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Synergistic anti-inflammatory effect of NSAIDs plus B vitamins administered pre and postoperatively in third molar surgery: randomized clinical trial

Efeito anti-inflamatório sinérgico da associação de AINEs e vitaminas do complexo B administrada no pré e pós-operatório de cirurgia de terceiros molares: ensaio clínico randomizado

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ABSTRACT

Objective: The aim of the present study was to evaluate the synergistic anti-inflammatory effect of Non-steroidal anti-inflammatory drugs (NSAIDs) plus B vitamins administered pre and postoperatively in surgeries of impacted mandibular third molars. **Material and Methods**: Double-blind randomized clinical trial, sixty-six patients participated and were randomized into 2 groups. The control group was administered meloxicam 15 mg intramuscularly plus placebo orally and to the experimental group, meloxicam 15 mg intramuscularly plus vitamins B [B1, B6, and B12] orally; both treatments were administered preoperatively. The anti-inflammatory effect was evaluated by pain intensity, facial swelling (facial contour measurements), and mouth opening (distance between the upper and lower incisors) during the post-surgical phase. Student's t-test was performed for independent samples. **Results**: In all the evaluated times (1 hour, 6 hours, 12 hours, 24 hours, 2 days, and 3 days after the end of the surgery) the experimental group presented a significantly lower intensity of pain compared to the control group ($p<0.05$). The highest pain intensity was recorded at 6 hours (17.7 ± 9.1 mm in the experimental group and 34.5 ± 21.3 mm in the control group). Swelling and mouth opening were similar in both groups, at all times evaluated ($p>0.05$). **Conclusion**: In the present study, the administration of NSAIDs plus B vitamins (B1, B6, B12) produced lower intensity of pain compared to the administration of only NSAIDs. Nevertheless, swelling and mouth opening were similar in all evaluations for both study groups.

KEYWORDS

Vitamin B complex; Inflammation; Meloxicam; Molar, third; Pain.

RESUMO

Objetivo: O objetivo do presente estudo foi avaliar o efeito anti-inflamatório sinérgico de anti-inflamatórios não esteroidais (AINEs) com vitaminas do complexo B administrados no pré e pós-operatório de cirurgias de terceiros molares inferiores impactados. **Material e Métodos:** Ensaio clínico randomizado duplo-cego, 66 participantes que foram randomizados em 2 grupos. O grupo controle recebeu Meloxicam 15 mg por via intramuscular + placebo por via oral e o grupo experimental, Meloxicam 15 mg por via intramuscular + vitaminas B [B1, B6 e B12] por via oral; ambos os tratamentos foram administrados no pré-operatório. O efeito anti-inflamatório foi avaliado pela intensidade da dor, edema facial (medidas do contorno facial) e abertura da boca (distância entre os incisivos superiores e inferiores) durante a fase pós-cirúrgica. Foi aplicado o teste t de Student para amostras independentes. **Resultados**: Em todos os tempos avaliados (1 hora, 6 horas, 12 horas, 24 horas, 2 dias e 3 dias após o término da cirurgia) o grupo experimental apresentou uma intensidade de dor significativamente menor

em relação ao grupo controle (p <0,05). A maior intensidade de dor foi registrada em 6 horas (17,7 ± 9,1 mm no grupo experimental e 34,5 ± 21,3 mm no grupo controle). Edema e abertura bucal foram semelhantes nos dois grupos, em todos os momentos avaliados (p>0,05). **Conclusão**: No presente estudo, a administração de AINEs com vitaminas do complexo B (B1, B6, B12) resultou em menor intensidade de dor em comparação com a administração apenas de AINEs. No entanto, o edema e a abertura da boca foram semelhantes em todas as avaliações para ambos os grupos de estudo.

PALAVRAS-CHAVE

Complexo vitamínico B; Inflamação; Meloxicam; Dente serotino; Dor.

