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Original Research Article

Can perioperative haemodynamics and opioid requirement in Abdominal Hysterectomy be influenced by a premedication drug?

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ABSTRACT

Background: Abdominal hysterectomy is a common surgery, usually done under Spinal anaesthesia. It would be greater if a premedication oral drug were available to reduce the perioperative use of opioids. The aim of the study was to find out whether gabapentin can reduce the perioperative dose of tramadol but without affecting perioperative haemodynamics.

Methods: This is a randomized double blinded controlled study. Patients undergoing Abdominal hysterectomy under Spinal anaesthesia were divided into two groups. One group was given gabapentin and another was given placebo as premedication drugs. Perioperative haemodynamics were monitored. Perioperative requirement of tramadol injection was estimated.

Results: No significant changes were noted in perioperative haemodynamics. Perioperative requirement of tramadol was reduced in gabapentin group.

Conclusions: Gabapentin does not affect perioperative haemodynamics. Gabapentin reduces perioperative requirement of tramadol.

Keywords: Abdominal hysterectomy, Gabapentin, Intraoperative haemodynamics

INTRODUCTION

Pain during perioperative period affects the recovery from anesthesia and surgery.¹ The most common reasons of prolonged recovery are drowsiness, sedation, vomiting, nausea and pain.² Opioids are used during perioperative period in several patients.^{3,4} The limitations of opioids include their side effects. Also not all patients respond well to opioids. Several mechanisms are involved in perioperative pain.⁵ So it is better to combine opioid and non-opioid analgesic drugs. This will result in efficient analgesia.⁶ There will be a reduction of opioid requirement also. Thus we will be able to avoid the side effects of opioids to a greater extent.⁷ Also we will be able to avoid opioids tolerance.

The chemical structures of gabapentin and γ -aminobutyric acid are similar. But gabapentin does not interact with GABA receptors. The concentration of GABA in the brain is increased by gabapentin. It is used as an anticonvulsant drug.⁸ Gabapentin is also used in diabetic neuropathy, reflex sympathetic dystrophy, postherpetic neuralgia and neuropathic pain.⁹⁻¹² The development of hyperalgesia can be avoided by pretreatment with gabapentin.¹³ One of the major causes for postoperative pain is central neuronal sensitization.¹⁴ Gabapentin acts very specifically on the neural mechanisms related to central neuronal sensitization.

Oral gabapentin as a single dose reduces postoperative opioid consumption.¹⁵ The aim of our study is to find out the effects of gabapentin on several factors in patients

who are undergoing total abdominal hysterectomy. Such factors are intraoperative surgical environment, intraoperative haemodynamics, early postoperative pain and overall perioperative tramadol requirement.

METHODS

Aims and Objectives

To assess the effect of gabapentin when given as a premedication drug on perioperative haemodynamics, perioperative pain and perioperative requirement of tramadol.

Design

The permission and consent of the Institutional Ethics Committee was obtained. Written informed consents were received from all the patients. Female patients posted for elective total abdominal hysterectomy under spinal anaesthesia were included in the study. Sixty patients were selected. They were of ASA Grade I or II, weighed above 40 kg and aged above 30 years. The patients with any of the following disorders were excluded from the study- allergy to tramadol or gabapentin, contraindications to tramadol or gabapentin, bleeding disorders, peptic ulcer, asthma or renal impairment.

Sample size

The sample size was calculated as 60 patients in total. The study was a randomized and double blinded clinical trial. Patients were randomly divided with the help of slip in box protocol. There were two groups with 30 patients in each.

Two hours before surgery gabapentin was given as an oral tablet of 300 mg to patients in the gabapentin group. Placebo tablet was given to the patients in the other group. In the operation theatre, an 18 G peripheral venous cannula was inserted in to a wide and straight vein over the dorsum of hand. Isotonic saline infusion was started. Spinal anaesthesia was performed with sub arachnoid injection of 25 µg fentanyl and 3.5 ml of 0.5% hyperbaric bupivacaine. The following variables were monitored - heart rate (HR), peripheral oxygen saturation (SpO₂), systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial blood pressure (MAP).

