esse vírus oncogênico interage com linfoma não Hodgkin B ainda é pouco compreendido. HBV é linfotrópico e pode se inserir no genoma do receptor, causando superexpressão de oncogenes e *downregulation* de genes supressores tumorais. Portanto, o estímulo crônico pelo HBV pode aumentar a proliferação de células B, promovendo expansão monoclonal dessas células, resultando em malignidade.

CONCLUSÃO: HBV pode estar implicado na patogênese desse linfoma, entretanto, uma associação direta entre essas duas entidades não pôde ser provada no presente estudo e investigações adicionais são necessárias.

INTRODUCTION

Splenic diffuse red-pulp small B-cell lymphoma was recognized as a provisional entity in the 2008 update of the World Health Organization (WHO) classification.[1] This new WHO update recognized two categories of primary splenic lymphomas; splenic marginal-zone lymphoma (SMZL) and the provisional group of splenic B-cell lymphoma/leukemia unclassifiable (SLLU), that includes splenic diffuse red-pulp small B-cell lymphoma and hairy-cell leukemia variant (HCL-v).[1] The median age at which patients are diagnosed with splenic diffuse red-pulp small B-cell lymphoma is 72 years (range: 69-74 years),[2] and the disease is seen predominantly among males, with a male/female ratio of 2.4:1.

Splenic diffuse red-pulp small B-cell lymphoma is a rare disease and represents less than 1% of all non-Hodgkin lymphomas (NHL) and 10% of B-cell lymphomas that are described in post-splenectomy series.[1] This malignancy is characterized by diffuse infiltrate of monomorphic small to medium-sized B-cells with cytoplasmic villi, going into the red pulp of the spleen. The bone marrow sinusoids and peripheral blood are frequently involved. Patients usually present with an advanced stage of disease when they are diagnosed. Peripheral lymph node involvement and B-symptoms are rarely reported and massive splenomegaly is common.[1] Splenic diffuse red-pulp small B-cell lymphomas have an indolent clinical course and there is no known standard treatment approach. So far, most of these patients have been treated with splenectomy.[3]

The pathogenesis of this lymphoma is still poorly understood and no risk factors associated with its development have been described. Recent studies have shown an association between B-cell NHL and hepatitis B virus (HBV), but the mechanism through which this oncogenic virus results in chronic lymphoproliferative B-cell disorders is not clearly understood. To the best of our knowledge, there is no case report in the literature correlating HBV with splenic diffuse red-pulp small B-cell lymphoma.

Here, we describe two cases of splenic diffuse red-pulp small B-cell lymphoma associated with chronic HBV infection.

CASE REPORTS

Case 1

A 62-year-old woman presented at our clinic complaining of weight loss, fever, night sweats and increasing abdominal size over the preceding two months. In her medical history, she reported having had rheumatoid arthritis, which was previously treated with chloroquine and methotrexate, and an untreated chronic non-replicating HBV infection (AntiHbC total +, AgHbe –, AntiHbe +, AgHbs +, AntiHbsAg -) with quantitative polimerase chain reaction (PCR) for HBV of 104 IU/ml (normal range of values: 20–170,000,000 IU/ml). Other viral serological tests for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) were negative. In her family history, her daughter had had a central nervous system (CNS) neoplasm, a 60-year-old brother had had prostate cancer and another 50-year-old brother had died of acute leukemia.

In her physical examination, she presented as emaciated and pale, with massive splenomegaly and no palpable hepatomegaly or peripheral lymphadenopathy. Computed tomography (CT) scans showed subtle hepatomegaly and greatly increased spleen size, with no lymphadenopathy (**Figure 1**).

Laboratory tests showed normocytic and normochromic anemia (hemoglobin 8.8 g/dl, platelet count of 124 x 10^9/l and total leukocyte count of 6.18 x 10^9/l); 21% of the lymphoid cells had a high nuclear-to-cytoplasmic ratio, with loose chromatin, small clear nucleolus and thin cytoplasmic projections. Immunophenotyping of peripheral blood cells showed that they were positive for CD19, CD20, FMC7, CD22, and CD23, with strong expression of CD79b and CD25, weak surface expression of immunoglobulin (Ig) M, and partial expression of CD5. No expression of CD200, CD10, CD11c or CD103 was seen. Monoclonality was demonstrated through restriction of

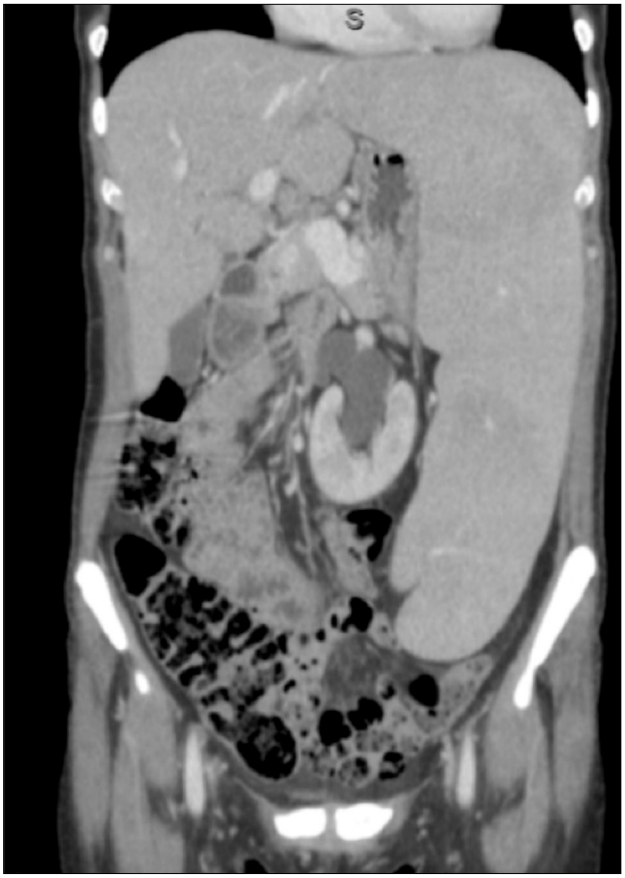

Figure 1. Computed tomography (CT) scan demonstrating subtle hepatomegaly and greatly increased spleen size.

cytoplasmic light kappa chain Ig. Bone marrow biopsy revealed intrasinusoidal infiltration by small B lymphoid cells.

