Effect of Premedication with Anti-inflammatory Drugs on Post-Endodontic Pain: A Randomized Clinical Trial

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In spite of advances in root canal therapy and better knowledge of pulpal and periapical inflammation, up 40% of endodontic patients report varying degrees of pain. The aim of this present study was to compare the effect of single preoperative dose of ibuprofen or dexamethasone on post-endodontic pain. Sixty volunteers were divided into three groups (n=20 per group): PL, placebo; IB, 400 mg of ibuprofen; and DE, 8 mg of dexamethasone. The primary outcome was the post-endodontic pain intensity measured with a numerical rating scale (4, 8, 12, 24, and 48 h). Secondary outcomes included number of anesthetic cartridges used and consumption of rescue medication. Data were analyzed by one-way ANOVA, chi-square and Kruskal-Wallis tests. There was no significant difference among groups (p>0.05) considering the pain intensity. Only 37% of IB group patients and 28% of DE group patients used some rescue medication. On the other hand, 74% of PL group patients mentioned the consumption of rescue medication; PL group had a statistically significant difference (p<0.05) in comparison with IB and DE groups. The number of anesthetic cartridges used had no statistically significant difference among the groups (p>0.05). Significant differences were not found in the reduction of pain intensity and the number of anesthetic cartridges used. Considering the consumption of rescue medication (secondary outcome), preoperative administration of Ibuprofen or dexamethasone reduces post-endodontic pain and discomfort in comparison with a placebo. Premedication with anti-inflammatory drugs drugs could be contributed to control of the post-endodontic pain, mainly in patients more sensible for pain.

Introduction

The incidence and severity of post-operative pain are associated with specific dental treatments; the highest of which is root canal therapy (1). In spite of advances in root canal therapy and better knowledge of pulpal and periapical inflammation, up 40% of endodontic patients report pain of different degrees (2-4). Post-endodontic pain, particularly after initial endodontic treatment, should ideally be eliminated by the therapy; however, analgesics and/or anti-inflammatory drugs are frequently required to reduce pain (5-7).

A variety of approaches have been recommended for the management of post-endodontic pain. One of them is the prescription of analgesics and steroidal and non-steroidal anti-inflammatory agents. In this sense, drugs that regulate the inflammatory reaction should be considered for the prevention and control of post-endodontic pain (7-9). However, a definitive anti-inflammatory protocol to prevent and control the occurrence of post-endodontic pain has not yet been established (2,6,10,11).

Non-steroidal (NSAID) and steroidal (SAID) anti-inflammatory drugs can reduce inflammation at different levels in the inflammatory process. Ibuprofen is an NSAID that exerts its analgesic and anti-inflammatory effects by inhibiting the cyclooxygenase (COX) enzymes COX-1 and COX-2 (6,8,10,12,13). Dexamethasone is a SAID that can have an effect on inflammation by suppressing vasodilation, PMNs migration, and phagocytosis. SAIDs are capable of down-regulating many pro-inflammatory cytokines associated with an inflammatory reaction and immune response (2,9,14-17).

In comparison to repeated doses during the postoperative period, a preoperative, single oral dose of anti-inflammatory agents can regulate the release of inflammatory mediators and reduce the occurrence of side effects (2,7-9). The optimal oral ibuprofen or dexamethasone dosages for the prevention and control of endodontic pain was not yet determined. Therefore, the purpose of the present study was to compare the effect of ibuprofen (400 mg) or dexamethasone (8 mg) administered as a single, preoperative oral dose for the prevention and control of the post-endodontic pain. Three null hypotheses were tested: (i) the preoperative consumption of ibuprofen or dexamethasone has no influence on post-operative pain; (ii) the preoperative consumption of ibuprofen or dexamethasone has no influence on the number of local

anesthetic cartridges required for comfortable endodontic treatment; and (iii) the preoperative consumption of ibuprofen or dexamethasone has no influence on the level of consumption of rescue medication for control of post-endodontic pain.

