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Comparison Between Ibuprofen Arginine and Ibuprofen in Tooth Extraction

Comparación entre ibuprofeno arginina e ibuprofeno en la extracción dental

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Abstract

Introduction: Postoperative pain after extraction of mandibular third molars is a common complaint, requiring effective approaches for its management. **Objective**: To perform a Pilot Study providing information on the management of postoperative pain after extraction of mandibular third molars, comparing the analgesic efficacy and onset of action of ibuprofen associated with arginine with ibuprofen alone. **Methodology**: Prospective, randomized, split-mouth, blinded clinical study involving 14 outpatients, totaling 28 bilateral symmetrical mandibular third molars. Each patient underwent separate surgeries with a regular interval of 15 days between them. At the end of each stage, patients were medicated with ibuprofen (600 mg) associated with arginine (555 mg) or ibuprofen alone (600 mg). Study participants recorded pain intensity using the Visual Analogue Numeric Rating Scale (VAS) over 3 days. **Results**: The onset of analgesia showed statistically significant differences, assessed as the median time to significant pain relief was achieved after 24.8 minutes with ibuprofen associated with arginine, and within 40.2 minutes with ibuprofen ($p = 0.0245$). Analgesic quality was similar between the two groups ($p = 0.2156$). **Conclusions**: Ibuprofen with arginine provides analgesia, achieving pain relief rates similar to the conventional formulation, but with a significantly faster onset of pain relief. The results corroborated the results of previous studies on the efficacy of ibuprofen in acute pain after surgical removal of impacted mandibular third molars.

Keywords: Ibuprofen; Arginine; Analgesia; Oral Surgery; Third Molar.

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Resumen

Introducción: El dolor postoperatorio después de la extracción de terceros molares mandibulares es una queja común, que requiere enfoques efectivos para su manejo. **Objetivo**: Presentar un estudio Piloto proporcionando información sobre el manejo del dolor postoperatorio luego de la extracción de terceros molares mandibulares, comparando la eficacia analgésica y el inicio de acción del ibuprofeno asociado a arginina con el ibuprofeno solo. **Metodología**: Estudio clínico prospectivo, aleatorizado, de boca dividida, ciego, en el que se incluyeron 14 pacientes ambulatorios, con un total de 28 terceros molares mandibulares simétricos bilaterales. Cada paciente fue sometido a cirugías separadas con un intervalo regular de 15 días entre ellas. Al final de cada etapa, los pacientes fueron medicados con ibuprofeno (600 mg) asociado con arginina (555 mg) o ibuprofeno solo (600 mg). Los participantes del estudio registraron la intensidad del dolor utilizando la Escala Numérica Analógica Visual (EVA) durante 3 días. **Resultados**: El inicio de la analgesia mostró diferencias estadísticamente significativas, evaluadas como el tiempo medio hasta el alivio significativo del dolor se logró después de 24,8 minutos con ibuprofeno asociado a arginina, y dentro de los 40,2 minutos con ibuprofeno ($p = 0,0245$). La calidad analgésica fue similar entre los dos grupos ($p = 0,2156$). **Conclusiones**: El ibuprofeno con arginina proporciona analgesia, lográndose tasas de alivio del dolor similares a la formulación convencional, pero con un inicio del alivio del dolor significativamente más rápido. Los resultados corroboraron los resultados de estudios previos sobre la eficacia del ibuprofeno en el dolor agudo después de la extracción quirúrgica de terceros molares mandibulares impactados.

Palabras Clave: Ibuprofeno; Arginina; Analgesia; Cirugía Oral; Tercer molar.

Introduction

The use of non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, has been reported to be effective in controlling postoperative pain in dental surgeries. NSAIDs are indicated for the control of inflammation, pain, and postoperative edema. Additionally, they promote tissue repair, enabling patients to return more quickly to their daily routines [1-4].

Ibuprofen belongs to the class of NSAIDs derived from propionic acid. In addition to its anti-inflammatory properties, it possesses analgesic and antipyretic effects [3]. Its analgesic efficacy has been confirmed in managing pain related to soft tissue trauma and in the postoperative period of oral surgeries [3, 5, 6, 7].

