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*Clinical Study*

# Effect of Two Different Doses of Gabapentin on the Intraocular Pressure and Hemodynamic Stress Responses to Laryngoscopy and Tracheal Intubation

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*Background*. The stress response to laryngoscopy and intubation causes an undesirable increase in heart rate, blood pressure, and intraocular pressure. This study was designed to compare the effect of two doses of gabapentin on the stress response to laryngoscopy and intubation. *Patients and Methods*. (ASA I and II) 60 patients, aged from 18 to 60 years undergoing elective eye surgery requiring endotracheal intubation, were randomly allocated into 3 groups, 20 patients each. 2 hours before the surgery, group I received oral placebo, and groups II and III received oral gabapentin 800 mg and 1200 mg, respectively. Heart rate (HR), mean arterial pressure (MAP), and intraocular pressure (IOP) were measured before and after induction of anesthesia, immediately after, 5 minutes, and 10 minutes after intubation. *Results*. Gabapentin 1200 mg prevented the increase in HR, MAP, and IOP, secondary to laryngoscopy and intubation, and kept them below the baseline till 10 minutes after intubation ($P < 0.001$), while with gabapentin 800 mg, the increase in HR, MAP, and IOP was nonsignificant ($P > 0.05$) and returned to levels below the baseline at 5 and 10 minutes after intubation. *Conclusion*. Preoperative gabapentin 1200 mg effectively prevented the stress response to laryngoscopy and intubation; meanwhile, gabapentin 800 mg only prevented significant stress response.

## 1. Introduction

Laryngoscopy and endotracheal intubation can evoke a transient but marked response manifested as hemodynamic changes such as hypertension, tachycardia, even dysrhythmias, and an increase in intraocular pressure [1, 2].

The hemodynamic responses to laryngoscopy and intubation can be tolerated by a normal subject but they may be dangerous increasing the morbidity and mortality in patients with hypertension and ischemic heart disease [3].

The control of intraocular pressure (IOP) is of prime importance in eye surgery especially in penetrating eye injury and glaucoma surgery [4]. Many pharmacologic agents have been proposed to attenuate the stress response to laryngoscopy and intubation such as systemic and local lidocaine, B blockers, calcium channel blockers, vasodilators, and opioids [5–7].

In the past few years gabapentin has been used in anesthetic practice as an analgesic in the perioperative setting and has been noticed to provide hemodynamic stability, so some studies have been conducted to test the effect of gabapentin by different doses on the stress response to laryngoscopy and intubation and yielded different results [8, 9].

This study was designed as a prospective randomized double-blinded controlled clinical trial to investigate the effect of two doses of gabapentin on the hemodynamic and IOP response to laryngoscopy and endotracheal intubation.

## 2. Patients and Methods

After obtaining hospital board approval and written informed patient consents, this study was done prospectively on 60 patients aged from 18 to 60 years, ASA I and II undergoing

Table 1: Demographic characters of studied patients.

| | Control (no. 20) | Gaptin 800 (no. 20) | Gaptin 1200 (no. 20) | $F$ | $P$ |
|---|---|---|---|---|---|
| Age (y) | 32.61 ± 12.65 | 31.45 ± 12.01 | 30.65 ± 9.65 | 0.14 | 0.86 |
| Sex (male/female) | 10/10 | 9/11 | 11/9 | 0.40[@] | 0.81 |
| Weight (kg) | 73.15 ± 11.49 | 75.45 ± 10.85 | 72.80 ± 11.24 | 0.33 | 0.71 |

Data were expressed as mean ± SD.
[@]Data were expressed as ratio. $\chi^2$ test was used.

