A comparative clinical evaluation of analgesic efficacy of Tapentadol and ketorolac in mandibular third molar surgery

ABSTRACT

Introduction: The surgical removal of impacted mandibular third molars is one of the most commonly performed dentoalveolar procedures in oral and maxillofacial surgery and is associated with varying degrees of postoperative discomfort. Pain, trismus, and swelling are the most common postoperative complaints, and these influence a patient's quality of life in the days after surgery.

Materials and Methods: A comparative study of the 32 patients, 16 were allocated to receive ketorolac and 16 patients were allocated to receive tapentadol. As the data for this study were collected at different time points, analysis for the longitudinal study was done. The main outcome variable, pain level was measured in five-ordered categories. As we had ordinal data in our study, we first checked for marginal homogeneity through Cochran–Mantel–Haenszel test.

Results: In the present study, the results show that there is no statistically significant difference between the two treatment groups (P = 0.1184). According to results, there is no significant group by time interaction, which means both drugs have shown almost equal efficacy at different time points. Similarly, there is no difference in efficacy of the two drugs across gender level.

Conclusion: The present findings showed that there is no statistically significant difference between the two treatment groups, although ketorolac is more effective for immediate pain reduction than tapentadol. However, the overall reduction of pain using both groups has no significant difference.

Keywords: Impaction, nonsteroidal anti-inflammatory drugs, opioid analgesics, third molar

INTRODUCTION

Pain is the most common complaint of the human beings. Dental pain specifically third molar extraction is said to be one of the most acute postsurgical painful conditions.[1] Extractions of the third molars account for a large volume of cases in contemporary oral surgical practice and require much planning and surgical skill during both preoperative diagnosis and postoperative management.[3] The pain experienced following the third molar surgery under local anesthesia has been shown to be of short duration and reaches its maximum intensity in the early postoperative period and in the most cases, patients require some form of analgesic to deal with it.[3]

Treating the patient before the development of significant pain is a more humane, enlightened approach to patient care and is consistent with the current trends toward more aggressive, preventive, and systematic approaches to pain management. Moreover, it has become recognized that longer the pain remains uncontrolled, more sensitive patient may become to the painful stimuli.[4] It is generally accepted that pain following the third molar surgery reaches
moderate-to-severe intensity within the first 5 h after surgery. However, there are studies showing that the postoperative pain reaches its peak intensity during the first 8 h after surgery.[5]

Opiates are the standard of care for moderate-to-severe postoperative pain. Most opioids used in clinical practice produce analgesia by activating opioid receptors on neurons within the pain transmission pathway.

Tapentadol is a centrally acting analgesic with a dual mode of action (i.e., m-opioid receptor agonism and norepinephrine uptake inhibition), distinguishing it from other commercially available opioids.[6] Opioid receptor binding has shown that tapentadol has higher binding affinity to m-opioid receptors than for delta(d)- and kappa(k)-opioid receptors.

Ketorolac having prolonged analgesic activity (Power et al., 1990) has neither sedative nor anxiolytic properties (Brown et al., 1990). Ketorolac does appear to have a significant analgesic efficacy and has been used successfully to replace opioid in some situation involving mild-to-moderate postsurgical pain.[7]

This study focuses on the comparison of the efficacy of two different analgesics. The use of tapentadol has not reported very widely after extraction of the third molar, so we compared its pain relief efficiency.

**MATERIALS AND METHODS**

This study was done at the Department of Oral and Maxillofacial Surgery, where 32 patients who required surgical extraction of impacted mandibular third molars. All the patients who were included in the study were given information regarding the procedure. The patients were randomly divided into two groups. Patients were allocated to Group A and B in which an odd number of patients were included in Group A, and even number of patients were included in Group B. Group A patients were given ketorolac 10 mg BD, and Group B patients were given tapentadol 50 mg BD postoperatively.

**Inclusion criteria**
- Age group 18–60 years
- Patients who are willing to participate.

**Exclusion criteria**
- Medically compromised patients
- Patients who have had any type of analgesic in the past 48 h
- Patients who are not willing to participate
- Patients allergic to the drugs.

