Original Research Article

Indian Journal of Anesthesia and Analgesia
2019; 6(5) (Part - I): 1641-1646
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6519.23

Outcome of Oral Gabapentin in Total Abdominal Hysterectomies on Post-operative Epidural Analgesia

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Abstract

Background: Pre-emptive analgesia is defined as an anti-nociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies post-operative pain. *Objective:* To evaluate the role of gabapentin as pre-emptive analgesic in patients undergoing total abdominal hysterectomy. *Methods:* Aprospective, randomized clinical study was conducted and the patients were randomly allocated to two groups of 15 each with ASA Grade I and II. Patients in Group A were given oral gabapentin 1200 *mg 1 hour* before surgery whereas placebo was given to patients belonging to Group B. Epidural block is achieved in both groups with a bolus dose of 0.5% bupivacaine (maximum allowable dose–*2 mg/kg*) prior to surgery. After skin closure, the infusion dose is reduced to a lower concentration of Bupivacaine (0.0625%) at the rate of *2 ml/hr* and the patient will be shifted to HDU (high dependency unit). Data collected includes patients age, body weight, post-operative VAS scores, and tramadol *50 mg* I.V. doses given at *1, 4, 8, 12, 16, 20, 24 hours. Results:* Study revealed that the mean VAS score in the post-operative period is lower in group A (Gabapentin) as compared to group B (placebo). Mean number of total top ups with tramadol is lower in Group A (Gabapentin) as compared to Group B (Placebo). *Conclusion:* Pre-emptive use of gabapentin *1200 mg* orally significantly reduces the number of post-operative analgesic dose requirements and post-operative pain in patients undergoing total abdominal hysterectomy under epidural anesthesia.

Keywords: Gabapentin; Total abdominal hysterectomy; Pre-emptive analgesia.

How to cite this article:

Thomas P George, Kiron KG, Joe Joseph. Outcome of Oral Gabapentin in Total Abdominal Hysterectomies on Post-operative Epidural Analgesia. Indian J Anesth Analg. 2019;6(5 Part-1):1641-1646.

Introduction

Post-operative pain is typically regarded as a type of nociceptive pain involving peripheral mechanoreceptor stimulation, inflammatory, and neurogenic and visceral mechanisms, with a transient, reversible type of neuropathic pain[1] Gabapentin [1-(aminomethyl) cyclohexane acetic acid] is a structural analogue of gamma amino butyric acid (GABA), which was initially introduced in 1994 as an antiepileptic drug, particularly for partial seizures. It was soon found to be promising in treating neuropathic pain associated with post-herpetic neuralgia (PHN)[2,3], post-poliomyelitis neuropathy[4], and reflex sympathetic dystrophy[5].

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Received on 08.06.2019, **Accepted on** 24.07.2019

Placebo-controlled clinical trials also have indicated a role of gabapentin in treating pain related to diabetic neuropathy (DNP)[6] and PHN[7]. The concept of pre-emptive analgesia to reduce post-operative pain was founded on a series of successful animal experimental studies that showed central nervous system plasticity and sensitization after nociception.[8] Pre-emptive analgesia is defined as an anti-nociceptive treatment that prevents the establishment of alteredcentral processing of afferent input, which amplifies post-operative pain.[9] Gabapentin has demonstrated analgesic effects in clinical trials as a pre-emptive analgesic and in acute post-operative pain management. So, the rationale behind the study to investigate whether pre-emptive use of gabapentin *1200 mg* orally could reduce post-operative pain and number of additional analgesics in the initial *24 hours* in patients undergoing total abdominal hysterectomy.

Materials and Methods

Study Design

A randomized control study involving 30 patients belonging to ASA 1 & 2, who were posted for elective total abdominal hysterectomies.

Study Setting

Tertiary care teaching hospital–major operation theatre, Department of Anesthesiology, Pushpagiri Institute of Medical Sciences, Thiruvalla, Kerala.

Sample Size

For a significant level of 5% and a power of 90%, and equal number in both groups,a pooled variance of 16; to find a difference of *6 hour* between the 2 Groups, the sample size required is 11. For accounting dropouts, the sample size is rounded to 15.

Study Population

30 female patients with American Society of Anesthesiologists (ASA) physical status 1 or 2 aged *35–60 years* scheduled for total abdominal hysterectomy.

