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Study of comparison of Pre-Emptive and post-operative Analgesic Efficacy of Oral tapentadol on postoperative pain following Mandibular Third Molar Surgery

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Abstract

Background: Pre-emptive analgesia aims at preventing the central nervous system from reaching a hyper-excitable state known as central sensitization, in which it responds excessively to afferent inputs. The clinical implication would be more effective pain management, thereby reducing post-operative pain and analgesic requirements.

Objective: The study was carried out to examine whether tapentadol administered 60 minutes before surgical extraction of lower wisdom teeth provides effective postsurgical analgesia and reduces rescue analgesic intake compared with tapentadol administered 60 minutes after surgery.

Methodology: The 101 patients were placed into three groups: pre-group (tapentadol 60 minutes preoperatively); post-group (tapentadol 60 min postoperatively); and no-group (placebo 60 minutes preoperatively).

Results: Study interventions had a significant effect on pain sensations in initial 3 hours and at the 12 hours after surgery. 100 miligramtapentadol tablet given preoperatively or postoperatively provides significant analgesic effectiveness and longer pain free intervals. The analgesic effectiveness is increased during first three hours after surgery when tapentadol is given one hour before the surgery, then when administered postoperatively, following third molar surgical removal. Patients in the pre and postgroups required significantly less rescue analgesics than those in the no-group.

Conclusion: Tapentadol administered before third molar surgery provides more effective pain control in initial

postoperative periods than tapentadol administered after the surgery or placebo.

Keywords: pre-emptive analgesia; tapentadol; third molar surgery; oral surgery; pain; numeric rating scale.

Introduction

Post-traumatic or postsurgical pain occasionally develops into chronic pain, hyperaesthetic pain or allodynia, which may limit a patient's daily activity level and sometimes require regularanalgesic medication[1]. The pathophysiological mechanisms of such neuropathic pain have been elucidated and a number of interventions have been attempted to prevent or reduce postoperative pain.Current drug treatment options for management of pain include opioids, nonsteroidal anti-inflammatory drugs (NSAIDs). [2] NSAIDs are limited by ceiling effect and are appropriate for relief of mild to moderate pain. NSAIDs are contraindicated in patients with acid peptic disease, renal impairment, and bleeding tendency. COX-2 inhibiting NSAIDs overcome some of these side effects, but some of them increase the risk of cardiovascular side effects, including MI. [3] Opioids are considered as gold standard for treatment of moderate to severe pain. However, opioids are underutilised, as doctors may be reluctant to prescribe them and patients may be reluctant to take them due to potential risk of adverse effects, abuse, tolerance, withdrawal, and liability. Suboptimal use of opioids can lead to unrelieved pain, which can lead to poor patient outcome and potentially life-threatening complications. Analgesics having similar effectiveness with improved compliance in comparison to opioids are valuable additions to the analgesic armamentarium. [4,5] One strategy aimed at improving the compliance of mu-opioid receptor (MOR) agonists is to combine MOR agonism with monoamine reuptake inhibition. Tapentadol is a novel, next generation, centrally acting analgesic with dual mechanism of action that offers analgesic efficacy that is similar to that provided by a pure MOR agonist, but with an improved side-effect profile.In this randomized prospective double-blind study, it was tested whether tapentadol premedication prevented postoperative pain in patients undergoing unilateral mandibular 3rd molar extraction under local anaesthesia.

Materials and Methods

Study includes total 101 participants who visited Department of Dentistry, Parul Institute of Medical Sciences and Research, Parul University, Vadodara, Gujarat, India from July 2020-May 2021.

The study protocol followed a prospective, single-centre, randomized, double-blinded and active-controlled clinical trial design. All surgical procedures and postoperative controls were performed by the same surgeon. Signed informed written consent was obtained from all the patients prior to the surgery.

