

Effects of the Preoperative Administration of Dexketoprofen Trometamol on Pain and Swelling After Implant Surgery: A Randomized, Double-Blind Controlled Trial

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The fear of postoperative pain is often mentioned by patients as one of the factors that is most frequently associated with dental implants. To reduce this factor, a single oral dose of 25 mg dexketoprofen trometamol (DKT) or placebo was administered 15 minutes before implant surgery. One hundred patients who required single-implant treatments were randomly assigned to 1 of 2 blinded groups. The patients in the test group were given 25 mg DKT (DKT group), and those in the control group were given 500 mg vitamin C as a placebo (PLACEBO group). A subjective visual analogue scale of 100 mm in length was used to evaluate pain. Inflammation and complications were assessed using a 5-point Likert scale. An analysis of variance, *t*-tests, and a Mann-Whitney *U* test were performed. Among the 100 patients, 83 completed the study (there were 8 dropouts in the PLACEBO group and 9 in the DKT group). The patients who received DKT reported a lower pain intensity during the immediate postoperative period. The inflammatory response was weaker in the DKT group than the control group at 48 hours, but bleeding was greater. There were no other complications in either of the groups. In conclusion, the preemptive use of 25 mg soluble DKT administered orally 15 minutes before implant surgery can reduce the severity of immediate postoperative pain.

Key Words: *preemptive analgesia, dental implants, dexketoprofen trometamol, postoperative/drug therapy, dental implants/adverse effects.*

INTRODUCTION

The fear of pain is often mentioned by patients as one of the factors that is most frequently associated with dental treatment.^{1,2} Pain related to previous dental treatment has a highly subjective component, and patients perceive such pain as a real threat that generates a high level of anxiety.³ In extreme cases, such fear may prevent these patients from seeking future dental treatment.⁴

The justification for our work is that among the dental treatments that generate the greatest fear among patients, mention must be made of surgical procedures, including implantology.⁵⁻⁷ In general, the pain perceived after the placement of an implant is described as mild to moderate, although it may occasionally be intense, and the duration of

this pain is usually limited.⁸⁻¹⁰ The origin of this pain may be surgical trauma or/and the subsequent inflammatory process.¹¹

One therapeutic approach for alleviation of the perception of pain after surgery is based on the preemptive administration of nonsteroidal analgesics. Dexketoprofen trometamol (DKT) is one of the most powerful inhibitors of prostaglandin synthesis *in vitro*.^{12,13} Among the advantages of DKT is a 5-fold reduction in the risk of ulcers compared with the isomeric form of the drug. Another important feature of DKT is its rapid absorption, which allows administration of the drug between 15 and 20 minutes before surgery.¹⁴

However, there is limited information about the effects of preemptive administration of DKT on the pain perceived by patients after surgery and, more specifically, after implant procedures. Therefore, the objective of this work was to determine the pain perceived after the insertion of implants in patients who were administered a single 25-mg dose of DKT 15 minutes before surgery. Our working hypothesis was that DKT administered 15 minutes before implant surgery would be effective in reducing postoperative pain.

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DOI: 10.1563/aid-joi-D-17-00185

TABLE 1
Demographics of the study population*

Parameter	DKT	Placebo
Number	50	50
Male	12	23
Female	38	27
Age (CI)	52.9 (49.2–55.6)	53.84 (49.9–57.7)
Withdrawals	9	8

*DKT indicates dexketoprofen trometamol.

MATERIALS AND METHODS

Materials

Clinical Sample

A total of 100 consecutive patients (November 2013 to October 2015) scheduled for implant surgery in the University Dental Clinic (Murcia, Spain) were included in this study. Only 1 implant was placed per patient, and a total of 100 dental implant surgeries were performed. All patients were older than 18 years of age and free of medical and surgical contraindications, as well as systemic disease that would conflict with the treatment (American Society of Anesthesiologists [ASA] I or II). The body mass index was not calculated. All participants in the study were able to read, understand, and respond to the health questionnaire and signed an informed consent document. This study was performed in accordance with the 2014 revision of the Declaration of Helsinki¹⁵ and was registered in ClinicalTrials.gov under Identifier NCT03107338.

