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Evaluation of postoperative pain management after impacted third molar surgery with preoperative oral lamotrigine: An observational study

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Abstract

Introduction: Extraction of the impacted third molar is often associated with severe postoperative pains, management of which are a big challenge. Lamotrigine is a new antiepileptic drug with pre-emptive analgesic properties, which is hypothesized to alleviate postoperative pain.

Aim of study: This study aimed to evaluate the efficacy of pre-operative administration of single oral 200 mg lamotrigine in reducing the postoperative pain of impacted third molar surgery.

Materials and Method: In this randomized controlled trial, 80 adult patients were divided into two groups (n= 40) to receive either 200 mg oral lamotrigine for 1 hour before the removal of impacted third molar. The patients were monitored for 4 hours in the recovery room and pain intensity was measured through visual analogue scale (VAS) for the next 12 hours at 30-minute intervals. The time and number of rescue analgesics used in 12 hours was also recorded.

Results: Two groups were not statistically significantly different regarding the severity of postoperative pain. (p= 0.523)

Conclusion: Accordingly, pre-emptive administration of lamotrigine was not effective in diminishing the postoperative acute pain of impacted third molar extraction

Keywords: lamotrigine, third molar, visual analogue scale (VAS), impacted teeth

Introduction

The surgical extraction of lower third molars is the most frequent intervention in oral surgery [1]. This procedure is often associated with significant postsurgical sequelae that may have both biological and social impact. Besides severe complications such as dysaesthesia, severe infection, fracture, and dry socket, patients frequently complain of pain, swelling, and limitation in mouth opening (Trismus) throughout the postoperative course due to the inflammatory response following the surgical injury [2]. Surgical removal of lower third molar can vary in difficulty and in the degree of trauma caused to the surrounding tissue. The greater amount of tissue injury leads to an increased amount of inflammation in the peri-surgical area. Swelling may be particularly significant when the surgery is prolonged and when large amounts of bone, gingiva, and oral mucosa are manipulated. Careful surgical technique is effective in limiting tissue damage and swelling; therefore, attention should be taken to avoid prolonged periods of tissue elevation and retraction [3].

Pain management after third molar surgery is more crucial and should be treated before the development of significant intensity of pain. Longer the pain remain uncontrolled more sensitive the patient may become to painful stimuli. Pain following third molar surgery reaches to severe intensity or peak with in first 5-8 hrs after the surgery [4].

Lamotrigine is a medication from phenyltriazine group and is chemically dissimilar to other antiepileptic medications. The drug is presented as standard oral tablets (25 to 200 mg) and chewable, dispersible tablets (2 to 25mg), and a new extended release tablet is available in some parts of the world [5]. Lamotrigine is a new generation antiepileptic medication employing its anticonvulsant effect by influencing the sodium channels. It is reported that the medications, which block sodium channels, could be helpful in the treatment of neuropathic pain [6, 7]. An animal model study has reported the efficacy of lamotrigine use in neuropathic pain and showed its effect in experimental pain models such as cold induced pain in humans [6, 8, 9]. The role of lamotrigine as a pre-emptive analgesic to reduce post surgical pain has

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also been reported [7, 10]. Observations indicate that increased activity of sodium channels is seemingly the basis for hyperalgesia, like the positive effect of sodium channel inhibitors (e.g. lidocaine) on increasing the pain threshold [7, 11]. Lamotrigine inhibits the function of neuronal sodium channels in a concentration and voltage-dependent manner, decreasing the release of excitatory neurotransmitters, especially glutamate and aspartate [5, 9, 12, 13, 14]. However, up to now, the exact principles responsible for the lamotrigine-induced anticonvulsive effect remain obscure, and probably other targets might control and regulate such effect [9]. The frequent plausible side effects of lamotrigine are dizziness, tremors, sleepiness, loss of coordination, headache, double vision, blurred vision, nausea, vomiting, stomach pain, dry mouth, changes in menstrual periods, back pain, sore throat, runny nose, or sleeping problems (insomnia), however, the reported incidence is low and clinically insignificant [12-17]. Hence, the current study decided to assess the effect of pre-emptive administration of this medication after this surgical procedure because of the mild to moderate postoperative pain experienced in recovery, which necessitates analgesics