Selection was based on inclusion and exclusion criteria:

Inclusion criteria

1. Age between *35–60 years.*
2. Physical status: American Society of Anesthesiologists (ASA) 1 or 2.

Exclusion criteria

(1) Patients with cerebrovascular disease, cardiovascular disease.

(2) Poorly controlled arterial hypertension.

(3) Coagulation defects.

(4) History of renal in-sufficiency.

(5) History of hepatic insufficiency.

(6) Hypersensitivity to the drug in study.

(7) Patients with baseline pulse < *60 bpm* and systolic BP < *100 mm Hg*.

(8) History of peptic ulcer.

Ethical Considerations

The study was conducted after attaining approval from research and ethical committee.

Informed Consent

Written informed consent was taken from all patients.

Methodology

Patient will be assigned to two groups of 15 each. Patients in Group A will be given oral gabapentin *1200 mg 1 hour* before surgery whereas placebo willbe given to patients belonging to Group B.

Pre-operative Evaluation

A thorough pre-anesthetic check-up was carried out. Detailed history was taken, airway and systems were examined. Pulse rate, blood pressure and bodyweight were noted. Routine investigations like hemogram, blood sugar, renal function test, liver function test, bleeding and clotting time, prothrombin time, international normalized ratio (INR), chest *X*-ray (PA) viewand electocardiogram were done and reviewed in all the subjects.

Pre-operative Preparation

All patients were kept fasting for *six hours* before surgery. All the subjects were pre-medicated with Tab. Ranitidine *150 mgTab*. Alprazolam *0.25 mg* on previous night and *two hours* prior to surgery.

Procedure

Epidural block was achieved in both group patients with a bolus dose of 0.5% bupivacaine (maximum allowable dose–*2 mg/kg*) prior to surgery. Intra-

operatively analgesia was maintained with 0.5% bupivacaine infusion at the rate of *4 ml/hr*. After skin closure, the infusion dose was reduced to a lower concentration of bupivacaine (0.0625%) at the rate of *2 ml/hr* and the patient was shifted to HDU (high dependency unit). VAS scores were assessed by an independent physician who was not aware of the group allocation on a scale of *0–10 cm* (0 mean no pain, 10 equals to worst imaginable pain) after *1, 4, 8, 12, 16, 20 and 24 hrs* after the surgery and at the same time patients were asked for any complication suffered by them. Whenever the VAS score was above 4 additional analgesia with *50 mg* tramadol I.V. was given. Total numbers of tramadol top ups received by each patient were also noted.

Data collection

Post-operative assessment of pain was done using VAS (visual analogue scale). Other parameters like, additional analgesic requirements, hemodynamic variables (HR) were also monitored at specific time intervals. All collected data were recorded in a tabular fashion on a printed study proforma that was prepared earlier.

Statistical methods

Data was analysed using computer software, statistical package for social sciences (SPSS). The categorical variableswere presented as percentages and frequencies. Continuous variables were expressed as means and standard deviations. Changes in variables were analyzedusing repeated measures ANOVA. Other outcome variables were tabulated and subjected to chi-square test. A *p* - value of less than 0.05 was considered statistically significant.

Results

Table 1: Age wise distribution of the study participants

Group	Sample	Mean	Standard deviation	*p* - value
Gabapentin	15	45.47	5.475	0.645
Control	15	46.40	5.501	

Mean age in Group A (Gabapentin) and Group B (Control) were *45.47 ± 5.475 years* and *46.40 ± 5.501 years* respectively. This difference in the ages between the two groups was statistically not significant (*p* - value = 0.645 > 0.05) (Table 1).

Table 2: Weight wise distribution of the study participants

Group	Sample	Mean	Standard deviation	p - value
Gabapentin	15	63.93	8.447	0.315 > 0.05
Control	15	66.93	7.583	

Mean weight in Group A (Gabapentin) and Group B (Control) were *63.93 ± 8.447 years* and *66.93 ± 7.583 years* respectively. This difference in the ages between the two groups was statistically not significant (*p* – value = 0.315 > 0.05) (Table 2).