Table 2: HR (beat/min.) at various intervals.

| | Control group I (no. 20) | Gaptin 800 group II (no. 20) | Gaptin 1200 group III (no. 20) | $F$ | $P$ |
|---|---|---|---|---|---|
| Baseline | 81.250 ± 11.69 | 81.05 ± 10.51 | 83.0 ± 12.63 | 0.17 | 0.84 |
| After induction | 77.20 ± 10.43[*] | 76.10 ± 8.93[**] | 76.4 ± 11.51[**] | 0.06 | 0.94 |
| After intubation | 93.30 ± 12.48[#**] | 83.20 ± 8.9 | 80.8 ± 11.39[**] | 6.46 | 0.002 |
| 5 min | 89.40 ± 11.53[#*] | 80.5 ± 8.85 | 77.10 ± 11.63[**] | 6.72 | 0.002 |
| 10 min | 86.55 ± 10.79[#] | 80.2 ± 9.23 | 74.95 ± 11.14[**] | 6.21 | 0.003 |
| $P$ | 0.000 | 0.000 | 0.000 | | |

Data were expressed as mean ± SD.
[#]Means that control group was significantly different from both groups ($P < 0.05$).
[@]Means that gabapentin 800 group was significantly different from gabapentin 1200 group ($P < 0.05$).
[*]Means significant difference from baseline value ($P < 0.05$).
[**]Means highly significant difference from baseline value ($P < 0.001$).

elective cataract surgery under general anesthesia with endotracheal intubation. Exclusion criteria included raised IOP, systemic hypertension, and expected difficult airway. Patients on medications that affect heart rate or blood pressure such as B blockers, calcium channel blockers, or vasodilators and those who received sedatives, hypnotics, or antidepressant drugs on regular basis were also excluded. Patients who were not intubated from the 1st intubation attempt were also excluded. The patients were randomly allocated, using randomization software generator, into three groups each consisted of 20 patients: group I (the control group), group II (gabapentin 800 mg group), and group III (gabapentin 1200 mg group). Two hours before surgery, patients of group I received oral placebo while patients of groups II and III received gabapentin 800 and 1200 mg, respectively (Gaptin 400 mg Delta Pharma).

On arrival to the operating room an 18 G intravenous cannula was inserted into a peripheral vein and crystalloid infusion was started. Routine monitoring included five-lead ECG, noninvasive mean arterial pressure (MAP), oxygen saturation, and end tidal $CO_2$ monitoring. Benoxinate HCl 0.4% eye drops were applied to the nonoperated eye and IOP was measured using indentation tonometry (Schiötz tonometry).

After 3 minutes of preoxygenation general anesthesia was induced by propofol 2 mgl/kg, fentanyl 2 ug/kg, and cisatracurium 0.15 mg/kg to facilitate endotracheal intubation. After 3 minutes endotracheal intubation was performed by an experienced anesthesiologist to limit the duration of intubation to the least time possible and the lungs were mechanically ventilated. Anesthesia was maintained by isoflurane 1.2–2% and incremental doses of cisatracurium.

For each patient HR, MAP, and IOP were recorded before induction of anesthesia (baseline), after induction of anesthesia, immediately after endotracheal intubation and cuff inflation (1 min), 5 minutes after intubation, and 10 minutes after intubation. All data were collected by an observer unaware of the patient group.

Based on initial pilot observation, it was found that 15% difference had been the minimum detectable difference in the mean of HR, MAP and IOP between the studied groups to ensure an 80% power of calculation and 95% confidence interval. So the calculated sample size was minimally 17 patients for each group.

Statistical analysis: numeric data are summarized as means and standard deviation; comparison between several means was done by one way analysis of variance ($F$) and comparison of means at repeated interval on the same group was done by repeated measure of ANOVA. Sex variable was presented as number and ratio and the testing association was done by chi-square test. Probability ($P$) less than 0.05 is considered significant.

## 3. Results

The demographic data of the patients in the three groups were comparable showing no significant difference regarding the age, sex (male to female ratio), and body weight as shown in Table 1.

The baseline values of HR and MAP showed no significant difference regarding the baseline values (Tables 2 and 3) (Figures 1 and 2). All the studied groups showed significant reduction in HR and MAP after induction of general anesthesia compared to the baseline.