Splenectomy was performed as a therapeutic procedure and the histological analysis showed that the spleen weighed 1.818 kg, measured 27 x 14.3 x 8.3 cm and presented diffuse infiltrate in the red pulp of the spleen, with both cord and sinusoid infiltration by small B-cell lymphocytes (**Figure 2**) expressing CD20 and DBA-44 antigens. These cells had a low Ki67 proliferative index and were negative for CD3, CD5, CD10, CD23 and cyclin-D1. A hepatic biopsy revealed mixed inflammatory infiltration and stage 1 steatohepatitis, with an activity index of 5.

The patient improved clinically and her laboratory parameters normalized after splenectomy. However, 10 months later, the patient presented with weight loss, fever, night sweats, asymmetrical eyelid edema and pleural effusion. At that time, laboratory examinations showed leukocytosis of 30.18 x 10^9/l; 22% of the cells were of moderate size and presented loose chromatin and evident peripheral nucleoli, which were morphologically suggestive of centroblasts. Her laboratory values showed hypercalcemia and elevated lactate dehydrogenase (LDH), of more than 3,000 U/l (normal values range from 240 to 480 U/l). Pleural fluid showed infiltration by neoplastic cells. New immunophenotyping of peripheral blood cells revealed aberrant lymphoid cells expressing B antigens, including CD19, surface IgM (sIgM), strong CD20 expression, heterogeneous partial CD79b expression and FMC7 with a lack of CD5 antigen. Bone marrow karyotyping revealed 46,XX [20]. The bone marrow biopsy was hypercellular due to infiltration by B cells.

Brain and orbit magnetic resonance imaging (MRI) showed infiltration of the optic nerve, bilateral lacrimal glands and CNS. Restaging CT scans revealed renal infiltration and axillary and abdominal lymph node enlargement. It was concluded that transformation to high-grade B-cell lymphoma had occurred, and treatment with R-CHOP was started, with the following given on day 1 of each cycle: intravenous rituximab, 375 mg/m^2; intravenous cyclophosphamide, 750 mg/m^2; intravenous doxorubicin, 50 mg/m^2; and intravenous vincristine, 1.4 mg/m^2. In addition, oral prednisone, 100 mg once daily, was given on days 1–5. R-CHOP was administered in combination with intrathecal chemotherapy containing methotrexate (12 mg), cytarabine (60 mg) and dexamethasone (2 mg) (MADIT) and two cycles of methotrexate (3 g/m^2 intravenously) after the last cycle of R-CHOP and radiotherapy to the orbits (24 Gy). Tenofovir (300 mg/day) was started along with the chemotherapy to avoid replication of HBV. The patient achieved a complete response, and autologous bone marrow transplantation was performed as a consolidation strategy. However, unfortunately, the patient died due to infectious complications during the transplantation.

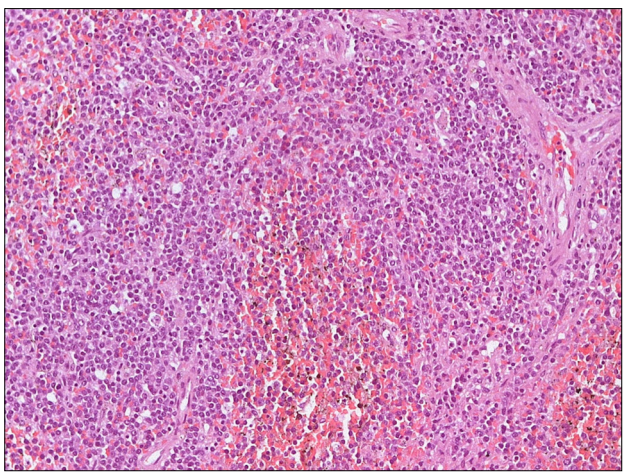

Figure 2. Diffuse infiltrate of small B-cell lymphocytes in the red pulp of the spleen (hematoxylin and eosin, x 200).

Case 2

A 29-year-old female patient with a seven-year history of splenomegaly, without portal hypertension and with chronic non-replicating HBV infection (AntiHbC total +, AntiHbe +, AgHbe –, AgHbs +, AntiHbs –) showing quantitative PCR for HBV of less than 20 IU/ml (normal range of values: 20-170,000,000 IU/ml) presented to our service complaining of progressive spleen enlargement and B symptoms (fever, night sweats and weight loss) for the past two months. Laboratory tests showed hemoglobin 8.1 g/dl, platelets 80 ×10^9/l and white blood cells 12 × 10^9/l, with 85% atypical lymphoid cells. Immunophenotyping demonstrated strong expression of CD45, positivity for the B-cell antigens CD20 and CD19, weak expression of CD25, partial expression of CD23 and CD200 and negativity for CD11c and CD103. Monoclonality for kappa light chain Ig was demonstrated in both the peripheral blood and bone marrow.

The karyotype was complex, with structural abnormalities in the 14q32 region, deletions on chromosomes 6 and 7, isochromosomes 8 and 17 and trisomy 18. Fluorescence in situ hybridization analysis revealed an extra copy of the MYC gene and a p53 deletion. ^{18}FDG-PET-CT showed splenomegaly (standard uptake value [SUV]: 6.1), hepatomegaly (SUV: 3.2), abdominal lymph node enlargement (SUV: 6.3) and cervical and mediastinal lymphadenopathy (**Figure 3**).

