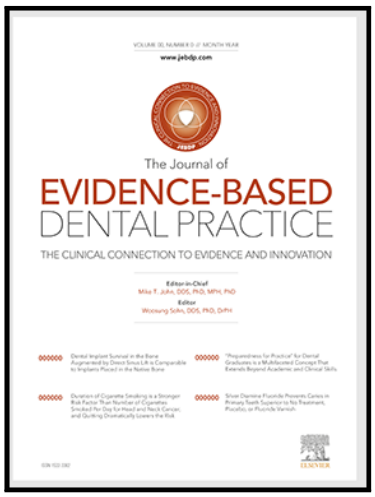

Analgesic efficacy of tramadol/dexketoprofen versus ibuprofen after impacted lower third molar extraction: A randomized controlled clinical trial

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Title: Analgesic efficacy of tramadol/dexketoprofen *versus* ibuprofen after impacted lower third molar extraction: A randomized controlled clinical trial.

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Declaration of interest: None

Abstract

Objective: Impacted third molar extraction is associated with acute moderate-to-severe pain for up to 48h post-surgery. This trial was designed to compare the analgesic effectiveness, swelling, and adverse events after impacted third molar surgery following multimodal therapy with 75 mg tramadol hydrochloride plus 25 mg dexketoprofen or monotherapy with 400mg ibuprofen.

Patients and methods: Seventy-two patients were randomly assigned to receiving ibuprofen (n=36) or tramadol-dexketoprofen (n=36). Postoperative pain intensity and swelling were measured using a visual analog scale (VAS); pain relief experienced was reported using a four-point verbal rating scale (VRS); the rescue medication requirement, adverse effects, and global impression of the medication were recorded.

Results: No statistically significant between-group difference in pain intensity was observed at any time point; however, pain relief was significantly higher in the tramadol-dexketoprofen treated-group at 6 and 36 h. Self-reported VRS assessments showed significantly lower swelling in the tramadol-dexketoprofen group at 24 h post-surgery but not at 48 or 72 h, and VAS-swelling scores showed no significant between-group difference. The frequency of postoperative nausea and dizziness was significantly higher in the tramadol-dexketoprofen group.

Conclusions: Multimodal therapy proved more effective to manage moderate-severe pain after impacted third molar surgery in comparison to monotherapy. However, the improvement in relief must be balanced against the increased risk of adverse effects when considering this multimodal approach.

Key words: Pain Management, Analgesia, Acute pain, Multimodal treatment, Oral Surgery

INTRODUCTION

Impacted lower third molar extraction is one of the most frequent procedures in oral and maxillofacial surgery, and patients can experience post-operative pain and inflammation [1]. This acute pain is usually of moderate-severe intensity but can become chronic and more severe if not appropriately treated [2]. Different treatments and ways to manage this acute pain have been investigated, but no clear consensus has been reached on the optimal therapeutic approach. Anti-inflammatory analgesics are among the drugs most commonly used for this purpose [3]. One of the best documented is the non-steroidal anti-inflammatory drug (NSAID) dexketoprofen, a well-known peripheral analgesic characterized by the rapid onset of its effect [3]. An oral dose of 25 mg every 8 hours is recommended to treat acute pain of medium to moderate intensity is recommended, with a maximum dose of 75 mg/day [4,5]. Dexketoprofen has an analgesic efficacy similar to that produced by other COX-2 inhibitors but with fewer adverse effects than other NSAIDs[3]. Opioid analgesics have also been administered to treat this type of pain, and one of the most frequently prescribed is tramadol. Unlike classic opioids, tramadol also modulates the monoaminergic system by inhibiting noradrenergic and serotonergic reuptake, leading to its wide prescription for pain of moderate to severe intensity [6]. At a dose of 100 mg every 8 hours, the analgesic efficacy of tramadol for postoperative pain after lower third molar removal is similar to that of traditional NSAIDs [7]. However, it is recommended to limit the use of tramadol [8,9] or reduce the dose by administering it in combination with other drugs [3,10], because of the potential for abuse and addiction and the high rate of complications and adverse effects.

The need to reduce opioids in patients with acute pain has led to proposals of a multimodal approach to analgesia [3,8,11–13]. Multimodal analgesia consists of the combination of two or more analgesics, each one providing a different mechanism of

action and working together in an additive way, which allows to improve analgesic effect while reducing the dose and side effects of any individual analgesic [8,14,15]. Furthermore, pain is often the result of multiple mechanisms that respond to different pharmacological interventions [11]. Among the different combinations investigated for postoperative pain, the administration of an opioid together with a NSAID has been proposed as the best option [11]. NSAIDs and opioids have distinct mechanisms of action and target different pain pathways, potentiating their additive effects [8]. Research into the most appropriate combination [14] has led to the proposal of 25 mg dexketoprofen and 75 mg tramadol for a multimodal approach to moderate-severe acute pain, offering central analgesic effects, peripheral analgesic effects, and anti-inflammatory activity [11,12,16,17]. These doses have been found to provide improved analgesia in comparison to monotherapy with 100 mg tramadol or with either drug at the same doses (25 mg dexketoprofen or 75 mg tramadol) [3,8,11–13].

The objective of this study was to compare analgesic effectiveness, swelling, and adverse effects after impacted lower third molar extraction between the combination of 75 mg tramadol hydrochloride plus 25 mg dexketoprofen (Enanplus) and 400 mg ibuprofen, widely prescribed in monotherapy for acute post-surgical pain. The main study hypothesis was that patients receiving 75 mg tramadol hydrochloride/25 mg dexketoprofen would experience greater pain relief and need lesser rescue medication in comparison to those receiving ibuprofen and would have no major adverse events.

MATERIAL AND METHODS

Study design and patient selection

A single-center, double-blind, parallel-group, randomized controlled clinical trial was conducted in patients undergoing scheduled impacted lower third molar extraction at the Clinic of the School of Dentistry of the University of Granada (Spain) between January and June 2019. Inclusion criteria were: age ≥ 18 yr., need for surgical extraction of at least one fully or partially impacted lower third molar with a degree of difficulty of 5 points or more on the Pedersen scale, ASA I-II status according to the American Society of Anesthesiologists, and no allergy to the drugs under study. Exclusion criteria were: pregnancy or breastfeeding; ASA III, IV, or V status; consumption of antibiotics in the week before surgery; and apical radiolucent image in target tooth. All participants signed informed consent to participate in the study, which followed the guidelines of the Helsinki Declaration and was approved by the ethics committee (nº: 474/CEIH/2018) of the University of Granada. The trial was registered in the Australian New Zealand clinical trial registry (ANZCTR), number ACTRN12619001709134 and follows the recommendations of the CONSORT 2010 statement for reporting randomized trials [18,19].