Immediately after intubation the HR increased significantly in group I and nonsignificantly in group II but remained below the baseline in group III. The MAP increased significantly above the baseline in group I, remained below

Table 3: MAP (mmHg) at various intervals.

| | Control (no. 20) | Gaptin 800 (no. 20) | Gaptin 1200 (no. 20) | $F$ | $P$ |
|---|---|---|---|---|---|
| Baseline | 90 ± 12 | 89.2 ± 7.02 | 91.86 ± 7.06 | 0.47 | 0.62 |
| After induction | 84 ± 9$^{*}$ | 81.58 ± 6.10$^{**}$ | 83.93 ± 5.99$^{**}$ | 2.1 | 0.11 |
| After intubation | 108 ± 17$^{\#**}$ | 88.93 ± 5.95 | 85.26 ± 5.81$^{**}$ | 21.04 | 0.000 |
| 5 min | 102 ± 8$^{\#**}$ | 84.21 ± 5.66$^{**}$ | 81.43 ± 5.74$^{**}$ | 51.31 | 0.000 |
| 10 min | 95 ± 16$^{\#}$ | 80.07 ± 5.77$^{**}$ | 78.46 ± 5.69$^{**}$ | 13.5 | 0.000 |
| $P$ | 0.000 | 0.000 | 0.000 | | |

Data were expressed as mean ± SD.
$^{\#}$Means that control group was significantly different from both groups ($P < 0.05$).
$^{*}$Means significant difference from baseline value ($P < 0.05$).
$^{**}$Means highly significant difference from baseline value ($P < 0.001$).

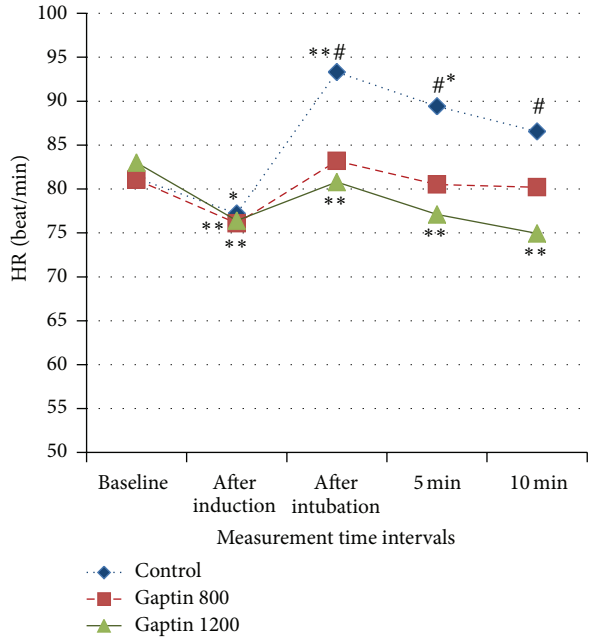


Figure 1: HR (beat/min.) at various intervals. Data were expressed as mean ± SD. $^{\#}$Means that control group was significantly different from both groups ($P < 0.05$). $^{@}$Means that gabapentin 800 group was significantly different from gabapentin 1200 group ($P < 0.05$). $^{*}$Means significant difference from baseline value ($P < 0.05$). $^{**}$Means highly significant difference from baseline value ($P < 0.001$).

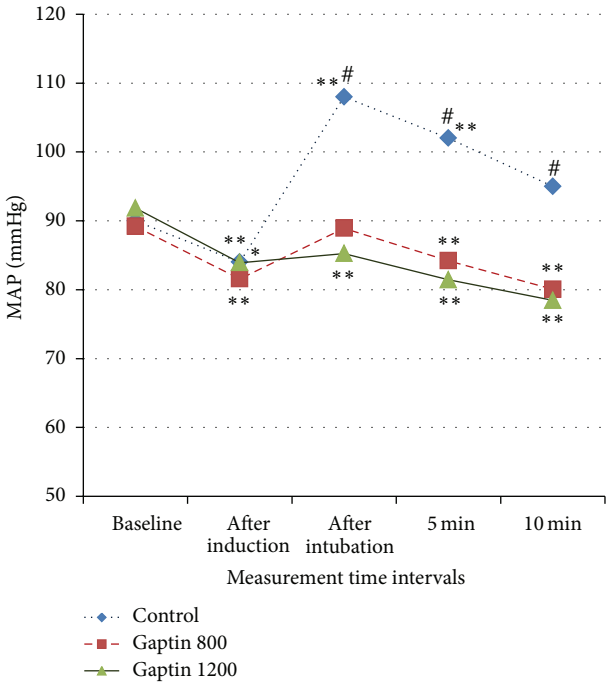


Figure 2: MAP (mmHg.) at various intervals. Data were expressed as mean ± SD. $^{\#}$Means that control group was significantly different from both groups ($P < 0.05$). $^{*}$Means significant difference from baseline value ($P < 0.05$). $^{**}$Means highly significant difference from baseline value ($P < 0.001$).

