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Effect of Preemptive Amitriptyline on Postoperative Pain after Impacted Mandibular Third Molar Extraction: A Randomized Clinical Trial

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A B S T R A C T

Objectives: Extraction of impacted mandibular third molars is one of the most common procedures in oral and maxillofacial surgery, which is usually associated with significant postoperative pain. This study aimed to evaluate the effect of preemptive amitriptyline on postoperative pain after impacted mandibular third molar extraction.

Materials and Methods: This randomized double-blind placebo-controlled clinical trial included 20 patients (n=40 teeth) who referred to the Department of Oral and Maxillofacial Surgery of Tabriz Dental School for bilateral extraction of impacted third molars. After obtaining ethical approval and informed consent, the participants were randomly assigned to two groups: the intervention group received 25 mg amitriptyline preemptively while the control group received a placebo. The primary outcomes included postoperative pain score measured by a visual analog scale (VAS), and the frequency of analgesics taken during the postoperative period. Data were analyzed by paired samples t-test (alpha=0.05).

Results: A total of 20 patients (10 males and 10 females) participated in this study, with a mean age of 22.2 years. The mean duration of surgery was almost similar in the two groups (P=0.847). The intervention group consumed significantly lower number of analgesics during the postoperative period than the control group (P<0.001). The time interval from surgery to the first analgesic intake was significantly longer in the amitriptyline group (P<0.001).

Conclusion: Preemptive consumption of amitriptyline can effectively reduce postoperative pain and analgesic consumption following impacted mandibular third molar extraction surgery.

Keywords: Amitriptyline; Pain, Postoperative; Analgesia; Pain Management

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INTRODUCTION

Surgical extraction of impacted mandibular third molars is among the most commonly performed procedures in oral and maxillofacial surgery [1]. Despite being a routine procedure, this surgery is often associated with significant postoperative pain, which can hinder patient recovery and diminish overall patient satisfaction [2]. Pain following third molar extraction is complex, with both inflammatory and neuropathic components contributing to its intensity [3]. Standard postoperative pain management for such surgical procedures typically involves the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids [4]. However, both options come with notable limitations: NSAIDs may cause

gastrointestinal or renal side effects; while, opioids carry risks of addiction and other adverse effects [5]. Consequently, there is an obvious need for alternative pain management strategies that can provide effective analgesia with fewer side effects [6].

One promising approach is the use of preemptive analgesia, which involves administration of analgesics before the occurrence of surgical trauma to prevent central sensitization that contributes to postoperative pain [7,8]. Amitriptyline, a tricyclic antidepressant, has garnered attention for its analgesic properties, particularly in neuropathic pain syndromes [9]. While its primary clinical use is for the management of mood disorders, amitriptyline's ability to modulate pain pathways, through the inhibition of serotonin and norepinephrine reuptake, as well as sodium channel and N-methyl-D-aspartate receptor antagonism, suggests that it could play a beneficial role in managing postoperative pain after third molar surgery [10]. However, its specific efficacy and safety in this context remain underexplored, highlighting the need for further research [11].

The severity of postoperative pain following third molar extraction varies, influenced by factors such as the depth of impaction, surgical technique, and individual pain threshold. Inadequate pain control can prolong recovery, increase reliance on analgesics, and contribute to complications such as edema, trismus, and infection [12]. While conventional analgesics like NSAIDs primarily target inflammation, they may not sufficiently address the neuropathic pain that arises from nerve injury during the procedure. The amitriptyline's multimodal mechanism of action, which affects both inflammatory and neuropathic pathways, positions it as a potential adjunct or alternative to traditional analgesics, possibly reducing the need for opioids and enhancing overall pain control [13].

Amitriptyline's off-label use for chronic pain management, particularly in conditions like fibromyalgia, diabetic neuropathy, and post-herpetic neuralgia, has been well-documented. These conditions share similarities with the neuropathic component of pain that can follow third molar surgery, making amitriptyline a logical candidate for preemptive use in this setting [14]. By modulating central pain pathways before the nociceptive stimulus occurs, it is hypothesized that amitriptyline could attenuate postoperative pain, and thereby improve recovery outcomes and reduce the need for additional analgesics. However, lack of robust relevant clinical trials in dental surgery limits the ability to draw definitive conclusions about its efficacy [15].

