The use of Gabapentin, Clonidine, or Esmolol to attenuate the haemodynamic response to laryngoscopy and intubation

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ABSTRACT

Laryngoscopy and intubation increases blood pressure and heart rate. The study aims to investigate the effect and safety of gabapentin, clonidine or esmolol on the haemodynamic response to laryngoscopy and intubation. Fifty-six ASA I and II patients undergoing elective surgery were randomly allocated to one of the four groups. First study drug was administered orally as gabapentin 1200mg or clonidine 200 µg or placebo. Second study drug was administered intravenously as esmolol 1.5mg/kg or normal saline. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded at baseline and at 0, 1, 3 and 5 minutes after tracheal intubation. Rate pressure product (RPP) was calculated. Baseline values were compared with the values at various time intervals within the same group. Inter-group comparison was made for each time point. In Gabapentin group there was no increase in SBP and MAP in response to laryngoscopy and intubation but HR and RPP were significantly high at 0, 1, 3 and 5 minutes. In Esmolol group, there was no increase in HR response to laryngoscopy and intubation but there was significant high SBP and MAP at 0, 1, 3 and 5 minutes of intubation. In clonidine group, there was significant increase in HR, SBP and MAP at 0 minute, which returned to baseline at 1 minute. The variables were similar to baseline at 3 and 5 minutes. No side effects were observed during the study. Gabapentin at 1200mg blunts mainly the hypertensive response to laryngoscopy and intubation while Esmolol at 1.5 mg/kg blunts mainly increase in heart rate response. Clonidine at 200mcg blunts both increase in blood pressure and heart rate response to laryngoscopy and intubation. Multicentered comparative studies involving larger patient population, is required to generalize our result. Also further studies regarding the combination of these agents and in sicker group of population (ASA III and IV) are to be considered.

Keywords: attenuation of haemodynamic response, Clonidine, Esmolol, Gabapentin, laryngoscopy and intubation

INTRODUCTION

Direct laryngoscopy and tracheal intubation lead to increase in heart rate and blood pressure.[1] Mechanism of cardiovascular response to intubation is considered to be a reflex sympathetic response to the mechanical stimulation of larynx and trachea. Significant increase in circulating cathecolamines with laryngoscopy with or without tracheal intubation has been described.[2,3]

Various anaesthetic drugs and techniques have been described to control the haemodynamic response to the laryngoscopy and intubation, such as omitting cholinergic medications,[4] deepening of anaesthesia,[5] pretreatment with nitrglycerine,[6] administration of beta-blockers,[7] calcium channel blockers,[8] gabapentin,[9] clonidine[10] and opioids like fentanyl[11] & remifentanyl.[12] The technique or drug of choice depends upon the necessity and duration of the operation, choice of anaesthetic technique, route of administration, and medical condition of the patient.[6,13]

Gabapentin, a structural analog of gamma-aminobutyric acid, is a multimodal perioperative drug which attenuates haemodynamic response to laryngoscopy and intubation,[9,14] reduces preoperative anxiety,[15] prevents postoperative nausea and vomitting,[16] reduces the postoperative requirement of analgesics[17] and decreases postoperative delirium.[18]

The mechanism by which gabapentin attenuates the pressor response to laryngoscopy and intubation is unidentified. The drug inhibits membrane voltage-gated calcium channel, therefore acting like calcium channel blocker.[19] The most common adverse effects of gabapentin are somnolence (20%), ataxia (13%), fatigue (11%), and dizziness (8%). The other complications are nystagmus, headache, diplopia, tremor and nausea, each one less than 10%.[20] At the dose of 1200 mg, Gabapentin was demonstrated to be effective in attenuating the response to laryngoscopy and intubation.[21]

Clonidine activates the α-2 receptor of the brain and spinal cord to decrease the sympathetic outflow, causing sedation, analgesia, hypotension and bradycardia without significant respiratory depression.[10] It is well absorbed after oral administration with peak plasma

concentration in 75 to 90 minutes. Preoperative use decreases the intraoperative stress response by reducing the nociceptive transmission and decreases norepinepherine concentration in serum, provided haemodynamic stability.[22,23] Laisalmi M et al concluded that premedication with clonidine blunts the stress response to surgical stimuli and reduces the requirement of narcotic and anaesthetic agents.[24]

