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Fixed and on-demand regimens of acetaminophen in periodontal surgery: randomized clinical trial

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Aim: to evaluate the clinical efficacy of an acetaminophen analgesic by comparing its prescription in fixed versus on-demand schedules after periodontal surgery. The hypothesis of the study was that the fixed regimen would be more effective than the on-demand regimen for postoperative analgesics following periodontal surgery. **Methods:** An open randomized clinical trial was conducted. The 68 patients who needed total flap surgery to restore supracrestal tissue attachment or surgical treatment of periodontitis were randomized". Visual Analogue Scale was used to assess pain. The fixed group (n = 34) received 500 mg of acetaminophen every 4 hours for 2 days. The on-demand group (n = 34) was instructed to use the acetaminophen "as needed," at intervals of no less than 4 hours between doses. Ibuprofen was the rescue medication for both groups. Pain scores and medication use were recorded 2, 6, 12, 24 and 48 hours after the surgical procedure. The study was registered at the Brazilian Registry of Clinical Trials under RBR-7wv259. **Results:** The two groups did not differ in relation to the frequency or the intensity of pain in a 48-hour period (n=20 in the fixed group, and n=22 in the on-demand group), or even in the intention-to-treat (n=34 in each group). Individuals who experienced moderate to severe pain used rescue medication more frequently in both groups. No adverse events were reported. **Conclusion:** Both regimens were effective in controlling postoperative pain after periodontal surgery.

Keywords: Pain, postoperative. Randomized controlled trials as topic. Periodontal diseases. Acetaminophen.

Introduction

Surgical procedures are routine in a periodontal clinic[1], and the most commonly performed surgeries involve total flaps[2], either for surgical treatment of periodontitis, or for the reestablishment of supracrestal attached tissues. The intensity of postoperative pain in periodontal surgery varies greatly, and the prevalence of patients who do not need postoperative analgesic medication is not consistent in the literature. In a cross-sectional study that included different types of periodontal surgery, 32% of the patients did not use postoperative analgesics[3]. In another study, 20,6% of the patients undergoing periodontal surgery for different indications reported absence of postoperative pain[4]. In yet another study involving periodontal surgery to treat periodontitis, only 8.6% of the patients reported no postoperative pain[5]. Different factors may interfere with the intensity of pain during the postoperative period, including anxiety[6-8] and such surgical factors as surgery duration and osteotomy[9]. The disparity in the occurrence of postoperative pain raises doubts about the indication and prescription of analgesic drugs.

The vast clinical efficacy of analgesic protocols can be seen in the literature, specifically in the cases that compare different medications used either alone or in combination to treat dental pain. A variety of studies can be found that test non-opioid analgesics for postoperative pain control[10-12]. Among these, acetaminophen is one of the most commonly used agents available on the market. Its widespread use can be attributed to its efficacy in relieving dental pain, its low incidence of adverse events[12], and particularly its distinction as a first-choice medicine for pregnant women and the elderly, or for situations when non-steroidal anti-inflammatory drugs are contraindicated[13].

Acetaminophen is commonly prescribed in fixed or on-demand schedules in dental clinical practice. In the latter case, it is important for the doctor to inform the maximum daily dose and the minimum interval between doses, since the patients are in charge of their own pain management. The on-demand schedule has potential risks that include the use of doses beyond those recommended as the daily maximum limit. On the other hand, a fixed regimen poses the risk of a potential increase in adverse effects due to continued, higher total drug consumption. This is because the pain level at the moment of administration is not under consideration, unlike on-demand use[14].

Regarding the management of postoperative pain after periodontal total flap surgery, the literature shows variable and conflicting data that may hinder establishing an effective and safe postoperative analgesic regimen. Thus, the aim of the present study was to compare the efficacy of acetaminophen analgesics, when prescribed in a fixed or an on-demand regimen, in patients undergoing periodontal total flap surgery. The hypothesis of the present study was that the fixed regimen would be more effective than the on-demand regimen for postoperative analgesics following periodontal surgery.

