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ATTENUATION OF PRESSURE RESPONSE DURING LARYNGOSCOPY AFTER USING NITROGLYCERINE AND ESMOLOL –A COMPARATIVE STUDY .

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ABSTRACT

BACKGROUND- Pressure response after direct laryngospy produces deleterious effects on patients. Different drugs and methods are tried to abolish this responces. Efficacy of a continuous infusion of esmolol and nitroglycerine in attenuating the haemodynamic response to direct LI in elective surgery under general anaesthesia evaluated in this study.

Materials and Methods- 150 patients randomly allocated in three equal groups. Group E received esmolol 100 µg/kg/minute intravenous, Group N received nitroglycerine 0.5 µg/kg/minute i.v. and Group C (control) received 50 cc normal saline infusions. Pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) compared in three groups.

Results- Esmolol showed lowest pulse rate 1, 3, 5 post intubation minutes (4.94±9.91, 1.56±7.96,-1.96±7.222) respectively. At 3 and 5 minutes esmolol has reduced mean SBP below the pre-intubation level (-4.4 and –10.34 respectively). Whereas in nitroglycerine group reduction of mean SBP below pre-intubation level found at 5 minutes after intubation (-6.98). Esmolol effectively bring down the DBP at normal level at 3 minutes **(0.78±7.49)**. At 5 minutes after intubation both nitroglycerine **(-4.14±5.96)** and esmolol **(-3.48±7.34)** has brought down the DBP below pre-intubation level. At 3 minutes mean MBP in esmolol group reduced to below pre-intubation level (-0.96) and the same changes occurred in both esmolol and nitroglycerine group at 5 minutes after intubation (-5.71 and -5.08 respectively) .

Conclusion- We conclude that Esmolol was more effective than Nitroglycerine in controlling the hemodynamic responses to direct laryngoscopy and endotracheal intubation

KEYWORDS : Nitroglycerine,esmolol, Direct Laryngospy, Pressure Response

INTRODUCTION

Direct laryngoscopy and endotracheal intubation(LI) frequently induces a transient cardiovascular stress response characterized by tachycardia, hypertension, tachyarrhythmia and increased serum concentration of catecholamines[1,2,3] ,transient rise in central venous pressure[4,5]. Recent evidence also suggests that tracheal intubation is a strong stimulus for coronary vasoconstriction[6]

Stimulation of the receptors in the epipharynx, laryngopharynx and the tracheobronchial tree, during laryngoscopy and intubation results in reflex cardiovascular responses and marked increase in the elaboration of the sympathomimetic amines [7].These responses are more pronounced during the stimulation of the epipharynx than during stimulation of the tracheobronchial tree[7]. Also they are most likely during light levels of anesthesia and in association with hypoxia, hypercarbia and acidosis[8].

In healthy patients these haemodynamic effects are generally well tolerated but may produce deleterious effects in the presence of coronary or cerebral atheromas or preexisting hypertension[9,-12]

Various drugs have been used to attenuate these haemodynamic responses with a varying degree of success like, intravenous and topical lignocaine[13,14]; narcotic analgesics[15,16]; deep general anaesthesia[17]; beta blockers[18,19]; calcium channel blockers[20,21]; sodium nitroprusside (SNP)[22]. Phentolamine, clonidine, nitroglycerine and hydralazine have also been used[23,24,25,26-32]. Each of these drugs has some disadvantages.

Esmolol hydrochloride is a cardio selective intravenous (i.v) beta adrenoceptor(β-AR) antagonist. It has rapid onset of action, exerts a peak haemodynamic effect within minutes and short elimination half time of nine minutes[30, 32]. Likewise nitroglycerine is short acting vasodilator acting on venous capacitance and arteriolar resistance vessels thereby increasing oxygen supply to the myocardium[33, 34]. The effect can be titrated safely and quickly.

The present study was undertaken to compare the efficacy of a continuous infusion of esmolol and nitroglycerine in attenuating the haemodynamic response to direct LI elective surgery under general anaesthesia.

OBJECTIVES OF THE STUDY-

1. To observe the effects of intravenous nitroglycerine at a dose of 0.5 µg/kilogram/minute in attenuating pressor responses to laryngoscopy and intubation.

2. To observe the effects of intravenous esmolol at a dose of 100 µg/kilogram/minute in attenuating pressor responses to laryngoscopy and intubation.

