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Tramadol combined with local anesthesia for postoperative pain in third molar surgery

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Abstract

Background Postoperative pain is a significant challenge in oral surgery. Tramadol exhibits both systemic and local analgesic effects, with proven efficacy in combination with local anesthetics.

Purpose This study evaluated the efficacy of local anesthetics combined with tramadol in reducing pain and analgesic use after third molar surgery.

Study design, setting, sample This randomized, double-blind trial included ASA I–II patients aged 18–50 years and weighing 70–80 kg who were undergoing impacted third molar surgery. Patients requiring extra anesthesia, those with tramadol hypersensitivity, or those who recently used sedatives were excluded.

Independent variables Two local anesthetic solutions were compared: the LT group (tramadol and articaine with epinephrine) and the LA group (articaine with epinephrine, control).

Main outcome variable Postoperative pain was measured as the primary outcome via a visual analog scale (VAS) at multiple time points (10 min and 1, 2, 4, 6, 12, 24 and 48 h postsurgery). The secondary outcomes included the timing of the first analgesic intake and the total number of analgesic doses consumed within 48 h.

Covariates The covariates included age, sex, BMI, surgical duration, and adverse effects (nausea, vomiting, burning).

Analyses Age and surgical duration were analyzed with t tests; VAS scores and analgesic use were analyzed with Mann–Whitney U tests; and categorical data were analyzed with Fisher's exact test or Yates' correction ($p < 0.01$).

Results Sixty patients were randomized into the LT ($n = 30$) and LA ($n = 30$) groups. Age, sex, and BMI distributions were similar between the groups. VAS pain scores were lower in the LT group at 1, 2, and 6 h (mean difference: -4.9, -1.9, and − 1.4; $p < 0.01$) but higher at 4 h (mean difference: 1.5; $p < 0.01$). The LT group required their first analgesic later (5.2 ± 0.8 vs. 2.0 ± 0.6 h; mean difference: 3.1; $p < 0.01$) and consumed fewer analgesics (1.8 ± 0.5 vs. 3.6 ± 0.8 doses; mean difference: -1.8; $p < 0.01$). A transient higher VAS score was observed at 4 h in the LT group, likely reflecting delayed analgesic use. Adverse effects were minimal and not significantly different between groups.

Conclusion and relevance Local anesthetics combined with tramadol reduce pain and analgesic use after third molar surgery. This strategy improves recovery and warrants further research for broader applications.

Trial registration ClinicalTrials.gov NCT05614440, Date of registration 14 November 2022.

Keywords Tramadol, Third molar surgery, Postoperative pain, Local anesthesia, Nerve block

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Introduction

Surgical removal of impacted third molar teeth is a procedure frequently encountered in oral and maxillofacial surgery practices. Given the invasive nature of the procedure, effective anesthesia is mandatory to ensure patient comfort during surgery. Conventional local anesthetics, such as articaine or lidocaine with epinephrine, are commonly administered via traditional dental syringes to achieve regional nerve blocks or infiltration anesthesia. While advancements in delivery systems, such as single-tooth anesthesia (STA) devices and computer-controlled local anesthetic delivery (CCLAD) systems, have been developed to improve this intraoperative experience [1, 2], a significant challenge remains.

Despite these intraoperative advancements, postoperative pain following impacted third molar removal remains profound due to inflammatory mediators released during bone and soft tissue manipulation [3]. This postoperative pain is one of the most significant factors affecting patient satisfaction, as it directly impacts recovery and comfort levels [4].

Several pain-management strategies are available, including oral, parenteral, and local administration methods. Oral analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), are commonly used but their systemic use may lead to side effects including gastrointestinal disturbances and cardiovascular risks [4, 5]. Parenteral administration, such as intravenous or submucosal injection, results in a faster onset of action and more consistent drug levels at the injury site but may also increase systemic side effects, such as nausea, dizziness, or the risk of dependency when opioids are involved [6–8].