Post operative pain was assessed with the aid of Visual Analogue Scale (VAS). In VAS, 0 cm = no pain and 10 cm = severe pain. During pre anaesthetic assessment, VAS was explained to the patients. Intravenous tramadol was administered to alleviate post operative pain. All the patients received intravenous tramadol post operatively. First dose of tramadol was 50 mg. After that as per patient's demand, every time 25 mg tramadol was given but at an interval of greater than 30 minutes. Also it was made sure that tramadol never exceeded 400 mg over a

period of 4 hours. An anaesthetist not involved in the study assessed the patients. Evaluation was done at 2 hours, 4 hours, 8 hours, 12 hours, and 24 hours. Evaluation was done for sedation, intensity of pain, tramadol requirement and total perioperative tramadol consumption. Haemodynamic vital parameters viz., heart rate, respiratory rate, SpO₂ and blood pressure were recorded. The presence or absence of side effects was also noted. The side effects noted were sedation, nausea and vomiting. All the sixty patients took part in the study. Data was analyzed using Wilcoxon- Mann- Whitney test and Fisher Exact Test. Data was considered as significant if $p \leq 0.05$.

Statistical analysis

Statistical analysis was done with the SPSS software. Demographic data was analyzed for the comparability of both groups. Age and weight were compared using Wilcoxon- Mann- Whitney test. ASA status was compared using Fisher Exact Test. Intra operative haemodynamic variables were compared using Wilcoxon- Mann- Whitney test. Analgesic requirement and VAS score over 24-hour period were analyzed with Wilcoxon- Mann- Whitney test. A 'p' value of <0.05 was considered to be statistically significant.

RESULTS

The groups could be comparable with respect to the age (Table 1).

Table 1: Comparison of sample based on age.

Parameter	Placebo (Sum of ranks)	Gabapentin (Sum of ranks)	U statistic	p value
Age	794.5	1035.5	329.5	0.074827

Since the p-value is ≥ 0.05 , the groups can be comparable with respect to the age.

The groups were comparable with respect to weight (Table 2).

Table 2: Comparison of sample based on weight.

Parameter	Placebo (Sum of ranks)	Gabapentin (Sum of ranks)	U statistic	p value
Weight	933	897	432	0.790147

Since the p-value is ≥ 0.05 , the groups can be comparable with respect to the weight.

The groups were comparable with respect to ASA status (Table 3).

Table 3: Comparison of sample based on ASA status.

Fisher exact test			
	Placebo	Gabapentin	Marginal row totals
ASA I	19	17	36
ASA II	11	13	24
Marginal column totals	30	30	60 (Grand Total)

The Fisher exact test statistic value is 0.792494. The result is not significant at $p < 0.05$. Hence the groups were comparable with respect to ASA status.

The groups were comparable with respect to intra operative haemodynamic variables (Table 4).

Since the p-value is ≥ 0.05 , the groups can be comparable with respect to the intra operative haemodynamic variables. Statistically there is no significant difference in

the intra operative haemodynamics between two groups. Thus we can infer that gabapentin does not influence intra operative haemodynamics.

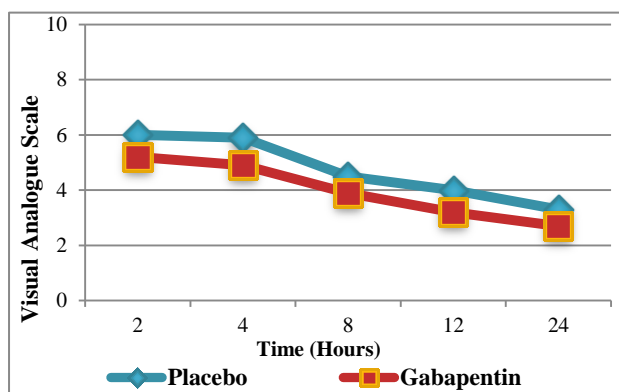
Table 4: Comparison of sample based on intra operative haemodynamic variables.

Parameter	Placebo (Sum of ranks)	Gabapentin (Sum of ranks)	U statistic	p value
Heart rate	885.5	944.5	420.5	0.662735
Systolic Bp (SAP)	944.5	885.5	420.5	0.662735
Diastolic Bp (DAP)	944	886	421	0.668106
SpO ₂	900.5	929.5	435.5	0.830255

Post-operative pain was assessed using the Visual Analogue Scale. It was observed that the Gabapentin group showed lower scores at 2, 4, 8, 12 and 24 hours consistently following surgery.

