Preoperative Gabapentin or Clonidine Decreases Postoperative Pain and Morphine Consumption after Abdominal Hysterectomy

Mohammad Hossein Ghafari, Majid Akrami, Behrang Nouralishahi and Ali Sadegh
1Department of Anesthesiology and Critical Care, Dr. Ali Shariati Hospital,
2Department of Anesthesiology and Critical Care, Bahar Lou Hospital,
3Department of Anesthesiology and Critical Care, Arash Hospital,
Tehran University of Medical Sciences, Tehran, Iran

Abstract: Gabapentin and clonidine have been used to decrease pain after variety of surgical procedures. We investigated, in a randomized, placebo-controlled, double-blind study, the efficacy and safety of gabapentin or clonidine on pain after abdominal hysterectomy and on morphine consumption in patients. The 99 patients, ASA physical status I-II were randomized to receive either oral placebo or gabapentin 300 mg or clonidine 100 µg at night (10:00 pm) before surgery and 1 h pre-operatively. Anesthesia was induced by midazolam 0.03 mg kg⁻¹, fentanyl 2.5 µg kg⁻¹, sodium thiopental 5 mg kg⁻¹ and atracurium 0.5 mg kg⁻¹ and continued by 1 MAC isoflurane, 4 L min⁻¹ fresh gas flow (50% N₂O in O₂). Heart rate, SPO₂, mean arterial pressure, respiratory rate, opioid consumption and patient’s pain intensity (according to VAS) were recorded at the time of recovery and 1, 4, 8, 12, 24 and 48 h post-operatively. All enrolled patients received postoperative intravenous analgesia delivered through a PCA pump. Total morphine consumption and patient’s pain intensity (according to VAS) were lower in gabapentin and clonidine group in comparison to control group (p<0.05). Meanwhile, gabapentin administration significantly decreased morphine consumption after hysterectomy in comparison to clonidine. There were no significant differences between groups in case of complications. Preoperative oral gabapentin (low dose) or clonidine lowers pain score and total morphine consumption for analgesia after abdominal hysterectomy.

Key words: Gabapentin, clonidine, postoperative pain, abdominal hysterectomy, morphine, consumption

INTRODUCTION

Postoperative pain affects recovery from surgery and anesthesia (Alparslan et al., 2004). For effective postoperative pain relief, a multimodal therapy is required, which is the use of 2 or more analgesic agents or techniques in combination (Rachakrishnan et al., 2005). Combination of opioids and non opioid analgesics improve the quality of postoperative analgesia, reduce opioid requirement and associated side effects (Eckhardt et al., 2000). The under-treatment of postoperative pain has been recognized to delay patient recovery and discharge from hospital. Various noxious mechanisms are involved in postoperative pain, including sensitization of peripheral noxious nerve terminals and central neurons apparently central neuronal sensitization in particular contributes to postoperative pain hypersensitivity (Dirks et al., 2002). The mechanistic approach to pain management, based on current understandings of the peripheral and central mechanisms involved in noxious transmission, provide newer options for clinicians to manage pain effectively. Gabapentin, has a selective effect on the noxious process involving central sensitization (Lee et al., 2005). This drug is relatively well tolerated and belongs to a class of drugs that have anxiolytic properties. Each of these properties suggests that gabapentin may be useful preoperatively (Mengaoux et al., 2005). Gabapentin, a structural analog of gamma-aminobutyric acid, is a novel anticonvulsant drug and has analgesic effects on neuropathic pain, diabetic neuropathy, post herpetic neuralgia and reflex sympathetic dystrophy (Mengaoux et al., 2005; Whitley, 2005; Cutrer and Maskowicz, 2004). The use of gabapentin in the perioperative setting has been evaluated in recent studies. Some studies report promising reductions in postoperative pain and morphine consumption (Mengaoux et al., 2005), but the exact role played by gabapentin in relieving postoperative pain still remains controversial (Jiannren and Chen, 2000).