Clinical Materials

The study protocol was approved by the Ethics Committee of the University of Murcia.

The study was conducted under a double-blind randomized design using a visual analogue scale (VAS) of 100 mm to measure pain intensity. The degree of complications was measured using a 5-point Likert scale (4, extremely; 3, very; 2, present; 1, somewhat; 0, not). Gastrointestinal upset was evaluated as yes or no.

The patients signed 2 informed consent forms: one for implant surgery and the other for participation in the study. The latter explicitly mentioned the patients' ability to leave the study at any time.

A local anesthetic composed of lidocaine hydrochloride and epinephrine (20 mg/mL + 0.0125 mg/mL, respectively) was applied (never alveolar nerve block). All patients in this study were administered only a local lidocaine anesthetic, and the dose for each patient never exceeded 2 cartridges (20 mg × 1.8 mL = 36 mg lidocaine).

All implants had sandblasted and acid-etched surfaces (TiCare Inhex, Mozo Grau, Valladolid, Spain). The implants were all placed by the same surgeon (ASP) following the recommendations of the manufacturer (total = 100 implants).

The test group received a 25-mg dose of DKT in an oral suspension 15 minutes before surgery, and the control group received 500 mg vitamin C 15 minutes before surgery. Both solutions were administered in a disposable orange cup to mask the slight difference in color.

Methods

Selection of the Study Sample

All of the patients involved in this study were selected via a sequential nonprobability method as they attended the clinic for dental treatment (consecutive cases). X-ray examinations were performed previously (panoramic and/or scanner images). This study was conducted under a parallel group design.

The sample size was calculated according to the following formula: $n \geq 2 \times (Z_{\alpha} + Z_{\beta})^2 \times S^2/d^2$, with a result of 42 patients per group, with N = sample size, α (type I error) = 0.05, β = 0.2 (type 2 error; estimated power of 80%), S^2 = variance in control group = 147.42, and d = measurement error of 1.5 mm.

The required sample size was estimated to be 42 patients per group. We assumed a loss of 20% of the patients, and the final sample adjusted for patient losses was 97 patients, which was ultimately rounded up to 100.

The patients were instructed about the mechanical control of plaque and were provided written instructions concerning oral hygiene. The demographics of the population study sample can be seen in Table 1.

No changes were made regarding the admitted patients, except when the exclusion criteria were met or dropout occurred. Any changes in outcomes were made after the trial commenced.

Inclusion Criteria

The patients who were included in the study met the following inclusion criteria: good systemic health status (ASA I or II), no current pain, no use of painkillers in the prior weeks, older than 18 years of age, an oral hygiene index of <2 ,¹⁶ a minimum of 2 mm of adhered gum, a minimum of 8 mm of vertical bone, a minimum of 7 mm of vestibule-lingual bone, scheduled to receive a unitary implant, and willing to participate in this controlled study.

Exclusion Criteria

Patients meeting the following criteria were excluded: pregnant or nursing women, the use of any type of medication that might affect the perception of pain, a level of pain greater than 40 mm on the VAS before surgery, a history of alcohol or drug abuse, a requirement for guided regeneration or sinus-lifting procedures, and failure to comply with the study protocol.

Study Design

This study was conducted as a prospective randomized double-blind study with a placebo. The checklist items proposed in the consolidated standards of reporting trials (CONSORT) statement were considered in this work. The process can be summarized as follows:

- Initial screening: Patients who attended the clinic were interviewed and evaluated to ensure that they met the inclusion criteria.
- Distribution: Allocation to the test and control groups was performed prior to the treatments.
- Randomization: To ensure effective randomization, all patients were entered into a computer program (<https://www.random.org>). Fifty patients were assigned to the test

group, and 50 were assigned to the control group, according to a list that matched the order of the surgical procedure that was to be accomplished (A.S.P.). The result was kept in a numbered envelope that was opened on the day of surgery (J.M.P.), indicating the assigned treatment option.

