

## **Gabapentin pre-treatment for pressor response to direct laryngoscopy and tracheal intubation: a randomized, double-blind, placebo-controlled study**

**Vikram Bhandari<sup>1,2\*</sup>, Dilip C. Dhasmana<sup>1</sup>, Sheveta Dureja<sup>3</sup>, Jagdish P. Sharma<sup>4</sup>, Praveendra K. Sachan<sup>5</sup>, Aditi Chaturvedi<sup>1</sup>**

<sup>1</sup>Department of Pharmacology, Himalayan Institute of Medical Sciences Dehradun, Uttarakhand, India, <sup>2</sup>Department of Pharmacology, Sri Guru Ram Das Institute of Medical Sciences and research, Amritsar, Punjab, <sup>3</sup>Department of Physiology, Chintpurni Medical College, Pathankot, Punjab, India, <sup>4</sup>Department of Anaesthesia, Himalayan Institute of Medical Sciences Dehradun, Uttarakhand, India, <sup>5</sup>Department of Surgery, Himalayan Institute of Medical Science, Dehradun, Uttarakhand, India,

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**\*Correspondence to:**

Dr. Vikram Bhandari,  
Email: vik\_bhandari@yahoo.com

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### **ABSTRACT**

**Background:** Laryngoscopy and endotracheal intubation are associated with an increase in blood pressure (BP) and heart rate (HR). The present study was conducted to evaluate the role of gabapentin in attenuation of these hemodynamic changes.

**Methods:** Forty patients undergoing elective laparoscopic cholecystectomy under general anesthesia with standardized premedication and anesthetics were randomized to receive gabapentin or a matching placebo. The patients of Group I received gabapentin 600 mg orally 2 hrs before surgery and patients in Group II received a matching placebo. Patient's HR, systolic BP (SBP), diastolic BP (DBP), mean BP (MBP), were monitored before and after 1, 2, 5, and 10 mins of endotracheal intubation.

**Results:** Comparison of SBP, DBP, and MBP at 1, 2, 5 and 10 mins after endotracheal intubation showed statistically significant attenuation in the gabapentin group when compared to placebo. Changes in the HR were not significant.

**Conclusion:** Gabapentin 600 mg, given 2 hrs before induction is effective in attenuating the pressor response to laryngoscopy and tracheal intubation.

**Keywords:** Gabapentin, The pressor response, Laryngoscopy, Endotracheal intubation, Hemodynamic

### **INTRODUCTION**

Laryngoscopy and endotracheal intubation which form an integral part of the process of general anesthesia are

associated with cardiovascular changes like hypertension, tachycardia and dysarrhythmias.<sup>1</sup> These changes result from reflex sympathetic activity involving baroreceptors, which get activated by the stimulation of epipharynx and

laryngopharynx.<sup>2</sup> Hemodynamic changes start within seconds of direct laryngoscopy and the magnitude of response depends upon many factors like the technique and expertise of the person performing the procedure.<sup>3</sup> Premedication and drugs used for induction may attenuate these responses.<sup>4</sup> Hypertensive and patients with cardiovascular diseases are more vulnerable to such changes. Several techniques have been tried to prevent or mitigate these hemodynamic changes, prominent being, increasing the depth of anesthesia, avoiding anticholinergics, pre-treatment with vasodilators such as beta-adrenergic blockers, nitrates, calcium channel blockers and opioids.<sup>1</sup>

Gabapentin was developed as an anticonvulsant.<sup>5,6</sup> It has shown promising results in the treatment of chronic pain which led to its approval by US Food and Drug Administration for treatment of post-herpetic neuralgia.<sup>7</sup> Gabapentin has over the years shown promising results in reducing post-operative pain and opioid requirement and is remarkably free from serious side effects and interactions with food and concomitantly administered drugs.<sup>5</sup> During these studies it was observed that the patients were hemodynamically stable during laryngoscopy and endotracheal intubation.<sup>8</sup> Considering this information, we planned to evaluate the role of gabapentin in reducing pressor responses to laryngoscopy and endotracheal intubation in patients undergoing laparoscopic cholecystectomy.

## METHODS

This study was carried out after approval from the Institutional Ethics Committee. Prior to initiation of the study, written informed consent from the patient/legal guardian of the patient was obtained after full explanation of elements contained in the research protocol.

### Study design

It was a “randomized, double-blind placebo-controlled parallel group study” done in patients undergoing elective laparoscopic cholecystectomy under general anesthesia with standardized premedication and anesthetics. A total number of 40 patients were included in the study.