This reality underscores the need for multimodal pain management strategies that combine optimized anesthetic techniques with adjunctive pharmacological agents such as NSAIDs, tramadol and non-pharmacological interventions (cold therapy, warm compresses, etc.) can mitigate both acute and delayed postoperative discomfort [9, 10].

Among the available pharmacological agents, Tramadol is a centrally acting opioid that provides adequate analgesia. It reduces the transmission of pain impulses by inhibiting serotonin and norepinephrine reuptake. In addition to its systemic analgesic effects, the local anesthetic and analgesic effects of tramadol on peripheral nerves have been presented in multiple clinical and laboratory studies [4]. The local mechanisms of action of tramadol include an anesthetic effect mediated by sodium channel blockade, an antinociceptive effect due to potassium channel blockade, and analgesia mediated through peripheral opioid receptors [11–13].

While these strategies have shown efficacy in managing postoperative pain, gaps remain in the literature regarding detailed evaluations of their clinical outcomes. For example, there are often insufficient data comparing the amount of analgesic required postoperatively, the timing of the first analgesic intake, and detailed assessments of pain intensity scores (e.g., VAS scores) during the early postoperative hours. Furthermore, the term "local administration" for tramadol often encompasses a wide range of techniques, including intra-socket application or submucosal infiltration. A distinct gap remains regarding the specific efficacy of tramadol when used as part of a true regional anesthetic technique, such as the inferior alveolar nerve block.

Therefore, this study was specifically designed to address this critical gap by clarifying the novelty and clinical efficacy of using tramadol as an adjunct within a conventional inferior alveolar nerve block. Unlike previous studies focusing on broader "local administration" techniques such as submucosal or intra-socket applications, our trial provides a focused evaluation of this distinct regional anesthetic technique. By utilizing a highly homogenous patient cohort with a standardized, low level of surgical difficulty (Pell & Gregory Class I, Position A), this study aimed to isolate and assess key clinical outcomes—namely, the duration of postoperative analgesia, the timing of first analgesic intake, and total analgesic consumption.

Materials and methods

Study design and ethical approval

This prospective, randomized, placebo-controlled, double-blind study was conducted at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Marmara University, Istanbul, Turkey. The study was approved by the Ethics Committee of Marmara University, School of Medicine (153/011), and all participants provided informed, written consent. Patients and the public were not involved in the design, conduct, or reporting of this study. There were no important changes to the methods or outcomes after the trial commenced. This study was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Inclusion and exclusion criteria

The inclusion criteria for participants were: (1) age between 18 and 50 years, (2) American Society of Anesthesiologists (ASA) physical status I or II, (3) no known hypersensitivity to tramadol or other study medications, and (4) no use of sedatives, tranquillizers, or analgesic medications within the 24 h prior to surgery.

A planned exclusion criterion was the need for a supplemental dose of anesthetic solution during surgery. However, sufficient anesthesia was achieved in all 60 participants, and consequently, no patients were excluded from the study post-randomization.(Fig. 1).