Considering the direct relationship between peak ibuprofen concentrations, peak analgesic effect, and duration of analgesia [8, 9, 10,] researchers have investigated various oral formulations and different ibuprofen salts to enhance absorption properties and speed of onset of action. The objective is to achieve a rapid increase in plasma concentrations for a quicker analgesic effect. These formulations include lysine ibuprofen [11], sodium ibuprofen [12], arginine ibuprofen [11, 13-16], and liquigel ibuprofen [5,] popularly known as fast-acting formulations. Fast-acting ibuprofen formulations appear to lead to higher plasma concentrations within one hour [17].

Ibuprofen arginine is a medication created by adding the amino acid arginine, possessing analgesic, antipyretic, and anti-inflammatory effects. The inclusion of arginine seems to facilitate rapid absorption through the gastric and enteric mucosa [11, 13, 14, 16, 17].

The data from this study aim to contribute to postoperative pain management in oral surgery and assist healthcare professionals in selecting appropriate analgesic strategies. As such, the study seeks to answer the following questions: Is postoperative pain relief faster with ibuprofen arginine when compared to regular ibuprofen? And, is the quality of analgesia equivalent?

Methodology

Study Design

The study was designed as a study, single-centre, prospective, split-mouth, randomized, blinded, clinical trial. The measurement of postoperative pain in impacted third molar extraction procedures is shown to be an effective model for testing, analyzing, and evaluating the action of analgesic and anti-inflammatory drugs [18-20].

Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of: Ethics Committee.

Study Population

Study participants were recruited from patients referred for the surgical removal of bilateral impacted mandibular third molars to the department of oral and maxillofacial surgery at the Federal University of Espírito Santo, between March and September 2019. Each subject signed a detailed informed consent form prior to participation in the study.

Patient selection used as inclusion criteria: healthy volunteers (male and female), age between 18 and 30 years, with third mandibular molars with indication for extraction where both were in the same position according to the Pell and Gregory classification [21]. Exclusion criteria were patients with history of hypersensitivity to the active ingredient ibuprofen arginine or to any of the excipients; history of hypersensitivity reactions in response to acetylsalicylic acid (ASA) or other non-steroidal anti-inflammatory drugs; active peptic ulcer/bleeding or history of recurrence (two or more different episodes of demonstrated ulceration or bleeding); active bleeding, such as cerebrovascular or ulcerative colitis; signs of severe liver or kidney failure; signs of uncontrolled severe heart failure; bleeding in the stomach or intestine, or any type of bleeding at the time associated or not with anti-inflammatories or acetylsalicylic acid; black stools or bloody diarrhea; hemorrhagic diathesis (clotting disorder); bleeding or blood clotting disorders, or were taking blood thinners; gestational or postpartum period[22].

An estimate of the sample calculation is made in relation to the number of patients treated in the service, taking into account that the sample will only be those patients who meet the inclusion criteria, estimating in the first instance approximately 27 third molar surgery procedures, with a confidence level of 95% and a margin of error of 5%. This will be contrasted by performing an exact count of the sample obtained.

Blinding

Patients, surgeons, clinical and statistical investigators were blinded by analgesic treatments administered with package indistinguishable in appearance. The only non-blinded person was an external collaborator involved in the verification of doses.

Surgical Procedure

The volunteers underwent anamnesis (standard medical records), with registration of vital signs, blood pressure and heart rate, according to pre-established techniques. All patients signed informed consent forms for the research.

Interventions were performed in an outpatient setting, under local anesthesia with Alphacaine® (association of 2% lidocaine hydrochloride and 1:100,000 adrenaline). The pre-operative protocol included amoxicillin (2g) according to American Heart Association. All procedures were performed by one surgeon and assistant experienced in oral surgery. The surgeries were performed in the morning to avoid influence of circadian rhythms.

All the procedures followed the biosafety rules. An envelope mucoperiosteal flap was raised, osteotomy and tooth sectioning were performed, and both two parts of the tooth were extracted [21]. After the socket debridement, the flap was repositioned and stabilized with 4/0 non-absorbable interrupted sutures (Mononylon Ethilon®, Ethicon S. p. A. Johnson & Johnson). Surgical techniques and procedure duration were identical on both sides. The operation time was measured from anesthesia to the last stitch. Sutures were removed 1 week later.

Postsurgical instructions were given to each patient concerning food consumption as well as hygiene at surgical site. Patients were also asked to report any adverse events occurring during the study period.

