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Comparing Oral Gabapentin Versus Clonidine as Premedication on Early Postoperative Pain, Nausea and Vomiting after General Anesthesia

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Abstract: This study was designed to compare the effects of small dose of oral gabapentin with clonidine as premedication; on early postoperative pain, nausea and vomiting (PONV) in patients undergoing elective abdominal surgeries under general anesthesia. In a randomized placebo controlled study, 120 ASA I and II patients scheduled for elective abdominal surgeries were randomly assigned to receive either 0.2 mg oral clonidine (n = 40), 300 mg gabapentin (n = 40) or placebo (n = 40) 1 h before surgery. They anesthetized with the same technique. Demographic data, post operative pain scores, nausea and vomiting and total morphine consumption by PCA pump after the operation were recorded in the recovery room and during first 6 h after the operation. VAS score more than 3 points assumed clinically important for postoperative pain management. Demographic data was not statistically different between the study groups. Two patients in gabapentin compared with 13 patients in Clonidine group (p = 0.01) and 29 patients in placebo group (p = 0.014) had VAS >3 in recovery room. The mean morphine consumption were 4.75±7.5 mg in placebo, 1.95±5.51 mg in Clonidine and 1.56±1.5 mg in gabapentin group in recovery (Clonidine vs placebo, p = 0.032; gabapentin vs placebo, p = 0.024; gabapentin vs Clonidine, p = 0.045). These measurements were 18±15.8, 13.1±12.6, 12.1±12.9 mg during first 6 h after operation; in placebo, Clonidine and gabapentin groups, respectively (Clonidine vs placebo, p = 0.017; gabapentin vs placebo, p = 0.023; gabapentin vs Clonidine, p = 0.067). PONV was not statistically different between the study groups in the recovery room and during first 6 h after the operation. This study showed that oral premedication with 300 mg gabapentin reduce postoperative pain and total morphine consumption but not PONV during recovery and first 6 h after abdominal surgeries.

Key words: Gabapentin, clonidine, pain, nausea, vomiting, postoperative

INTRODUCTION

Prevention and treatment of postoperative pain and complications such as nausea and vomiting, continues to be a major challenge in postoperative care and plays an important role in the early mobilization and well-being of the surgical patient.

Opioid analgesics, with their well-known side-effects, continues to represent a cornerstone in postoperative pain control and testing new analgesics as well as combinations of analgesics in order to reduce the need for opioids, is a key area in acute pain research (Rose and Kam, 2002).

Gabapentin is an anticonvulsant that has antinociceptive and antihyperalgesic properties. In pain models it has shown anti-hyperalgesic properties, possibly by reducing central sensitization, a prerequisite for postoperative hyperalgesia. It binds the $\alpha^2\delta$ subunits of voltage dependent calcium ion channels and blocks the development of hyperalgesia and central sensitization (Rose and Kam, 2002).

After a single oral dose of 300 mg gabapentin, mean maximum plasma concentrations attained in 2-3 h. Absorption kinetics of gabapentin are dose dependent, possibly due to a saturable transport system. Bio-availability of a single 300 mg oral dose of gabapentin is 60% and decreases with increasing dose. Elimination of gabapentin is by renal clearance and is about 5-7 h after a single oral dose of 200 to 400 mg (Goa and Sorkin, 1993).

The α^2-agonist clonidine has also shown properties that are potentially beneficial for premedication to reduce sympathetic activity, the incidence of shivering and oxygen consumption during recovery from anesthesia, to decrease anesthetic and analgesic requirement and minimize postoperative pain, nausea and vomiting (Ghignone *et al*., 1987; Quintin *et al*., 1991).

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Recently an open clinical study demonstrated the anti-emetic effect of gabapentin in chemotherapy-induced acute (within 24 h) and delayed onset (days 2-5) of nausea and vomiting; Mitigation of tachykinin neurotransmitter activity by gabapentin has been postulated to play a role (Guttuso *et al*., 2003).

In the study by Pandey *et al.* (2006) on two hundred and fifty patients scheduled for laparoscopic Cholecystectomy, gabapentin as premedication effectively suppresses nausea and vomiting and post-operative rescue analgesic requirement (Pandey *et al*., 2006).

Therefore we conducted a study to compare the effects of 300 mg oral gabapentin doses with 0.2 mg clonidine as premedication; on early postoperative pain, nausea and vomiting in patients undergoing elective abdominal (gynecological or general) surgeries under general anesthesia.

MATERIALS AND METHODS

This randomized, double-blind clinical trial was performed in Dr. Shariati Hospital of Tehran University of Medical Sciences in 2007. The study protocol conformed to the ethical guidelines of the 1989 Declaration of Helsinki and was approved by the investigational review board of Dr. Shariati hospital.

Hundred and twenty ASA physical status I or II patients aged 20 to 60 year scheduled to undergo elective abdominal (gynecological and general) surgeries under general anesthesia, were studied and written informed consent was obtained from all subjects. Patients with mental impairment, chronic pain, history of cardiovascular and psychiatric disease, use of psychotropic drugs and pregnancy were excluded.