Material and Methods

Sixty patient volunteers of both genders between 18 and 66 years of age were selected to participate in this double-blind parallel-randomized clinical trial. Study subjects were enrolled from the pool of patients referred to the Department of Endodontics for root canal treatment. Upon approval by the Joint Research and Ethics Committee (CAAE - 09736212.9.0000.0105; Clinical Trials Registry: Primary Id Number: RBR-6rp3ds), all patients signed a consent form before taking part in treatment. The primary outcome was the post-endodontic pain intensity measured with a numerical rating scale (NRS). Secondary outcomes included number of anesthetic cartridges used during the endodontic procedure and consumption of rescue medication for control of post-endodontic pain.

A specific clinical report containing all patient information was compiled. Our control variables were gender, age, teeth, diagnosis (vital or non-vital), pain symptomatology (asymptomatic or symptomatic), duration of endodontic treatment and dental anxiety (Corah Dental Anxiety) (18,19).

The initial examination included periodontal probing, a mobility assessment, thermal (cold) test, percussion and palpation evaluation and a periapical radiograph. All past and present symptoms were recorded and a diagnosis was determined based on clinical and radiographic features. Two operators performed all clinical examinations.

The inclusion criteria were single or multi-root teeth with a clinical diagnosis of symptomatic/asymptomatic, irreversible pulpitis or non-vital teeth that require nonsurgical endodontic therapy. Exclusions were made according to the following criteria: severe periodontal diseases; requirement for prophylactic antibiotics; analgesic and inflammatory drugs consumed within the last 12 h; pregnancy or lactation; systemic diseases that contra indicated the endodontic therapy; mental disabilities; patients with self-reported gluten sensitivity; and any known sensitivity or other adverse reactions to ibuprofen and dexamethasone.

The volunteers were randomized into 3 experimental groups (n=20 per group), stratified according to age, gender, teeth, diagnosis and dental anxiety by the generation of random computer numbers (http://www.randomizer.org). Group PL, placebo control received four capsules containing wheat flour, Group IB, received two coated tablets with 200 mg of ibuprofen (Advil™, Wyeth Indústria Farmacêutica

Ltda, Itapevi, SP, Brazil) for a total of 400 mg, and Group DE, received two tablets of 4 mg dexamethasone (Decadron™, Aché Laboratórios Farmacêuticos S.A, Guarulhos, SP, Brazil) for a total of 8 mg.

All medications were removed from their original containers and placed in new ones in accordance with the following protocols: Protocol 1, two placebo capsules 1 hour before the procedure and two placebo capsules 15 min before the procedure; Protocol 2, two placebo capsules 1 hour before the procedure and two Ibuprofen coated tablets (total 400 mg) 15 min before the procedure; and Protocol 3, two tablets of dexamethasone (a total of 8 mg) 1 hour before the procedure and two placebo capsules 15 min before the procedure.

The volunteers were selected and received one code according to the randomization process. In order to maintain blinding of patients, a third researcher (F.A.S.) gave the tablets and capsules to the volunteers and determined that they were used correctly. The tablets were disguised so that the patients would not know what medication they were taking.

In all groups, root canal treatment was performed under local anesthesia with a solution of 2% mepivacaine with epinephrine (Mepiadre™, DFL Indústria e Comércio S.A., Rio de Janeiro, RJ, Brazil) by infiltration technique or inferior alveolar nerve block, according to region, followed by rubber dam isolation, coronal and root access, cleaning and shaping of canals. The number of anesthetic cartridges used during the endodontic procedure by each volunteer (secondary outcome) was recorded.

