

A Comparative Study of Oral Tramadol against oral Ketorolac for the pain management in the dry socket: A Randomised clinical trial

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How to citation this article: Abid Majeed Rather, Umer Mukhtar, Mohammad Muneeb Mubashir, “A Comparative Study of Oral Tramadol against oral Ketorolac for the pain management in the dry socket: A Randomised clinical trial”, IJMACR- November – December - 2021, Vol – 4, Issue - 6, P. No. 159 – 165.

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Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Pain in the dry socket is severe and challenging to manage. The current treatment modalities for pain control are not potent enough to provide relief and pain management remains a problem to be solved. The oral tramadol and ketorolac tablets are both suitable options for pain management in a dry socket. This study aimed to compare the efficacy of oral tramadol with oral ketorolac for pain control in dry socket patients. An open-label, randomized controlled trial was conducted from November 2018 to October 2020. A total of 50 patients were selected and were divided into two groups 1. Group tramadol (n = 25) in which Tab Tramadol 75mg thrice daily was given and 2. Group Ketorolac (n = 25) Tab ketorolac 10mg thrice daily was used for pain management. The primary objective of the study was the evaluation of the pain scores for six consecutive days by visual analog scale (VAS). Secondary measures included the safety and tolerability of drugs and the amount of

rescue analgesic medication. The mean VAS pain scores were less in both groups as compared to baseline data on all follow-up days. The amount of rescue analgesic medication was comparable in both groups. Side effects were seen in both the groups with Nausea (40%), constipation (28%), and Vomiting (32%) more in the Tramadol group and Headache (46%) and GIT upset (28%) more in the ketorolac group. Thus, it would be concluded that both the drugs are potent enough for pain management in dry socket pain and tramadol is a good option for patients having GIT upset with the use of NSAIDs.

Keywords: Dry socket; Tramadol; Ketorolac; Pain management

Introduction

A 'dry socket' also known as 'fibrinolytic alveolitis' or 'localized osteomyelitis', is one of the most common complications after tooth extraction.¹Blum described dry socket as “postoperative pain in and around the

extraction site, which increases in severity at any time between one and three days after the extraction, accompanied by a partially or totally disintegrated blood clot within the alveolar socket, with or without halitosis.² Incidence has been seen ranging from (0.5%-68%) with more incidence among females.³

The etiology of dry socket is very complex and multifactorial with different mechanisms and factors influencing the incidence of this condition. The most common causes for this condition include traumatic extractions, bacterial microbiota, bone & root fragments in extraction wounds, aggressive curettage & irrigation, smoking, oral contraceptives and dislodgement of extraction wound clot by focal fibrinolytic activity or by exaggerated mouth rinsing by patients.^{3,4,5} Diagnosis can be made by clinical history of persistent throbbing pain radiating to head and neck regions and other signs and symptoms like halitosis, foul taste along with the presence of localized swelling and extraction wound devoid of a blood clot on clinical examination.^{3,4}

Different methods that include perioperative rinsing with chlorhexidine or other antiseptic solutions, use of systemic antibiotics, plaque control measures, and placement of antibiotics or other antiseptic pastes in the extraction sockets have been used as a preventive measure for the dry socket.^{4,6} Various treatment options for the management of dry sockets had been recommended from time to time by various authors. Use most of these treatment modalities are based on symptomatic pain relief in dry sockets. Treatment modalities that include use of analgesics, irrigation of extraction sockets, placement of intra socket medicaments (antibiotics, obtundants, anesthetic agents) e.g, zinc oxide eugenol dressings, ribbon gauzes impregnated with BIPP paste (bismuth subnitrate and

iodoform paste), alveogyl, a combination of lidocaine with metronidazole pastes, honey and combination of turmeric with mustard oil have been used.^{4,3,7,8} New forms of treatment options like management with plasma-rich growth factors, and by low-level laser therapy had also been advocated for the management of this dreaded complication.^{9,10} Symptoms in the dry socket including the pain can even persist for 10 days. Pain in the dry socket is so severe that even the strongest analgesic cannot relieve the symptoms and pain management remains a problem to be solved.^{3,4}