Corresponding Author: Mohammad Hossein Ghafari, Department of Anesthesiology and Critical Care, Dr Ali Shariati Hospital, Tehran University of Medical Sciences, North Karegar, P.O. Box 1411713135, Tehran, Iran
On the other hand, the α2-agonist clonidine has shown properties that are potentially beneficial for premedication to reduce sympathetic activity, to minimize fluctuations in the hemodynamic profile during anesthetic induction and to decrease anesthetic requirement for both opioid and volatile anesthetics. Clonidine provides significant benefits for preoperative anxiety and analgesia (Hidalgo et al., 2005). Clonidine has nonopioid antinoceptive properties, which might be used as an alternative to postoperative analgesia without opioid-induced side effects. The major clinical place of clonidine may thus be as an adjuvant to other analgesics, as shown in a number of studies in which clonidine has been investigated in combination with local anesthetics, opioids and ketamine (Tryba and Gehling, 2002). However, the analgesic effect of oral clonidine has been controversial. Some investigation showed that oral clonidine had not only a good analgesic effect, but also a synergic effect with opioids administered by the neuroanalgesic route (Goyagi et al., 1999). We designed this study to find out whether oral gabapentin (low dose) or clonidine reduces postoperative pain and hence, morphine consumption in patients undergoing abdominal hysterectomy. Another purpose of performing this study is to compare the effect of low dose gabapentin with clonidine on decreasing morphine consumption and pain intensity after abdominal hysterectomy according to VAS pain score.

MATERIALS AND METHODS

The protocol was approved by the institutional ethics committee and informed written consent was obtained from the patients. Ninety nine female patients, 20-60 years old, classified as ASA physical status I-II, who were candidates for elective total abdominal hysterectomy and salpingo-oophorectomy and underwent general anesthesia were selected. Cooperative patients with minimum age of 20 years old who were over 40 kg and had no psychologic problem could participate in this protocol. Patients with opioid allergy, asthma, renal insufficiency, history of peptic ulcer or bleeding diathesis, mental impairment, chronic pain, cardiovascular, hepatic or renal diseases, BMI over 35, patients who received analgesic or opioids 48 h before surgery, drug or alcoholic abusers and surgery time over 2.5 h all were excluded. Patients were visited and educated about study plan and VAS system and the way of post operative pain control and how to use the PCA system by an anesthesiologist the day before surgery. Under study drugs administration, anesthetized patients management, post operative pain assessments and patients opioid needs all were done by 3 residents of anesthesiology not involved in this study who were totally unaware of the patients groups. So, the study was done as randomized, double blind clinical trial. All patients underwent standard psychological tests and their demographic characteristics were extracted from their files. Patients were randomly assigned into 3 groups according to randomization Table 1.

Group 1 (control): Thirty three patients received placebo at 10:00 pm the night before and 1 h before, the surgery.

Group 2 (gabapentin): Thirty three patients received 300 mg gabapentin at 10:00 pm the night before and 1 h before the surgery.

Group 3 (clonidine): Thirth three patients received 100 μg clonidine at 10:00 pm the night before and 1 h before the surgery.

Patients did not take other drugs preoperatively. All the drugs in this study were in the form of capsules with appropriate code numbers. On arrival in operating room patients received saline normal 0.9% solution 7 mL kg⁻¹. Standard monitoring was established and heart rates, SPO₂, MAP were measured before induction of anesthesia. All patients were premedicated with midazolam 0.03 mg kg⁻¹ plus fentanyl 2.5 μg kg⁻¹ 3 min before induction of anesthesia. Anesthesia was induced with sodium thiopental 5 mg kg⁻¹ and atracurium 0.5 mg kg⁻¹ and was maintained with 1 MAC isoflurane inspired at a fresh gas flow rate of 4 L min⁻¹ in combination with nitrous oxide 50% in oxygen.

Further, boluses of fentanyl 1 μg kg⁻¹ and atracurium 0.2 mg kg⁻¹ were given every 30 min. Operation was performed via Pfannenstiel incision. BIS of the patients were maintained between 45 and 55. We also, maintained the end expiratory CO₂ values between 30 and 32 mmHg by mechanical ventilation. At the end of surgery neuromuscular blockade was antagonized with neostigmine 2.5 mg and atropine 1.25 mg.

After tracheal extubation patients were transferred to PACU and finally all the patients were discharged to the ward with Aldrete score of 9. Post operative pain assessment was done according to 10 cm VAS, where 0 = no pain and 10 = the worse possible pain.