Despite its potential, the use of amitriptyline as a preemptive analgesic must also account for its side effect profile. Its use is associated with sedation, dizziness, dry mouth, and, at higher doses, cardiovascular effects, which could limit its application to certain patient populations, particularly younger individuals or those undergoing elective surgeries [16]. Therefore, the potential benefits of improved pain control must be carefully balanced against the risks of adverse effects. Additionally, the optimal dosing regimen for amitriptyline in this context remains unclear, underscoring the need for further research to establish safe and effective dosing protocols that maximize its analgesic benefits while minimizing side effects [11].

A critical need exists for safe and effective pain management strategies that minimize opioid use following mandibular third molar surgery. Amitriptyline, with its broad-spectrum analgesic properties, represents a promising candidate for preemptive analgesia in this context. However, its clinical effectiveness, optimal dosing, and safety profile must be rigorously assessed to determine whether it should be integrated into routine practice for managing postoperative pain in oral surgery. Although previous studies on other surgical populations have shown mixed results regarding the analgesic effects of amitriptyline, no research has specifically evaluated its preemptive use in mandibular third molar extraction. This study sought to address this gap by exploring whether amitriptyline can significantly reduce postoperative pain and improve recovery outcomes in this commonly

performed oral surgery. By answering these key questions, the research could drive important advances in postoperative care and enhance patient satisfaction in dental surgical procedures. Thus, this study aimed to evaluate the effect of preemptive amitriptyline on postoperative pain after impacted mandibular third molar extraction.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (Ethics Code: IR.TBZMED.VCR.REC.1402.752). It was also registered in the Iranian Registry of Clinical Trials (IRCT Code: IRCT20240419061526N1).

Study design:

This randomized double-blind placebo-controlled clinical trial was conducted on patients referred to the Department of Oral and Maxillofacial Surgery of Tabriz Dental School, requiring extraction of bilateral impacted mandibular third molars as part of their treatment plan. Written informed consent was obtained from all patients before their inclusion in the study.

Sample size calculation:

The sample size was calculated based on the pain severity outcome according to a study by Levine et al [17]. With a power of 80% and an alpha level of 0.05, a minimum of 16 participants were required in each group. Considering the possibility of some patients experiencing postoperative complications and dropping out, 20 participants were included in each group. The study only included patients with bilateral impaction, resulting in a total of 20 patients (40 teeth).

Eligibility criteria and settings:

The inclusion criteria for this study included patients aged 18 to 25 years with bilateral impacted mandibular third molars with similar type of impaction at both sides. All patients were required to provide informed consent for participation.

The exclusion criteria included pregnancy, use of analgesics, anti-inflammatory drugs, or sedatives within the past 12 hours, known allergies to amitriptyline, systemic diseases such as diabetes mellitus or hypertension, substance abuse or smoking, ongoing radiotherapy or chemotherapy, and development of postoperative complications (e.g., infection or dry socket). Patients who were unwilling to continue participation were also excluded from the study.

Following ethical approval, sampling was conducted using a convenience sampling method, selecting patients who met the inclusion criteria among those referred to Tabriz Dental School.

Randomization and blinding:

Twenty patients (n=40 teeth) were randomly assigned to one of the two study groups using simple randomization. The R software was used for random allocation of patients to the study groups. Initially, a dataset containing the list of all participants was created. Then, using the "random" package and the sample function, patients were randomly assigned to either the intervention or the control group. The allocations were generated directly by the software, ensuring that each patient was assigned to only one group. To prevent any bias, the group assignments were kept concealed from both the surgeon and the data analyst. Since the surgeries were performed 6-8 weeks apart, patients who were assigned to the intervention group for the first surgery remained in the same group for the second surgery. The second author, who was aware of the group allocations, distributed the respective medications. The surgeon (corresponding author of the study) and the data analyst, who was external to the research team, were blinded to the group assignments. Therefore, the study was conducted as a double-blind trial. For allocation concealment, the randomization process was managed by an independent person not involved in the study, who generated the group assignments and kept them confidential. The surgeon and data analyst were unaware of the group assignments until the study was completed. This ensured that neither the patients nor the investigators could influence the allocation process, maintaining the integrity of the study design.

Intervention:

Intervention group: Patients with impacted mandibular third molars who received 25mg

amitriptyline before surgery.

Control group: Patients with impacted mandibular third molars who received a placebo (sugar pill) instead of amitriptyline before surgery.

To ensure consistency across all participants, the same standardized surgical technique was employed for all cases. The procedure was performed by experienced oral and maxillofacial surgeons following established protocols, and any variations, if present, were carefully monitored and documented to minimize potential biases. Additionally, preoperative assessments and postoperative care were uniformly applied to all participants, ensuring comparability of outcomes.

