



Effect of Intravenous Ketorolac on Postoperative Pain in Mandibular Fracture Surgery; A Randomized, Double-Blind, Placebo-Controlled Trial

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► ABSTRACT

Objective: To evaluate the effects of intravenous ketorolac on early postoperative pain in patients with mandibular fractures, who underwent surgical repair.

Methods: This prospective, randomized, placebo-controlled clinical trial was conducted in Shahid Rajaei Hospital, affiliated with Shiraz University of Medical Sciences during a 1-year period from 2015 to 2016. We included a total number of 50 patients with traumatic mandibular fractures who underwent surgical repair. Patients with obvious contraindications to ketorolac such as asthma, renal dysfunction, peptic ulceration, bleeding disorders, cardiovascular disease, mental retardation, or allergy to ketorolac or NSAIDs, were excluded. The patients were randomly assigned to receive intravenous ketorolac (30 mg) at the end of operation in post anesthesia care unit immediately upon the onset of pain (n=25), or intravenous distilled water as placebo (n=25). Postoperative monitoring included non-invasive arterial blood pressure, ECG, and peripheral oxygen saturation. The postoperative pain was evaluated by a nurse using visual analog scale (VAS) (0–100 mm) pain score 4 hours after surgery and was compared between the two study groups.

Results: Overall we included 50 patients (25 per group) in the current study. The baseline characteristics including age, gender, weight, operation duration, anesthesia duration and type of surgical procedure were comparable between two study groups. Those who received placebo had significantly higher requirements for analgesic use compared to ketorolac group (72% vs. 28%; $p=0.002$). Ketorolac significantly reduced the pain intensity 30-min after the operation ($p<0.001$). There were no significant side effects associated with ketorolac.

Conclusion: Intravenous single-dose ketorolac is a safe and effective analgesic agent for the short-term management of mild to moderate acute postoperative pain in mandibular fracture surgery and can be used as an alternative to opioids.

Keywords: Ketorolac; Postoperative pain; Mandibular Fracture; Surgery; Analgesic.

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Introduction

Maxillofacial injury occurs in approximately 5-33% of patients experiencing severe trauma [1]. Injuries to the maxillofacial region may be particularly debilitating. It is the region of specialized functions such as vision, hearing, olfaction, respiration, mastication and speech. Important vascular and neural structures which are intimately associated are present in this region and the psychological impact of disfigurement may also add to the level of resulting morbidity [2]. The prevalence of mandible fractures was more prevalent in male patients, especially during the 3rd decade of their lives. The most common cause was road traffic accident and the more frequently affected region was condyle of the mandible [3, 4]. Inadequate postoperative pain relief may delay recovery, lead to a prolonged hospital stay, and increased medical costs [5]. Ketorolac is an injectable non-steroidal anti-inflammatory drug (non-selective cyclooxygenase inhibitor), blocks cyclooxygenase in the arachidonic acid cascade, thereby inhibiting the formation of prostaglandins with strong analgesic activity. When the ketorolac is administered intravenously, the initial analgesic response occurs within 30 minutes, and the time interval before which the peak of concentration is reached is 1 to 2 hours [6]. The onset of ketorolac analgesia is much slower than the onset of opioid analgesia. Compared with opioids, ketorolac 30 mg exhibited analgesic activity and pain relief equivalent to that of meperidine 50 mg and 100 mg intramuscularly and may be more cost-effective than intravenous morphine [7-9]. Previous studies investigated the administration of ketorolac wide acceptance in the treatment of postoperative pain in a variety of surgical procedures. It reduces opioid consumption by 25 to 45 percent and thereby lowers opioid-related side effects such as ileus, nausea, vomiting and shorter stay in hospital [5, 10, 11]. Ketorolac is used for moderate pain relief; and it may be used to treat severe pains when combined with opioids, reducing the opioid dose [12, 13]. The adverse effects of ketorolac are gastrointestinal disturbances and renal impairment; however, the reported incidence is low and clinically insignificant [6]. We postulated that single dose administration of ketorolac in patients undergoing maxillofacial surgeries will significantly reduce the postoperative pain. Thus, the aim of this study was to determine the effects of intravenous ketorolac during the immediate postoperative period on postoperative pain in patients undergoing mandibular fracture surgery.

