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Diclofenac sodium vs. dexketoprofen trometamol: selecting NSAIDs for managing postoperative inflammatory complications after third molar surgery—a randomized clinical trial

Mahmut Erkal[1] and Cennet Neslihan Eroglu[1*]

Abstract

Background After surgical procedures involving bone and soft tissue, such as impacted tooth extraction, profen and diclofenac derivatives are commonly prescribed. Diclofenac sodium (DS) and dexketoprofen trometamol (DT), derivatives of diclofenac and profen, exhibit clinical differences from their parent compounds. Despite their widespread use, comparative studies of their effects on postoperative complications remain limited. This randomized controlled trial was performed to compare the analgesic and anti-inflammatory effects of DS and DT following impacted tooth extraction.

Methods This split-mouth, randomized clinical study included healthy individuals aged 18 to 40 years with bilaterally impacted third molars. Left and right teeth were randomly assigned to either the DT or DS group. Participants took 25 mg of DS or 36.9 mg of DT twice daily for 7 days, beginning 1 h before extraction. Postoperative pain was assessed using a visual analogue scale at 4, 8, 12, and 24 h postoperatively, as well as on days 2 through 7. Trismus was evaluated by the interincisal distance, and edema was anatomically measured preoperatively and on postoperative days 2 and 7. The surgical duration and rescue analgesic use were also recorded.

Results In total, 35 patients (28 women, 7 men) aged 18 to 31 years (mean, 21.31 ± 3.19 years) participated. The mean operation duration was 12.94 ± 2.26 min for the DT group and 13.26 ± 2.19 min for the DS group ($p > 0.05$). No statistically significant difference was observed between the groups regarding pain, edema, or trismus development ($p > 0.05$). However, from days 2 to 7, the DS group exhibited a greater reduction in edema than did the DT group ($p < 0.05$). Additionally, the DS group required 10% more frequent use of rescue analgesics than the DT group.

Conclusion Following impacted tooth extraction, administering DT during the initial days—when pain is more intense and the inflammatory response is developing—followed by DS in the later recovery phase may enhance postoperative comfort.

*Correspondence:
Cennet Neslihan Eroglu
neslihanakca2003@yahoo.com

Full list of author information is available at the end of the article

Trial registration This clinical trial was retrospectively registered on 03.10.2023 with the number TCTR20231003006.
Keywords Diclofenac sodium, Dexketoprofen trometamol, Third molar, Pain, Edema, Trismus

Introduction

Impacted tooth extractions are routine maxillofacial surgeries that often result in pain, swelling, and trismus, with symptoms generally subsiding within the first week. Depending on the procedure, clinicians typically select either analgesic medications or a combination of analgesic and anti-inflammatory drugs [1]. To address these postoperative complications, non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed as the most practical option. NSAIDs are available in various forms, dosages, and salt derivatives [2, 3].

The formation of salt compounds is a well-established technique for creating safe and effective drug dosage forms. This approach significantly influences the physicochemical and biological properties of active pharmaceutical ingredients [4, 5]. The selection of an appropriate salt depends on several factors, including the drug's chemical characteristics, the intended dosage form, and its pharmacokinetic profile. Choosing the optimal salt can enhance therapeutic efficacy and pharmaceutical performance by affecting drug dissolution rates and clinical outcomes [5]. As a result, different formulations may lead to variations in pharmacodynamic effects among individuals [6].

Diclofenac is a derivative of benzene acetic acid. Among its salt forms, diclofenac sodium (DS) demonstrates good oral absorption and is exclusively used in extended-release dosage forms. By contrast, diclofenac potassium is absorbed more rapidly, providing faster onset of action and making it the preferred option for pain relief. However, it is argued that the sodium salt form is more effective for managing inflammation [5, 7].

Dexketoprofen trometamol (DT), a water-soluble tromethamine salt of ketoprofen from the aryl propionic acid NSAID family, exhibits unique clinical effects compared with ketoprofen. Studies indicate differences in the analgesic and anti-inflammatory properties of racemic ketoprofen, dexketoprofen, and DT [8–11]. Pharmacokinetic data reveal that DT is absorbed more rapidly, reaching peak plasma concentrations within 0.25–0.75 h when taken orally, compared with 0.5–3.0 h for racemic ketoprofen [8]. Approximately 10% of racemic ketoprofen is metabolized into dexketoprofen in the body, and it has been reported that dexketoprofen provides anti-inflammatory effects equivalent to a dose of ketoprofen that is twice as high [9, 10]. Products marketed as 25 mg actually contain 36.9 mg of DT which is bioequivalent to 25 mg of dexketoprofen [12]. Furthermore, DT is particularly effective in managing pain within the first few hours after surgery, with an analgesic effect lasting up to 5.5 h, maintaining high efficacy even at low doses [13, 14].