Esmolol is a β_1-adrenoceptor blocker. It has a very short diffusion (2 minutes) and elimination half-life (9 minutes). Peak effects with bolus injections of esmolol are seen in 1-2 minutes.[25] Several studies showed esmolol to be effective in blunting the pulse rate response[26,27] to laryngoscopy and intubation, but blood pressure response was attenuated only at higher dose.[28,29] Esmolol is effective in attenuating the haemodynamic response in a dose dependent manner.[30] When used in a dose of 1.5 mg/kg, it was safe and predominantly suppressed the heart rate response.[26,31,32]

There are no studies comparing the efficacy of gabapentin, esmolol and clonidine to blunt the haemodynamic response to laryngoscopy and intubation. So this study was conducted to compare the efficacy and safety of these agents.

MATERIALS AND METHODS

After obtaining approval from Institution Review Board (IRB) and written informed consent from all patients, fifty-six American Society of Anaesthesiologist (ASA) I and II patients, aged 18-65 years and weighing 40 to 70 kgs, scheduled for elective surgery under general anaesthesia requiring endotracheal intubation, were enrolled in our study. 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 allocated to one of the four study groups PN, GN, PE or CN using a sealed envelope method. In each group 14 patients were enrolled. First study drug was administered orally two hours before induction. It was placebo capsules for group PN and PE. Two gabapentin tablets (600 mg in each) were administered as first study drug in group GN and two clonidine tablets (100 mcg in each) were administered in group CN. Second study drug was administered intravenously two minutes before laryngoscopy and intubation. It was 11 ml of normal saline in group PN, GN and CN and Esmolol 1.5 mg/kg, diluted to 11 ml, in the group PE. The study drugs containing placebo, gabapentin, clonidine and esmolol were prepared in a double blind fashion, by a collaborator not involved in the data recording and an appropriate code number was assigned. The same collaborator administered the drugs while a blind observer collected data.

Patients were fasted for 6 hours before surgery. No premedication was administered. Any side effects of first study drug like nausea and vomiting, dizziness, somnolence, ataxia and headache were noted before induction. In the operating room, IV access was secured with 18-20 G IV cannula in the dorsum of hand and Ringer's lactate was administered intravenously at 7ml/kg/hour. Pre-induction heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and rate pressure product (RPP) were recorded as baseline value. 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 1 minute after administration of vecuronium. Patients were intubated using Macintosh 3 blade with appropriate sized tube. Patients were mechanically ventilated with tidal volume of 8ml/kg and a respiratory rate of 12-14/min. In each patient, HR, SBP, DBP & MAP were recorded immediately after laryngoscopy and intubation (0 minute) and at 1 min, 3min 5 mins and 10 mins by an independent investigator unaware of the group assignment. The rate pressure product was calculated by multiplying HR and SBP. Surgical incision was delayed for 5 minutes after intubation.

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 3 mg. 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%.

Statistical analysis

ANOVA was used with Bonferroni test for group differences. Paired t test was used for comparison with baseline. Independent t test was use 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 calculation

Sample size (56 patients) was calculated to ensure power of 0.80 using Russell-Lenth's power/sample-size calculator.[33] Pretest of 20 cases was done for sample size calculation.

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

Variable	Group PN	Group GN	Group PE	Group CN	p value
Age (yrs)	33.21±10.35	38.29±14.23	29.50±12.04	31.00±13.13	0.27
Weight (kg)	58.86±6.18	54.50±8.47	51.00±8.12	53.71±7.14	0.06

RESULTS

Demographic characteristics were similar in the four groups (Table 1).

The preoperative heart rate (HR), systolic blood pressure (SBP), mean arterial blood pressure (MAP) and rate pressure product (RPP) values were similar in the three groups (Table 2). After induction, HR increased in group PN and GN but HR decreased in group PE and CN but all the changes were non significant. Immediately after intubation, HR increased significantly in group PN ($p<0.01$), GN ($p<0.01$) and CN ($p<0.01$) but the increase in HR was not significant in group PE. At 1 and 3 minutes, there was significant increase in HR in group PN ($p<0.01$) and GN ($p<0.01$) but was not significant in group PE and CN. At 5 minutes, there was increase in HR in group PN and GN but there was decrease in HR in group PE and CN, but all the changes were not significant.