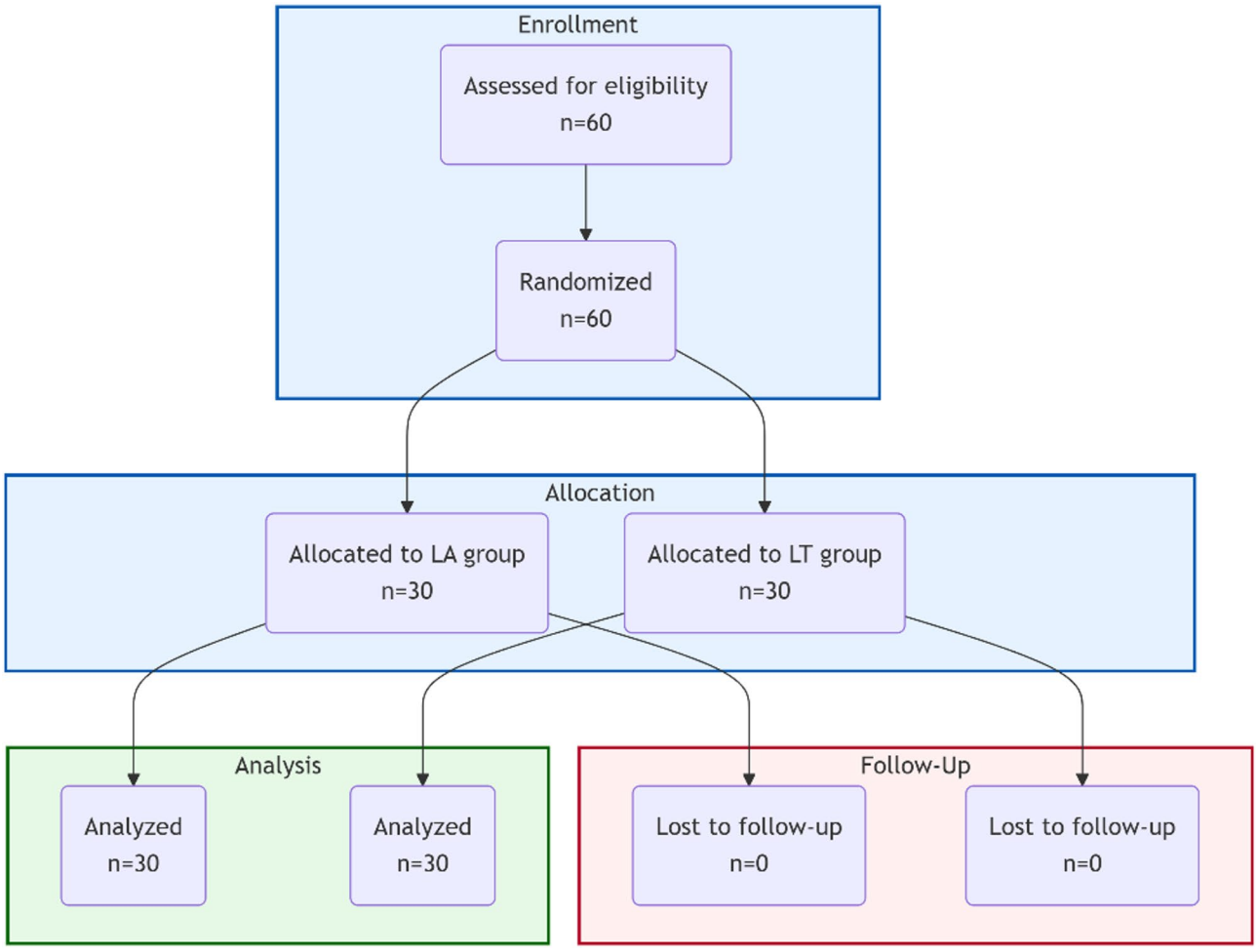

Fig. 1 CONSORT flow diagram of the study. The diagram illustrates the flow of participants through each stage of the trial, from eligibility assessment to randomization, allocation, follow-up, and analysis

Sample size

A formal a priori power analysis was not performed for this study. The sample size of 60 participants (30 per group) was determined based on sample sizes used in similar published studies investigating postoperative pain management after third molar surgery [13–17]. This sample size was considered adequate to detect clinically significant differences between the groups.

Randomization, blinding, and interventions

The 60 participants enrolled in the study were each assigned a unique patient identification number, from 1 to 60. A randomization sequence, allocating each number to either the LA or LT group, was generated using a computer by a clinical staff member not involved in patient recruitment or treatment.

To ensure allocation concealment, this sequence was implemented using the sealed envelope method. For each patient number, the corresponding group assignment ('LA Group' or 'LT Group') was written on a card and placed inside an opaque, sealed envelope marked only with that patient's identification number. On the day of their scheduled surgery, the anesthetic nurse—who was not involved in the surgery or postoperative assessment—would take the specific envelope corresponding to the patient being treated. The envelope was then opened to reveal the group assignment, and the appropriate anesthetic solution was prepared and brought to the operating room. This procedure ensured that both the operating surgeon and the patient remained blind to the group allocation throughout the study.

