

# Use of Gabapentin, Esmolol or Their Combination to Attenuate Haemodynamic Response to Laryngoscopy and Intubation

Shrestha GS, Marhatta MN, Amatya R

Department of Anaesthesiology  
Maharajgunj Medical Campus  
Tribhuvan University Teaching Hospital  
Maharajgunj, Kathmandu, Nepal

## Corresponding Author

Gentle Sunder Shrestha  
Department of Anaesthesiology  
Maharajgunj Medical Campus  
Tribhuvan University Teaching Hospital  
Maharajgunj, Kathmandu, Nepal  
Email: gentlesunder@hotmail.com

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## ABSTRACT

### Background

Laryngoscopy and intubation increases blood pressure and heart rate.

### Objective

The study aims to investigate the effect and safety of gabapentin, esmolol or their combination on the haemodynamic response to laryngoscopy and intubation.

### Methods

A total of 72 patients undergoing elective surgery were randomly allocated to one of the four groups. First study drug was administered orally as gabapentin 1200mg or placebo. Second study drug was administered intravenously as esmolol 1.5mg/kg or normal saline. Heart rate, rate pressure product, systolic blood pressure and mean arterial pressure were recorded at baseline and at zero, one, three and five minutes after tracheal intubation.

### Results

Baseline values were compared with the values at various time intervals within the same group. In group PE (placebo, esmolol), there was significant decrease in heart rate and rate pressure product at five minutes. In group GN (gabapentin, normal saline), there was significant decrease in systolic blood pressure and mean arterial pressure at five minutes. In group GE (gabapentin, esmolol), there was significant decrease in heart rate at zero, three and five minutes. Systolic blood pressure, mean arterial pressure and rate pressure product was significantly lower at three and five minutes. In group PN (placebo, normal saline), there was significant increase in heart rate at zero, one, three and five minutes; systolic blood pressure at zero and one minutes; mean arterial pressure at zero and one minutes & rate pressure product at zero, one and three minutes. In group GN (gabapentin, normal saline), there was significant increase in heart rate at zero, one and three minutes & rate pressure product at zero, one and three minutes. In group PE (placebo, esmolol), there was significant increase in systolic blood pressure at zero and one minutes & mean arterial pressure at zero and one minutes. However, in group GE (gabapentin, esmolol) none of the variables showed statistically significant increase at any time.

Inter-group comparison was made for each time point. At zero minute, there was significant difference in heart rate between groups PN and GE, GN and PE & GN and GE. Significant difference was also noted in rate pressure product between PN and GE at zero minute. At one minute there was difference in heart rate between PN and PE, PN and GE, GN and PE & between GN and GE. Significant difference was observed in rate pressure product between PN and PE & between PN and GE at one minute. No significant side effects of the study drugs were observed.

### Conclusions

Combination of gabapentin and esmolol in this study design is safe and better attenuates both the pressor and tachycardic response to laryngoscopy and intubation, than either agent alone.

## KEYWORDS

attenuation of haemodynamic response, Esmolol, Gabapentin, laryngoscopy and intubation

## INTRODUCTION

Laryngoscopy and tracheal intubation are associated with hypertension, tachycardia and increased circulating catecholamines.<sup>1,2</sup> Haemodynamic changes are usually transient and without sequelae. However, in patients with pre-existing coronary artery disease, hypertension or cerebrovascular disease, these changes may precipitate myocardial ischaemia, arrhythmias, myocardial infarction and cerebral haemorrhage.<sup>3,4</sup>

Various techniques have been studied to prevent or attenuate the haemodynamic response to laryngoscopy and intubation, such as omitting cholinergic medications, deepening of anaesthesia, pretreatment with nitroglycerine, beta-blockers, calcium channel blockers, gabapentin and opioids like fentanyl and remifentanyl.<sup>5-12</sup>

Gabapentin was shown to be effective in decreasing post-operative analgesic consumption and pain, prevention of postoperative nausea and vomiting, reduction of postoperative delirium, preoperative anxiolysis and attenuation of haemodynamic response to laryngoscopy and intubation.<sup>10,13-17</sup> This multimodal perioperative drug is a structural analog of  $\gamma$ -aminobutyric acid. It acts by decreasing the synthesis of neurotransmitter glutamate and by binding to  $\alpha\delta$  subunit of voltage dependent calcium channel.<sup>18,19</sup> Action similar to calcium channel blockers may be responsible for blunting haemodynamic response to laryngoscopy and intubation.<sup>20</sup>

