Comparison Effect of Pre-Emptive Gabapentin and Oxycodone on Pain After Abdominal Hysterectomy: A Double Blind Randomized Clinical Trial

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Abstract- Gabapentin is popular analgesic adjuvants for improving postoperative pain management. The aim of this study was to compare the preventive effects of pre-emptive oxycodone and gabapentin on acute pain after elective abdominal hysterectomy. One hundred patients undergoing abdominal hysterectomy were randomly assigned to oxycodone group received 10 mg of oxycodone and gabapentin group received 10 mg of gabapentin 1 hour before surgery. The anesthetic technique was standardized, and the postoperative assessments included the amount of meperidine consumption, PONV and VAS for postoperative pain at arrival to recovery, 6, 12 and 24 h after surgery. Bleeding loss assessed during surgery. Postoperative pain scores were significantly lower in the gabapentin group compared with the oxycodone group. (P=0.0001) The total meperidine used in the gabapentin group was significantly less than in the oxycodone group. Postoperative nausea and vomiting (PONV) and blood loss during surgery were significantly decreased in gabapentin group. Based on the results of this study, Pre-emptive use of gabapentin 1200 mg orally, significantly decreases postoperative pain and PONV, rescues analgesic requirements and also bleeding loss during surgery in patients who undergo abdominal hysterectomy. Significant side effects were not observed.

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Keywords: Gabapentin; Pain relief; Oxycodone; PONV; Bleeding loss; Abdominal hysterectomy

Introduction

Early and late relief postoperative pain is an important challenge for anesthesiologists and surgeons. Thus, not only surgical procedures, preoperative interventions, need to be examined in clinical trials (1). Postoperative pain affects recovery from anesthesia and surgery (2).

Prevention and treatment of postoperative pain and complications such as nausea and vomiting, keep being significant challenge in postoperative care and plays an important role in the early mobilization and well-being of the surgical patient. Given the plurality of mechanisms involved in postoperative pain, a multimodal analgesia regimen using a combination of opioid, non-opioid analgesics, and regional anesthesia has become the treatment of choice for simplifying the recovery period (3).

Opioid analgesics, with their side-effects, likewise use in postoperative pain control; and testing new analgesics also combinations of analgesics in order to decrease the demand for opioids is a key region in acute pain research (4).

Management of postoperative pain due to reducing suffering and due to earlier mobilization, shortened hospital stay, decreased hospital costs and raised patient's satisfaction. Generally, the goal in all patients is to minimize exposure to the side effects of relatively high doses of systemic narcotics, while supplying sufficient analgesia (5-7).

Gabapentin binds to the α2 δ subunit of voltage-gated calcium channels, so preventing the release of nociceptive neurotransmitters including noradrenaline, substance P, and glutamate (8).

Evidence offered that, in addition to being an effective analgesic for patients with chronic pain

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syndromes or, neuropathic, gabapentin also provides effective postoperative analgesia when received before surgery (9-10).

Gabapentin is an anticonvulsant that has been shown to be effective in the treatment of chronic pain and neuropathic (11-12).

The analgesic effect of its perioperative use has not been entirely definite (9). Hysterectomy is one of the most major gynecologic surgery (10) thus we designed the present study to investigate whether the pre-emptive use of gabapentin 900 mg orally could decrease postoperative pain, meperidine consumption and postoperative nausea and vomiting (PONV) during 24 h after hysterectomy.

Materials and Methods

In this double blinded randomized clinical trial, between 2013-2014, 100 patients who were candidate for abdominal hysterectomy in Rasoul Hospital, Tehran, Iran, was enrolled in the study. All ASA class I-II, patients that candidate for abdominal hysterectomy, 18-60 aged, Consent to participate in the study enrolled in the study. Those without informed consent, Allergy to study drugs, History of drug abuse or alcohol dependence, Neuromuscular disease or a history of neurological or psychiatric, history of chronic pain syndromes excluded from the study.

The study protocol was approved by ethics committee of Iran University of Medical Sciences, and the trial is registered at Iranian Registry of Clinical Trials, number IRCT139208011580N2. Each patient signed informed consent before enrollment in the study. The selected patients were randomly divided into two groups, oxycodone group (n=50) and gabapentin group (n=50), using block randomization in blocks containing four patients and non-blinded. The oxycodone group received oral oxycodone capsules 10 mg (Co: Razak-Iran), and gabapentin group received oral gabapentin capsules 900 mg (Co: Razak-Iran) 1 hour before induction of anesthesia.

For all the patients, the operation and anesthesia were performed by the same surgeon and anesthetist. After pre-oxygenation for 5 minutes, and access to IV line and under essential monitoring including automated non-invasive blood pressure monitoring (NIBP), the baseline hemodynamic parameters such as HR, systolic and diastolic blood pressure, and mean arterial pressure recorded using automated non-invasive blood pressure monitoring.