Materials and methods

Study design and sample

An open label randomized controlled trial was conducted to test the analgesic efficacy of acetaminophen in two different prescription schedules, according to the CONSORT statement. Although it was an open study, participants were unaware of the working hypothesis. The participants were recruited from the Periodontology Residence Clinic at the Federal University of Rio Grande do Sul (UFRGS), in Porto Alegre, Brazil. Data collection took place between May 2016 and July 2017. Adult patients who needed either total flap surgery to restablish supracrestal tissue attachment or surgical treatment of periodontitis were included. Patients using systemic analgesic, anxiolytic, anti-infective or anti-inflammatory agents, muscle relaxants or antidepressants were excluded, as well as those who had a previous condition of chronic or acute pain, or those who found it difficult to understand the instructions given by the research team.

This study was performed according to the Declaration of Helsinki. The Research Ethics Committee of the Federal University of Rio Grande do Sul approved this study (CAAE 38637714.2.0000.5347). The registration at the Brazilian Registry of Clinical Trials can be found at http://www.ensaiosclinicos.gov.br/rg/RBR-7wv259/.

Data collection

After reading and signing the informed consent form, the participants answered questions about gender, age, years of schooling, and smoking. The Visual Analogue Scale (VAS)[15,16] was applied to assess the basal level of pain before the beginning of the dental procedure. The following scales were applied to assess the degree of anxiety: (a) the Corah Dental Anxiety Scale (CDAS), proposed by Corah[17] and validated in Brazil by Hu et al.[18], and (b) the reduced version of the State-Trait Anxiety Inventory (STAI), proposed by Kaipper et al.[19] and validated in Brazil by Biaggio et al.[20]. The CDAS comprises four questions concerning how patients feel about dental treatments. The CDAS scores range from 4 to 20, with greater scores indicating higher levels of anxiety[18]. The STAI scores range from 13 to 52 (state section) and 13 to 48 (trait section), with greater scores indicating higher levels of anxiety. Two previously trained researchers conducted the interview. The surgical treatments were performed by dentists from the Periodontology Residence Clinic of the School of Dentistry, UFRGS.

Surgical procedures

The surgeries were performed using full thickness flaps as follows: the initial incision was performed parallel to the long axis of the tooth and placed approximately 1 mm from the buccal/palatal gingival margin, or intracrevicular when esthetic considerations were important. Buccal and palatal full-thickness flaps were carefully elevated. Subsequently, intracrevicular incisions were made around the teeth to the alveolar crest and the third and last incision was made in a horizontal direction and in a position close to the surface of the alveolar bone crest separates the soft tissue collar of the root surfaces from the bone. The granulation tissues were removed by

means of manual curettes. Ostoeotomy was performed to reestablish supracrestal tissues dimensions or radicular debridement took place in cases of surgical treatment of periodontitis. Local anesthesia was administered with both infiltrative and regional techniques. The duration of the surgeries was recorded. Chlorhexidine digluconate solution (0.12%) was prescribed for topical use every 12 hours for 14 days.

Allocation

After the surgical procedures were completed, the participants were randomly assigned to one of the two groups for postoperative pain control: (1) fixed-time or (2) on-demand analgesic regimens. Simple randomization was performed using a computer-generated table. Allocation was concealed using numbered opaque envelopes, which contained the code generated by the random number table, set up by an individual not involved in the study.

In the fixed-time regimen group, the patients were instructed take 500 mg of acetaminophen every 4 hours for 48 hours, as prescribed. Administration was to start 2 hours after surgery ended. The patients received a written form to record the time periods when they used the medicine. The proposed total dose of acetaminophen in this group was 3 g/day.

In the on-demand regimen group, the patients were instructed to use 500 mg of acetaminophen when they felt pain, with an interval of no less than 4 hours between two doses, during a period of 48 hours, as prescribed. They received a written form to record the time periods when they used the medicine. The total daily dose of acetaminophen in this group could differ, up to a maximum dose of 3 g/day.

Ibuprofen 600 mg was prescribed as a rescue analgesic for both groups. The patients were instructed to use it when pain persisted after 1 hour following administration of acetaminophen, with an interval of no less than 6 hours between two doses. The total daily dose of rescue analgesic could differ, up to a maximum dose of 2.4 g/day. Each participant received 16 acetaminophen tablets (500 mg each) in a non-electronic container that could be opened manually, identified by a blue label, and 6 ibuprofen tablets (600 mg each), identified by a yellow label.