Pain score, heart rate, SPO₂, MAP, RR, sedation level and total morphine dose were assessed at 1, 4, 8, 12, 24 and 48 h after surgery. All enrolled patients received postoperative intravenous analgesia delivered through a PCA pump (Gemstar, Abbott). The PCA pump was loaded with morphine hydrochloride 1 mg mL⁻¹ diluted in 0.9% NaCl and was programmed to deliver, on request, a 1 mg morphine bolus with a lock-out period of 7 min between 2
RESULTS

Ninety-nine eligible patients were evaluated from December 1st, 2006 to April 1st, 2008. Nine of the patients was excluded from the study so data of all 99 patients were analyzed. The groups were compared by age, ASA physical status, anesthesia time, weight, opioid taken during surgery and there were no significant differences among different groups (Table 1). VAS pain score comparison resulted in the following.

There were significant differences between gabapentin and clonidine groups with control group at 1, 12, 24 and 48 h post operation. VAS pain score in these hours was significantly lower in these 2 groups than in control group (Table 2). Meanwhile, gabapentin group in comparison with clonidine or control group had significantly lower VAS at 8 h after surgery (Table 2). VAS pain score was significantly lower in the gabapentin group than the control group 4 h after surgery (Table 2).

Total morphine consumption during the first 24 h in the control group, clonidine group and gabapentin group were 26.9 ± 2.28, 20.05 ± 1.28 and 15.78 ± 1.15 mg, respectively. Morphine consumption in gabapentin and clonidine groups were significantly lower than control group at 24 h post operation.

<p>| Table 1: Subjects' demographic and clinical data |</p>
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control</th>
<th>Gabapentin</th>
<th>Clonidine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (No.)</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>44.5±4.1</td>
<td>44.65±3.31</td>
<td>43.72±4.25</td>
<td>0.854</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.74±2.10</td>
<td>70.22±1.80</td>
<td>70.93±1.76</td>
<td>0.845</td>
</tr>
<tr>
<td>ASA (II)</td>
<td>27±6</td>
<td>27±6</td>
<td>26±7</td>
<td>0.867</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>duration (min)</td>
<td>135.6±7.02</td>
<td>137.5±6.5</td>
<td>97</td>
</tr>
<tr>
<td>Fernamly (µg)</td>
<td>321.9±8.29</td>
<td>307.4±6.63</td>
<td>320.6±8.42</td>
<td>0.346</td>
</tr>
</tbody>
</table>

Data are represented as mean±SEM or number of patients; All between groups differences are significant (one-way ANOVA, Tukey)

<p>| Table 2: Subjects' pain score |</p>
<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Control</th>
<th>Gabapentin</th>
<th>Clonidine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 *</td>
<td>6.39±0.48</td>
<td>4.24±0.54</td>
<td>4.48±0.58</td>
<td></td>
</tr>
<tr>
<td>4 †</td>
<td>5.81±0.40</td>
<td>4.25±0.35</td>
<td>4.62±0.44</td>
<td></td>
</tr>
<tr>
<td>8 †</td>
<td>6.10±0.47</td>
<td>3.51±0.31</td>
<td>4.86±0.41</td>
<td></td>
</tr>
<tr>
<td>12 *</td>
<td>4.94±0.40</td>
<td>2.92±0.32</td>
<td>3.43±0.38</td>
<td></td>
</tr>
<tr>
<td>24 *</td>
<td>3.48±0.40</td>
<td>1.81±0.30</td>
<td>1.76±0.30</td>
<td></td>
</tr>
<tr>
<td>48 *</td>
<td>2.17±0.38</td>
<td>0.64±0.19</td>
<td>1.12±0.28</td>
<td></td>
</tr>
</tbody>
</table>

Data are represented as mean±SEM, Pain score (cm); *: Significant difference between control group with gabapentin and clonidine groups (one-way ANOVA, Tukey); †: Significant difference between Control group with Gabapentin group (one-way ANOVA, Tukey); †: Significant difference between gabapentin group with control and clonidine groups (one-way ANOVA, Tukey)

<p>| Table 3: Subjects' complications |</p>
<table>
<thead>
<tr>
<th>Complications</th>
<th>Control (n=33)</th>
<th>Gabapentin (n=33)</th>
<th>Clonidine (n=33)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>0.389</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td>0.087</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.867</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0.401</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0.587</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0.318</td>
</tr>
</tbody>
</table>

Data are represented as number of patients; There were no significant differences in complications among the study groups

On the basis of ANOVA test, there is a significant difference between gabapentin and clonidine groups with control group (p<0.05). Due to Post Hoc Tukey test, there is a significant difference in the amount of morphine consumption in the first 24 h after surgery among gabapentin and clonidine groups (p<0.05). In the 2nd 24 h after surgery, no significant statistic differences were noted between the 3 groups.