the baseline in group II, and was significantly below the baseline in group III ($P < 0.05$). The HR and MAP decreased gradually at 5 and 10 minutes after intubation but remained above the baseline in group I. Intergroup comparison showed that HR and MAP were significantly lower in group II (gabapentin 800) and group III (gabapentin 1200) than in group I (the control group) at 1, 5, and 10 minutes after intubation with no significant difference between groups II and III.

The results of the present study showed that IOP was comparable among the three groups regarding the baseline value (Table 4) (Figure 3). After induction IOP decreased significantly below the baseline in the three groups ($P < 0.05$). Immediately after intubation, the IOP increased significantly in group I and nonsignificantly in group II but remained below the baseline in group III. The IOP then decreased gradually in the three groups at 5 and 10 minutes after intubation.

Intergroup comparison showed that IOP was significantly lower in group III than group I and group II at 1, 5, and 10 minutes after intubation.

## 4. Discussion

The present study showed that gabapentin 1200 mg given to the patient 2 hours before surgery effectively prevented the increase in HR, MAP, and IOP secondary to laryngoscopy

Table 4: IOP (mean) at various intervals in the different groups.

| | Control (no. 20) | Gaptin 800 (no. 20) | Gaptin 1200 (no. 20) | $F$ | $P$ |
|---|---|---|---|---|---|
| Baseline | 15.05 ± 2.704 | 16.27 ± 2.67 | 15.7 ± 2.61 | 1.1 | 0.33 |
| After induction | 12.35 ± 2.39$^{*}$ | 12.95 ± 2.33$^{**}$ | 11.77 ± 2.18$^{**}$ | 1.31 | 0.27 |
| After intubation | 18.950 ± 2.98$^{\#**}$ | 16.37 ± 2.51$^{@}$ | 13.6 ± 2.28$^{**}$ | 31.05 | 0.000 |
| 5 min | 17 ± 2.59$^{\#*}$ | 15.15 ± 2.32$^{@**}$ | 12.65 ± 2.05$^{**}$ | 17.55 | 0.000 |
| 10 min | 15.95 ± 2.63$^{\#}$ | 14.15 ± 2.65$^{@**}$ | 12.02 ± 2.11$^{**}$ | 12.62 | 0.000 |
| $P$ | 0.000 | 0.000 | 0.000 | | |

Data were expressed as mean ± SD.
$^{\#}$Means that control group was significantly different from both groups ($P < 0.05$).
$^{@}$Means that gabapentin 800 group was significantly different from gabapentin 1200 group ($P < 0.05$).
$^{*}$Means significant difference from baseline value ($P < 0.05$).
$^{**}$Means highly significant difference from baseline value ($P < 0.001$).

