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

Seyed Mojtaba Marashi, Ali Akbar Morabi, Mohammad Hossein Ghaafari, Omid Azimaraghi and Ali Movafegh*

Department of anesthesiology and critical care, Dr. Ali Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

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). 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). 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 morbidity complications, and extra hospital costs.

The opioids are the most effective classes of drugs used in post-operative 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 y-aminobutyric acid (GABA) is an anticonvulsant drug. Recently, it has been shown that this drug has some analgesic and antihyperalgesic properties. Regarding its 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 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...
All drug preparation and administration were done by an anesthesiologist who 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 clonidine 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. We randomized 66 patients. There were no protocol violations, and all of the patients were included in the analysis.

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; periparative fluid administration; and distribution of sex and ASA physical status were the same in the three groups (Table 1).

TheVAS 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 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; periparative fluid administration; and distribution of sex and ASA physical status were the same in the three groups (Table 1).

TheVAS 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.](image)

<table>
<thead>
<tr>
<th>Table 1: Patients characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female/Male)*</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>ASA Physical Status Class (III)*</td>
</tr>
<tr>
<td>Age (years)**</td>
</tr>
<tr>
<td>Weight (kg)**</td>
</tr>
<tr>
<td>Duration of Surgery (min)**</td>
</tr>
<tr>
<td>Fluid administration (L)**</td>
</tr>
</tbody>
</table>

* Values are expressed as mean ± SD.
<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n=22)</th>
<th>Clonidine Group (n=22)</th>
<th>Gabapentin Group (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female/Male)*</td>
<td>16/6</td>
<td>19/3</td>
<td>17/5</td>
</tr>
<tr>
<td>ASA Physical Status Class (III)*</td>
<td>13/9</td>
<td>12/10</td>
<td>11/11</td>
</tr>
<tr>
<td>Age (years)**</td>
<td>38.2 ± 10.0</td>
<td>41.8 ± 7.9</td>
<td>38.5 ± 10.1</td>
</tr>
<tr>
<td>Weight (kg)**</td>
<td>67.1 ± 12.3</td>
<td>67.6 ± 17.3</td>
<td>70.5 ± 10.2</td>
</tr>
<tr>
<td>Duration of Surgery (min)**</td>
<td>133 ± 20.5</td>
<td>126 ± 20.5</td>
<td>129 ± 20.5</td>
</tr>
<tr>
<td>Fluid administration (L)**</td>
<td>5.13 ± 0.9</td>
<td>6.45 ± 0.9</td>
<td>5.42 ± 1.0</td>
</tr>
</tbody>
</table>

a Values are expressed as mean ± SD.

* There were not significant differences between groups.
have been evaluate the gabapentin as a part of multimodal analgesia and antihyperalgesic properties [5,6]. In the recent years some studies 0.2 mg clonidine could only decrease post-operative pain intensity post-operative VAS for pain and morphine consumption compared premedication with gabapentin 900 mg had a significant decrease in size was simply too small to show any differences in the incidence of PONV. Surprisingly, this incidence increased in patients who received placebo. On the other hand, clonidine, an α2- adrenoceptor agonist with rise in incidence of PONV in clonidine group can’t be attributed to methods 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 pre-medication [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 whist 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.

References