To date, no definitive conclusion has been reached in the literature on this issue because the limited number of clinical studies comparing diclofenac and ketoprofen do not adequately represent DS and DT [5, 7–11, 15]. Moreover, the majority of these studies have primarily focused on evaluating analgesic efficacy, with limited or no comparative analysis of their anti-inflammatory effects [13–15].

The aim of this study was to compare the efficacy of DS and DT when administered preemptively following impacted tooth extraction. Specifically, the study aimed to evaluate the progression of pain, edema, and trismus between the groups and assess the need for rescue analgesics in each group. We hypothesized that the side treated with DT would experience less pain, edema, and trismus, along with a significantly reduced need for rescue medication.

Materials and methods

A single-center, parallel-group, randomized clinical trial was conducted on patients scheduled for impacted lower third molar extractions at the oral and maxillofacial surgery department between February 2019 and February 2022. Eligible participants were non-smoking individuals aged 18 to 40 years, had an American Society of Anesthesiologists physical status of 1, had no known allergies to the medications used in the study, and had no medication use within the previous 3 months. Participants had asymptomatic teeth with no history of infection, characterized by bilateral symmetric bone retention in Class II, Class B (Pell-Gregory), and mesioangular (Winter) positions, with a Pedersen difficulty score of 10–11. Bone removal and tooth sectioning were required in all procedures.

The study was approved by the Clinical Research Ethics Committee (KAEK-155/16032022) of Akdeniz University Faculty of Medicine.

In accordance with the guidelines of the Helsinki Declaration, all participants provided written informed consent after being fully informed about the drugs, surgical procedures, potential side effects, and complications. The clinical trial was registered retrospectively under the number TCTR20231003006 and adheres to the recommendations of the CONSORT 2010 statement for reporting randomized trials.

Study sample and design

The sample size for this study was calculated with a power of at least 80% and a type 1 error of 5% (paired design) [16], resulting in a total of 35 patients (Fig. 1). The left- and right-side teeth of the same individual constituted the experimental groups, with simple randomization used to assign the teeth to either the DS group or DT group. In the DS group, participants were administered 25 mg diclofenac sodium (Dikloron 25 mg, enteric tablet; Deva Holding Inc., Istanbul, Turkey) orally 1 h before surgery, followed by the same dose twice daily for 7 days postoperatively. In the DT group, participants received 36.9 mg dexketoprofen trometamol (Arveles 25 mg tablet; Menarini Drug Industry and Trade Inc., Istanbul, Turkey) orally 1 h before surgery, with the same dosing regimen continued postoperatively for 7 days. A minimum washout period of 4 weeks was observed between the extraction of the right and left teeth to ensure adequate drug clearance.

Blinding

The clinician responsible for collecting preoperative and postoperative clinical data, as well as the surgeon and the statistician, were blinded to the group allocation. The administration of the drugs was carried out by a trained dental assistant who was not involved in the study.

All patients with recorded preoperative measurements underwent procedures under local anesthesia containing articaine hydrochloride + epinephrine. Standard surgical techniques were employed, including a horizontal incision from the crest of the wisdom tooth to the anterior border of the ramus mandibulae, a sulcular incision of the second molar, and vertical relaxing incisions from the mesial aspect of the second molar, which together facilitated the elevation of a triangular full-thickness flap. Bone removal was performed under saline irrigation, and the teeth were extracted by sectioning. Following the extraction, the sockets were irrigated with physiological saline and the flaps were closed primarily using 3/0 silk sutures, with three sutures for the horizontal incision and two for the vertical component. All surgical procedures were conducted by a single highly skilled oral surgeon (M.E.). The duration of the operation was recorded from the initiation of the incision to the placement of the final suture. Postoperatively, all patients were prescribed 1000 mg of amoxicillin and instructed to use a chlorhexidine gluconate + benzydamine hydrochloride gargle orally twice daily for 7 days. Additionally, 500 mg of paracetamol was provided as a rescue analgesic to be used if needed. No postoperative cold compresses were applied for any patient.