To account for the potential influence of tooth impaction type on the patient's perceived pain, it was ensured that each patient had the same type of impaction on both sides; thus, maintaining homogeneity between the two groups. All surgeries were standardized by being performed by the same clinician, and extraction of bilateral impacted molars was spaced 6-8 weeks apart. To assess postoperative pain, each patient was provided with a visual analog scale (VAS) pain chart. Patients were instructed to record their pain level over the next 48 hours along with the dose of ibuprofen taken during this period. Patients were instructed to take the prescribed analgesic whenever they experienced significant pain and to record the time of each medication intake.

Statistical analysis:

Statistical analyses included the Kolmogorov-Smirnov test to assess normality, paired samples t-test to compare normally distributed surgical duration and time intervals between analgesic administrations, Chi-square test to analyze analgesic intake frequency between the two groups, and Wilcoxon test to analyze non-normally distributed pain score data. A P-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 25 (SPSS Inc., IL, USA).

RESULTS

A total of 10 (50%) females and 10 (50%) males participated in this study. The youngest patient was 18 and the oldest was 25 years old, with a mean age of 22.2±2.56 years. Figure 1 shows the CONSORT flow-diagram of patient selection and allocation.

The duration of surgery was recorded in minutes for each group, and compared between the control and intervention groups. Given that the distribution of the surgical time was normal (P>0.05) as assessed by the Kolmogorov-Smirnov test, comparison of surgical time between the two groups was conducted using the paired samples t-test. The results indicated that the mean duration of surgery was 19.9±3.58 minutes in the control group and 19.8±2.81 minutes in the intervention group. This difference was not statistically significant (P=0.847).

In the control group, all 20 participants received at least three analgesics, with 14 patients subsequently receiving the fourth analgesic and 10 patients receiving the fifth analgesic. In the intervention group, all 20 patients received the first analgesic; 18 patients received the second analgesic, 12 patients received the third analgesic, and 7 patients received the fourth analgesic, with no patients receiving the fifth analgesic. The relationship between the frequency of analgesic intake and the control/intervention group was analyzed using the Chi-square test, revealing a statistically significant difference between the two groups (P<0.001, Table 1).

To compare the time intervals between analgesic intakes, all durations were converted to minutes, and their normality was assessed using the Kolmogorov-Smirnov test. The results indicated that all time intervals in both groups had a normal distribution (P>0.05). Therefore, the paired samples t-test was employed to compare these values between the control and intervention groups. The mean difference in the time interval between completion of surgery and intake of the first analgesic was approximately 2 hours and 16 minutes, which was statistically significant (P<0.001). The mean difference in the time interval between the first and second analgesics was reported to be 53 minutes, which was not statistically significant (P=0.139). Similarly, the mean difference in