Table 5: Comparison of VAS.

Parameter (VAS Score)	Placebo			Gabapentin			p value
	Mean	SD	Sum of ranks	Mean	SD	Sum of ranks	
2 hours	6.0	1.0	1112.5	5.2	0.9	717.5	0.003501
4 hours	5.9	1.2	1138.5	4.9	1.0	691.5	0.000952
8 hours	4.5	0.9	1068	3.9	0.9	762	0.023696
12 hours	4.0	0.9	1141	3.2	0.9	689	0.000834
24 hours	3.3	1.0	1061.5	2.7	1.0	768.5	0.030317

**Figure 1: Comparison of VAS scores.**

Consistently the p-value is ≤ 0.05 . So the difference between placebo and gabapentin is statistically significant.

The analgesic requirement was also assessed at 0-2, 2-4, 4-8, 8-12 and 12-24 hours following surgery. Gabapentin group showed lower tramadol consumption consistently at all-time intervals (Table 6).

The p-value is ≥ 0.05 for 0-2 and 12-24 hours which is statistically not significant.

Table 6: Comparison of tramadol requirement.

Parameter (Tramadol requirement)	Placebo			Gabapentin			p value
	Mean	SD	Sum of ranks	Mean	SD	Sum of ranks	
0-2 hours	80.8	15.7	1016	72.5	16.5	814	0.135378
2-4 hours	98.3	27.8	1182.5	70.0	19.0	647.5	0.000077
4-8 hours	64.2	15.7	1165.5	45.0	17.9	664.5	0.000213
8-12 hours	61.7	17.0	1267.5	32.5	11.7	562.5	0.000000
12-24 hours	59.2	13.9	1034	50.0	20.8	796	0.078519
Total	363.3	51.2	1275	270.0	49.3	555	0.000000

The p- value is ≤ 0.05 for 2-4, 4-8, 8-12 hours and total requirement of tramadol. This is statistically significant.

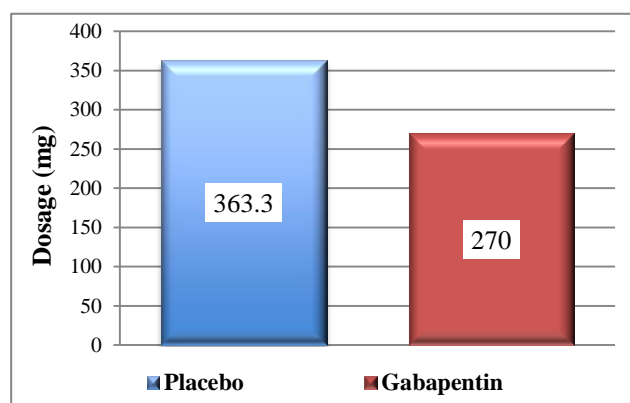


Figure 2: Comparison of tramadol requirement.

The side effects noted were nausea, vomiting and sedation.

Table 7: Side effects.

	Placebo	Gabapentin
Nausea	4	3
Vomiting	1	0
Sedation	3	4

We compared the incidence of side effects between both the groups. It was not significant.

DISCUSSION

Our clinical trial was studying the effects of gabapentin premedication in patients who were undergoing total abdominal hysterectomy under spinal anaesthesia. We could not find any significant difference in surgical environment or intraoperative haemodynamics. But postoperative pain scores and perioperative total tramadol consumption got reduced by gabapentin premedication. Also there were not much side effects with gabapentin premedication.

When different analgesic drugs are combined, the analgesic effect gets augmented.¹⁶ The doses of individual drugs can be reduced. Thus we can minimise the side effects of the drugs. This is possible by combining analgesics which have different locations of actions.¹⁷ One of the commonest drugs used for postoperative pain relief is tramadol. Tramadol acts by stimulating μ opioid receptors. Tramadol also acts on the noradrenergic and serotonergic systems. By this action, tramadol inhibits the reuptake of serotonin and norepinephrine. Due to the two different mechanisms of action, tramadol is an effective analgesic drug.¹⁸

Gabapentin reduces hypersensitivity associated with inflammation, nerve injury and postoperative pain.¹⁹

Central neuronal sensitization is one of the mechanisms of hyperalgesia. Postoperative pain to some extent results from central neuronal sensitization.²⁰ Gabapentin is an antihyperalgesic drug. It can very well be used for the alleviation of perioperative pain. When combined with another analgesic drug, gabapentin produces augmented analgesia. Thus gabapentin amplifies the analgesic effects of tramadol.²¹ The combination of gabapentin and tramadol produces better analgesia than with tramadol alone.