Study Medication

In the first surgical procedure, the mandibular right third molar was extracted, using SPIDUFEM 600® (oral solution 1155 mg, equivalent to 600 mg of ibuprofen and 555 mg of arginine) as postoperative medication in a dose of 1 envelope of 600 mg every 8 hours for 3 days.

The second surgical procedure, realized 15 days after the first one, consisted of extracting the mandibular left third molar, using BUPROVIL® 600 mg (600 mg ibuprofen tablet) as a postoperative medication in a dose of 1 tablet every 8 hours for 03 days.

The patients were instructed to take the medication from the moment they felt the end of the anesthesia action. During the postoperative period, paracetamol 500mg was prescribed to patients as rescue therapy. All research medications were provided to patients at no cost.

Assessement

At the end of each phase, patients performed self-assessment at regular intervals of 12 hours for 3 days after administration of the first dose of medication selected through the Visual Analogue Scale (VAS), marking 0 to 10, being 0, no pain and 10, severe pain [23]. After taking the first dose, patients were instructed to set the necessary time for significant pain relief.

Patients were not allowed to receive analgesic opioids, anti-inflammatories, and tranquilizers before surgery and throughout the study period. The use of any concomitant medication, including psychotropics, antidepressants, sedative-hypnotics, or other NSAIDs that could potentially confound pain relief assessments, was also not allowed. The only exception was the use of "rescue medication" (Paracetamol 500 mg) postoperatively if the patient did not obtain pain relief with the research medication.

Patient identification and number, medication per procedure, vital signs before surgery, surgery start and end time, number of anesthetic tubes and possible intercurrences were recorded on a control form.

Statistical Methods

The survey data are presented in graphs and tables where the mean and standard deviation for the quantitative data were calculated. The times for comparing the onset of analgesia with the drugs were analyzed using the Wilcoxon test, and the significance level used was $p = 0.05$. All patients who received the study medication were included in the calculation of medians and in the comparison of results of analgesia onset times. The levels of analgesia obtained (analgesic quality) were compared using the statistical software SPSS version 22 and ANOVA test (two-way ANOVA), the significance level used was $p = 0.05$.

Results

Fourteen patients were included in the study, who underwent extraction of mandibular thjrd molars bilaterally according to the standard of surgical care. After the extraction sujrgery of the mandibular third molar on the right side, *Spidufen*® (Ibuprofen with arginine) was used and for the left side *Buprovil*® (Ibuprofen) for each patient, thus totaling twenty-eight surgical procedures. Two patients chose to leave the research, one patient developed alveolitis at the postoperative period and the other had inferior alveolar nerve's paresthesia being excluded. The final sample consisted of 10 patients, 6 were female and 4 were male. The age of the patients ranged from 21 to 27 years, with a mean of 23.6 years (**Table 1**).

Table 1- Distribution of patients according to gender and age

N	Sex	Age
1	Masculine	20
2	Feminine	27
3	Feminine	25
4	Feminine	21
5	Masculine	25
6	Feminine	23
7	Feminine	24
8	Masculine	24
9	Masculine	24
10	Feminine	23
Arithmetic Mean		23.6

Onset of Analgesic Action

The onset of analgesic action of ibuprofen with arginine (IBUA) was on average 24.8±15.7 minutes (TMed), with a minimum time (Tmin) of 5 minutes and a maximum (Tmax) of 60 minutes. Onset of action of ibuprofen (IBU) was on average 40.2±26.4 minutes, with a minimum time of 15 minutes and a maximum of 94 minutes. The values referring to the time of onset of action are shown in **Figure 1.**

