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ORIGINAL ARTICLE

Drug Interactions and Adverse Events in a Cohort of Warfarin Users Attending Public Health Clinics

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Abstract

Background: Warfarin is an oral anticoagulant involved in important interactions with foods and other drugs.

Objectives: To evaluate the occurrence of adverse events reported by warfarin users and their relationship with drug interactions.

Methods: This was an open cohort, prospective study conducted in an 18-month period with warfarin users attending public health clinics of the city of Ijuí, Brazil. Data were collected by means of interviews administered at patients' home every month. Patients' responses were confirmed by review of medical records when patients sought medical care. Data were analyzed by descriptive statistics. Potential drug interactions were evaluated in a database and vitamin K consumption was quantified using a validated method.

Results: A total of 68 patients were followed-up; 63 completed the study and 5 died in the study period. Mean number of medications taken by the patients was 9.6 ± 4.5, and mean number of interactions involving warfarin was 2.91 ± 1.52. Most potential interactions increased the risk of bleeding, 61 of them severe interactions and 116 moderate interactions. Eighty-seven episodes of bleeding and 4 episodes of thrombosis were reported by a total of 37 and 4 patients, respectively. At the occurrence of these events, 56.5% of warfarin users were also taking omeprazole, 35.9% were taking simvastatin and 25.0% paracetamol. Most patients had a low vitamin K intake.

Conclusions: A high frequency of potential interactions between warfarin and other drugs was detected, but a low intake of foods that could possibly affect the effects of warfarin was observed. Based on our results, it seems prudent to follow patients on warfarin therapy for drug-drug interactions, aiming to control adverse effects and to promote a safe and effective therapy. (Int J Cardiovasc Sci. 2019;32(2)110-117)

Keywords: Anticoagulants / adverse effects; Warfarin; Pharmacovigilance; Drug Interactions; Drug Incompatibility; Omeprazole; Simvastatin; Acetaminophen; Vitamin K; Delivery Health Care / statistics & numeral data.

Introduction

Warfarin is one of the most used oral anticoagulants. According to the Food and Drug Administration, it is among the top ten drugs in terms of the risk of severe side effects.[1] Warfarin is characterized by a narrow therapeutic window, high interaction with other drugs and frequent bleeding.[2]

The effect of warfarin may be either increased or decreased when combined with some drugs or foods. These interactions can be potentially harmful to patients and caused increased health-related costs,[3] which justifies the need to identify potential interactions involving warfarin that may lead to adverse effects.

The risk for adverse events caused by drug interactions with warfarin increases with the number of drugs administered concomitantly,[4] whereas vitamin K-rich diets may decrease warfarin therapeutic effect.[5] The occurrence of adverse events may be prevented by monitoring of the therapy by health providers involved in its prescription, delivery and follow-up of anticoagulated patients.[6]

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The high frequency of interactions of warfarin with other drugs has been described in studies with hospitalized patients.[7,8] Nevertheless, studies evaluating drug-drug interactions in primary health care are less common. If, on the one hand, these patients generally use less medication than hospitalized patients due to their less severe conditions, monitoring of diet and medication use is less frequent. The aim of this study was to evaluate the occurrence of adverse effects related to drug-drug interactions in warfarin users in the primary health care.

Methods

Study design and subjects

This was an open cohort, prospective study with descriptive analysis with all warfarin users attending public health clinics of the city of Ijuí, located in the south of Brazil. Patients were followed for an 18-month period between April 2014 and October 2015, by monthly interviews conducted in patients' home. This was an open cohort because patients were prospectively recruited in the first six months of follow-up.

Warfarin users were identified using copies of drug prescriptions, filed at Ijui Secretary of Health Central Pharmacy. It is the place where all prescriptions issued in the city are filed. Patients' address and telephone number registered in the medical records were used for scheduling of visits.