Pain assessment

After the surgical procedure, the participants were given instructions on how to fill out a postoperative pain control form (or a "pain diary"). The pain control form was composed of the VAS[21], and included a section to record analgesic consumption (yes/no), and time of use. For detailed information about the pain scale, see Schirmer et al.[8]. The patients were instructed to fill out the pain control form 2, 6, 12, 24 and 48 hours after surgery. To improve adherence, the patients received a phone call every 24 hours reminding them to fill out the postoperative pain control form.

In the return visit for postoperative evaluation and suture removal, the participants were instructed to bring back the pain diary and remaining medication, to determine adherence. The number of tablets left was counted and recorded. Patients were also questioned about the occurrence of drug-related adverse events.

Adherence to treatment

Adherence to the randomized scheme in both regimens was based on the participants' notes in their pain diary, and the number of remaining tablets. Adherence in the fixed regimen was assumed when the participants (a) used the acetaminophen as indicated in the prescription, and (b) respected the period of 1 hour following its administration before taking the rescue medication. Forgotten doses, observed from the records in the pain diary, were considered non-adherence to treatment. The presence of a high number of tablets in the acetaminophen container suggested non-use, and a lower number of tablets than estimated suggested excessive use, and was also considered as non-adherence. Adherence in the on-demand regimen was affirmed when the individual used the acetaminophen respecting intervals of no less than 4 hours between doses, and 1 hour after its administration before taking the rescue medicine, according to the pain diary. The presence of fewer acetaminophen tablets than estimated suggested excessive use, and constituted non-adherence.

Sample Calculation

The sample calculation considered 70% prevalence of analgesic use in the fixed scheme group, and 35% in the on-demand group[3,5]. A significance level of 5%, and a beta error probability of 20% were assumed. Based on these data, a sample size of 31 individuals per group was estimated. Considering a 10% attrition rate in both groups, 34 subjects were randomized to each group, totaling 68 participants.

Data analysis

The data were expressed as either absolute or relative frequencies, mean and standard deviation, or median and interquartile range. The continuous variable comparisons between groups were performed using the Student *t*-test for independent samples, or the Mann-Whitney *U* test. The data of categorical variables were expressed as absolute frequencies and percentages. Comparisons were made using the chi-square test.

The value of the 75th percentile was considered the reference point to analyze the anxiety levels. Participants within the 75th percentile and with higher scores were categorized as "high anxiety," and those with lower scores, as "without high anxiety." This procedure was used for the "CDAS level variables," and the "state" (32) and "trace" levels (30) of the State-Trait Anxiety Inventory (STAI) (11). For example, subjects with "high anxiety" presented values equal to or higher than the 75th percentile for each variable.

VAS data were categorized as mild (VAS 1-39), moderate (VAS 40-69), or severe (VAS ≥70) pain, according to Collins et al.[15] and Al-Hamdan[5]. Participants were dichotomized into those with mild pain and those with moderate to severe pain within 6 hours after surgery. A period of 6 hours was selected because it is used routinely in the literature for acute postoperative pain analysis, inasmuch as it is the period of highest pain intensity for the surgical procedure in quesion[22-24].

The results were shown in intention-to-treat and protocol analyses. In the intention-to-treat analysis, all 68 subjects in the sample were considered. The analysis by protocol included only participants categorized as adherent to the scheme proposed by

the study. Statistical software SPSS® for Windows, version 18.0, was used for data analysis. The individual was considered the unit of analysis, and the significance level was established at 5%.

Results

Regarding the study eligibility criteria, 97 individuals indicated to undergo periodontal surgery were evaluated (Figure 1). Of these, 29 were excluded either because they did not meet the criteria (n=22), or because they did not return to perform the procedure (n = 7). The remaining 68 participants who agreed to participate were included.