MATERIALS AND METHODS ---- Following Institutional Ethics Committee approval, written consent from 150 adult ASA physical status I & II of age 17-45 years of both sexes scheduled for elective non-cardiac surgery requiring general anaesthesia with endotracheal intubation were enlisted in the study. Patient refusal,Extremes of age,ASA physical status III, IV&V patients,Mallampati grade III&IV,Distorted neck anatomy,Duration of laryngoscopy ≥15 seconds,Bronchial asthma,Chronic obstructive pulmonary disease,History of previous Cerebrovascular accident,Raised intracranial tension,Cerebral aneurys, Cardiovascular, hepatic, metabolic disorders,History of taking

antihypertensive, antidiabetic, and anti-asthma drugs,Raised intraocular pressure were excluded from the study.

A detailed history, systemic examination and laboratory findings were checked .Patients were randomly allocated in three groups of 50 (n=50) according to the drugs received.

Group E received esmolol 100 µg/kg/minute intravenous and Group N received nitroglycerine 0.5 µg/kg/minute i.v. and Group C (control) received 50 cc normal saline infusions. Both the drugs diluted to prepare 50 cc infusion solutions. Person A injected study drug as per study protocol. Person B monitored pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) with respect to time, while Person C intubated the patient (Person C was kept constant throughout the study). Person B was kept unaware of the drug injected.

All the patients in three groups were premedicated with Alprazolam 0.5mg p.o. in the morning on the day of surgery. They were weighed and reassured. On arrival in the operation theatre and after ten minutes patients were connected to a non-invasive blood pressure (NIBP) monitoring & ECG & Pulse Oximeter and patients pulse rate, systolic, diastolic & mean blood pressure were recorded. Intravenous access was secured and infusion of RL 5ml/kg/hr was started. The infusion of study drug was started 5 minutes before intubation. Patients were pre oxygenated with 100% oxygen for 5 minutes. Patients of all the groups were induced with Thiopentone sodium 5mg/kg body wt in incremental doses until loss of eyelash reflex occurred and this was followed by intravenous Inj. Vecuronium Bromide 0.1 mg/kg body weight. Controlled ventilation was continued with 66% Nitrous oxide in oxygen for 180 seconds. Antisialogogue and analgesic were intentionally avoided. Intubation was performed with Macintosh laryngoscope. The laryngoscopy was limited to 15 seconds. Tube fixed and secured. Following intubation, the lungs were ventilated with nitrous oxide: oxygen = 66: 33 % with intermittent doses of vecuronium. PR,SBP,DBP,MBP was recorded at 1, 3 and 5 minutes interval after intubation. The infusion was stopped 5 minutes after intubation. Inj. Glycopyrrolate 0.2mg was administered after stoppage of infusion. Intravenous pethidine 0.5 mg / kg was administered before surgical incision.

At the end of the surgery patients were reversed with i.v. neostigmine 0.06mg/kg and atropine 0.02mg/kg body weight.

Statistical tests-Groups were compared by Unpaired't' test. Paired't' test was done between baseline and post intubation parameters in control group to show effect of intubation. For interpretation of statistical test result following significance level was set. $p \leq 0.05$ - significant. $p \leq 0.01$ - highly significant.

Results-

Table shows demographic profile of three groups.

Group			
	Control	Nitroglycerine	Esmolol
Age (mean±SD) in years	34.16 ±7.611	35.22 ± 6.129	34.28 ± 7.806
Body weight (mean±SD) in inches	54.00 ±10.381	53.70± 7.129	53.14± 8.018
Gender ratio (M:F)	25:25	27:23	22:28

All the three groups are comparable as statistically ($p \geq 0.05$).

From the above table it is seen that difference of mean PR at 1 minute and baseline for control group remained highest, esmolol lowest and nitroglycerine in .Similar type of changes is also noted at 3 and 5 minutes after intubation.

Table 2. Summary of paired't' test of difference in mean pulse rate between baseline and at different time intervals in study groups.

Group	PR1-PR				PR3-PR				PR5-PR			
	Mean	SD	t value	p value	Mean	SD	t value	p value	Mean	SD	t value	p value
N	18.6	12.88	10.21	<0.01	20.42	11.27	12.81	<0.01	15.48	11.65	9.39	<0.01
O	34.86	7.77	31.72	<0.01	30.16	8.33	25.59	<0.01	23.22	9.32	17.61	<0.01
E	4.94	9.91	3.52	<0.01	1.56	7.96	1.39	>0.05	-1.96	7.222	-1.92	>0.05

At 5 minutes it is interesting to see that esmolol causes reduction of pulse rate below pre intubation level (-1.96). Whereas some elevation of pulse rate remained at 5 minutes in subjects of nitroglycerine group (15.48) .On applying statistical test it is seen that upto 5 minutes mean pulse rates of control and nitroglycerine group remain significantly elevated (<0.01) except for the esmolol group which showed insignificant differences at 3 and 5 minutes.It can be summarized that esmolol is the most effective drug to bring down the pulse rate at normal level at 3 and 5 minutes after intubation.