Subjects were divided in three groups by random allocation using lottery method

Group I – Patients receiving 100 mg tapentadol tablet orally 60 minutes preoperatively, followed by placebo tablet orally 60 minutes postoperatively

Group II – Patients receiving placebo tablet orally 60 minutes preoperatively, followed by 100 mg tapentadol tablet orally 60 minutes postoperatively

Group III- Patients receiving placebo tablet orally 60 minutes preoperatively, followed by placebo tablet orally 60 minutes postoperatively

The basic criterion for including a patient in the study was a need for surgical extraction of a retained lower third molar. The molars to be extracted had not caused inflammation and were in at least a partial bony

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impacted state, requiring bone removal. The criteria for exclusion were: age under 18 or over 60 years; pregnancy; allergy to tapentadol, aspirin or any other NSAID; any digestive diseases; inflammation in the area of the tooth to be extracted; and any analgesic intake within the previous 3 days. Patients were not administered any antibiotic prophylaxis for the surgical procedure. Qualification, elimination of contraindications and written consent were obtained by the blinded surgeon performing the surgery. The time from tapentadol/placebo administration to anaesthesia was standardized to 60 minutes for every patient. Investigators confirmed that the pain prior to the beginning of the anaesthesia and immediately after the completion of surgery was absent or negligible. All patients received perineural anaesthesia into the inferior alveolar and lingual nerves and infiltrative anaesthesia in the vestibular region. Local anaesthesia was delivered using 1.8 ml of a 2% solution of lignocaine with 1:80,000 epinephrine. After 50 min, surgery was initiated and its duration (the period between incision of the mucosa and completion of the last suture) was recorded in the patient's record. Number of sutures taken was also counted.The surgical procedure was standardized and involved creating a flap with Ward's incision followed by bone removal using a drill cooled with water. After surgical removal, the wound was rinsed with a sterile solution of normal saline, and after achieving local haemostasis, the wound was sutured. Each patient was given an explanation about how to measure pain intensity on the numeric rating scale (NRS) of 0– 10 mm, with 0 representing no pain and 10 representing the worst pain imaginable. Study participants were asked to record the pain intensity score every hour for 6 hours from the end of surgery, and then during 8^{th}, 10^{th}, 12^{th}, 24^{th}, 36^{th}, 48^{th}, 60^{th}, 72^{nd} and 84^{th} hours postsurgically. Additional analyses included the first episode of pain that compelled the patient to take a rescue analgesic (500 miligram paracetamol with Diclofenac sodium 50 miligram tablet) as well as the total consumption of analgesic rescue medication was recorded.Demographic data was analysed using the ANOVA tests, where appropriate. The Kruskal–Wallis rank test was used to analyse the duration of surgery, quantity of total analgesic intake, time to the first pain episode and the level of pain in each of the fixed time intervals. The differences in rescue analgesic intake between the groups were analysed using the Mann–Whitney U-test. To establish the mutual influence of both within-group (along the time axis) and between-group factors, the pain score differences between groups during the entire 84 hours observation period were assessed using analysis of variance with repeated measures (RM-ANOVA, within-between designs). In all calculations, a P-value of less than 0.05 was considered significant.

Results

One hundred one patients were statistically analysed. There were no significant differences in gender (P = 0.77) or age (P = 0.63, ANOVA) between the three groups (Table 1).

Subjective assessment by Kruskal Wallis Rank test amongst 3 groups showed significant p value from 1^{st} to 84^{th} hours, except for the 5^{th} hour. Amongst group I, II and III, p value was <0.0001 from 1^{st} to 4^{th} hour. P value was 0.414 at 5^{th} hour. P value was 0.009 for 6^{th} and 8^{th} hour, 0.007 for 10^{th} and 12^{th} hours. P value was <0.0001 at 24^{th} hours ,0.005 at 36^{th} hours, 0.008 at 48^{th} hours, p value was <0.0001 during 60^{th} , 72^{nd} and 84^{th} hours.

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No statistically significant difference in the demographic factors, mean duration of the surgery and the baseline pain scores permitted a comparative assessment of the study results.

The pair wise comparison was conducted between the groups using the Mann-Whitney U test. Subjective assessment of pain during 1st ,2nd and 3rd hour after surgery by the group I and II showed stastically significant difference (p - <0.0001).