Esmolol is a  $\beta$ 1-adrenoceptor (cardioselective) blocker. It has a very short diffusion (two minutes) and elimination half-life (nine minutes). Peak effects with bolus injections of esmolol are seen in one to two minutes.<sup>21</sup> Several studies showed esmolol to be effective in blunting the pulse rate response to laryngoscopy and intubation, but blood pressure response was blunted only at higher dose.<sup>22-25</sup>

Gabapentin is a multimodal perioperative drug. It has a favourable side effect profile and has less interaction with other drugs.<sup>26,27</sup> There are no studies comparing the efficacy of gabapentin and esmolol to blunt the haemodynamic response to laryngoscopy and intubation. So this study was conducted to compare the efficacy and safety of these agents alone or in combination.

## METHODS

Patients scheduled for elective surgery with American Society of Anaesthesiologists (ASA) physical status I and II, weighing 40 to 70 kgs and with age 18 to 65 years were enrolled in the study. The study was conducted in Tribhuvan University Teaching Hospital between January to March 2011. Patients with pre-existing cardiopulmonary disease, with contraindications or known hypersensitivity to study drug or on antihypertensive medications or drugs with effect on central nervous system were excluded. Patients with anticipated difficult airway and with duration of

laryngoscopy more than 30 seconds or with more than one attempt at intubation were also excluded from the study.

Patients were randomly assigned to one of the four study groups PN (placebo normal saline), PE (placebo, esmolol), GN (gabapentin, normal saline) or GE (gabapentin, esmolol) using a sealed envelope method. In each group 18 patients were enrolled. First study drug was administered orally two hours before induction. It was placebo capsules for group PN and PE. Two gabapentin capsules with 600mg in each were administered as first study drug in group GN and GE. Second study drug was administered intravenously two minutes before laryngoscopy and intubation. It was 11 ml of normal saline in group PN and GN. Esmolol 1.5 mg/kg, diluted to 11 ml, was given as second study drug in group PE and GE.

Patients were fasted for six hours before study. Any side effects of first study drug like nausea and vomiting, dizziness, somnolence, ataxia and headache were noted before induction. Ringer's lactate seven milliliters per kilogram was given intravenously before induction. Heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were noted at baseline, after induction, immediately after intubation (zero minute) and at one, three and five minutes after intubation. Mean arterial pressure (MAP) and rate pressure product (RPP) were calculated from these parameters. Pethidine 0.75mg/kg was given as an analgesic. Patients were induced with propofol 2 to 2.5 mg/kg and vecuronium 0.1 mg/kg was given as a muscle relaxant. Second study drug was administered two minutes after giving vecuronium. HR less than 45 beats/min was treated with Inj. atropine in increments of 0.3 mg and fall in SBP of more than 30% below the baseline for longer than 60 seconds was treated with Inj. mephentermine in increments of three milligrams. Increase in SBP of more than 30% of baseline for longer than 60 seconds or HR of more than 130 beats/min for longer than 60 seconds was managed by increasing the inspired Halothane concentration in increments of 0.5%. Surgical incision was delayed for five minutes after intubation.

ANOVA was used with Bonferroni test for group differences. Paired t test was used for comparison with baseline. Independent t test was used for comparison between the groups. Chi square test was used for studying association between categorical variables. Statistical analyses were done with SPSS 17.0 package program for Windows.

Sample size (72 patients) was calculated to ensure power of 0.80 using Russell-Lenth's power/sample-size calculator.<sup>28</sup> Pretest of 50 cases was done for sample size calculation.

## RESULTS

Demographic variables did not differ significantly between the groups (table 1).

