RESEARCH ARTICLE

The Clinical Effect of Oral Gabapentin/Clonidine Premedication on Postoperative Outcomes in Patients Undergoing Orthognathic Surgery

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Background: Postoperative acute pain management after 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 analgesic effect of oral gabapentin and clonidine combination and opioids requirements after surgery.

Methods: This study was a randomized clinical trial (RCT) on 70 patients (18-55 yr old ASAI to II) undergoing various types of Orthognathic surgeries in Sina hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran in 2016. The patients were randomly divided in two groups. Both groups received 1 gr (IV acetaminophen) 0.5 hour before the end of surgery. The control group received placebo and gabapentin/clonidine group received 300 mg gabapentin and clonidine 0.2mg orally 60 minutes before the induction of anesthesia. The pain severity score (assessed by VAS scale, the level of sedation (assessed by Sedation Agitation Scale), opioids requirement, nausea and vomiting were recorded in the post anesthesia care unit (PACU) 5 10, 20, 30 minutes and 3 hours after surgery. For rescue pain management intravenous morphine was administered.

Results: Seventy patients were enrolled in this study. Gabapentin/ Clonidine increase extubation time (20.3±9.3min) ($P<0.05$) compared to control group (14.8±6.2 min). Gabapentin/ Clonidine decline the pain intensity, level of agitation and morphine requirement in the early minutes in recovery room. The incidence of PONV was also lower in gabapentin/clonidine group (5.7%) compared to control group (14.7%) $p=0.005$.

Conclusion: Premedication of oral gabapentin/ Clonidine increases extubation time and sedation score in patients recovering from Orthognathic surgery and could reduce postoperative pain scores and opioids consumption in recovery room.

Keywords: gabapentin; clonidine; postoperative acute pain; orthognathic surgery

Pain is the most common stressful and worrisome outcome for patients who undergo surgical procedures. Postoperative acute pain management provides early postsurgical mobilization, shortened hospitalization, decreased post surgery chronic pain and patient satisfaction [1].

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 [2]. An analgesic strategy that controls postoperative pain with minimal side effects is a necessary and undeniable reality in modern hospitals. 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].

Clonidine by stimulating presynaptic α2 receptors in the vasomotor center in the brainstem inhibiting the release of Norepinephrine and lead to a decrease in sympathetic tone. It has some mild sedative and analgesic effect, which has been used extensively as premedication before surgery or procedures [4].

Gabapentin a lipophilic structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) is used primarily to treat seizures and neuropathic pain [5]. It also has an analgesic and opioids-sparing effect in acute postoperative pain management [6]. 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 [7].

Pain control after Orthognathic surgeries due to severity of pain and limitations of opioids use in these patients are of particular importance. In a previous study, we evaluated the postoperative analgesic effects of gabapentin and ketorolac after Orthognathic surgeries and suggested that ketorolac as

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Received: 20 December 2017, Revised: 12 January 2018, Accepted: 27 January 2018
The authors declare no conflicts of interest.
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well as gabapentin could decline the pain intensity and opioids requirement with less complication in this procedure [8].

The α2-adrenergic agonist clonidine has antinociception effect and produces postoperative analgesia in humans.

The aim of this study was to evaluate the combination effect of oral gabapentin and clonidine by two mechanisms of action in brain with intravenous acetaminophen for acute pain control and other postoperative outcomes after Orthognathic surgeries.

Methods

This randomized clinical trial was conducted on 70 consecutive patients with ASA I-II undergoing various types of Orthognathic surgeries in Sina hospital in Tehran in 2016. 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 control group (n= 35) took placebo and the Gabapentin group (n= 35) received 300 mg Gabapentin and clonidine 0.2mg orally 30 minutes 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 sodium5 mg/kg, and lidocaine 1.5 mg/kg. Continuous infusion of remifentanil 0.2 µg/kg/hr and propofol were maintained during the anesthesia period.

At the end of surgery, muscle relaxant effect was reversed by neostigmine50 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 10,20,30 minutes and 3 hours in ward by using a10-cm VAS score. Secondary postoperative outcomes were sedation score that was assessed simultaneous with pain evaluation by using Sedation Agitation Scale and incidence of nausea and vomiting. 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 during the recovery period 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 version16 (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant

Results

In this study, 70 patients, with a mean age of 45.31±0.6years and an age range of 18-55 years were studied over 12 months. There were no significant differences between the demographic variables, anesthesia and surgery duration, between each group (Table 1).

Table 1- Demographic Characteristics of the Patients in two groups

Variables	Gabapentin /clonidine group N=35	Control group N=35	P value
Age (year)	45.13±9.7	45.3±9.7	0.5
Male/female(n)	18/17	21/14	0.4
Anesthesia Duration(h)	4.14±1.2	4.57±1.38	0.5
Surgery Duration(h)	3.47±1.1	3.83±1.2	0.5
Opioids requirements(n)	13 (37%)	20(57%)	0.02

The mean extubation time in control group (14.8±6.2 min) was significantly lower than intervention group (20.3±9.3min) (P<0.05).

