

Postoperative Multimodal Analgesic Effect of Gabapentin and Ketorolac with Acetaminophen after Remifentanyl Infusion in Traumatic Maxillofacial Surgery

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Background: Pain control after traumatic maxillofacial surgery due to severity of pain and limitations of opioids use in these patients is of particular importance. The aim of this study was to evaluate the multimodal analgesic effect of oral gabapentin and intramuscular ketorolac in combination with intravenous acetaminophen for pain control after remifentanyl infusion in this surgery.

Methods: This study was a randomized clinical trial (RCT) on 60 patients (18-45 yr old ASA I to II) undergoing traumatic maxillofacial surgery in Sina Hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran from July 2014 to September 2015. The patients were randomly divided in 2 groups. Both groups received 1 gr (IV acetaminophen) 0.5 hour before the end of surgery. The Ketorolac group (n= 30) received 30 mg IM Ketorolac after induction of anesthesia and the Gabapentin group (n= 30) received 600 mg Gabapentin orally 30 minute before the induction of anesthesia. The pain severity score (assessed by VAS scale, the level of sedation (assessed by Ramsey scale), opioid requirement, nausea and vomiting was recorded in the postanesthesia care unit (PACU) and at 1-12-24 hours after surgery. For rescue pain management intravenous morphine was administered.

Results: Sixty patients were enrolled in this study. Use of Ketorolac and Gabapentin declines the pain intensity, level of agitation and morphine requirement in the recovery room and early hours in the ward. Mean arterial pressure and heart rate changes were significantly lower in ketorolac group compared with gabapentin group in the recovery room ($P < 0.05$).

Conclusion: The results of this study suggest that single intramuscular ketorolac in combination with intravenous acetaminophen can decline the pain intensity and opioid requirement with less nausea and vomiting and good hemodynamic control after traumatic maxillofacial surgery.

Keywords: multimodal analgesia; traumatic maxillofacial surgery; gabapentin; ketorolac

Pain is the most common undesirable and treatable outcome for patients who undergo surgical procedures. Postoperative pain management provides early postsurgical mobilization, shortened hospitalization, decreased hospital expenses and improved patient satisfaction. Opioids are generally the preferred analgesic agents during the early postoperative period but their use is associated with multiple adverse effects, such as nausea, vomiting, respiratory depression and delayed recovery [1]. This emphasizes the need for an analgesic strategy that controls postoperative pain with minimal side effects [2]. In recent years, the combination of some analgesics with different mechanisms of action as a multimodal analgesic

approach may reduce postoperative opioids requirement and its side effects [3].

Gabapentin a lipophilic structural analogue of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) is used primarily to treat seizures and neuropathic pain [4]. It also has an analgesic and opioid-sparing effect both at rest and with movement in acute postoperative pain management [5-7].

Gabapentin appears to be an acceptable alternative for cyclooxygenase-2 inhibitors for perioperative pain management and short-term use as an adjuvant to opioid analgesics [8]. Based on a systematic review, perioperative oral gabapentin is a useful adjunct for the management of postoperative pain that provides analgesia through a different mechanism from opioids and other analgesic agents and would make a reasonable addition to a multimodal analgesic treatment plan [9].

Ketorolac is a non-steroidal anti-inflammatory drug (NSAID), that is used as an analgesic for short-term management of moderate to severe pain.

Smith et al. evaluated the efficacy of a single dose of ketorolac given postoperatively for the treatment of moderate to severe postoperative pain in a quantitative review and their results demonstrated a beneficial effect

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[10].

Paracetamol is a centrally non-opioid analgesic but its precise mechanism of action has not yet been elucidated [11]. It was used in the management of postoperative pain, alone or in combination with others analgesics [12]. Combining paracetamol with opioids may improve analgesia, and by lowering the required doses of both medications, tolerability may be enhanced without increasing the incidence of postoperative nausea and vomiting (PONV) or respiratory depression effects associated with the use of opioids [13].

Traumatic maxillofacial surgery is one of the major maxillofacial procedures that produces strong noxious stimulations. The use of opioids as a painkiller after these procedures because of their side effects has some limitations. In a recent study we evaluated the postoperative analgesic effects of gabapentin and ketorolac after orthognathic surgeries and we suggest that ketorolac as well as gabapentin can decline the pain intensity and opioid requirement with less complication in this procedure [14].

Therefore we designed the present clinical study to evaluate the effectiveness of preoperative oral gabapentine and single intramuscular dose ketorolac after induction of anesthesia in combination with intravenous paracetamol at the end of traumatic maxillofacial surgeries.