Inclusion criteria were patients living in Ijui, Brazil, on oral warfarin therapy for chronic diseases or who initiated therapy in the first six months of the study, and who had their medication dispensed from Ijui public health centers. All participants signed an informed consent form. Patients living in other cities, patients treated with other anticoagulants, and those who acquired medications in private pharmacies were excluded.

Data were collected with the aid of a questionnaire containing questions about the patient – socioeconomic and demographic characteristics; medications – use of warfarin and other drugs prescribed; and foods – types and amounts of certain foods consumed.

Data analysis

Medications were classified at the first level of the Anatomical Therapeutic Chemical (ATC) coding system,[9] used for the classification of drugs according to their sites of action and therapeutic and chemical properties. Results related to the medications used by the patients are presented as mean and standard deviation.

Drug interactions were classified according to Micromedex[10] database, and only severe and moderate interactions were considered for analysis. Assessment of drug interactions was performed at two time points – first, at the 18th month of patients' follow-up and then at the occurrence of a clinical event (bleeding or venous thromboembolism). These events were identified by self-report and confirmed by data documented in the medical records. Bleeding and venous thromboembolism were categorized by the site of occurrence only, not considering the severity. For analysis of drugs and their interactions, we included only continuously used medications, based on their prescriptions.

Because of the high use of simvastatin and its potential interaction with warfarin, patients' cardiovascular risk was assessed by the Framingham score, which evaluates and scores each of the following risk factors – age, systolic and diastolic blood pressure, smoking, diabetes mellitus (DM), total cholesterol (TC) and HDL-TC. Results were expressed as absolute risk of fatal (death) and non-fatal (acute myocardial infarction and angina pectoris) cardiovascular events in ten years. Individuals with a risk equal to or lower than 9% were classified as "low-risk" (LR); those with a risk between 10% and 19% as "moderate risk" (MR) and patients with a risk equal to or higher than 20% were classified as high risk (HR).[11] Age, smoking and DM were self-reported, and DM was confirmed by the use of glucose lowering drugs. Blood pressure was measured at the first interview, and TC and HDL-CT at month 18.

Frequency and amount of vitamin K consumed was evaluated using an instrument developed for the Portuguese population and validated by Ferreira.[11] Based on their responses, patients were classified by vitamin K consumption into one of the four categories – high, moderate, low and very low consumption.

Values of international normalized ratio (INR) were used for calculation of the Time in Therapeutic Range (TTR), according to the method adapted and validated by Schimidt et al.[12] Results were expressed as interquartile range.

Statistical analysis was performed using the SPPSS software version.

All patients signed the informed consent form. The study was approved by the ethics committee of the Federal University of Rio Grande do Sul (approval number 336.259/2013).

Results

Sixty-eight patients were followed for 18 months. Sixty-three (92.6%) completed the follow-up and 5 (7.3%) died during the study period. Of the 68 patients, 55.1% were female, with mean age of 64 ± 14 years. Most patients (63.2%) had some elementary school and 51.5% had an income of one minimum age.

Mean number of medications taken by patients was 10 ± 4, and all patients were taking at least one medication in addition to warfarin. In descending order, the most frequent medications were drugs acting on the cardiovascular system (49.2%), blood and hematopoietic organs (16.0%), nervous system (14.8%) and alimentary tract and metabolism (13.5%).

Analysis of drug-drug interactions showed that 66 (97.1%) of patients were subjected to interactions involving warfarin, and 51 (73.9%) and 65 (94.2%) patients were at risk of experiencing one or more severe and moderate interaction, respectively. The mean of potential interactions involving warfarin was 3 ± 1.5 per patient (Figure 1). All interactions identified can affect the effect of warfarin. In 177 patients, this effect would be increased, thereby increasing the risk of bleeding. In 23 patients, the effect of warfarin would be decreased, increasing the risk of thromboembolic events.