All the patients were operated under local anesthesia using infiltration or inferior alveolar nerve block of involved side. Incision was given, and the operation site was exposed by reflecting mucoperiosteal flap, guttering of buccal bone, and sectioning of the third molar was done if required as per the standard impacted third molar surgery. After the surgery, operating site was irrigated with betadine and saline. Then, the flap was primarily closed with 3-0 silk. Patients were asked to take medicine 1 h after the surgery in both groups. Pain intensity was recorded at 1 h, 4 h, 10 h, 1 day, 2 day, and 3 day after the procedure using the visual analog scale as said by the patients through telephonic conversation. The patients were recalled at the 7th day postoperatively for suture removal.

**RESULTS**

Of the 32 patients, 16 were allocated to receive ketorolac and 16 patients were allocated to receive tapentadol. As the data for this study were collected at different time points, analysis for the longitudinal study was done. The main outcome variable, pain level was measured in five-ordered categories. Figure 1 shows the results of 1 h after surgery, Figure 2 shows the results of 4 h after surgery, Figure 3 shows the results of 10 h after surgery, Figure 4 shows the results of the 1st postoperative day, Figure 5 shows the results of the 2nd postoperative day, and Figure 6 shows the results of the 3rd postoperative day.

**DISCUSSION**

Postoperative pain control is one of the most important aspects of management of surgical patients. Various drugs, which are used to control the postoperative pain, are mainly categorized into two groups, i.e., nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids.[8]

Surgical removal of impacted third molar is the most common outpatient procedure in oral surgery. Normally, it is followed by an inflammatory reaction characterized by pain, swelling, and trismus.[9] The management of this postoperative pain has been extensively studied with several NSAIDs.[10] Sometimes, the patients experience severe pain after the surgical removal of the impacted teeth. NSAIDs have become popular for pain relief after different major and minor surgical procedures.

NSAIDs reduce the biosynthesis of prostaglandins by inhibition of the enzyme cyclooxygenase (COX). Mechanism of action of NSAIDs prostaglandins, prostacyclin (PGI2), and thromboxane A2 (TXA2) are produced from arachidonic acid by the enzymes cyclooxygenase which exists in a
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**COX-1 and COX-2 isoforms:**
- COX-1: “housekeeping” functions and present in most of the cells of the body.
- COX-2: Normally not present but induced by certain serum factors, cytokines, and other signal molecules at the site of inflammation.[11-15]

**Opioid analgesics:**
- Act as agonists at opioid receptors in the central nervous system, although some opioids have both agonist and antagonist effects.
- Compared to pure agonists, agonist-antagonist drugs have less potential for abuse in patients with a known history of abuse/addiction, and studies have shown.

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**Table 1: Comparison after 1st h**

| Drugs         | Nos of Patients |
|---------------|-----------------|
| Tablet ketorolac | 6 6 7 6 5 6 7 8 8 6 6 5 6 8 8 6 |
| Tablet tapentadol | 7 5 7 7 6 6 6 6 7 8 6 6 6 7 8 7 |

**Figure 1: One hour after surgery**

**Table 2: Comparison after 4 h**

| Drugs         | Nos of Patients |
|---------------|-----------------|
| Tablet ketorolac | 4 4 5 5 4 5 5 6 7 3 5 4 5 6 7 3 |
| Tablet tapentadol | 4 5 5 5 5 4 5 5 5 7 4 5 5 5 7 7 |

**Figure 2: Four hours after surgery**
that they may not induce a withdrawal syndrome in patients already physically dependent on opioids, although caution is advised in this setting. However, agonist-antagonist medications have a ceiling effect for analgesia. In general, acute pain is best treated with short-acting pure agonist drugs, whereas chronic pain is best treated with longer-acting pure agonist drugs. Adverse effects related to opioids include sedation, constipation, nausea, vomiting, and pruritus. Respiratory depression is also possible but rare when opioids are given in appropriate doses.\cite{16}

Ketorolac is a member of the pyrrolopyrrole group of nonsteroidal anti-inflammatory drugs. Ketorolac is also a NSAID, which has been compared and found effective with pethidine 50–100 mg, morphine 6–12 mg, and pentazocine 30 mg.\cite{16} Ketorolac has been proved to be more potent than several other NSAIDs studied under similar experimental conditions.