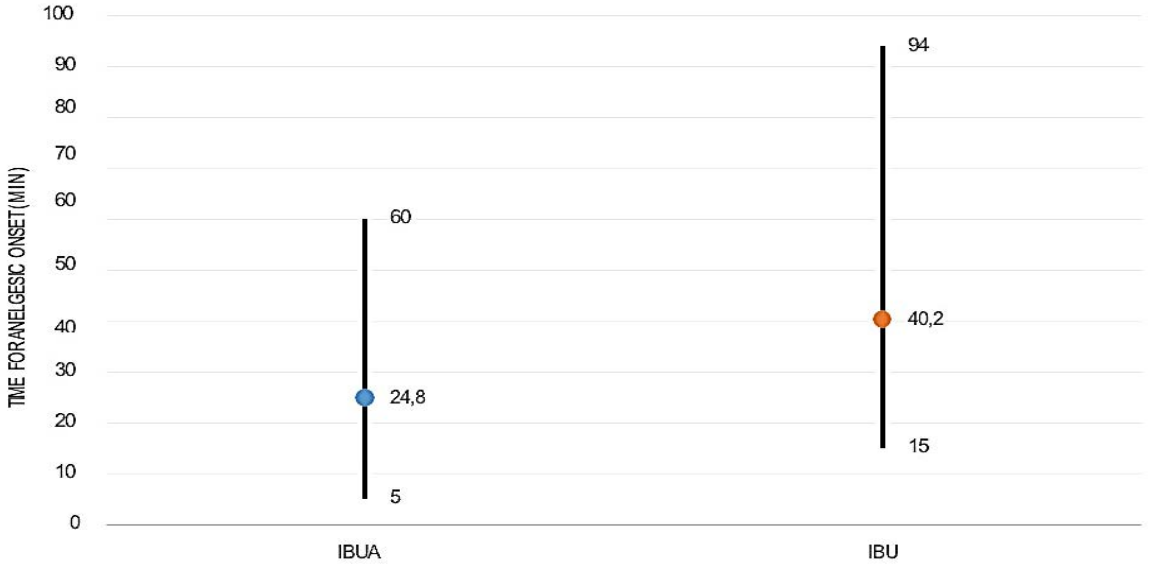

Figure 1 - Time required (means, minimum and maximum) to start analgesia with ibuprofen and ibuprofen arginine reported by the patients
IBUA- Ibuprofen with arginine. IBU- Ibuprofen

The onset of analgesia was clinically faster, and statistically significant (p= 0.0245), in patients treated with ibuprofen arginine when compared to patients treated with ibuprofen, using significant pain relief as a parameter.

Analgesic Quality

Next, shown in **Figure 2**, the comparison of the mean values of VAS obtained in the morning (first value of the category) and in the afternoon (second value of the category) of the three postoperative days. Patients medicated with IBUA had similar pain scores to IBU, being statistically non-significant (p= 0.2156). This relationship can also be seen in **Firuge 3.**

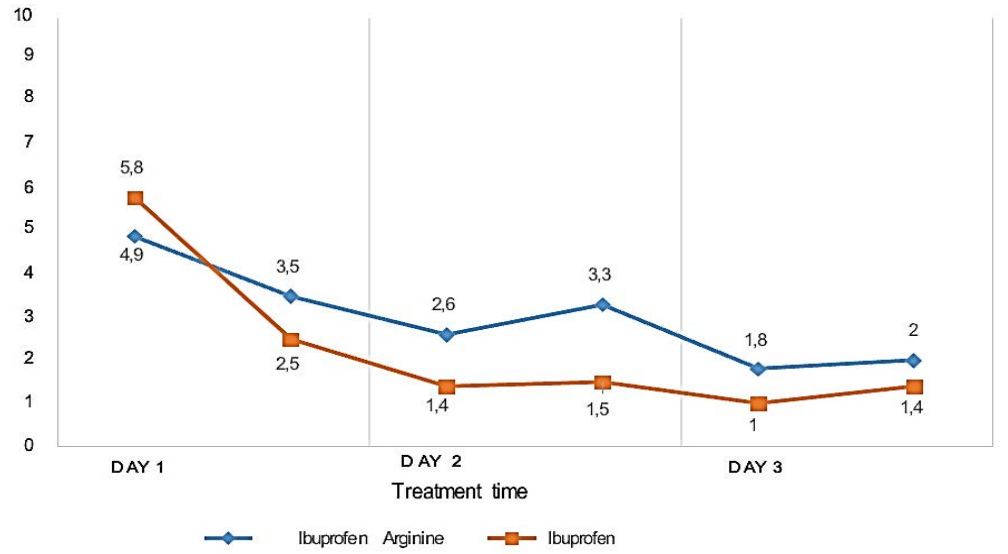

Figure 2 - Comparison of mean VAS values obtained in the morning (first value of the category) and in the afternoon (second value of the category) of the three days of treatment.
VAS: Visual Analogue Scale