Splenectomy was indicated and the anatomopathological analysis showed that the spleen dimensions were 33.0 x 20.6 x 7.5 cm. The spleen showed infiltration by small to intermediate-sized mature lymphoid cells, with large cells among them, primarily in the red pulp and sinusoidal space of the spleen and secondarily in the white pulp of the spleen (**Figure 4**). Immunohistochemical analysis showed expression of CD20 and DBA44, with Ki67 of 40%. The cells were negative for CD5, CD10, CD23, CD3 and cyclin D1. A hepatic biopsy demonstrated nodular lymphoid

infiltrate involvement, with suspected lymphoid neoplasia. A hilum splenic lymph node (measuring 2.6 x 1.1 x 1.0 cm) showed lymphoid neoplasia of mature cells with predominance of intermediate to large cells with a nodular pattern.

The diagnosis of splenic diffuse red-pulp small B-cell lymphoma was made and treatment was then instituted, consisting of eight cycles of R-CHOEP: intravenous rituximab (375 mg/m^2), intravenous cyclophosphamide (750 mg/m^2), intravenous doxorubicin (50 mg/m^2), and intravenous vincristine (1.4 mg/m^2) on day 1; intravenous etoposide (100 mg/m^2) on days 1–3; and oral prednisone (100 mg orally once daily) on days 1–5. It was proposed that this would be followed by autologous stem cell transplantation. After eight cycles of R-CHOEP, the patient achieved complete response, but she became pregnant and chose not to undergo the transplantation. Nonetheless, she continues not to present any evidence of disease today (three years after the treatment). Administration of tenofovir (300 mg/day) was started along with the chemotherapy.

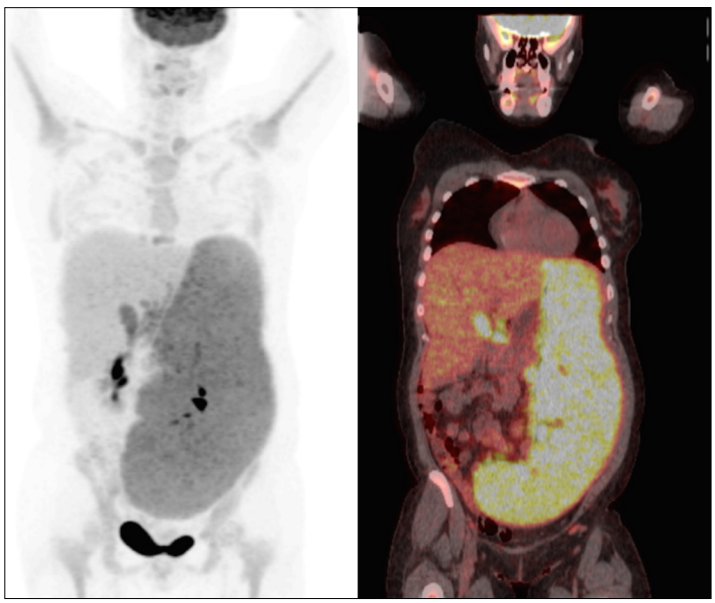

Figure 3. 18FDG-PET-CT (fludeoxyglucose F18 position emission computed tomography) demonstrating major splenomegaly (standard uptake value [SUV]: 6.1) and hepatomegaly (SUV: 3.2)

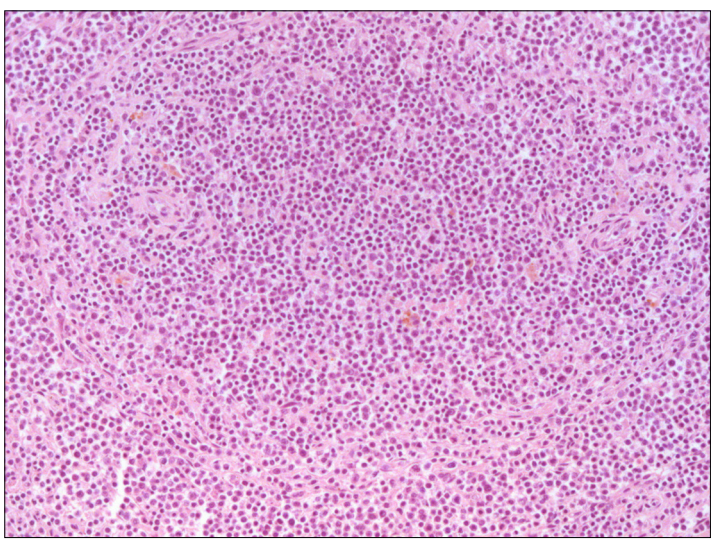

Figure 4. Small and few large lymphoid cells in splenic red pulp (hematoxylin and eosin, x 200)

DISCUSSION

We have reported on two patients with chronic non-replicating HBV who developed splenic diffuse red-pulp small B-cell lymphoma. The diagnosis of primary chronic lymphoproliferative disorders of the spleen is established based on analysis on splenectomy tissue, or on integration of clinical data, assessment of lymphocyte morphology in peripheral blood, immunophenotyping of these lymphocytes and evaluation of bone marrow infiltration pattern from biopsy. For our patients, we used both criteria in order to be sure of the diagnosis. In both cases, the splenectomy product demonstrated diffuse neoplastic infiltration consisting of small mature lymphocytes with primary immunophenotype B of the red pulp of the spleen. With this presentation, the diagnosis of splenic marginal-zone lymphoma was ruled out, since this entity is characteristically a primary neoplasm of the splenic white pulp, usually with nodular architectural arrangement.