Within individual groups, baseline haemodynamic variables were compared with variables at various time intervals

**Table 1. Patient characteristics. (Values are Mean±SD)**

Variable	Group PN	Group PE	Group GN	Group GE	p value
Age (yrs)	32.11±9.74	31.11±12.26	37.78±12.56	34.00±10.66	0.31
Weight (kg)	56.67±7.17	51.61±6.99	53.72±9.40	57.11±8.25	0.14

**Table 2. Comparison of haemodynamic variables with baseline.**

	Group PN Mean±SD	Group GN Mean±SD	Group PE Mean±SD	Group GE Mean±SD
<b>Heart Rate (beats/min)</b>				
Baseline	77.72±13.62	80.17±14.54	87.22±11.72	87.94±14.51
Induction	79.83±15.70	82.56±18.65	81.78±11.46	87.67±14.74
Intubation	94.39±15.06**	100.17±19.33**	84.78±13.37	82.78±14.88#
1 min	101.28±16.73**	96.28±14.82**	83.78±11.99	84.17±17.15
3 min	93.22±14.86**	92.50±11.92*	84.44±14.51	82.83±17.21#
5 min	85.83±15.92*	81.83±16.72	81.72±14.57#	78.89±13.08##
<b>Systolic Blood Pressure (mm of Hg)</b>				
Baseline	117.28±18.08	125.94±15.90	117.67±14.78	128.56±16.96
Induction	105.78±13.22	112.56±17.98	109.67±13.99	117.06±18.57
Intubation	134.50±17.91**	123.44±17.33	129.94±19.53*	125.50±20.67
1 min	134.50±18.87**	124.06±14.77	128.94±15.83**	122.78±21.06
3 min	122.61±19.55	121.44±16.15	120.78±14.39	116.67±17.61#
5 min	116.28±19.08	116.17±16.43#	113.06±14.07	113.50±19.36#
<b>Mean Arterial Pressure (mm of Hg)</b>				
Baseline	88.05±13.08	94.28±9.94	88.96±11.56	96.85±15.19
Induction	79.04±11.14	84.11±13.30	81.81±12.52	87.87±15.61
Intubation	103.76±15.20**	96.48±12.28	102.72±16.77*	95.06±16.49
1 min	101.98±14.69*	95.20±11.76	98.43±14.64*	93.22±17.23
3 min	92.06±14.55	93.04±11.03	93.52±13.68	89.30±16.45#
5 min	87.39±17.05	87.24±9.86#	86.35±13.98	86.02±16.27#
<b>Rate Pressure Product (beats . mm Hg/min)</b>				
Baseline	9233.11±2817.85	9994.67±1733.24	10313.89±2262.02	11456.17±3012.55
Induction	8432.94±1931.33	9141.56±1861.94	8967.72±1747.33	10416.33±2998.95
Intubation	12832.44±3281.53**	12311.67±2841.93**	11118.44±3029.77	10537.06±3222.62
1 min	13670.11±3402.72**	11973.89±2548.82**	10879.72±2539.17	10557.39±3473.41
3 min	11471.89±2933.95**	11231.56±2123.22*	10276.11±2628.31	9879.44±3368.19#
5 min	10040.17±2605.75	9525.22±2581.54	9282.83±2253.37#	9131.39±2823.11##

\* p<0.05 (increase), \*\* p< 0.01 (increase), # p<0.05 (decrease), ## p< 0.01 (decrease)

(Table 2). In group PE, there was significant decrease in HR at five minutes (p<0.05) & RPP at five minutes (p<0.05). In group GN, there was significant decrease in SBP at five minutes (p<0.05) & MAP at five minutes (p<0.05). In group GE, there was significant decrease in HR at zero minute (p<0.05), three minutes (p<0.05) and five minutes (p<0.01); RPP at three minutes (p<0.05) and five minutes (p<0.01); SBP at three minutes (p<0.05) and five minutes (p<0.05) & MAP at three minutes (p<0.05) and five minutes (p<0.05).