INTRODUCTION

Worldwide, the prevalence of third molar impaction is 24.4%, with the mandible being the most likely impaction site with 57.6%. Third molar surgery leads to soft and hard tissue trauma to varying degrees [1]. This depends on several factors such as its anatomical location, obstruction of the adjacent teeth, and the depth of embedding of the tooth in the bone tissue (imaging studies usings radiographs or images free of ionizing radiation [2,3]) [1].

According to some studies, preventive analgesia with NSAIDs and particularly with cyclooxygenase 2 (Cox-2) inhibitors has shown to be effective in reducing central and peripheral sensitization, avoiding the amplification of the nociceptive stimulus [4-6].

Meloxicam is a preferential Cox-2 inhibitor with a rapid onset of action (30 minutes) and a long half-life (15 to 20 hours). Also risk of adverse effects is significantly lower compared to other conventional NSAIDs [7]. In addition, this surgery can trigger mixed-type pain, which makes pain management even more complex. The therapeutic option for this problem is the association of NSAIDs with vitamin B, since the B vitamins have an antinociceptive, antihyperalgesic and antiallodinic effect [8]. The B vitamins when associated with NSAIDs could produce a synergistic effect, enhancing their analgesic and anti-inflammatory effects, reducing adverse effects by requiring lower doses of NSAIDs. However, these beneficial effects have been little studied [9-13].

The aim of the present study was to evaluate the synergistic anti-inflammatory effect of NSAIDs plus B vitamins administered pre and postoperatively in surgeries of impacted mandibular third molars.

MATERIAL AND METHODS

Ethical considerations

The present study followed CONSORT guidelines for clinical trials. The study was approved by the ethics committee of the Hipólito Unanue National Hospital (Code Nº121-2019) and according to the International Conference on Harmonization Good Clinical Practice (ICH-GCP), considering the 1975 Declaration of Helsinki, as revised in 2000 [14]. Participants who accepted the conditions of the study signed the informed consent, which detailed the potential benefits and harms of participating in the study.

Design

A single-center, prospective, parallel, double-blind randomized clinical trial was performed.

Sixty-six patients with impacted mandibular third molars who were recruited in 2019 at the Hipólito Unanue National Hospital.

The inclusion criteria were ASA I patients between 18 and 30 years of age, with mandibular third molars with partial or complete impaction, requiring osteotomy for their extraction. Patients who did not receive NSAIDs and/or analgesics until one week before the surgical procedure were included. Patients with a history of alcoholism, smoking, consumption of illicit substances, hypersensitivity to NSAIDs or paracetamol, and symptoms associated with the third molar up to one week before extraction were excluded. For the included patients, the Gbotolorun surgical difficulty index was obtained, which considers age, body mass index, depth of the elevation points of the tooth, and curvature of the roots [15].

Participants were randomly assigned to two groups of 33 members. The control group received meloxicam 15 mg (Flodin®, Tecnofarma, Lima, Perú) intramuscularly plus placebo (starch tablet)

orally and the experimental group received meloxicam 15 mg (Flodin®) intramuscularly plus B vitamins [thiamine 100 mg, pyridoxine 100 mg, and cyanocobalamin 5000 mcg] (Neurobion 5000® tablet, Merck, Lima, Perú) orally. Both treatments were administered 30 minutes before the start of surgery. The patients were unaware of the treatment they received. The outcomes to be evaluated were pain, swelling, and trismus.

The sample size was calculated with a power of 80% and an alpha of 5%. According to the visual analog scale (VAS) the standard deviation of the first group was 1.47 and of the second group 1.45; furthermore, as differences of means, 1.12 was considered.[12] The sample size was 60 patients. In addition, it was considered to add 10% of missing data, so the sample size is 66.

The random assignment codes were made by simple randomization (random number table), and allocation concealment was performed by means of opaque envelopes. For masking, the placebo tablets exhibited similar shape, size, and taste characteristics to the Neurobion 5000® tablets. Neither the surgeon nor the patients knew to which study group they were assigned.

