Original Research Article

Comparative Efficacy of Preoperative Ketorolac and Tramadol for Postoperative Pain Management in Third Molar Surgery

Jingade Krishnojirao Dayashankara Rao*

MDS, FDSRCPS (Glasgow),
Associate Professor, Dept. of Maxillofacial Surgery and Diagnostic Science, College of Dentistry, Qassim University, Saudi Arabia
*Corresponding author email: **j.rao@qu.edu.sa**

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Abstract

Introduction: Surgical extraction of impacted third molars often causes moderate to severe postoperative pain. Patient comfort and recovery depend on pain management. IV pain management may include ketorolac, an NSAID, and tramadol, a centrally acting analgesic. This study examined whether preoperative ketorolac and tramadol reduce third molar surgery postoperative pain.

Materials and methods: A double-blind randomized controlled trial involving 100 participants of 20–30-year-old with ASA I were included. Participants were randomly assigned to receive ketorolac (30 mg IV) or tramadol (50 mg IV) preoperatively. Pain assessments were conducted using Visual Analog Scales (VAS), and the time to rescue analgesic was monitored. Total analgesic consumption over the first five postoperative days and global pain assessment were recorded. Statistical analyses were performed using Student's t-test and chi-square test.

Results: Demographic data showed no significant age or sex differences between ketorolac and tramadol groups. The tramadol group had a significantly higher mean weight. In operation details and efficacy parameters, tramadol had a longer action time but not statistically significant. VAS scores showed higher tramadol pain perception and a shorter rescue analgesic time. Tramadol users used more analgesics postoperatively. Global assessment scores showed tramadol increased pain perception statistically. Ketorolac was significantly more effective than tramadol in relieving pain, with a higher percentage of participants rating it as Very Good or Excellent.

Conclusion: In third molar surgery, ketorolac managed postoperative pain better than tramadol. More participants reported Very Good and Excellent pain relief with ketorolac, which delayed the need for

rescue analgesics. These findings may help clinicians choose postoperative painkillers. Larger studies are needed to confirm these findings and identify possible causes of the pain management differences between ketorolac and tramadol.

Key words

Ketorolac, Tramadol, Efficacy, Preoperative, Postoperative pain, Third molar surgery.

Introduction

Maxillofacial surgeons are frequently sought out for surgical extraction of impacted third molars for a variety of reasons, including infection, orthodontic treatment, trauma, and others. The surgical removal of impacted mandibular third molars is a repeatable surgical trauma that can produce moderate to severe pain. As a result, patients typically require an effective analgesic for at least twenty-four hours after the procedure (Schou, et al., 1998) [1]. After having third molar surgery, effective postoperative pain management may contribute to faster recovery in terms of oral function and overall quality of life [2, 3] Ketorolac, tramadol, paracetamol, nalbuphine, and buprenorphine are some of the several analgesics that can be administered using intravenous (IV) procedures.

Ketorolac is classified as a non steroidal anti-inflammatory medication (NSAID), specifically belonging to the pyrrolopyrrole family. It is available for administration via intravenous (IV), intramuscular, or orally, and it exhibits analgesic, anti-inflammatory, and antipyretic effects. It has been shown to be considerably beneficial for postoperative dental pain [4, 5]. It would appear that the major activity of ketorolac is to block the cyclooxygenase enzyme. This enzyme is responsible for the metabolism of arachidonic acid into endoperoxide intermediates and prostaglandins, both of which contribute to the sensation of pain.

An analogue of codeine that was synthesized is called tramadol. It is a central analgesic that has low affinity for opioid receptors [6], and it has been shown to be clinically useful in treating moderate to moderately severe pain. Additionally, it has been shown to have a low addiction potential and to cause minor respiratory depression [4, 7, 8]. Inhibition of the neuronal absorption of norepinephrine and serotonin at synapses in the descending inhibitory pain pathways is largely responsible for its activity [6]. When compared to the adverse effect profiles of traditional opioids, the one associated with tramadol seems to be more tolerable for individuals undergoing ambulatory surgery. It has been demonstrated that tramadol taken orally is beneficial for the treatment of postoperative dental pain [9, 10].

