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Original Research Article

Mitigation of Hemodynamic Response to Intubation with Esmolol, Diltiazem and Magnesium Sulphate: A Comparative Evaluation

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Conflict of interest: Nil

Abstract:

Introduction: Laryngoscopy and tracheal intubation are frequently associated with hypertension and tachycardia which sometimes results in grave complication like intracranial haemorrhage, various modalities can be implied to mitigate the stress response.

Objective: Objective of our study is to assess the efficacy of intravenous esmolol 2mg/kg, intravenous diltiazem 0.2mg/kg and intravenous magnesium sulphate 60mg/kg. to attenuate the stress response of laryngoscopy and intubation.

Study Design: Prospective, Randomised, Double blind.

Place of Study: NSCB Medical College Jabalpur.

Methods: 80 patients of ASA class I and II who were scheduled to undergo general anaesthesia were given study drugs at the above mentioned doses before laryngoscopy and intubation. Subjects were then assessed for hemodynamic perturbations immediately following intubation and at 1, 3 and 5 minutes after intubation.

Results: Patients in esmolol group showed minimum deviation of heart rate from mean which was 87.55±10.73, 76.9±7.76, 82.45±8.19, 82.65±8.31, 82.1±8.91 and 82.2±8.4 minutes respectively at baseline, immediately after study drug administration, immediately after intubation, at 1 minute, at 3 minute and at 5 minute after intubation.

The least variance in mean arterial pressure was observed with esmolol (96.53±6.35, 84.72±4.56, 95.37±6.91, 93.77±6.12, 90.05±6.56 and 87.22±4.88 mmHg) and with magnesium sulphate (94.57±5.5, 89.12±5.32, 92.53±6.74, 92.45±6.38, 90.37±5.77 and 87.2±5.5 mmHg) respectively at baseline, immediately after drug administration, immediately after intubation, at 1 minute, at 3 minute and at 5 minute after intubation.

Conclusion: The study concluded that Esmolol at a dose of 2mg/kg bolus 2 minute before intubation is more effective to attenuate the cardiovascular pressure response to laryngoscopy and intubation than Diltiazem 0.2mg/kg and Magnesium Sulphate 60mg/kg.

Keywords: Esmolol, Magnesium Sulphate, Diltiazem, Laryngoscopy, Intubation.

Introduction

Endotracheal intubation and laryngoscopy are integral part of airway management while giving general anesthesia and in critically ill patients. Procedure was first described by Rowbotham and Magill in 1921 [1]. The procedure is met with severe stress response akin to the surgical stimulus encompassing many reflex mechanisms and release of several neurohormones. Laryngeal, tracheal, and bronchial receptors are stimulated by mechanical and chemical irritants during laryngoscopy, intubation, and extubation [2].

Hypertension and tachycardia have been reported since 1950 during intubation under anesthesia. Surges in blood pressure and heart rate, due to reflex sympathetic and vagal discharges after laryngotracheal stimulation, increase the plasma norepinephrine concentration [3]. Prys Robert et al [4] demonstrated an exaggerated increase in noradrenaline concentration and moderate increases in adrenaline concentration following laryngoscopy in hypertensive patients. This change is of limited significance in healthy but may prove fatal in patients with cardiovascular instability and pulmonary disorders, causing sudden deaths [5]. King et

al [6] confirmed the adverse effect of pressor response. This pressor response manifests within 5 seconds of initiation of laryngoscopy and further elevates while endotracheal tube enters inside trachea. Average rise of SBP is 25 –50 mmHg [7-11] following a plateau at or above this peak pressure, which is sustained for 1-2 min. It takes about 5 –10 min for the pressures to return to pre laryngoscopic value [12,13]. Even patients with controlled hypertension are prone to elevations in pressures. Patients with limited cardiovascular reserve, example having coronary artery disease, cardiac dysrhythmias, cardiomyopathy, congestive heart failure, hypertension, patients with limited intracranial compliance, and geriatric population may face life threatening complications such as myocardial ischemia, acute cardiac failure, and cerebrovascular haemorrhage [14,15].