- Prospective: Assignment to the groups was performed prior to the surgical treatments, and the treatments were administered before evaluating the outcomes of the procedures.
- Masking: The patients and the evaluator of the VAS (M.M.V.) were unaware of the results of randomization and the treatment received. Randomization was performed by A.S.P.

Evaluation of Pain and Inflammation

Pain was assessed using a VAS of 100 mm at the following times: before anesthesia (before sample dose administration), after anesthesia, immediately postoperatively, 2, 8, 12, 24, 36, and 48 hours after surgery, and late postoperatively (3 and 7 days). The degree of inflammation was measured by the evaluator (M.M.V.) after 48 hours using a 5-point Likert scale (4, extremely inflamed; 3, very inflamed; 2, inflamed; 1, somewhat inflamed; 0, not inflamed). The same examiner trained and calibrated performed all clinical measurements during follow-up examinations, as well as the presence or absence of any other complications.

Surgical Procedure

The placement of the implants was performed according to the manufacturer's recommendations at a drilling speed of 800 rpm and a torque of 20 N with abundant sterile cooling. Local anesthesia was administered using the minimum amount necessary to avoid potential complications related to ischemia during healing. In all cases, the incisions were mid-crestal with no vertical releasing incisions, and the incisions were extended mesially and distally to assure accessibility. The incisions were extended as needed to expose at least 5 mm of bone.

Postoperative Care

Antibiotic treatment (500 mg of amoxicillin or 300 mg of clindamycin for patients with penicillin allergies) was administered every 8 hours for 7 days. Treatment was initiated after surgery. Similarly, the analgesic and anti-inflammatory treatments involved the administration of 600 mg of ibuprofen every 8 hours for 48 hours starting 2 hours after surgery. No provisional prostheses were used during the healing period.

Dropouts

Of the 100 initial patients, 17 dropped out (8 from the PLACEBO group and 9 from the DKT group). Of the 8 dropouts from the PLACEBO group, 4 were male, and 4 were female. The causes were as follows: 1 failed to understand the instructions; 1 made mistakes in completing the questionnaire; 1 completed the form irregularly; and 5 never returned the questionnaire. Of the 9 patients in the DKT group who dropped out, 2 were male, and 7 were female. The causes were as follows: 2 failed to understand the instructions; 1 patient scored higher than 70 mm on the pain VAS preoperatively; and 6 patients never returned their questionnaires.

Statistical Analysis

The data were processed using the SPSS version 19 program (SPSS Inc, Chicago, Ill) for Microsoft Windows. Descriptive statistics (mean and CI) were used to present the data using Tukey's exploratory analysis. The difference in age between the groups was analysed with a *t*-test. Pain perception over time between groups (PLACEBO vs DKT) was analysed via a 2-way analysis of variance (ANOVA) with repeated measures through the general linear model (GLM) procedure.

Inflammation and postoperative complications recorded using the Likert scale were analyzed using the Mann-Whitney *U* test. Gastrointestinal upset (yes or no) was analysed with the χ^2 test.

The level of statistical significance was set at $P < .05$. The Kolmogorov-Smirnov test and Shapiro-Wilk test were performed to determine the normality of the distribution. The power obtained in the tests was 80%.

Results were reviewed by an independent statistician (<http://estadisticamurcia.com/web/#2>).

RESULTS

Of the 83 patients who completed the study, 29 were men, and 54 were women. The average age was 52.7 years (CI, 50–55.4). The mean age of the men was 52.2 years (CI, 46.9–57.5), and the mean age of the women was 53 years (CI, 49.8–56.2). There was no statistically significant difference.

