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The Effect of Pre-operative Oral Clonidine or Gabapentin on Post-operative Pain intensity, Morphine Consumption and Post-operative Nausea and Vomiting in Patients Who Undergone Thyroidectomy: A Double-blind Placebo-control Study

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Abstract

Background: This prospective, randomized, double-blind study evaluated the effect of clonidine and gabapentin premedication on postoperative pain intensity, morphine consumption, nausea and vomiting.

Methods: Sixty-six ASA I-II patients, aged 20 to 55 were randomly allocated to orally receive either clonidine 0.2 mg (group C,n=22), placebo (group P,n=22) or gabapentin 900 mg (group G, n=22) two hours before operation. Postoperative visual analog scale for pain (VAS), nausea and vomiting were measured in the recovery room and 2,6,12 and 24 hours following the surgery as well.

Results: The patients' characteristics were alike in three groups. The VAS pain scores at measured times were significantly lower in the clonidine (3.4 ± 0.9, 4.2 ± 0.75, 4.8 ± 1.0, 4.9 ± 1.3, 3.3 ± 0.6) and gabapentin groups (3.1 ± 0.6, 4.1 ± 1.0, 3.6 ± 0.7, 4.7 ± 0.8, 3.5 ± 0.7) than in the placebo group (5.1 ± 1.6; 6.5 ± 1.5; 5.9 ± 0.9; 5.5 ± 0.8, 3.5 ± 0.7, (repeated-measures ANOVA, between-subjects effects, P<0.001) The post-operative morphine consumption in gabapentin group (18.3 ± 15.6 mg) was significantly less than clonidine (47.1 ± 29.1 mg, P=0.02) and placebo groups (65.7 ± 31.1mg, P<0.001). The incidence of PONV in the first 24 hour after surgery was significantly more in clonidine (40.9%) than gabapentin (9.1%%) and placebo (9.1%%) groups (P<0.01).

Conclusion: Oral premedication with gabapentin or clonidine significantly decreases the post-operative pain and morphine consumption, without any decrease in PONV.

Keywords: Gabapentin; Clonidine; Postoperative nausea and vomiting; Analgesia

Introduction

Postoperative pain management is still one of the topics of interest of the both anesthesiologists and surgeons. Postoperative pain has a direct role on excess hospital stay that leads to more morbid complications, and extra hospital costs.

The opioids are the most effective classes of drugs used in postoperative pain control, however, due to their side effects, physicians are more inclined to utilize other classes of analgesics [1]. In the recent years many studies have paid attention to clonidine and more recently on gabapentin premedication for pain managing after surgical procedures. Clonidine is an α2- adrenoceptor agonist with sedative and analgesic effects; it's low cost has made it an interesting drug for pain control [2,3]. Gabapentin, a structural analogue of the γ-aminobutyric acid (GABA) is an anticonvulsant drug. Recently, it has been shown that this drug has some analgesic and antihyperalgesic properties. Regarding it's well-tolerated side effects it can play a role in multi-modal analgesia approach [1,4].

The main objectives of the present study were to compare the effect of clonidine and gabapentin premedication on postoperative pain intensity and post-operative morphine consumption; postoperative nausea and vomiting (PONV) were considered to be as the secondary outcome.

Materials and Methods

The protocol was approved by the Institutional Ethics Committee and an informed written consent was obtained from the patients. Sixty-six patients, aged between 20-55, classified as ASA physical status I and II whom underwent total thyroidectomy without lymph node dissection were enrolled in this randomized, double-blind and placebo-control study. Patients studied were previously diagnosed with multinodular goiter.

Patients with the following criteria were excluded: history of cardiovascular, hepatic or renal disease, chronic pain, hypertension, motion sickness, history of any kinds of allergy to clonidine, gabapentin or common drugs that are used during general anesthesia, history of drug or alcohol abuse and taking clonidine or gabapentin regimen before the surgery except for the study protocol.

As administration of clonidine to patients with a history of hypertension and cardiovascular disease may cause adverse effects they were not included in the study. The prevalence of PONV is higher in patients with renal insufficiency and motion sickness, subsequently they were also not included in the study. Liver is the site of metabolism of gaba-

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pentin. Also some hepatic side effects have been previously reported. As a result patients with hepatic disease were not included in the study.

Participants were computer randomized to three groups with 22 patients in each group.

All patients received a tablet and three capsules, two hours before the surgery. The study was double-blind. So, neither the patient not the anesthesiologist, who was responsible for data collection of the patient, was aware of the content of the tablet and capsules. Using a computer-generated randomization list patients were allocated into three groups. All drug preparation and administration were done by an anesthesiologist who was not involved in the patient care or data collection. The randomization list was concealed from investigators. Patients in group C (n=22) received a tablet containing 0.2 mg clonidinee and three placebo capsules. In group-P (n=22), both tablet and three capsules were placebo. In group-G (n=22), patients received three capsules, each containing 300 mg (a total of 900 mg) gabapentin and a placebo tablet.

On arrival to the operating room, all patients were routinely monitored with an electrocardiogram (ECG), noninvasive blood pressure and pulse oximetry.