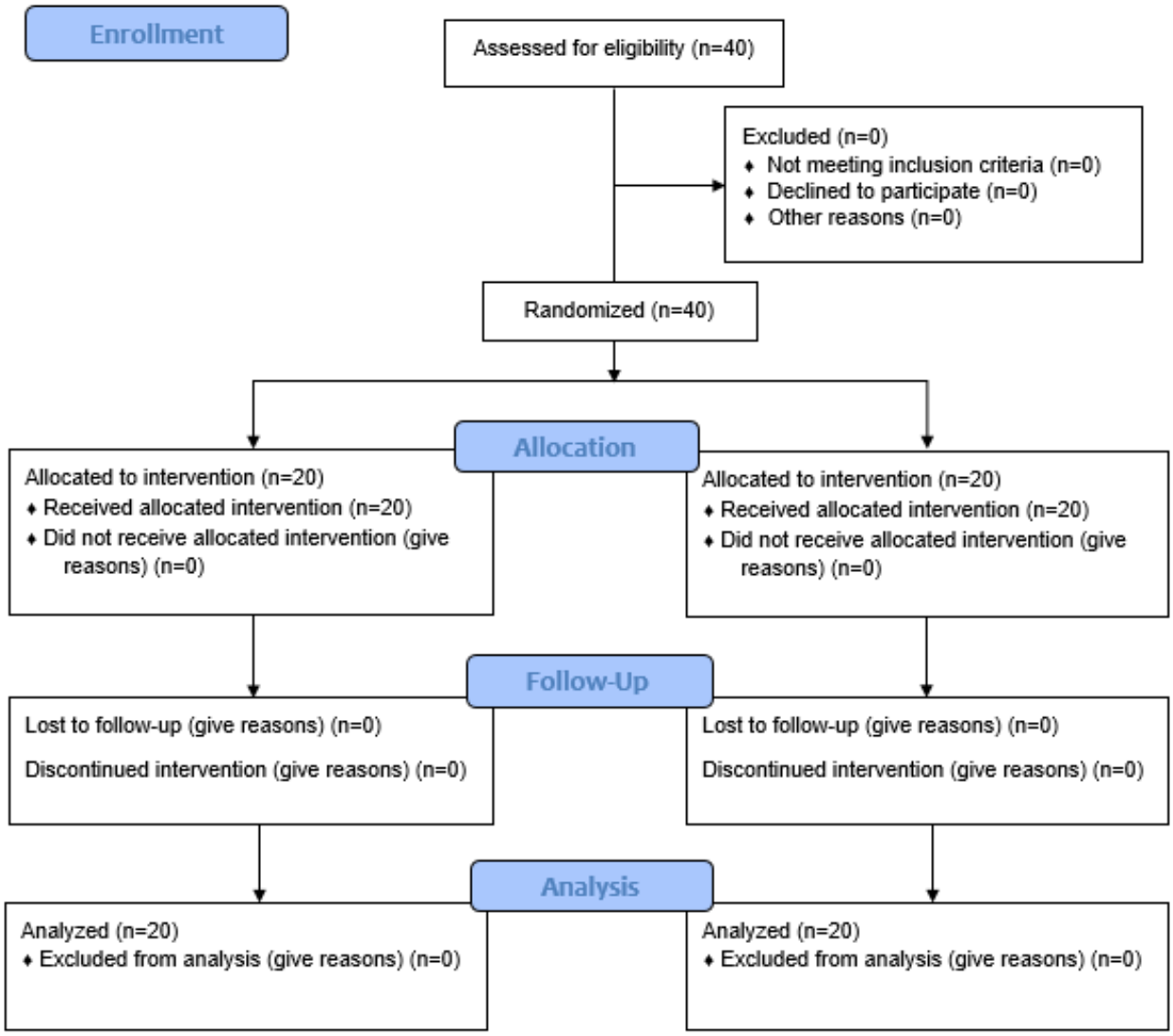

Fig 1. CONSORT flow-diagram of patient selection and allocation

Table 1. Comparison of analgesic administration frequency between the control and intervention groups

Groups	Taken analgesics	Number of patients
Control	First analgesic	20
	Second analgesic	20
	Third analgesic	20
	Fourth analgesic	14
	Fifth analgesic	10
Intervention	First analgesic	20
	Second analgesic	18
	Third analgesic	12
	Fourth analgesic	7
	Fifth analgesic	0

the time interval between the second and third analgesics was 23 minutes, which was not statistically significant either (P=0.719). Additionally, the mean difference in the time interval between the third and fourth analgesics was reported to be 49 minutes, which was not statistically significant (P=0.479, Table 2).

The intensity of pain experienced by patients was evaluated at different stages before and after surgery. Given the non-normal distribution of all values, the Wilcoxon test was employed to compare pain intensity between the pre- and postoperative periods within each group. The results are presented in Table 3, indicating statistically significant differences in pain scores before and one hour after the administration of analgesics in both groups (P<0.05).

The intensity of pain after surgery was also compared between the two groups. Due to the non-normal distribution of all values (P<0.05), the Wilcoxon test was applied to assess the differences in pain intensity between the two groups. The findings are summarized in Table 4, revealing statistically significant differences in all pain scores one hour after administration of the first, second, third, and fourth analgesics between the control and intervention groups (P<0.05).

We compared the side effects between the participants in the two groups, and it was found that none of the patients in the control group experienced any side effects. In contrast, two patients in the intervention group developed drowsiness, one experienced palpitation, and one developed dry mouth, which were the side effects associated with the medication used in the intervention group. Comparison of side effects between the two groups showed no statistically significant difference (P = 0.215, Table 5).

DISCUSSION

The findings of this study provided compelling evidence regarding the optimal efficacy of amitriptyline for management of postoperative pain in patients after impacted mandibular third molar surgery. The results indicated a significant reduction in pain intensity in patients receiving amitriptyline compared to those on standard analgesic protocols. This reduction can be attributed to several pharmacological mechanisms that highlight the role of amitriptyline as a multi-modal analgesic agent [18].