The sample size was determined to detect a between-group difference of ≥ 2 points in the average VAS-pain score over a 48-hour period, considering this to be a clinically relevant difference, with a confidence interval of 95 % and statistical power of 90 %, a common standard deviation of 2.5 (a quarter of the rank of the scale proposed by Machin et al., 1997 [20] and a between-group ratio of 1:1. The "power twomeans" command in Stata was used for calculations. A total sample size of 68 patients was estimated, 34 in each group.

Patients were consecutively admitted in the study following a scheme of balanced randomization every 8 patients (4 patients per group) using a computer-generated randomization sequence, up to have 72 patients. Each participant was assigned (1:1 ratio) to a random code (A or B). The code A represented the ibuprofen group for the receipt of one oral capsule of 400 mg Ibuprofen (Kern Pharma, Terrasa, Spain) every 8 h during the first 48 h post-extraction and the code B the tramadol-dexketoprofen group for the receipt of one oral capsule of 75 mg tramadol hydrochloride plus 25 mg dexketoprofen (Enanplus; Laboratorios Menarini, Badalona, Spain) at the same time points. The assignments were stored in numbered sealed envelopes and opened after surgery by a clinician not involved in the perioperative evaluation to provide medication to patients. The medication was prepared in capsules that were identical in size, color, and shape by the pharmacy to ensure blinding. All data were gathered by the main researcher, who was blinded to the group assignment of patients but, also, none of the patients or surgeons were aware of the treatment condition. Even the statistical consultant did not know to which group the patient belonged until the study was completed.

Surgical protocol

All surgical procedures were conducted by the same surgeons (C.V., M.V.R.). Immediately before the intervention, patients rinsed their mouths for 2 min using 10 mL of 0.12 % chlorhexidine mouthwash (Perio-Aid; Dentaid, Barcelona, Spain), and their lips and perioral facial skin were treated with 10 % povidone-iodine (Corsodyl; SmithKline Beecham, Brendford, United Kingdom) using sterile injectors. All patients received local anesthesia using 4 % articaine with 1: 100,000 epinephrine (Ultracain; Normon, Madrid, Spain). According to the radiologically-evaluated extraction difficulty, a linear or bayonet incision was performed, lifting a full-thickness flap to

expose the molar and adjacent bone. Osteotomy was conducted using a straight handpiece and round bur, sectioning the tooth when necessary with a turbine bur, and closing the wound with 3.0 silk suture (Normon). A gauze with 0.20 % chlorhexidine gel (Lacer, Barcelona, Spain) was then placed on the wound, and patients were asked to keep it firmly in place for 30 min. Patients were prescribed with a 0.12 % chlorhexidine mouthwash (Perio-Aid; Dentaid) to use after toothbrushing during one week. Sutures were removed at one-week post-surgery.

Patients not feeling adequate pain relief at 1 h after taking the study medication received 1 g paracetamol as rescue analgesic. As antibiotic therapy, all patients were prescribed with 750 mg amoxicillin (or 300 mg clindamycin for penicillin-allergic patients) every 8 h for 6 days.

Study variables

Study variables were classified as primary and secondary variables. The primary outcome variables were; postoperative pain intensity by visual analogue scale (VAS) (0 = no pain to 10 = worst imaginable pain) at 1, 2, 4, 6, 8, 12, 24, 36, and 48 h; pain relief provided by the medication at 1, 2, 4, 6, 8, 12, 24, 36, and 48 h by verbal rating scale (VRS) (1 = no relief, 2 = slight relief, 3 = acceptable relief, and 4 = complete relief); and need for rescue analgesia with 1 g paracetamol (yes/no) and, when the response was "yes", the number of paracetamol tablets consumed.

Secondary variables were; swelling intensity on a VAS (0 = no swelling to 10 = maximum imaginable swelling) at 24, 48, and 72 h; limitation of mouth opening (in mm) measured from the distance between the upper and lower incisal edges of central incisors at 48 h and 7 days for trismus assessment; the presence/absence of wound infection (presence of purulent fluid in wound; the presence of fever (> 38º C); and the presence of intense pain with no pain relief and/or persistent swelling); adverse effects

(nausea, vomiting, somnolence, dizziness, trembling, sweating, dyspepsia, diarrhea, bleeding, disorientation...) with their intensity (mild, moderate, or severe); and the general perception of the effects of the medication received (poor, acceptable, good, very good).

Although the study has a randomized trial design, i.e., all other variables are distributed by chance, variables related to the patient, tooth to be extracted, and surgery were also analyzed in order to evaluate the homogeneity of the sample. Patient-related variables were: sex, age, presence of general disease (yes/no), medication, and tobacco consumption (0 = No, 1 = ≤10 cigarettes/day, 2 = > 10 cigarettes/day). Tooth-related variables were: extracted third molar (38/48), extraction difficulty according to the Pedersen index (0-10) [21,22], and history of pericoronitis (yes/no). Surgery-related variables were: surgery duration (min), type of incision (linear/bayonet), periosteum tear (yes/no), osteotomy (none, mesial-vestibular, mesial-distal-vestibular, mesial-distal-vestibular-lingual, occlusal), tooth sectioning (yes/no), and number of sutures.

Statistical analysis

Differences in general characteristics between treatment groups were compared using the *chi-square test* or *Fisher's exact test,* as appropriate, for categorical variables, the *Mann-Whitney U test* for ordinal variables, and the *Student's t-test* for continuous variables.

Pain was analyzed in three ways: 1) as the mean of pain intensity VAS score evaluated at 0, 1, 2, 4, 6, 8, 12, 24, 36, and 48 h post-extraction); 2) as the maximum pain experienced by patients during the first 48 h; and 3) as the time period before maximum pain was reached. Swelling was analyzed in the same three ways. Between-group differences in outcome variables were analyzed with the *Mann-Whitney U test*

when the *normality* and *skewness* conditions were met and with the *Student's t-test* when they were not.

Generalized Estimating Equations (GEE) models were constructed, integrating the pain or swelling scores at all times of measurement (0, 1, 2, 4, 6, 8, 12, 24, 36, and 48 h post-extraction). An exchangeable correlation structure, a Gauss family for modelling the dependent variable and the identity link function were used to construct the models. In a first stage, univariate GEE models were constructed controlling for each potential confounding factor, selecting factors showing a *p*-value > 0.20 for the association with the response variable. Finally, a multivariate GEE model was constructed with treatment group as independent variable and the selected covariates. Stata v14 (StataCorp, College Station, Texas, USA) was used for statistical analyses, and $p<0.05$ was considered significant in all tests.