The patients were randomly assigned to receive either 0.2 mg oral clonidine (C group, n = 40), 300 mg gabapentin (G group, n = 40) or placebo (P group, n = 40) 1 h before surgery. Randomization was based on computer-generated codes that were concealed until interactions were assigned.

The day before surgery, patients were instructed about the Verbal Analog Scale (VAS) in which 0 = no pain and 10 = worst pain imaginable and how to use the PCA pump for postoperative pain management (Pain Management Provider, Abbott Laboratories and Eczacibasi-Baxter, Ireland).

Drugs were given by an independent anesthetist in the ward, there fore both the anesthesiologist and the patient were blinded to the group assignment.

On arrival in the operating room, ECG electrodes and non Invasive Blood Pressure (NIBP) monitor were applied and oxygen saturation was monitored by pulse oxymeter.

Patients were anesthetized with the same technique including fentanyl 3 μg kg^{-1} (Amp 10 mL, Fentanyl-Janssen™, Belgium), thiopentone 5 mg kg^{-1} (Vial 1 g, Biochemie GmbH, Kundl-Austria) and atracurium 0.5 mg kg^{-1} (Amp 10 mg mL^{-1} Mayne Pharma Plc™, UK) to facilitate orotracheal intubation. General anaesthesia was maintained with isoflurane (0.4-1.6%) and 50% nitrous oxide in oxygen. Intra operative analgesia was maintained by fentany l μg kg^{-1} h^{-1}.

Neuromuscular blockade was then reversed with intravenous neostigmine 2.5 mg and atropine 0.5 mg. Demographic data, duration and type of surgery was recorded by resident of anesthesia. Postoperative nausea and vomiting (PONV), total amount of morphine consumption along with VAS scores at rest and on movement (deep breathing and coughing) were also recorded in the recovery, first and 6 h after the operation; by trained nurse staff who was blinded to randomization.

Postoperative PCA orders were written in a standardized fashion and were activated in the recovery room. Patients were treated by morphine sulfate as opioid titration with the following protocol: MS 2 mg IV Q 10 min, up to VAS < 3.0. The patients who were severely sedated were omitted from the opioid titration. PCA Pump set-up was as follow: Bolus Dose: 1 mg and an intermittent dose of 0.02 mg kg^{-1}. The lockout interval was set at ten minutes; there was no continuous infusion.

Statistical analysis: A sample size of 40 patients in each group will be sufficient to detect a 30% difference in the incidence of postoperative pain between the study groups assuming power of 85% and a significance level of 5%. Normality of distribution was tested by Kolmogorov Smirnov test. Data were analyzed by SPSS version 11.5 (SPSS Inc., Chicago, IL) and were compared by using one way ANOVA and post hoc-Tukey tests, Kruskal wallis and Chi-square. $p<0.05$ was considered statistically significant.

RESULTS

Demographic data, duration and type of surgery (gynecologic/general) were not statistically different between the study groups (Kruskal wallis, one way ANOVA, Chi-square, Table 1).

VAS score more than 3 points assumed clinically important for postoperative pain management.

Two patients in gabapentin compared with 13 patients in Clonidine and 29 patients in placebo group had VAS >3 in recovery room (Chi-square, $p = 0.001$ and $p = 0.014$, respectively).

Table 1: Comparing demographic data, type and duration of surgery between the study groups

Variables	Placebo (n = 40)	Clonidine (n = 40)	Gabapentine (n = 40)
Age (year)	40.1±11.9	35.2±12.9	39.9±12.6
Weight (kg)*	54.5±18.2	58.1±14.3	57.7±13.4
ASA (I/II)	18/22	20/20	19/21
Surgery time (min)*	90.2±25.7	91.6±26.7	95.5±25.9
Surgery type (Gyn/Gen†)	25/15	23/17	24/16

*Data are presented as mean±SD, †Gynecological versus general surgeries

Table 2: Comparing VAS scores more than three points in the recovery, first and 6 h after the operation, between the study groups

VAS>3	Placebo No. (%)	Clonidine No. (%)	Gabapentin No. (%)	p-value
In the recovery	29 (72.5)	13 (32.5)	2 (5)	0.001
1st h after operation	37 (92.5)	36 (90)	19 (47.5)	0.001
Six h after operation	39 (97.5)	37 (92.5)	33 (82.5)	0.027

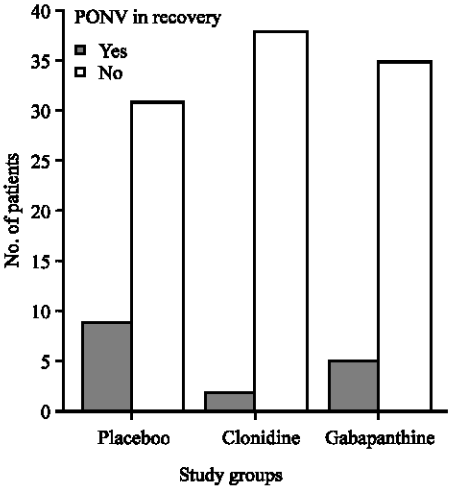

Fig. 1: Comparing postoperative nausea and vomiting in recovery room between the study groups

Patients in placebo and Clonidine group had statistically more pain than gabapentin group during first 6 h after operation (Chi-square, $p<0.05$, Table 2).