The goal of the strategy that involves administering the analgesic before the surgery is to not only pre-position the drug at the surgical site, but also to establish effective blood levels for maximum analgesic effect. This not only predicts less pain during the initial postoperative period, but it also reduces the intensity of pain during the days after the surgery (Ong, et al., 2004) [11]. When the level of pain experienced during recovery is reduced, the amount of analgesic medication taken is reduced as well. This, in turn, leads to fewer side effects of the medication, which in turn reduces the number of events that may complicate the postoperative course (Ong and Tan, 2004) [12].

Rarely do researchers conduct trials comparing the analgesic efficacy of different intravenous analgesics in patients undergoing third molar surgery. There are no research that we are aware of that compare the effectiveness of intravenous tramadol to that of ketorolac when it comes to third molar surgery. This is to the best of our knowledge. We thought it would be relevant to compare the analgesic performance of preoperative tramadol and ketorolac in avoiding postoperative pain in a somewhat homogenous

group of third molar surgical patients because the efficacy of different analgesics can be influenced by the type of surgery that is being performed. Ketorolac was found to be more effective than tramadol in this regard.

Materials and methods

The present double blind randomized trial was carried out at the dept. of oral and maxilla facial surgery, After receiving institutional ethical approval, the study's sample of 100 participants - 50 of whom were randomly assigned to the Tramadol group and 50 to the Keterolac group - was started. Using G Power software, the sample size was calculated with a confidence interval of 95% and an 80 percent power. Based on the prevalence of prior studies, the lowest prevalence was used. The number of participants needed to reject the null hypothesis was 100, 50 in each arm. The study included patients with physical status ASA I and age 20 to 30 years of both sexes. Clinical examinations, intraoral periapical radiographs, and orthopantomograms were performed on the patients. Patients other than those with ASA I, those with a history of allergic reactions to tramadol or ketorolac, those taking other nonsteroidal anti-inflammatory drugs (NSAIDs) within the previous 21 days, and those with acute pericoronitis were excluded from the study. Patients were chosen based on the difficulty index, and those who ever fall under the categories of moderately difficult and very difficult were selected.

Study Procedure: Participants' informed consent was obtained prior to the study's start. Two study groups - one receiving 30 mg IV of ketorolac, the other receiving 50 mg IV of both ketorolac and tramadol - were given codes, and samples were randomly assigned to each group. The effort made to keep patient and group information hidden from the primary investigator and sample itself. This task was taught to and calibrated out to an independent assistant. The principle investigator was told how to administer the necessary medication, but the assistant investigator entered the data. Fifteen minutes prior to surgery, a loaded syringe containing either tramadol 50 mg/ml or ketorolac 30 mg/ml was injected into the cephalic vein in the antecubital fossa. The same dentist and an assistant removed all of the patients' third molars under local anesthesia (2 percent lignocaine with 1:200,000 adrenaline) to block the lingual and long buccal nerves as well as the inferior alveolar nerve. Strict aseptic procedures were used, and the surgical field was prepared. Following the standard T. Wards incision, the tooth was extracted using an osteotomy technique and tooth sectioning, after which the wound was stitched shut with a 3 0 mersilk suture. Antibiotics, antiemetics, and rescue oral analgesics (aceclofenac 100 mg + paracetamol 500 mg + serratiopeptidase 10 mg) were prescribed, along with postoperative instructions.

Patients were admitted on a daycare basis for six hours following surgery, during which time they were asked to report the moment they first felt pain. At that point, an hourly pain assessment using visual analogue scales was initiated (VAS). The scale ranged from 0 (no pain) to 10 (worst pain). This provides a comprehensive evaluation of the patient's pain. Patients were discharged and given the recommendation to undergo routine follow-up appointments after the time when the pain subsided was noted and the immediate postoperative complications were ruled out. Additionally, patients were asked to record how many rescue analgesics they had taken daily up until the fifth postoperative day, and sutures were removed on the seventh day after confirming satisfactory healing. At the conclusion of the trial, patients were also given a global assessment and asked to provide an overall assessment of the effectiveness of the surgery with regard to pain on a five-point categorical scale. The scale had four levels: 0 for poor, 1 for fair, 2 for good, 3 for very good, and 4 for excellent. Excellent is the opposite of poor, which is a lot of pain. Regular follow-up exams also included a review of potential side effects brought on by the study drugs.