LA group (Control): This group received 2 mL of local anesthetic mixed with 2 mL of saline, resulting in a total solution volume of 4 mL.

LT group (Intervention): This group received 2 mL of local anesthetic mixed with a solution containing 50 mg of tramadol (from a 1 mL ampoule) and 1 mL of saline, resulting in a total solution volume of 4 mL.

The study drug was tramadol (Tramal; Sanofi-Synthelabo, Grunenthal GmbH, Aachen, Germany) 50 mg/mL

injectable ampoules. The local anesthetic was 4% articaine HCl + 1:100,000 epinephrine (Ultracaine DS Forte, Aventis, NJ, USA).

Surgical procedure and monitoring

To ensure consistency and minimize procedural variability, all local anesthetic and surgical procedures were performed by a single, experienced oral and maxillofacial surgeon using a standardized technique. During the procedure, patients were maintained in a semisupine position and monitored with electrocardiography (ECG), pulse oximetry, and noninvasive blood pressure. While no formal interim analyses for efficacy were planned, these monitoring procedures served as the basis for safety-driven stopping guidelines. Any clinically significant adverse event, such as hemodynamic instability (e.g., severe arrhythmia, hypotension) or oxygen desaturation, was a prespecified criterion for discontinuing the intervention for that participant. However, no such events occurred during the study.

To ensure a homogenous sample with a consistent level of surgical difficulty, only mandibular third molars classified according to the Pell & Gregory system as Class I, Position A, were included. Additionally, all teeth had a vertical angulation (Winter's classification) and were covered only by soft tissue (mucosal retention). A standardized surgical protocol was followed for extraction. A classic envelope flap with a sulcular incision extending from the first to the second molar and a distal relieving incision to the mandibular ramus was used. The buccal bone was removed via a round bur and handpiece with copious irrigation. The tooth was elevated and relocated, and the surgical site was closed with 3–0 silk sutures. The application of local anesthesia was designated as time zero, and the duration from the start of the surgery to its completion was recorded.

Table 1 Demographic data, BMI, duration of operation and adverse effects

	Group LA	Group LT	Sum	*p*
	Mean ± Sd (Median)	Mean ± Sd (Median)	Mean ± Sd (Median)	
Age (year)	23.93 ± 2.83	22.90 ± 4.14	*23.42 ± 3.55*	**0.263**[1]
Sex, ***n (%)***				
Male	17 (56.7%)	17 (56.7%)	*34 (56.7%)*	[2]**1.000**
Female	13 (43.3%)	13 (43.3%)	*26 (43.3%)*	
BMI (kg/m²)	22.83 ± 1.58	21.74 ± 2.86	*22.28 ± 2.36*	[1]**0.074**
Duration of operation	48.00 ± 4.19	42.30 ± 6.37	*45.15 ± 6.07*	[1]**0.001** **
Nausea	2 (6.7%)	3 (10%)	*5 (8.3%)*	[2]**1.000**
Vomit	2 (6.7%)	0 (0%)	*2 (3.3%)*	[2]**0.492**
Burn	3 (10%)	0 (0%)	*3 (5%)*	[1]**0.237**

[1] Student's t test. [2] Continuity (Yates) correction and Fisher's exact test. ** Statistically significant difference ($p < 0.01$)

Outcome measures

The primary outcome was postoperative pain intensity, evaluated using a visual analog scale (VAS) ranging from 0 (no pain) to 10 (excessive pain). Patients were asked to score their pain at 10 min and 1, 2, 4, 6, 12, 24, and 48 h postsurgery. These specific time points were selected for two primary reasons. First, they were chosen based on the expected pharmacokinetics of the agents to capture the dynamic pain profile, including the period of waning local anesthesia and the onset of tramadol's local and systemic effects. Second, this assessment schedule is consistent with methodologies used in previous key studies on postoperative pain after third molar surgery, ensuring the comparability of our findings with the existing literature [14, 16, 18].