A crown-down technique was used. Canals were enlarged to a size 25 file or larger (depending on the root canal), 1.0-1.5 mm short of the radiographic apex. The site was irrigated with 2.5% sodium hypochlorite between each file, leaving irrigant inside the canal throughout the entire procedure. The root canals were also irrigated with 17% EDTA prior obturation. When instrumentation was completed, the canals were washed and dried with paper points and filled with calcium hydroxide paste. A cotton pellet was placed inside the cavity of access, which was restored with intermediate restorative material (Coltosol™; Coltene Brasil, Rio de Janeiro, RJ, Brazil). Two researchers (A.C.A.J.A. and M.T.P.) performed all of the endodontic instrumentation.

Due to the possibility of pain after the root canal instrumentation, the patients were instructed to use analgesic rescue medication if they had any uncomfortable sensation, regardless of the experimental group. The patients were given a "rescue bottle" that contained 4 tablets of 750 mg acetaminophen (Tylenol™, Janssen-Cilag Farmacêutica LTDA, São José dos Campos, SP, Brazil), with the recommendation to use a tablet orally every 6 h. If

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they did not use this drug, they were asked to return it for evaluation of medication consumption.

The preoperative and postoperative pain intensity was analyzed in the interval between appointments of instrumentation and root canal obturation, through numeric rating scale (NRS)(20) after 4, 8, 12, 24 and 48 h following the root canal instrumentation. A clinical record diary with the pain scale was delivered to patients and returned in the second session. The patients were guide to write down a number between 0 to 100 to express the degree of pain intensity, where the number 0 represents "no pain" and 100 signifies "unbearable pain" (5,9). The pain intensity was assigned to 4 categoric scores according to each pain scale: 1, none (0); 2, mild (1-33); 3, moderate (34-66); and 4, severe (67-100) (14).

The sample size calculation was performed based on pain intensity (primary outcome) using data previously published which a report of the effect of premedication with anti-inflammatory on the post-endodontic pain (9). When the sample size in each experimental group was 18 (allocation ratio 1:1:1), a two-sided test would have 82% power at an effect size of 0.80 and a 0.05 significance level to detect a minimum clinically important difference of 15 units on the NRS. The sample size was increased to 20 participants per group to account for the potential loss of patients during the study. Sample size was calculated using sample-size calculating software G*Power version 3.1.9.2 (http://www.gpower.hhu.de).

Data were analyzed by using parametric or non-parametric statistical models. Comparisons among the groups for gender, teeth, diagnosis and pain symptomatology (qualitative variables) were analyzed by chi-square test. Quantitative variables such as age, duration of treatment, dental anxiety, anesthetic cartridges number and consumption of rescue medication were evaluated by one-way ANOVA with Bonferroni post-hoc tests. Once the NRS did not show normal distribution and homogeneity of variance, the Kruskal-Wallis non-parametric test was used to determine the difference among groups within each time point (preoperative, 4, 8, 12, 24 and 48 h). The tests were considered to be statistically significant when $p < 0.05$ (GraphPad Prism version 6.00 for Windows ; GraphPad Software, La Jolla, CA USA).

Results

Four patients were excluded from the study (2 presented incomplete pain diaries, 1 had a post-instrumentation infection and 1 did not return for the second appointment). The remaining 56 volunteers (Group PL = 19, Group IB = 19 and Group DE = 18) completed the study (Fig. 1). There were no patients with lack of adherence to the medications.

Table 1 shows the demographic and clinical feature variables (control variables). There were no statistically significant differences among groups considering age, gender, teeth, diagnosis, pain symptomatology, duration treatment and dental anxiety scale ($p > 0.05$, chi-square and ANOVA tests).

The pain intensity in each time point with the NRS is shown in Figure 2. There was no statistically significant difference among groups, and the pain intensity decreased over time ($p > 0.05$, Kruskal-Wallis).

The percentage of subjects reporting no pain after a 4- and 8-h period was more than 50% for the PL and IB groups and 70% DE group. After a 12- 24-h those percentages rose to 60% for the PL an IB groups and 80% DE group. After the 48-h period, no pain was observed in more than 80% of the patients in all groups (Fig. 3). Further, no side effects were reported for any of the medications used.