Other entities that might have formed differential diagnoses were hairy-cell leukemia and hairy-cell leukemia variant. However, the clinical data in association with morphological and immunophenotyping data made it possible to safely rule out diagnoses of hairy-cell leukemia (absence of pancytopenia, no cells with the classical morphology of "hairy cell" and immunophenotyping not characterized by strong expression of CD11c, CD25, CD103 and CD123 antigens) or hairy-cell leukemia variant (no lymphocytes with morphology characterized by the presence of central vesicular nucleolus, cytoplasm similar to hairy cell and absence of strong expression of CD11c and CD20 antigens).

Thus, integration of all these findings, i.e. lymphoproliferative malignancy of small B cells, diffuse infiltration of the spleen and primary from splenic red pulp, with exclusion criteria for "hairy cell" and its variant form, enabled the definitive accurate diagnosis of splenic diffuse red-pulp small B-cell lymphoma in both cases reported here.

We conducted a systematic search in the main electronic databases (PubMed, Google Scholar and Lilacs Library), to find articles relating to splenic diffuse red-pulp small B-cell lymphoma in association with hepatitis B infection. In order to make the search as wide as possible, no limits were applied regarding the date of publication, the language or the research design

(**Table 1**). There were fewer than 100 search results and none of them described any association between splenic diffuse red-pulp small B-cell lymphoma and hepatitis B.

Mollejo et al. first proposed this lymphoma as a new subtype in 2002,[4] consequent to reviewing 85 cases of SMZL. These authors identified four cases with predominance of monomorphic infiltration in the red pulp of the spleen instead of the typical micronodular component in the white pulp commonly seen in SMZL. Later on, two series of cases of splenic diffuse red-pulp small B-cell lymphoma were published by Traverse-Glehen et al.[5] and Kanellis et al.[2]

Similarly to our two patients, all cases previously reported were also in stage IV at diagnosis. Diffuse infiltration of the red pulp of the spleen, affecting both cords and sinuses, along with marked DBA-44 positivity, was frequently found by Kanellis et al.[2] (88.2% of their cases), as well as in our cases. Additionally, previous studies described situations of lymph node replacement by diffuse neoplastic infiltrate, with preserved sinuses.[2,4]

The most common finding in the bone marrow biopsies was predominance of intrasinusoidal lymphoid infiltration, sometimes associated with interstitial and nodular involvement, along with hematopoietic tissue and absent or mild fibrosis. The malignant cells presented with round to slightly irregular nuclei, vesicular chromatin and moderate amounts of pale cytoplasm and cytoplasmic projections similar to SMZL villous cells. These cells expressed CD20, DBA44 and IgG. Presence of annexin A1, CD25, CD3, CD5, CD23, CD103, CD123, CD11c, CD38, CD10, Bcl6, bcl2, cyclin D1 and IgD was uncommon.[1,4] Our cases are consistent with those presented in the literature regarding the pathological and immunophenotypic findings of splenic diffuse red-pulp small B-cell lymphoma. The majority of the cases reported in the literature had a normal karyotype and the most frequent chromosomal abnormalities were 7q and 3q deletions and trisomy 18.[1,6] One of our cases showed a complex karyotype.

Table 1. Systematic search of the literature performed on April 4, 2016

Electronic databases	Search strategy	Results	
		Found	Paper used
Medline (via PubMed)	"Lymphoma, B-Cell"[Mesh] AND "Hepatitis B"[Mesh] AND Case Reports[ptyp]	62	0
Lilacs (via Bireme)	("Linfoma de Células B OR Lymphoma, B-Cell OR Linfoma de Células B " [Decs] AND Hepatite B OR Hepatitis B OR Hepatitis B [Decs])	0	0
Embase (via Ovid)	(Lymphoma, B-Cell) and (Hepatitis B)). All fields. Search terms cross-referenced: b; b-cell; hepatitis; hepatitis b; lymphoma; lymphoma, b-cell	10	0

Kanellis et al.[2] found p53 inactivation in all cases of splenic diffuse red-pulp small B-cell lymphoma, comprising either p53 mutation (2/4 cases) or anomalous p53 staining. Mollejo et al.[4] reported that TP53 abnormality was present in 2 out of 13 cases (15.3%): one of these patients showed disease progression and ultimately died of the disease. In the same way as described by these authors, one of our patients also had a p53 deletion and evolved to aggressive disease. Splenic diffuse red-pulp small B-cell lymphoma is an indolent lymphoma and patients can be maintained using a watchful waiting approach or may undergo splenectomy.

Compared with SMZL, splenic diffuse red-pulp small B-cell lymphoma has demonstrated better disease-free survival, but overall survival is not statistically different. At diagnosis, our patients presented with anemia, which is associated with worse prognosis according to Kanellis et al.,[2] and both of them had HBV infection as a comorbidity. HBV infection may be associated with worse prognosis, since both patients evolved with aggressive disease.

Virus-induced carcinogenesis is known to occur in several lymphoid malignancies in which the virus has a pathogenic role, such as in Burkitt's lymphoma with Epstein-Barr virus (EBV), adult T-cell leukemia with human T-cell lymphotropic virus-1, and primary effusion B-cell lymphoma with human herpes virus 8. Some malignancies may be caused by chronic stimulation such as in mucosa-associated lymphoid tissue lymphoma, which is associated with *Helicobacter pylori*, or through an indirect mechanism. While EBV has a direct carcinogenic effect on Burkitt's lymphoma through activating the c-Myc oncoprotein, HIV acts on the immune system to reduce immune surveillance.[7,8]

HBV is a small DNA virus that is a member of the Hepadnaviridae family. It replicates through a RNA intermediary and can integrate into the host genome. HBV infection is highly prevalent worldwide, with around 350 million chronically infected individuals. It is endemic in Asia, Africa, the Middle East, Eastern Europe and South America.[9] There are 500,000 to 1.2 million deaths due to chronic hepatitis B annually, out of a total of 350 million cases worldwide,[8] and about 340,000 cases of liver cancer relating to HBV.[10]

