Original Article

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Comparison of Pain Relief from Different Intravenous Doses of Ketorolac after Reduction of Mandibular Fractures

Surgery Section

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ABSTRACT

Introduction: Pain is an unpleasant feeling due to tissue destruction, which disturbs an individual's daily routines even at its lowest levels. The majority of surgeons and anaesthesiologists are increasingly trying to administer non-opioid analgesics because excessive use of opioids after surgery results in patient dissatisfaction.

Aim: To evaluate the analgesic effect of intravenous injection of different doses of ketorolac at different intervals in patients undergoing surgery for unilateral fractures of the mandible.

Materials and Methods: In the present randomized clinical trial (March 2016 to January 2017, in Tabriz Imam Reza Treatment/Educational Center), 50 patients were assigned to five groups with simple randomization method. In Group 1 and 2, immediately before the induction of general anaesthesia 30 and 60 mg of ketorolac and in Group 3 and 4, immediately before termination of surgery 30 and 60 mg of ketorolac was injected intravenously. In Group 5, ketorolac was not administered. After each patient regained complete consciousness, the severity of pain was determined using VAS up to 24 hours at baseline and at 2, 4, 6, 12 and 24-hours intervals. The total dose of the opioid analgesic agent (morphine-pethidine) and the time for the first request for an analgesic agent were recorded for each patient and their means were compared in each group with suitable statistical tests.

Results: The patients in Group 5 and 4 exhibited the highest and lowest mean pain scores (5.03±0.9 and 3.5±1), respectively. ANOVA for repeated measures and post-hoc Tukey tests showed significant differences only between Group 3 and 5 ($p=0.002$) and Group 4 and 5 ($p=0.001$), with no significant differences between the other groups ($p>0.005$). The highest dose of the analgesic agent was in Group 5 (5.3±1.4 mg) and the lowest dose was recorded in Group 4 (1.6±0.6 mg). Patients in the control group received significantly higher doses compared to the other groups ($p<0.05$). The patients in Group 1 and 2 received higher doses of analgesics compared to Group 3 and 4 ($p<0.05$). The longest time for the request for the first dose of analgesic agent after surgery was 73.4±12.03 minutes in Group 4. The patients in the control group had requested analgesics after surgery at a significantly shorter time compared to the patients in all the study groups ($p<0.05$). The patients in Group 1 and 2 had requested analgesics at a shorter time after surgery compared to the subjects in Group 3 and 4 ($p<0.05$).

Conclusion: Intravenous administration of 30 and 60 mg of ketorolac, immediately before termination of surgery, decreases the pain severity and the need for opioid analgesics after surgery.

Keywords: Nonsteroidal anti-inflammatory drugs, Opioid, Postoperative pain

INTRODUCTION

One of the most fearful experiences for patients is postoperative pain because millions of cells are injured during surgery [1]. The efficacy of pain relief after surgery is one of the most important factors necessary for the discharge of patients from the hospital [2,3].

Opioid analgesics are usually administered and side effects have been reported for these medications, including postoperative ileus, urinary retention, poor respiration, itching, confusion, dependence, tolerance and increased rates of nausea and vomiting [3,4].

Considering the problems above, the majority of surgeons and anaesthesiologists are increasingly trying to administer non-opioid analgesics such as NSAIDs [4].

Currently, NSAIDs are considered a component of multimodal analgesic treatments [5]. In the past, there was an increasing inclination to use NSAIDs in the management of postoperative pain, in combination with opioids or alone. Use of this group of medicines has been reported to be effective in the management of mild to moderate pain, including pain after maxillofacial surgeries, minor orthopaedic surgeries or outpatient surgeries [6].

Ketorolac is an injectable NSAID with analgesic and anti-inflammatory properties that belongs to the heterocyclic acetic acid family and provides moderate anti-inflammatory and strong analgesic effects. It brings its effect through inhibition of the synthesis of prostaglandins and inhibition of cyclo-oxygenase, similar to the majority of NSAIDs [1,7,8]. The longest permissible period of use of the oral form of this medication is five days, with two days for its injectable type (intravenous or intramuscular). The chief contraindication of this medication is hypersensitivity [1].

Some studies have reported that intravenous injection of 30 mg of ketorolac has resulted in the relief of postoperative pain, even compared to the preoperative injection of 50 mg of tramadol [9,10]. However, some other studies have reported that administration of 30 mg of ketorolac before orthopaedic surgeries [11] or prescription of ketorolac before surgical removal of impacted third molars has not affected the mount of narcotics received or even not receiving narcotics after surgery [12]. Considering the controversies and the fact that previous studies have not evaluated the proper time for prescription of analgesics, it seems further studies are necessary. Therefore, the present study was undertaken to compare the analgesic effect of intravenous injection of different doses of ketorolac at different intervals in patients undergoing surgery for unilateral fractures of the mandible.