Among the interactions that would increase the effect of warfarin, 61 patients had severe and 116 moderate interactions. Simvastatin and amiodarone can cause severe interactions with warfarin, and were found in 47.5% and 14.8% of patients, respectively. The most frequent drugs with potential moderate interactions with warfarin were omeprazole (33.1% of patients) and paracetamol (18.6%). All interactions that would reduce the effect of warfarin were classified as moderate, and the most common drug was spironolactone (60.9%).

A total of 87 bleeding episodes were detected in 37 patients, and 4 venous thromboembolism events were detected in 4 patients; 56.5% of these patients used omeprazole), 35.9% simvastatin and 25.0% paracetamol.

Figure 2 depicts the distribution of patients by risk (present or not) of drug interactions, TTR and frequency of bleeding and venous thromboembolism events. Among the 66 patients at risk of drug interactions involving warfarin, in only 14 patients the INR was maintained within the recommended therapeutic range during most of the follow-up period (51-100%), with 16 bleeding events and one venous thromboembolism event reported. Bleeding and thromboembolism events were more frequently reported by patients whose INR values were maintained within therapeutic range for a shorter time. Patients without potential drug interactions involving warfarin (n = 2), showed a TTR lower than 50%, with bleeding reported by one of them. In addition, 25 (37.3%) of patients at risk of drug interactions did not show any INR value within therapeutic range during follow-up. Considering INR values outside the therapeutic range, 70% of them were below and 30% above recommended range.

With respect to cardiovascular risk, 8 (11.6%) patients had a low risk, 10 (14.5%) a moderate risk and 51 (73.9%) a high risk. Among those with low cardiovascular risk, 3 were taking simvastatin.

Potential interactions between warfarin and foods (particularly vitamin K- rich foods) were assessed by food records of the patients, and a low vitamin K intake was detected in most patients (Table 1).

Discussion

In an 18-month follow-up of 68 patients using warfarin, we found that almost all of them (97.1%) were at risk of drug interactions (± 3 interactions per patient). These interactions were either severe (61) or moderate (116), and probably contributed to the occurrence of adverse events (84 bleeding and 4 thrombosis events). Dietary assessment revealed a low vitamin K intake, excluding the possibility of interactions between warfarin and foods. Nevertheless, many drugs could be implicated in the development of adverse events, mainly simvastatin, omeprazole and paracetamol.

Mean number of drugs was 9.6 ± 4.5 per day, higher than that reported in studies on the use of warfarin among patients in outpatient treatment (4.2 - 4.8 drugs/day.[13-15] The number of medications taken by a patient is considered an exposure factor to drug interactions. Cruciol-Souza et al.,[16] reported that the use of 7 or more medications significantly increased the risk of patients to drug interactions.

The percentage of estimated interactions with warfarin was comparable to that reported in other studies (81-100%).[2,7,8,17,18] Mean number of drug interactions involving warfarin (2.91 ± 1.52 per patient) was similar to that found by Teklay et al.,[17] despite to different methods, setting and time of follow-up between the studies. One peculiarity of our study cohort was the fact that they were