In group PN, there was significant increase in HR at zero minute (p<0.01), one minute (p<0.01), three minutes (p<0.01) and five minutes (p<0.05); SBP at zero minute (p<0.01) and one minute (p<0.01); MAP at zero minute

(p<0.01) and one minute (p<0.05) & RPP at zero minute (p<0.01), one minute (p<0.01) and three minutes (p<0.01). In group GN, there was significant increase in HR at zero minute (p<0.01), one minute (p<0.01) and three minutes (p<0.05) & RPP at zero minute (p<0.01), one minute (p<0.01) and three minutes (p<0.05). In group PE, there was significant increase in SBP at zero minute (p<0.05) and one minute (p<0.01) & MAP at zero minute (p<0.05) and one minute (p<0.05). However, in group GE, none of the variables showed statistically significant increase at any time.

Inter-group comparison was made for each time point

**Table 3.** Inter-group comparison for each time point.

	Group PN Mean±SD	Group GN Mean±SD	Group PE Mean±SD	Group GE Mean±SD
<b>Baseline</b>				
Heart Rate (beats/min)	77.72±13.62	80.17±14.54	87.22±11.72	87.94±14.51
SBP (mm Hg)	117.28±18.08	125.94±15.90	117.67±14.78	128.56±16.96
MAP (mm Hg)	88.06±13.08	94.28±9.94	88.96±11.56	96.85±15.19
RPP (beats.mmHg/min)	9233.11±2817.85	9994.67±1733.24	10313.89±2262.02	11456.17±3012.55
<b>Induction</b>				
Heart Rate (beats/min)	79.83±15.70	82.56±18.65	81.78±11.46	87.67±14.74
SBP (mm Hg)	105.78±13.22	112.56±17.98	109.67±13.99	117.06±18.57*
MAP (mm Hg)	79.04±11.14	84.11±13.30	81.81±12.52	87.87±15.61
RPP (beats.mmHg/min)	8432.94±1931.33	9141.56±1861.94	8967.72±1747.33	10416.33±2998.95*
<b>Intubation</b>				
Heart Rate (beats/min)	94.39±15.06	100.17±19.33	84.78± 13.37 <sup>!!</sup>	82.78±14.88 <sup>**§</sup>
SBP (mm Hg)	134.50±17.91	123.44±17.33	129.94±19.53	125.50±20.67
MAP (mm Hg)	103.76±15.20	96.48±12.28	102.72±16.77	95.06±16.49
RPP (beats.mmHg/min)	12832.44±3281.53	12311.67±2841.93	11118.44±3029.77	10537.06±3222.62*
<b>1 minute</b>				
Heart Rate (beats/min)	101.28±16.73	96.28±14.82	83.78±11.99 <sup>^!!</sup>	84.17±17.15 <sup>***§</sup>
SBP (mm Hg)	134.50±18.87	124.06±14.77	128.94±15.83	122.78±21.06
MAP (mm Hg)	101.98±14.69	95.20±11.76	98.43±14.64	93.22±17.23
RPP (beats.mmHg/min)	13670.11±3402.72	11973.89±2548.82	10879.72±2539.17 <sup>^^</sup>	10557.39±3473.41*
<b>3 minute</b>				
Heart Rate (beats/min)	93.22±14.86	92.50±11.92	84.44±14.51	82.83±17.21
SBP (mm Hg)	122.61±19.55	121.44±16.15	120.78±14.39	116.67±17.61
MAP (mm Hg)	92.06±14.55	93.04±11.03	93.52±13.68	89.30±16.45
RPP (beats.mmHg/min)	11471.89±2933.95	11231.56±2123.22	10276.11±2628.31	9879.44±3368.19
<b>5 minute</b>				
Heart Rate (beats/min)	85.83±15.92	81.83±16.72	81.72±14.57	78.89±13.08
SBP (mm Hg)	116.28±19.08	116.17±16.43	113.06±14.07	113.50±19.36
MAP (mm Hg)	87.39±17.05	87.24±9.86	86.35±13.98	86.02±16.27
RPP (beats.mmHg/min)	10040.17±2605.75	9525.22±2581.54	9282.83±2253.37	9131.39±2823.11

\* p<0.05 (Group PN Vs Group GE), \*\* p<0.01 (Group PN Vs Group GE), § p<0.05 (Group GN Vs GE), §§ p<0.01 (Group GN Vs Group GE), ^^ p<0.01 (Group PN Vs PE), !! p<0.01 (Group GN Vs PE)