The number of anesthetic cartridges used during the endodontic procedures had no statistically significant difference among the groups ($p = 0.168$, ANOVA). Anesthetic supplementation was necessary in 47% (n=9), 58% (n=11) and 39% (n=7) of patients, respectively for PL, IB and DE groups (Fig. 4A).

Figure 4B demonstrates the rescue medication tablets that were taken by each volunteer. There was a statistically significant difference between placebo and experimental groups ($p < 0.05$, ANOVA with Bonferroni post-hoc tests). The rescue medication consumption was 50% (IB group) and 64% (DE group) lower than the placebo group. Only 37% of IB group patients and 28% of DE group patients used some rescue medication during the course of the study. On the other hand, 74% of placebo group patients mentioned the consumption of rescue medication.

Discussion

Based on the results of this present study, the null hypothesis (i) was accepted whereas the pain intensity (primary outcome) did not show statistically significant difference among groups. However, the null hypothesis (iii) was rejected, the results showed that the placebo group members experienced more post-endodontic pain and discomfort since they had an increase of rescue medication consumption (secondary outcome) in comparison with the ibuprofen and dexamethasone groups. On the other hand, there was no statistical difference between the ibuprofen and dexamethasone groups. In our study, considering the possibility of pain after root canal instrumentation, the patients were advised to use analgesic rescue medication if they had some pain, regardless of the experimental group. Several studies have considered the use of rescue medication as a pain indicator for the evaluation of postoperative pain (5,7-10,14,15). The null hypothesis (ii) was accepted since and number of anesthetic cartridges

used during the endodontic treatment (secondary outcome) did not show statistically significant difference among groups. Although there is moderate evidence to support the use of oral anti-inflammatory drugs before the administration of inferior alveolar nerve block local anesthetic to provide additional analgesia to the patients (21). In our study, neither ibuprofen nor dexamethasone had decreased the needs for anesthetic supplementation.

The sample in each group was distributed similarly (control variables), take into account of age, gender, teeth, diagnosis, pain symptomatology, duration of the treatment and anxiety rating. In the present study, 61% of patients had no or mild anxiety, and only 7% had severe anxiety. These results are similar to other studies (18,19). The control of these variables was important to minimize bias as much as possible. Our sample size was adequate for the evaluation of the preoperative administration of anti-inflammatory drugs in controlling pain after endodontic instrumentation. Other studies had used similar-sized sample (2,8,14). The sample size of the present study was consistent, and the randomization process was considered appropriate since no difference was observed among groups

for control variables.

For the prevention and control of post-endodontic pain, drugs that modulate the inflammatory response should be considered, such as analgesics and anti-inflammatory drugs. The inflammatory response can be modulated by a preoperative single oral dose of anti-inflammatory drugs, but not interfere with wound healing by blocking key inflammatory events (13,17). This dose can reduce side effects compared with repeated doses during the postoperative period (2,6). The maximum benefit of an anti-inflammatory is achieved when it reaches therapeutic levels before tissue manipulation (5,7-9).

Before endodontic therapy, the preoperative use of NSAIDs such as ibuprofen, can block the COX pathway and, consequently, the sensation of pain before it starts, thus resulting in a decreased pain level in the initial h after root canal therapy. Ibuprofen is largely prescribed, safe and inexpensive. A preoperative dose of 400 mg of ibuprofen was used, according to the literature, doses between 150 mg to 800 mg of ibuprofen had good efficacy in dental studies (5,6,8,10,11,21).