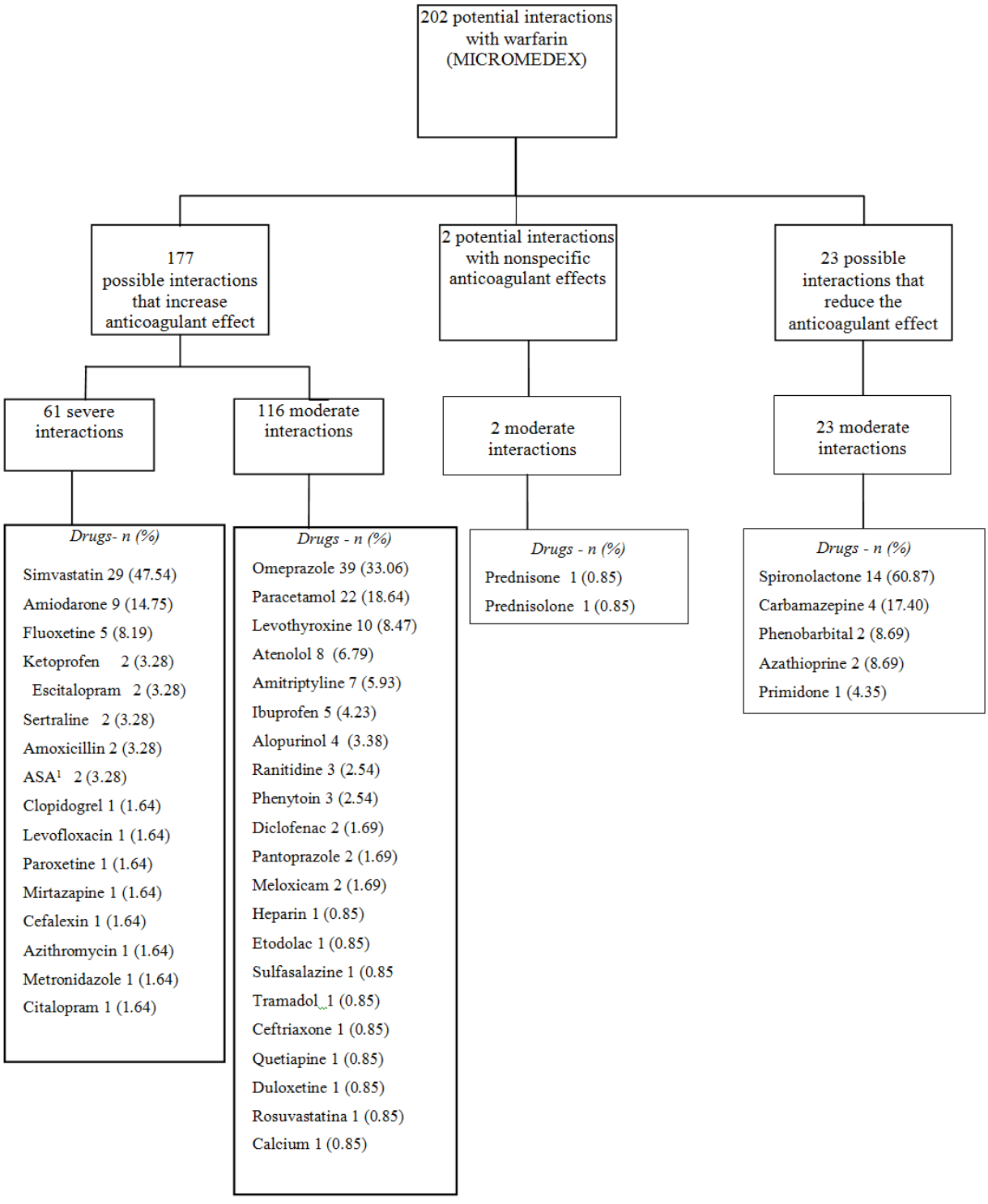

Figure 1 - Potential drug interactions involving warfarin in warfarin users (n = 68) of a cohort of Ijui, Brazil.
ASA: acetylsalicylic acid.