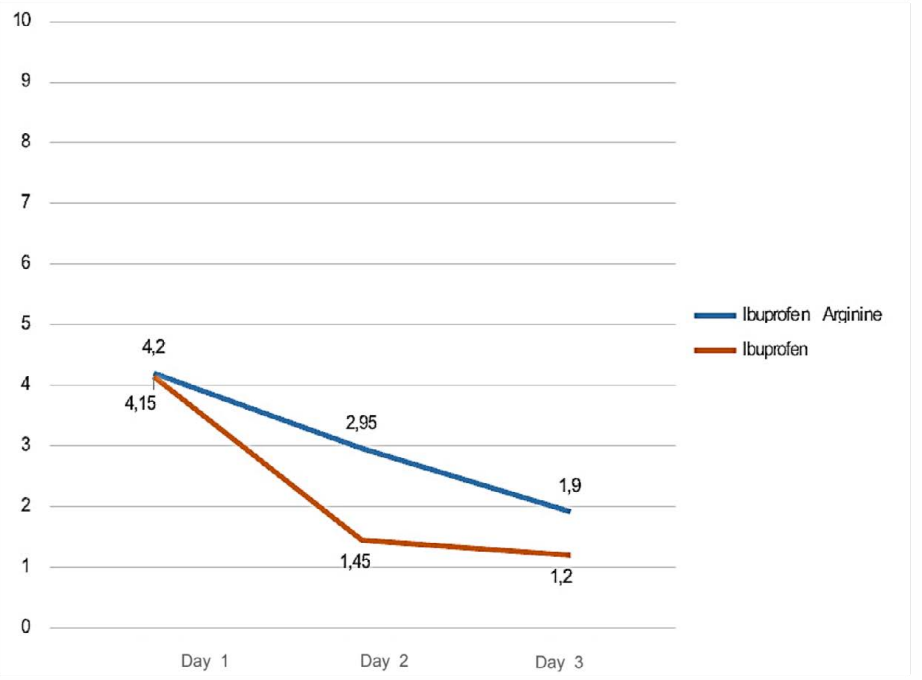

Figure 3 - Comparison of the overall average of VAS values per day for the three days of treatment.
VAS: Visual Analogue Scale

The use of emergency medication was reported by only 20% (n= 2) of the patients in the sample, both on the first day of treatment with ibuprofen associated with arginine.

Tolarance and Safety

None of the patients during treatment with either ibuprofen-arginine or ibuprofen, reported adverse reactions to the use of the medications.

Discussion

The use of ibuprofen at dosages of 400mg, 600mg, and 800mg, as observed in clinical studies, provides analgesia of identical quality to the paracetamol-codeine combination, making it a viable alternative for pain management. Furthermore, 600 mg of ibuprofen demonstrated a longer duration of analgesia when compared to paracetamol-codeine, thereby reducing the frequency of analgesic intake [24, 25]. Moreover, regarding analgesic equivalence, another study suggests that the addition of 60 mg of codeine to 1000 mg of paracetamol or 400 mg of ibuprofen does not offer superior analgesia compared to non-opioid medications. This finding questions the common practice of combining opioids with non-opioid analgesics [25]. These studies collectively demonstrate that ibuprofen is as effective as opioid analgesics.

Ibuprofen arginine was developed with the aim of maintaining the well-established efficacy and safety of ibuprofen as an analgesic and anti-inflammatory while accelerating the absorption of pure ibuprofen for quicker pain relief in acute conditions [26, 27]. For our clinical investigation, we utilized the extraction of third molars as it serves as an effective model for testing, analyzing, and evaluating the action of analgesic and anti-inflammatory drugs [18-20].

In vitro studies have revealed that saline forms of ibuprofen, when associated with sodium or arginine, dissolve more rapidly than the corresponding free acid. This effect is more pronounced in low pH environments, mimicking the gastric conditions [28, 17]. Subsequently, in vivo studies have confirmed a higher bioavailability of ibuprofen salts compared to the free acid due to increased water solubility, drug dissolution rate, and greater absolute bioavailability in healthy volunteers [17]. The enhanced bioavailability of the drug does not result in a shorter elimination half-life compared to pure ibuprofen [29].

Clinical studies have demonstrated that the ibuprofen-arginine combination yields a faster analgesic effect when compared to ibuprofen alone [14-16]. Additionally, ibuprofen-arginine has shown significant superiority over ibuprofen in terms of pain and swelling control [16].