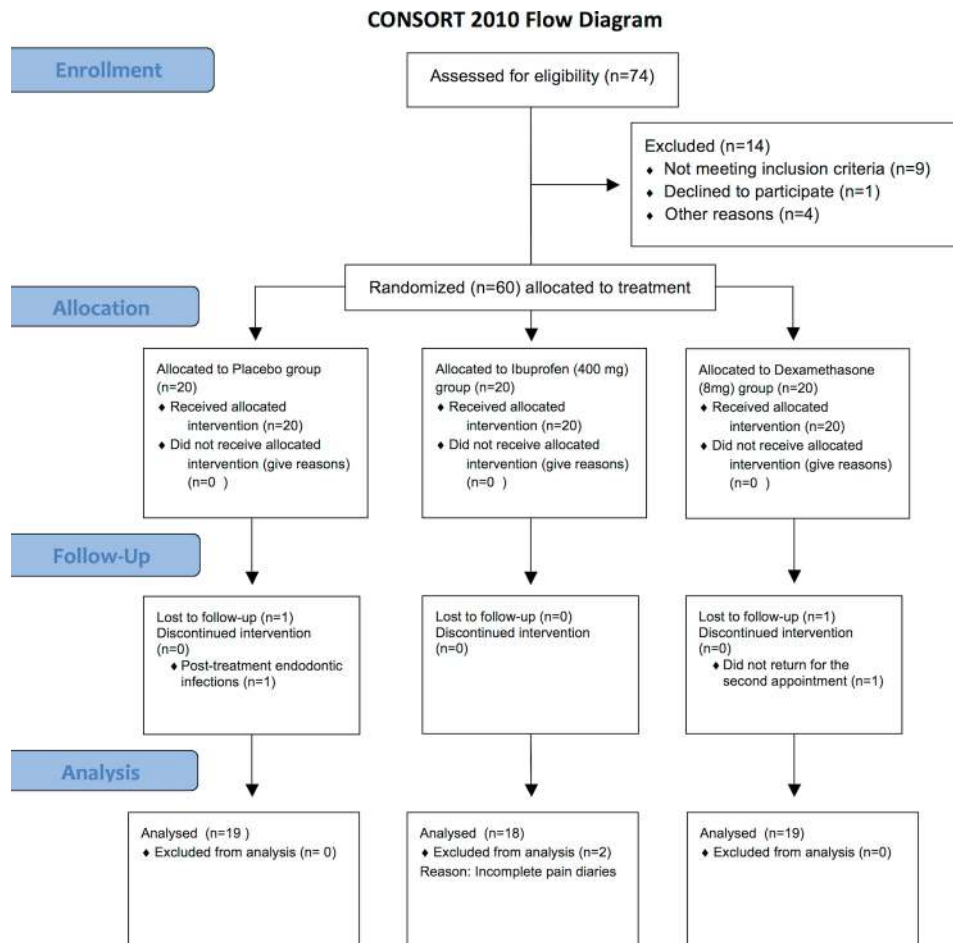The preoperative use before root canal therapy of SAIDs

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Figure 1. Flow diagram for the included volunteers in each step of the study.

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such as dexamethasone also can reduce post-endodontic pain (11,14-16). Dexamethasone inhibits the production by multiple cells factors that are important in producing the inflammatory response. SAIDs inhibit the activity of phospholipase-A2 which reduces the release of arachidonic acid (14,16). Another mechanism by which steroids have an anti-inflammatory effect is by activation of cytoplasmic glucocorticoid receptors which regulate the transcription of some primary response (17). It is at this cellular level in which regulatory effects on the immune system, including regulation of several pro-inflammatory cytokines (17,22). Such a mechanism may also be important for the suppress effect of glucocorticoids on COX-2. As a consequence of the time required for changes in gene expression and protein synthesis, most effects of corticosteroids are not immediate. This fact is of clinical significance, because a delay generally is seen before the beneficial effects of corticosteroid therapy become evident (9,12,22).