The secondary outcomes were: (1) the time of the first analgesic intake, (2) the total number of analgesic doses consumed within 48 h, and (3) the incidence of adverse events, including nausea, vomiting, fatigue, hallucinations, and burning sensations.

Standard postoperative medication included amoxicillin at 1000 mg twice daily and naproxen sodium at 550 mg twice daily if the VAS score exceeded 5. Sutures were removed on day 7.

Statistical analysis

Statistical analysis was performed via SPSS Statistics 22 software (IBM SPSS, Istanbul, Turkey). The data are presented as the means ± standard deviations (SDs) and 95% confidence intervals (CIs), where applicable. Student's t test was used to compare continuous variables, such as age, BMI, and duration of operation, between the groups. Continuity (Yates) correction and Fisher's exact test were used for categorical variables, such as sex and side effects. The Mann–Whitney U test was used to compare nonparametric data, including VAS pain scores and total analgesic intake. The statistical significance threshold was set at $p < 0.01$. All tests were two-sided.

Results

A total of 60 patients (34 males (56.7%) and 26 females (43.3%)) were enrolled in this study; each of the test groups contained 30 patients. The mean age of the LA group was 23.93 ± 2.83 years, whereas the LT group had a mean age of 22.90 ± 4.14 years. The BMI values were 22.83 ± 1.58 kg/m² in the LA group and 21.74 ± 2.86 kg/m² in the LT group. The sex distribution was identical in both groups, with 17 males (56.7%) and 13 females (43.3%) in each. No statistically significant differences were observed in age, BMI, or sex between the groups ($p > 0.05$, Table 1). However, a statistically significant difference was found in the duration of operations between the groups. The mean operation time was shorter in

the LT group (42.30 ± 6.37 min) than in the LA group (48.00 ± 4.19 min, $p = 0.001$; Table 1).

Nausea was reported in 2 patients (6.7%) in the LA group and 3 patients (10%) in the LT group. Vomiting occurred in 2 patients (6.7%) in the LA group but was not observed in the LT group. Burning sensations were reported by 3 patients (10%) from the LA group, whereas none were reported in the LT group. These differences in side effects between the groups were not statistically significant ($p > 0.05$, Table 1).

According to the VAS scores, patients in the LT group had significantly lower pain levels at 1 h (1.47 ± 0.78 vs. 6.37 ± 0.85), 2 h (1.70 ± 0.75 vs. 3.63 ± 0.61), and 6 h (1.90 ± 1.35 vs. 3.33 ± 1.45) postsurgery than did those in the LA group ($p < 0.01$, Table 2). Interestingly, at 4 h postsurgery, patients in the LT group reported significantly greater pain levels (4.57 ± 1.01) than did those in the LA group (3.07 ± 0.69, $p < 0.01$; Table 2). By 12, 24, and 48 h postsurgery, the pain levels in both groups were minimal, with no statistically significant differences observed (Table 2; Fig. 2).

The LT group required their first analgesic intake significantly later (5.16 ± 0.75 h) than the LA group did (2.02 ± 0.59 h, $p < 0.001$). Additionally, the total analgesic intake was significantly lower in the LT group (1.83 ± 0.46 doses) than in the LA group (3.60 ± 0.81 doses, $p < 0.001$; Table 3).