All patients' 0.01 mg/kg midazolam and 3 micro/kg fentanyl were administered preoperatively.

Anesthesia induction performed in all patients in the same method, using Thiopental sodium (Thiopentone, Sandoz GmbH, Koundl, Astra) 4 mg/kg and after the loss of consciousness, atracurium 0.5 mg/Kg/IV administrated. Anesthesia maintained with propofol 100 µg/Kg/IV/min and intermittent doses of atracurium administered with Controlled breathing. If necessary, 50 micro fentanyl were administered.

After surgery, another physician who was not the part of the anesthesia team and not informed of the drug group assignment recorded the occurrence of PONV and pain by asking the patients.

Pain score, after arrival in the recovery, at 1, 4, 8, 12 and 24 h after surgery, using the VAS (where 0=no pain to 10=worst possible pain) at rest for pain assessment.

When VAS scores were >3, for the patient 0.3-0.4 mg of meperidine was given bolus. Calculated total blood volume of blood loss during surgery is collected in suction, and the number of blood gases was obtained. The occurrences of postoperative side effects such as PONV were recorded at follow-up intervals.

All data were recorded in prepared checklists and were coded for statistical analysis.

Results were reported as mean±standard deviation (SD) for quantitative variables and percentages for categorical variables. The groups were compared using the Student's t-test and repeated measurement ANOVA for continuous variables and the Chi-square test (or Fisher's exact test if required) for categorical variables. All the statistical analysis were performed using SPSS version 19 (SPSS Inc, Chicago, IL, USA) for Windows. $P<0.05$ were considered statistically significant.

Results

Table 1 shows a summary of the baseline characteristics of both groups. There was no significant difference between the groups regarding any of the studied parameters. Mean arterial blood pressure; heart rate values did not differ between the groups at any of the measured time intervals.

The VAS pain scores were significantly lower in the gabapentin group compared with the oxycodone group at all measurements for 24 h ($P=0.0001$) (Figure 1).

The mean amount of meperidine used in the oxycodone group (47.2±14.3 mg) was significantly more than in the gabapentin group (25±0 mg, $P=0.0001$) (Figure 2).

The mean amount of bleeding loss in the oxycodone

group (415±50.8 mL) was significantly more than in the gabapentin group (333.4±38.09 mL, *P*=0.0001) (Figure 3).

In addition, none of the patients in the gabapentin group have PONV, and PONV were significantly more common in the oxycodone group compared with the gabapentin group (*P*=0.0001).

Table 1. The demographic and clinical data of the study patients

Variable	Gabapentin(n=30)	Oxycodone (n=30)	*P**
Age	47.8±8.1	49.4±9.1	0.356
Weight (Kg)	68.7±13.2	68.1±4.1	0.803
Duration time of surgery (h)	2.75±0.45	3±0.4	0.004
Duration time of anesthesia (min)	77±10	76±9	0.057
ASA Class I	25 (50%)	22 (44%)	0.216
ASA Class II	25 (50%)	28 (56%)	

* Student's t-test, *P*<0.05 assumed meaningful

Table 2. Mean VAS in different time after surgery between two groups

Variable	Gabapentin(n=30)	Oxycodone (n=30)	*P**
Arrival time to recovery	**3.2±0.4**	**3.9±1.2**	**0.015**
6 (h)	**4.7±0.9**	**4.9±1.06**	**0.884**
12 (h)	**4.7±1.2**	**5.3±1.2**	**0.006**
24 (h)	**2.9±0.6**	**3.7±1.3**	**0.001**

* Student's t-test, *P*<0.05 assumed meaningful

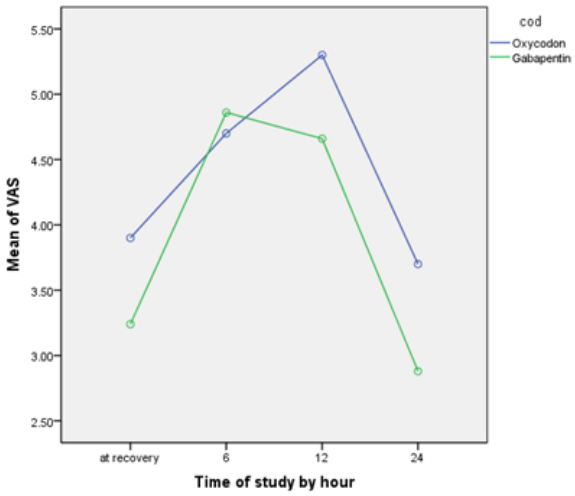

Figure 1. VAS scores of patients in different postoperative time between two groups (*P*=0.0001)