Subjective assessment of pain during 2nd , 8th ,10th ,12th hour after surgery by the group I and III showed stastically significant difference (p - <0.0001). Subjective assessment of pain during 1st, 4th,8th, 10th ,72nd , 84th hour after surgery by the group II and III showed stastically significant difference (p - 0.0001).

The mean time to first rescue analgesic medication was 6.61 hours for group I, 7.62 hours for group II and 2.92 for group III, which was stastically significant between group I and III (p - <0.0001); and also between group II and III(p - <0.0001). There was no stastically significant difference between group-I and group-II for time to first rescue analgesia.(p-0.346).

The mean total consumption of rescue analgesic during 7 postoperative days period was 7.14 for group I, 8.63 for group II and 11.33 for group III patients, which was stastically significant between group I and III (p - <0.0001); and also between group II and III(p - <0.0001). There was no stastically significant difference between group-I and group-II for total consumption of rescue analgesia during 7 postoperative days period. (p-0.433).There was stastically significant between group I and III (p - <0.0001); and also between group II and III(p - <0.0001).

There was no stastically significant difference between group-I and group-II for intensity of pain when first rescue analgesic medication taken. (p-0.01)

Table 1: Demographic and objective measurement data.

	Pre-group	Post-group	Placebo-group	P-values
Number of patients	35 (35.4%)	33 (31.2%)	33 (33.3%)	0.8
Age (years)	22.6	21.5	23.1	0.63
Sex (female/male)	26/9	19/14	17/16	0.77
Duration Of Surgery (Minutes)	48.4	51.2	46.9	0.210
Time to first rescue analgesia (Hours)	6.61	7.62	2.92	0.346
Total rescue analgesic consumed during 7 post operative days	7.14	8.63	11.33	0.433
Intensity of pain when first rescue analgesic taken , NRS scale (cm)	0.97	1.3	2.81	0.01

Discussion

The surgical removal of impacted third molar teeth is a common procedure that has been routinely performed in oral and maxillofacial surgical practice on an outpatient

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basis. Normally, it is followed by an inflammatory reaction characterized by pain, swelling, and trismus.

Moderate to severe pain associated with this surgical extraction is a frequent complaint that may affect the patients' quality of life and chance of an early recovery. [6,7]

In response to tissue damage, peripheral nociceptors are stimulated, giving rise to acute or nociceptive pain, which is usually limited in time.If pain input persists, as with postoperative pain, an inflammatory reaction may occur by a variety of C-fiber dependent neuropeptides in the spinal dorsal horn (for instance substance P, somatostatin, corticotropin-releasing factor), excitatory amino acids (glutamate, aspartate), and other chemical mediators (cytokines, chemokines, bradykinin, prostaglandins) [8,9,10,11].

Prostaglandins are derived from the precursor arachidonic acid. Arachidonic acid metabolism can proceed along 1 of 2 major pathways: the cyclooxygenase pathway (cox-1 and cox-2) or the lipooxygenase pathway. The end products of these pathways are TxB2, PGE2, PGD2, PGF2a, LTB4 and LTE4, which have a central role in the inflammatory processes occurring in injured tissue. [12]

With ongoing nociceptive input, there is modulation of the central nervous system through activation-dependent plasticity. As a result, allodynia (i.e. a reduction in pain threshold) and hyperalgesia (i.e. an increase in responsiveness to peripheral nociceptor signals) may occur; this process is called peripheral sensitization. [13,14]

Once peripheral neuronal excitability is increased and the pain threshold is lowered, minor nociceptive stimuli can trigger modulation of central pain pathways. Via afferent C-fiber stimulation, dorsal horn neurons and higher structures become sensitized. Sensitization is reflected by increased spontaneous neuronal activity, reduced pain threshold, or increased responsiveness to stimulation, prolonged discharge to repeated stimulation (''wind-up'') and expansion of the peripheral receptive fields of the dorsal horn neurons, a phenomenon called central sensitization. [15,16]

This leads to inadequate pain control during the immediate postoperative period which may contribute to the development of hyperalgesia leading to greater pain during postoperative recovery. [17]

Opioid analgesics act as agonists at opioid receptors in thecentral nervous system, Tapentadol is a centrally active analgesic with a dual mode ofaction (i.e., m-opioid receptor agonism and norepinephrineuptake inhibition), distinguishing it from other commerciallyavailable opioids. Tapentadol is an immediate-release (IR)formulation for the relief of acute pain in adults, Clinical trials of patients with varioustypes of moderate-to-severe acute pain have shown that tapentadol provides analgesia comparable to that ofthe pure m-opioid agonist, oxycodone IR, with improvedgastrointestinal tolerability (lower incidence of nausea, vomiting, and constipation). [18]

We evaluated tapentadol for effects on moderate-to-severepain after minor oral surgery, which is an established pain.