For patients who underwent abdominal hysterectomy, during the post operative period gabapentin markedly decreases pain.²² Also gabapentin to a greater extent reduces tramadol administration. In our study we could find that there was a reduction in pain scores for a period of 24 hours.

Some of the prevalent analgesics in the postoperative pain management are nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs reduce postoperative pain. They also reduce the postoperative consumption of opioids. They are well known, potent, and less expensive. Since NSAIDs have adverse renal, gastrointestinal and haemostatic effects in some patients, their role is limited in some situations.^{23,24} Gabapentin is a less well known drug. To make use of gabapentin widely, we have to prove several things about gabapentin. We have to prove that it significantly reduces opioid consumption. We have to prove that it provides better pain relief than NSAIDs. Also we have to prove that gabapentin has fewer adverse effects.²⁵

Turan et al studied the patients who underwent abdominal hysterectomy.²⁶ They studied the effect of gabapentin 1200 mg on postoperative pain. They also monitored tramadol consumption. Both pain and tramadol consumption got reduced in the gabapentin group. In our study we used only 300 mg dose of gabapentin. However patients had a comfortable level of analgesia preoperatively. Also the side effects caused by the high dosage of gabapentin are much less in our study.

Durmus et al studied the patients who underwent abdominal hysterectomy.²⁷ They assessed the effects of gabapentin and acetaminophen. The patients were given drugs one hour before surgery. One group received 1200 mg gabapentin. Another group received acetaminophen 20 mg per kg with 1200 mg gabapentin. Third group received placebo. The pain score between the gabapentin and gabapentin plus acetaminophen group did not differ significantly. So ultimately the authors suggested only gabapentin and not any combination with acetaminophen.

1200 mg gabapentin and placebo were compared in abdominal hysterectomy patients by Dierking et al.²⁸ The drugs were given one hour before surgery. There was significant reduction of pain in gabapentin group. Also the incidences of side effects viz., nausea and vomiting were less. In our study, there minimal side effects.

Elective vaginal hysterectomy patients were studied by Rorarius et al.²⁹ They gave gabapentin 1200 mg to one group. Another group was given oxazepam 15 mg. In the initial postoperative hours gabapentin reduced patient-controlled analgesia by 40%. Comparing with gabapentin group, the placebo group had more pain during the initial postoperative period. In our study also we got similar findings.

Fassoulaki et al studied the nature and course of postoperative pain for five days and much more.³⁰ For one group they gave gabapentin 600 mg. For another group they gave placebo. The drugs were started 18 hours preoperatively. The drugs were repeated 6th hourly till five days. Morphine was also given for three days. The patients were followed for one month postoperatively. Gabapentin decreases morphine consumption for two days only. After 48 hours, could not have any impact on the pain. So we can know that gabapentin usage is limited to early post operative period only. Gabapentin is a good choice for perioperative usage.

Frouzanfard et al compared gabapentin 1200 mg and placebo in hysterectomy patients.³¹ In the gabapentin group, pain and morphine consumption decreased significantly. In the immediate postoperative period few side effects were noted. The side effects included nausea and vomiting. These side effects were attributed to the high dosage of gabapentin. In our study gabapentin was given at a dose of 300 mg. The lesser incidence of side effects in our study could be attributed to the smaller dose of gabapentin.

Patients tolerate the single dose of gabapentin well. Gabapentin has fewer side effects. The drug interactions are less for gabapentin. When gabapentin is given as single small dose say 300 mg, the side effects are not very significant. Thus, gabapentin can be a very good premedication drug. The ideal time for the gabapentin premedication is one to two hours preoperatively. By this way we can get the maximum effect of gabapentin premedication at the required and most appropriate time.

CONCLUSION

We conclude that a single oral premedication of gabapentin does not interfere with perioperative haemodynamics. Also preoperatively gabapentin increases the analgesic effect of tramadol and decreases tramadol consumption. Gabapentin at single oral dose of 300 mg does not create any significant side effect. So gabapentin is a good choice as the premedication drug.

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