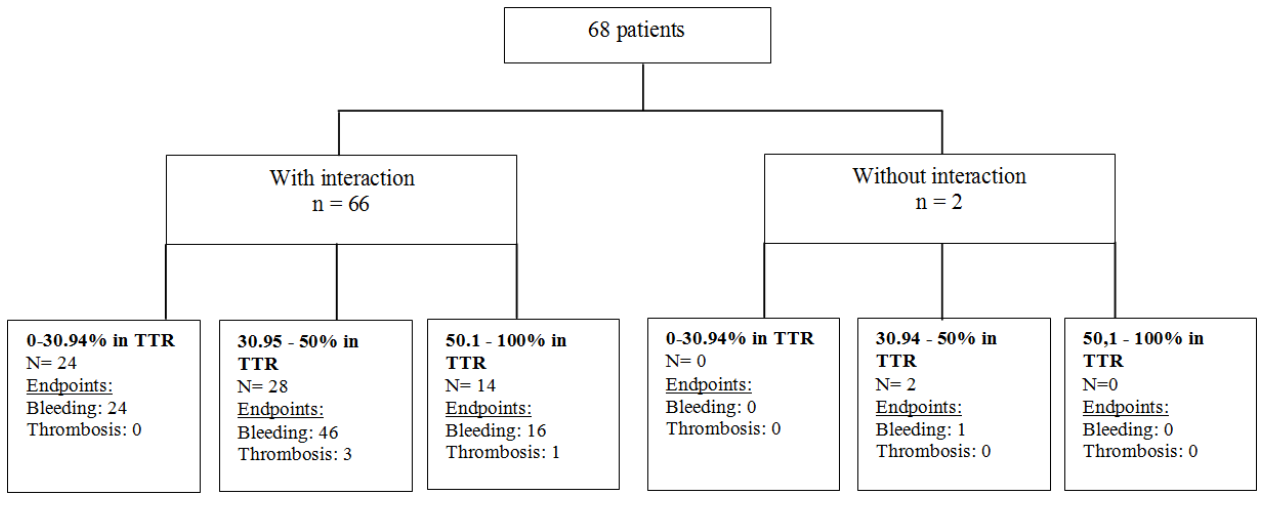

Figure 2 - Drug interactions and Time in Therapeutic Range (TTR) of a cohort of warfarin users (n = 68) in Ijui, Brazil.

Table 1 - Stratification of vitamin K consumption among warfarin users (n = 68) attending public health centers of Ijui, Brazil

Consumption	Vitamin K n (%)[a]
Very low	10 (14.7)
Low	53 (77.9)
Moderate	5 (7.4)
Elevated	-

[a] *number of patients.*

neither followed in an anticoagulation outpatient clinic nor followed for pharmacotherapy, and hence were more vulnerable to drug interactions.

The most cited drugs and drug classes that have the potential to interact with warfarin are antibiotics,[18,19] anticoagulants (heparin and enoxaparin),[7,17] diuretics (spironolactone),[17] betablockers,[17,20] proton-pump inhibitors,[7,18,21] nonsteroidal inflammatory drugs,[8,17,18,22] serotonin selective reuptake inhibitors,[19] amiodarone,[22] paracetamol,[8,14,19] simvastatin,[7] tramadol,[7] levothyroxine.[21] All these drugs were prescribed and taken by our study group.

Many patients who reported bleeding and thromboembolism episodes were exposed to omeprazole, simvastatin and paracetamol. These drugs interact with warfarin by means of competition for the cytochrome P450 metabolism. Nearly 30% of our patients had CYP2C9 polymorphism (data not shown), which would increase the risk for drug interactions. A careful evaluation of risks and benefits would be useful in prescribing simvastatin to anticoagulated patients, due to high severity of the interaction of this drug with warfarin and questionable benefit for patients with low cardiovascular risk.[23] Three patients with low cardiovascular risk were taking simvastatin, who may benefit from simvastatin deprescribing. Deprescribing is the process of discontinuing drugs when existing or potential harms outweigh the benefits, considering patient's need of treatment, level of functioning, life expectancy, values, and preferences. Deprescribing should be a patient-centered intervention; it is not free of uncertainties, and requires shared decision making, informed patient consent, and close monitoring of effects.[24] With respect to omeprazole, it would be prudent to advise patients about safe limits of its use, since important increases in INR may occur during one to two weeks of initiation of moderate/high doses (2-4 g/day) of omeprazole.[10] For omeprazole users, INR monitoring should be performed, with necessary changes in the dosage, or even discontinuation of treatment, aiming to maintain INR at desirable levels.[10] Similar to simvastatin, the use of both omeprazole[25] and paracetamol[26] have been pointed out as excessive and irrational, emphasizing the need to evaluate the real need for its use.