MATERIALS AND METHODS

The present randomized clinical trial was carried out from March 2016 to January 2017 in Imam Reza Educational/Treatment center, Tabriz, Iran. Fifty patients with unilateral fractures in the body, angle or the symphysis of the mandible, with an indication for open reduction with the intraoral approach, were selected using simple

random sampling technique and included in the study after signing informed consent forms.

To determine the sample size, the results of a study by Alexander R et al., were used by considering α=0.05 and a study power of 90% and a difference of 1.5 in pain scores between the two groups [13]. The sample size was estimated at eight subjects in each group but the sample size increased to 10 subjects in each group, i.e., a total of 50 subjects, to increase the accuracy of the study.

Inclusion criteria: Signing an informed consent form and an interest in taking part in the study, Subjects with unilateral fractures of the mandibular symphysis, body or angle, with less than three months since the fracture (in fractures longer than three months, there is a possibility of prolongation or complication of the surgery), An age range of 20-60 years, due to the higher prevalence rate of traumas to the face and jaw at these ages [14], ASA I subjects (healthy subjects) and ASA II subjects (subjects with mild systemic conditions and no functional limitations) [15].

Exclusion criteria: The patients with, surgical operations lasting for more than two hours (due to complicated surgery), use of habit-forming drugs by the subjects, psychopathic subjects (all the subjects taking medications for psychosis were excluded due to the sedative effect of these medications), allergy to medications, systemic conditions due to the possibility of exacerbation of the conditions due to the effects of the medication, a history of convulsions (due to the sedative effects of anticonvulsants), more than one location for incision; were excluded from the study.

Study Groups

The subjects were assigned into five study groups with the use of the Randlist (Version 1.2) by an operator blinded to the aims of the study (simple randomization method). The type of intervention for each patient was placed in a closed envelope and handed to the anaesthesiologist to act accordingly during the induction of general anaesthesia.

In Group 1, immediately before the induction of general anaesthesia one ketorolac vial containing 30 mg of the medication was injected intravenously. In Group 2, immediately before the induction of general anaesthesia 60 mg of ketorolac was injected intravenously. In Group 3, immediately before termination of surgery (placing the last suture) 30 mg of ketorolac was injected intravenously and in Group 4, immediately before termination of surgery (placing the last suture) 60 mg of ketorolac was injected intravenously. In Group 5, ketorolac was not administered.

Evaluation of Study Outcomes

The primary outcome of the present study was postoperative pain relief after intravenous injection of different doses of ketorolac at different time intervals. After each patient regained complete consciousness, the severity of pain was determined using VAS up to 24 hours at baseline and at 2, 4, 6, 12 and 24-hours intervals. To this end, each patient was asked to determine his/her pain severity using a numeric value from 0 (absence of pain) to 10 (severe intolerable pain). The mean pain scores of patients in different study groups and at different time intervals were recorded and compared. Finally, the total dose of the opioid analgesic agent (morphine-pethidine), in terms of mg per the first 24 hours for each patient and also the time for the first request for an analgesic agent in minutes were recorded for each patient and their means were compared in each group.

Before initiating the study, all the nurses and the patients were briefed on the study procedures and steps and the scoring technique. All the subjects completed the study and none was excluded from the study.

In the present study, the surgeon, the patients and the nurses who recorded pain scores, the dose of the analgesic agents administered and the time of the first administration of the analgesic agent were blinded to the study (a double-blinded scheme). All the surgeries were carried out by one oral and maxillofacial surgeon.

All the patients went through a routine procedure for the diagnosis and treatment planning and none was deprived of routine treatment. All the ethical aspects of the present study were approved by the Ethical Committee of Tabriz University of Medical Sciences under the code IR.TBZMED.REC.1395.639.

STATISTICAL ANALYSIS

Data were analysed with the use of descriptive statics (frequencies, percentages, means and standard deviations), one-way ANOVA and repeated measures ANOVA, using SPSS 19.0. Kolmogorov-Smirnov test was used for the evaluation of normal distribution of data. Statistical significance was set at p<0.05.

RESULTS

In the present study, 50 patients (37 males and 13 females), with a mean age of 33.08±9.1 years, were evaluated [Table/Fig-1,2].