Tramadol is an atypical centrally-acting synthetic opioid analgesic. It works by acting as an opioid agonist and an aminergic (noradrenaline and serotonin reuptake inhibitor) thus having double actions. It has a good analgesic efficacy and produces fewer side effects at equianalgesic doses compared to other opioids. The appropriate dosage regimen for dental pain ranges from 50-100mg every 4-6 hours and not to exceed 400mg per day. Its metabolic half-life is 6-9 hours with a duration of analgesia ranges from 4- 6 hours. The most common side effects are nausea, vomiting, somnolence, and dizziness. It has fewer effects on GIT functions, less risk of causing respiratory depression and less seizure risk as compared to other prototypes of opioids.^{11,12,13} Thus, Opioids having both central and peripheral effects have been seen to be more efficient in severe pain management conditions and thus can be a good option for pain management in dry socket

Ketorolac is a non-selective cox inhibitor drug that acts by inhibiting the synthesis of prostaglandins, prostacyclin's and thromboxane's which are the mediators of pain and inflammation.^{14,15} It is rapidly absorbed with bioavailability reaching approximately 80% to 100% following oral or i.m route. Oral ketorolac

administration after a single 10 mg dose has a much slower onset of action about 30 to 60 minutes with peak analgesia reaching about 90 to 240 minutes. The Plasma half-life in the normal adult is about 5 to 6 hours. After oral administration analgesia can be maintained for up to 6-8 hrs. Ketorolac has been seen to cause various adverse effects like nausea, vomiting, GIT symptoms like (Epigastric pain, peptic ulceration, dyspepsia, and GIT bleed) as compared to opioids where the effects on GIT are mild and effects on the central nervous systems are prominent.¹⁴ It also prolongs bleeding time by inhibiting platelet aggregation and possesses no sedative or anxiolytic properties.^{14,15, 16,17} Ketorolac should be avoided in patients with kidney and coagulation disorders as it interferes with renal and platelet functions.¹⁵

So, it is now evident from the previous studies that the pain in the dry socket is quite severe that even the commonly given analgesics are not adequate for pain management therefore potent analgesics (Tramadol, ketorolac)are a good option for pain management, Thus, there is a need to study these treatment modalities for pain management in a dry socket.

So, the purpose of this clinical trial was to compare the efficacy and safety of oral tramadol with oral ketorolac for pain management in dry sockets.

Patients and Method

Study design

The study was an active-controlled open-label, randomized clinical trial conducted from November 2018 to October 2020 after being approved by Institutional Ethical Committee. A total of 50 patients who were diagnosed with dry socket within the age range of 18-65 years of either sex were recruited from the outpatients, who reported at the Oral Health Sciences

Centre, Postgraduate Institute of Medical Science and Research, Chandigarh. Patients allergic to tramadol or ketorolac, having cancerous or ulcerative lesions, pregnant and lactating females, or having migraine, asthma, and alcoholic or narcotic abusers were excluded from the study.

Sample size calculation

A convenient sample of 50 patients was randomly assigned in the Tramadol Group or Ketorolac Group with 25 in each group.

1. Tramadol Group = (n=25)

2. Ketorolac Group = (n=25).

Randomization was done by Computer generated list and allocation concealment of patients in the respective groups by sequentially numbered opaque sealed envelopes.

Procedure

After the diagnosis of dry socket, preoperative radiographs were taken to rule out any remaining root piece in extraction sockets and preoperative pain evaluation was done by Visual analog scale^{20,26} (VAS) and patients were then allocated to their respective treatment groups.

1. **Tramadol Group-** Patients were given Tablet Tramadol (Tab Tramadol 75mg Dr. Reddy's Laboratories Ltd Mumbai, India), thrice daily for six consecutive days.

2. **Ketorolac Group** - Patients were given Tablet ketorolac(Tab ketorolac DT 10mg Dr. Reddy's Laboratories Ltd Mumbai, India), 20mg of loading dose on Day one followed by 10mg thrice daily for six consecutive days.