Table 2 VAS scores

VAS	Group LA	Group LT	*p*
	Mean ± Sd (Median)	Mean ± Sd (Median)	
10 min	0 ± 0 (0)	0 ± 0 (0)	**1.000**
1 h	6.37 ± 0.85 (6)	1.47 ± 0.78 (1.5)	**0.001 ****
2 h	3.63 ± 0.61 (4)	1.70 ± 0.75 (2)	**0.001 ****
4 h	3.07 ± 0.69 (3)	4.57 ± 1.01 (5) †	**0.001 ****
6 h	3.33 ± 1.45 (3.5)	1.90 ± 1.35 (1.5)	**0.001 ****
12 h	0.63 ± 0.76 (0.5)	0.93 ± 0.78 (1)	**0.107**
24 h	0.23 ± 0.43 (0)	0.10 ± 0.31 (0)	**0.169**
48	0.07 ± 0.25 (0)	0 ± 0 (0)	**0.154**

† Note: Unexpected higher VAS score in the LT group. Mann–Whitney U test.

** Statistically significant difference ($p < 0.01$)

Table 3 First analgesic intake and total analgesic intake

	Group LA	Group LT	Sum	*p*
	Mean ± Sd (Median)	Mean ± Sd (Median)	Mean ± Sd (Median)	
First analgesic intake	2.02 ± 0.59 (2)	5.16 ± 0.75 (5)	*3.59 ± 1.72 (3.5)*	**0.001 ****
Total analgesic intake	3.60 ± 0.81 (4)	1.83 ± 0.46 (2)	*2.72 ± 1.11 (2)*	**0.001 ****

Mann–Whitney U test.

** Statistically significant difference ($p < 0.01$)

Discussion

Tramadol is an effective and reliable pain control drug. Adding tramadol to a local anesthetic agent increases the duration of regional and postoperative analgesia [8, 14].

Tramadol also demonstrates local anesthesia–like activity by blocking nerve conduction, with a potency comparable to that of local anesthetic agents such as prilocaine and lidocaine. The nerve conduction blocking effects of opioids, including tramadol, have been shown to be fully reversible [12].

Al-Haideri et al. [15] conducted a study on 100 patients requiring the extraction of a single upper molar via conventional methods. Their results suggested that tramadol combined with adrenaline could be a viable alternative to traditional local anesthetics in oral and maxillofacial

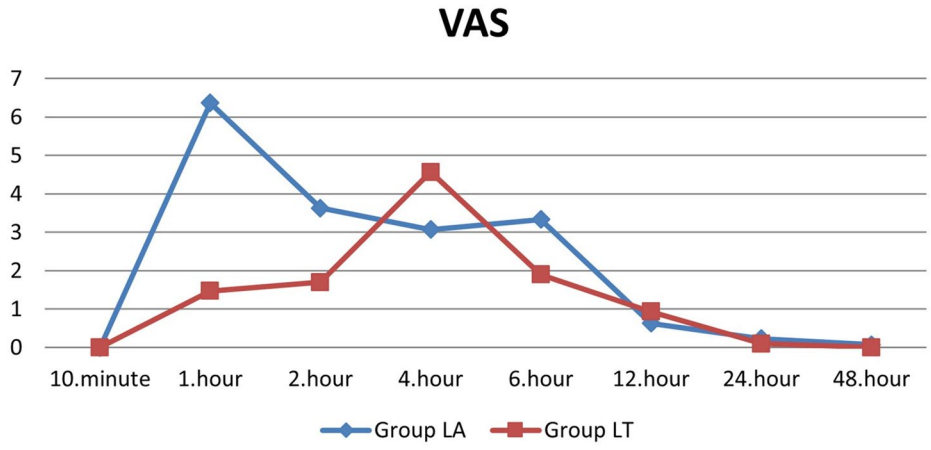

Fig. 2 Mean postoperative pain scores (VAS) over 48 h. The graph compares mean Visual Analog Scale (VAS) scores between the local anesthetic group (LA) and the local anesthetic with tramadol group (LT). The LT group reported significantly lower pain scores at all early time points, except for the 4-hour mark. For data on variability (Standard Deviation), please refer to Table 2

surgery, particularly for patients who cannot tolerate conventional anesthetics. This aligns with our findings, where tramadol demonstrated effective analgesic properties when combined with a local anesthetic.