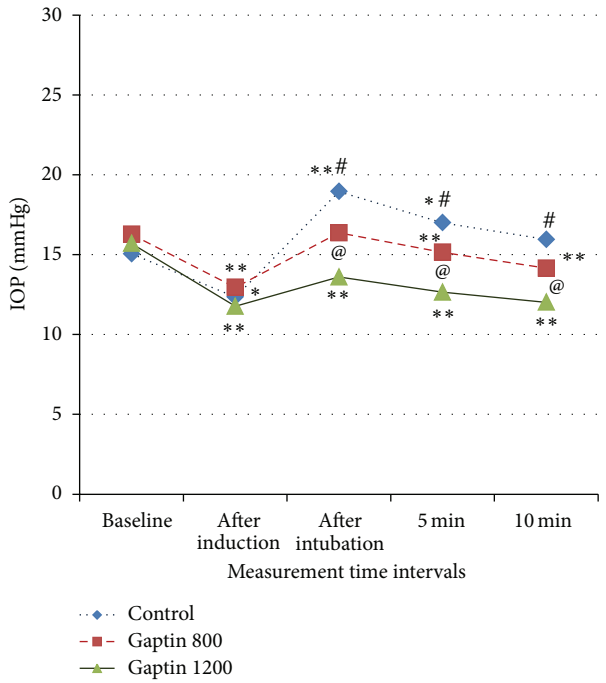


Figure 3: IOP (mmHg.) at various intervals. Data were expressed as mean ± SD. $^{\#}$Means that control group was significantly different from both groups ($P < 0.05$). $^{@}$Means that gabapentin 800 group was significantly different from gabapentin 1200 group ($P < 0.05$). $^{*}$Means significant difference from baseline value ($P < 0.05$). $^{**}$Means highly significant difference from baseline value ($P < 0.001$).

and endotracheal intubation. With gabapentin 800 mg the increase in HR and IOP due to laryngoscopy was nonsignificant and the MAP remained below the baseline.

Laryngoscopy and endotracheal intubation are known to produce a pressor response which may cause significant increase in HR, MAP, and IOP [10, 11].

Many drugs have been used to reduce this response; however most of them have side effects that limit their use [12].

Gabapentin, a structural analogue of gamma aminobutyric acid, was originally introduced as antiepileptic drug and was shown to be effective in management of neuropathic pain and in the perioperative setting as an analgesic [13, 14].

Recently the effect of gabapentin on the pressor response to laryngoscopy and intubation has been tested in some studies but with different dose regimen and conflicting results.

In a study done by Fassoulaki and coworkers [9], they found that gabapentin 1600 mg given orally in four divided doses every six hours the day before surgery attenuated the hypertensive but not the tachycardic response to laryngoscopy and tracheal intubation.

Memis and colleagues [15] reported that gabapentin 800 mg, given 1 hour before surgery, significantly reduced MAP and HR during the first 10 minutes after intubation compared to gabapentin 400 mg which failed to inhibit the pressor response to laryngoscopy and intubation.

In the study done by Bafna and associates [16], gabapentin 1000 mg given to the patient one hour before surgery resulted in significant reduction in both MAP and HR within 10 minutes after laryngoscopy and intubation, meanwhile patients who received gabapentin 600 mg showed increased MAP and HR during the study period.

In our study, single dose of gabapentin 800 mg, given 2 hours preoperative, can attenuate the hypertensive and tachycardic response to laryngoscopy and intubation; while single dose of gabapentin 1200 mg given at the same time keeps both MAP and HR below baseline values; also both doses of gabapentin (800 & 1200 mg) succeeded to reduce the MAP and HR during the first 10 minutes after intubation compared with control group in which the hemodynamic variables remained elevated during the study period.

In agreement with our study, Kaya and associates reported that oral gabapentin 800 mg given orally to the patient two hours before surgery effectively suppressed the increase in IOP and MAP secondary to endotracheal intubation [12].

The mechanism by which gabapentin attenuates the stress response to laryngoscopy and intubation is still unclear but it was proposed to be related to its antinociceptive mechanism, which most likely modulates the calcium current by selective binding to (3H) gabapentin (a radio legend), the $\alpha_2\gamma_1$ subunit of voltage dependent Ca channels, so it is possible that gabapentin acts in a way similar to calcium channel blockers

in controlling hemodynamics. It could also be suggested that there is a possible relaxing effect of gabapentin on the ciliary muscle that might decrease the IOP by improving the aqueous humor flow [17–19].

Two cases in the gabapentin 1200 mg showed a significant reduction in MAP and HR which was transient and responded rapidly to IV fluid boluses and ephedrine 3 mg while another two cases among the same group presented with bradycardia and both responded to atropine.

Limitation of the current study was the small sample size, so further studies are needed to test the efficacy and safety of gabapentin use for attenuation of pressor response and rise of IOP associated with laryngoscopy and intubation.

The current study demonstrated the beneficial effect of using either oral gabapentin 800 or 1200 mg, when given 2 hours before surgery, in attenuation of hypertension, tachycardia, and rise of IOP associated with laryngoscopy and intubation in dose-dependent manner.

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