Outside the hospital environment, particularly in non-specialized health settings, warfarin may be prescribed without a routine assessment of INR, potential interactions with foods and other drugs, and clinical outcomes. According to Holbrook et al.,[27] INR should be monitored every 2-4 days after initiation of anticoagulant therapy until therapeutic range is achieved, and as INR stabilization is achieved, monitoring can be weekly. INR monitoring intervals may be gradually increased to every four weeks, as long as INR is within therapeutic range. A monitoring frequency of up to once every 12 weeks may be considered for patients with stable INR, whose treatment remained unchanged within at least three months before. Based on our results, few patients had INR values maintained within recommended range.

The low intake of vitamin K in our study group rules out the possibility of interactions between warfarin and vitamin K-rich foods. Dietary sources of vitamin K, such as leafy vegetables (spinach, broccoli, lettuce), fish, cereals, grains, nuts and cashew apple,[28] are not part of the diet of low income population in Brazil. We did not find any Brazilian study assessing the consumption of vitamin K among patients taking warfarin. A study by Ferreira[11] conducted in Portugal, though, reported a moderate consumption of these foods by most of warfarin users. Cultural, dietary, and income factors may explain this difference. Chang et al.,[28] support that a high or irregular consumption of vitamin K significantly contributes to INR variation. For Violi et al.,[29] however, restriction of vitamin K intake does not seem to be an adequate strategy to improve anticoagulation quality with warfarin. Rather, the authors recommend a balanced and stable dietary habit.[30]

Figure 2 depicts the distribution of patients according to the risk of drug interactions, INR values within therapeutic range and clinical events. Of 66 patients at risk of interactions involving warfarin, only 14 patients had INR values within therapeutic ranges during most of the following-up period (51-100%). These patients reported 16 bleeding events and one episode of thrombosis. Bleeding and thrombosis events were more frequent in the other two groups of patients with a shorter TTR. Both patients not at risk of drug interactions involving warfarin had a TTR shorter than 50% and one of them reported bleeding. In addition, among patients at risk of bleeding, 25 (37.3%) did not show any INR value within therapeutic range during follow-up. Considering INR values outside the therapeutic range, 70% of them were below and 30% above recommended range.

It is worth pointing out that the causes of adverse effects are multifactorial. In addition to the drug interactions discusses in the present study, other factors like low adherence to treatment, self-medication, lack of a continuing monitoring of therapy,[6] age older than 70 years, first month of anticoagulation therapy, uncontrolled hypertension, renal insufficiency, previous gastrointestinal bleeding, and alcohol abuse,[30] may have contributed to the occurrence of bleeding and venous thromboembolism reported by our patients.

Conclusions

Warfarin users in primary care were subjected to a mean of three moderate/severe drug interactions. Exposure to a variety of drugs probably contributed to high occurrence of bleeding. On the other hand, a low vitamin K intake was observed, indicating a low probability of an influence of diet on coagulation in response to warfarin.

Therefore, there is an urgent need for effective interventions aimed at preventing drug interactions and promoting a safe use of warfarin among its users. For this purpose, it is recommended a higher integration between highly qualified health staff members.

Besides, results of this study will serve as a basis for the next step of this investigation that will focus on pharmacotherapy monitoring of anticoagulated patients, aiming at minimizing adverse events from warfarin.

Author contributions

Conception and design of the research: Colet CF, Amador TA, Heineck I. Acquisition of data: Colet CF. Analysis and interpretation of the data: Colet CF, Amador TA, Heineck I. Statistical analysis: Colet CF, Amador TA, Heineck I. Obtaining financing: Colet CF, Amador TA, Heineck I. Writing of the manuscript: Colet CF, Amador TA, Heineck I. Critical revision of the manuscript for intellectual content: Colet CF, Amador TA, Heineck I.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Federal University of Rio Grande do Sul under the protocol number 36.259/2013. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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