Amitriptyline, a tricyclic antidepressant, primarily exerts its analgesic effects through inhibition of the reuptake of norepinephrine and serotonin in the central nervous system. This mechanism enhances the availability of these neurotransmitters, which are crucial for modulating pain pathways [14]. By increasing the concentration of norepinephrine and serotonin, amitriptyline promotes the activation of descending inhibitory pathways, which effectively dampen pain transmission and enhance overall pain relief [15].

Moreover, amitriptyline has been shown to interact with N-methyl-D-aspartate receptors; thereby reducing excitatory neurotransmission and inhibiting central sensitization, a process that can lead to chronic pain syndromes following surgical trauma [19]. By addressing both peripheral and central mechanisms of pain, amitriptyline not only reduces acute postoperative pain but may also prevent the development of persistent pain conditions, enhancing the overall recovery experience of patients [20].

Table 2. Comparison of time intervals (minutes) between analgesic intakes

Time interval	Control (mean ± SD)	Intervention (mean ± SD)	Mean diff
Time from surgery to first analgesic	171.45 ± 74.21	308.25 ± 78.03	-136.8
Time from first to second analgesic	452.11 ± 68.71	505.88 ± 123.84	-53.77
Time from second to third analgesic	562.00 ± 146.45	539.00 ± 136.27	23
Time from third to fourth analgesic	434.33 ± 55.44	483.33 ± 145.52	-49
Time from fourth to fifth analgesic	505.80 ± 67.96	0.00	---

SD: Standard deviation; diff: difference

Table 3. Comparison of pain score before and after surgery in the two groups

Groups	Time	Minimum pain	Maximum pain	Pain score (mean ± SD)	P-value*
Control	Before the first analgesic	0	10	6.9 ± 2.19	< 0.001
	1 hour after the first analgesic	0	5	2.7 ± 1.3	
	Before the second analgesic	3	8	5.9 ± 1.16	< 0.001
	1 hour after the second analgesic	1	4	2.15 ± 0.93	
	Before the third analgesic	3	7	5.2 ± 0.95	< 0.001
	1 hour after the third analgesic	0	4	1.6 ± 1.09	
	Before the fourth analgesic	4	6	5 ± 0.67	< 0.001
	1 hour after the fourth analgesic	0	3	1.64 ± 0.92	
	Before the fifth analgesic	4	6	4.8 ± 0.63	0.004
	1 hour after the fifth analgesic	0	2	1.3 ± 0.82	
Intervention	Before the first analgesic	3	7	5.4 ± 1.27	< 0.001
	1 hour after the first analgesic	0	3	1.7 ± 1.03	
	Before the second analgesic	2	8	4.44 ± 1.46	< 0.001
	1 hour after the second analgesic	0	3	1.11 ± 1.07	
	Before the third analgesic	4	6	4.66 ± 0.65	0.002
	1 hour after the third analgesic	0	2	0.83 ± 0.93	
	Before the fourth analgesic	3	4	3.85 ± 0.37	0.015
	1 hour after the fourth analgesic	0	1	0.28 ± 0.48	
	Before the fifth analgesic	0	0	0	0.999
	1 hour after the fifth analgesic	0	0	0	

Table 4. Comparison of pain intensity after surgery between the groups

Groups	Pain intensity (mean ± SD)	P value*
Control group 1 hour after the first analgesic	2.7 ± 1.3	0.028
Intervention group 1 hour after the first analgesic	1.7 ± 1.03	
Control group 1 hour after the second analgesic	2.15 ± 0.93	0.004
Intervention group 1 hour after the second analgesic	1.11 ± 1.07	
Control group 1 hour after the third analgesic	1.6 ± 1.09	0.004
Intervention group 1 hour after the third analgesic	0.83 ± 0.93	
Control group 1 hour after the fourth analgesic	1.64 ± 0.92	0.026
Intervention group 1 hour after the fourth analgesic	0.28 ± 0.48	

Wilcoxon signed-rank test; SD: Standard deviation

Table 5. Comparison of side effects between the two groups

Side effect	Control	Intervention	P value*
Drowsiness	1(5%)	2(15%)	
Palpitation	0(0%)	1(5%)	
Constipation	0(0%)	0(0%)	0.115
Blurred vision	0(0%)	0(0%)	
Dry mouth	0(0%)	1(5%)	

*Chi-square test

These findings align with previous findings documenting the effectiveness of amitriptyline in various pain management contexts. For instance, Sharav et al. [21] demonstrated the successful use of a 30 mg daily dose of amitriptyline in controlling chronic orofacial pain. Similarly, McQuay et al. [22] reported that a 25mg daily dosage of amitriptyline effectively managed diverse chronic pain types, including facial, back, and abdominal pain. Additionally, Goldenberg et al. [23] highlighted the success of a 25 mg daily regimen of amitriptyline in fibromyalgia patients, further emphasizing on the amitriptyline's versatility as an analgesic agent.