Materials and Method

90 patients who underwent surgical removal of impacted mandibular third molars were included. Inclusion criteria: Clinically healthy patients at the age of 15 to 50, with indications for extraction of a mandibular third molar; No evidence of pain related to the mandibular third molar to be extracted. Exclusion criteria: Patients at age outside the age range for the study; Pregnancy; Allergy to nimesulide, metamizole or to lactose - the main ingredient of the placebo; Acute inflammation in the area of the tooth to be extracted; Taking antibiotic preparations and nonsteroidal anti-inflammatory drugs (NSAIDs) in the last seven days; Patients needing antibiotic prophylaxis. The participation of each patient in this study was voluntary, and the patient was enrolled after obtaining written informed consent. 10 patients were excluded from the study for not meeting the inclusion criteria or not signing the consent form. All the enrolled participants met the inclusion criteria determined by good medical, clinical and systemic

The remaining 80 patients were divided into two groups (n=40). The experimental group received lamotrigine, and 40 patients under the control group in the preoperative setting one hour before the surgery. The side to undergo extraction first and the drug to be used were randomly chosen by using the relevant website (www.randomization.com) regarding the Consort guidelines [18, 19].

The patient underwent extraction of the right or left lower third molar, randomly chosen by the research assistant. Then, the patient was orally administered with 200 mg lamotrigine 1 hour before the extraction of the other lower third molar. Neither the surgeon nor the patient was aware which drug was administered for which side. An assistant collected the data regarding the operation sides and drug treatments. The surgical intervention was surgical removal of an impacted mandibular third molar. 4% solution of articaine hydrochloride with epinephrine concentration of 1:100000 were used for analgesia. The operations for surgical removal of an impacted mandibular third molar were performed using a standard technique with access through a triangular mucoperiosteal flap.

The patients with any postoperative complications such as bleeding, dry, or purulent alveolitis were treated and excluded from the study. Throughout the surgery, the heart rate, blood

pressure, and blood oxygen saturation were recorded at specified intervals. By the end of the operation, the analgesics usage according to the patients' self-assessment of pain in the VAS was also registered. After the surgery, the patients were monitored for up to 5 hours in the recovery room. A blind operator assessed the severity of the postoperative pain by using visual analogue scale (VAS, 100-mm) at 30-minute intervals at rest. VAS is an accepted method for assessment of post-operative pain [20, 21]. It is considered as the most valid scale of subjective self-reported pain and probably the most frequently used self-rating instrument for the measurement of pain in clinical and research settings. It can be easily administered by any health professional [21, 22]. The patients were instructed to record the time and number of rescue analgesics (Acetaminophen 500 mg) used within the next 12 postoperative hours. The record of analgesic ingestions could reveal whether any of the treatments provided sufficient analgesia. Moreover, the postoperative complications were asked through questionnaires. The obtained data were statistically analyzed by using SPSS software. Chi-square, Fisher's exact test, and Mann-Whitney U test were employed as appropriated. Significance level was set at $p < 0.05$.

Results

This study was first concerned with the pain intensity over the first 12 postoperative hours, and second with the efficacy, measures included analgesic consumption as well as the safety and tolerability of lamotrigine. The mean age of the studied patients was $25. \pm 5$ years, the oldest being 55, and the youngest 25. Regarding the sex, 45% of patients were male and 55% were female, although the study was not looking for sex based findings. Table 1 shows the demographic characteristics of patients in the two studied groups.

The outcome of VAS was subjected to Chi-square test to find out the difference between the groups. The results indicated that the two groups were not statistically significantly different in terms of the severity of postoperative pain. ($p = 0.523$)

Table 1: Demographic characteristics of the patients in lamotrigine group

Features	Group		p Value
	Lamotrigine 40	Control 40	
Male	18	15	0.633
Female	22	25	0.649
Age years	$25. \pm 5.1$	26.4 ± 6.9	0.022
Weight kg	68.1 ± 12.6	67.3 ± 10.2	0.833
Height cm	166.3 ± 8.5	168.7 ± 7.3	0.734

Table 2: Comparison of clinical characteristics and postoperative outcome after impacted third molar surgery

Features	Lamotrigine 40	Control 40	p Value
Type of impacted tooth			
Mesioangular	20	18	
Vertical	7	12	
Distoangular	3	0	0.181
Horizontal	10	10	
Length of operation (min)	35	35	0.344
Duration of local anesthesia (hr)	2	2.25	0.912
Surgery duration (hr)	2	2.25	.088
Pain (VAS)			
Mild	10	14	0.522
Moderat	2	5	
Severe	28	21	

Discussion

It is said that “the pain of mind is worse than the pain in body” and its management would require alleviating both the mental and physical pain, making the patient comfortable. Postoperative pain is considered a form of acute pain due to surgical trauma^[23].