The mean VAS score is lower in Group A (Gabapentin) as compared to Group B (Control) at *1 hour, 4 hours, 12 hours, 16 hours, 20 hours, 24 hours* after surgery. Statistical analysis proved that there is significant difference in mean heart rate of the two groups at *1 hour, 4 hours,16 hours, 12 hours* after surgery (Table 3).

Comparison of baseline heart rate in the two groups indicates that there is no significant difference between the two groups. The mean heart rate is lower in Group A (Gabapentin) as compared to Group B (Control) at *1, 4, 12, 16, 20, 24 hours* after surgery. Statistical analysis proved that there is

Table 3: Distribution of VAS score in terms of hours after surgery

VAS Score (Hours after surgery)	Group	Mean	Standard deviation	*f* - value	*p* - value
1 hr	Gabapentin	0.67	0.724	147.875	0.000 < 0.05
	Control	4.13	0.834		
4 hr	Gabapentin	2.47	1.246	41.600	0.000 < 0.05
	Control	5.93	1.668		
8 hr	Gabapentin	4.80	1.568	0.257	0.616 > 0.05
	Control	4.53	1.302		
12 hr	Gabapentin	4.07	2.219	2.949	0.97 > 0.05
	Control	5.33	1.799		
16 hr	Gabapentin	3.47	0.315	4.9000	0.035 < 0.05
	Control	4.40	1.352		
20 hr	Gabapentin	4.13	0.915	12.785	0.001< 0.05
	Control	5.60	1.298		
24 hr	Gabapentin	4.07	1.223	0.980	0.331 > 0.05

significant difference in mean heart rate of the two groups at *4 hours, 12 hours, and 20 hours* after surgery (Table 4).

The mean MAP is lower in Group A (Gabapentin) as compared to Group B (Control) at 1 hour, 4 hours, 12 hours, 16 hours, 20 hours, 24 hours after surgery. Statistical analysis proved that there is no significant difference in mean MAP of the two groups at various time periods (Table 5).

Comparison of baseline Sp02 in the two groups indicates that there is no significant difference between the two groups. The mean Spo2 is lower in Group A as compared to Group B at *1, 4, 8, 12, 16, 20, 24 hours* after surgery. Statistical analysis proved that there is no significant difference in mean saturation of the two groups at various time periods (p – value > 0.05) (Table 6).

Table 4: Comparison in the Heart Rate among the study groups

Heart rate	Group	Mean	Standard deviation	*f* - value	*p* - value
Baseline	Gabapentin	67.27	6.497	0.116	0.736 > 0.05
	Control	68.13	7.396		
1 hr after surgery	Gabapentin	72.93	11.548	0.085	0.773 > 0.05
	Control	74.20	12.307		
4 hrs after surgery	Gabapentin	75.33	9.926	8.970	0.006 < 0.05
	Control	84.13	5.566		
8 hrs after surgery	Gabapentin	83.20	13.007	3.181	0.085 > 0.05
	Control	74.33	14.196		
12 hrs after surgery	Gabapentin	77.00	9.554	4.234	0.049 < 0.05
	Control	84.07	9.254		
16 hrs after surgery	Gabapentin	74.47	8.766	0.005	0.946 > 0.05
	Control	74.73	12.372		
20 hrs after surgery	Gabapentin	75.67	12.760	7.766	0.009 < 0.05
	Control	87.07	9.392		
24 hrs after surgery	Gabapentin	75.53	8.903	0.489	0.490 > 0.05
	Control	78.53	14.030		

Table 5: Comparison in the Mean Arterial Pressure among the study groups

MAP	Group	Mean	Standard deviation	*f* - value	*p* - value
Baseline	Gabapentin	75.60	9.804	5.103	0.032 < 0.05
	Control	69.97	4.667		
1 hr after surgery	Gabapentin	76.87	10.439	0.020	0.88 > 0.05
	Control	77.53	14.952		
4 hrs after surgery	Gabapentin	78.13	14.530	8.104	0.008 < 0.05
	Control	92.67	13.409		
8 hrs after surgery	Gabapentin	87.07	15.691	1.461	0.237>0.05
	Control	81.07	11.113		
12 hrs after surgery	Gabapentin	80.13	10.862	3.840	0.060 > 0.05
	Control	87.80	10.564		
16 hrs after surgery	Gabapentin	79.47	12.682	0.005	0.943 > 0.05
	Control	79.80	12.497		
20 hrs after surgery	Gabapentin	82.33	16.800	1.952	0.173>0.05
	Control	89.47	10.426		
24 hrs after surgery	Gabapentin	78.20	12.214	1.235	0.276 > 0.05