In the present study, the reduction in pain intensity was accompanied by a notable decrease in the need for rescue analgesics in patients treated with amitriptyline. This finding suggests that amitriptyline not only effectively alleviates pain but also enhances the overall analgesic efficacy of the treatment regimen. By reducing reliance on additional opioids or non-opioid analgesics, amitriptyline can mitigate the potential side effects associated with higher opioid consumption, addressing a critical concern in the current clinical landscape marked by an opioid crisis [24].

The results of this study demonstrated that preemptive amitriptyline significantly reduced postoperative pain intensity following mandibular third molar extraction. This reduction was notably greater compared to the control group that received standard analgesics. Similar findings have been reported in other studies; for example, NSAIDs such as ibuprofen are effective in managing pain, although their effect may be less pronounced than that of amitriptyline. Opioids, such as morphine or codeine, are also commonly used for pain relief but are associated with serious side effects, including dependency and nausea. In contrast, amitriptyline offers a promising alternative, providing effective pain relief with fewer side effects, making it a potentially better option for managing postoperative pain in oral surgeries [1,9,11].

Based on the present findings, comparison of side effects between the intervention and control groups revealed that none of the patients in the control group experienced any side effects. In contrast, several side effects were observed in the intervention group, including drowsiness in two patients, palpitations in one patient, and dry mouth in one patient. These side effects are likely attributed to the amitriptyline medication used in the intervention group. Amitriptyline is a tricyclic antidepressant that works by inhibiting the reuptake of norepinephrine and serotonin in the central nervous system. This mechanism increases the concentration of these neurotransmitters in synapses, leading to pain relief [11-13]. Additionally, amitriptyline has sedative effects, which may cause drowsiness, and it can also affect the autonomic nervous system, leading to palpitation and dry mouth. Despite these side effects, comparison between the two groups showed no statistically significant difference. This finding suggests that, although some side effects were observed in the intervention group, they were not sufficient to negatively impact the overall effectiveness of the drug in pain management. Future studies with a larger sample size may be necessary to examine the frequency, severity, and potential impact of these side effects on clinical outcomes of amitriptyline as a premedication in dental surgeries.

While the results of this study are promising, certain limitations must be acknowledged. The sample size, although adequate for preliminary insights, may restrict the generalizability of the findings. Future research with larger and more diverse cohorts will be essential to confirm these results and to explore the long-term safety and effectiveness of amitriptyline in various surgical populations. Furthermore, the subjective nature of pain measurement presents challenges; incorporating objective pain assessment tools could provide a more comprehensive evaluation of treatment efficacy.

We estimated the sample size using the sample size calculation formula, which ensures that the results are statistically generalizable. However, it appears that the sample size and the study's focus on the 18 to 25-year-old age group may limit the generalizability of the findings to real-world populations. Therefore, it is recommended that future studies include a larger and more diverse patient population to enhance the validity and applicability of the results. The concern regarding subjective biases in patients after bilateral surgery (with a 6-8-week gap) has been acknowledged. To minimize these biases, all surgical procedures were performed by one single clinician, and standard methods were used to assess the patients. However, future studies should pay more attention to the potential impact of the first surgical experience on the outcomes. Unfortunately, this aspect was not addressed in our study, and it can be considered as a limitation of our research. In this study, a 48-hour follow-up period post-surgery was considered to assess the short-term effects of amitriptyline on pain and recovery. However, it is true that a longer follow-up period could aid in examining the long-term effects of the drug and sustainability of its outcomes. In future studies, adding longer follow-up periods (such as one week or more) would be valuable in evaluating the sustained effects of amitriptyline.

CONCLUSION

This study underscores the importance of incorporating amitriptyline into multi-modal pain management strategies for postoperative care. The significant reduction in pain scores and the decreased need for additional analgesics highlight amitriptyline's potential to enhance patient outcomes following surgery. Continued research into optimal dosing regimens and long-term effects of amitriptyline will be vital for refining pain management protocols and improving surgical recovery experiences.

CONFLICT OF INTEREST STATEMENT

None declared.

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