The issues related to achieving good postoperative analgesia are many and various - insufficient competence, fear of complications, poor knowledge of analgesic drugs, poor assessment of pain, etc.^[24]. There are numerous techniques for analgesic treatment of postoperative pain, but the interest in recent years has been focused on the preemptive analgesia. This is due to the development of the fundamental sciences associated with the discovery of central sensitization by Woolf^[25]. According to a number of authors, the combination of preemptive analgesia with local anaesthesia makes the control of postoperative pain more effective^[26, 27].

There has also been discussion on the efficacy of lamotrigine as a pre-emptive analgesic to reduce postsurgical pain^[28]. Moreover, the intensity of acute postoperative pain was reported to be associated with the development of chronic pain. More recently, it has been shown that neuronal alpha-4-beta2-nicotinic acetylcholine receptors may be a target for lamotrigine, which may regulate its antiepileptic effects^[29, 30, 31, 32].

McCleane *et al.*^[30]. Reported that treatment of neuropathic pains could benefit from agents that block sodium channels. Likewise, Bonicalzi *et al.*^[28]. Discussed the effect of lamotrigine as a preemptive analgesic on decreasing the postoperative pain. Systematic reviews performed by Wiffen *et al.*^[29, 30, 32]. Reported that Bonicalzi *et al.* introduced the use of lamotrigine for acute pain, however, in their study all patients were given buprenorphine, a potent analgesic^[28]. Seven other research studied the central post stroke pain, diabetic neuropathy, HIV related neuropathy, intractable neuropathic pain^[33]. Spinal cord injury related pain and trigeminal neuralgia^[34].

As mentioned earlier, lamotrigine has been studied in the past for management of painful neuropathic conditions with only few establishing their efficacy in trigeminal neuralgia. In addition, this drug has negligible effects on hematological and biochemical indices; does not induce hepatic enzyme, has very slight drug interactions and protein binding which makes them proper for use in older patients^[35]. Likewise, in comparison to other drugs, this medication requires only twice daily prescription, which consequently increases the patient's compliance. The adverse-effect reported this medication has also been recognized to be acceptable^[35].

The present investigation was focused on the efficacy of lamotrigine monotherapy in postoperative pain management after extraction of the mandibular third molar since there is little or no study on the use of lamotrigine and similar drugs as pre-emptive agents in acute pain, or other forms of chronic pain particularly after oral and dental surgeries. The enrolled systematic reviews did not recruit any studies regarding the efficacy of this drug in management of pains after orodental surgeries. There have not yet been any studies evaluating the clinical pain control and postoperative benefits of lamotrigine when used as pre-emptive analgesia after third molar surgical extraction. The literature seems to lack results from studies on acute dental pains whilst this pain is recognized as one of the most annoying post-surgical conditions in general and third molar extraction in particular, for the control of which, various medicines are used^[36, 37]. Management of surgical patients is challenging in several aspects, one of which is

postoperative pain control. The pain experienced within the first 24 hours after the surgery is called the immediate postoperative pain; it demands help from the physicians. Meanwhile, the attempts to provide satisfying postoperative analgesia might fail due to several reasons including inadequate knowledge, poor pain evaluation, limited staffs, and worrying about the complications of analgesic agents^[36, 37]. According to Leach *et al.*^[38] by decreasing the severity of postoperative pain, lamotrigine might also decrease the upcoming adverse events. Aiming to investigate the advantages of lamotrigine in neuropathic pains, consequent systematic reviews of all the placebo-controlled found no evidence to confirm the efficacy of lamotrigine as a therapy for pain syndromes up to date of their study^[5, 7].

The results of the current study indicated that the difference between study and control group was not statistically significant considering the severity of acute postoperative pain which confirms and adds to the results yielded by Wiffen *et al.*^[7]. That lamotrigine does not have a significant place in therapy based on available evidence.

Conclusion

Within the limitations of a small sample size and the subjective nature of the assessments, the current results revealed that lamotrigine was not effective in controlling the postoperative pain of third molar surgery.

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