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

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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% N_2O in O_2). Heart rate, SPO_2, 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 (Alparsalan *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 (Radhakrishnan *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 nociceptive mechanisms are involved in postoperative pain, including sensitization of peripheral nociceptive nerve terminals and central neurons apparently central neuronal sensitization in particular contributes to postoperative pain hyper-sensitivity (Dirks *et al*., 2002). The mechanistic approach to pain management, based on current understandings of the peripheral and central mechanisms involved in nociceptive transmission, provide newer options for clinicians to manage pain effectively. Gabapentin, has a selective effect on the nociceptive 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 (Menigaux *et al*., 2005). Gabapentin, a structural analog of gama-aminobutyric acid, is a novel anticonvulsant drug and has analgesic effects on neuropathic pain, diabetic neuropathy, post herpetic neuralgia and reflex sympathetic dystrophy (Menigaux *et al*., 2005; Whitley, 2005; Cutrer and Maskowitz, 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 (Menigaux *et al*., 2005), but the exact role played by gabapentin in relieving postoperative pain still remains controversial (Jianren and Chen, 2000).

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On the other hand, the α_2-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 nonopiate antinociceptive 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 analgesic, 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 neuroaxial 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 salpingoophorectomy 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, SPO_2, 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 CO_2 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 worst possible pain.

Pain score, heart rate, SPO_2, 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

consecutive boluses (Reservoir volume = 100 mL and continuous flow = 0). We used PCA intravenous pump under monitoring in recovery room (Chumbley *et al*., 1998). The patient could freely trigger her pump in case of pain sensation and repeat it until her pain was relieved. The patients were visited by another resident of anesthesiology at 1, 4, 8, 12, 24 and 48 h and the amount of morphine displayed on the PCA pump monitor was recorded on the patients control sheet. Sedation was assessed according to Ramsay sedation scale. Complications such as nausea and vomiting, constipation, dizziness, somnolence and etc. were recorded. Nausea and vomiting were treated with metoclopromide (10 mg). The treatment was repeated if necessary. No other analgesia was administered for the patients.

Sample size of 33 patients by group was calculated to detect a significant difference of 30% or more in morphine consumption with a power of 85% and a significance level of 5%. Data are expressed as mean±SEM. Parametric data were analyzed with one-way analysis of variance or (chi-square) χ^2 as appropriate. When overall among group significance was present, pair-wise multiple comparisons of means testing (Tukey's method) or (chi-square) χ^2 or Fisher's exact test was performed as appropriate. Statistical calculations were performed using SPSS (SPSS Inc., Chicago, IL) ver. 14.0. Differences were considered significant at $p<0.05$.

RESULTS

Ninety nine eligible patients were evaluated from December 1st, 2006 to April 1st, 2008. None of the patients was excluded from the study so data of all 99 patients were evaluated. 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 26.94±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.

Table 1: Subjects' demographic and clinical data

Characteristics	Control	Gabapentin	Clonidine	p-value
Number (No.)	33	33	33	-
Age (year)	44.55±1.12	44.65±1.31	43.72±1.25	0.854
Weight (kg)	71.74±2.10	70.22±1.80	70.93±1.76	0.845
ASA (I/II)	27/6	27/6	26/7	0.867
Anesthesia duration (min)	135.65±7.02	137.50±5.97	126.00±6.74	0.439
Fentanyl (μg)	321.97±8.29	307.43±6.63	320.69±8.42	0.346

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

Table 2: Subjects pain score

Time (h)	Control	Gabapentin	Clonidine
1*	6.39±0.48	4.24±0.54	4.48±0.58
4†	5.81±0.40	4.25±0.35	4.62±0.44
8‡	6.10±0.47	3.51±0.31	4.86±0.41
12*	4.94±0.40	2.92±0.32	3.43±0.38
24*	3.48±0.40	1.81±0.30	1.76±0.30
48*	2.17±0.38	0.64±0.19	1.12±0.28

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)

Table 3: Subjects complications

Complications	Control (n = 33)	Gabapentin (n = 33)	Clonidine (n = 33)	p-value
Nausea	7	5	3	0.389
Vomiting	9	4	3	0.087
Dizziness	2	2	1	0.867
Constipation	2	2	0	0.401
Somnolence	3	2	1	0.587
Pruritus	4	2	1	0.318

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 (Jianren 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 laparascopic 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 laparascopic 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 (α_2) agonists are assuming greater importance as anesthetic adjuvant and analgesic. Their primary effect is sympatholytic. They reduce peripheral norepinephrine release by stimulation of prejunctional inhibitory (α_2) adrenoreceptors.

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 (α_2), 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 (Ilfeld *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 synergic 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 (α_2) 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.

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