No side effects following the dexamethasone or ibuprofen treatment were observed. Single oral dose of anti-inflammatory drugs is safe over the short term, without side effects or contraindications. Both anti-inflammatory drugs showed no significant difference in the intensity of postoperative pain and rescue medication consumption. Ibuprofen is rapidly absorbed with onset action between 0.5-1 h, plasma half-life of 2-4 h and duration of action approximately 4-6 h (13,17). Dexamethasone has a plasma half-life approximately 1.5-4 h and duration of action of 36-54 h (17,22). Therefore, ibuprofen and dexamethasone had different prescriptions. They must be administered before the infliction of tissue damage, not during or after endodontic treatment. A single oral dose of ibuprofen (15 min) or dexamethasone (1 h) before the endodontic procedures could be suitable, because by the time that the endodontic instruments and/or irrigating solutions reach the periapical region, the drugs will have achieved therapeutic levels in the tissues. Dentists can administer ibuprofen 15 min before the endodontic procedure. Dexamethasone needs patient cooperation to take 1 hour before the dental appointment. Thus, it can be used either ibuprofen or dexamethasone, but ibuprofen could be a more practicable alternative because of its lower latency time. On the other hand, dexamethasone could be indicated in patients who have a history of allergy to ibuprofen, aspirin or other NSAIDs, or have experienced gastrointestinal bleeding or ulcer related to the use of NSAIDs (11).

Placebo groups are frequently used in clinical trials. For ethical reasons, all patients were informed about the chance of receiving a "sham" drug to control pain. There was a balanced 1:1:1 randomization ratio among the placebo, ibuprofen and dexamethasone groups. Maximal differences between the test drugs and placebo are achieved with a balanced ratio (23). In the present study, a parallel clinical design was established, where the patients have received only once the preoperative single oral dose of anti-inflammatory agents could contribute to

Table 1. Demographic and clinical features (control variables)

Variables	Placebo (PL, n=19)	Ibuprofen (IB, n=19)	Dexamethasone (DE, n=18)	p value
Age (years)[†]	33.3±10.9	34.3±12.7	38.1±12.8	0.464 ns
Gender (%)[‡]				
Male	7 (37)	7 (37)	7 (39)	0.989 ns
Female	12 (63)	12 (63)	11 (61)	
Teeth (%)[‡]				
Upper	14 (74)	13 (68)	9 (50)	0.290 ns
Lower	5 (26)	6 (32)	9 (50)	
Single-rooted	9 (47)	7 (37)	8 (44)	0.796 ns
Multi-rooted	10 (53)	12 (63)	10 (56)	
Diagnosis (%)[‡]				
Vital	10 (53)	9 (47)	10 (56)	0.880 ns
Non-vital	9 (47)	10 (53)	8 (44)	
Pain symptomatology (%)[‡]				
Asymptomatic	8 (42)	8 (42)	9 (50)	0.857 ns
Symptomatic	11 (58)	11 (58)	9 (50)	
Duration of treatment (mim)[†]	72.2±26.6	78.4±31.4	85.0±45.3	0.531 ns
Corah's Dental Anxiety Scale[†]	9.6±2.9	10.0±4.1	9.8±3.5	0.949 ns
Frequency Corah's Dental of Anxiety Scores (%)				
4-5 no anxiety	2 (11)	4 (21)	2 (11)	
6-10 mild anxiety	10 (52)	8 (42)	8 (44)	
11-15 moderate anxiety	6 (32)	5 (26)	7 (39)	
16-20 severe anxiety	1 (5)	2 (11)	1 (6)	

Values are % or mean ± SD. Four patients were excluded from analysis (2 presented incomplete pain diaries, one had a Post-treatment endodontic infections and one did not return for the second appointment). [†]ANOVA. [‡]Chi-square. s, significant. ns, not significant.

reduce any bias.