Table 6: Comparison in the Spo2 among the study groups

Pulse oximeter	Group	Mean	Standard deviation	*f* - value	*p* - value
Baseline	Gabapentin	99.00	0.378	1.909	0.178 > 0.05
	Control	99.20	0.414		
1 hr after surgery	Gabapentin	99.00	0.655	0.085	0.772 > 0.05
	Control	99.07	0.594		
4 hrs after surgery	Gabapentin	98.93	0.258	0.000	1.000 > 0.05
	Control	98.93	0.258		
8 hrs after surgery	Gabapentin	98.80	0.414	1.909	0.178 > 0.05
	Control	99.00	0.378		
12 hrs after surgery	Gabapentin	98.87	0.352	2.154	0.153 > 0.05
	Control	99.00	0.000		
16 hrs after surgery	Gabapentin	98.93	0.458	0.318	0.577 > 0.05
	Control	99.00	0.000		
20 hrs after surgery	Gabapentin	99.00	0.000	0.318	0.577 > 0.05
	Control	99.07	0.458		
24 hrs after surgery	Gabapentin	98.93	0.258	0.00	1.000 > 0.05
	Control	98.93	0.258		

Discussion

Gabapentin is a structural analogue of gamma-amino butyric acid. It has been first reported to be effective for the treatment of neuropathic pain and diabetic retinopathy. It has also been used successfully as a non- opoid analgesic adjuvant for post-operative pain management. It is effective in reducing narcotic usage post- operatively and is helpful in neuropathic pain due to cancer.

The mean VAS score is lower in Group A (Gabapentin) as compared to group B (Control) *at 1 hour, 4 hours, 12 hours, 16 hours, 20 hours, 24 hours* after surgery. This was similar to the studies done by Turan *et al.*[10] and Anil verma *et al.*[11] However, VAS score in gabapentin group was higher than control group at the *8 hour*.

The mean heart rate is lower in Group A (Gabapentin) as compared to Group B (Control) at *1 hour, 4 hour, 12 hours, 16 hours, 20 hours, 24 hours* after surgery. Statistical analysis proved that there is significant difference inmean heart rate of the two groups at *4 hour,12 hour*, and *20 hours* after surgery (p - value < 0.05). Turan, G *et al.*[10], found out in their study that oral gabapentin (*1.2 g* day) as an adjunct to epidural analgesia decreased pain and analgesic consumption. The VAS pain scores were significantly greater at *1, 4, 8, 12,* and *16 hr* after operation in patients receiving placebo than in those receiving gabapentin ($p < 0.001$). Compared with the placebo group, PCA requirements were significantly reduced in the gabapentin-treatment group at *24, 48*, and *72 hr* after surgery. In addition, oral analgesic consumption was less in the gabapentin-treated patients compared with the control group. Verma *et al.*[11] found out in their study that single oral dose of gabapentin given *2 hrs* before surgery provides better pain control as compared to the placebo and also reduces the requirement of epidural boluses in patients undergoing total abdominal hysterectomy without increase in frequency of side effects. Patients in the Group G (gabapentin) had significantly lower VAS scores at all times *2, 4, 8, 12* and *24 hrs* than those in the Group P (placebo). The total number epidural boluses demanded after surgery in the first *24 hr* in the Group G (gabapentin) (3.4 ± 1.6, mean ± SD) was significantly less than in the Group P (placebo) (5.6 ± 2.1, $p < 0.05$).[12,13]

Conclusion

Pre-emptive analgesia is defined as an anti-nociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies the post operative pain.[9] Many drugs have been proposed to attain the same. Our study found out that the mean VAS score in the post-operative period is lower in Group A (gabapentin) as compared to Group B (placebo). Hence, we conclude that a single oral dose of gabapentin given *1 hr* before surgery provides better pain control as compared to the placebo and also reduces the requirement of additional analgesics in patients undergoing total abdominal hysterectomies receiving epidural bupivacaine infusion.

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