RESULTS

Seventy-two patients were enrolled in the study and randomly assigned to Ibuprofen treated group (n=36) or tramadol-dexketoprofen treated group (n=36). Two patients in the ibuprofen group were lost to the follow up, one for missing the suture removal appointment and the other for failure to comply with the assigned drug regimen. The final study sample therefore comprised 70 patients (30 males and 40 females), for whom data on all variables were available and analyzed. The flow of patients through the study is depicted in Figure 1. The mean ± SD age of participants was 26.00 ± 0.43 years. There were no differences between treatment groups in age (p=0.765), sex (p=0.241), medical disease (p=0.543), tobacco consumption (p=0.670), or any tooth-related or surgery-related variable. Table 1 summarizes results obtained for the predictor variables.

As reported in Table 2, no between-group difference was found in pain intensity. VAS-pain values were lower in the tramadol-dexketoprofen group at all measurement time points, but the difference was never statistically significant, Supplementary Figure 1. However, the pain relief was greater in the tramadol-dexketoprofen group than in the ibuprofen group at 6 h (12% with no pain in the ibuprofen group *versus* 17% in tramadol-dexketoprofen group; p=0.049); 8 h (9% with no pain in the ibuprofen group *versus* 25% in tramadol-dexketoprofen group; p=0.075); and 36 h (9% with no pain in ibuprofen group *versus* 44% in tramadol-dexketoprofen group; p=0.032). Supplementary Figure 1.

As shown in Table 3, the VRS-swelling score was lower in the tramadol-dexketoprofen group than in the ibuprofen group at 24 h (24% with no or some swelling in ibuprofen group *versus* 53% in tramadol-dexketoprofen group; p=0.039), but there was no between-group difference at 48 h or 7 days. VAS-swelling scores did not differ between groups at any time point, although a slightly lower score was observed at 24 h in the tramadol-dexketoprofen group (mean difference 1.16; 95% CI: -0.18 to 2.52). No wound infection was detected in 94.3% of the patients, with no difference between the groups. (Supplementary Figure 2).

No between-group difference was observed in maximum mouth opening measured at 48 h (mean difference -2.76; 95% CI: -8.37 to 2.85) or 7 days (mean difference -0.80; 95% CI: -4.16 to 2-56). There was a reduction in mouth opening between pre-surgery values and those measured at 48 h and 7 days post-surgery**.**

Rescue medication was required by 25 (35.7 %) of the 70 patients. Although it was more frequently required by patients in the ibuprofen group than in the tramadol-dexketoprofen group (15 [44,1%] *vs.* 10 [27,8; p= 0.154), as indicated in Table 2, these groups did not differ in the number of rescue medication tablets consumed (mean

difference 0.82; 95% CI: -0.99 to 2.39). The perception by patients of their treatment did not differ between the groups, being perceived as good (45.7%) or very good (31.4%) by most patients and poor by only one patient (in the tramadol-dexketoprofen group) (Table 3).

Adverse effects were recorded in 41.7% of the tramadol-dexketoprofen group *versus* 8.8 % of the ibuprofen group (p=0.002). There was a higher frequency of nausea (0% in ibuprofen group *vs.* 19% in tramadol-dexketoprofen group; p=0.011) and dizziness (0% in ibuprofen group *vs.* 25% in tramadol-dexketoprofen group; p=0.002) in the tramadol-dexketoprofen group. Adverse effects were always mild in the ibuprofen group, whereas they were mild in 33.3 %, moderate in 26.7%, and severe in 40 % of patients in the tramadol-dexketoprofen group (p=0.201), details are depicted in Table 4 and Supplementary Figure 3.

Regression models revealed a higher pain score of 0.99 points for females (95% CI: 0.21 to 1.76; p=0.013), 1.61 points for smokers of ≥ 10 cigarettes/day (95% CI: 0.15 to 3.07; p=0.030), 1.82 points for patients with periosteal tear (95% CI: 0.89 to 2.75; p<0.001), and 0.44 points (95% CI: 0.13 to 0.75; p=0.006) for patients with post-extraction trismus at 48 h, rising to 0.66 points at 7 days (95% CI: 0.17 to 1.15 p= 0.008), regardless of the treatment received (Table 5).

The multivariate model indicates that the VAS-swelling scale score was 1.11 points lower (95% CI: -2.15 to 0.08; p=0.035) in the tramadol/dexketoprofen *versus* ibuprofen group after adjusting for confounding variables. (Table 6).

DISCUSSION

In this study, post-operative pain after impacted lower third molar extraction was well controlled by the administration of 75 mg tramadol combined with 25 mg dexketoprofen and also by monotherapy with 400 mg ibuprofen, although greater pain relief was obtained with the multimodal approach.

The dose of ibuprofen selected (400 mg) is widely used to manage postoperative pain after third molar extraction. It remains controversial whether the dose should be increased to 600 mg, although a Cochrane review reported no increase in its effect as monotherapy in moderately intense post-surgical pain at higher doses [23]. Motov *et al.* also observed no differences in the analgesic efficacy profile of ibuprofen among single oral doses of 400, 600, or 800 mg for the short-term treatment of acute moderate-to-severe pain in the emergency department [24]. They concluded that NSAIDs are commonly prescribed at doses above their analgesic ceiling, offering no increase in analgesic effectiveness and potentially increasing the risk of harm. Studies in the setting of dental and oral surgery have recommended an analgesic ceiling dose of 400 mg ibuprofen per dose (1200 mg/day) [24]. Since Dexketoprofen began to be used in clinical practice in 1996, numerous studies have evaluated its application in third molar surgery at different doses, establishing 25 mg every 8 hours as the most appropriate [3]. An oral fixed dose of dexketoprofen, reported by several RCTs [25–28], is effective for the treatment of patients with acute pain of medium to moderate intensity after dental surgery. However, after surgical extraction of third molars, the pain is acute and moderate to severe intensity, hence the need to increase the analgesic efficacy of this drug increasing its dose or combining it with another analgesic that supposes an extra route of action allowing to increase the coverage of this type of pain, such as tramadol

[11]. In addition, dexketoprofen 25 mg is being used in combination with tramadol to decrease the dose of tramadol and therefore its side effects [3,10].