In a study, the efficacy and safety of NSAIDs analgesic in the treatment of acute postoperative dental pain have revealed that ketorolac has a greater global efficacy. In another study of the third molar extraction, Fricke et al.\cite{17} found 30 mg of ketorolac was significantly better than 50 and 100 mg pethidine. Ketorolac exhibits analgesic activity mediated
by peripheral effects. At analgesic doses, it has minimal anti-inflammatory and antipyretic activities. It is also a potent platelet aggregation inhibitor. Ketorolac is not an anesthetic agent and possesses no sedative or anxiolytic properties. It is stated that ketorolac is a useful alternative to opioid and to other nonsteroidal analgesics in ameliorating moderate-to-severe postsurgical pain.[17]

Tapentadol is a centrally active analgesic with a dual mode of action (i.e., m-opioid receptor agonism and norepinephrine uptake inhibition), distinguishing it from other commercially available opioids. It is stated that ketorolac is a useful alternative to opioid and to other nonsteroidal analgesics in ameliorating moderate-to-severe postsurgical pain.[17]

Tapentadol is a centrally active analgesic with a dual mode of action (i.e., m-opioid receptor agonism and norepinephrine uptake inhibition), distinguishing it from other commercially available opioids.Tapentadol is an immediate-release (IR) formulation for the relief of acute pain in adults, as an extended-release formulation for the management of chronic pain in adults, and in the US, for neuropathic pain associated with diabetic peripheral neuropathy. Tapentadol is also approved as an oral solution for the relief of acute pain in adults.[18,19] Clinical trials of patients with various types of moderate-to-severe acute pain have shown that tapentadol IR provides analgesia comparable to that of the pure m-opioid agonist, oxycodone IR, with improved gastrointestinal tolerability (lower incidence of nausea, vomiting, and constipation).[16]

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

| Drugs          | Comparison after 2\textsuperscript{nd} day |
|----------------|------------------------------------------|
| Tablet ketorolac | 2 2 1 1 2 1 1 1 0 1 2 1 1 1 1 0          |
| Tablet tapentadol | 2 2 2 2 3 2 2 2 3 4 3 2 2 3 2 2          |

Figure 5: Second postoperative day

| Drugs          | Comparison after 3\textsuperscript{rd} day |
|----------------|------------------------------------------|
| Tablet ketorolac | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0          |
| Tablet tapentadol | 0 0 0 0 1 2 0 1 0 1 1 0 1 0 1 0          |

Figure 6: Third postoperative day
model for the assessments of analgesia, the results of which can be generalized to other surgical procedures. The model is ideal for evaluating analgesia for a number of reasons. The pain model employs standardized surgical and anesthetic procedures, with less interpatient variability in pain. Furthermore, patients undergoing surgery experience a predictable and sustained level of moderate-to-severe pain following the procedure that requires analgesic treatment for several days.

We evaluated both drugs comparison after 1 h which shows no significant difference with \( P = 0.850 \) and after 4 h also no significant difference with \( P = 0.428 \). Both drugs give a significant different after 10 h, 1st day, 2nd day, and 3rd day with \( P < 0.005 \). So, basically with a comparison of both drugs, there is no significant difference between these two drugs for pain control postoperatively, but for immediate pain relief, ketorolac is marginally superior in compare with tapentadol.

Of the 32 patients, 16 were allocated to receive ketorolac and 16 patients were allocated to receive tapentadol. As the data for this study were collected at different time points, analysis for the longitudinal study was done. The main outcome variable, pain level was measured in five-ordered categories. As we had ordinal data in our study, we first checked for marginal homogeneity through Cochran–Mantel–Haenszel test. The results show that there is no statistically significant difference between the two treatment groups \( (P = 0.1184) \). According to the results, there is no significant group by time interaction, which means both drugs have shown almost equal efficacy at different time points. Similarly, there is no difference in efficacy of the two drugs across gender level.

**CONCLUSION**

Hence, we conclude that there is no statistically significant difference between the two treatment groups, although ketorolac is more effective for immediate pain reduction than tapentadol. However, the overall reduction of pain using both groups has no significant difference. Hence, we can use both drugs for the management of mild-to-moderate pain.

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**Conflicts of interest**

There are no conflicts of interest.

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