Hemodynamic response to laryngoscopy and intubation in anesthetized patients was first reported by Donegan et al [16]. Tomori et al [17] extensively elucidated the exaggerated cardiovascular response due to autonomic overactivity. They observed that mechanical stimulation of four areas of the upper respiratory tract, the nose, the epipharynx, the laryngopharynx and the tracheobronchial tree is associated with enhanced neuronal activity in the cervical sympathectic efferent fibers. These responses were most pronounced during stimulation of epipharyrnx. Prys Robert et al. [18] differentiated between the effects of laryngoscopy and tracheal intubation and found that reflex tachycardia and hypertension were produced well before the act of intubation. Several measures have been carried out to attenuate or prevent these responses such as shortening the time of laryngoscopy, smooth intubation, airway anesthesia by blocking superior and recurrent laryngeal nerve, use of local anesthetics, beta blockers, calcium channel blockers and other agents such as magnesium sulphate, labetalol, nitroprusside and nitroglycerine [19- 22]. The inhibition of reflex stimulation of the sympathetic pathway can be broadly subdivided into three parts i.e. inhibition of afferent limb by use of topical airway anesthesia or application of nerve blocks then inhibiting central integrating system by use of opioids and α2 agonists and finally the effect on the efferent limb by blocking peripheral β and calcium channel receptors [23]. However, none of them have proved to be ideal due to their limitations and side effects. Thus, the search for an ideal agent to negate the hemodynamic responses of laryngoscopy and intubation has never ceased.

In our study, esmolol was selected, as it is cardio selective β blocker, ultra short acting, water soluble, have rapid onset and can be administered intravenously [24]. Its metabolism is not influenced by renal or hepatic functions. These above characteristics make esmolol, useful for prevention and treatment of adverse increase in systemic pressures and heart rate that occur perioperatively in response to noxious stimulus such as laryngoscopy and intubation.

Diltiazem, a calcium channel blocker was also used in our study as it has a rapid onset of action when given intravenously and causes myocardial depression. It blunts hemodynamic response because of its vasodilating effect. It effectively decreases the rise in blood pressure, but not the changes in heart rate associated with stress response.

Magnesium sulphate is preferred because it has minor cardiovascular sideeffects and potentiate the action of NMBAs. It has bronchodilating, antiarrhythmic properties and used for prophylaxis against seizures in pre-eclampsia. It's also used nowadays to control hypertensive responses. It blocks the release of catecholamines from both adrenergic nerve terminals and adrenal glands and is also a directly acting vasodialator.

Aims & Objectives

Aim

- To compare the efficacy between intravenous Esmolol, Diltiazem, & Magnesium sulphate in attenuating the hemodynamic responses to intubation.

Objectives

Primary objective:

- To find out whether drugs like Esmolol, Diltiazem, & Magnesium sulphate can attenuate hemodynamic responses to intubation.

Secondary Objectives:

- To observe the changes in systolic blood pressure, diastolic blood pressure, heart rate during intubation.
- To assess the role of intravenous esmolol, diltiazem and magnesium sulphate, in attenuating cardiovascular response to intubation.

Material and Methods

Place of Work

- Department of Anesthesiology N.S.C.B Medical College &Hospital, Jabalpur (M.P.)

Duration of the Study

- March 2021 to August 2022.

Inclusion Criteria

- Patients with age between 20 and 40 years
- ASA class I and II
- Normotensive
- Elective surgery
- Samson and Young class I and II

- Cormack Lehane grade I and II

Exclusion Criteria

- Patient refusal
- Emergency surgery
- Psychologically ill patients
- History of allergy to the study drugs
- Anticipated difficult airways
- Patients in whom laryngoscopy and intubation required >1 attempt.
- Uncontrolled hypertension or chronic respiratory disease
- Hepatic disease or renal disease
- Diabetes mellitus
- Ischemic heart disease and cardiac dysfunction
- Morbid obesity
- Pregnancy or lactating
- Patients with elevated intracranial pressure and intraocular pressure.

Study Design

This study was a prospective, randomized, double blind comparative study. For the study purpose, all the 80 patients were randomized into 4 groups of 20 patients each using the sealed envelope method.

- **Group I** – Received normal saline as control.
- **Group II**- Received injection diltiazem 0.2mg/kg intravenous bolus 1 minute before laryngoscopy and intubation.
- **Group III** – Received injection esmolol 2mg/kg intravenous bolus 2 minute before laryngoscopy and intubation.
- **Group IV** - Received injection magnesium sulphate 60mg/kg intravenous 1 minute before laryngoscopy and intubation.

Method of Study

The patients who met inclusion criteria were randomized into four groups. Informed written consent was obtained after explaining the anesthesia procedure.