HBV and HCV are known to induce acute and chronic hepatitis and are strongly associated with hepatocellular carcinoma (HCC). HBV carriers have a 200 times higher risk of HCC, and this is one of the highest risks for a human malignancy.[11] Its pathogenesis involves multiple pathways, including oxidative stress, hepatic inflammation leading to genetic damage and integration of HBV DNA into the host genome, thereby leading to genetic alterations such as chromosomal and gene translocations

and deletions or generation of fusion transcripts. These alterations may change oncogenes, tumor-suppressor genes and expression of small non-coding RNA molecules (miRNAs).[12]

Non-structural HBV X protein is a key regulatory protein that modulates viral replication and pathogenesis. It is transcribed in human HCC tumor cells, even when HBV replication is absent, due to viral DNA integration. This protein modulates gene expression, since it interacts with transcription factors, activates mitogenic signaling cascades and interacts with cellular proteins, including p53. Consequently, DNA repair, tumor suppressor genes and the cell cycle could become deregulated.[13]

The relationship between NHL and HCV has already been proven, with evidence demonstrating a causal relationship.[11,14-17] There is a known multicausal process involving direct lymphocytic activation mediated by viral proteins and chronic antigenic stimulation, for promoting B-cell transformation.[18] A recent prospective cohort study conducted in South Korea evaluated 603,585 participants, among whom 53,045 (9%) tested positive for HBsAg. The HBsAg-positive patients were at higher risk of NHL than those who were HBsAg-negative (hazard ratio: 1.74; 95% CI: 1.45–2.09), especially for diffuse large B-cell lymphoma and immunoproliferative diseases. In this study, HBsAg was not associated with follicular lymphoma, T-cell NHL, Hodgkin's lymphoma, multiple myeloma or leukemia.[19] A meta-analysis on 17 case-control and five cohort studies found that HBV-infected individuals had an odds ratio (OR) of 2.24 (95% CI: 1.80-2.78; $P \leq 0.001$) for developing NHL.[20] Another meta-analysis on 12 case-control studies, comprising 11 studies evaluating HBV infection in NHL and one study that had investigated NHL in HBV infection, reported that the OR of detecting HBV infection in lymphoma patients was 2.5 times higher than in controls.[21] These studies suggest a possible relationship between HBV and NHL. The pathogenic association is less well studied than relationships with HCV, but it appears to result from different HBV-driven events.[22]

HBV is a hepatotropic virus and replicates within hepatocytes, but it can also cause lymphotropism for lymphocytes in the peripheral blood, bone marrow, spleen, lymph nodes, and thymus.[23-26] This lymphotropism of HBV is a fundamental property favoring causality between HBV and B-cell malignancies. Additionally, a study evaluating CD20 cell expression in the liver of HBsAg-positive and HBeAg-negative patients found that all of them were CD20-positive.[27]

Wang et al.[28] found higher prevalence of HBeAg and anti-HBe in NHL cases than in controls, thus suggesting that viral replication may be required to support neoplastic proliferation. HBV integrates into the host genome and can lead to overexpression of cellular oncogenes or downregulation of tumor suppressor gene expression. Introduction of whole-genome sequencing identified several preferred sites for HBV integration, some of which have also been described in lymphomas, CCNE (cyclin E1)[29] and the PDGF receptor.[30] Also, the HBX protein transactivates cellular promoters and enhancers, including the binding site for NF-KB.[12] The HBX protein is involved in blocking p53-mediated apoptosis, which has been implicated in the pathogenesis of splenic diffuse red-pulp small B-cell lymphoma.[12,28,31,32] A second mechanism for lymphomagenesis could relate to chronic stimulation by HBV antigens, thereby leading to incremental proliferation of B-lymphocytes and, consequently, monoclonal malignant expansion. The incremental B-cell proliferation may lead to predisposition towards genetic aberrations, thus promoting neoplastic transformation.[28]

CONCLUSION

We have described two cases of splenic diffuse red-pulp small B-cell lymphoma associated with HBV. Although we hypothesized that HBV might be implicated in the pathogenesis of this lymphoma, no direct association between these two entities could be proved in this study, and further investigations are necessary.

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Pilates for low back pain

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Tiê P. Yamato, Christopher G. Maher, Bruno T. Saragiotto, Mark J. Hancock, Raymond W. J. G. Ostelo, Cristina M. N. Cabral, Luciola C. Menezes Costa, Leonardo O. P. Costa

The independent commentary was written by Anamaria Jones

ABSTRACT

BACKGROUND: Non-specific low back pain is a major health problem worldwide. Interventions based on exercises have been the most commonly used treatments for patients with this condition. Over the past few years, the Pilates method has been one of the most popular exercise programmes used in clinical practice.

OBJECTIVES: To determine the effects of the Pilates method for patients with non-specific acute, subacute or chronic low back pain.

METHODS:

Search methods: We conducted the searches in CENTRAL, MEDLINE, EMBASE, CINAHL, PEDro and SPORTDiscus from the date of their inception to March 2014. We updated the search in June 2015 but these results have not yet been incorporated. We also searched the reference lists of eligible papers as well as six trial registry websites. We placed no limitations on language or date of publication.

Selection criteria: We only included randomized controlled trials that examined the effectiveness of Pilates intervention in adults with acute, subacute or chronic non-specific low back pain. The primary outcomes considered were pain, disability, global impression of recovery and quality of life.