Materials and Methods

Study Population

This randomized double-blind placebo-controlled trial was carried out from March 2015 to April 2016, in Shahid Rajaei Hospital, affiliated with Shiraz

University of Medical Sciences. Institutional review board (IRB) and medical ethics committee approvals were obtained from the Shiraz University of Medical Sciences (IR.SUMS.REC.1394.55). The trial was registered with Iranian registry of Clinical Trials (IRCT201607271674N13). The study was conducted in accordance with the Declaration of Helsinki, October 2008 (49th General Assembly of the World Medical Association). Written informed consents were obtained from eligible patients or by their legally authorized representative. We include those with mandibular fracture who were candidate for surgery under general anesthesia in the Department of Oral and Maxillofacial Surgery. All the included patients were ASA I and aged between 16 and 47 years. Patients were included if they had no systemic diseases and no history of any drug consumption. Patients with a previous history of allergy to non-steroidal anti-inflammatory drugs, asthma, ischemic heart disease, renal failure and those who did not sign the informed consent were excluded from the study.

Randomization and Intervention

Patients were randomized in a 1:1 ratio using a computer-generated table of random numbers. According to this table, numbers between 0 and 4 were allocated to the placebo and numbers between 5 and 9 were allocated to ketorolac groups. The first group of patients was given 30 mg of intravenous Ketorolac (C.T. Pharma, Rasht, Iran) at the end of the operation in post anesthesia care unit (PACU) immediately upon the onset of pain (n=25). The second group of patients was given intravenous placebo (1cc distilled water) immediately upon the onset of pain. The drug was administered by a nurse who was blind toward the study groups. The patients were also blind toward the drug they were receiving.

Anesthesia Protocol

The general anesthesia method was similar for all patients. Intravenous 0.1 mg/kg morphine was administered to induce anesthesia. Induction was achieved with 2.5 mg/kg of propofol, 3 µg/kg of fentanyl, and 0.5 mg/kg of atracurium. Maintenance of anesthesia was achieved by infusion of 100 µg/kg/min propofol and 0.1 µg/kg/min remifentanyl. All patients were monitored intraoperatively for heart rate, continuous ECG, non-invasive blood pressure (NIBP), and peripheral oxygen saturation by pulse-oximeter.

Outcome Measurement

The nurses who recorded the data of pain and drug complications were blind regarding the grouping. The difference in postoperative pain between pretreated and post-treated side in each patient was assessed by three primary end-points: pain intensity as measured by a 100-mm visual analogue scale for 4 hours, time to rescue analgesic, postoperative analgesic consumption. Secondary endpoint included

incidence of any adverse events of ketorolac in the recovery room. Pain intensity at rest was measured at selected intervals with a 100-mm visual analog scale (VAS; 0 - no pain to 100 - worst possible pain). The pain severity was assessed by a blind operator every 5 minutes until 30 min, 1, 2, and 4 hours postoperatively. Rescue analgesia was administered at VAS \geq 40 mm, in the form of intravenous pethidine 1 mg/kg. All the patients were monitored in the post-anesthesia recovery room for the first 4 hours (every 5 minutes until 30 min, 1, 2, and 4 hours postoperatively regarding heart rate, non-invasive blood pressure, and pulse oximetry. Adverse events and postoperative complications were recorded throughout the study period.

Statistical Analysis

To estimate the required sample size, a pilot study was conducted by measuring VAS after surgery on 10 patients receiving intravenous ketorolac or distilled water. The VAS scores 4 hours after surgery in Groups "Placebo" and "Ketorolac" were 43.1 \pm 14.9 and 20.0 \pm 10.1, respectively. We aimed to demonstrate a difference of 100 mm in the VAS pain score 2 hours after surgery between the groups. With a two-tailed $\alpha=0.05$ and a power of 80%, 24 patients needed in each group. Considering a loss to follow up rate of 10%, we entered 55 patients in the study. Descriptive analyses were performed on all baseline variables including means and standard deviations, medians, frequency and percentages, as appropriate.

Independent t-test was used for comparing parametric variables and chi-square test for proportions between groups. To compare baseline pain score and time to onset analgesia, Mann-Whitney test was used. In addition, Wilcoxon signed Ranks was used for the comparison of pain score before and after of ketorolac administration. Statistical analysis was performed by statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA) version 17. A 2-sided p -value of less than 0.05 was considered statistically significant.