Surgical procedure

All surgeries were performed by the same oral and maxillofacial surgeon, using a standard surgical technique of bone removal and tooth sectioning with a No. 0541 26 mm surgical fissure drill (Denstsply Maillefer® Dentsply International, Ballaigues, Suiza). Subsequently, the primary closure of the surgical wound was performed with a 3-0 silk suture.

Immediately following the surgical procedure, all patients were given routine postoperative indications and were prescribed clindamycin 300 mg orally every 08 hours for 07 days. Additionally, after 12 hours, the control group was prescribed diclofenac 50 mg (Voltaren® Novartis, Lima, Perú) orally every 8 hours for 5 days and the experimental group, diclofenac 50 mg plus B vitamins [thiamine 50 mg, pyridoxine 50 mg and cyanocobalamin 1000 mcg] (Doloneurobion Forte®, Merck, Lima, Perú) orally every 8 hours for 5 days.

For pain assessment, each patient was instructed to measure postoperative pain intensity with the VAS. The extreme point on the left represented zero (no pain) and the extreme point on the right represented one hundred (maximum pain imaginable). The patients recorded the intensity of pain during the postoperative phase (1 hour, 6 hours, 12 hours, 24 hours, 2 days, and 3 days after the end of the surgery).

The swelling was evaluated by summation of 5 lines of facial contour measurement using craniometric points (mm) [Figure 1]. Measurements were made with tapes and a calibrated electronic vernier, recording a baseline value (before surgery) and after 1 hour, 24 hours, 3 days, and 7 days after the end of the surgery.

The mouth opening was evaluated by measuring the distance between the incisal edges of pieces 11 and 41 (mm). It was performed with a calibrated electronic vernier, recording a baseline value (before surgery) and after 1 hour, 24 hours, 3 days, and 7 days after the end of the surgery.

Statistical analysis

Statistical analysis was performed using Stata software version 16.0. The numerical variables were expressed as mean and standard deviation. In addition, an intention-to-treat analysis was performed considering the last observation made. For the evaluation of outcomes, a parametric

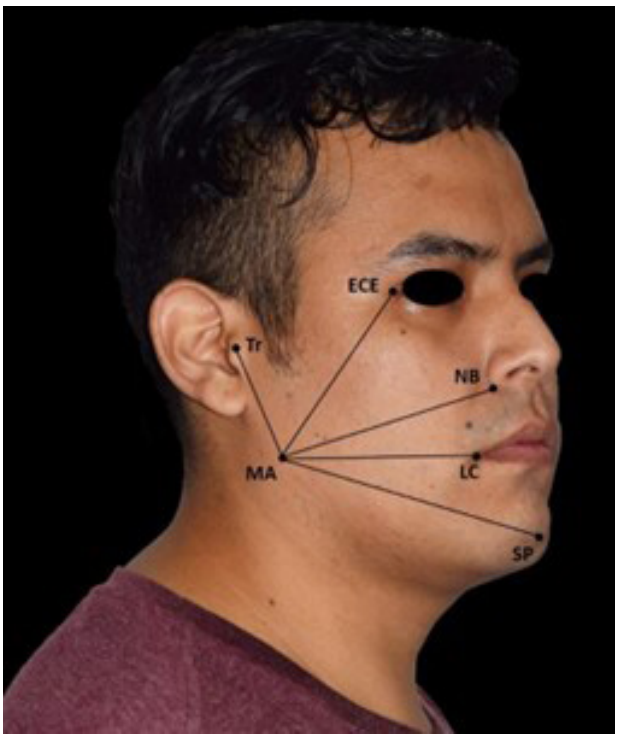

Figure 1. Facial measurements taken from the study groups for the evaluation of facial swelling. Tr: tragus, MA: mandibular angle, ECE: external angle of the eye, NB: external wing of the nose, LC: labial commissure and SP: soft pogonion.