Tab Paracetamol 650mg (Tab Dolo 650 mg Micro Labs Ltd Mumbai India) was given as a rescue analgesic medication in both groups and, the number of pills taken

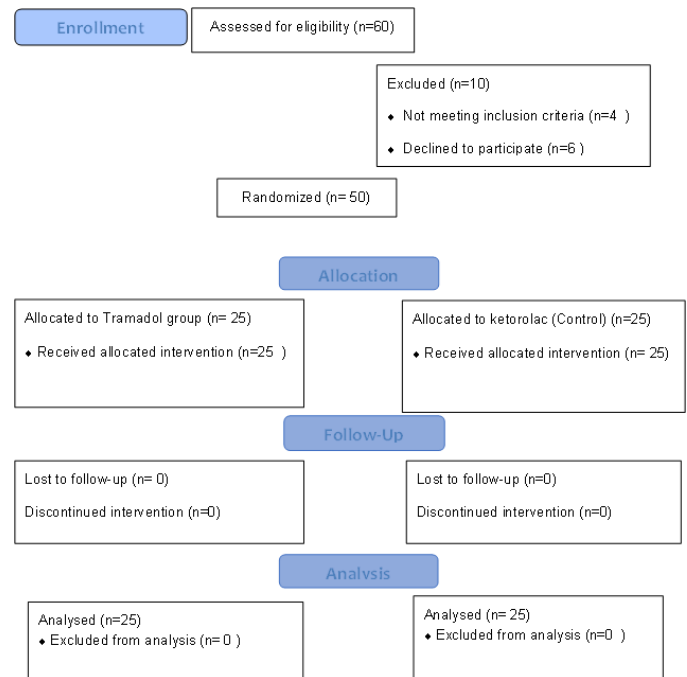
by patients in both the groups were noted and Tab Ondansetron 4mg (Tab Emset, Cipla Pharmaceuticals, Mumbai, India) was used as a rescue antiemetic to control vomiting in both the groups during the study. Irrigation of extraction sockets (dry socket) was done with saline and evaluation for side effects were done on 1st, 3rd, and 6th posttreatment day in both the groups. Maintenance of good oral hygiene at home by brushing and saltwater rinsing was also advised. Posttreatment pain measurements were noted by the patient each morning and evening for six consecutive days on pain dairy with an imprinted VAS pain scale given to each patient. The Safety and side effects were evaluated by noting the number of patients who experienced vomiting, headache, somnolence, constipation, dizziness, and epigastric pain.

Statistical analysis

The results were analysed by using SPSS version 18. Results on continuous measurements were presented on Mean ± SD (Min-Max) and categorical measurements in Frequency (Percentage). The normality of the data was assessed using the Shapiro-Wilk test and Chi-square test/Fischer exact test, Mann-Whitney U test was used to check the difference between the groups. P-value less than 0.05 were considered to be significant.

Observations and Results

Consort flow diagram



Mean pain scores at baseline (Day 1st morning) were statistically non-significant ($p > 0.05$) in both the groups (Tramadol and Ketorolac group). In both the groups mean pain scores (VAS in mm) decreased significantly on all post-treatment follow-up days as compared to the baseline pain scores. In comparison between the groups, tramadol showed a significant decrease on day 2 and day 5 postoperative as depicted in table 2. The number of patients taking the rescue analgesic medication was more in the tramadol group as compared to the ketorolac group but was statistically non-significant ($p > 0.05$) as depicted in table 3. Following side effects were seen in both groups (table no 4). More episodes of nausea, vomiting, and constipation occurred in the tramadol Group and Headache and GIT symptoms (Epigastric pain) was noted more in Ketorolac group patients

Discussion

Dry socket is one of the most common complications seen after the extraction of teeth. It is being commonly seen after extractions lower molar teeth with incidence up to 70 %¹. Our study also showed maximum incidence in the lower molars region (70%). It causes many

undesirable symptoms like halitosis, pain, and localized inflammation of the extraction socket. Severe pain most irritating symptom and can even persist for more than 10 days. So, pain management is still challenging and yet to be solved symptom^{1,5}.