Statistical analysis

Version 20.0 of SPSS software was used (IBM Corp. Armonk, NY. USA) and Student's t-test and chi-square test was used to analyze statistical data related to the onset of action, duration of action, sum of pain intensity, total number of analgesics consumed during the first five postoperative days, and postoperative analgesic efficacy. P values below 0.05 were regarded as statistically significant, P values above 0.01 as highly significant, and P values above 0.001 as extremely significant, whereas P values above 0.05 were regarded as statistically insignificant.

Results

The present study double blind randomized controlled trial was conducted among 100 participants. The **Table - 1** presents demographic data comparing two groups, one using Tramadol and the other using Ketorolac. The mean age of the Tramadol group (24.63 ± 6.81 years) is slightly lower than that of the Ketorolac group (26.73 ± 5.35 years), but this difference is not statistically significant (p = 0.299). The distribution of male and female participants was similar in both groups, with 23 males and 27 females in the Tramadol group and 24 males and 26 females in the Ketorolac group (p = 0.344). However, there was a statistically significant difference in weight between the two groups, with the Tramadol group having a higher mean weight (63.1 ± 9.8 kg) compared to the Ketorolac group (61.7 ± 11.6 kg) (p = 0.003). These findings suggested that while age and sex distribution are similar between the groups, there was a significant difference in weight, which may need to be considered in further analyses or when interpreting the study results.

Table - 1: Demographic data.

Variable	Tramadol	Ketorolac	p-value
Age	24.63±6.81	26.73±5.35	0.299
Sex (male/female)	24/26	23/27	0.344
Weight	63.1±9.8	61.7±11.6	0.003

Table - 2: Operation details and efficacy parameters.

Variable	Tramadol	Ketorolac	p-value
Duration of action	10.52±2.37	3.89±2.04	0.07
VAS (mm)	21.1±9.3	13.7±9.75	0.03
Mean time to rescue analgesic (h)	7.2±3.1	10.2±2.0	0.006
Median time to rescue analgesic (h)	6.8	0.007	7.00
Total number of analgesics consumed during 5 postoperative days	8.72±4.015	3.07±1.74	0.03
Global assessment	3.2±0.7	2.8±0.7	0.02

Table - 3: Overall Pain Assessment.

Overall pain assessment	Tramadol	Ketorolac
Fair	13.00%	9.00%
Good	34.00%	17.00%
Very good	26.00%	33.00%
Excellent	27.00%	41.00%

Chi-square test: p value <0.05, student ‘t’ test p value <0.05.

Table - 2 presents operation details and efficacy parameters comparing two groups, one using Tramadol and the other using Ketorolac. The duration of action for Tramadol (10.52 ± 2.37 hours) appears longer than for Ketorolac (3.89 ± 2.04 hours), although this difference was not

statistically significant (p = 0.07). The Visual Analog Scale (VAS) scores for pain in the Tramadol group (21.1 ± 9.3 mm) were significantly higher than in the Ketorolac group (13.7 ± 9.75 mm) with a p-value of 0.03, indicating greater pain perception in the Tramadol group. Tramadol users also had a shorter mean time to rescue analgesic (7.2 ± 3.1 hours) compared to Ketorolac users (10.2 ± 2.0 hours), which was statistically significant (p = 0.006). The median time to rescue analgesic was notably shorter in the Tramadol group (6.8 hours) compared to the Ketorolac group (7.00 hours). Moreover, the total number of analgesics consumed during 5 postoperative days was significantly higher in the Tramadol group (8.72 ± 4.015) compared to the Ketorolac group (3.07 ± 1.74) with a p-value of 0.03. Additionally, the global assessment scores indicate that the Tramadol group (3.2 ± 0.7) had a statistically higher pain perception compared to the Ketorolac group (2.8 ± 0.7) with a p-value of 0.02. These findings suggest that Ketorolac may be more effective in pain management and delaying the need for rescue analgesics compared to Tramadol in the context of this study.