Postoperative pain was evaluated using a visual analogue scale (VAS) at 4, 8, 12, and 24 h postoperatively, as well as on days 2, 3, 4, 5, 6, and 7. Pain intensity was scored on a scale from 0 to 10, with 0 representing no pain and 10 representing the worst possible pain.

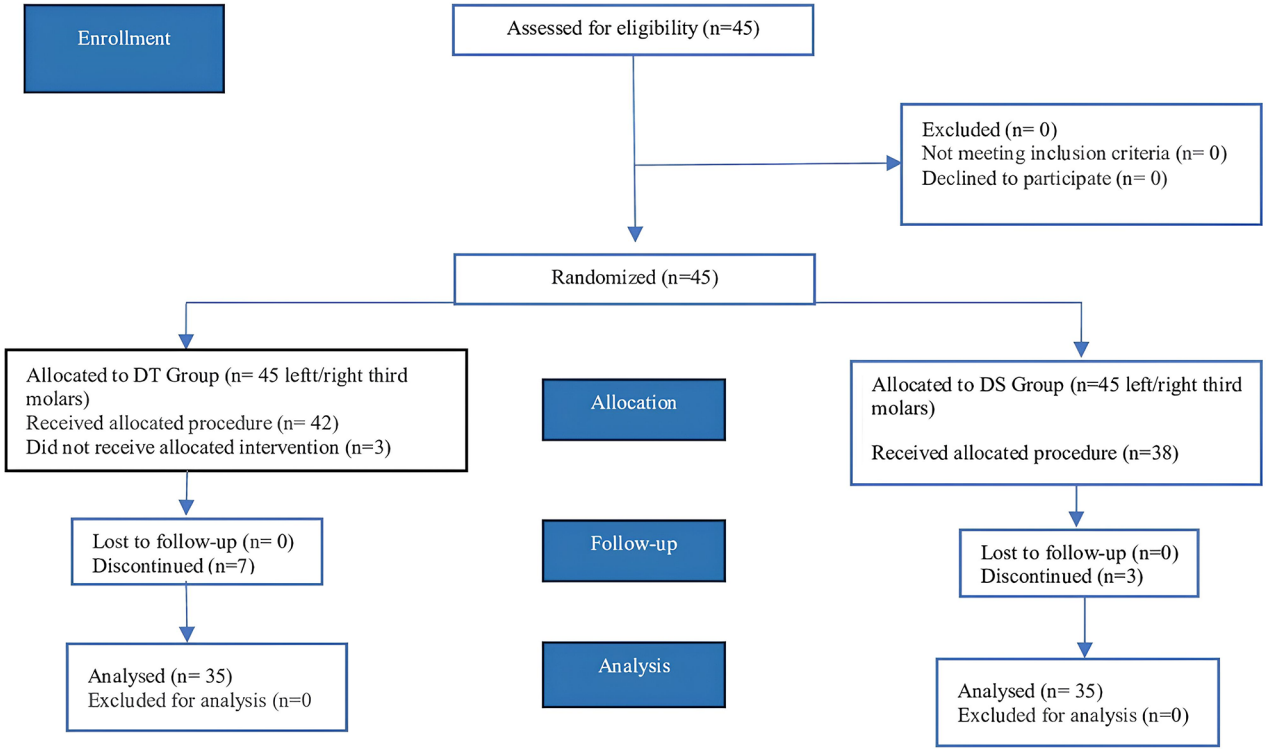

Fig. 1 CONSORT flow diagram of the present single-center, parallel-group randomized clinical trial

Edema was measured using preoperative anatomical reference points: gonion–external canthus (a), tragus–lip commissure (b), and tragus–pogonion (c). The distances between these points were recorded using a flexible ruler. Postoperatively, measurements were repeated on days 2 and 7, and the difference between the preoperative and postoperative values was calculated to determine the amount of edema.

For trismus assessment, the maximum mouth opening distance between the lower and upper central incisors was recorded preoperatively. Postoperative measurements of maximum mouth opening were taken on days 2 and 7, and the difference between these values and the preoperative measurement was calculated to assess the extent of trismus. Additionally, if rescue analgesics were used, the number of tablets consumed was recorded.