Results

A total of 55 patients were eligible to enter the study, of whom 2 patients refused to participate in the study and 3 did not meet the inclusion criteria, leaving 50 patients that signed consent forms (consisting of control group, 25; and experimental group, 25). No patient was lost from the study due to adverse events or study complications (Figure 1). The results showed no statistically significant difference between the two groups regarding age ($p=0.155$) and sex ($p=0.999$). The baseline characteristics of the patients in two study groups are summarized in Table 1.

Those who receive ketorolac had significantly shorter time to perceptible pain relief and onset of analgesia activity when compared to controls ($p<0.001$). The severity of baseline pain (the pain before intervention) was comparable between two study groups ($p=0.999$). The pain intensity did not

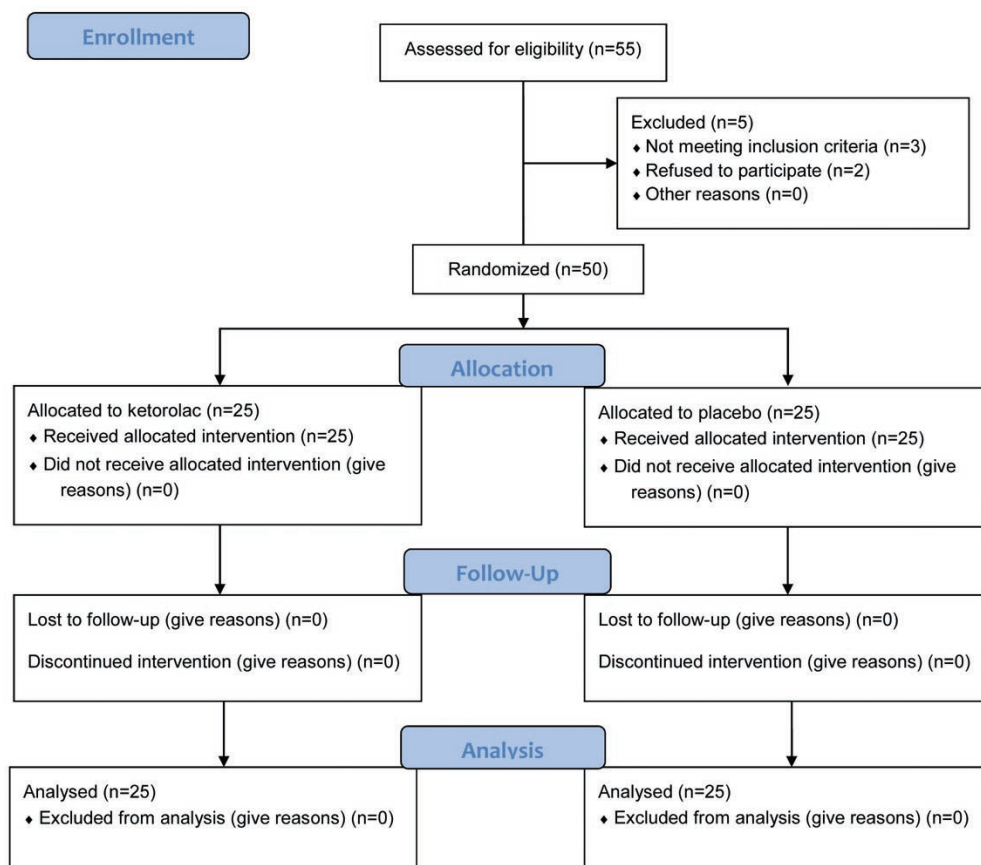


Fig. 1. CONSORT flow diagram of the study.

Table 1. Baseline characteristics of 50 patients with mandibular fractures undergoing surgery in two study groups

	Ketorolac (n=25)	Placebo (n=25)	p value
Age	29.64±8.225	26.40±7.599	0.155
Sex			
Men (%)	15 (60%)	15 (60%)	0.999
Women (%)	10 (40%)	10 (40%)	
BMI	21.46±3.07	21.30±2.55	0.840
Operation duration (hr)	2.56±0.939	1.94±0.666	0.010

decreased significantly within 30 minutes in placebo group while it decreased significantly in those who received ketorolac ($p<0.001$). The occurrence of VAS score >1 (need for treatment) evaluated serially from the recovery room did not reveal any significant difference between the ketorolac and placebo groups within 1 hour ($p=0.490$), 2 hours ($p=0.999$) and 4 hours postoperatively ($p=0.725$) (Table 2). The need for rescue analgesic within 1 hour after surgery was significantly lower in those who received ketorolac when compared to placebo (28% vs. 72%; $p=0.002$). However two study group were comparable regarding rescue analgesic after 4 hours (16% vs. 24%; $p=0.480$). There were no identifiable postoperative complications associated with the use of ketorolac. The study outcomes are summarized in Table 2.