Systolic blood pressure at baseline was similar in all the groups. There was fall in SBP immediately after induction however, the changes were not significant. Immediately after intubation, there was significant rise in SBP in group PN ($p<0.01$), PE ($p<0.01$) and CN ($p<0.05$) but there was no significant change in GN group. At 1 minutes, the rise in SBP was significant in group PN ($p<0.01$) and PE ($p<0.01$) but not significant in group

Table-2: Comparison of haemodynamic variables with baseline.

	Group PN	Group GN	Group PE	Group CN
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Heart Rate (beats/min)				
Baseline	77.71±14.71	80.79±15.64	83.86±11.11	76.57±14.60
Induction	79.21±17.12	85.36±20.17	79.50±11.78	75.36±18.33
Intubation	96.21±15.42**	98.43±20.31**	83.93±14.96	87.71±15.47**
1 min	102.93±17.48**	96.14±15.84**	83.29±13.10	80.93±14.70
3 min	92.36±15.92**	92.86±11.47**	84.07±15.98	75.14±13.72
5 min	85.21±16.48	83.57±18.30	80.79±15.80	73.50±11.69
Systolic Blood Pressure (mm of Hg)				
Baseline	120.93±18.52	125.50±16.68	116.64±12.13	115.57±15.73
Induction	107.43±13.00	113.79±19.02	110.21±13.09	101.86±8.05
Intubation	137.21±18.99**	122.36±18.56	132.43±20.10**	123.43±19.86*
1 min	135.86±20.71**	123.14±15.10	129.57±16.01**	121.00±21.80
3 min	123.43±21.25	121.79±16.89	120.07±13.64	116.71±18.44
5 min	117.64±20.21	117.71±18.07#	111.57±13.45	111.21±16.98
Mean Arterial Pressure (mm of Hg)				
Baseline	90.69±13.09	94.07±10.85	87.26±10.06	87.71±11.11
Induction	79.71±11.44	85.36±14.67	83.02±10.61	75.62±6.53
Intubation	105.31±15.49**	95.26±13.27	103.95±17.52**	95.62±16.49*
1 min	101.43±16.28*	94.38±12.54	99.24±14.40**	93.81±17.66
3 min	91.91±15.85	93.07±11.32	92.93±13.43	84.95±14.53
5 min	87.36±18.00	87.72±10.72#	85.09±13.49	79.98±14.40#
Rate Pressure Product (beats . mm Hg/min)				
Baseline	9554.29±3088.13	10039.00±1931.97	9796.07±1795.24	8793.71±1804.19
Induction	8503.79±2085.39	9509.21±1883.44	8718.14±1392.11	7729.86±2331.05
Intubation	13344.57±3418.99**	11932.50±2716.77**	11216.93±3253.92*	10877.43±2915.98**
1 min	14056.79±3724.42**	11868.50±2654.47**	10888.36±2765.57*	9837.14±2779.35*
3 min	11481.57±3315.60**	11270.14±1913.52*	10175.64±2766.55	8827.43±2356.33
5 min	10095.86±2748.08	9847.93±2806.60	9047.50±2282.48	8219.57±2055.05

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

GN and CN. At 3 minutes, the SBP was higher in group PN, PE and CN which were not significant, but there was insignificant fall in SBP in group GN. At 5 minutes, the SBP was lower than the base line in groups PN, PE and CN which were not significant but the fall in SBP was significant in group GN($p<0.05$).

MAP prior to induction was similar in all the groups. There was fall in MAP immediately after induction, however all the changes were not significant. Immediately after intubation there was significantly rise in MAP in group PN ($p<0.01$),PE ($p<0.01$) and CN ($p<0.05$) but there was no significant increase in MAP in GN group. At 1 minutes, the rise in MAP was significant in group PN ($p<0.05$) and PE ($p<0.01$) but not significant in group PE and CN. At 3 minutes, the MAP was higher in group PN and PE which were no significant but there was fall in MAP in group GN and CN which were also not significant. At 5 minutes, the MAP was lower than the baseline in groups GN ($p<0.05$) and CN ($p<0.05$) which were significant but the fall in MAP in group PN and PE were not significant.