Patients were kept nil by mouth for 8 hours. After shifting the patients to the operation theatre, IV access(18G) obtained, and Ringers lactate was started. Standard monitor attached and Pre-induction vitals were recorded. Patients were premedicated with IV Glycopyrrolate 0.005mg/kg. Preoxygenated done with 100% oxygen for three minutes, proceeded with Inj. Propofol followed by inj. Vecuronium bromide to facilitate the direct laryngoscopy and intubation. Then study drugs were given and after 3 minutes, proceeded for laryngoscopy and intubation. All the patients were mechanically ventilated and maintained to keep normoxia with oxygen saturation ≥ 98% and normocapnia.

All the parameters were recorded at following stages

- Preoperative
- After given the study drug
- Immediately after intubation
- At 1 min, 3 min, & 5 min after intubation.

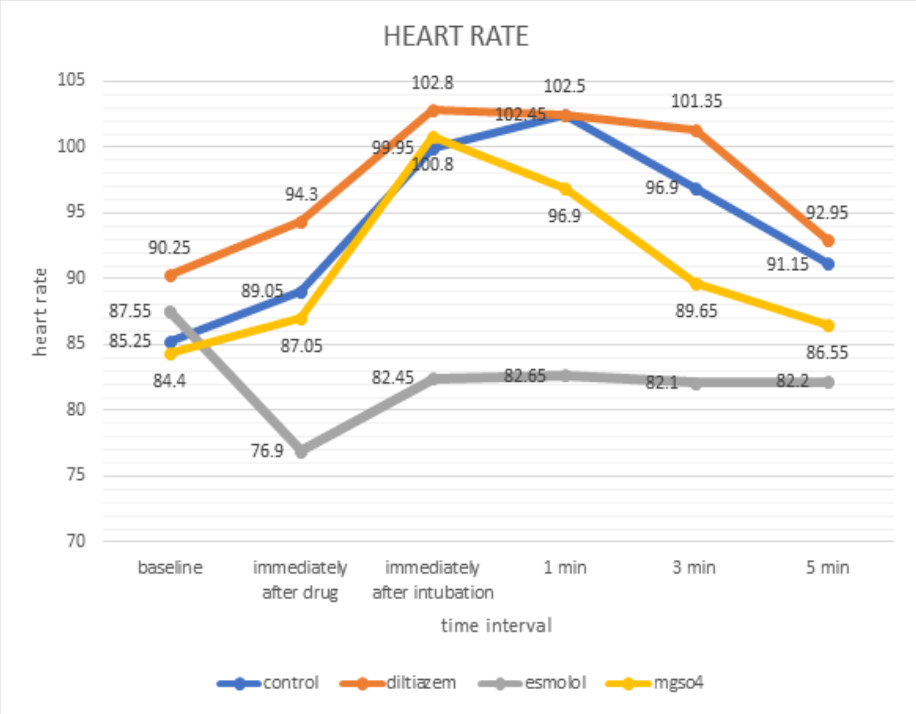
Observations & Results

Table no. – 1 Demographic data: age (years)

Variable	Group I (Control)	Group II (Diltiazem)	Group III (Esmolol)	Group IV (Mgso4)	p value
Age (years)	31.15±5.61	34.95±4.82	31.75±5.59	31.25±5.36	0.088

- Mean age group of patients in Group I, II, III and IV were 31.15, 34.95,

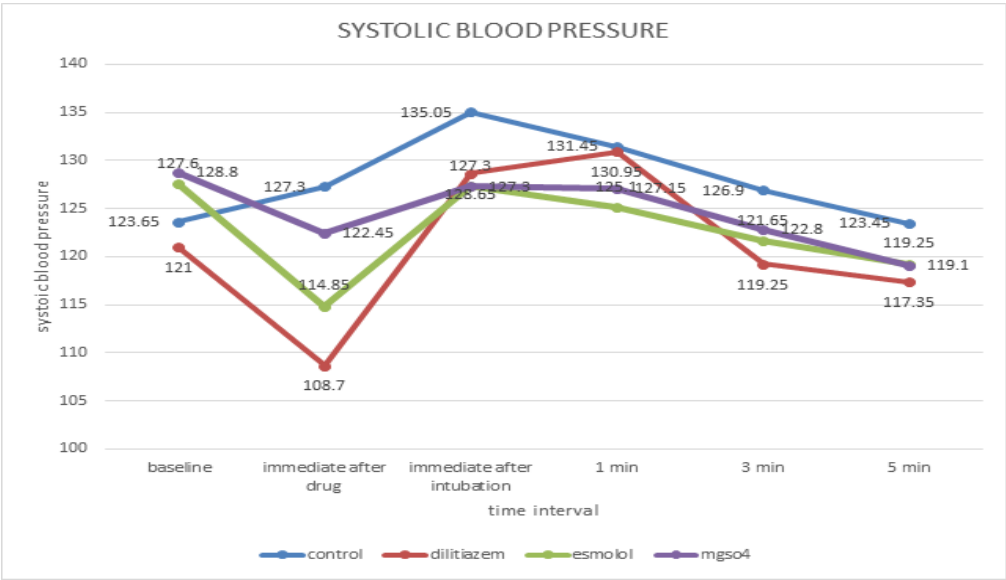
31.75 & 31.25 years respectively. The mean age of the patients did not differ significantly between the study groups (p = 0.088).