According to Collins et al. [16], tramadol has a significant effect on postoperative pain following third molar surgery. Similarly, in their crossover study of 20 patients, Kanto et al. [17] reported that tramadol significantly prolonged the time to first analgesic intake and reduced the overall need for analgesics. Consistent with these studies, our findings showed that the LT group reported significantly lower pain levels at all time points except 4 h post-surgery, as presented in Table 2.

The paradoxical finding of a higher VAS score in the LT group at the 4-hour mark warrants a detailed explanation, as it may be influenced by both pharmacological and methodological factors. A key consideration is the significant difference in the timing of first rescue analgesic intake. The LA group required their first dose at an average of 2.02 h, meaning that by the 4-hour assessment, most of these patients were likely under the analgesic effect of naproxen sodium. Consequently, their reported VAS score may represent a medicated, and thus suppressed, level of pain. In contrast, the LT group did not require rescue analgesia until an average of 5.16 h. Their 4-hour VAS score therefore reflects an unmedicated, "true" pain level at a critical "analgesic threshold" where the combined local and systemic effects of tramadol were beginning to wane, just before rescue medication became necessary.

This interpretation is supported by the pain scores at the 6-hour mark. After the majority of LT patients had also taken their first dose of rescue analgesic (around the 5th hour), their mean VAS score dropped sharply to 1.9. The LA group, despite having been medicated for a longer period, reported a significantly higher mean VAS score of 3.33 at the same time point. This suggests that even after rescue medication, the underlying analgesic effect of tramadol continued to provide superior pain control. Therefore, the delayed need for analgesia in the LT group, combined with the rapid pain reduction post-medication, serves as a more robust indicator of tramadol's prolonged clinical efficacy than a direct comparison of VAS scores at the potentially misleading 4-hour time point. These findings are in agreement with previous studies, which highlight tramadol's role in reducing overall pain intensity and the need for rescue analgesics [14, 16].

Studies by Pozos-Guillen et al. [13] and a recent meta-analysis [19] demonstrated that the use of submucosal tramadol is a safe and efficient method for reducing acute postoperative pain, particularly in the first 6 h following third molar surgery. Similarly, our study revealed that the total analgesic intake in the LT group was significantly lower than that in the LA group (Table 3), emphasizing the advantages of tramadol in postoperative pain management.

In terms of side effects, nausea, vomiting, fatigue, hallucinations, and burning sensations have been associated with tramadol use in some cases. However, these adverse effects are often dose dependent [17]. An interesting finding was the observation of adverse effects such as vomiting and burning sensations exclusively in the placebo (LA) group. While not statistically significant, this warrants discussion. The absence of a burning sensation in the LT group could be attributed to tramadol's known local anesthetic-like effect on peripheral nerve endings, which may have stabilized them against surgical trauma.

Furthermore, the adverse effects in the LA group could be multifactorial, potentially stemming from heightened patient anxiety or a nocebo effect, as patients were blinded but aware of potential side effects. The cases of vomiting, specifically, might be linked to a higher gag reflex in those individuals—a factor not screened for in this study. This could also speculatively explain the significantly longer mean operation time recorded for the LA group, as managing a patient with a sensitive gag reflex can introduce procedural delays. The shorter operation time in the LT group is therefore less likely to be a result of unblinding, but rather a reflection of smoother surgical conditions, possibly enhanced by the superior local stability provided by tramadol.

Vallecillo et al. reported that, compared with 400 g of ibuprofen, 75 mg of tramadol combined with 25 mg of dexketoprofen appears to be more efficacious at reducing pain after impacted third molar extraction. However, it is associated with an increased risk of adverse effects [20].

Our results and those of previous studies in the literature [6, 13, 15, 18] indicate that the local administration of 50 mg tramadol, as used in this study, does not lead to significant side effects.

In other studies on patients who underwent third molar extraction under general anesthesia, the incidence of nausea and vomiting was greater in patients who were administered intravenous tramadol [7]. In fact, the incidence of nausea and vomiting is lower after oral tramadol administration than after parenteral tramadol administration [5].