In our study, the ibuprofen-arginine combination exhibited a significantly faster onset of action compared to ibuprofen ($p = 0.0245$), which aligns with results from other clinical and in vitro studies [11, 13, 14, 16, 17, 28]. It's worth noting that the pharmaceutical presentation of the medication may also influence its rapid onset of action, as suggested by Li H and colleagues [30], who found that effervescent ibuprofen had faster absorption and onset of action compared to traditional tablets. This raises questions about whether the ibuprofen-arginine formulation with the effervescent presentation (Spidufen®) might offer even quicker relief due to the combination of arginine and the pharmaceutical presentation.

The increase in drug bioavailability, demonstrated in our study through the rapid onset of analgesic action, was not associated with a shorter elimination half-life when compared to pure ibuprofen, a pattern also noted by other researchers [11, 14, 13, 17, 29]. In a study by Lisboa & Pilatti [31], which evaluated analgesia provided by ibuprofen-arginine, no statistical difference was found in pain control and edema after mandibular third molar extractions between medications. This suggests that due to its fast action, arginine ibuprofen can be used as preemptive analgesia in third molar surgeries.

There was no difference in the quality of analgesia during the postoperative period between the two medications ($p = 0.2156$). This result differs from some authors whose findings indicate a greater analgesic potency of arginine ibuprofen compared to isolated ibuprofen [11, 16]. Other studies suggest at least identical analgesic efficacy of

ibuprofen-arginine in relation to analgesics combined with opioids [25, 24, 32-35]. The divergence in our data compared to other studies may be attributed to the smaller sample size. Despite similar analgesia scores between the groups, two patients used rescue medication on the first postoperative day when analyzing the VAS scores. The use of rescue medication could be related to individual pain perception, shaped by past experiences, traumas, and cultural factors.

The enhanced efficacy of the ibuprofen-arginine combination did not result in a higher rate of adverse reactions when compared to the standard formulation. No patients reported adverse reactions with either medication, which aligns with the findings of other studies [11, 13-15, 31, 33-40]. High-quality scientific evidence supports the use of ibuprofen in clinical practice after third molar extraction due to its analgesic efficacy and a safety profile similar to other traditional NSAIDs [26, 27]. Additionally, administering ibuprofen immediately after surgery is associated with lower pain intensity and reduced need for additional analgesic medications [22].

Meta-analytic evidence shows that paracetamol, over NSAIDs: I) has an opioid-sparing effect of approximately 40% (regardless of the type of surgery), and II) does not present differences with respect to the reduction of pain intensity at rest [40].Meta-analytic evidence also confirms the synergy of both and suggests the combination of paracetamol with NSAIDs for greater analgesia compared to paracetamol or NSAIDs alone [41] This suggests that the path to efficient analgesia should include both paracetamol and an NSAID (regardless of pain intensity and the route of administration of the opioid), So it's good as a rescue dose[42-43].

Conclusion

The results of this study are consistent with previous research on the efficacy of ibuprofen in managing acute pain following the surgical removal of impacted mandibular third molars. It supports the hypothesis that the combination of ibuprofen and arginine is as effective as ibuprofen in pain relief but offers a faster onset of action without increasing side effects. Based on the findings presented in this article, further studies are warranted better to understand the role of ibuprofen arginine in dental surgeries. It should be noted that this study is a pilot study, derived from a small sample, which limits its significance; however, when making predictions based on the number and quantity of patients treated and assessed in the service (At the beginning we estimated a sample of 27 procedures and there were 14 patients with 28 procedures, that is, the extraction of two third molars for each one). A new multicenter study is planned to provide additional information considering the limitations of this study (such as the small sample), with the goal of recruiting a larger sample that provides conclusive results if they occur and allows for a clear comparison of the analgesic effects in each case.

Authors' contributions

GSCF, conception or design of the work, data analysis and interpretation, drafting of the work, final approval of the version to be published. AIP, data analysis and interpretation, drafting of the work. GIT, data analysis and interpretation, drafting of the work. B-SB, conception or design of the work, data analysis and interpretation, critical review. RAGJ, conception or design of the work, data interpretation, critical review. SDN, conception or design of the work, data interpretation, critical review. BRM, conception or design of the work, data interpretation, critical review. GS, conception or design of the work, data analysis and interpretation, critical review, final approval of the version to be published. SMA, conception or design of the work, data analysis and interpretation, critical review, final approval of the version to be published.

Ethical considerations

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of: Ethics Committee of Federal University. The approval code for this study is: (Opinion n° 2,242,478).

Competing interests

The authors have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

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