The composition of the groups was as follows: 41 patients with a mean age of 51.8 years (CI, 48.0–55.6) completed the study in the DKT group, which was composed of 10 men (average age, 53.1 years; CI, 43.8–62.3) and 31 women (mean age, 51.4 years; CI, 47.0–55.7). There was no statistically significant difference in age. Forty-two patients with a mean age of 53.6 years (CI, 49.5–57.7) completed the study in the PLACEBO group, which was composed of 19 men (mean age, 51.7 years; CI, 44.6–58.9) and 23 women (mean age, 55.1 years; CI, 50.1–60.1). There was no statistically significant difference in age between the men and women.

The time spent on each surgical intervention varied between 40 and 60 minutes. Regarding the anatomical locations of the interventions, 10 implants were placed in the anterior maxilla (from canine to canine), 6 in the anterior mandibular region, 26 in the premolar maxillary area, 5 in the lower premolar region, 13 in the maxillary molar region, and 23 in the bottom molar region. The distribution according to bone density D1–D4 based on Misch criteria was as follows: 2 implants were placed in D1 bone; 61 implants were placed in D2; and 20 implants were placed in D3 bone. No implants were placed in D4 bone in either of the groups.

All of the analyzed variables followed a normal distribution. On the other hand, due to the sample size, the central limit theorem guaranteed the use of parametric tests.

To test whether the change in VAS over time was significant and whether this change influenced the group, we performed a 2-factor ANOVA with repeated measures through the GLM procedure.

Evaluation of the patients prior to anesthesia revealed that there were no statistically significant differences in the

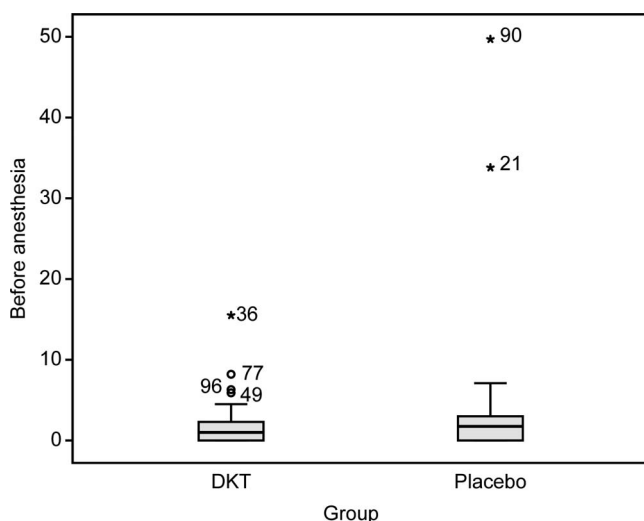


FIGURE 1. Before the initiation of the study, there were no significant differences between the groups. The plots show the minima, lower quartiles (Q1), medians (Q2), upper quartiles (Q3), and maxima. Circles, outliers (1.5× the interquartile range); asterisks, extreme outliers (3× the interquartile range).

perception of pain between the 2 groups (Figure 1). One patient from the test group was removed from the study at this time because this patient expressed a high level of pain (with a VAS score greater than 70 mm).

Immediately after anesthesia (15–20 minutes after the administration of DKT), there were no statistically significant differences between the 2 groups.

Immediately postoperatively, the pain was considered mild (<30 mm) or moderate (<60 mm) by the patients. More specifically, 80 patients reported feeling slight pain (96.4%), and only 3 patients reported moderate pain (3.6%). All patients who mentioned moderate pain belonged to the PLACEBO group; statistically significant differences were found between the 2 groups ($P < .023$). The average pain reported by the DKT group was 3.75 (CI, 2.0–5.41) compared with 8.52 (CI, 4.74–12.3) in the PLACEBO group (Figure 2). There were no significant differenc-