Data collection and analysis: Two independent raters performed the assessment of risk of bias in the included studies using the 'Risk of bias' assessment tool recommended by The Cochrane Collaboration. We also assessed clinical relevance by scoring five questions related to this domain as 'yes', 'no' or 'unclear'. We evaluated the overall quality of evidence using the GRADE approach and for effect sizes we used three levels: small (mean difference (MD) < 10% of the scale), medium (MD 10% to 20% of the scale) or large (MD > 20% of the scale). We converted outcome measures to a common 0 to 100 scale when different scales were used

MAIN RESULTS: The search retrieved 126 trials; 10 fulfilled the inclusion criteria and we included them in the review (a total sample of 510 participants). Seven studies were considered to have low risk of bias, and three were considered as high risk of bias.

A total of six trials compared Pilates to minimal intervention. There is low quality evidence that Pilates reduces pain compared with minimal intervention, with a medium effect size at short-term follow-up (less than three months after randomization) (MD -14.05, 95% confidence interval (CI) -18.91 to -9.19). For intermediate-term follow-up (at least three months but less than 12 months after randomization), two trials provided moderate quality evidence that Pilates reduces pain compared to minimal intervention, with a medium effect size (MD -10.54, 95% CI -18.46 to -2.62). Based on five trials, there is low quality evidence that Pilates improves disability compared with minimal intervention, with a small effect size at short-term follow-up (MD -7.95, 95% CI -13.23 to -2.67), and moderate quality evidence for an intermediate-term effect with a medium effect size (MD -11.17, 95% CI -18.41 to -3.92). Based on one trial and low quality evidence, a significant short-term effect with a small effect size was reported for function (MD 1.10, 95% CI 0.23 to 1.97) and global impression of recovery (MD 1.50, 95% CI 0.70 to 2.30), but not at intermediate-term follow-up for either outcome.

Four trials compared Pilates to other exercises. For the outcome pain, we presented the results as a narrative synthesis due to the high level of heterogeneity. At short-term follow-up, based on low quality evidence, two trials demonstrated a significant effect in favour of Pilates and one trial did not find a significant difference. At intermediate-term follow-up, based on low quality evidence, one trial reported a significant effect in favour of Pilates, and one trial reported a non-significant difference for this comparison. For disability, there is moderate quality evidence that there is no significant difference between Pilates and other exercise either in the short term (MD -3.29, 95% CI -6.82 to 0.24) or in the intermediate term (MD -0.91, 95% CI -5.02 to 3.20) based on two studies for each comparison. Based on low quality evidence and one trial, there was no significant difference in function between Pilates and other exercises at short-term follow-up (MD 0.10, 95% CI -2.44 to 2.64), but there was a significant effect in favour of other exercises for intermediate-term function, with a small effect size (MD -3.60, 95% CI -7.00 to -0.20). Global impression of recovery was not assessed in this comparison and none of the trials included quality of life outcomes. Two trials assessed adverse events in this review, one did not find any adverse events, and another reported minor events.

AUTHORS CONCLUSIONS: We did not find any high quality evidence for any of the treatment comparisons, outcomes or follow-up periods investigated. However, there is low to moderate quality evidence that Pilates is more effective than minimal intervention for pain and disability. When Pilates was compared with other exercises we found a small effect for function at intermediate-term follow-up. Thus, while there is some evidence for the effectiveness of Pilates for low back pain, there is no conclusive evidence that it is superior to other forms of exercises. The decision to use Pilates for low back pain may be based on the patient's or care provider's preferences, and costs.

The full text of this review is available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010265.pub2/full

The abstract is also available in Portuguese and English

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COMMENTS

This systematic review provides important data on the impact of the Pilates method regarding treatment of nonspecific low back pain. Among the 10 studies that fulfilled the inclusion criteria, 7 had low risk of bias and 3 had high risk. Six studies compared Pilates with minimal intervention and showed evidence of low and moderate quality regarding pain reduction and improvement of disability over the short and medium terms. One study showed low-quality evidence over the short term regarding function and the overall impression of recovery. Four studies compared the Pilates method with another kind of exercises: pain reduction was observed in two studies over the short term and in one over the medium term (low-quality evidence). Regarding disability, moderate-quality evidence was found in two studies over the short and medium term. For function over the short term, no significance difference was found. However, over the medium term, there was a significant effect in favor of other exercises. No adverse events were observed in this review, thus showing the safety of this method for this population.

This systematic review thus suggested that the Pilates method was slightly better than minimal intervention in relation to pain and disability. However, it did not show that the Pilates method was superior to other exercises. Since the benefits of Pilates seem to be similar to those of other exercises, the decision to use this as a treatment for patients with nonspecific low back pain should be based on the patient's or care provider's preferences, and on the costs. Other studies with more robust methodology should be conducted and the cost of this treatment should be analyzed.

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Yoga for asthma

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The independent commentary was written by Ana Luisa Godoy Fernandes

ABSTRACT

BACKGROUND: Asthma is a common chronic inflammatory disorder affecting about 300 million people worldwide. As a holistic therapy, yoga has the potential to relieve both the physical and psychological suffering of people with asthma, and its popularity has expanded globally. A number of clinical trials have been carried out to evaluate the effects of yoga practice, with inconsistent results.

OBJECTIVES: To assess the effects of yoga in people with asthma.

METHODS:

Search methods: We systematically searched the Cochrane Airways Group Register of Trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts. We also searched PEDro. We searched ClinicalTrials.gov and the WHO ICTRP search portal. We searched all databases from their inception to 22 July 2015, and used no restriction on language of publication. We checked the reference lists of eligible studies and relevant review articles for additional studies. We attempted to contact investigators of eligible studies and experts in the field to learn of other published and unpublished studies.

Selection criteria: We included randomized controlled trials (RCTs) that compared yoga with usual care (or no intervention) or sham intervention in people with asthma and reported at least one of the following outcomes: quality of life, asthma symptom score, asthma control, lung function measures, asthma medication usage, and adverse events.