Table 9. Summary of paired't' test of difference in mean systolic blood pressure between baseline and at different time intervals in study groups.

Group	SBP1-SBP				SBP3-SBP				SBP5-SBP			
	Mean	SD	t value	p value	Mean	SD	t value	p value	Mean	SD	t value	p value
N	3.06	12.87	1.68	>0.05	11.5	7.27	11.18	<0.01	-6.98	7.7	-6.41	>0.05
O	23.56	10.77	15.47	<0.01	17.58	10.98	11.32	<0.01	10.5	10.99	6.75	<0.01
E	1.44	11.16	0.91	>0.05	-4.4	10.51	-2.96	>0.05	-10.34	7.99	-9.15	>0.05

Above table is showing that the difference of mean SBP at 1 minute and baseline, at 3 minutes and baseline, at 5 minutes and baseline for control group remained highest , esmolol lowest and nitroglycerine group in between .At 3 and 5 minutes esmolol has reduced mean SBP below the pre-intubation level (-4.4 and –10.34 respectively). Whereas in nitroglycerine group reduction of mean SBP below pre-intubation level found at 5 minutes after intubation (-6.98).

On applying statistical test it is seen that upto 5 minutes mean systolic blood pressure remain significantly elevated in the control group. At 1 minute and 5 minutes after intubation the rise of mean systolic blood pressure was statistically insignificant in both nitroglycerine and esmolol group. At 3 minutes significant elevation in mean SBP present in nitroglycerine (<0.01) and in esmolol group it is insignificant.

It can be summarized that esmolol is the most effective drug to bring down the systolic blood pressure at or below normal level at 1 minute, 3 and 5 minutes after intubation than nitroglycerine.

Table 10. Summary of paired't' test of difference in mean diastolic bloodpressure between baseline and at different time intervals in study groups

Group	DBP1-DBP				DBP3-DBP				DBP5- DBP			
	Mean	SD	t value	p value	Mean	SD	t value	p value	Mean	SD	t value	p value
N	2.96	6.92	3.02	<0.01	4.54	4.83	6.65	<0.01	-4.14	5.96	-4.91	>0.05
O	19.44	9.5	14.47	<0.01	15.76	9.71	11.48	<0.01	0.2	12.49	0.11	>0.05

E	6.86	8.85	5.48	<0.01	0.78	7.49	0.74	>0.05	-3.84	7.34	-3.69	>0.05

From the above table it is seen that difference of mean DBP at 1 minute and baseline for control group remained highest, nitroglycerine lowest and esmolol in between. The difference of mean DBP at 3 minutes and baseline for control group remained highest, esmolol lowest and nitroglycerine in between. It is interesting to see that at 5 minutes, both esmolol and nitroglycerine reduced mean DBP below the pre-intubation level (-3.84 & -4.14 respectively). When statistically tested, at 1 minute in all the groups and at 3 minutes in nitroglycerine and control group the elevation of mean DBP is statistically highly significant(<0.01). Whereas at 3 minutes in esmolol group and at 5 minutes in all the study groups DBP rise was statistically insignificant. It can be summarized that esmolol is the most effective drug to bring down the DBP at normal level at 3 minutes. At 5 minutes after intubation both nitroglycerine and esmolol has brought down the DBP below pre-intubation level.

Table 11. Summary of paired't' test of difference in mean of mean blood pressure between baseline and at different time intervals in study groups.

Groups	MBP1-MBP				MBP3-MBP				MBP5-MBP			
	Mean	SD	t value	p value	Mean	SD	t value	p value	Mean	SD	t value	p value
N	3.04	7.37	2.92	0.01	6.9	4.63	10.54	0.01	-5.08	5.54	-6.48	0.05
O	20.74	8.56	17.13	0.01	16.46	8.5	13.69	0.01	3.7	9.88	2.65	0.05
E	5.06	8.52	4.19	0.01	-0.96	7.38	-0.92	0.05	-5.71	6.87	-5.88	0.05

The above table is showing that difference of mean of MBP at 1 minute and baseline for control group remained highest, nitroglycerine lowest and esmolol in between i.e. reduction of pulse rate at 1 minute was highest for nitroglycerine. The difference of MBP at 3 minutes and baseline for control group remained highest, esmolol lowest and nitroglycerine in between. It is interesting to see that at 3 minutes mean of mean blood pressure in esmolol group reduced to below pre-intubation level(-0.96) and the same changes occurred in both esmolol and nitroglycerine group at 5 minutes after intubation (-5.71 and -5.08 respectively) .