In the present study, superior pain relief was observed in the tramadol + dexketoprofen group. Previous studies found that the same combination and doses were more effective than monotherapy with 25 mg dexketoprofen or 100 mg tramadol [16,17] or a multimodal approach with 75 mg tramadol/650 mg paracetamol to relieve acute moderate-severe pain after impacted lower third molar extraction [29]. Increasing numbers of studies have described the benefits of this combination of drugs to treat acute postoperative pain of moderate to severe intensity [11,12,16,17,29,30], however, only one [29] uses it in the context of the extraction of the retained third molar and, unlike our study, compares it to another new combination of drugs. This study is the first to investigate the difference between the application of the tramadol/dexketoprofen combination and one of the treatments routinely used in this context, such as ibuprofen. An expert consensus recently supported the administration of the presented combination not only for postoperative pain but also for non-surgical pain, due to the speed with which effective analgesia was obtained and the improvement in patient adherence achieved when a smaller number of pills must be taken [12]. Taken together, these findings strongly support the use of 75 mg tramadol/25 mg dexketoprofen to relieve pain after third molar extraction.

Differing from other studies[16,17,29] the present study also included evaluations of postoperative swelling, need for rescue medication and drug-related adverse effect. Swelling which results from the release of inflammatory mediators into the surgical wound and from vascular dilatation and permeability [31]. NSAIDs are among the most widely prescribed drugs to control post-surgical edema [3,32], and a NSAID was administered to both groups, which may explain the relatively similar inflammatory

response in each group. It might therefore be interpreted that the addition of an opioid in multimodal analgesic therapy may improve pain relief but may possibly not reduce the swelling. Nevertheless, the multivariate analysis revealed that the VAS-swelling scale score lower in the tramadol/dexketoprofen group than in the ibuprofen group after adjustment for confounders suggesting that the inclusion of an opioid in a multimodal approach can contribute to a reduction in postoperative swelling.

It was hypothesized that less rescue medication would be required by patients in the 75 mg tramadol/25 mg dexketoprofen group. However, although a lesser use was observed in these patients than in those receiving 400 mg ibuprofen, this between-group difference did not reach statistical significance, which may be attributable to the small sample size. Patients receiving this combination were previously reported to need less rescue medication in comparison to those treated with 75 mg tramadol or 25 mg dexketoprofen alone or placebo [33], with a longer mean time to remedication [12].

Drug-related adverse events were significantly more frequent in the 75 mg tramadol/25 mg dexketoprofen group than in the 400 mg ibuprofen group. Previous studies of multimodal analgesia after third molar extraction, including a systematic review and meta-analysis, found that the opioids in combinations were responsible for the majority of adverse effects, including somnolence, dizziness, headache, and nausea [34,35]. Other authors who compared analgesic effectiveness and safety outcomes between tramadol and NSAIDs found a higher frequency of nervous system-related adverse effects, especially dizziness, in the tramadol group; however, they found no between-group difference in adverse effects on the digestive system except for nausea, which was also more frequent in the tramadol group [35–37]. In conclusion, as noted above, most adverse effects of the present multimodal approach can be attributed to the consumption of an opioid.

The results of this study could suggest a change in the routine treatment of postoperative pain after surgical extraction of the retained lower third molar, having found better pain management with the combination of tramadol/dexketoprofen. However, both therapies studied achieved satisfactory outcomes, the risk of adverse effects was higher in the tramadol/dexketoprofen group, and the lesser need for rescue medication observed in the tramadol/dexketoprofen group was not statistically significant. So, clinicians and patients must balance the improved pain management obtained with 75 mg tramadol/25 mg dexketoprofen against the increased risk of adverse effects and, perhaps, reserve it for clinical scenarios in which pain management is especially challenging or when more intense post-operative pain is expected.

Strengths and Limitations of the Study

Third molar extraction is widely used in the evaluation of pain control measures, and the analgesic efficacy observed after this procedure has been found to predict results obtained in other types of acute postoperative pain [3,23]. One advantage is the availability of samples of generally young and healthy patients who are not receiving any other type of medication [23,34]. The sample size was relatively small in the present study, although it proved adequate to yield statistically significant results; nevertheless, further significant between-group differences might have been detected if the sample had been larger. An additional limitation was the absence of a placebo arm in the trial, so that a placebo effect on pain intensity reduction cannot be ruled out. Finally, the evaluation of pain is always challenging, although this potential weakness was addressed by using standardized categorical VRS and VAS instruments and considering multiple outcomes (pain intensity, pain relief, and postoperative swelling).

CONCLUSIONS

In conclusion, analgesia with 75 mg tramadol/25 mg dexketoprofen appears to be more efficacious to reduce pain after impacted third molar extraction in comparison to monotherapy with 400 g ibuprofen. However, it is associated with an increased risk of adverse effects, suggesting that this multimodal approach should be reserved for patients predicted to experience more intense pain or whose pain is refractory to treatment with NSAIDs or paracetamol. However, further research is warranted in wider patient samples to verify these results and identify the patients who would obtain the greatest benefit from this combination.

DECLARATIONS

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Ethics approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of Ethics Committee on Human Research (nº: 474/CEIH/2018), University of Granada, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate

All participants signed informed consent to participate in the study.