The most common complications during the study were nausea and vomiting. There were no significant differences in complications among the study groups (Table 3). Meanwhile, there were no significant differences in pulse rate and blood pressure preoperation and 1 h post operation among the groups.

DISCUSSION

The effect of low dose gabapentin on decreasing postoperative morphine consumption has not been analyzed yet. Although, there are studies regarding gabapentin and clonidine effects on decreasing
postoperative pain, no randomized control trial has been
done for comparing these 2 drugs. The results from our
study administering oral gabapentin (low dose) or
clonidine before abdominal hysterectomy comparing
to the group receiving placebo show a VAS pain
score reduction in the former. Postoperative opioid
consumption was also reduced without any more
complications in relation to the control group. Despite
recognition of the importance of effective pain control, up
to 70% of patients still complain of moderate to severe
pain postoperatively (Pyati and Gun, 2007). Morphine is
the gold standard for treating severe pain. However, a
major drawback of morphine is the need to increase the
dose steadily, as a result of either increased pain or
developed tolerance. The use of opioids is limited both
by side effects (such as sedation, nausea, vomiting,
constipation and respiratory depression) and by the fact
that certain types of pain respond poorly to opioid
(Eckhardt et al., 2000). Opioids are administered with one
or more nonopioid analgesics to obtain a more favorable
balance between analgesia and side effects. Various
nociceptive mechanisms are involved in postoperative
pain, including sensitization of peripheral nociceptive
nerve terminals and central neurons. In particular,
central neuronal sensitization apparently contributes to
postoperative pain hypersensitivity (Woolf and Chong,
1993). Gabapentin is a novel antiepileptic agent that
binds to alpha 2 delta subunit of voltage-dependent
calcium channels (Field et al., 1997). Gabapentin is a
structural analog of GABA, which readily crosses the
blood-brain barrier when given systemically. It does no
bind to GABA receptors (Jiannen and Chen, 2000).
Gabapentin is effective for neuropathic pain, diabetic
neuropathy, postherpetic neuralgia, reflex sympathetic
dystrophy, acute neuritis, glossopharyngeal neuralgia,
multiple sclerosis and cancer related neuropathic pain
(Menigaux et al., 2005, Whitley, 2005; Cutrer and
Maskowitz, 2004; Mao and Chen, 2000).

One study suggests that both pharmacodynamic
and pharmacokinetic interaction between morphine
and gabapentin lead to increased analgesic effects
(Eckhard et al., 2000). Multimodal analgesia with
gabapentin and local anesthetics reduced acute and
chronic pain after breast surgery for cancer
(Fassoulaki et al., 2005). A single dose of 1200 mg oral
gabapentin administered preoperatively result in a 50% reduction in postoperative morphine consumption
and pain 2 and 4 h after radical mastectomy (Dirks et al.,
2002). But in our study the patients were evaluated for 48 h
postoperatively. VAS pain score in gabapentin and
clonidine at 1, 12, 24 and 48 h after operation was
significantly different with control group. Preoperative
oral gabapentin decreased pain score in the early
postoperative period and reduced postoperative morphine
consumption in patients with spinal surgery, while
decreasing some of morphine-associated side effects
(Turan et al., 2004), but in our study, significant difference
among different groups were not found after evaluating
complications. In some studies significant reduction in
postoperative analgesic requirements during the first
24 h after surgery was noted (i.e., abdominal
hysterectomy, spinal surgery, vaginal hysterectomy,
radical hysterectomy, radical mastectomy and
laparoscopic cholecystectomy).