Data analyses

The Shapiro–Wilk test was employed to assess the normality of the distribution of continuous variables. Descriptive statistics for continuous variables were presented as mean, standard deviation, median, and range. To compare measurements between the sides, the paired t-test was applied for parametric data, while the Mann–Whitney U test was used for non-parametric data.

For intra-group comparisons, the Wilcoxon test was used to analyze measurements on days 2 and 7. Additionally, the Friedman test was applied within each group to compare measurement differences between days 2 and 7, followed by a Bonferroni-corrected post-hoc test for pairwise comparisons. A statistical significance level of $p < 0.05$ was considered. Data analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA).

Results

The study included 28 women (80.0%) and 7 men (20.0%), with patient ages ranging from 18 to 31 years and a mean ± standard deviation of 21.31 ± 3.19 years. The mean operation duration was 12.94 ± 2.26 min for the DT group and 13.26 ± 2.19 min for the DS group, with no statistically significant difference between them ($p = 0.56$).

Statistical analysis revealed that the mean VAS scores of the two groups were similar ($p > 0.05$). However, the mean rescue analgesic usage was 0.57 ± 1.01 tablets (31.4%) in the DT group and 0.69 ± 0.93 tablets (41.2%) in the DS group. The difference in rescue analgesic usage between the groups was not statistically significant ($p = 0.62$).

When comparing the differences between maximum mouth openings on postoperative days 2 and 7 relative to preoperative measurements, the DS group showed higher mean differences. However, these differences were not statistically significant ($p > 0.05$) (Table 1).

For edema outcomes, the differences in the a, b, and c distances measured preoperatively and postoperatively on days 2 and 7 were analyzed between groups, and no significant differences were observed (Table 2). However, a statistically significant difference was found in favor of the DS group regarding the reduction in edema from days 2 to 7, with the DS group exhibiting greater edema reduction (Table 3; Fig. 2).

No recovery problems or drug-related side effects were observed during the study.

Discussion

In this study, we investigated whether preemptive administration of DT or DS would offer distinct advantages in managing pain, swelling, and trismus during the

Table 1 Comparison of postoperative pain (VAS scores) and trismus between DT and DS groups

	DT Group					DS Group					*p**
	Mean	SD	Median	Min.	Max.	Mean	SD	Median	Min.	Max.	
VAS (4 h)	5.23	3.12	6.00	0.00	10.00	5.09	3.28	5.00	0.00	10.00	*0.852*
VAS (8 h)	6.69	2.76	7.00	0.00	10.00	7.06	2.55	8.00	0.00	10.00	*0.561*
VAS (12 h)	5.63	3.05	5.00	0.00	10.00	5.80	2.71	6.00	0.00	10.00	*0.804*
VAS (1 day)	4.43	2.76	4.00	0.00	10.00	5.26	3.08	5.00	0.00	10.00	*0.240*
VAS (2 days)	3.60	2.45	4.00	0.00	10.00	3.51	2.49	3.00	0.00	10.00	*0.885*
VAS (3 days)	2.17	2.35	2.00	0.00	9.00	2.43	1.97	2.00	0.00	6.00	*0.621*
VAS (4 days)	1.26	1.85	0.00	0.00	9.00	1.57	1.52	1.00	0.00	4.00	*0.441*
VAS (5 days)	0.83	1.27	0.00	0.00	5.00	0.80	1.18	0.00	0.00	5.00	*0.923*
VAS (6 days)	0.60	1.03	0.00	0.00	4.00	0.46	0.70	0.00	0.00	3.00	*0.501*
VAS (7 days)	0.40	0.77	0.00	0.00	3.00	0.26	0.61	0.00	0.00	3.00	*0.395*
Trismus (2 days)	17.54	5.54	18.00	6.00	29.00	16.06	6.49	17.00	3.00	27.00	*0.306*
Trismus (7 days)	6.97	5.24	5.00	0.00	20.00	6.60	6.04	6.00	0.00	24.00	*0.784*

**According to the results of the paired t-test, significance levels for inter-side differences are indicated*

VAS = visual analogue scale, SD = standard deviation, Min. = minimum; Max. = maximum