AUTHOR STATEMENT

Vallecillo C: Methodology, Investigation, Data Curation, Writing - Original Draft. ***Vallecillo-Rivas M:*** Methodology, Investigation, Data Curation. ***Gálvez R:*** Conceptualization, Writing - Review & Editing, Supervision. ***Vallecillo-Capilla M:*** Conceptualization, Writing - Review & Editing, Supervision. ***Olmedo-Gaya MV:*** Conceptualization, Methodology, Writing - Review & Editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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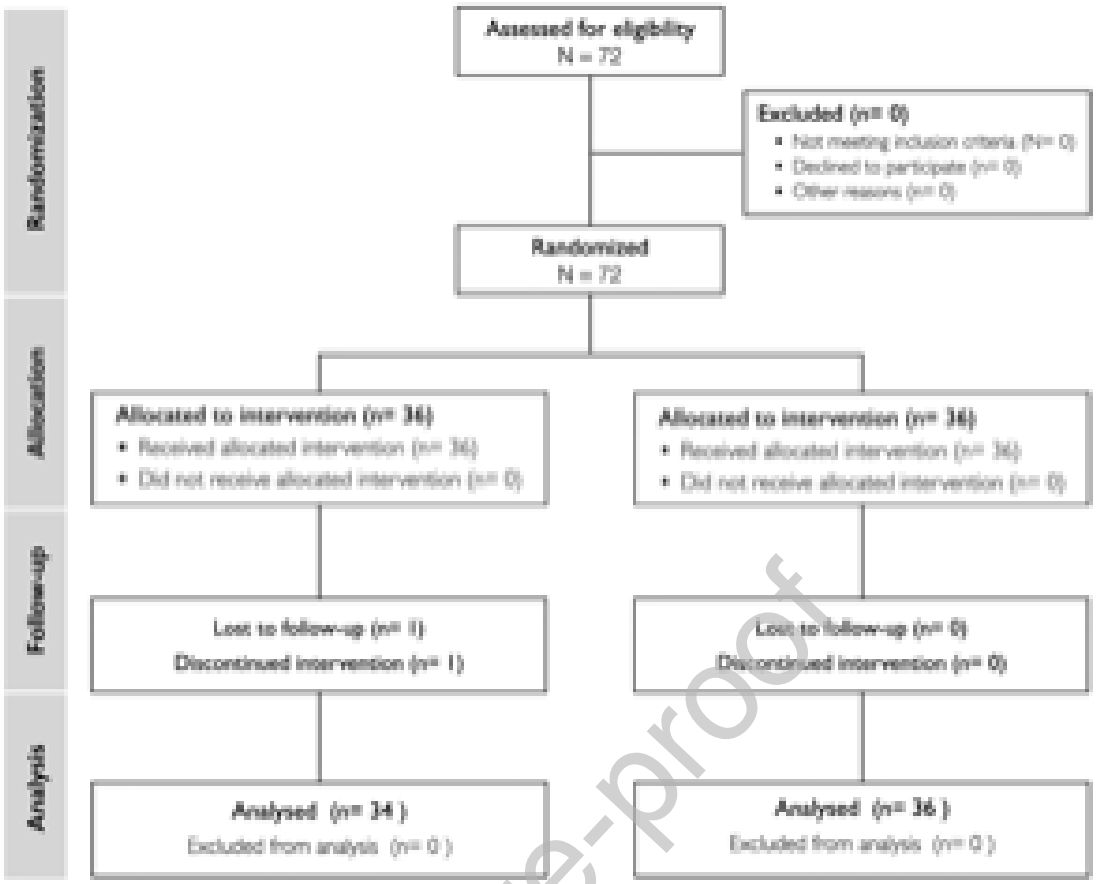

Figure 1. Flow diagram. The diagram shows a single-center trial with a parallel randomized group.

Table 1. Summary of predictor variables: patient-related, tooth-related, and surgery-related.

Table 2. Summary of primary study variables. Postoperative pain intensity on a VAS at different time-points; pain relief provided by the medication throughout different time-points by VRS; and rescue medication and number of tablets consumed.

Table 3. Summary of secondary variables. Swelling intensity by VAS; swelling by VRS; presence of wound infection; adverse effects (nausea, vomiting, somnolence, dizziness, trembling, sweating, dyspepsia, diarrhea, bleeding, disorientation...) with their intensity (mild, moderate, or severe); and the general perception of the effects of the medication received.

Table 4. Summary of adverse effects.

Table 5. GEE regression models for mean VAS pain score measured at 1, 2, 4, 6, 8, 12, 24, 36, and 48 h.

Table 6. GEE regression models for VAS swelling score (0-10) at 24, 48, and 72h.

Table 1. Summary of predictor variables: patient-related, tooth-related, and surgery-related.

PREDICTOR VARIABLES		IBUPROFEN		TRAMADOL/DEXKETOPROFEN		
		n	(%)	n	(%)	*p*-value
Age group	<20	7	(20.6)	11	(30.6)	0.765[c]
	20-24	13	(38.2)	11	(30.6)	
	25-29	8	(23.5)	5	(13.9)	
	≥30	6	(17.6)	9	(25.0)	
Sex	Male	17	(50.0)	13	(36.1)	0.241[a]
	Female	17	(50.0)	23	(63.9)	
General disease	No disease	29	(85.3)	28	(77.8)	0.543[a]*
	Anemia	1	(2.9)	0	(.0)	
	Anxiety	0	(.0)	1	(2.8)	
	Asthma	0	(.0)	1	(2.8)	
	Cholesterol and hypertension	0	(.0)	1	(2.8)	
	Diabetes	0	(.0)	1	(2.8)	
	Epilepsy	2	(5.9)	0	(.0)	
	Hemoglobinopathy	1	(2.9)	0	(.0)	
	Hypertension	0	(.0)	1	(2.8)	
	Hypothyroidism	1	(2.9)	1	(2.8)	
	Grom syndrome	0	(.0)	1	(2.8)	
	Thalassemia minor	0	(.0)	1	(2.8)	
Tobacco	Non-smoker	29	(85.3)	30	(83.3)	0.670[c]
	Smoker <10 cigarettes/day	4	(11.8)	2	(5.6)	
	Smoker >10 cigarettes/day	1	(2.9)	4	(11.1)	
Localization	Lower left third molar	16	(47.1)	20	(55.6)	0.477[a]
	Lower right third molar	18	(52.9)	16	(44.4)	
Extraction difficulty	Not/slightly difficult	4	(11.8)	12	(33.3)	0.172[c]
	Moderately difficult	20	(58.8)	15	(41.7)	
	Very difficult	10	(29.4)	9	(25.0)	
History of Pericoronaritis	No	22	(64.7)	26	(72.2)	0.498[a]
	Yes	12	(35.3)	10	(27.8)	
Type of incision	Linear	15	(44.1)	17	(47.2)	0.794[a]
	Bayonet	19	(55.9)	19	(52.8)	
Periosteal tear	No	25	(73.5)	25	(71.4)	0.845[a]
	Yes	9	(26.5)	10	(28.6)	
Osteotomy	No osteotomy	2	(5.9)	8	(22.2)	0.138[b]
	Mesial and vestibular	7	(20.6)	10	(27.8)	
	Mesial, vestibular, and distal	22	(64.7)	15	(41.7)	
	Mesial, vestibular, distal, and occlusal	3	(8.8)	3	(8.3)	
Tooth sectioning	No	17	(50.0)	23	(63.9)	0.241[a]
	Yes	17	(50.0)	13	(36.1)	
Number of sutures	1	2	(5.9)	1	(2.8)	0.209[c]
	2	5	(14.7)	11	(30.6)	
	3	13	(38.2)	13	(36.1)	
	4	8	(23.5)	8	(22.2)	
	5	4	(11.8)	3	(8.3)	
	6	2	(5.9)	0	(.0)	

(**a**) Chi-Square test; (**b**) Fisher's exact test; (**c**) Mann-Whitney test; (*****) *p*-value based in the presence /absence of pathologies

Table 2. Summary of primary study variables. Postoperative pain intensity on a VAS at different time-points; pain relief provided by the medication throughout different time-points by VRS; and rescue medication and number of tablets consumed.