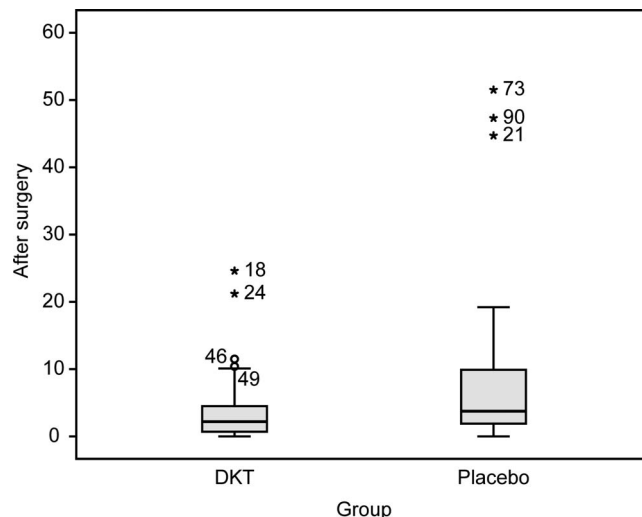


FIGURE 2. After the dental implant procedures, significant differences were noted between the groups. Less pain was reported by the dexketoprofen trometamol group than the PLACEBO group. The plots show the minima, lower quartiles (Q1), medians (Q2), upper quartiles (Q3), and maxima. Circles, outliers (1.5× the interquartile range); asterisks, extreme outlier (3× the interquartile range).

es between the groups during the late follow-up period. Summaries of these results are presented in Table 2 and Figure 3.

No statistically significant differences between the sexes were found during any of the evaluated periods, although the women in both groups exhibited a greater clinical perception of pain from 8 to 36 hours.

No differences were found with respect to bone density or pain at any time period.

There were significant differences between the groups regarding inflammation and bleeding after 48 hours (Mann-Whitney U test). The patients in the DKT group showed a lower degree of inflammation. However, they presented a greater degree of bleeding but did not reach a degree of 1 (somewhat).

Time	Group		Intrasubject Effects	
	DKT Mean (SD)	Placebo Mean (SD)	Time $F(d.f.); P$ Value (η^2)	Group \times Time $F(d.f.); P$ Value (η^2)
Before anesthesia	2.03 (2.92)	3.65 (8.95)	$F(10.800) = 9.273 < .001$ (0.104)	$F(10.800) = 2.186 .003$ (0.092)
After anesthesia	4.45 (6.17)	6.08 (10.38)		
Immediately postoperatively*	3.76 (5.32)	9.52 (12.14)		
2 h	12.39 (21.16)	15.44 (17.80)		
8 h	11.14 (15.26)	9.95 (13.83)		
12 h	11.76 (16.01)	7.08 (10.76)		
24 h	7.86 (13.29)	6.56 (11.60)		
36 h	8.69 (14.64)	7.05 (12.53)		
48 h	7.76 (14.15)	7.24 (13.27)		
3 d	7.61 (13.48)	6.89 (12.16)		
7 d	4.83 (12.27)	4.77 (6.74)		

*Statistically significant differences.

†ANOVA with repeated measures through the general linear model. DKT indicates dexketoprofen trometamol.

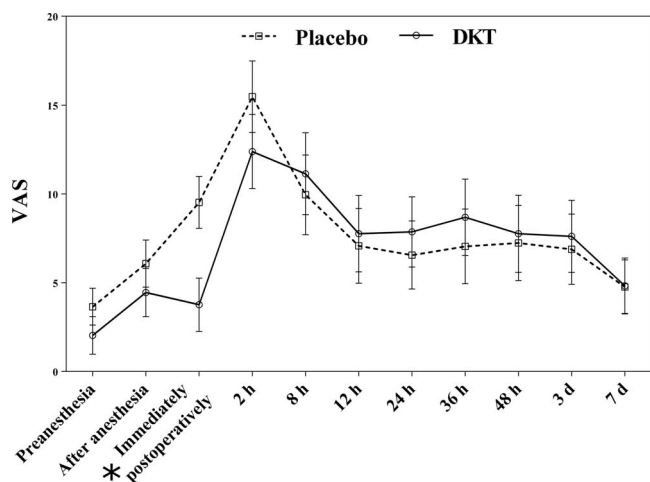


FIGURE 3. Patient pain evolution. The total follow-up period was 7 days. *Statistically significant differences.