Notably, our study revealed that side effects such as vomiting and burning were observed in the placebo (LA) group but not in the tramadol (LT) group, which may indicate that the local administration of tramadol facilitates more controlled absorption, reducing systemic effects than the oral or parenteral routes do.

A recent meta-analysis revealed that, compared with placebo or local anesthetics, submucosal tramadol has greater efficacy and fewer adverse effects in symptomatic irreversible pulpitis patients [11]. This finding supports

the hypothesis that local applications of tramadol are advantageous for controlling postoperative pain while minimizing systemic side effects.

Deshpande et al. [21]. compared the analgesic efficacy of intrasocket applications of tramadol and ketamine in third molar surgeries and reported that both are effective alternatives for postoperative pain management. Although this approach differs from ours, it underscores the versatility and potential applications of tramadol across various clinical contexts.

Our results, supported by previous studies in the literature, suggest that the local administration of tramadol is a safe and effective method for reducing postoperative pain with minimal adverse effects. These findings reinforce the role of tramadol as a valuable adjuvant in oral and maxillofacial surgeries.

Limitations

This study has several limitations that should be considered. First, it was conducted at a single academic center, which may limit the generalizability of our findings to other clinical settings. Similarly, all procedures were performed by a single surgeon; while this approach enhances procedural consistency, it may limit the generalizability of the findings to practitioners with different levels of experience. Second, although the sample size was comparable to other studies in the field, a larger, multi-center trial would be beneficial to confirm our results with greater statistical power.

Furthermore, we included a highly homogenous group of patients with a specific, low-difficulty type of impaction (Pell & Gregory Class I, Position A, vertical). While this strengthens the internal validity by reducing confounding variables, it may limit the applicability of our findings to more complex surgical cases. Additionally, we did not screen for patients based on their gag reflex sensitivity, which could be a confounding variable for adverse effects like nausea and vomiting and may have influenced surgical duration. Finally, the primary outcome of pain was assessed using a subjective measure (VAS), which relies on individual patient perception. Despite these limitations, this study provides valuable evidence on the efficacy of locally administered tramadol for postoperative pain management in third molar surgery.

Conclusions

This study demonstrated that the combination of tramadol with a local anesthetic agent during the surgical extraction of impacted third molars provides a significant clinical advantage. Compared with the LA group, the LT group consistently reported lower overall pain levels and required rescue analgesics both fewer in total number and significantly later. This prolonged duration of effective analgesia highlights the clinical benefits of tramadol's local administration. While a higher VAS score was noted in the LT group at the 4-hour mark, the interpretation of this finding is debatable, as it likely reflects an unmedicated pain level in contrast to the medicated state of the control group at that specific time point.

Moreover, the local application of tramadol in this study was associated with minimal adverse effects, further underscoring its favorable safety profile for this indication. These results align with those of previous studies, reinforcing the use of tramadol as an effective adjuvant for pain management in oral and maxillofacial surgery.

While this study provides valuable insights, its findings should be interpreted in the context of its limitations. Future research, ideally in the form of large-scale, multi-center trials involving multiple surgeons and more diverse patient populations, is necessary to confirm these results, determine optimal dosing strategies, and explore the broader clinical applications of this technique in different surgical procedures.

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Not Applicable.

Author contributions

I.M.A. and O.G. designed the study and developed the research methodology. I.M.A. conducted the surgical procedures, collected the clinical data, and performed the statistical analysis. T.S. supervised the anesthetic protocol and contributed to the clinical data interpretation. I.M.A. and O.G. wrote the main manuscript text. All authors reviewed, edited, and approved the final version of the manuscript.

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Data availability

The full trial protocol, statistical analysis plan, and the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Clinical Trials Registration Number: NCT05614440 (https://clinicaltrials.gov/study/NCT05614440).

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Marmara University, School of Medicine (153/011), and all participants provided informed, written consent to participate in the study. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors declare no conflicts of interest.

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