Data collection and analysis: We extracted bibliographic information, characteristics of participants, characteristics of interventions and controls, characteristics of methodology, and results for the outcomes of our interest from eligible studies. For continuous outcomes, we used mean difference (MD) with 95% confidence interval (CI) to denote the treatment effects, if the outcomes were measured by the same scale across studies. Alternatively, if the outcomes were measured by different scales across studies, we used standardized mean difference (SMD) with 95% CI. For dichotomous outcomes, we used risk ratio (RR) with 95% CI to measure the treatment effects. We performed meta-analysis with Review Manager 5.3. We used the fixed-effect model to pool the data, unless there was substantial heterogeneity among studies, in which case we used the random-effects model instead. For outcomes inappropriate or impossible to pool quantitatively, we conducted a descriptive analysis and summarized the findings narratively.

MAIN RESULTS: We included 15 RCTs with a total of 1048 participants. Most of the trials were conducted in India, followed by Europe and the United States. The majority of participants were adults of both sexes with mild to moderate asthma for six months to more than 23 years. Five studies included yoga breathing alone, while the other studies assessed yoga interventions that included breathing, posture, and meditation. Interventions lasted from two weeks to 54 months, for no more than six months in the majority of studies. The risk of bias was low across all domains in one study and unclear or high in at least one domain for the remainder.

There was some evidence that yoga may improve quality of life (MD in Asthma Quality of Life Questionnaire (AQLQ) score per item 0.57 units on a 7-point scale, 95% CI 0.37 to 0.77; 5 studies; 375 participants), improve symptoms (SMD 0.37, 95% CI 0.09 to 0.65; 3 studies; 243 participants), and reduce medication usage (RR 5.35, 95% CI 1.29 to 22.11; 2 studies) in people with asthma. The MD for AQLQ score exceeded the minimal clinically important difference (MCID) of 0.5, but whether the mean changes exceeded the MCID for asthma symptoms is uncertain due to the lack of an established MCID in the severity scores used in the included studies. The effects of yoga on change from baseline forced expiratory volume in one second (MD 0.04 liters, 95% CI -0.10 to 0.19; 7 studies; 340 participants; $I^2 = 68\%$) were not statistically significant. Two studies indicated improved asthma control, but due to very significant heterogeneity ($I^2 = 98\%$) we did not pool data. No serious adverse events associated with yoga were reported, but the data on this outcome was limited.

AUTHORS CONCLUSIONS: We found moderate-quality evidence that yoga probably leads to small improvements in quality of life and symptoms in people with asthma. There is more uncertainty about potential adverse effects of yoga and its impact on lung function and medication usage. RCTs with a large sample size and high methodological and reporting quality are needed to confirm the effects of yoga for asthma

The full text of this review is available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010346.pub2/full
The abstract is also available in English and French

REFERENCE

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COMMENTS

Asthma is a heterogeneous inflammatory disease and understanding of its physiopathogenesis has undergone constant development in the light of updates within immunopathology and molecular biology. These have provided descriptions of many inflammatory pathways mediated by cytokines that may play a role in modulating the disease and in establishing chronic inflammatory processes and lung remodeling.

Drug treatment is based on administration of combinations of inhaled corticosteroids and bronchodilators, but non-drug management is essential and includes teaching patients how to live with a chronic disease that limits the quality of life. One of the main recommendations is that regular physical exercise should be practiced in order to improve fitness and increase the aerobic threshold, thereby improving the functional conditions for withstanding exacerbation of symptoms. Recent research has also confirmed the effectiveness of regular physical exercise performed at 60% of maximum load. This practice has the capacity to reduce inflammatory mediators and consequently may be effective in treating asthma.

This systematic review included a large number of patients and examined the practice of yoga exercises in relation to the clinical expression of asthma. Reductions in symptoms and use of medication were observed, as well as significant improvements in quality-of-life scores among yoga practitioners, compared with non-practitioners. The data presented do not specify whether the patients had moderate or severe asthma, and no functional improvements were confirmed. These data support the conclusion that there is a benefit from from practicing yoga, but no physiopathological explanation for the observed benefits has been presented.

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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).

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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, ICMJE) 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:

Article in journal

- Hurt AC, Hardie K, Wilson NJ, et al. Community transmission of oseltamivir-resistant A(H1N1)pdm09 influenza. N Engl J Med. 2011;365(26):2541-2.

Chapter of book

- Miller WI, Achernabb JC, Fluck CE. The adrenal cortex and its disorder. In: Sperling M. Pediatric endocrinology. 3rd ed. Elsevier Health Sciences; 2008. p. 444-511.

Text on the internet

- Centers for Disease Control and Prevention. Children's food environment State Indicator Report, 2011. Available from: http://www.cdc.gov/obesity/downloads/ChildrensFoodEnvironment.pdf. Accessed in 2012 (Mar 7).

Figures and tables

Images must have good resolution (minimum of 300 DPI) and be recorded in ".jpg" or ".tif" format. Do not attach images inside Microsoft PowerPoint documents. If photographs are inserted in a

Microsoft Word file, the images should also be sent separately. Graphs must 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.

São Paulo Medical Journal/Evidence for Health Care is for now published in black-and-white in its printed version. Photographs, photomicrographs, bar and line graphs and any image to be published must be prepared considering that there will be no color differentiation (any color information will be discarded). Shades of gray and printing patterns (dots, stripes and others) should be used instead, with good contrast.

Original articles

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;[7,8]
4. Systematic reviews of the literature and meta-analyses: PRISMA[4]

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 final sample of patients included should be produced and inserted in the article.

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".