Student's t-test was performed for independent samples considering a p-value less than 0.05 to reject the two-tailed null hypothesis.

RESULTS

Of 76 patients who met the eligibility criteria, 10 patients were excluded. Of the 66 participants included, 27 were male and 39 females. The average age was 23.8 ± 4.9 years. The patients were randomized to the control and experimental group. Six patients were lost to follow-up. [Figure 2] The baseline characteristics of the subjects in the study groups are presented in Table I.

Pain (VAIN) scores

It was found that the intensity of pain, at all evaluated times, was significantly lower in the experimental group. The greatest intensity of pain occurred at 6 hours, with a value of 34.5 ± 21.3 mm (95%CI = 26.9-42.1) for the

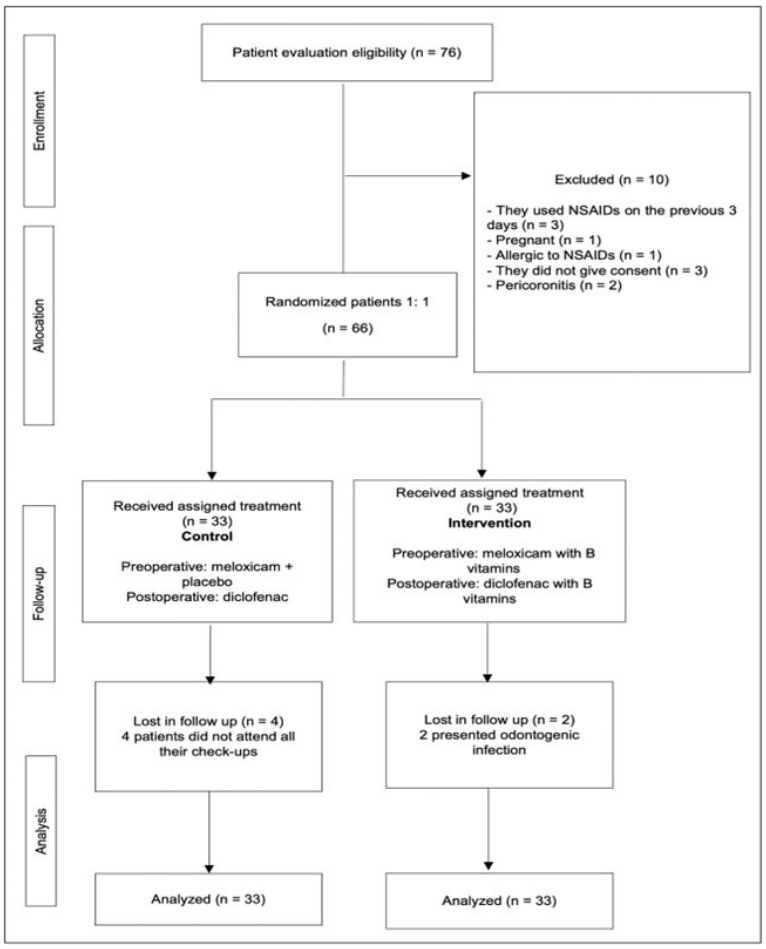

Figure 2. Flowchart of the participants in the clinical trial according to CONSORT.

Table I - Characteristics of the patients included in the two treatment groups

	NSAIDs (n=33)	NSAIDs with B vitamins (n=33)	Total (n=66)	p-value
Gender				0.226
Female	21 (63.6%)	18 (54.5%)	39 (59.1%)	
Male	12 (36.4%)	15 (45.5%)	27 (40.9%)	
Age (years)*	23.7 ± 4.5	24.3 ± 5.3	23.8 ± 4.9	0.092
Duration of surgery (min)*	27.1 ± 4.3	28.9 ± 6.6	27.6 ± 6.8	0.098
Surgical difficulty index (Gbotolorun)*	10.1 ± 2.3	9.4 ± 2.4	9.8 ± 2.4	0.084
Number of anesthesia cartridges *	3.82 ± 0.4	3.94 ± 0.4	3.9 ± 0.4	0.443

*Data are means ± standard deviation (numerical) or number (%) (nominal).

control group and a value of 17.7 ± 9.1 mm (95%CI = 14.5-20.9) for the experimental group; p=0.001 [Table II and Figure 3].