The numeric rating scale (NRS) was used to evaluate pain intensity. This pain scale is sensitive for the assessment of pain intensity (20). Few studies used the NRS to evaluate the severity of pain after endodontic treatment (5,9). NRS was used because it is easy to apply, does not require good vision, and avoids the use of standardized scales, paper and pen. One can even determine the intensity of pain accurately using telephone interview (20). The visual analog scale is the most frequently observed in endodontic clinical trials (2,3,6-8,12). Remarkably, both the NRS and visual analog scales agree well and are equally sensitive. The NRS lends itself to practical use owing to the ease with which it is

understood by most people (20).

No significant difference was found among groups considering the reduction of pain intensity (primary outcome) and the number of anesthetic cartridges used during the endodontic treatment (secondary outcome). However, it may be conclude that patients in the placebo group experienced more post-endodontic pain since they indicated an increased use of rescue medication consumption (secondary outcome) in comparison with the ibuprofen and dexamethasone groups. According to our results, premedication with anti-inflammatory drugs could be contributed to control of the post-endodontic pain, mainly in patients more sensible for pain. Further clinical
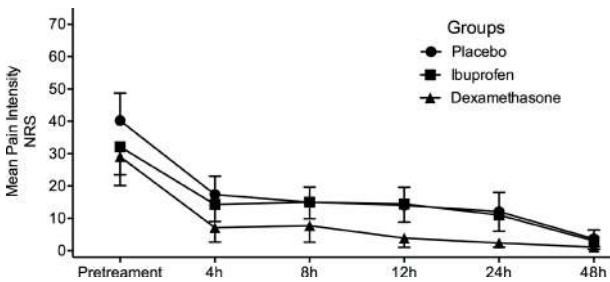

Figure 2. NRS, numerical rate scale. Mean and standard error of pain intensity values for each group at each time point. There was no significant difference among the three groups (p>0.05, Kruskal-Wallis test).
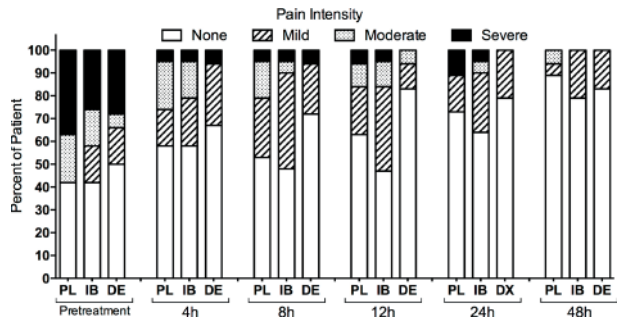

Figure 3. Percentage of subjects in placebo (PL), ibuprofen (IB) and dexamethasone (DE) groups who reported None, Mild, Moderate, and Severe preoperative and postoperative pain.
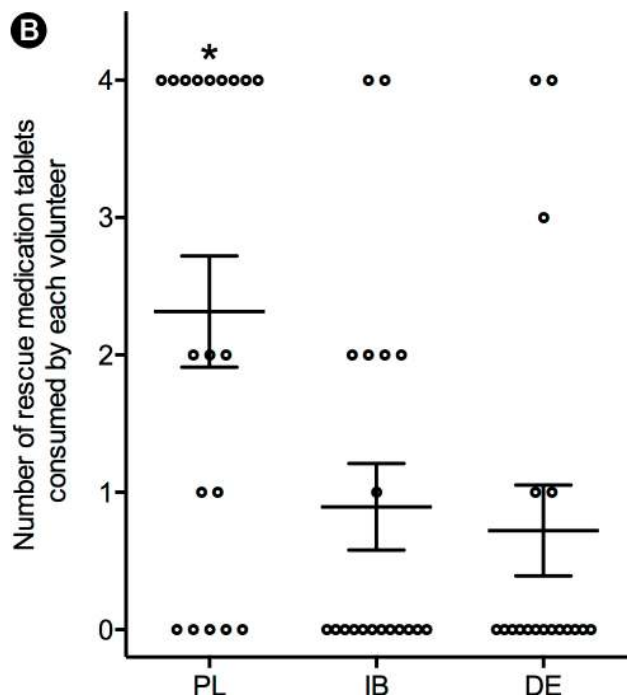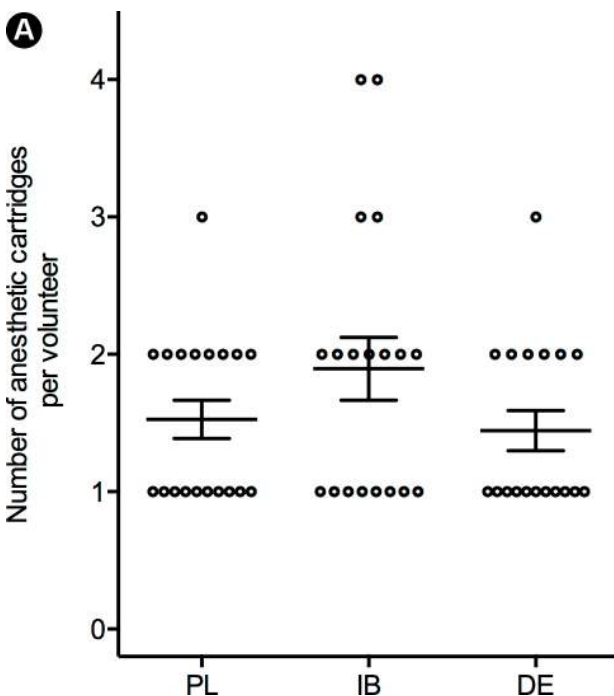