Analyses of VAS data from each time point revealed, however, that the differences in pain scores were most evident in the early postoperative minutes. The mean VAS scores were significantly reduced in clonidine/gabapentin group after extubation until early minutes of coming to recovery room (Table 2). Number needed to analgesia in gabapentin/clonidine group was 13 (37%) that was significantly lower than control group 20(57%) in recovery period.

Table 2- Postoperative mean VAS score in both studied groups

Time	Gabapentin/clonidine group	Control group	P value
5min	3.34	5.66	0.03
10min	3.15	5.46	0.01
20min	3.12	5.67	0.01
30min	4.11	5.78	0.01
3hr	5.76	5.89	0.2

The trend of mean sedation score (Sedation Agitation Scale) in gabapentin/clonidine was significantly lower in the early postoperative period (p=0.02) compare to control group but it was not significantly different between each group after this time (Table 3)

Table 3- Postoperative mean sedation score in both studied groups (Sedation Agitation Scale)

Time	Gabapentin/clonidine group	Control group	P value
5min	3.93	4.66	0.03
10min	3.15	4.43	0.02
20min	3.22	4.68	0.01
30min	3.21	4.28	0.01
3hr	4.76	4.89	0.4

The incidence of PONV was lower in gabapentin/clonidine

group (5.7%) compare to control group (14.7%) p=0.005.

Discussion

In this clinical study we demonstrated that the combination of preoperative oral gabapentin 300mg and clonidine 0.2mg, with intravenous paracetamol 1gr at the end of maxillofacial surgery in patients receiving continuous infusion of remifentanil resulted in an overall reduction in pain scores in the early postoperative period. This combination prolonged extubation time at the end of surgery and resulted in less agitation and PONV during PACU.

After a single oral dose of 300 mg gabapentin, mean maximum plasma concentrations are attained in two to three hours. It is eliminated by renal clearance and after a single oral dose of 300 mg the elimination half-life reach to seven hours [9].

In previous study we used 600mg gabapentin one hour before maxillofacial surgery, that reached to maximal plasma concentrations at the time of surgical stimuli and its analgesic effect sustained until early postoperative period [10].

The analgesic efficacy of gabapentin when used one hour before the surgical incision has been reported in a number of systematic reviews with meta-analyses. The results of our study show that gabapentin with clonidine couldn't reduce the intensity of pain in a prolonged time after surgery it just increased sedation and extubation time. It is close to a systematic review with meta-analyses by Fabritius et al that ruled out beneficial effect of postoperative analgesic effects of gabapentin especially when added to multimodal analgesia [11]. In this meta-analyses pain at rest was not significantly reduced at 6-h post-operatively, whereas pain during mobilization was reduced.

Gabapentin/clonidine reduced the incidence of PONV in postoperative period. In a quantitative analysis of evidence from randomized controlled clinical trials Achuthan et al, showed that preoperative administration of gabapentin in patients undergoing abdominal surgery were associated with a lower incidence of nausea and vomiting. They observed a reduction of 24% for nausea, 38% for vomiting and no significant reduction in the composite PONV [12]. The speculated mechanisms of anti-emetic properties of gabapentin include decreased tachykinin neurotransmission, decreased calcium influx in area postrema, reduced inflammation at the surgical trauma site [13-14].

Clonidine provides analgesia via both peripheral and central mechanisms. The peripheral effect apparently results from blocking C fibers and/or interaction with inhibitory G-proteins. Centrally, analgesia appears to result from stimulation of presynaptic a2-adrenergic receptors located in substantia gelatinosa of the dorsal horn at the central nervous system. This stimulation increases acetylcholine concentrations and inhibits neurotransmission by decreasing the release of substance P and glutamate. Supraspinal analgesia is mediated through noradrenergic neurons, stimulating neuronal firing in locus coeruleus and norepinephrine release [15].

However, the analgesic effect of oral clonidine has been controversial. Some authors have not detected improved postoperative analgesia or a reduction in morphine consumption [16]. In a large randomized control trial clonidine does not reduce opioids consumption or pain scores in patients recovering from non-cardiac surgery under general and spinal anesthesia [17].

In a rat model of postoperative pain evaluation, antiallodynic effect of intrathecal Gabapentin and its interaction with Clonidine was assessed by Jen-Kun Cheng et al. The results illustrate that intrathecal gabapentin and clonidine interact in a synergistic manner reducing postoperative allodynia and they suggest that such a combination may have clinical usefulness after surgery [18].

The combination of gabapentin and clonidine, was evaluated following spinal fusion surgery for Idiopathic Scoliosis in Children by DK Choudhry et al. They concluded that additions of postoperative transdermal clonidine and perioperative oral gabapentin together reduced opioid use and shorter hospital stay following spinal fusion surgery [19].

Conclusion

Premedication of oral gabapentin/ Clonidine increase extubation time and sedation score in patients recovering from orthogenetic surgery and could reduce postoperative pain scores and Opioids consumption just in recovery period. Anyway, further studies with higher doses may be necessary to evaluate effects of this combination on postoperative outcomes over time.

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