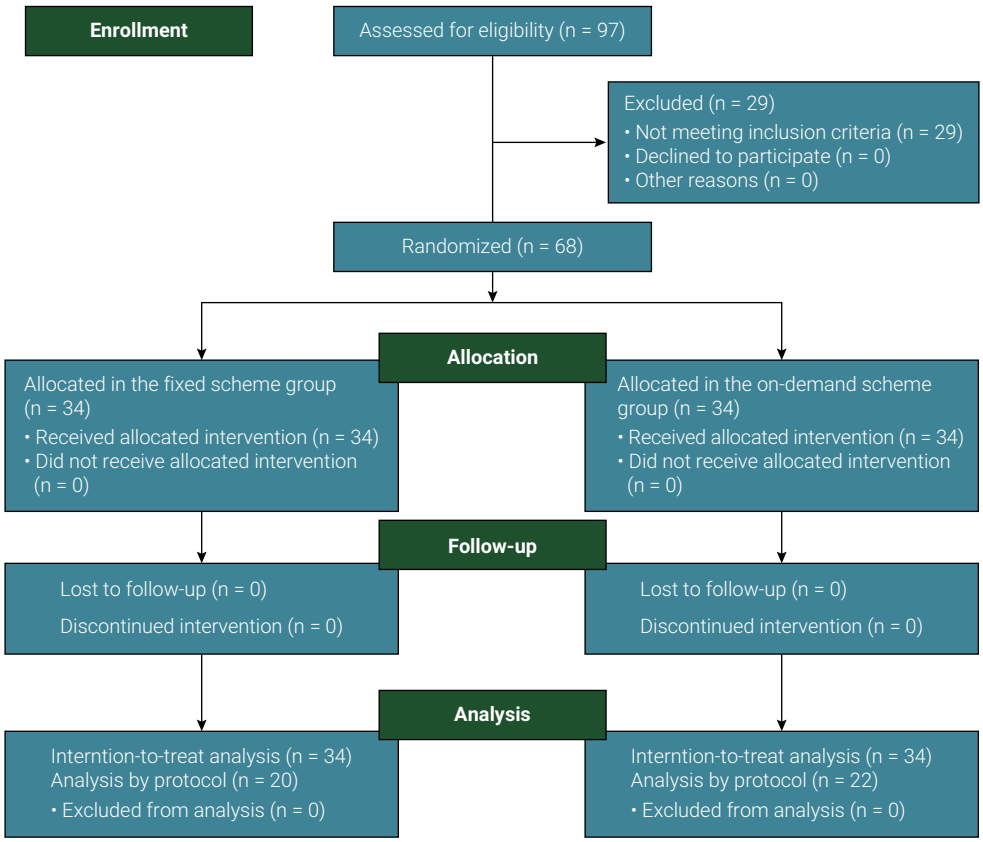

Figure 1. Flow diagram.

Characteristics of the sample and the surgical procedures are described in Table 1. There was no difference between the fixed and on-demand groups in regard to the variables analyzed. Adherence to the proposed schedule was observed in 61.76% of the total sample, with no statistically significant difference between the two groups (58.8% in the fixed regimen group versus 64.7% in the on-demand regimen group, $P = 0.54$; chi-square test).

Table 1. Demographic and descriptive data of groups who received prescription of acetaminophen in fixed or on-demand schemes for analgesics after periodontal procedures.

Variable	Fixed (n = 34)	On-demand (n = 34)	*P*
Age (± SD)	41.5 (± 16.15)	41.2 (± 14.31)	0.93 [a]
Sex – n (%)			
Male	11 (32.4)	11 (32.4)	0.60 [a]
Female	23 (67.6)	23 (67.6)	
Schooling – mean (years) (± SD)	10.5 (± 3.22)	11 (± 2.76)	0.49 [a]
Smoking habit – n (%)			
Non-smoker	27 (79.4)	24 (70.6)	
Smoker	4 (11.8)	7 (20.6)	0.60 [a]
Ex-smoker	3 (8.8)	3 (8.8)	
Reason for surgery – n (%)			
Reestablish supracrestal tissue attachment	29 (85.3)	31 (91.2)	0.71 [a]
Surgical treatment of periodontitis	5 (14.7)	3 (8.8)	
Local anesthetic solution – n (%)			
Lidocaine	18 (52.9)	23 (67.6)	
Mepivacaine	11 (32.4)	8 (23.5)	0.71 [a]
Prilocaine	2 (5.9)	2 (5.9)	
Not registered	3 (8.8)	1 (2.9)	
Number of local anesthetic tubes used – n (± SD)	2.72 (± 0.86)	2.49 (± 0.81)	0.26 [a]
Removal of bone tissue – n (%)			
No	11 (32.4)	8 (23.5)	0.59 [a]
Yes	23 (67.6)	26 (76.5)	
Duration of surgery (h & min) (mean ± SD)	1:31 (± 0:40)	1:23 (± 0:25)	0.37 [a]
Furcation injury – n (%)			
Yes	4 (11.8)	2 (5.9)	0.67 [a]
No	30 (88.2)	32 (94.1)	
Anxiety-Trace (IDATE) - Total scores Median (P25- P75)	26 (24.5-32.2)	27.5 (23-31.2)	0.48 [b]
Anxiety-State (IDATE) - Total scores Median (P25- P75)	28 (24-31)	26 (24-30)	0.53 [b]
CDAS - Total scores – Median (P25- P75)	8 (5-11.2)	8 (5-10.5)	0.29 [b]