Rate pressure product (RPP) at baseline was similar in all the groups. There was fall in RPP immediately after induction, however all the changes were not significant. Immediately after intubation, there was highly significant rise in RPP in groups PN ($p<0.01$), GN ($p<0.01$) and CN ($p<0.01$) and a significant rise in group PE ($p<0.05$). At 1 minutes, the rise in RPP was highly significant in group PN ($p<0.01$) and GN ($p<0.01$) and significant in group PE ($p<0.05$) and CN ($p<0.05$) when compared with baseline. After 3 minutes, the values of RPP were significantly higher than baseline value in group PN ($p<0.01$) and group GN ($p<0.05$) but the rise was non significant in group PE and CN. At 5 minutes, the RPP values in all the groups were insignificantly higher than baseline.

There was no incidence of nausea and vomiting, respiratory depression, dizziness, smonlence, ataxia and headache after administration of first study drug and before induction. None of the patients developed bradycardia and hypotension.

DISCUSSION

The present study compares the efficacy of Clonidine, Gabapentin and Esmolol administered prior to surgery for controlling cardiovascular responses to laryngoscopy and tracheal intubation. Clonidine and Esmolol were better in blunting the increase in heart rate response of intubation than the gabapentin and normal saline. Gabapentin and Clonidine were better in blunting the increase in blood pressure response to intubation than esmolol and normal saline. There were no cases of bradycardia, tachycardia, arrhythmia, ST segment or other ECG change and hypotension observed in our study.

To attenuate the pressure response to laryngoscopy and intubation, studies were done on gabapentin at various doses.[9,14,21,34,35] There are additional advantages with use of single dose of 1200 mg preoperatively, namely reduction of postoperative opioids consumption,[36] reduction of postoperative nausea and vomiting[37] with no significant adverse effects. Previous study using 1200mg of Gabapentin was shown to be safe and effective.[21] So, we chose a single preoperative dose of 1200mg.

In our study, Gabapentin blunted the increase in SBP and MAP in response to laryngoscopy and intubation but there was no effect on HR and RPP as observed at 0, 1, 3 and 5 minutes which was also observed in the study by Fassoulaki A et al.[9] However in other studies, gabapentin was effective in blunting both tachycardic and hypertensive response to intubation.[35,38]

Esmolol is effective in attenuating the haemodynamic response in a dose dependent manner.[33] When used in a dose of 1.5mg/kg, it was safe and predominantly suppressed the heart rate response.[39,40,41]So this dose was chosen in our study.

In our study, Esmolol blunted the response to laryngoscopy and intubation by predominantly suppressing the tachycardic response rather than hypertensive response at 0,1,3 and 5 minutes of intubation as observed in other studies.[39-41]

Clonidine is effective in attenuating the haemodynamic response to tracheal intubation.[10] Previous investigations showed that a dose of 300 microgram orally decreases the sympathetic response. With this dose intraoperaive and postoperative hypotension was observed to be significant.[42,43]Lower dose of 150-200 microgram also blunted haemodynamic response to intubation.[35,42,43] Thus, in our study we choose a single dose of 200 mcg clonidine, which was administered 90 minutes prior to laryngoscopy.

In clonidine group, there was significant increase in HR, SBP and MAP immediately after intubation, which returned to baseline at 1minute. After that, the measured variables were similar to base line at 3 and 5 minutes suggesting clonidine to be effective for controlling blood pressure and heart rate response to intubation. Similar results were observed in other studies.[35,38,44]

We did not measure the stress mediators such as plasma cathecolamines level or cortisone level and we did not calculate the sedation scores. The type of surgery and the quantity of surgical stimulus was not adjusted in first

5 minutes of the induction. These are the limitation of our study.

The advantage of using Gabapentin, Esmolol or Clonidine as a premedication to blunt haemodynamic response to laryngoscopy and intubation are easy administration, no significant side effects and availability at low cost. Besides, gabapentin and clonidine has additional antinociceptive property.

In conclusion, our study showed that oral gabapentin 1200 mg and oral clonidine 200 mcg administered 90 minutes prior to laryngoscopy & IV esmolol 1.5 mg/kg 90 seconds prior to laryngoscopy comparably blunted haemodynamic response to laryngoscopy and intubation. However, neither of the agents are ideal. Combination of the agents might be better. Multicentered studies involving larger population and involving ASA III and IV patients are recommended. Comparative study of these agents alone and in combination and also with other agents like dexmedetomidine will be prudent.

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