When statistically tested, rise in mean of MBP in all the study group at 1 minute; in control and nitroglecerine group at 3 minutes are highly significant(<0.01). In esmolol this change is insignificant at 3 minutes. At 5 minutes mean of MBP in both esmolol and nitroglycerine group showed insignificant differences except for the control group in which it remained elevated significantly.In summary, esmolol is the most effective drug to bring down the mean of MBP below pre-intubation level at 3 and 5 minutes whereas nitroglycerine is only effective at 5 minutes after intubation .

DISCUSSION -

Transient cardiovascular stress responses such as tachycardia, hypertension and tachyarrhythmia's occur during direct laryngoscopy and endotracheal intubation(LI).[1,2,3] These responses may produce deleterious effects in the presence of coronary or cerebral atheromas on preexisting hypertension [9,10,11]

Burnstein et al [35] observed that these changes could be related to the stimulation of cardio-accelerator nerves, implying on increasing in cardiac sympathetic tone rather than an increase in vagal tone. Subsequently **King and coworkers**[17] observed that direct LI were associated with a rise in blood pressure on increase in heart rate.

Derbyshire et al[1] demonstrated an increase in plasma concentrations of noradrenaline implying an increased sympathetic activity. Recent studies have reported increased in bispectral index along with heart rate and blood pressure associated with LI [36-38]

The magnitude of cardiovascular response to LI may vary with depth of anaesthesia[39], the duration[40] and the difficulties encountered during LI [41], age [42] and history of diabetes or cardiovascular disease[43]. The reflex cardiovascular response to LI may be influenced by age [44,-46], duration of laryngoscopy[47], types of blade[48,49].

Various drugs have been tried to attenuate these pressor responses such as intravenous and topical lignocaine[13,14]; narcotic analgesics [15,16]; deep general anaesthesia[17]; beta blockers[18,19]; calcium channel blockers [20,21]; sodium nitroprusside[22]; phentolamine; clonidine nitroglycerine and hydralazine [23,24,25,26] Magnesium sulphate adenosine triphosphate.

Esmolol and nitroglycerine were used in the present study be cause their quick onset and short duration of action [30,31,32].

Esmolol has been used attenuate the haemodynamic responses to LI in a varied dose range from 20mg to 200mg bolus to 0.2 to 3mg/kg body weight .

Nitroglycerine has been used in different doses and through different approach to attenuate the cardiovascular responses to intubation. .**Dutta et al**[50] administered 0.2 µg/kg/min GTN in a continues infusion 4 minutes before laryngoscopy and up to 5minutes after intubation .**Singh et al**[51] and **Firoozbakhsh**[52] used GTN in a 2 µg/kg bolus dose before intubation and **Swamy et al**[53] administered 30µg/kg of GTN prior to induction. In our study we used 0.5 microgram/kg/min of GTN 5 minutes before and after intubation.

The premedication, duration of infusion of studied drugs, induction technique, intubation technique, maintenance of anesthesia and antagonism of neuromuscular blockade was similar in the study groups.

There was no significant difference in values of mean pulse rate between the three groups before start of infusion. In Esmolol group at 1 minute after intubation there was significant rise in the pulse rate which was maximal and at 3 minutes the rise was insignificant and decreased below baseline after 5 minutes of intubation[117] .The pulse rate was significantly low as compared to the Nitroglycerine group. These findings are similar to those found by **Singh et al**[51] and **Dutta et al**[50] in comparison to GTN group.In the GTN group the pulse rate increased after intubation and remained at an elevated level at 5 minutes after intubation. Maximum rise was seen at 3 minutes after intubation. Longmire et al and Dutta et al have reported similar results with GTN infusion.

The initial SBP was comparable between three groups. In GTN group, the SBP increased following intubation.The maximum rise was at 3 minutes after intubation and was statistically significant as compared to initial value**.** The blood pressure decreased significantly below the initial value after 5 minutes. However, **Kamra et al**[54] found that the increase in SBP only lasted for 1 minute after intubation. **Fassoulaki et al**[34] reported no increase SBP immediately after intubation. However there was significant decrease at 3 and 5 minutes. Our observation was similar to the observation of **Fassoulaki et al**[34] at 5 minutes after intubation.