		IBUPROFEN		TRAMADOL/DEXKETOPROFEN		
PAIN INTENSITY (VAS)		Mean	95 % CI	Mean	95 % CI	*p*-value
At 0h		0.85	(0.20 - 1.51)	0.72		0.696 [a]
At 1h		1.74	(0.89 - 2.58)	1.17	(0.57 - 1.76)	0.378 [a]
At 2 h		2.12	(1.40 - 2.84)	1.53	(0.89 - 2.17)	0.144 [a]
At 4 h		2.94	(2.20 - 3.68)	2.56	(1.87 - 3.24)	0.520 [a]
At 6 h		3.71	(2.66 - 4.76)	2.69	(1.95 - 3.43)	0.180 [a]
At 8 h		3.88	(2.90 - 4.86)	2.86	(1.98 - 3.74)	0.104 [a]
At 12 h		3.26	(2.33 - 4.20)	2.42	(1.52 - 3.31)	0.091 [a]
At 24 h		3.15	(2.21 - 4.08)	2.78	(1.72 - 3.84)	0.207 [a]
At 36 h		3.03	(2.16 - 3.90)	2.61	(1.64 - 3.58)	0.225 [a]
At 48 h		2.41	(1.61 - 3.21)	2.78	(1.84 - 3.72)	0.812 [a]
PAIN RELIEF (VRS)		n	(%)	n	(%)	
At 1 h	No pain	19	(55.9)	21	(58.3)	0.621 [a]
	Some pain	8	(23.5)	12	(33.3)	
	Marked pain	7	(20.6)	3	(8.3)	
	Extreme pain	0	(.0)	0	(.0)	
At 2 h	No pain	12	(35.3)	16	(44.4)	0.243 [a]
	Some pain	15	(44.1)	17	(47.2)	
	Marked pain	6	(17.6)	3	(8.3)	
	Extreme pain	1	(2.9)	0	(.0)	
At 4 h	No pain	5	(14.7)	10	(27.8)	0.119 [a]
	Some pain	17	(50.0)	18	(50.0)	
	Marked pain	9	(26.5)	7	(19.4)	
	Extreme pain	3	(8.8)	1	(2.8)	
At 6 h	No pain	4	(11.8)	6	(16.7)	0.049 [a]
	Some pain	12	(35.3)	19	(52.8)	
	Marked pain	12	(35.3)	10	(27.8)	
	Extreme pain	6	(17.6)	1	(2.8)	
At 8 h	No pain	3	(8.8)	9	(25.0)	0.075 [a]
	Some pain	17	(50.0)	16	(44.4)	
	Marked pain	8	(23.5)	10	(27.8)	
	Extreme pain	6	(17.6)	1	(2.8)	
At 12 h	No pain	4	(11.8)	13	(36.1)	0.128 [a]
	Some pain	19	(55.9)	13	(36.1)	
	Marked pain	9	(26.5)	7	(19.4)	
	Extreme pain	2	(5.9)	3	(8.3)	
At 24 h	No pain	5	(14.7)	15	(41.7)	0.195 [a]
	Some pain	18	(52.9)	9	(25.0)	
	Marked pain	9	(26.5)	9	(25.0)	
	Extreme pain	2	(5.9)	3	(8.3)	
At 36 h	No pain	3	(8.8)	16	(44.4)	0.032 [a]
	Some pain	19	(55.9)	9	(25.0)	
	Marked pain	8	(23.5)	8	(22.2)	
	Extreme pain	4	(11.8)	3	(8.3)	
At 48 h	No pain	7	(21.2)	12	(33.3)	0.956 [a]
	Some pain	21	(63.6)	12	(33.3)	
	Marked pain	4	(12.1)	10	(27.8)	
	Extreme pain	1	(3.0)	2	(5.6)	
RESCUE MEDICATION		n	(%)	n	(%)	

	Yes	15	(44.1)	10	(27.8)	0.154 [b]
RESCUE MEDICATION		Mean	SD	Mean	SD	
Nª OF TABLETS		3.6	(2.9)	2.9	(1.8)	0.401 [c]
(**a**) Mann-Whitney test; (**b**) Chi-square test; (**c**) t-Student test						

Table 3. Summary of secondary variables. Swelling intensity by VAS; swelling by VRS; presence of wound infection; adverse effects (nausea, vomiting, somnolence, dizziness, trembling, sweating, dyspepsia, diarrhea, bleeding, disorientation...) with their intensity (mild, moderate, or severe); and the general perception of the effects of the medication received.

		IBUPROFEN		TRAMADOL/DEXKETOPROFEN		
SWELLING INTENSITY (VAS)		Mean	95 % CI	Mean	95 % CI	*p*-value
At 24 h		5.50	(4.60 - 6.40)	4.33	(3.30 - 5.36)	0.089 [a]
At 48 h		5.03	(4.20 - 5.86)	4.61	(3.57 - 5.65)	0.527 [a]
At 72 h		3.71	(2.89 - 4.52)	3.58	(2.61 - 4.55)	0.846 [a]
SWELLING (VRS)		n	(%)	n	(%)	
At 24 h	None	0	(.0)	5	(13.9)	0.039 [b]
	Some	8	(23.5)	14	(38.9)	
	Marked	19	(55.9)	10	(27.8)	
	Extreme	7	(20.6)	7	(19.4)	
At 48 h	None	0	(.0)	4	(11.1)	0.323 [b]
	Some	11	(32.4)	13	(36.1)	
	Marked	19	(55.9)	13	(36.1)	
	Extreme	4	(11.8)	6	(16.7)	
At 72 h	None	2	(5.9)	8	(22.2)	0.227 [b]
	Some	21	(61.8)	18	(50.0)	
	Marked	10	(29.4)	9	(25.0)	
	Extreme	1	(2.9)	1	(2.8)	
WOUND INFECTION		n	(%)	n	(%)	
	Yes	2	(5.9)	2	(5.6)	
ADVERSE EFFECTS		n	(%)	n	(%)	
	Yes	3	(8.8)	15	(41.7)	0.002 [c]
Intensity of adverse effects	Mild	3	(100)	5	(33.3)	0.138 [b]
	Moderate	0	(0)	4	(26.7)	
	Severe	0	(0)	6	(40.0)	
PERCEPTION OF THE MEDICATION		n	(%)	n	(%)	
	Poor	0	(.0)	1	(2.8)	0.884 [b]
	Acceptable	9	(26.5)	6	(16.7)	
	Good	14	(41.2)	18	(50.0)	
	Very good	11	(32.4)	11	(30.6)	

(**a**) t-Student test; (**b**) Mann-Whitney test; (**c**) Fisher's exact test

Table 4. Summary of adverse effects.