Swelling measurement (mm)

It was found that the level of swelling was similar between both study groups at all times evaluated. The highest level of swelling was recorded on the third postoperative day, with a swelling level of 482.3 ± 27.1 mm for the control group and a value of 478.8 ± 29.7 mm for the experimental group; p=0.627 [Table III].

Maximum Inter-Incisal Opening (mm)

It was found that the mouth opening was similar between both study groups in all the evaluated times. The lowest degree of mouth opening was recorded on the first postoperative day [Table IV].

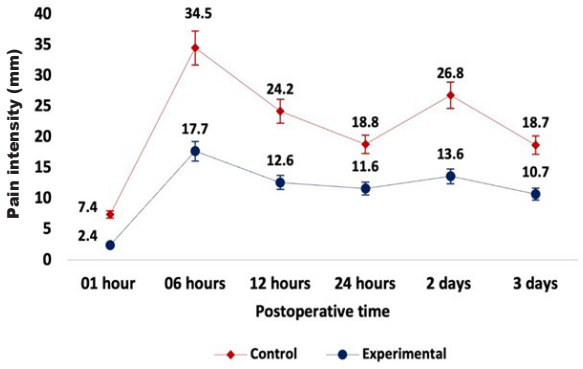

Figure 3. Comparison of pain intensity according to the VAS in both study groups. VAS (Visual Analogue Scale).

DISCUSSION

The present study found that patients who received NSAIDs plus B vitamins pre and postoperatively had a significantly lower intensity of pain compared to patients who received only NSAIDs pre and postoperatively. Oral swelling and opening were similar at all times evaluated in both groups.

Cetira et al. [16] mentioned that the preoperative administration of NSAIDs to third molar surgery significantly decreased pain (1 hour and 6 hours postsurgical), which would produce greater patient comfort in the postoperative.

The preoperative administration of meloxicam has been reported to produce a significantly superior analgesic and anti-inflammatory effect compared to other analgesic and/or anti-inflammatory drugs (diclofenac, tramadol, celecoxib) in mandibular third molar surgery [17-19]. In this study, treatment was started preoperatively with meloxicam administered intramuscularly since it is a long-acting NSAID; and that it has been shown to be useful in impacted third molar surgery [20,21]. This was followed by a short half-life NSAID such as diclofenac, which has also been shown to be

Table II - Comparison of pain between study groups at different postoperative times (VAS)

Postoperative time	NSAIDs (n=33)	NSAIDs with B vitamins (n=33)	P-value *
01 hour	7.4 ± 2.1	2.4 ± 1.1	0.033
06 hours	34.5 ± 21.3	17.7 ± 9.1	0.001
12 hours	24.2 ± 22.3	12.6 ± 8.6	0.025
24 hours	18.8 ± 14.8	11.6 ± 7.5	0.002
2 days	26.8 ± 23.1	13.6 ± 11.3	0.018
3 days	18.7 ± 13.1	10.7 ± 7.4	0.016

Values are means ± standard deviation. VAS (Visual Analog Scale). * Student's t-test for independent samples (p<0.05).

Table III - Comparison of swelling (mm) between study groups at different postoperative times

Postoperative time	NSAIDs (n=33)	NSAIDs with B vitamins (n=33)	p-value *
Basal	464.9 ± 22.7	456.9 ± 28.9	0.426
01 hour	467.8 ± 22.9	464.7 ± 27.7	0.623
24 hours	476.5 ± 25.8	474.1 ± 27.9	0.711
3 days	482.3 ± 27.1	478.8 ± 29.7	0.627
7 days	468.5 ± 23.9	461.7 ± 31.4	0.327

Values are means ± standard deviation. * Student's t-test for independent samples (p<0.05).