Tapentadolhad numerically lower incidences of nausea and vomiting compared with morphine sulphate 60 mg that werenot statistically significant. Possibly, this reduced level ofopioid-like side effects with tapentadol may be due to itslower affinity for the MOR Crile introduced the concept of ''pre-emptive analgesia'' on the basis of clinical observations at the beginning of the previous century. [19,20] Woolf proved this concept associated with post injury pain hypersensitivity in a

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series of animal studies in 1983 and stated that therapeutic interventions should be made in advance of the pain rather than in reaction to it. [21] Pre-emptive analgesia is defined as an antinociceptive treatment that prevents establishment of altered central processing of afferent input from injuries (central sensitization) or that starts before surgery, which amplifies postoperative pain.

However, only a small number of studies have been conducted in the field of dental surgery.

As it has been postulated that the pain existing before surgery may have already achieved central sensitization, thus making pre-emptive analgesia ineffective. Therefore asymptomatic impacted mandibular third molars were included in the current study.

The results of the present study support the opinion of Jung et al[22,23] that pre-emptive tapentadol when given 60 minutes before surgery provides effective pain control upto 3 hours after surgery as compared to when administered postoperatively or with placebo, supporting that since the desired effect of presurgically administered analgesic drug is to prevent prostaglandin production in the area of injury and thereby reduce central and peripheral sensitization,.

Time required to first rescue medication was longer in group I (pre-emptive tapentadol tablet given 60 minutes before surgery) patients than group III (pre-emptive placebo tablet given 60 minutes before surgery). Jung et al. [22] had suggested that the longer duration to first rescue analgesic may be due to a pre-emptive effect as the study drugs were given before the surgical incision suggestive of a relatively longer post-operative pain free interval without actually increasing the dosage or the dosing frequency of the study drug. [23]

Time required to first rescue medication was longer in group II (postoperative tapentadol tablet given 60 minutes after surgery) patients than group III. Junget al. [22] had also suggested that local anaesthetics might also have a pre-emptive analgesic effect in reducing sensory inflow from the periphery to the CNS. Therefore, patients receiving medication postsurgery may experience the longest period of analgesia because the tapentadol was administered at the longest interval after local anaesthesia.

The total analgesic intake during 7 postoperative days was significantly reduced in pre-emptive and postoperative tapentadol groups compared with placebo. The strategy of administering the analgesic before surgery will pre-position the drug at the surgical site & establish effective blood levels for a maximum analgesic effect. This predicts not only less pain during the initial post-operative period, but also lowers the intensity of pain during the days after the surgery. By lessening the pain during recovery, fewer analgesics would be consumed, there by resulting in fewer overall adverse effects of the analgesics.

The duration of operation has been related to factors such as severity of impaction and tooth position and to the experience of the surgeon involved. According to Hidemichi Yuasa[24] severe pain and average pain were related to the depth of impaction and the difficulty of extraction. Ingibjoj et al[25]in their case observed that the time taken to perform impaction surgery was not found to be a risk indicator for postoperative complication, in contrast to our study, there was no correlation of requirement of analgesics with difficulty index of surgery and duration of procedure amongst 3 groups.

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Conclusion

Hence on the basis of the present study and as per the support of the literature, it can be stated that 100 miligramtapentadol tablet given preoperatively or postoperatively provides significant analgesic effectiveness and longer pain free intervals. The analgesic effectiveness is increased during first three hours after surgery when tapentadol is given one hour before the surgery, then when administered postoperatively, following third molar surgical removal.

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