DT = dexketoprofen trometamol

DS = diclofenac sodium

Table 2 Comparison of edema measurements between DT and DS groups over time

	DT Group				DS Group				*p**
	Mean	**SD**	**Median**	**Range**	**Mean**	**SD**	**Median**	**Range**	
D2E a	0.74#	0.56	1.00	2.00	0.89#	0.63	1.00	3.00	*0.379*
D7E a	0.14	0.36	0.00	1.00	0.09	0.28	0.00	1.00	*0.456*
D2E b	0.66#	0.48	1.00	1.00	0.71#	0.57	1.00	2.00	*0.749*
D7E b	0.20	0.41	0.00	1.00	0.11	0.32	0.00	1.00	*0.328*
D2E c	0.40#	0.50	0.00	1.00	0.46#	0.51	0.00	1.00	*0.632*
D7E c	0.03	0.17	0.00	1.00	0.00	0.00	0.00	0.00	*0.317*

**Significance levels for inter-group differences are indicated byp values (Mann–Whitney U test)*

#Statistically significant intra-group differences between D2E and D7E (Wilcoxon test)

D2E = edema measurement on postoperative day 2

D7E = edema measurement on postoperative day 7

a, b, c = different anatomical reference points used for edema measurement

DT = dexketoprofen trometamol

DS = diclofenac sodium

SD = standard deviation

Table 3 Comparison of intra-group changes in edema measurements over time

	DT Group				DS Group				
	Mean	**SD**	**Median**	**Range**	**Mean**	**SD**	**Median**	**Range**	***p****
D2E a – D7E a	0.600	0.604	1.000	2.000	0.800[a]	0.484	1.000	3.000	*0.144*
D2E b – D7E b	0.457	0.505	0.000	1.000	0.600[a]	0.301	1.000	3.000	*0.249*
D2E c – D7E c	0.371	0.490	0.000	1.000	0.457[b]	0.205	0.000	1.000	*0.470*
*p***	*0.302*				***0.039***				

**According to the results of the Mann–Whitney U test, significance levels for inter-group differences are indicated byp values*

***Significance levels for measurement differences between days 2 and 7 were determined using the Friedman test: a, b indicate statistically significant differences according to the Bonferroni-corrected post-hoc test*

D2E–D7E = difference in edema measurement between postoperative days 2 and 7

DT = dexketoprofen trometamol

DS = diclofenac sodium

SD = standard deviation

postoperative period. While clinical differences between the two groups were observed, these did not reach statistical significance. Clinically, rescue analgesia was required less frequently on the side treated with DT, and less edema was initially observed. Conversely, DS proved significantly more effective than DT in reducing edema between postoperative days 2 and 7. These findings suggest that DT may be particularly beneficial during the first 48 h, when pain is most severe and edema is increasing, while DS could be more effective in the later recovery phase for resolving postoperative edema more rapidly. Based on these results, tailoring NSAID prescriptions to the specific needs of the recovery period—using analgesic-anti-inflammatories during the early postoperative phase—could be a promising strategy. We believe this study provides "novelty value" by offering clinicians a new perspective on postoperative NSAID prescription strategies.

The use of rescue analgesics has been identified as a potential factor that can obscure the true effects of study drugs within a research group [17]. In our study, rescue analgesics were used, and this provided valuable data regarding the efficacy and duration of action of the NSAIDs administered. Because NSAIDs are generally dosed twice daily, the use of rescue analgesics helps to determine whether the prescribed regimen is sufficient to manage pain effectively at the given dosage. Increasing the dosage of analgesics raises the risk of side effects and toxicity; therefore, it is critical to establish the minimum effective dose and an appropriate dosing regimen tailored to the clinical scenario. The need for rescue analgesics in the DS group raises the question of whether a higher dosage or alternative analgesics should be considered for managing acute pain more effectively.

The patients in our study began their medications 1 h before the procedure, with 31.4% of the DT group and 41.2% of the DS group requiring paracetamol as a rescue analgesic. Although this approximately 10% lower usage in the DT group did not reach statistical significance, it may indicate a clinical advantage. Notably, although paracetamol is generally considered to have minimal anti-inflammatory effects, a previous study reported a contradictory finding [18]. This raises the possibility that the use of paracetamol as a rescue analgesic may have