[a] Chi-square test for categorical variables, and Student *t* test for independent samples for continuous variables.
[b] Mann-Whitney test. IDATE: Trait-State Anxiety Inventory. CDAS: Corah Dental Anxiety Scale. P25 e P75 (P25- P 75): interquartile range

The frequency of the postoperative pain levels at 2, 6, 12, 24 and 48 hours for participants who received an analgesic prescription in a fixed or on-demand schedule is shown in Table 2. When the frequency of the pain levels was compared with each of the schemes in the different periods, no statistically significant difference was

observed (*P*>0.05 for all the time periods, using the Friedman test). The pain scores of patients who received a prescription for fixed or on-demand analgesics is shown as supplementary material (Supplementary Table 1). The frequency of participants using rescue medication at each time interval is shown in the Supplementary Table 2. There was no difference between the groups in any of the periods evaluated in the protocol analysis or the intention-to-treat analysis.

Table 2. Distribution frequency of pain levels assessed at 2, 6, 12, 24 and 48 hours after periodontal procedures for the groups that received a prescription of acetaminophen in fixed or on-demand regimens, in an intention-to-treat analysis (n = 68). The VAS scores are categorized as follows: mild pain scores = from 1 to 39; moderate pain scores = from 40 to 69; severe pain scores = ≥ 70.

Pain levels	Analgesic scheme	2 hours	6 hours	12 hours	24 hours	48 hours
Mild	Fixed	85.3%	82.4%	91.2%	97.1%	97.1%
	On-demand	85.3%	73.5%	79.4%	85.3%	85.3%
Moderate	Fixed	11.8%	14.7%	2.9%	2.9%	2.9%
	On-demand	5.9%	11.8%	14.7%	8.8%	8.8%
Severe	Fixed	2.9%	2.9%	5.9%	0%	0%
	On-demand	8.8%	14.7%	5.9%	5.9%	5.9%
	P [a]	0.92	0.30	0.20	0.85	0.85

[a] Friedman test.

In Table 3, the sample was categorized into two groups according to the reported pain intensity over a period of 6 hours – participants with mild pain or those with moderate to severe pain. There were no significant differences between the two groups regarding sociodemographic variables related to the surgical procedure or anxiety. Patients that experienced moderate to intense pain used rescue medication more frequently than those feeling mild to moderate pain. There were no reports of adverse events related to consumption of the prescribed drugs in either group.

Table 3. Distribution of individuals who presented mild pain or moderate to severe pain 6 h after periodontal procedures, according the sociodemographic and surgical characteristics, anxiety scores and prescription of acetaminophen in fixed or on-demand schemes.

Variable	Mild pain n=53	Moderate to severe pain n=15	*P*
Age (years) (mean±SD) [a]	40.2 (±15.2)	45.0 (±15.37)	0.28
Sex – n (%) [c]			
Female	35 (66)	11 (73.3)	0.59
Male	18 (34)	4 (26.7)	

Continue

Continuation			
Smoking habit – n (%) [c]			
Smoking	9 (17.0)	2 (13.3)	0.76
Non-smoking	40 (75.5)	11 (73.3)	
Ex-smoker	4 (7.5)	2 (13.3)	
Duration of the surgery (h & min) (mean±SD) [a]	01:26 (±00:35)	01:29 (±00:26)	0.73
Osteotomy [c]			
Yes	39 (73.6)	10 (66.7)	0.59
No	14 (26.4)	05 (33.3)	
Anxiety-Trace (IDATE)[d] - Median (P25- P 75) [b]	27 (24-30)	26 (24-31)	0.43
Anxiety-State (IDATE)[d] - Median (P25- P 75) [b]	29 (24-32)	28 (23-31)	0.86
CDAS[d] - Median (P25- P75) [b]	8 (5-11)	9 (5-12)	0.32
Acetaminophen administration scheme - n (%)[c]			
Fixed	28 (52.8)	6 (40.0)	0.38
On-demand	25 (47.2)	9 (60.0)	
Adherence to the scheme prescribed - (n %)[c]			
Yes	36 (67.9)	9 (60.0)	0.49
No	17 (32.1)	6 (49.0)	
Use of acetaminophen in the proposed period - n (%)[e]			
Yes	48 (90.6)	14 (93.3)	0.60
No	5 (9.4)	1 (6.7)	
Use of rescue medication - n (%)[e]			
Yes	8 (15.1)	9 (60)	0.001
No	45 (84.9)	6 (40)	
Dose of ibuprofen used in the proposed period (mg) - Median (P25- P75) [b]	0 (0/0)	600 (0/600)	0.001