Table - 3 presents the overall pain assessment results for two groups, one using Tramadol and the other using Ketorolac. The data show the distribution of participants' ratings for pain relief, categorized into four groups: Fair, Good, Very Good, and Excellent. In the Tramadol group, 13.00% rated their pain relief as Fair, 34.00% as Good, 26.00% as Very Good, and 27.00% as Excellent. In contrast, in the Ketorolac group, 9.00% rated their pain relief as Fair, 17.00% as Good, 33.00% as Very Good, and 41.00% as Excellent. Both the Chi-square test (p value <0.05) and the Student's t-test (p value <0.05) indicate statistically significant differences between the two groups in terms of overall pain assessment. These results suggest that Ketorolac may provide better pain relief as rated by the participants compared to Tramadol, with a larger proportion of participants in the Ketorolac group reporting Very Good and Excellent pain relief ratings.

Discussion

Inducing acute pain that ranges from mild to severe, surgical removal of impacted mandibular third molars has proven to be an effective clinical trial model for research on pain management and treatment. There are a number of factors that relate to the peripheral inflammatory reaction that is initiated by surgical trauma, which is why non-steroidal anti-inflammatory drugs and opioid analgesics have been reported to be effective for the pain that occurs after surgical extraction and have been used as a form of pre-emptive analgesia. The goal of administering analgesia following surgery to remove an impacted third molar is to provide enough pain relief while also having only minimum adverse effects. It is possible that the development of pain hypersensitization could be decreased or eliminated with the administration of analgesics prior to the painful stimuli, which would then result in less postoperative pain [5, 13].

According to Raffa (2001), pre-emptive analgesia, which involves the administration of various types of analgesic and anti-inflammatory medications such as Dexamethasone, Ibuprofen, Acetaminophen, Codeine, Tramadol, Aceclofenac, and Ketorolac, might lessen the amount of postoperative pain that a patient experiences [14]. Because it has been hypothesized that the pain that was previously present before to surgery may have already gained central sensitization, rendering preemptive analgesia ineffective, asymptomatic impacted mandibular third molars were included in the present investigation [5, 15].

There is a growing demand for clinical models that are able to provide an accurate reflection of the efficacy of the many different analgesics that are frequently used. Because the method causes pain that is often consistent in degree, it is commonly used as a model to assess the efficacy of analgesics. This allows for accurate differentiation between analgesics that are weak and those that are strong [16]. Because the pain that occurs after the surgical removal of a third

molar is related to a peripheral inflammatory reaction that is initiated by surgical trauma, non-steroidal antiinflammatory drugs like ketorolac and ibuprofen, as well as opioids like tramadol, have been found to be effective for controlling postoperative pain (Jung et al., 2004) [17].

Recently, ketorolac has been introduced as a parenteral nonsteroidal anti-inflammatory drug (NSAID) for the treatment of postoperative pain. Studies have shown that the analgesic effectiveness of ketorolac is comparable to that of morphine. Studies comparing the two medications have indicated that ketorolac suppositories had a greater effect than diclofenac [18, 19]. Tramadol can be used regularly despite the fact that it is an opioid because there is no tolerance to the drug and it does not cause respiratory depression. It is hypothesized that tramadol has a multimodal action, as it possesses an analgesic efficacy that is comparable to that of ketorolac [18].

Because of this, any significant difference that was found in terms of pain levels between the two study groups in this particular research can be attributed to the action of the medicine. Ong et al. conducted a study in which they compared the analgesic potency of IV ketorolac and IV tramadol after third molar surgery. The researchers came to the conclusion that the duration of analgesic was greater with ketorolac than with tramadol, with an overall reduction in the consumption of rescue analgesics [15].

In a prior study that took place in Singapore's National University Hospital, the author examined 64 patients who were given the drugs Tramadol 50 mg and Ketorolac 30 mg intravenously. The level of discomfort was rated on a visual analogue scale of 100 millimetres on an hourly basis for twelve hours. (Ong et al., 2004; Ong and Tan, 2004) [11, 12] In this investigation, a regular intravenous sedation procedure was used, and impacted third molars were extracted while the patient was under the influence of local anesthesia.