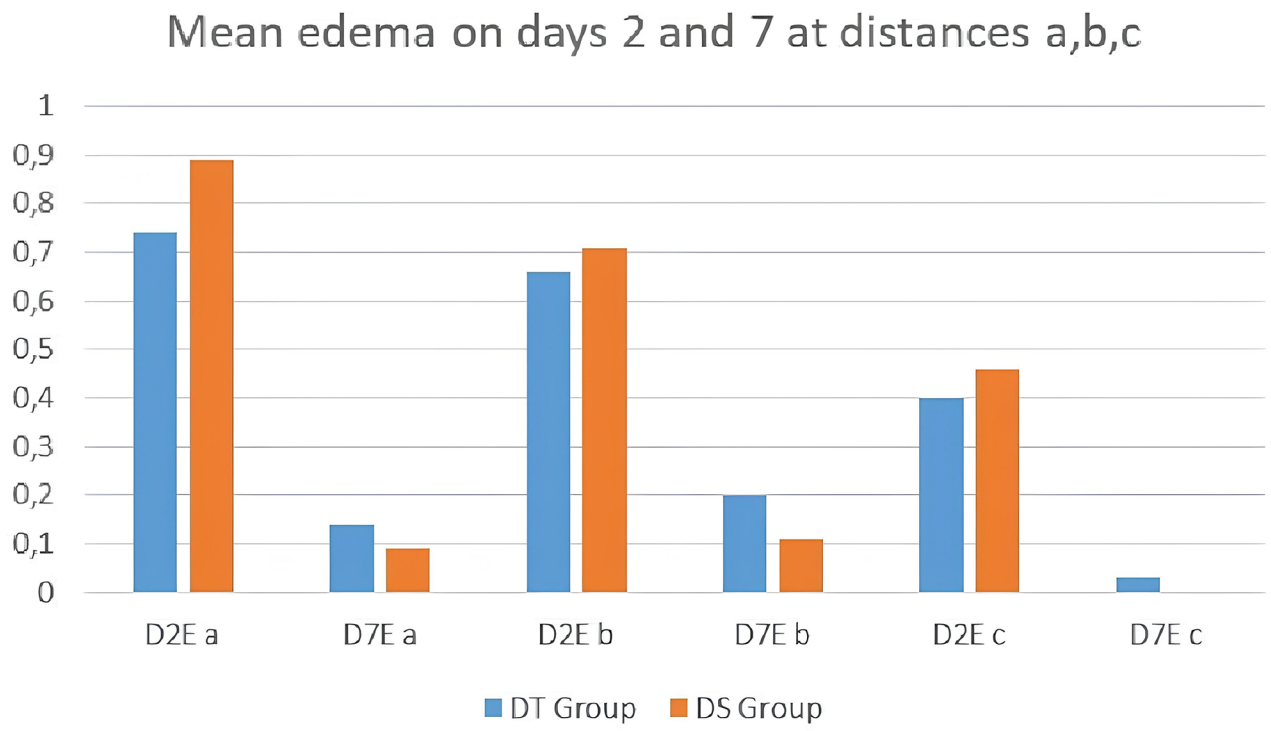

Fig. 2 Variation in mean edema measurements over time for each group

contributed to the faster reduction of edema observed in the DS group than in the DT group between days 2 and 7.

The time to reach the maximum plasma concentration for DT is 25–45 min, while that for DS is approximately 2 h [8, 19]. Although no statistically significant difference was found in the peak edema levels, clinically, less edema was observed on postoperative day 2 in the DT group than in the DS group. This clinical difference may be attributed to DT's rapid attainment of the maximum plasma concentration, potentially making it more effective in suppressing early-stage inflammation during the period of surgical trauma. By day 7, the edema levels were similar in both groups, with the DS group showing greater success in reducing edema between days 2 and 7. This could be associated with the hydrophilic nature of the sodium salt compared with the trometamol salt, which may enhance its effectiveness in resolving edema. Future studies could explore whether administering DS 2 h before the procedure might produce different clinical and statistical outcomes regarding its effect on edema. However, because of diclofenac's short plasma elimination half-life, preemptive administration 2 h prior is unlikely to extend the pain-free period provided by local anesthesia [15, 18, 20–22]. Additionally, initiating diclofenac preemptively 1 day before surgery has been reported to have no effect on trismus [23]. In our study, no statistically significant difference was observed between the groups in terms of trismus outcomes.