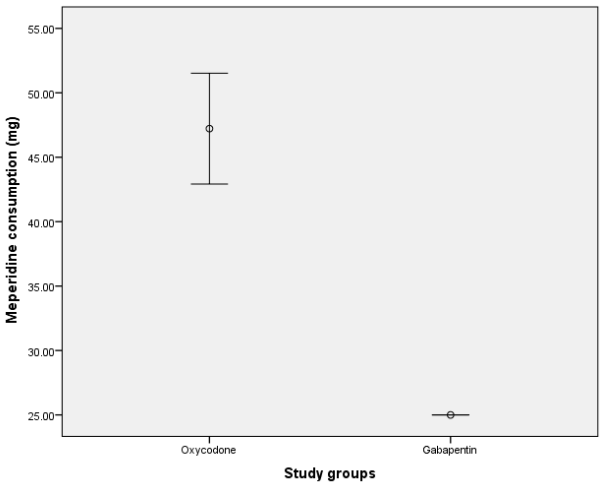

Figure 2. Postoperative meperidine consumption in two groups (*P*=0.0001)

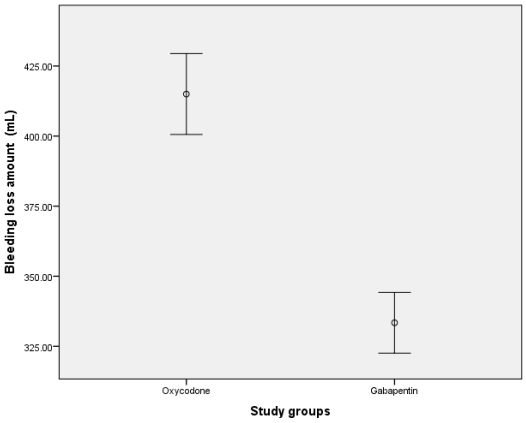

Figure 3. Intraoperative bleeding loss amount in two groups (*P*=0.0001)

Discussion

The present study showed that 900 mg gabapentin administered 1 h before surgery reduced pain and opioid consumption. Pain after surgery is due to both surgical stimulation and neurogenic factors.

Several methods are used to reduce postoperative pain such as non-steroidal anti-inflammatory drugs (NSAIDs), opioids, pre-emptive medications and local anesthetics (13).

Gabapentin is firstly used as an anticonvulsant drug, but recent studies have demonstrated that also has antihyperalgesic effects especially before surgery process (14).

In animal studies have been shown that pre-operative treatment with gabapentin may prevent pain more effectively than when received after surgery (15).

Probably, gabapentin mechanism through postsynaptic binding to the α2 and μ1 subunits of the voltage-dependent calcium channels of the dorsal horn neurons in the spinal cord, decreasing calcium entry into the nerve endings and inhibiting the release of neurotransmitters (16).

However, different results exist regarding the effects of gabapentin on pain and opioid consumption. Turan *et al*. reported that 1200 mg gabapentin on pain and tramadol consumption after hysterectomy was reduced in the gabapentin group (2). In another study by Durmus *et al*., demonstrated that 1200 mg gabapentin and gabapentin with acetaminophen were compared with placebo in hysterectomy patients were significantly decreased pain intensity and morphine requirement after surgery (17). Some studies revealed like results (15,18).

In contrast to the studies showing positive effect of gabapentin on pain and opioid requirement, some studies have reported no or low effects.

Dierking *et al*. reported no difference in pain after hysterectomy between patients treated with 3000 mg gabapentin and placebo (19).

Radhakrishnan *et al*., found pain level and opioid consumption after lumbar laminectomy and discectomy in patients receiving 800 mg gabapentin or placebo, no difference between groups (20).

These findings are likely due to either difference in the time of opioid administration, or the fact that each patient in the test group was administered 25 mg/h, of morphine regardless of reported pain level. Also, local anesthetic which blunts the anti-hyperalgesic effects of gabapentin. In previous research has reported that gabapentin requires 1 h to 2 h to take effect. Also, the short duration of surgery is insufficient time for the drug to take effect. PONV observed commonly after anesthesia and surgery with an overall incidence of 25-30%. It is one of the most common causes for poor patient satisfaction ratings in the postoperative period (21-23). In our study, a significant decrease in PONV was found in gabapentin group. Our clinical study on postoperative pain found that a pre-emptive 900 mg oral dose of gabapentin reduces the pain scores and meperidine requirement in the immediate period and also reduces nausea and vomiting in patients undergoing abdominal hysterectomy.

Pain after abdominal hysterectomy can be multifactorial including incisional, dynamic pain and visceral pain, such as during straining, coughing, or mobilizing, like to any abdominal surgery. According to this study, we suggest that administration of pre-emptive gabapentin 900 mg for reducing postoperative pain and PONV after hysterectomy or any abdominal surgery.

In summary, perioperative administration 900 mg of gabapentin decreases postoperative pain, PONV and the requirement for opioids in the post- operative period in patients who undergo abdominal hysterectomy. Also, significant side effects were not observed.

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