Methods

This randomized clinical trial was conducted on 60 consecutive patients with ASA I-II undergoing various types of traumatic maxillofacial surgeries in Sina hospital in Tehran in 2015. The study was approved by the institutional review board and for the all patients written informed consent was obtained. Patients with known sensitivity to gabapentin, history of seizure, positive history of gabapentin consumption, and those patients with the history of opium or alcohol use, history of psychological disorders, renal impairment, and definite liver disease were all excluded.

In the operating room, the patients were randomly assigned by using a computer random number generator to divided two groups. The Ketorolac group (n= 30) received 30 mg IM Ketorolac after induction of anesthesia and the Gabapentin group (n= 30) received 600 mg Gabapentin orally 30 minute before the induction of anesthesia. Both groups received 1 gr (IV acetaminophen) 0.5 hour before the end of surgery.

Midazolam 0.04 mg/kg and fentanyl 2 µg/kg were used as premedication for all patients. Anesthesia induction was achieved by using atracurium 0.5 mg/kg, thiopental sodium 5 mg/kg, and lidocaine 1.5 mg/kg. Continuous infusion remifentanyl 0.2 µg/kg/hr and Isoflurane with 1 minimum alveolar concentration were maintained during the anesthesia period.

At the end of surgery, muscle relaxant effect was reversed by neostigmine 50 µg/kg and atropine 20 µg/kg. After extubation, patients were transferred to the post anesthesia care unit (PACU), where an anesthesiologist and nurse unaware of the study objectives, observed the patients. As the primary objective, pain scores were measured at the time of arrival in the PACU as well as 5 and 30 minutes thereafter and postoperatively at 1,12, and 24 hours using a 10-cm VAS score. Secondary objectives of the study were as following: Sedation score was assessed during the first 30 minutes after arriving to PACU using Ramsay Sedation

Scale simultaneously with pain scores. Heart rate and mean arterial pressure was assessed during recovery period.

In recovery room and in any cases without properly pain control, morphine (0.03mg/kg, intravenously) was infused every 5 minutes and the administrated dosages of morphine within the first 24 hours of drugs injection was also recorded.

Statistical analysis

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Categorical variables were compared using chi-square test or Fisher's exact test. Quantitative variables were also compared with student t test or Mann- Whitney U test. For the statistical analysis, the statistical software SPSS version 16 (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

The 60 patients enrolled in the study were divided into gabapentin (n = 30), Ketorolac (n = 30). There were no significant differences in the demographic data of the participants (Table 1).

Analyses of VAS data from each time point revealed, however, that the differences in pain scores were most evident in the early postoperative hours. The mean VAS score were significantly reduced in Ketorolac group with high Sedation score compared with the Gabapentin group during recovery period until early hours of coming to ward (Table 2).

The mean intensity of pain score was not significantly different between each group after this time. The mean arterial pressure and heart rate, frequency of PONV and were also significantly reduced in Ketorolac group (Table 3).

Patients in the Ketorolac group requested a smaller amount of morphine than those in the Gabapentin group (Table 3) but the difference between groups was not significant in the ward. The 24 h morphine consumption was 7.2±3.2 mg and 3.5±1.2mg in the Gabapentin and Ketorolac group respectively (P<0.05).

Table 1- Patients characteristics

Variable	Gabapentin group	Ketorolac group	p Value
Age (yr)	27.81±8.25	28.61±11.56	0.46
Male/female	19/11	20/10	0.23
MAP before surgery(mmHg)	92.12±12.61	93.81±14.19	0.68
HR(min)	81.6±13.4	81.6±13.4	0.39
Operation time (min)	151.2±11.2	154.3±11.3	0.28

Data are mean ± standard deviation. P value < 0.05 is considered statistically significant.

Table 2- Postoperative VAS score in both studied groups

Time	Gabapentin group	Ketorolac group	p Value
5min	4.0±1.60	2.0±0.74	0.002
30min	2.54±0.50	1.80±0.64	0.02

Table 2- Postoperative VAS score in both studied groups (Continued)

Time	Gabapentin group	Ketorolac group	p Value
1hr	4.78±1.22	2.12±0.90	0.001
12hr	3.0±0.86	3.50±0.84	0.1
24hr	3.0±0.86	3.50±0.84	0.1

VAS: Visual analogue scale, Mean± Standard deviation. P value for difference= 0.011. P value for trend= 0.48

Table 3- Variable outcome in recovery

Variable	Gabapentin group	Ketorolac group	P value
MAP(mmHg)	98.11±14.9	90.12±10.6	0.043
HR(min)	82.3±11.4	72/2±8/3	0.045
PONV(n)	10	8	0.055
Sedation score (RSS)	2.3±0.9	5.3±0.3	0.024
Morphine requirement(mg)	7.2±3.2	3.5±1.2	0.002
Recovery time(min)	30.2±12.4	21.3±8.5	0.045

Ramsay Sedation Scale: RSS

Discussion

In this clinical study we demonstrated that the combination of preoperative oral gabapentine 600mg or intraoperative intramuscular ketorolac 30mg, with i.v paracetamol 1gr at the end of traumatic maxillofacial surgery in patients receiving continuous infusion of remifentanyl resulted in an overall reduction in pain scores in the early postoperative hours.