Gender	Study groups*					
	Group 1	Group 2	Group 3	Group 4	Group 5	Total
Male	7	8	8	7	7	37
Female	3	2	2	3	3	13

[Table/Fig-1]: The frequencies of patients participating in the study in terms of gender. *group 1: injection of 30 mg of ketorolac immediately before the induction of general anaesthesia; group 2: injection of 60 mg of ketorolac immediately before the induction of general anaesthesia; group 3: injection of 30 mg of ketorolac immediately before termination of surgery; group 4: injection of 60 mg of ketorolac immediately before termination of surgery; group 5: no intervention

Study groups	Mean age ± SD
Group 1	34.4±11.2
Group 2	33.3±7.7
Group 3	34.1±6.9
Group 4	33±11.5
Group 5	30.6±9.09
Total	33.08±9.1

[Table/Fig-2]: The mean ages of the subjects included in the study.

[Table/Fig-3] presents the mean pain severity scores of the subjects in different study groups pre-operatively and post operatively at different time intervals. As shown in the [Table/Fig-3], the pain was most severe immediately after regaining consciousness in all the study groups; however, the severity of pain decreased gradually in 24 hours.

The patients in Group 5 (the control) and 4, exhibited the highest and lowest mean 24-hour pain scores (5.03±0.9 and 3.5±1), respectively. Patients in Group 1 and 2, experienced more severe pain compared to patients in Group 3 and 4, respectively. One-way ANOVA and Post-hoc Tukey tests showed significant differences only between Group 3 and 5 (p=0.002, CI: -2.4,-0.3) and Group 4 and 5 (p=0.001, CI: -2.5,-0.5), with no significant differences between the other groups (p>0.005) [Table/Fig-4].

The dose of the analgesic agent administered during the first 24 hours after surgery was recorded separately for each group [Table/Fig-5].

The results showed the highest dose of the analgesic agent in Group 5, with a mean of 5.3±1.4 mg; the lowest doses were recorded in Group 3 and 4, with means of 1.9±0.8 and 1.6±0.6 mg, respectively. One-way ANOVA showed significant differences in this respect (p<0.001). Post-hoc Tukey tests were used for the comparison of the mean doses of analgesics administered in different study groups, indicating that patients in the control group received significantly higher doses compared to the other groups

Study groups	The patients' pain severity scores at different time intervals (mean ± SD)							
	Before surgery	Immediately after regaining consciousness	After 2 hours	After 4 hours	After 6 hours	After 12 hours	After 24 hours	Total (Mean 24-hour pain scores)
Group 1	1±0.9	5.6±1.5	5.1±1.1	4.8±1.1	4.4±0.8	3.2±0.6	2.2±0.6	4.2±0.7
Group 2	1.5±1.08	5.4±1.4	5.1±0.9	4.7±0.6	4.3±0.6	3.3±0.6	2.1±0.9	4.1±0.4
Group 3	1.5±1.2	4.9±1.1	4.6±1.07	4.4±0.9	4±0.9	2.9±0.8	1±0.8	3.6±0.6
Group 4	2±0.9	4.8±1.6	4.5±1.6	4.3±1.4	3.9±0.9	2.7±0.8	0.8±0.7	3.5±1
Group 5	1.7±1.1	6.5±1.3	6±1.2	5.7±1.05	5.2±1.3	3.9±0.9	2.9±0.9	5.03±0.9
ANOVA Test (p-value)	0.35	0.76	0.79	0.046	0.039	0.022	0.001	0.001

[Table/Fig-3]: The means and standard deviations of pain severity scores at different time intervals.

(p<0.05). The patients in Group 1 and 2 received higher doses of analgesics compared to Group 3 and 4 (p<0.05). However, there were no significant differences between Group 1 and 2 and Group 3 and 4 (p>0.05) [Table/Fig-6].

In addition, in the present study, the time of the first request for analgesic agent was recorded in minutes for each patient and their means were compared between the groups [Table/Fig-7].

The results showed that the longest time for the request for the first dose of analgesic agent after surgery was 72.9±11.08 minutes in Group 3, followed by 73.4±12.03 minutes in Group 4. The shortest time was recorded in Group 5, with 28±4.5 minutes. One-way ANOVA showed a significant difference in this respect (p<0.001). Post-hoc Tukey tests were used for comparison of the times for the request for the first dose of analgesic agent between different study groups. The results showed that the patients in the control group had requested analgesics after surgery at a significantly shorter time compared to the patients in all the study groups (p<0.05). The patients in Group 1 and 2 had requested analgesics at a shorter time after surgery compared to the subjects in Group 3 and 4 (p<0.05). However, there were no significant differences between Group 1 and 2 on one hand and Group 3 and 4 on the other hand (p>0.05) [Table/Fig-8].