Converting drugs into water-soluble salt forms enhances their dissolution, absorption, and bioavailability after oral administration [24]. As a result, the clinical duration of action, absorption rate, dosage, and maximum effect value of ketoprofen and diclofenac differ from those of their salt forms, DT and DS. Studies comparing ketoprofen and diclofenac with their salt derivatives show that higher doses of the main active ingredients are often used, and the salt forms typically have a shorter onset of action. For instance, studies comparing the parent compounds typically administer ketoprofen and diclofenac at higher dosages than their salt forms [25, 26]. In one study, a single 100-mg dose of ketoprofen was compared with 75 mg of DS following impacted tooth extraction, and although pain scores favored ketoprofen, the difference was not statistically significant. However, the time to first analgesic intake was noted to be longer with ketoprofen [25]. Similarly, another study by Bahrgava et al. compared single doses of a 20 mg/70 cm^2 ketoprofen patch with a 200 mg/50 cm^2 diclofenac patch after impacted premolar tooth extraction, with ibuprofen as a rescue analgesic. Although ketoprofen demonstrated analgesic superiority, no statistically significant difference was found [26].

Anıl et al. administered a single dose of 50 mg DT and 75 mg DS parenterally during laparoscopic cholecystectomy [27]. In patients who received DT, both controlled morphine use and rescue analgesic requirements were lower than in the DS group, and the time to first analgesic use after surgery was longer [27]. Additionally, in the

management of acute musculoskeletal injuries, orally administered DT has been shown to provide faster pain control than DS [28]. Our findings align with the literature; however, we did not identify any studies comparing the analgesic and anti-inflammatory effects of these two drugs on both soft and bone tissues.

One limitation of our study is the lack of homogeneity in the female-to-male ratio. This imbalance is largely due to a general trend observed in the literature, where women are more likely to undergo tooth extractions [29]. Male patients, even when extraction is indicated, tend to be less likely to proceed with the procedure. Additionally, the patient groups were formed during the active phase of the COVID-19 pandemic, a time when patients were still hesitant to seek dental treatment in hospitals, further contributing to this imbalance.

Another limitation is the absence of a placebo group in the study. However, the superiority of the NSAIDs used in this study over placebo has been repeatedly demonstrated in prior research. Furthermore, the use of experimental groups created within the same individual eliminates individual variability in drug response, enhancing the reliability and significance of the results.

The doses used in this study were selected based on typical daily requirements encountered in clinical practice and determined with consideration of the therapeutic efficacy of both drugs. While the dose ranges provided in product labeling allow for a broad therapeutic window, the risk of adverse effects increases with higher doses. For instance, DT doses of ≥ 50 mg are associated with a higher incidence of local bleeding [11, 14]. Furthermore, because pharmaceutical products on the market containing 25 mg of DT actually include 36.9 mg of DT, the threshold for potential side effects may be reached more quickly. This highlights that the optimal dose for each drug may not be universally applicable across all clinical scenarios. Therefore, pharmaceutical research should prioritize evaluating whether the desired clinical effects can be achieved with the minimum effective dose in the shortest possible time frame.

For pain, edema, and trismus following the extraction of impacted teeth, even minimal relief—such as a decrease of 1 point on the VAS or a slight improvement in mouth opening—can translate into significant comfort for patients. In split-mouth studies, the results hold particular clinical value because patients can directly compare the effects on the right and left sides. Therefore, even minor clinical differences are meaningful in terms of patient comfort and benefit, and a statistically significant difference may not always reflect clinically relevant improvements [30]. What truly matters is the impact on patients' quality of life and its implications for clinical practice [31].

Conclusion

Our findings suggest that instead of relying on a single anti-inflammatory analgesic throughout the postoperative period, different drug requirements may arise depending on the clinical progression of inflammation. Although no statistically significant difference was observed between DT and DS, DT demonstrated clinical benefits such as reduced rescue analgesic use and less edema development on day 2. On the other hand, DS was more effective in resolving postoperative edema over time. Based on these findings, it may be beneficial to admisnister DT during the first 48 h, when pain is severe and edema is increasing. Changing the medication to DS after 48 h could potentially lead to a faster resolution of postoperative edema. This drug regimen should be further evaluated. In other words, the postoperative period may be better managed by tailoring NSAID use to the stages of the healing process.

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Author contributions
M. E. and C.N.E. wrote the main text and prepared Figs. 1 and 2. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Clinical Research Ethics Committee (KAEK-155/16032022) of Akdeniz University Faculty of Medicine. All participants provided written informed consent to participate in the study, which adhered to the principles outlined in the Helsinki Declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Akdeniz University, Antalya 07058, Turkey

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