Discussion

Acute postoperative pain is a predictable consequence following operations, and inadequately controlled pain after surgery is a challenge facing anesthesiologists [14]. The use of NSAIDs is considered for acute postoperative pain management. Although these agents may be insufficient as a single regimen to treat severe pain, they may be acceptable augmentation to opioids and may result in a substantial decrease in opioid requirements, which is associated with the decrease or possible avoidance of opioid related side effects [15]. Intravenous ketorolac was commonly well tolerated by patients which reduces

prostaglandin synthesis by non-selective competitive inhibition of cyclo-oxygenase (COX-1 and COX-2), producing peripherally-mediated analgesia [16, 17].

The aim of this study was to evaluate the analgesic efficacy and safety of a single dose intravenous ketorolac in comparison with placebo in patients experiencing moderate pain after mandibular fracture surgery. The safety and analgesic efficacy of single-dose intravenous ketorolac has been reported in early postoperative period in laparoscopic cholecystectomy with reduced consumption of rescue analgesic [18]. Cepeda *et al.* observed that in spite of superior analgesic properties of morphine, compared with ketorolac in postoperative pain, addition of a strong opioid to an NSAID decreases the risk of opioid side effects in the early postoperative period due to a considerable reduction in opioid requirements [19]. However, the evidence of a meta-analysis demonstrated systemic single dose of ketorolac benefits postoperative analgesia. Postoperative nausea and vomiting outcomes can be achieved by using a 60-mg dose and intramuscular route may provide greater opioid-sparing effects than the intravenous route [11]. In our study, the patients who received 30 mg intravenous ketorolac in post anesthesia care unit, immediately upon the onset of pain, were found to have less pain intensity and analgesic consumption in immediate postoperative period, as compared to placebo group. Moreover, use of intravenous ketorolac was effective in reducing postoperative pain scores and amount of rescue analgesic in immediate postoperative period after mandibular fracture surgery. Ketorolac, when

Table 2. Comparing the study outcomes in 50 patients with mandibular fractures undergoing surgery in two study groups

	Ketorolac (n=25)	Placebo (n=25)	p value
Time to onset of analgesia (min)	18.8±6.65	30±1.85	0.001
Pain intensity			
Baseline	2.76±0.87	2.72±0.73	0.999
1 hour	0.40±0.50	0.52±0.65	0.131
2 hours	0.96±0.54	0.69±0.68	0.108
4 hours	1.08±0.49	1.04±0.68	0.135
VAS^a >1			
1 hour	0 (0%)	2 (8%)	0.490
2 hours	3 (12%)	3 (12%)	0.999
4 hours	4 (16%)	6 (24%)	0.725
Analgesic requirement			
1 hour	7 (28%)	18 (72%)	0.002
4 hours	4 (16%)	6 (24%)	0.480

^aVAS: Visual Analogue Scale

used as part of a multimodal therapy in conjunction with other analgesics such as paracetamol or when given as multiple doses, may reduce postoperative pain; however, further studies are necessary to confirm it. Ketorolac decreases pain in the immediate postoperative period, compared with those of the placebo and achieves good potency only as an additive to narcotics. Careful patient selection is essential if use of ketorolac is considered. The risk for adverse events, however, increases with high doses, prolonged therapy (>5 days) or in vulnerable patients (e.g. the elderly). Ketorolac should be prescribed at the lowest dosage necessary to control pain; the duration of therapy should also be limited to as few days as possible [20]. More studies examining the efficacy of different dose regimens of systemic ketorolac to prevent postoperative pain are necessary to help anesthesiologists achieve the very much needed improvement in the management of postoperative pain. The main limitations to our study were assessed pain scores at specific time intervals (four hours) in recovery room and the small sample size.

In conclusion, single-dose ketorolac, when administered post-operatively for mandibular

fracture, was effective in the management of mild to moderate acute postoperative pain after surgery. Ketorolac has a low potency against acute pain, but in combination with opioids allows a reduction in opioid dose with improved analgesic effect.

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