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1	2	0.06667	0.35420	1.000	-0.9398	1.0731
	3	0.58333	0.35420	0.476	-0.4231	1.5898
	4	0.71667	0.35420	0.272	-0.2898	1.7231
	5	-0.81667	0.35420	0.162	-1.8231	0.1898
2	3	0.51667	0.35420	0.594	-0.4898	1.5231
	4	0.65000	0.35420	0.367	-0.3564	1.6564
	5	-0.88333	0.35420	0.110	-1.8898	0.1231
3	4	0.13333	0.35420	0.996	-0.8731	1.1398
	5	-1.40000	0.35420	0.002*	-2.4064	-0.3936
4	5	-1.53333	0.35420	0.001*	-2.5398	-0.5269

[Table/Fig-4]: The results of one way ANOVA and Post-hoc Tukey tests for equality of mean 24 hours pain scores between study groups.
* The mean difference is significant at the 0.05 level.

Study groups	Mean ± SD	Min	Max	95% confidence interval	p-value
Group 1	3.7±1.3	1	5	2.7–4.6	<0.001
Group 2	3.8±1.3	2	6	2.8–4.7	
Group 3	1.9±0.8	1	3	1.2–2.5	
Group 4	1.6±0.6	1	3	1.09–2.1	
Group 5	5.3±1.4	3	8	4.2–6.3	

[Table/Fig-5]: The mean doses of the analgesic agent (mg) administered in different study groups.

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1	2	-0.10000	0.52957	1.000	-1.6047	1.4047
	3	1.80000	0.52957	0.012*	0.2953	3.3047
	4	2.10000	0.52957	0.002*	0.5953	3.6047
	5	-1.60000	0.52957	0.032*	-3.1047	-0.0953
2	3	1.90000	0.52957	0.007*	0.3953	3.4047
	4	2.20000	0.52957	0.001*	0.6953	3.7047
	5	-1.50000	0.52957	0.051	-3.0047	0.0047
3	4	0.30000	0.52957	0.979	-1.2047	1.8047
	5	-3.40000	0.52957	<0.001*	-4.9047	-1.8953
4	5	-3.70000	0.52957	<0.001*	-5.2047	-2.1953

[Table/Fig-6]: The results of one way ANOVA and Post-hoc Tukey tests for equality of mean analgesic agent administered in different study groups.
*The mean difference is significant at the 0.05 level.

Study groups	Mean ± SD	Min	Max	95% confidence interval	p-value
Group 1	54.6±8.6	43	67	60.7-48.4	<0.001
Group 2	60.7±8.6	50	77	54.5-66.8	
Group 3	72.9±11.08	58	93	64.9-80.8	
Group 4	73.4±12.03	52	91	64.7-82.01	
Group 5	28±4.5	20	35	24.7-31.2	

[Table/Fig-7]: The times for the first request for analgesic agent (in minutes) in different study groups.

(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1	2	-6.10000	4.18240	0.594	-17.9841	5.7841
	3	-18.30000	4.18240	0.001*	-30.1841	-6.4159
	4	-18.80000	4.18240	<0.001*	-30.6841	-6.9159
	5	26.60000	4.18240	<0.001*	14.7159	38.4841
2	3	-12.20000	4.18240	0.042*	-24.0841	-0.3159
	4	-12.70000	4.18240	0.031*	-24.5841	-0.8159
	5	32.70000	4.18240	<0.001*	20.8159	44.5841
3	4	-0.50000	4.18240	1.000	-12.3841	11.3841
	5	44.90000	4.18240	<0.001*	33.0159	56.7841
4	5	45.40000	4.18240	<0.001*	33.5159	57.2841

[Table/Fig-8]: The results of one way ANOVA and Post-hoc Tukey tests for equality of mean first request time for analgesic agent in different study groups.
* The mean difference is significant at the 0.05 level.

DISCUSSION

New evidence indicates that opioid analgesics have many side effects, resulting in patient dissatisfaction [2-4]. In contrast, agents affecting the central and peripheral nervous systems and use of

multimodal techniques are more effective in alleviating patient's pain [16,17]. NSAIDs are component of multimodal treatment modality for pain relief and have been reported to be effective in alleviating mild to moderate pain, including pain after maxillofacial surgeries, minor orthopaedic surgeries or outpatient surgeries [5,6]. Ketorolac is an NSAID, belonging to the heterocyclic acetic acid family, which provides a high level of analgesic properties, with moderate anti-inflammatory properties [7,8].