This combination resulted to less agitation and PONV and more hemodynamic stability during PACU. Morphine consumption, the secondary end point of the study, was significantly reduced for patients in the Ketorolac group compared with Gabapentin group in early hours after surgery.

After a single oral dose of 300 mg gabapentin, mean maximum plasma concentrations are attained in two to three hours. Because of decreasing compliance of transport system with increasing dose, the bioavailability of a single oral dose of gabapentin declined that may be reached to sixty percent. Gabapentin is eliminated by renal clearance and after a single oral dose of 300 mg the elimination half-life reach to seven hours [15]. We used 600mg gabapentin one hour before surgery, that reach to maximal plasma concentrations at the time of surgical stimuli and its analgesic effect sustained until early postoperative period. The analgesic efficacy of gabapentin when it was used one hour before the surgical incision has been established by Dirks et al. who found a significant reduction in postoperative opioid consumption without considerable side effects [16].

In a study by Hussain Khan, pre and post-incision gaba-pentin administration was found effective in pain management [17]. In this study, doses of gabapentin were 900 or 1200 mg which are higher than that of the current study.

Paracetamol is one of the most commonly used agents for relieving mild to moderate pain. Intravenous paracetamol infusion results in a rapid elevation in plasma concentrations and higher peak levels that clinical analgesic effect appear within 5-15 min of administration and lasts for approximately 4-6 hours [18]. These pharmacokinetic properties of paracetamol make it suitable as a component of multimodal analgesia for postoperative pain control and reduction of opioids consumption in a wide variety of surgical patients [19].

In this clinical study, we found that gabapentin and paracetamol combination reduced pain intensity from the end of surgery till sixth hours postoperatively.

Ketorolac is a non-selective cyclooxygenase inhibitor that causes postoperative reduction of inflammatory mediators and analgesia effects.

The onset time of analgesic effect following both IV and IM administration is about 30 minutes and maximum analgesia occurs after one to two hours. Analgesia normally lasts for four to six hours. Ketorolac was used as an analgesic in many studies. A quantitative systematic review to evaluate the efficacy of a single dose of preoperative ketorolac on postoperative analgesia show that intramuscular administration of single dose ketorolac is an effective multimodal approach to reduce postoperative pain. The 60mg IM route of administration provides greater postoperative analgesia and opioid sparing effects [20]. In this study our analysis demonstrated, that a single dose of ketorolac 30 mg as part of a multimodal therapy in conjunction paracetamol reduces postoperative pain, opioid consumption, agitation and PONV in the early postoperative period. The incidence of PONV is higher in Gabapentin group in comparison to the Ketorolac group, which may be due to more opioid consumption in this group.

In our study, we compared postoperative outcome of gabapentin and ketorolac in combination with acetaminophen. According to the trend of postoperative pain score both gabapentin and ketorolac in combination with paracetamol decreased the pain score in the early period following operation, but ketorolac had a little better outcome and less PONV and high level of sedation.

Opioid maintenance in our study was remifentanyl. Remifentanyl is an ultra short acting opioid which facilitates hemodynamic and neurologic management. Because of its short half-life, it is recommended to be used as an infusion. The main problem of remifentanyl based anesthesia is the rapid disappearance of its analgesic effect after the termination of infusion and the possible development of acute opioid tolerance [21]. According to the pharmacokinetic properties of remifentanyl, rapid development of opioid tolerance would be expected. Recent studies showed different results and there is still controversy whether remifentanyl induces hyperalgesia or not Yeom et al. in a study used remifentanyl (0.03 µg/kg/min and 0.16 µg/kg/min) as an adjuvant in general anesthesia and reported that remifentanyl showed no evidence of having developed acute opioid tolerance and opioid-induced hyperalgesia [22]. Cortinez et al. also suggested that there was no development of opioid-induced hyperalgesia after remifentanyl (0.1 µg/kg/min) based anesthesia [23]. In our study prophylactic analgesic treatment was started before the end of surgery, therefore evaluation of hyperalgesia after termination of remifentanyl infusion was not possible.

In conclusion, the combination of oral gabapentine 600mg

one hour before surgery or intraoperative intramuscular ketorolac 30mg, with i.v paracetamol 1gr as a multimodal approach at the end of traumatic maxillofacial surgery under infusion of remifentanyl resulted in an overall reduction in pain scores, opioid consumption, agitation and PONV in the early postoperative hours.

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