Forty patients were randomized using table of random numbers with odd numbers assigned to gabapentin group and even numbers assigned to placebo group. The randomization schedule was maintained by a person not directly involved in observation of patients. The treatment was blinded by the use of placebo capsules which were identical to the capsules of gabapentin in color, shape, size and weight. Placebo was prepared by filling the empty capsules with finely powdered sugar. Neither, the patient nor the prescriber knew about the treatment given.

Patients between 18 and 60 years of age and having American Society of Anesthesiologist Physical Status I and II, who

were diagnosed on ultrasound of having uncomplicated gall stones were included in the study.<sup>9</sup> Patients with anticipated difficulty in intubation, gastro esophageal reflux, overweight and those taking sedatives, anti-hypertensive medication, antidepressants were excluded in the study. Patients of both sexes, fulfilling the criteria given above, having normal investigations and scheduled for surgery were randomized into two groups: Group-I (the gabapentin group) and Group-II (the placebo group).

The patients of Group I received gabapentin 600 mg orally 2 hrs before surgery. The patients in Group II received a matching placebo orally 2 hrs before surgery. The treatment was double blinded. Anesthesia was induced by propofol 2 mg/kg and fentanyl 3 µg/kg. Intubation was facilitated with vecuronium bromide 800 µg/kg. Patient’s heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), were monitored just before (0 min) and after 1, 2, 5 and 10 mins of endotracheal intubation. All intubations were performed by an experienced anesthesiologist in a single attempt, in all the patients. Anesthesia was maintained with isoflurane (1%) and 70% nitrous oxide with oxygen and intermittent vecuronium when indicated. After the completion of surgery neuro-muscular block was reversed with atropine 0.02 mg/kg and neostigmine 0.04 mg/kg. When the patient fulfilled the criteria for extubation, they were extubated and shifted to post anesthesia care unit.

Power of the study and sample size: sample size calculation indicated that, for the power of 0.8 and to detect a clinically significant decrease in HR and blood pressure (BP) by 10-20%, a minimum 20 patients should be included in each group. Alpha error was taken as 0.05.

### Statistics

Data were analyzed using Microsoft excel. Results were expressed as mean±Standard error. Inter-group comparison of patient SBP, DBP, MBP and HR at 0, 1, 2, 5 and 10 mins after endotracheal intubation was done using unpaired t-test. P value <0.05 was taken as significant.

**Table 1: Demographic profile of patients in gabapentin and placebo groups.**

Parameter	Gabapentin	Placebo
Age (years)	44.8±2.7	41±2.4
Male:Female ratio	7:13	1:2
Height (cm)	158.1±1.8	159.7±2.2
Weight (kg)	65.4±2.2	66.4±2.04
ASA grade		
I (%)	18 (90)	17 (85)
II (%)	2 (10)	3 (15)

ASA: American Society of Anesthesiologist

## RESULTS

Both the groups were comparable in the demographic profile, i.e., age, sex, weight, height and physical status (Table 1). SBP just before (0 min) and at 1, 2, 5 and 10 mins after endotracheal intubation was compared between gabapentin and placebo groups using unpaired t-test. SBP, before intubation did not differ significantly in the gabapentin and placebo groups ( $p=0.48$ ). The p values for intergroup comparison were 0.0024, 0.024, 0.019 and 0.038 for 1, 2, 5 and 10 mins, respectively. Hence at all times after intubation the SBP values in the gabapentin group were significantly lower than those in the placebo group (Table 2).

DBP, before intubation did not differ significantly in the gabapentin and placebo groups ( $p=0.09$ ). The p values for intergroup comparison at 1, 2, 5 and 10 mins were 0.014, 0.018, 0.021 and 0.05, respectively. So at all times after intubation the DBP values in the gabapentin group were significantly lower than those in the placebo group (Table 2).

Similarly, the MBP at 1, 2, 5 and 10 mins after endotracheal intubation was found to be significantly lower in the gabapentin group when compared with placebo. MBP, before intubation did not differ significantly in the gabapentin and placebo groups. The p values for corresponding inter-group comparison at 1, 2, 5, 10 mins were 0.002, 0.003, 0.012 and 0.026 respectively. So at all times after intubation the MBP values in the gabapentin group were also lower than those in the placebo group (Table 2). Thus, gabapentin attenuated the pressor response (SBP, DBP, and MBP) to endotracheal intubation.

Comparison of HR in both groups did not show any significant difference. The p values were 0.85, 0.16, 0.36 and 0.16 for inter-group comparisons at corresponding time

intervals respectively. Hence, gabapentin did not show any significant difference in HR, before and after endotracheal intubation as compared to placebo. Gabapentin attenuated the pressor response to endotracheal intubation but had no effect on the HR (Table 3).