The mean morphine consumption were 4.75±7.5 mg in placebo, 1.95±5.51 mg in Clonidine and 1.56±1.5 mg in gabapentin group during recovery (Clonidine vs placebo, $p = 0.032$; gabapentin vs placebo, $p = 0.024$; gabapentin vs Clonidine, $p = 0.045$).

These measurements were 18±15.8, 13.1±12.6, 12.1±12.9 mg during first 6 h after operation; in placebo, Clonidine and gabapentin groups, respectively (Clonidine vs placebo, $p = 0.017$; gabapentin vs placebo, $p = 0.023$; gabapentin vs Clonidine, $p = 0.067$) (One way ANOVA, Post Hoc Tueky test).

No patients received any other oral or IV rescue medication.

PONV was not statistically different between the study groups in the recovery room and during first 6 h after the operation (Chi-square, $p>0.05$, Fig. 1, 2).

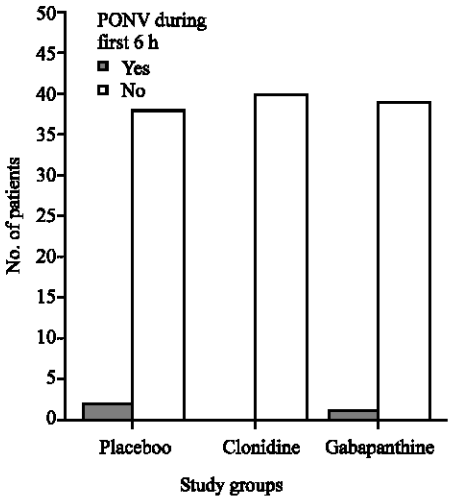

Fig. 2: Comparing postoperative nausea and vomiting during first 6 h after the operation between the study groups

Two patients in gabapentin group had dizziness and headache and 3 patients in Clonidine group had dry mouth preoperatively.

DISCUSSION

This study showed that oral premedication with 300 mg gabapentin reduce postoperative pain and total morphine consumption compared with 0.2 mg clonidine; but PONV was not statistically different between the study groups during recovery and first 6 h after abdominal surgeries.

The main aim in combining different analgesic drugs is to obtain synergistic or additive analgesia, allowing a smaller dose of each drug with an improved safety profile. This can be achieved by combining analgesics acting at different locations (e.g., centrally and peripherally acting analgesics). Anti-hyperalgesic drugs such as gabapentin may have a role in postoperative pain and the combination with other antinociceptive drugs may produce synergistic analgesia effects (Turan *et al*., 2004).

Gabapentin enhanced the analgesic effect of morphine in healthy volunteers and the combination produced better analgesia in comparison with morphine alone (Eckhardt *et al*., 2000; Turan *et al*., 2004).

In this study we compared the effect of oral gabapentin with Clonidine and placebo on acute postoperative pain, total postoperative morphine consumption and if they have anti emetic effects or not.

We found that both gabapentin and Clonidine; reduced postoperative pain and total morphine consumption compared with placebo group, but

gabapentin group was more effective than Clonidine group. Present results for gabapentin was similar to results presented in a systemic review about qualitative and quantitative effects of gabapentin on postoperative pain presented by Mathiesen *et al.* (2007).

Turan *et al.* (2004) investigated the efficacy of gabapentin on postoperative pain and tramadol consumption after abdominal hysterectomy in 50 patients who were randomized to receive either oral placebo or gabapentin. They found that preoperative oral gabapentin decreased pain scores and postoperative tramadol consumption in patients after abdominal hysterectomy and there were no differences between groups in adverse effects.

These finding were similar to our study but with different doses (Turan *et al.*, 2004).

We found that 9 patients in placebo, 2 patients in clonidine and 5 patients in gabapentin during recovery and two, zero and one patient in the same groups, respectively had PONV during first 6 h after surgery that was not statistically different.

These results were not correlated with Pandy *et al.* (2006) study in which 600 mg gabapentin as premedication for laparascopic cholecystectomy effectively suppresses nausea and vomiting. These difference may be due to their different doses of gabapentin compared with present study.

Gabapentin has been also reported by Guttuso *et al.* (2003) to be effective in the treatment of emesis in patients receiving cytotoxic drugs. The precise mechanism of gabapentin in the prevention of nausea and vomiting induced by cytotoxic drugs is not known but mitigation of tachykinin neurotransmitter activity has been postulated to be useful. There is evidence that tachykinins activity is part of the pathogenesis of chemotherapy-induced emesis in ferrets and a selective tachykinins-receptor antagonist improves both acute and delayed nausea and emesis induced by chemotherapy (Guttuso *et al.*, 2003).

The lower incidence of PONV in the gabapentin group in Pandey *et al.* (2006) study may be due to a decrease in opioid-related side effect. It will be interesting to see if gabapentin reduces the incidence of PONV when compared with placebo in patients undergoing non-painful procedures under general anesthesia.

The authors recommend further study with different doses of gabapentin for efficacy of this drug on postoperative pain and PONV reduction.

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