[a] Student *t* test for independent samples
[b] Mann-Whitney *U* test
[c] Chi-square test
[d] Total scores
[e] Exact Fisher test

Discussion

The present clinical trial compared the analgesic efficacy of two acetaminophen prescription schedules—fixed-dose or on-demand—in the postoperative period of total flap periodontal surgery. Both prescribed regimens were found to be effective in reducing pain levels, and rescue medication was used more frequently by patients who experienced moderate to intense pain.

Few studies have compared fixed to on-demand schedules – the latter is known as the pro-rata regimen, or "as needed" in more popular vernacular. Only two studies were found for the postoperative period of periodontal surgery. One compared the preop-

erative use of etodolac in a fixed regimen with acetaminophen and hydrocodone in a pro-rata regimen, and found no difference between the pain scores for the two regimens[25]. The other study compared the preoperative use of ibuprofen associated to a fixed prescription of the same drug in the postoperative period with the preoperative use of placebo associated to ibuprofen in an "as needed" regimen in the postoperative period of periodontal surgery[26]. There was no difference in the postoperative pain levels, thus corroborating the results of the present study. However, the design of these studies is not adequate enough to allow an effective comparison to be made between the prescription drug regimens.

The reason there is no difference between the two analgesic regimens tested could be attributed to the fact that postoperative pain after periodontal surgery is predominantly mild and moderate in intensity[3]; this would make the efficacy of acetaminophen suffice even when used sporadically[22]. In the present clinical trial, there was a predominance of mild pain throughout the 48 hours of observation.

Pain peaks, expressed as the highest median scores on the VAS scale, were observed at the 2nd and 6th postoperative hours, in both the fixed and on-demand groups. In fact, the literature shows that pain is more intense in the first 6 to 12 hours after periodontal surgery. One clinical trial involving surgery and reestablishment of supracrestal attached tissues observed a reduction in pain scores after the 6th and the 8th postoperative hour[23.] Another study with surgical treatment of periodontitis showed higher levels of pain in 6 hours, and a reduction in pain levels between 24 and 72 hours[24].

It is of fundamental importance to evaluate adverse events in drug studies, with the aim of drawing a safety profile of the studied drug[12]. In this study, there were no reports of adverse events associated with acetaminophen or ibuprofen. However, the sample size calculation was not based on this outcome; therefore, there could be a beta error. In two systematic reviews, the adverse effects attributed to acetaminophen (nausea, vomiting, and drowsiness) were classified as mild and transient, similar to those described by the placebo group[12,22].

Several additional factors have been associated with reports of higher levels of postoperative pain, including longer surgical procedures and bone tissue removal[3,6,9]. These variables were analyzed in our study, and no significant association with pain intensity was observed. Non-adherence to the proposed scheme was not related to pain intensity either. Our findings corroborate those of another study, which also used acetaminophen to control acute pain, and observed no association between adherence to fixed or on-demand protocols and pain levels[27]. Smoking is another condition that may also be associated with higher levels of postoperative pain. In a study on factors associated with pain and analgesic consumption, smokers were 47% more likely to report pain after non-surgical scaling and root planing than nonsmokers[8]. However, in the present study, no association was found between smoking and higher levels of postoperative pain, in line with the findings of Beaudette[6] involving the occurrence of pain following soft tissue grafting or implant surgery. It should be pointed out that only 20 to 30% of the participants in this study were smokers, which may not be enough to show a statistical difference.

Anxiety is also a factor that can influence pain levels[28-32], but the state and trait anxiety, and the dental anxiety scores in the present study did not show any significant differences between patients who reported mild pain or moderate to severe pain. It can be postulated that periodontal patients who undergo surgical procedures as part of their entire periodontal treatment are already familiar with the periodontist and dental staff, hence representing a anxiety-reducing factor. At the same time, procedures involving periodontal surgery most commonly receive mild postoperative pain scores, associated with less anxiety and fear.