Our research was carried out on hundred patients in the age range of 18–40 years who underwent third molar surgery under local anaesthesia all of the participants had asymptomatic impacted mandibular molars and they were randomly allocated into one of the two groups (50 in each group). The study was conducted as a triple-blind, randomised controlled trial with a sample size of 100 patients (50 males and 50 females). Both groups were given intravenous painkillers prior to the operation; however, Group I was given ketorolac 30 mg and Group II was given tramadol 50 mg.

The findings of this investigation were consistent with the findings of the current study. In orthopaedic surgeries, Lanzetta, et al. examined the effects of these two medicines on the level of pain that they caused. According to hourly assessments of pain, the pain alleviation brought on by tramadol was felt sooner than that brought on by ketorolac [20]. It's possible that tramadol's central mechanism of action is responsible for its quicker beginning of effect, but this is just a theory. When compared to patients in the tramadol group significantly less pain was experienced among patients in the ketorolac group. This comparison was made by Ong et al. following third molar surgery for a period of six hours. Postoperative pain was evaluated during this time [15].

The Visual Analogue Scale (VAS) scores for pain in the Tramadol group (21.1 9.3 mm) are substantially higher than in the Ketorolac group (13.7 9.75 mm) in our study, with a p-value of 0.03, showing stronger pain perception in the Tramadol group, the study that was done by Pathi, et al., Ketorolac administered intravenously before surgery was shown to provide higher pain relief with reduced pain intensity scores. Because of its peripheral modes of action, ketorolac was found to be a more effective medicine for the management of postoperative pain following surgery on the third molar. Tramadol was shown to be an appropriate and safe analgesic for the alleviation of post extraction pain in a study that was carried out by

Shaik and colleagues. This study also demonstrated that tramadol is more effective than ketorolac at providing extended analgesia with minimum adverse effects. It's possible that oral analgesic usage is to blame for the discrepancy [21].

In addition to this, the total number of analgesics taken in during the first five postoperative days was substantially higher in the group that received tramadol (8.72 4.015) as opposed to the group that received ketorolac (3.07 1.74) in the same vein Tuzuner, et al. noticed that the total number of analgesic intake was higher in the tramadol group compared to the diclofenac group for the purpose of pain reduction following bimaxillary osteotomy procedures. Pathi, et al. showed that this was the case [22]. However, Vitterio Colletti, et al. carried out a clinical trial to compare the therapeutic tolerability and postoperative analgesic effect of tramadol administered through IV injection as compared to ketorolac, and discovered that the mean number of ampoules for ketorolac was 1.5 0.1 on the day of surgery, dropping to 0.6 0.1 on day 1 and 0.1 0.1 on day 2 [23].

Ong, et al. found that the ketorolac group consumed significantly less postoperative analgesics overall than the tramadol group in order to prevent postoperative pain following third molar surgery [15]. In the current study, it was discovered that the ketorolac group consumed fewer analgesics overall than the tramadol group. Because NSAIDs have been shown to produce excellent dental pain relief while Tramadol does not affect prostaglandin synthesis or have anti-inflammatory effects, it is possible that Group I has better analgesic efficacy than Group II for third molar surgical pain.

The majority of patients in the ketorolac group (41.00%) rated the surgery as excellent in terms of having the least amount of pain following the surgery as compared to the Tramadol group, according to a study by Ong, et al. to compare preoperative IV tramadol and ketorolac for preventing postoperative pain after third molar surgery [15]. In the Tramadol group, 13.00% reported fair pain relief, 34.00% good pain relief, 26.00% very good pain relief, and 27.00% excellent pain relief. On the other hand, in the Ketorolac group, 9.00% reported fair pain relief, 17.00% good pain relief, 33.00% very good pain relief, and 41.00% excellent pain relief.

The main side effects of tramadol while using for preoperative analgesia are nausea and vomiting. Patients who received oral dosages of ketorolac and tramadol both experienced severe side effects, including epigastric pain, bleeding at the site of tooth extraction, nausea, and sweating (Shaik et al., 2010) [24]. Similar to this, ten patients in our study reported experiencing nausea and vomiting. Other side effects of parenteral tramadol include sweating and respiratory depression. None of the study participants reported experiencing sweating after receiving a tramadol injection. According to Vickers et al., there was a decrease in respiratory rate after IV tramadol administration, but it was noticed for longer than just the first five minutes after injection, whereas it persisted with morphine.