An 18-gauge cannula was inserted in a peripheral vein, and lactated ringer solution 7 mL/kg was administered. Anesthesia was induced with 2.5 μg/kg fentanyl and 0.03 mg/kg midazolam and 5 mg/kg thiopental sodium, and the trachea was intubated 3-5 minutes after the 0.5 mg/kg intravenous atracurium. After intubation, anesthesia was maintained with 0.6-1.3% isoflurane in a mixture of O_2/N_2O (50%/50%) and by intermittent injection of fentanyl 1 μg/kg and atracurium 0.2 mg/kg every 30 minutes. At the end of the surgery, the patients were extubated after administration of 1.25 mg atropine and 2.5 mg neostigmin (1:2) to reverse neuromuscular blockade.

Postoperative pain intensity, nausea and vomiting (PONV) were measured in the recovery room, and 2,6,12 and 24 hours following surgery. The PONV was assessed by "yes" or "no" survey and treated by 10 mg IV metoclopramide, if needed. Also total solution intake and opioid consumption during the first 24 hours of surgery were recorded. The severity of postoperative pain was measured and recorded using a 10-cm visual analog scale (VAS), where 0=no pain and 10=the worst possible pain. In the cases of postoperative pain with the VAS score over of four, 0.1 mg/kg morphine was administered for the patients. If more analgesic was required, the interval between two injections was at least four hours. All assessments were done by an anesthesiologist who was not involved in the patients' management in the operating room and was blind to patient's group assignment.

Based on previous studies, we determined that a sample size of 22 patients in each group would be sufficient to detect a difference of three scores in the mean of VAS, a power of 95%, and a significance level of 5%.

The distribution of age, weight, surgery time, and VAS for pain was checked by the Kolmogorov-Smirnov test. They followed a normal distribution. Age, weight, peri-operative fluid administration, surgery time, metoclopramide consumption and morphine consumption were compared between three groups by one way ANNOVA. The repeated measures analysis of variance was used to assess the differences of VAS for pain in three groups and the changes of them over time in each group. The PONV was the ordinal scale measurement. To compare them between three groups in each time of measurement, chi-square and Fisher exact tests (when appropriated) were used. The sex and ASA physical status class were compared with chi-square test. Two tailed P<0.05 was taken as significant. Statistical analysis was performed using SPSS 13.5 for Windows (SPSS Inc., Chicago, Illinois).

Results

We randomized 66 patients. There were no protocol violations, and all of the patients were included in the analysis.

The mean patients' age, weight; the duration of surgery; perioperative fluid administration; and distribution of sex and ASA physical status were the same in the three groups (Table 1).

The VAS pain scores at measured times were significantly lower in the clonidine (3.4 ± 0.9, 4.2 ± 0.75, 4.8 ± 1.0, 4.9 ± 1.3, 3.3 ± 0.6) and gabapentin groups (3.1 ± 0.6, 4.1 ± 1.0, 3.6 ± 0.7, 4.7 ± 0.8, 3.5 ± 0.7) than in the placebo group (5.1 ± 1.6; 6.5 ± 1.5; 5.9 ± 0.9; 5.5 ± 0.8, 3.5 ± 0.7, between subjects difference, P<0.001) (Figure 1). The changes in VAS for the pain during the time was significant in each group (within subject test, P<0.001).

The post-operative morphine consumption in gabapentin group (18.3 ± 15.6 mg) was significantly less than clonidine (47.1 ± 29.1 mg, P=0.02) and placebo groups (65.7 ± 31.1 mg, P<0.001). Post hoc Tukey test showed no differences in morphine consumption between clonidine and placebo groups (Table 1).

The incidence of PONV in the first 24 hours after the surgery was significantly more in clonidine (40.9%) than gabapentin (9.1%%) and

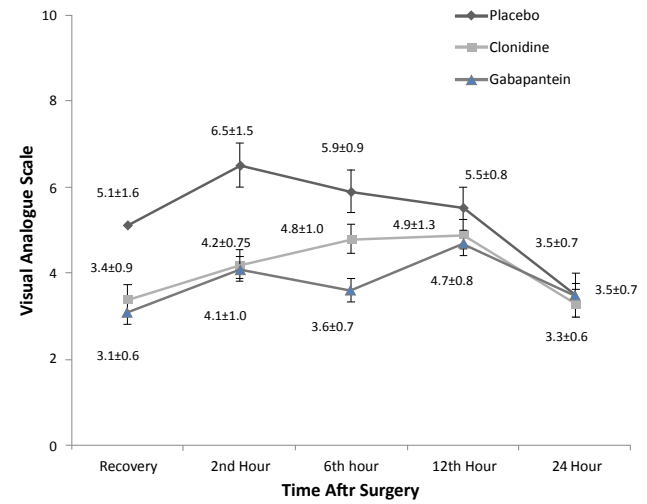

Figure 1: VAS in measured times P<0.001.