Table IV - Comparison of mouth opening (mm) between study groups at different postoperative times

Postoperative time	NSAIDs (n=33)	NSAIDs with B vitamins (n=33)	p-value *
Basal	44.2 ± 5.2	44.5 ± 5.7	0.828
01 hour	36.6 ± 7.9	36.2 ± 8.1	0.832
Day 1	30.7 ± 8.3	30.3 ± 8.5	0.848
Day 3	32.4 ± 8.1	30.9 ± 9.0	0.470
Day 7	39.1 ± 6.5	39.2 ± 8.1	0.963

Values are means ± standard deviation. * Student's t-test for independent samples ($p<0.05$).

effective in impacted third molar surgery [13]. In addition, diclofenac has presentations alone and is also associated with B vitamins, which makes it easier for the patient to take single tablet every 8 hours.

Recent investigations have reported that vitamins B associated with NSAIDs or corticosteroids have decreased pain after mandibular third molar surgery. This is due to a supra-additive synergistic effect, so lower doses of NSAIDs or corticosteroids could be prescribed (minimizing the risk of adverse drug reactions) [8,13].

In the present investigation, we found that the group treated with NSAIDs plus B vitamins manifested a lower intensity of postsurgical pain in all the hours evaluated (1 hour, 6 hours, 12 hours, 24 hours, 48 hours, and 72 hours) compared with the group treated with only NSAIDs ($p<0.05$).

These results were similar to those reported by Chumpitaz Cerrate et al. [13] who found that the combination of diclofenac plus B vitamins (B1, B6, and B12) had a significantly higher analgesic effect at 9 hours, 12 hours and 24 hours postoperatively compared to diclofenac-only therapy. In the same way, Chávez et al. [8] reported a significantly higher analgesic effect in the group of dexamethasone plus B vitamins (B1, B6, and B12) compared to the dexamethasone group at 3 hours, 6 hours, 12 hours, 24 hours and 48 hours after mandibular third molar surgery. This could be because vitamins B1, B6, and B12 are involved in regulating nociceptive pathways. Vitamin B1 modulates neuronal excitability and sodium currents in damaged neurons. Vitamin B6 has analgesic effects, blocking purinergic receptors (P2X), promoting the biosynthesis of neurotransmitters that inhibit pain (dopamine, serotonin, and GABA), and providing a neuroprotective capacity in the regulation of GABA and glutamate [10,11,22]. Moreover, vitamin B12 blocks the synthesis of pain and inflammation mediators and increases brain-derived neurotrophic factor, contributing to the remyelination of nerve cells [23,24].

Ponce-Monter et al. [12] reported that the addition of B vitamins to diclofenac increased its analgesic effect in a model of acute pain due to fracture and lower limb surgery. Rajaran and Choi [9] mentioned that B vitamins reduced the pain of temporomandibular joint disorder. Mauro et al. [25] reported that the administration of vitamin B12 in patients with low back pain significantly decreased pain and the consumption of rescue analgesics.

The postoperative pain of third molar surgery varies from moderate to severe in the first 12 hours and reaches its maximum intensity between 6 and 8 hours. This coincides with an increase in the synthesis of chemical mediators of pain in the surgical area [26,27].

In the present investigation, it was found that the greatest intensity of pain was at 6 hours (25.1 ± 15.6 mm). These results are similar to those reported by Paiva-Oliveira et al. [27], who reported the maximum postoperative pain evaluated using the Visual Box Scale-11 (BS-11) at 6 hours (34 ± 19 mm). Nevertheless, they differ from the study by Chávez et al. [8] and Chumpitaz Cerrate et al. [13], who reported that the greatest intensity of pain occurred at 24 hours (58.11 ± 14.7 mm and 35.25 ± 22.39 mm respectively). This could be due to the different anti-inflammatory and analgesic rescue therapies employed.