There were no significant differences between the groups regarding other possible complications, such as hematoma, infection, dehiscence, emphysema, sensory disturbances, or bone necrosis, at 48 hours (Mann-Whitney *U* test). No difference in gastrointestinal discomfort was observed between the groups (χ^2 test). These data should be interpreted with caution because of the very low incidence of recorded complications (Table 3).

DISCUSSION

The aim of the present study was to test the underlying principle of preemptive analgesia. It has been suggested that therapeutic interventions should begin before the onset of pain rather than in response to pain.¹⁷ Preemptive analgesia reduces postoperative pain and the consumption of analgesics and appears to be the most effective means of decreasing postoperative pain.¹⁸

To evaluate the pain reported by patients, we used a VAS.¹⁹ The VAS is a simple, solid, sensitive, and reproducible tool for

assessing pain in a given patient at different points in time. Additionally, VAS data can be analyzed with the use of parametric statistical techniques.

However, many clinical trials designed to test the analgesic efficacy of medicines do not consider values <50 in VAS for statistics.

Despite the fact that the surgery for single implant placement is a procedure where low intensity pain is expected (VAS: 15.44, 2 hours after surgery), we considered that in the absence of a gold standard for pain, this approach was the only way to obtain a similar stimulus for all patients and in this way to be able to compare the results of administering a preventive analgesic treatment. Most studies that assess pain after oral surgery (mainly lower third molars) follow a similar methodology and register pain levels <50.

On the other hand, the perception of pain involves a multiplicity of factors. Among the factors that are significantly correlated with postoperative pain are the following: (1) systemic diseases, (2) surgical procedures, (3) premedication, (4) bone quality, (5) presurgery anxiety, (6) postoperative swelling, and (7) sex.

Systemic diseases, such as diabetes mellitus and arterial hypertension, have been associated with higher rates of postoperative complications, such as pain and lack of wound healing,²⁰ which result from either the disease itself or medications used to control the disease. In our study, all patients were in good health (ASA I or II), and both of the aforementioned diseases were specifically avoided. Thus, systemic diseases did not affect our results.

Regarding the anesthesia used, we preferred lidocaine over other anesthetics such as articaine. The main reason for this choice is the short half-life of lidocaine (1.5–2 hours) and its wide therapeutic range. For instance, articaine has a half-life of 6 hours. The choice of lidocaine seemed appropriate because none of our interventions lasted more than 60 minutes. Furthermore, the rapid dissipation of the anesthetic effects allowed us to reliably evaluate the effect of DKT at an early stage.

In our study, we chose the administration of ibuprofen as a pain relief medication. The prescription of ibuprofen 600 mg as postoperative analgesic certainly masked the effect of DKT on pain perception. Both are nonsteroidal anti-inflammatory drugs (NSAIDs) that prevent inflammatory prostaglandin production by cyclooxygenase 1 and 2 (COX 1 and 2), as well as prostacyclin and thromboxane.

Another option would have been the prescription of acetaminophen. Acetaminophen is a drug used to relieve pain and reduce fever. Its mechanism of action does not interfere with the activity of COX 1 and 2. However, after surgery, it is imperative to also control inflammation, and this possible side effect involves not only the use of analgesics but the use of anti-inflammatories as well. The obvious reasons to control both are of an ethical nature, given that we do not know which patients will have it. On the other hand, we also looked for the continuity of the inhibitory effect on COX initiated by the DKT.

In any case, the taking of ibuprofen started 2 hours after the surgery and does not explain the differences found in the immediate postoperative period, because both arms of the study follow the same analgesic and anti-inflammatory pattern.