But in their study, Bouloux GF, et al. found that when used for postoperative pain control after nasal surgeries, tramadol was superior to ketorolac [23]. In a study, Shah et al. compared the effectiveness of tramadol hydrochloride and diclofenac sodium as analgesics during dentoalveolar surgery. The goal of this study was to identify a NSAID-free analgesic for patients undergoing dentoalveolar surgery who were unable to tolerate them. Tramadol performed better than diclofenac despite the two medications' equal analgesic efficacy. After dentoalveolar surgery, tramadol may be used for postoperative analgesia, particularly when NSAIDS are not recommended [26].

Because third molar surgery-related pain is different from other types of pain, ketorolac performed better than tramadol in our study. Dental pain and general surgical pain have

different pathogenetic mechanisms. Since dental pain is primarily inflammatory, NSAIDs are preferable over opioids for treating it. Pain and skin reactions at the injection site are the most frequent side effects of parenteral ketorolac, but in our study, only five patients reported severe pain at the injection site and none of them experienced local skin reactions.

Conclusion

Examining operation details and efficacy parameters in this study, it was observed that the duration of action of Tramadol appeared longer than Ketorolac, although this difference was not statistically significant. However, the Tramadol group reported significantly higher pain levels as indicated by higher Visual Analog Scale (VAS) scores, a shorter time to rescue analgesic, and a greater number of analgesics consumed during the postoperative period. Additionally, the global assessment scores demonstrated that the Tramadol group had a statistically higher pain perception compared to the Ketorolac group. The overall pain assessment results further support the superiority of Ketorolac in pain relief, with a significantly higher proportion of participants in the Ketorolac group rating their pain relief as Very Good and Excellent compared to the Tramadol group. Taken together, these findings suggest that Ketorolac may be more effective in postoperative pain management and provide better pain relief compared to Tramadol. These results have important implications for clinical practice and may guide healthcare professionals in selecting the most appropriate analgesic for postoperative pain control. However, further research and larger studies may be necessary to confirm these findings and explore potential factors contributing to the observed differences in pain management between the two medications.

References

1. Schou S, Nielsen H, Nattestad A, Hillerup S, Ritzau M, Branebjerg PE, et al. Analgesic dose-response relationship of ibuprofen 50, 100, 200, and 400 mg after surgical removal of third molars: a single-dose, randomized, placebo-controlled, and double-blind study of 304 patients. J Clin Pharmacol., 1998; 38: 447e454.
2. Cecche t i MM, Negra t o GV, Pere s MP, Deboni MC, Naclério-Homem Mda G. Analgesic and adjuvant anesthetic effect of submucosal tramadol after mandibular third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol., 2014; 117: e249-54.
3. Snyder M, Shugars DA, White RP, Phillips C. Pain medication as an indicator of interference with lifestyle and oral function during recovery after third molar surgery. J Oral Maxillofac Surg., 2005; 63: 1130-7.
4. Ong KS, Tan JM. Preoperative intravenous Tramadol versus oral Tramadol for preventing post operative pain after third molar surgery. Int J Oral Maxillofac Surg., 2004; 33: 274-278
5. Garibaldi JA, Elder MF. Evaluation of ketorolac (Toradol) with varying amounts of codeine for postoperative extraction pain control. Int J Oral Maxillofac Surg., 2002; 31: 276-80.
6. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. Drugs, 2000; 60: 139–176.
7. Pozos-Guillen A, Martinez-Rider R, Aguirre-Banuelos P, Perez-Urizar J. Pre-emptive analgesic effect of tramadol after mandibular third molar extraction: A pilot study. J Oral Maxillofac Surg., 2007; 65: 1315-20.
8. Pozos AJ, Martínez R, Aguirre P, Pérez J. Tramadol administered in a combination of routes for reducing pain after removal of an impacted mandibular third molar. J Oral Maxillofac Surg., 2007; 65: 1633-9.
9. Collins M, Young I, Sweeney P, Fenn GC, Stratford ME, Wilson A, Harris M. The effect of tramadol on dento-alveolar surgical pain. Br J Oral Maxillofac Surg., 1997; 35: 54–58.

10. Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo. Pain, 1997; 69: 287–294.
11. Ong K, Seymour R, Chen F, Ho V. Preoperative ketorolac has a preemptive effect for postoperative third molar surgical pain. Int J Oral Maxillofac Surg., 2004; 33: 771e776.
12. Ong K, Tan J. Preoperative intravenous tramadol versus ketorolac for preventing postoperative pain after third molar surgery. Int J Oral Maxillofac Surg., 2004; 33: 274e 278.
13. Isiordia-Espinoza MA, Sánchez-Prieto M, Tobías-Azúa F, Reyes-García JG, Granados-Soto V. Pre-emptive analgesia with the combination of tramadol plus meloxicam for third molar surgery: A pilot study. Br J Oral Maxillofac Surg., 2012; 50: 673-7.
14. Raffa R: Pharmacology of oral combination analgesics: rational therapy for pain. J Clin Pharmacol Thera, 2001; 26: 257e264.
15. Ong KS, Seymour RA, Chen FG, Ho VC. Preoperative ketorolac has a preemptive effect for postoperative third molar surgical pain. Int J Oral Maxillofac Surg., 2004; 33: 771-6.
16. Mehlisch DR. The efficacy of combination analgesic therapy in relieving dental pain. J Am Dent Assoc., 2002; 133: 861-71.
17. Jung YS, KimDK, KimMK, KimHJ, Cha IH, Lee EW. Onset ofanalgesia and analgesic efficacy of tramadol/acetaminophen and codeine/acetaminophen/ibuprofen in acute postoperative pain: a single-center, single-dose, randomized, active-controlled, parallel-group study in a dental surgery pain model. Clin Ther., 2004; 26: 1037e1045.
18. Tarkkila P, Tuominen M, Rosenberg PH. Intravenous ketorolac vs diclofenac for analgesia after maxillofacial surgery. Can J Anaesth., 1996; 43: 216-20.
19. Isiordia-Espinoza MA, Sánchez-Prieto M, Tobías-Azúa F, Reyes-García JG, Granados-Soto V. Pre-emptive analgesia with the combination of tramadol plus meloxicam for third molar surgery: A pilot study. Br J Oral Maxillofac Surg., 2012; 50: 673-7.
20. Lanzetta A, Vizzardi M, Letiza G, Matorona U, Sanfillipo A, Osti L, et al. Intramuscular tramadol versus ketorolac in patients with orthopedic and traumatologic postoperative pain. Curr Ther Res., 1998; 59: 39-46.
21. Shaik MM, Kumar J, Mobina S, Satyanarayana N, Sunitha P. Comparative study of tramadol and ketorolac in the pain management of third molar tooth extraction. J Coll Med Sci., 2010; 6: 35-43.
22. Tuzuner AM, Ucok C, Kucukyavuz Z, Alkis N, Alanoglu Z. Preoperative diclofenac sodium and tramadol for pain relief after bimaxillary osteotomy. J Oral Maxillofac Surg., 2007; 65: 2453-8.
23. Bouloux GF, Punnia-Moorthy A. Bupivacaine versus lidocaine for third molar surgery: A double-blind, randomized, crossover study. J Oral Maxillofac Surg., 1999; 57: 510-4.
24. Shaik M, Kumar J, Mobina S, Satyanarayana N, Sunitha P: Comparative study of tramadol and ketorolac in the pain management of third molar tooth extraction. J College Medical Sciences-Nepal, 2010; 6: 35e44.
25. Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J. Tramadol: Pain relief by an opioid without depression of respiration. Anaesthesia, 1992; 47: 291-6.
26. Shah I, Zaeem K, Ibrahim MW, Hussain I, Hassan A. Comparison of analgesic efficacy of tramadol hydrochloride with diclofenac sodium in dento-alveolar surgery. Pak Oral Dent J, 2007; 28: 241-4.