Ketorolac an NSAID is a potent analgesic for pain management in different acute and chronic conditions. It acts by blocking the cyclooxygenase enzymes, thus prevents the synthesis of mediators of pain and inflammation. NSAIDs are less efficient than opioids for pain management and cause severe gastrointestinal upset in many patients. So, opioids being more potent and efficient with fewer GIT effects can be used as a good treatment modality for pain management in dry sockets.^{15,16}

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic. It tramadol exerts a double action by acting both on opioid receptors and also reduces inhibits serotonin and norepinephrine re-uptake thus inhibits the transmission of pain impulses. It has good analgesic efficacy with fewer effects on the GIT system and more effects on the CNS. The most common side effects seen are nausea, vomiting, drowsiness, somnolence headache, and dizziness. Opioids also exert a depressive effect on the cardiovascular and respiratory systems. Although it is an opioid, it produces fewer adverse effects as compared to other opioids at the equianalgesic dosages thus can be used as a safe and potent analgesic for the management of pain in dry socket.^{11, 12, 13, 18}

This is the novel study that had compared the efficacy and safety of Tab tramadol with oral ketorolac for pain management in dry sockets. We recruited 50 patients that were equally separated into two groups with 25 patients in each group.

The primary objective of our study was to compare the efficacy of tramadol and ketorolac for pain management in dry socket patients, assessed by VAS (mm) scale. Safety of drugs as evaluated by side effects and mean amount of rescue analgesic medication, which was evaluated by the total percentage of the patients who took rescue analgesic medication were the secondary endpoints. We believed, tramadol resulted in satisfactory analgesia in severe pain in dry socket patients and evaluation of pain was done by using the most simple, reliable, well-validated VAS scale¹⁹.

In this study, the patients in both groups had a significant decrease in mean pain scores measured from baseline (day one morning) to Day six with the highest mean pain differences between the baseline and day six ($p < 0.001$). On Comparison between the two groups decrease in mean pain scores was seen more in the tramadol group as compared to ketorolac group, which was statistically non-significant ($p > 0.05$) except on few postop days (Day 1 and Day 5) ($p = 0.05$) which could be due to better control of moderate to severe pain by opioids as they act on both central and peripheral action on pain management as compared to NSAIDs that act by inhibiting local mediators of pain¹⁴. The study results in terms of decrease in mean pain scores are similar to the following authors. Mm Shaik et al.¹² found tramadol safe and efficient analgesic as compared to ketorolac for post-extraction pain. Collins et al.²⁰ also found tramadol successful in complete pain relief after dentoalveolar operations. Medve et al.²¹ also noted tramadol or tramadol acetaminophen combinations as an efficient and potent analgesic for dental pain. Paul Moore et al.¹¹ also found tramadol a better analgesic as compared to codeine for dental extraction pain. Mishra H et al.¹⁴ also concluded from a placebo-controlled study that tramadol

is equally potent as ketorolac and safe in patients who are intolerant to NSAIDs.

Tab paracetamol 650 mg (Tab Dolo 650 mg Glaxo Smith Klein Pharmaceutical's Mumbai India) was used as rescue analgesic medication to prevent episodes of severe pain during breakthrough pain periods and inadequate analgesia due to main study drugs. The mean amount of rescue analgesic medication taken was comparable in both the groups with more amounts needed in ketorolac patients as compared to tramadol but was statistically non-significant. This could be due to better analgesic efficacy of opioids and more metabolic half-life of tramadol that decreases the need for rescue analgesic medication in breakthrough periods.

Side effects were seen in both the groups as depicted in table no.4. In tramadol group patients, more episodes of nausea and vomiting, and constipation were seen this is because Opioids are known to cause nausea, vomiting, and constipation as their main side effects. All these effects were mild which were managed by the rescue antiemetic medication tab Ondansetron 8mg for vomiting and syrup Cremaffin (Abbot Pharmaceuticals, Mumbai India) for constipation. Ketorolac group patients experienced epigastric pain and headache as common adverse effects (36.6%). GIT upset is the common side-effect of NSAIDs. Due to less relief in pain in the ketorolac group as compared to tramadol, referred pain from the extraction socket could be the reason for the headache in Ketorolac patients.

In conclusion, both drugs were effective for pain management in dry socket patients. The amount of rescue analgesic medication needed was almost comparable in both the groups with more amount needed by ketorolac group patients. Side-effects were seen in both the groups, with more patients experienced

vomiting, nausea, and constipation in the tramadol group while Ketorolac group patients had more GIT symptoms (epigastric pain) and headache.

Ethics statement/confirmation of patients' permission

Ethical approval was given by Institutional Ethics Committee, All the participants gave their written informed consent.

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