TABLE 3

Complications and side effects observed during follow-up§

	Placebo (n = 42), DKT (n = 41),		P Value
	Median; IQR	Median; IQR	
Inflammation†	0; 0–1	1; 1–0	.025*
Bleeding†	0; 0–0	0; 0–0	.04*
Hematoma†	0; 0–0	0; 0–0	.674
Infection†	0; 0–0	0; 0–0	.317
Dehiscence†	0; 0–0	0; 0–0	.399
Emphysema†	0; 0–0	0; 0–0	1
Sensory disturbances†	0; 0–0	0; 0–0	.317
Bone necrosis†	0; 0–0	0; 0–0	.165
Gastrointestinal upset‡	0; 0–0	0; 0–0	.494

*Statistically significant differences.

†Mann-Whitney *U* test.

‡ χ^2 test.

§IQR indicates interquartile range; DKT, dexketoprofen trometamol.

It has been claimed that patients who undergo more complicated surgical procedures are prone to have more pain. The factors that are relevant to the procedures used in the present study that should be mentioned include procedures that lasting more than 60 minutes,²¹ graft technique,⁹ placement in posterior sectors,¹⁰ the number of implants placed,⁹ overheating of the surgical bed,^{22,23} insertion torque,²⁴ the administration of too much local anesthesia,²⁵ and surgeon experience.⁸ If an appropriate protocol for implant placement is followed, there should be few adverse effects. In this respect, adequate irrigation and intermittent drilling with low pressure will decrease postoperative pain.²⁶

In our study, we attempted to control all these variables and excluded complex cases that might have required treatment via regenerative techniques. We were extremely scrupulous regarding the surgical technique; we applied abundant irrigation in combination with discontinuous and progressive drilling in addition to using the minimum effective amount of local anesthesia. We also applied 20 N of insertion pressure in an electronically controlled manner. Additionally, a single surgeon performed all the interventions according to the manufacturer's instructions.

One worrying aspect is the premedication consumed by the patient. Two types of medications can affect wound healing. Some drugs, such as antidepressants, antipsychotics, mood stabilizers, anxiolytics, sedatives, and sleeping pills, alter the perception of pain,²⁰ whereas some drugs affect the osseointegration process (particularly NSAIDs).²⁷⁻³⁰

Patients who may have taken any medication that might affect pain perception or osseointegration during the previous 2 months were excluded from the study.

In our study, none of the patients mentioned gastrointestinal upset, and when the degree of wound healing was evaluated at 48 hours, no significant differences between the groups were found. These data are in agreement with those published by other authors and demonstrate that the use of NSAIDs for short periods does not jeopardize dental implants in the early healing phase.³¹

However, to avoid this possible risk, the use of single doses and/or short-duration regimens of analgesic treatment is recommended. There is a wealth of reliable evidence regarding the analgesic efficacy of single-dose oral analgesics. Fast-acting formulations and fixed-dose combinations of analgesics can produce good and often long-lasting analgesia at relatively low doses.³² In contrast, studies of single oral doses of analgesics have provided evidence that adverse event rates are generally similar between placebo and treatment groups in these circumstances, with the exception of the application of higher doses of some drugs and drug combinations that include opioids.³³ These data reinforce our support for the preventative administration of DKT in a single dose prior to implant surgery.

The objective of this study was to evaluate the efficacy of pain control with a single dose of DKT. Given that the half-life of DKT is approximately 1.6 hours, the follow-up on pain could be evaluated only with a period of 12 or 24 hours. However, the control of the surgery side effects not only is limited to the first 12 or 24 hours, but often appear even 7 days later. This 7-day follow-up sought to record all the possible complications of both the surgery and the use of the pharmacologic treatment

used. Furthermore, the follow-up was established in different periods of time and analyzed independently from each other.