4.4) *Procedures (*intervention, diagnostic test or exposure): describe the principal characteristics of any intervention, including the method, the timing and the duration of its administration or of data collection. Describe the differences in interventions administered to each group (if the study is controlled). Detail the procedures in such a way that other researchers will be able to repeat them in other localities.

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.

4.7) *Randomization*: describe the method used to implement the random allocation sequence (for example, sealed envelopes containing random sequences of numbers or software for generating random numbers). If appropriate, report that the study used "quasi-randomization".[12] In addition, describe who generated the random sequence, who assigned the participants to each group (in the case of controlled trials) and who recruited the participants.

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.

5.3) *Adverse events*: describe any side effect, adverse event or complication.

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 further 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.

Systematic reviews with or without meta-analyses should comply with the same publication norms established for original articles, and be produced in accordance with PRISMA[4] and the Cochrane Collaboration's systematic review Handbook.[13] The text should not exceed 5,000 words (excluding tables, figures and references)

Short communications, case reports or case series

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 observational studies and these should be structured in accordance with the norms of the STROBE Statement.[5]

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.

The São Paulo Medical Journal/Evidence for Health Care is interested in publishing rare or instructive case reports, accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[14] The results from the systematic search of the main databases — Medline (via PubMed), Embase, Lilacs and Cochrane Library — should be presented in a table with the search strategy for each database and the number of articles obtained.

Narrative reviews

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[1] 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 Bireme). For the search strategies, MeSH terms must be use 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).

Letters to the editor

Letters to the editor may address articles published in the São Paulo Medical Journal/Evidence for Health Care publication 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.

Documents cited

1. Internal Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals, writing and editing for biomedical publications. Available from: http://www.icmje.org. Accessed in 2012 (Aug 6).
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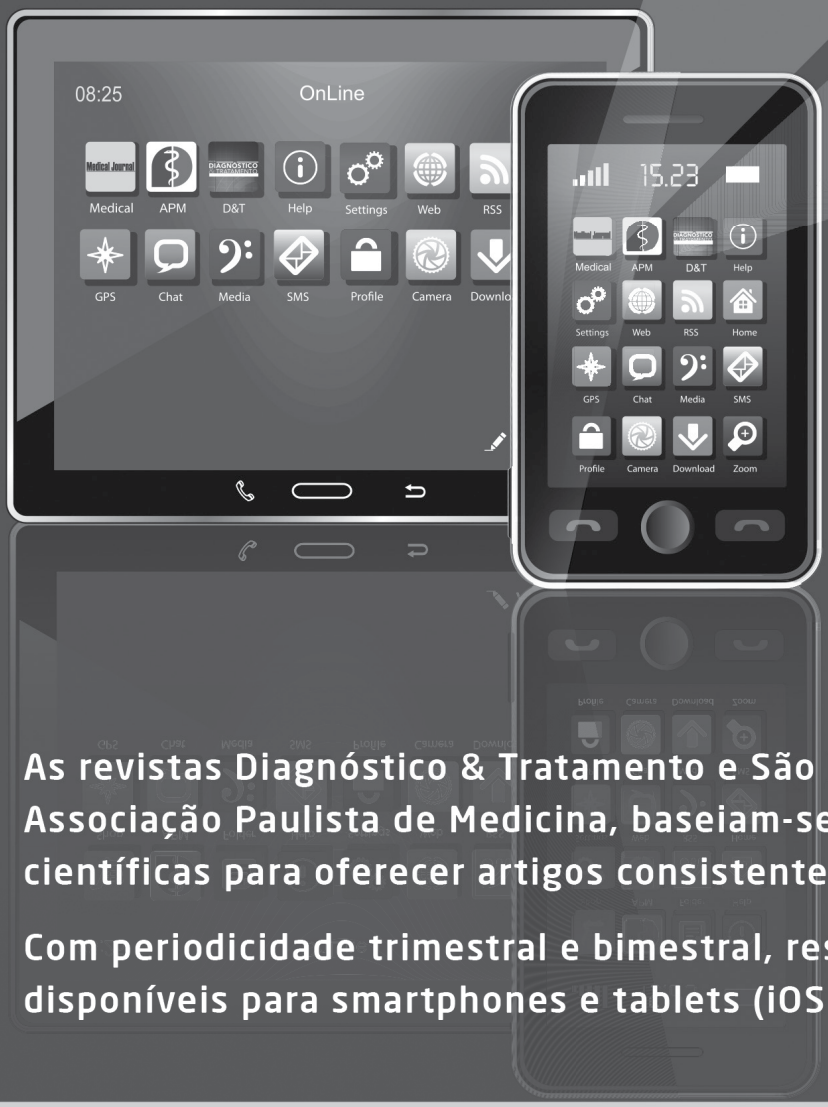

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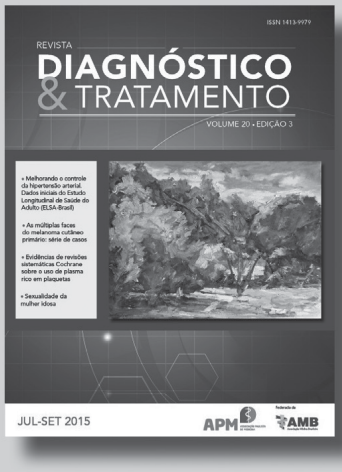

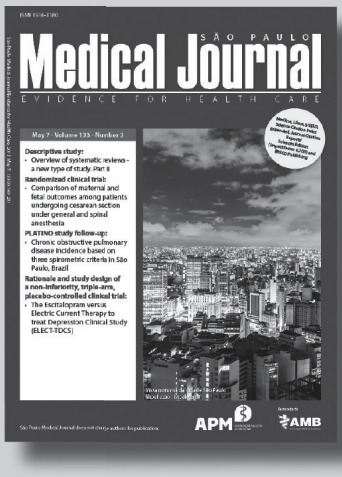

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