## DISCUSSION

Tracheal intubation during anesthesia elicits marked sympathetic response that manifests as tachycardia and hypertension, which can cause serious complications in patients with cardiovascular morbidity. Such patients require careful hemodynamic control during induction and endotracheal intubation.<sup>10</sup> A variety of drugs with varying mechanism of actions have been tried to provide hemodynamic stability. As gabapentin is already used as adjuvant for postoperative pain, its effects on hemodynamic parameters would be more than welcome. The absorption of gabapentin is dose dependent due to saturable I-aminoacid transport mechanism in the intestine. Thus, the oral bioavailability varies inversely with a dose. After a single dose of 300 mg or 600 mg, the bioavailability is approximately 60% and 40% respectively. Moreover, the peak concentration is obtained after 2 hrs of oral administration.<sup>7,11</sup> We used 600 mg, 2 hrs before surgery based on the results of dose escalation study which concluded that 600 mg given 2 hrs before surgery is the optimal dose for pain.<sup>12</sup> So we decided to evaluate its effect on the pressor responses to endotracheal intubation with the above dose. Recently, gabapentin has shown improvement in hemodynamic parameters in the patient undergoing general anesthesia. Gabapentin in the present study attenuated the pressor responses to endotracheal intubation by reducing SBP, DBP and MBP when compared to the placebo group, with no effect on HR. The findings of the present study are similar to those of Fassoulaki et al., who used 1600 mg gabapentin, in

**Table 2: SBP, DBP, MBP in mmHg (mean±SE), just before (0 min) and 1, 2, 5 and 10 mins after endotracheal intubation in Group I (gabapentin) and Group II (placebo groups).**

Time after intubation (mins)	SBP (mmHg)		DBP (mmHg)		MBP (mmHg)	
	Gabapentin	Placebo	Gabapentin	Placebo	Gabapentin	Placebo
0	123.5±3.61	126.6±2.47	78.05±2.12	84.55±3.04	93.15±2.41	98.65±2.76
1	131.35±2.85**	144.9±3.06	84.8±2.2*	94.05±2.83	100.3±2.27**	111.15±2.4
2	132.95±3.35*	144.7±3.73	82.3±1.79*	90.55±2.84	99.2±1.68**	108.6±2.54
5	124.55±2.8*	133.55±2.37	76.2±2.6*	84.70±2.41	92.6±2.29*	101.1±2.28
10	117.85±3.67*	126.65±1.83	77.05±2.68	83.35±1.62	90.65±2.87*	98.4±1.72

\* $p<0.05$ , \*\* $p<0.01$ , versus corresponding values in placebo group, SBP: Systolic blood pressure DBP: Diastolic blood pressure, MBP: Mean blood pressure, SE: Standard error

**Table 3: HR in beats per minute (mean±SE) before and 1, 2, 5 and 10 mins after endotracheal intubation in Group I (gabapentin) and Group II (placebo).**

Group	Before intubation 0 min	1 min	2 mins	5 mins	10 mins
I (gabapentin)	79.85±2.79	86.05±2.87	88.85±2.99	79.75±2.75	73.75±3.09
II (placebo)	81.25±1.81	86.65±1.67	84.2±1.35	82.65±1.59	78.7±1.61

SE: Standard error, HR: Heart rate

4 divided doses at 6 hourly intervals, starting the day before abdominal hysterectomy with use of propofol for induction. There was a marked decrease in SBP, DBP by gabapentin without effect on HR. The authors are of the opinion that as they used propofol for induction of anesthesia, which is known to cause bradycardia thus tachycardia which is caused by intubation may have been attenuated to some extent by propofol in patients of both the groups, thus masking the effect of gabapentin on HR.<sup>1</sup> Memis et al. found that 800 mg gabapentin given 1 hr before abdominal hysterectomy was effective in attenuating BP changes and also controlling the HR variability after endotracheal intubation therefore supporting in part, the present study.<sup>8</sup> Our study did not find a benefit in controlling HR variability; possibly due to the lower dose used. The mechanism by which gabapentin attenuates the pressor response to laryngoscopy and intubation is unknown. The drug has been found to inhibit membrane voltage-gated calcium channels, thus may act in a manner similar to calcium channel blockers in affecting cardiovascular responses.<sup>13</sup> Limitations of the study: the catecholamines and cortisol levels as a measure of stress were not evaluated to confirm or reject the finding observed in the present study.

## CONCLUSION

Pre-treatment with 600 mg gabapentin 2 hrs before induction attenuates the pressor response associated with laryngoscopy and tracheal intubation with no effect on HR.

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