	Placebo Group (n=22)	Clonidinee Group (n=22)	Gabapentin Group (n=22)
Gender (Female/Male)*	16/6	19/3	17/5
ASA Physical Status Class (I/II)*	13/9	12/10	11/11
Age (years)a*	38.2 ± 10.0	41.8 ± 7.9	38.5 ± 10.1
Weight (kg)a*	67.1 ± 12.3	67.6 ± 17.3	70.5 ± 10.2
Duration of Surgery (min)a*	133 ± 20.5	126 ± 20.5	129 ± 20.5
Fluid administration (L)a*	5.13 ± 0.9	6.45 ± 0.9	5.42 ± 1.0

a Values are expressed as mean ± SD.
* There were not significant differences between groups.

Table 1: Patients characteristics.

	Placebo Group (n=22)	Clonidinee Group (n=22)	Gabapentin Group (n=22)
Postoperative Morphine Consumption(mg) a	65.7 ± 31	47.1 ± 49.1	18.3 ± 15.6**
24 Hour PONV (%)	2(9.1%)	9(40.9%)**	2(9.1%)
Metoclopramide consumption (mg)a*	12.7 ± 4.7	14.1 ± 5.1	10 ± 0.0

a Values are expressed as mean ± SD.
** P<0.001
* There were not significant differences between groups.

Table 2: Postoperative Morphine Consumption; nausea and vomiting.

placebo(9.1%%) groups (P<0.01, Table 1). Metoclopramide request wasn't different significantly in the groups (Table 2).

Discussion

The current study demonstrates that patients who received oral premedication with gabapentin 900 mg had a significant decrease in post-operative VAS for pain and morphine consumption compared with patients who received placebo. However, oral premedication with 0.2 mg clonidine could only decrease post-operative pain intensity without morphine consumption. The incidence of PONV was more in clonidine group.

Gabapentin is a known anticonvulsant drug with antinociceptive and antihyperalgesic properties [5,6]. In the recent years some studies have been evaluate the gabapentin as a part of multimodal analgesia approach, and also the effect of this drug on PONV has been showed. In 2006, Ho and et al [4] performed a systematic review of 16 randomized clinical trials regarding postoperative pain management by gabapentin and demonstrated administration of single preoperative dose, 1200 mg or less, efficiently reduced VAS score, opioid consumption and vomiting in the first 24 hours of the surgery; however multiple preoperative doses, could not reduce pain score. They also showed gabapentin makes a trend toward lower incidence of nausea, but it did not show statistical significant differences. Although gabapentin has been used successfully for postoperative pain relief in various type surgeries [1,7], some studies have not confirmed these reports [8]. These different results seem affected by different dosage of gabapentin administration and the type of surgery.

On the other hand, clonidine, an α2- adrenoceptor agonist with analgesic effect is another option for attenuating postoperative pain as a part of multimodal analgesia that has been fairly noticed in the recent decade [2,9,10]. Its efficacy on reducing postoperative nausea and vomiting alone or in combination with opioids is well established. Some previous studies demonstrated that clonidine and gabapentin could reduce PONV [3,11,12], but the incidence of PONV in our study was alike in gabapentin and control groups. Perhaps our sample size was simply too small to show any differences in the incidence of PONV. Surprisingly, this incidence increased in patients who received clonidine. Higher incidence of PONV in clonidine group can be designated to more morphine consumption. However, in both clonidine and placebo groups, the post-operative morphine consumption was significantly more than gabapentin group. As the incidence of PONV in placebo group didn't differ significantly with gabapentin group, the rise in incidence of PONV in clonidine group can't be attributed to more morphine consumption. On the other hand, the metoclopramide request was the same in the groups. In this study, the severity of PONV wasn't assessed. The patients in the clonidine group might have experienced mild nausea; as a result they didn't get medicine. To clear this controversy, another study is likely expected to be done in the future.

As in our Center the PCA usage is not routine, we couldn't use this method for post-operative morphine consumption estimation, and it can be a limitation for our study.

In the PubMed, ISI and other famous data bases, we haven't manage to find any manuscript which compares gabapentin and clonidine effects on post-operative pain or morphine consumption, yet there were some works in which had studied the effects of gabapentin or clonidine on the post-operative pain and morphine consumption, as well as the incidence of PONV were evaluated. Oral gabapentin has been used successfully for post-operative pain and morphine consumption with doses ranged from 300 to 1200 mg. However, the lower doses were recommended, considering the potential risk of adverse effects [5]. As result, the 900 mg gabapentin was chosen in this study. Oral clonidine doses between 0.1 to 0.3 mg have been used as a premedication [2,13]. In a study, 0.15 mg oral clonidine had the best effect on prolongation of spinal anesthesia [14]. Some previous studies used 0.1 and 0.2 mg clonidine for post-operative pain reduction [2,13]. But 0.1 mg clonidine was not successful in the reduction of post-operative morphine consumption [2]. Consequently, 0.2 mg oral clonidine was chosen in this study.

We chose thyroidectomy patients in our study due to the following reasons. First, the thyroidectomy is a common procedure in our Center. Furthermore, the incidence of PONV following this procedure is rather high; consequently, we could to evaluate PONV whit less sample size.

In conclusion our study demonstrates that oral premedication with gabapentin significantly decreases the post-operative pain, morphine consumption, without any decrease in PONV. However, clonidine can only decrease post-operative pain without morphine consumption.

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