The present study has limitations. All the efforts made in data collection focused on increasing adherence to a patient-randomized scheme. However, in addition to cases of non-adherence (35.3%), there were also cases where the information on medication use and pain control recorded on a specific form by patients may not have reflected exactly what occurred in the postoperative period. It is also important to consider that a small group of patients in both groups experienced pain 48 hours after the procedure. A longer follow-up period should be considered for these patients. Considering that the anesthetic used was not standardized, the pain levels reported may have been influenced by the duration of the different anesthetics. In addition, the surgeries were performed by different professionals and although they were all in the periodontics residency course, they could be at different stages of training and with different clinical and surgical skills.

In conclusion, the present study demonstrated that the use of acetaminophen, in a fixed-dose or on-demand regimen is effective in postoperative pain control after periodontal total flap surgery. Since both regimens were effective, other parameters, such as patient safety and convenience, should be considered before prescribing either one or the other.

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Conflict of interest

None.

Data availability

Datasets related to this article are available upon request to the corresponding author.

Author contribution

C. Piardi originated and designed the study, acquired data, analyzed and interpreted data, drafted the manuscript and critically revised it; C. G. Vaz acquired and interpreted data and critically revised the manuscript; M. B. C. Ferreira originated and designed the study, analyzed and interpreted data, and revised the manuscript for important intellectual content; D. Pilger analyzed and interpreted data, and revised the manuscript for important intellectual content M. I. Fernandes originated and designed

the study, analyzed and interpreted data, and revised the manuscript for important intellectual content the manuscript; P. Weidlich originated and designed the study, analyzed and interpreted data, and critically reviewed the manuscript for important intellectual content. All authors approved the final version of the document to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the manuscript were appropriately investigated and resolved.

Supplementary Table 1. Visual Analog Scale (VAS) scores for pain evaluated 2, 6, 12, 24 and 48 hours after periodontal procedures, in the groups that received acetamoniphen prescription in fixed or on-demand schedules, based on intention-to-treat and per protocol analysis. Data are expressed as median and interquartile range (P25- P 75).

		VAS 2 h	VAS 6 h	VAS 12 h	VAS 24 h	VAS 48 h
Intention-to- treat analysis (n=68)	Fixed (n=34)	10.5 (1.5–30.7)[a]	10.0 (7.5–30.0)[a]	3.0 (0–18.5)[ac]	2.0 (0–8.2)[bc]	1.0 (0–4.0)[b]
	On-demand (n=34)	8.5 (0.75–27.7)[ac]	14.0 (1.0–2.5)[a]	5.5 (0.75–21)[ac]	2.0 (0–11.2)[bc]	2.0 (0–10.7)[bc]
Per protocol analysis (n=42)	Fixed (n=20)	12.0 (0.5–36.2)[a]	10.0 (0.25-2.0)[a]	2.0 (0–36.0)[ab]	2.0 (0–10.0)[b]	1.0 (0–4.0)[b]
	On-demand (n=22)	6.0 (0–29.75)[a]	11.0 (1.0–9.5)[a]	5.5 (0–26.75)[a]	2.0 (0–10.5)[a]	2.0 (0–7.75)[a]

Different letters represent intragroup differences, Friedman and Dunn's test.

Supplementary Table 2. Frequency of individuals who used rescue medication at 6, 12, 24 and 48 hours after periodontal procedures, in the groups that received acetamoniphen prescription in fixed or on-demand schemes, based on intention-to-treat and by per protocol analysis.

Analysis period	Frequency of use of rescue medication					
	Intention-to-treat analysis (n=68)			Per protocol analysis (n=42)		
	Fixed group n=34	On-demand group n=34	*P* [a]	Fixed group n=20	On-demand group n=22	*P* [a]
6 h	14.7%	35.3%	0.17	0%	18.2%	0.13
12 h	8.8%	29.4%	0.85	0%	13.6%	0.23
24 h	5.9%	17.6%	0.31	0%	4.5%	0.33
48 h	11.7%	20.6%	0.17	5%	9.0%	0.62

[a] Chi-square test, comparing fixed and on-demand groups using or not using rescue medication, in each period of time.

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