Figure 4. Scatter dot plots. (A) number of anesthetic cartridges used during the endodontic procedure, p=0.168, not significant (ANOVA). (B) number of rescue medication tablets consumed, *p<0.05, significant difference with IB and DE groups (ANOVA with Bonferroni post hoc test). Lines represent Mean and SEM. Dots correspond to each volunteer. PL (Placebo), IB (Ibuprofen) and DE (Dexamethasone).

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studies examining other clinical conditions, different endodontic modality treatments and other regimens of ibuprofen and dexamethasone should be conducted to demonstrate the potential of these drugs in the context of endodontic treatment.

Resumo

Apesar dos avanços no tratamento do canal radicular e melhor conhecimento da inflamação pulpar e periapical, 40% dos pacientes submetidos ao tratamento de endodôntico relatam diferentes graus de dor. O objetivo deste estudo foi comparar o efeito pré-operatório (dose única) de ibuprofeno ou dexametasona na dor pós-endodôntica. Sessenta voluntários foram divididos em três grupos (n=20 por grupo): PL, placebo; IB, 400 mg de ibuprofeno; e DE, 8 mg de dexametasona. O desfecho primário foi a intensidade da dor pós-endodôntica medida com uma escala numérica (4, 8, 12, 24 e 48 h). Os desfechos secundários incluíram o número de tubetes anestésicos utilizados e o consumo de medicação resgate. Os dados foram analisados com os testes ANOVA, qui-quadrado e Kruskal-Wallis. Não houve diferença entre os grupos (p>0,05) considerando a intensidade da dor. Apenas 37% dos pacientes do grupo IB e 28% do grupo DE utilizaram alguma medicação resgate. Por outro lado, 74% dos pacientes do grupo PL mencionaram o consumo de medicação resgate; o grupo PL apresentou diferença significativa (p<0,05) em comparação com os grupos IB e DE. O número de tubetes anestésicos utilizados não apresentou diferença significativa entre os grupos (p>0,05). Não encontramos diferença significativa na redução da intensidade da dor e no número de tubetes anestésicos utilizados. Considerando o consumo de medicação resgate (desfecho secundário), a administração pré-operatória de ibuprofeno ou dexametasona reduz a dor pós-endodôntica e o desconforto em comparação com placebo. A pré-medicação com anti-inflamatórios poderia contribuir para o controle da dor pós-endodôntica, principalmente em pacientes mais sensíveis à dor.

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