In Esmolol group, SBP after intubation**.**Then it came down below baseline value at 3 and 5 minutes after intubation. Our findings were similar to those of **Yuanet al,**[55] **Kar et al**[56]**, Liu et al**[57]**, Sheppard et al**[58] and **Helfmann et al**[59], but differed from **Ebert et al**[19]**, Jacque et al**[32] **and Atlee et al**[60]. Increase in blood pressure was not significant

following intubation in our study, a finding confirmed by **Taneja et al[61].** The values of mean DBP before infusion of study drug were comparable in all the three groups.In group-N, there was significant increase in DBP at 1 and 3 minutes following intubation**.** It decreased below pre intubation value at 5 minutes. According to Sahare et al[121] topical GTN is effective in attenuation of haemodynamic responses to LI . Firoozbakhsh et al[172] did not notice any difference in DBP in their study.

In group-E DBP increased following intubation before returning below the preintubation value at 5 minutes**.** Significant rise in blood pressure was present at 1 minute after intubation**. Ebert et al[19]** and **Atlee et al[60]** found no change in DBP. **Liu et al[57]** found DBP decreased to significant levels 4 minutes after intubation. However, **Ahuja et al[62]** and **Kumar et al[63]** reported a significant increase in DBP at 1 minute after intubation and **Kar et al[56]** reported significant decrease at 5 minutes after intubation these findings were confirmed in the present study.

The initial MBP was comparable in the three groups. In group- N MBP increased after intubation,was significant at 1 and 3 minutes. Then it decreased below the initial value at 5 minutes following intubation. The significant increase in MBP at 1 minute after intubation was corroborated by **Sood et al [64]**,**Mikawa et al[65]** noticed significant decrease in MBP after LI. In group E, MBP increased following LI, with a maximum at 1 minute .At 3 and 5 minutes post intubation, it was below preintubation value. The increase in MBP was statistically significant at 1 minute and this finding was confirmed by **Taneja et al[61]** and significant decrease at 5 minutes was confirmed by **Dutta et al[51,] Singh et al[51]** and **Liu et al[57]** found MBP increased after LI though the increase was not statistically significant.

We did not encounter any episode of hypotension, bradycardia, bronchospasm or any other side effect in any of the patients studied.

SUMMARY -

It was a one and half year long study having 50 subjects in each of Control, Nitroglycerine and Esmolol group. Group E received esmolol 100 µg/kg/minute intravenous and group N received nitroglycerine 0.5µg/kg/minute i.v. and group C 50 cc normal saline infusion started. Both the drugs diluted to prepare 50 cc infusion solutions.

All the patients in three groups (n=50 in each group) were premedicated with Alprazolam 0.5mg p.o. in the morning on the day of surgery. They were weighed and reassured. On arrival in the operation theatre and after ten minutes were connected multipara monitor and parameters recorded. The infusion of study drug was started 5 minutes before intubation. Patients were pre oxygenated for 5 minutes. Patients of both the groups were induced with intravenous Thiopentone sodium 5mg/kg BWt and intubation was performed with intravenous Vecuronium Bromide 0.1 mg/kg BWt. Controlled ventilation was continued with oxygen & intubation was performed 180 seconds after administration of vecuronium bromide. Antisialogogue and analgesic were intentionally avoided before intubation to exclude the effect of the drug on hemodynamic response during LI. Intubation was performed with Macintosh laryngoscope. The LI was limited to 15 seconds. Intubation of trachea was done with 7.0-7.5 mm internal diameter PVC tube in female & 8.0-8.5 mm internal diameter PVC tube in male following LI , the lungs were ventilated with $N_2O : O_2 = 66:33$ % with intermittent doses of vecuronium. (Pulse rate, systolic, diastolic & mean blood pressure was recorded at 1, 3 and 5 minutes interval after intubation. The infusion was stopped 5 minutes after intubation. Inj. Glycopyrrolate 0.2mg was administered after stoppage of infusion. Intravenous pethidine 0.5 mg / kg was administered before surgical incision. All surgical stimuli, analgesic supplements and inhalational anaesthetics were avoided during study. At the end of the surgery patients in all three groups were reversed with i.v. neostigmine 0.06mg/kg and atropine 0.02mg/kg body weight.

Conclusion-

We conclude that Esmolol was more effective than Nitroglycerine in controlling the hemodynamic responses to direct laryngoscopy and endotracheal intubation

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