		TOTAL		IBUPROFEN		TRAMADOL/ DEXKETOPROFEN		
ADVERSE EFFECTS		n	(%)	n	(%)	n	(%)	*p*-value*
Adverse effects	No	52	(74.3)	31	(91.2)	21	(58.3)	**0.002**
	Yes	18	(25.7)	3	(8.8)	15	(41.7)	
Nausea	No	63	(90.0)	34	(100.0)	29	(80.6)	**0.011**
	Yes	7	(10.0)	0	(.0)	7	(19.4)	
Vomiting	No	67	(95.7)	34	(100.0)	33	(91.7)	0.240
	Yes	3	(4.3)	0	(.0)	3	(8.3)	
Somnolence	No	66	(94.3)	33	(97.1)	33	(91.7)	0.615
	Yes	4	(5.7)	1	(2.9)	3	(8.3)	
Dizziness	No	61	(87.1)	34	(100.0)	27	(75.0)	**0.002**
	Yes	9	(12.9)	0	(.0)	9	(25.0)	
Trembling	No	69	(98.6)	34	(100.0)	35	(97.2)	1.000
	Yes	1	(1.4)	0	(.0)	1	(2.8)	
Dyspepsia	No	70	(100.0)	34	(100.0)	36	(100.0)	-
	Yes	0	(.0)	0	(.0)	0	(0.0)	
Diarrhea	No	70	(100.0)	34	(100.0)	36	(100.0)	-
	Yes	0	(.0)	0	(.0)	0	(0.0)	
Bleeding	No	69	(98.6)	33	(97.1)	36	(100.0)	0.486
	Yes	1	(1.4)	1	(2.9)	0	(0.0)	
Disorientation	No	69	(98.6)	34	(100.0)	35	(97.2)	1.000
	Yes	1	(1.4)	0	(.0)	1	(2.8)	
Others	No	69	(98.6)	33	(97.1)	36	(100.0)	0.486
	Yes	1	(1.4)	1	(2.9)	0	(.0)	
Intensity	Mild	8	(44.4)	3	(100)	5	(33.3)	0.201
	Moderate	4	(22.2)	0	(0)	4	(26.7)	
	Severe	6	(33.4)	0	(0)	6	(40.0)	

(*****) Fisher's exact test

Table 5. GEE regression models for mean VAS pain score measured at 1, 2, 4, 6, 8, 12, 24, 36, and 48 h.

		Mean Pain (0-10 scale)		Maximun Pain (0-10 scale)		Time to max. pain (h)		Univariate models (adjusted for baseline pain)		Multivariate model (adjusted for baseline pain and remaining covariates)	
		Mean	SD	Mean	SD	Mean	SD	Beta	95 % CI	Beta	95 % CI
Group	Ibuprofen	2.9	(2.0)	5.4	(2.2)	7.3	(7.9)	Ref.	-	Ref.	-
	Tramadol/ dexketoprofen	2.4	(1.9)	4.8	(3.0)	12.6	(15.4)	-0.49	(-1.33;0.35)	0	(-1.39;0.06)
Sex	Male	2.3	(1.6)	4.5	(2.1)	5.9	(7.3)	Ref.	-	Ref.	-
	Female	2.9	(2.1)	5.5	(3.0)	13.1	(14.7)	0.92	(0.07;1.76)	0.99	(0.21;1.76)
Tobacco	Non-smoker	2.5	(2.0)	4.8	(2.7)	10.1	(12.6)	Ref.	-	Ref.	-
	<10 cig/day	3.6	(1.8)	6.7	(1.5)	12.2	(17.7)	1.07	(-0.43;2.57)	0.59	(-0.74;1.91)
	>10 cig/day	3.0	(1.5)	5.8	(2.6)	6.2	(4.1)	0.26	(-1.38;1.90)	1.61	(0.15;3.07)
Disease	No	2.7	(1.9)	5.1	(2.5)	10.3	(13.1)	Ref.	-	Ref.	-
	Yes	2.5	(2.3)	4.8	(3.2)	9.0	(10.2)	0.02	(-1.08;1.11)	0.98	(-0.12;2.08)
Localization	Lower left 3rd molar	2.4	(2.0)	4.7	(2.4)	8.6	(10.6)	Ref.	-	Ref.	-
	Lower right 3rd molar	2.8	(1.9)	5.5	(2.9)	11.5	(14.3)	0.40	(-0.45;1.24)	0.41	(-0.31;1.13)
Difficulty	Not/slightly	2.5	(1.7)	4.7	(2.8)	8.4	(12.2)	Ref.	-	Ref.	-
	Moderately	2.8	(2.2)	5.3	(2.7)	11.2	(12.3)	0.31	(-0.76;1.38)	0.38	(-0.65;1.42)
	Very difficult	2.4	(1.8)	5.1	(2.5)	9.2	(13.8)	1.12	(-1.09;1.33)	0.34	(-0.84;1.52)
Pericoronaritis	No	2.9	(1.9)	5.5	(2.4)	10.4	(12.7)	Ref.	-	Ref.	-
	Yes	2.0	(1.9)	4.2	(2.9)	9.1	(12.5)	-0.71	(-1.62;0.20)	-0.47	(-1.34;0.39)
Incision type	Linear	2.8	(2.1)	5.4	(2.7)	13.0	(15.1)	Ref.	-	Ref.	-
	Bayonet	2.5	(1.9)	4.8	(2.6)	7.5	(9.4)	-0.08	(-0.94;0.78)	-0.27	(-1.11;0.57)
Periosteal tear	No	2.3	(1.6)	4.8	(2.6)	11.3	(13.9)	Ref.	-	Ref.	-
	Yes	3.7	(2.4)	5.9	(2.6)	7.3	(7.6)	1.14	(0.24;2.05)	1.82	(0.89;2.75)
Osteotomy	No osteotomy	2.0	(1.7)	4.6	(3.0)	16.2	(19.6)	Ref.	-	Ref.	-
	Mesial and vestibular	2.8	(2.0)	5.4	(3.2)	11.9	(15.3)	0.61	(-0.80;2.02)	0.49	(-0.69;1.67)
	Mesial, vestibular, and distal	2.6	(2.0)	4.9	(2.4)	7.6	(7.7)	0.42	(-0.85;1.68)	-0.37	(-1.63;0.89)
	Mesial, vestibular, distal, and occlusal	3.2	(1.6)	6.0	(2.3)	9.2	(13.3)	0.83	(-1.01;2.67)	-0.87	(-2.6;0.87)
Tooth sectioning	No	2.5	(2.0)	4.9	(2.8)	10.3	(13.4)	Ref.	-	Ref.	-
	Yes	2.9	(1.8)	5.3	(2.4)	9.7	(11.5)	0.34	(-0.52;1.19)	0.73	(-0.16;1.62)
Wound infection	No	2.7	(2.0)	5.0	(2.7)	10.3	(12.8)	Ref.	-	Ref.	-
	Yes	2.1	(1.5)	5.5	(1.7)	4.8	(3.0)	-0.62	(-2.44;1.21)	-0.67	(-2.29;0.96)
Age (per 10-year increase)								-0.44	(-0.88;-0.01)	-0,28	(-0.7;0.14)
Nº sutures (per unit increase)								0.18	(-0.20;0.56)	-0,09	(-0.53;0.34)
Time from incision to suture completion (per 10-min increase)								0.07	(-0.20;0.34)	-0,07	(-0.37;0.23)
Difference in opening at 48 h (per 10-mm increase)								-0.77	(-1.34;-0.21)	0,44	(0.13;0.75)
Difference in opening at one week (per 10-mm increase)								-0.56	(-0.88;-0.24)	0,66	(0.17;1.15)