In other studies, same effects were found after 2 days
(mastectomy) (Rowbotham, 2006). In our study, morphine
consumption in gabapentin and clonidine groups was
significantly lower during the first 24 h after surgery
compared to the control group too (p=0.05). VAS pain
score in clonidine or gabapentin groups was less than
control group in all evaluating postoperative hours. There
were significant differences at 1, 12, 24 and 48 h. In our
study, gabapentin 600 mg (300 mg in 2 separated dose)
was administered and this dose was effective in reducing
morphine consumption and VAS pain score but some
other studies showed opposite results. Gabapentin 600
mg had no effect on hyperalgesia associated with an
ultraviolet induced inflammation (Rowbotham, 2006).

In a study, investigating day-case laparoscopic
procedure, gabapentin 300 mg had no significant
effect on postoperative pain (Rowbotham, 2006;
Radhakrishnan et al., 2005). In another study, a single
preoperative dose of gabapentin 800mg does not augment
postoperative analgesia in patients given interscalene
brachial plexus blocks for arthroscopic shoulder surgery
(Adam et al., 2006). Differences between results can be
attributed to differences in types of surgery and in use of
different types of analgesics. In another study,
gabapentin in a total dose of 3000 mg, administered
before and during the first 24 h after abdominal
hysterectomy reduced morphine consumption with 32%,
without significant effects on pain score (Dierking et al.,
2004). In our study, VAS pain score and opioid
consumption were lower in clonidine group and
gabapentin group compared to the control group and the
patients experienced no more complications than usual.

The (α2) agonists are assuming greater importance as
anesthetic adjuvant and analgesic. Their primary effect
is sympatholytic. They reduce peripheral norpinephrine
release by stimulation of presynaptic inhibitory (α2)
adenoreceptors.

They inhibit central neural transmission in the dorsal
horn by presynaptic and postsynaptic mechanisms
and in spinal preganglionic sympathetic neurons
(Eisenach et al., 1996). In recent years (α2), agonists have found wider applications, particularly in the field of anesthesia and pain management. It has been noted that these agents can enhance analgesia provided by traditional analgesics, such as opiates and may result in opiate-sparing effects (Whitley et al., 2005; Howard and Jennifer, 2001; Khan et al., 1999). Several experimental studies have shown that clonidine may improve the analgesic effect of anti-inflammatory agents and also have significant peripheral antinociceptive effects (Tryba and Gehling, 2002; Khan et al., 1999).

In one study, the analgesic effects of 2 μg kg⁻¹ clonidine intramuscularly in adenotonsillectomy surgery were evaluated and no analgesic properties for clonidine were proved (Freeman et al., 2002). In another study, adding clonidine 2 μg mL⁻¹ to ropivacaine solution for aggravating post operative analgesia in interscalene block has not been successfully shown (Ilfield et al., 2005). Many other studies have shown the effectiveness of clonidine in pain reduction. It seems that the kind of surgery, age spectrum of the patients and route and dosage of clonidine influence the result in different studies.

Oral clonidine 5.5 μg kg⁻¹ has been effective in pain control after propofol injection (Yoshikawa et al., 2001). Other study has shown the effectiveness of intravenous clonidine in delaying the onset of pain and need for first request opioid dose (Jean et al., 1991). Other investigations showed that oral clonidine had not only a good analgesic effect, but also a synergistic effect with opioids administered by the neuroaxial route (Goyagi et al., 1999; Goyage and Nishikawa, 1996). Whether, the analgesic effect of clonidine varies due to the kind of surgical procedure or by route of administration is a matter to be investigated (Hidalgo et al., 2005). Oral dose between 100 and 300 μg have been used for premedication. Doses >150 μg resulted in more adverse effects. Bradycardia and hypotension were adverse effects of (α2) adrenergic agonists (Pertovaara et al., 1994). The patients in our study never experienced hypotension and cardiac arrhythmias. Of course all of our patients were ASA physical status I-II with no heart diseases, so additional studies must be done in patients with cardiac diseases.

CONCLUSION

We found that administration of low dose gabapentin (600 mg) or clonidine (200 μg) preoperatively was effective in lowering postoperative VAS pain score and opioid consumption for analgesia. On the other hand, it was also shown that gabapentin (600 mg) significantly decreases morphine consumption and postoperative pain intensity after abdominal hysterectomy comparing to clonidine.

REFERENCES