In this investigation, when evaluating the anti-inflammatory effect, no significant difference was found between both groups. A finding similar to that found by Chávez et al. [8], who reported similar values of facial swelling between the group that received dexamethasone plus B vitamins and

the group that received only dexamethasone at all times evaluated (1 day, 3 days and 7 days) after the extraction of the mandibular third molar. However, it differs from the study by Reategui et al. [28], who reported a greater anti-inflammatory effect of dexamethasone plus B vitamins (B1, B6, and B12) at 24 hours, 48 hours, and 96 hours after the extraction of the mandibular third molar, compared to the group treated with dexamethasone alone. This could be due to the fact that different techniques were used to evaluate swelling, in the study by Chávez et al. [8] the sum of five facial planes was used (similar to the present study), and in the study by Reategui et al. [28] only two facial planes were used (intersection of the tragus-pogonion and gonion-external angle of the eye). The potential mechanism of action of B vitamins as an anti-inflammatory is unknown, but some studies show that cyanocobalamin has anti-inflammatory effects by reducing nuclear factor kappa-Beta (NF-kB) and tumor necrosis factor-alpha (TNF-α) [29,30].

In the present investigation, in relation to mouth opening, the measurements were similar in both groups. The greatest limitation in mouth opening occurred 24 hours after surgery. Similar results were reported by Orozco-Solís et al. [17] who observed the greatest limitation of mouth opening 24 hours after surgery. Nonetheless, they differ from the study by Paiva-Oliveira et al. [27] who reported that it was 48 hours after surgery. This difference could be due to the different anti-inflammatory and analgesic rescue therapies used.

Because pain and inflammation are responses that vary between people, they could be assessed by split-mouth trials. Split-mouth trials were not used in the present study due to the infrequency of patients with bilaterally impacted third molars. Nevertheless, a validated instrument (VAS) was used for pain assessment and both groups had the same surgical difficulty index of Gbotolorun. Likewise, the comparison with other studies was limited due to the scarce report of the use of vitamins B1, B6, and B12 in third molar surgery. The present study is the first to evaluate the efficacy of NSAIDs plus B vitamins (administered pre and postoperatively) in a third molar model.

CONCLUSION

In the present study, the administration of NSAIDs with B vitamins (B1, B6, and B12) produced less intensity of postsurgical pain in all the hours evaluated in comparison with the group that received only NSAIDs. There was no significant difference in relation to swelling and mouth opening between both groups.

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Author's Contributions

VRPJ: Concepts, design, definition of intellectual, literature search, clinical studies, experimental studies, data acquisition, data analysis, manuscript preparation, manuscript edition, manuscript review. VMCC: Concepts, design, definition of intellectual, literature search, experimental studies, data analysis, manuscript preparation, manuscript edition, manuscript review. LKCR: Concepts, design, definition of intellectual, literature search, experimental studies, data analysis, statistical analysis, manuscript preparation, manuscript edition, manuscript review. DEMV: Clinical studies, experimental studies, data acquisition, manuscript edition, manuscript review. AARF: Clinical studies, experimental studies, data acquisition, manuscript edition, manuscript review.

CIFQ: Concepts, literature search, data analysis, manuscript preparation, manuscript edition, manuscript review. CHEP: Literature search, clinical studies, data analysis, manuscript preparation, manuscript edition, manuscript review.

Conflict of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the guidelines and policies of the ethics committee of the Hipólito Unanue National Hospital and according to the

International Conference on Harmonization Good Clinical Practice (ICH-GCP), considering the Declaration of Helsinki (revised in 2000). The approval code for this study is: Nº121-2019.

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