The present study was designed to compare the analgesic effects of intravenous injection of different doses of ketorolac at different time intervals of the surgery in patients undergoing surgery for unilateral fractures of the mandible. The results showed that the mean pain scores in all the study groups immediately after regaining consciousness were the maximum, decreasing gradually over a 24-hour period. Patients in the control group (Group 5) exhibited maximum pain and the patients in Group 3 and 4, in which 30 mg and 60 mg of ketorolac was injected immediately before the termination of surgery reported the least pain severity. In addition, from a clinical viewpoint, injection of 60 mg of ketorolac was more effective than 30 mg of ketorolac in relieving patients' pain; however, the difference was not significant statistically.

De Oliveira GS et al., carried out a systematic review and reported that intramuscular injection of ketorolac before surgery, reduces patient's pain after surgery and injection of 60 mg of ketorolac was more effective in relieving patients' pain [7].

Ong K et al., carried out a study on 34 patients who were candidates for the surgical removal of impacted third molars in order to evaluate the effect of intravenous administration of 30 mg of ketorolac before surgery. They reported that administration of ketorolac before surgery was effective in decreasing postoperative pain [10].

Gopalraju P et al., carried out a study on 40 patients to compare the analgesic effects of ketorolac and tramadol. In one group, 30 mg of ketorolac and in another group 50 mg of tramadol were injected intravenously 10 minutes before surgery. The results showed a better analgesic effect of ketorolac in decreasing postoperative pain compared to tramadol [9], consistent with the results of the present study; however, the results of some other studies are different from those of the present study.

Vanlersberghe C et al., carried out a study on 60 patients who were candidates for orthopaedic surgeries. Administration of 30 mg of ketorolac before surgery had no effect on decreasing postoperative pain. It should be pointed out that the samples in that study were followed up to six hours after surgery [11].

Cabell CA et al., carried out a study on 49 patients who were candidates for outpatient laparoscopy and reported that administration of ketorolac before surgery was not more effective than its administration after surgery in relieving pain [18].

The discrepancies between the results of studies above can be justified by differences in surgeries and in study methodologies.

In addition, the results of the present study showed that intravenous administration of 30 and 60 mg of ketorolac, immediately before induction of general anaesthesia or termination of surgery, not only results in a decrease in pain severity and lengthening of time for requesting analgesic agents after surgery, but also it decreases the need for opioid analgesics after surgery. Since there is evidence that the dose of analgesics administrated after surgery is a sufficient indication for demonstrating the real preventive effect of a medication [10,19], it can be concluded that intravenous administration of ketorolac before induction of general anaesthesia or termination of surgery has a preventive effect. However, some studies have shown that other members of the NSAID family have no preventive effect [11,20,21]. In a study by Ong K et al., too, preoperative administration of ketorolac resulted in an increase in the time for requesting analgesics and a decrease in the use of analgesics after surgery [10]. However, there are reports indicating that administration of ketorolac before surgery has no effect on decreasing the dose of narcotics. Gutta R et al., carried out a study on 85 patients who were candidates for the surgical removal of impacted third molars. The results showed that, compared to the control group, preoperative administration of ketorolac resulted in a decrease in pain and discomfort during the first 8 hours after surgery. However, no significant differences were observed in the amount of narcotics received between the case and control groups. It was concluded that in general there was no significant difference between receiving and not receiving ketorolac in relation to the amount of narcotics received after surgery [12].

As discussed above, several studies have evaluated the effects of administration of ketorolac before and after surgery on alleviation of postoperative pain; however, there is a limited number of studies in the field of maxillofacial surgery. Other studies in this respect, too, have exhibited definite differences in the results.

LIMITATION

Although all the surgeries were carried out by one oral and maxillofacial surgeon, it was not possible to match all the other conditions for all the subjects, including duration of surgery, traumas inflicted on the surgical site during surgery, the type of fracture and the emotional status of the patients, which might have affected the results of the study. Another limitation of the present study was the limited number of subjects; in this context, it is suggested that further studies be carried out with larger sample sizes. In addition, in the present study, only intravenous administration was evaluated, while some studies have reported that intramuscular injection is more effective. Therefore, it is suggested that further studies be carried out by taking into account all the variables above in the field of maxillofacial surgery.

CONCLUSION

The results of the present study showed that intravenous administration of 30 mg and 60 mg of ketorolac, immediately before termination of surgery, results in a decrease in pain severity, lengthening of time for requesting analgesic agents after surgery and decreases the need for opioid analgesics after surgery.

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