(Table 3). At zero minute, there was significant difference (p<0.05) in HR between groups PN and GE (94.39±15.06 Vs 82.78±14.88), GN and PE (100.17±19.33 Vs 84.78±13.37) & between GN and GE (100.17±19.33 Vs 82.78±14.88). Significant difference (p<0.05) was also noted in RPP between PN and GE (12832.44±3281.53 Vs 10537.06±3222.62) at zero minute. At one minute there was difference (p<0.05) in HR between PN and PE (101.28±16.72 Vs 83.78±11.99), PN and GE (101.28±16.72 Vs 84.17±17.15), GN and PE (96.28±14.82 Vs 83.78±11.99) & between GN and GE (96.28±14.82 Vs 84.17±17.15). Significant difference (p<0.05) was observed in RPP between PN and PE (13670.11±3402.72 Vs 10879.72±2539.17) & between PN and GE (13670.11±3402.72 Vs 10557.39±3473.41) at one minute.

There was no incidence of nausea and vomiting, respiratory depression, dizziness, somnolence, ataxia and headache

before induction of anaesthesia. One patient in Group PE developed bradycardia with heart rate upto 40 beats per minute, 25 minutes after administering the second study drug. It was treated with Inj. Atropine 0.3mg. None of the patients needed Mephentermine for correction of hypotension.

## DISCUSSION

To attenuate the pressor response to laryngoscopy and intubation, studies were done on gabapentin at various doses.<sup>10,17,29-31</sup> Results are variable and most of the studies showed predominantly blood pressure attenuating effect of gabapentin.<sup>10,29-31</sup> A meta-analysis on the use of gabapentin for postoperative analgesia showed the dose of 1200mg to be more effective than the dose of 300mg or 400mg for reducing postoperative opioid consumption.<sup>32</sup> Moreover, a

single 1200mg dose before surgery was found to reduce the incidence of postoperative nausea and vomiting.<sup>33,34</sup> Gabapentin was found to be safe and devoid of significant side effects. So, a single preoperative dose of 1200mg was chosen in our study.

Esmolol is effective in attenuating the haemodynamic response in a dose dependent manner.<sup>35</sup> When used in a dose of 1.5 mg/kg, it was safe and predominantly suppressed the heart rate response.<sup>22,36,37</sup> So this dose was used in our study.

When compared with baseline values, in Group GN, there was significant increase in heart rate, but the systolic blood pressure was decreased at five and 10 minutes and mean arterial pressure was decreased at five minutes. The findings are consistent with the study by Kumari I and colleagues.<sup>30</sup> As in our study, Kaya FN and colleagues did not find gabapentin to be effective to blunt the heart rate response, but blood pressure response was better attenuated, probably due to use of Fentanyl before intubation in their study.<sup>29</sup>

In Group PE, blood pressure increased at intubation and one minute, but the heart rate and rate pressure product decreased at five and 10 minutes. Findings are consistent with the study by Ugur B et al.<sup>22</sup> Similarly, in a study by Rathore A and colleagues, heart rate response was blunted at the dose of 50 and 100mg.<sup>25</sup> Blood pressure response was blunted only at the dose of 150mg.

In Group GE, when compared with baseline, there was no significant increase in variables at any time. There was significant decrease in heart rate at intubation, three, five and 10 minutes. Systolic blood pressure, mean arterial pressure and rate pressure product was decreased at three, five and 10 minutes.

Comparison between the groups showed significant decrease in heart rate, systolic blood pressure and rate pressure product at various times when Group GE was compared with Group PN and GN. Also, there was significant reduction in heart rate and rate pressure product in Group PE when compared with Group PN and GN. Except for an episode of bradycardia in Group PE, treated with Inj. Atropine, other significant adverse effects were not noted.

There are few limitations of this study. Patients with ASA physical status I and II were enrolled in the study, so the results cannot be generalized to the patients with higher ASA status. Fixed dose of gabapentin and esmolol were used, so further studies may help find the optimal safe dose. The study was conducted in a single centre. A multicentered larger study may be more informative.

## CONCLUSION

Combination of gabapentin and esmolol in this study design is safe and better attenuates both the heart rate and blood pressure response to laryngoscopy and intubation,

than either agent alone.

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