Table 6. GEE regression models for VAS swelling score (0-10) at 24, 48, and 72h.

		Mean swelling (0-10 scale)		Maximun swelling (0-10 scale)		Time to max. swelling (h)		Univariate models (adjusted for baseline pain)		Multivariate model (adjusted for baseline pain and remaining covariates)	
		Mean	SD	Mean	SD	Mean	SD	Beta	95 % CI	Beta	95 % CI
Group	Ibuprofen	4.7	(2.2)	5.8	(2.5)	27.5	(8.6)	Ref.	-	Ref.	-
	Tramadol/dexketoprofen	4.2	(2.7)	5.3	(3.2)	36.7	(15.7)	-0.57	(-1.72;0.59)	-1.11	(-2.15;-0.08)
Sex	Male	4.0	(2.3)	5.0	(2.7)	32.0	(11.5)	Ref.	-	Ref.	-
	Female	4.8	(2.6)	5.9	(2.9)	32.4	(14.9)	0.83	(-0.33;1.99)	1.05	(-0.06;2.15)
Tobacco	Non-smoker	4.3	(2.5)	5.4	(2.9)	32.9	(14.0)	Ref.	-	Ref.	-
	<10 cig/day	4.5	(2.3)	5.5	(1.9)	24.0	(.0)	0.17	(-1.88;2.23)	-0.84	(-2.73;1.05)
	>10 cig/day	5.9	(3.2)	7.4	(2.8)	33.6	(13.1)	1.54	(-0.70;3.77)	2.69	(0.61;4.77)
Disease	No	4.6	(2.4)	5.7	(2.7)	33.3	(14.2)	Ref.	-	Ref.	-
	Yes	3.8	(2.9)	4.8	(3.5)	27.7	(9.0)	-0.74	(-2.23;0.74)	0.15	(-1.42;1.71)
Localization	Lower left 3rd molar	4.6	(2.4)	5.8	(2.7)	32.0	(12.8)	Ref.	-	Ref.	-
	Lower right 3rd molar	4.3	(2.6)	5.2	(3.0)	32.5	(14.3)	-0.29	(-1.45;0.87)	-0.21	(-1.24;0.82)
Difficulty	Not/slightly	4.4	(2.7)	5.6	(3.0)	37.5	(15.1)	Ref.	-	Ref.	-
	Moderately	4.6	(2.7)	5.6	(3.1)	30.2	(12.1)	0.16	(-1.30;1.63)	1.20	(-0.28;2.67)
	Very difficult	4.2	(2.1)	5.4	(2.3)	31.6	(14.0)	-0.17	(-1.82;1.48)	0.94	(-0.74;2.62)
Pericoronaritis	No	4.8	(2.4)	5.9	(2.7)	31.0	(11.0)	Ref.	-	Ref.	-
	Yes	3.6	(2.5)	4.7	(3.2)	34.9	(17.7)	-1.19	(-2.41;0.03)	-1.08	(-2.32;0.15)
Incision type	Linear	4.6	(2.6)	5.8	(2.9)	32.3	(14.4)	Ref.	-	Ref.	-
	Bayonet	4.3	(2.5)	5.3	(2.9)	32.2	(12.8)	-0.26	(-1.42;0.90)	-0.11	(-1.31;1.08)
Periosteal tear	No	4.2	(2.4)	5.3	(2.8)	32.2	(13.4)	Ref.	-	Ref.	-
	Yes	5.4	(2.4)	6.5	(2.7)	32.8	(14.3)	1.15	(-0.11;2.41)	1.41	(0.09;2.73)
Osteotomy	No osteotomy	4.7	(3.2)	5.7	(3.5)	33.6	(16.8)	Ref.	-	Ref.	-
	Mesial and vestibular	4.2	(2.8)	5.2	(3.2)	33.9	(14.8)	-0.48	(-2.41;1.45)	-0.18	(-1.86;1.5)
	Mesial, vestibular, and distal	4.4	(2.2)	5.5	(2.6)	30.5	(10.8)	0.88	(-2.01;1.44)	-1.65	(-3.45;0.15)
	Mesial, vestibular, distal, and occlusal	4.9	(2.7)	6.0	(3.2)	36.0	(20.1)	0.24	(-2.26;2.75)	-2.14	(-4.62;0.34)
Tooth sectioning	No	4.3	(2.7)	5.4	(3.1)	30.6	(12.1)	Ref.	-	Ref.	-
	Yes	4.7	(2.2)	5.7	(2.6)	34.4	(15.0)	0.43	(-0.74;1.60)	0.51	(-0.76;1.78)
Wound infection	No	4.4	(2.6)	5.5	(2.9)	32.4	(13.6)	Ref.	-	Ref.	-
	Yes	4.8	(1.4)	6.8	(1.9)	30.0	(12.0)	0.32	(-2.19;2.82)	1.38	(-0.94;3.7)
Age (per 10-year increase)								-0.80	(-1.35;-0.18)	-0,31	(-0.91;0.29)
Nº sutures (per unit increase)								0.49	(-0.02;0.99)	-0,17	(-0.79;0.45)
Time from incision to suture completion (per 10-min increase)								0.50	(0.11;0.81)	0,43	(0;0.85)
Difference in opening at 48 h (per 10-mm increase)								-0.90	(-1.69;-0.13)	0,43	(-0.02;0.89)
Difference in opening at one week (per 10-mm increase)								-0.50	(-0.98;-0.09)	0,81	(0.11;1.51)