An association between bone quality and pain has been described. The explanation for this association could be that hard bone requires a lengthier surgical duration. Furthermore, hard bone could require greater contact pressure and thus elicit a necrotic response.³⁴ Therefore, a positive correlation between hard bone and postoperative pain would also be plausible and reasonable.

Additionally, some authors have identified a relationship between the position of the implant and the perceived pain,⁹ whereas others have not found such an association.^{35,36} This inconsistency is probably due to the pressure to which the high-density bone is subjected during the insertion of the implant. In our study, the compression during insertion was controlled and did not exceed 20 N. If the pressure exceeds this limit during milling, the drill provided in the surgical kit is altered (Mozo Grau/Ticare, Valladolid, Spain) and adapts itself to the bone density.

In our study, there were no significant differences in pain according to either the anatomic region of the implant or bone density.

It seems clear that anxiety can influence and amplify the pain response in early stages.^{6,10,35,37} However, some authors claim that the effect of anxiety at 7 days does not appear to be markedly important.³⁵

In our study, anxiety traits/states were not evaluated beyond the interviews completed by the patients on recruitment. Therefore, we cannot assess the influence of anxiety on immediate postoperative pain.

Some degree of postoperative swelling should be expected following dental implant surgery. The placement of dental implants physically insults both the mucosal and alveolar tissues, which causes classical acute inflammation.¹¹ In accordance with a previous study, swelling can be increased depending on the number of inserted dental implants, placement in an edentulous location, the presence or absence of sinus elevation and any bone reconstruction procedures that are performed.⁹

Our results demonstrated that swelling was lower in the DKT group at 48 hours. However, bleeding was greater at the same time (although with a low intensity). Both effects could be expected due to the administration of NSAIDs. No other complications were observed.

Finally, several authors have reported that women complain of pain more frequently than men.^{26,38,39} Similar to other authors,⁴⁰ we observed no differences in the perception of pain between the sexes, although in the placebo group, there was a clinical tendency for the women to report more pain after 8, 12, 24, and 36 hours, but this difference was not statistically significant.

The limitations of this study include the use of ibuprofen as an analgesic medication. All patients were prescribed 600 mg ibuprofen every 8 hours for 48 hours after the first 2 hours of surgery. This therapeutic action might partially explain why the perception of late postoperative pain did not differ between the 2 groups. However, this limitation arose from the obligation to help prevent the occurrence of pain in the patients to the

fullest extent possible. The application of no analgesic protocol would be unethical and therefore cannot be considered.

Notably, the ibuprofen was not supplied in a container that had to be returned at the end of the follow-up period. Despite our insistence that the patients maintain a strict pattern of administration, we cannot be sure that they followed this recommendation or that they did not take doses higher than those recommended.

Neither the reliability nor validity of the VAS was quantified in this study. However, we have used VAS as it was used in similar studies.

Another limitation of this work involves the lack of consideration for anxiety status, which would depend on individual differences in personality or expectations. We did not evaluate this variable, so we cannot determine to the degree to which anxiety might have affected the perception of pain.

Bone density was evaluated, but the limited number of implants placed in D1 bone and the absence of implants placed in D4 bone preclude appropriate conclusions regarding this variable.

Finally, osseointegration was not evaluated in the present study, and thus, we cannot speculate as to whether DKT or NSAIDs altered osseointegration in the long term.

CONCLUSIONS

Within the limitations of this study, the preemptive use of 25 mg soluble DKT administered orally 15 minutes before implantation showed statistically significant effects on immediate postoperative pain vs placebo administration.

ABBREVIATIONS

ANOVA: analysis of variance
 ASA: American Society of Anesthesiologists
 CONSORT: consolidated standards of reporting trials
 COX 1: cyclooxygenase 1
 COX 2: cyclooxygenase 2
 DKT: dexketoprofen trometamol
 GLM: general linear model
 NSAIDs: nonsteroidal anti-inflammatory drugs
 VAS: visual analog scale

NOTE

The authors declare no conflicts of interest or funding sources.

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