Graph 1: Heart Rate variation among different groups

Table 2; Comparison of mean heart rate at various intervals between each of the four treatment groups using Bonferroni Post-hoc test for multiple comparison in oneway ANOVA

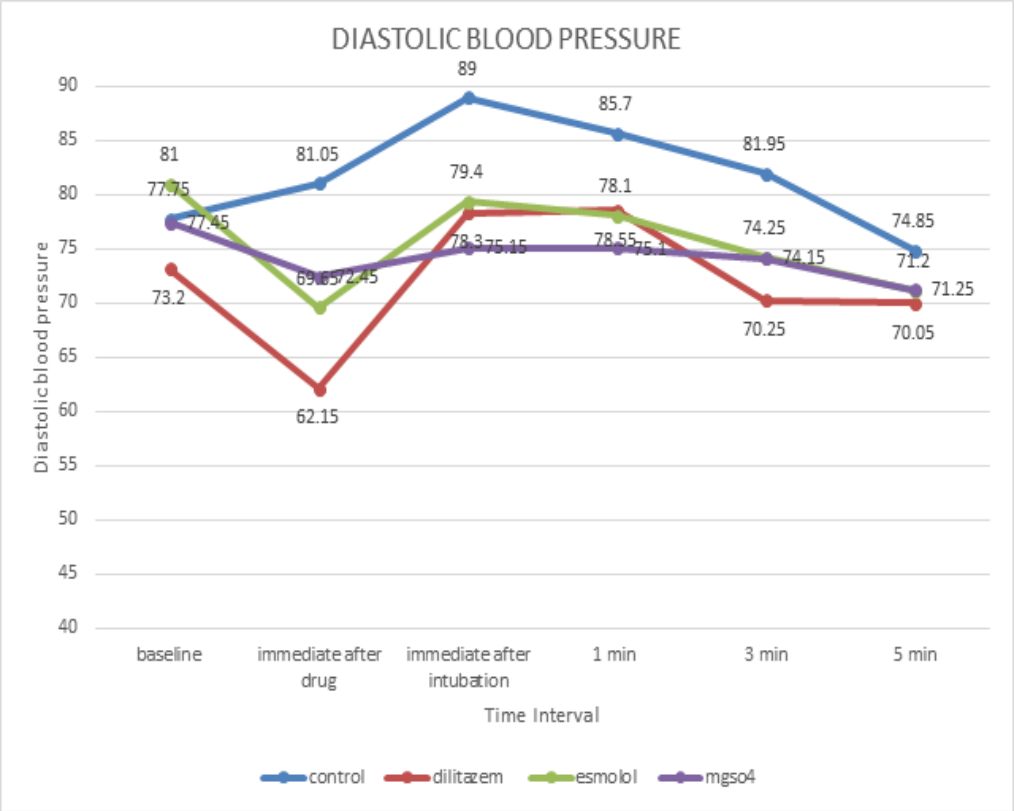
Time of follow up	p values					
	Ctrl Vs D	Ctrl Vs E	Ctrl Vs M	D Vs E	D Vs M	E Vs M
At Baseline	1	1	1	1	0.763	1
Immediately after drug	0.825	**0.005**	1	**<0.0001**	0.249	**0.029**
Immediately after intubation	1	**<0.0001**	1	**<0.0001**	1	**<0.0001**
After 1 min	1	**<0.0001**	0.995	**<0.0001**	0.973	**0.003**
After 3 min	1	**0.001**	0.325	**<0.0001**	**0.014**	0.271
After 5 min	1	**0.046**	0.982	**0.009**	0.324	1



Graph 2: Systolic Blood Pressure variation among different groups

Table 3: Comparison of mean systolic blood pressure at various intervals between each of the four treatment groups using Bonferroni Post-hoc test for multiple comparison in oneway ANOVA

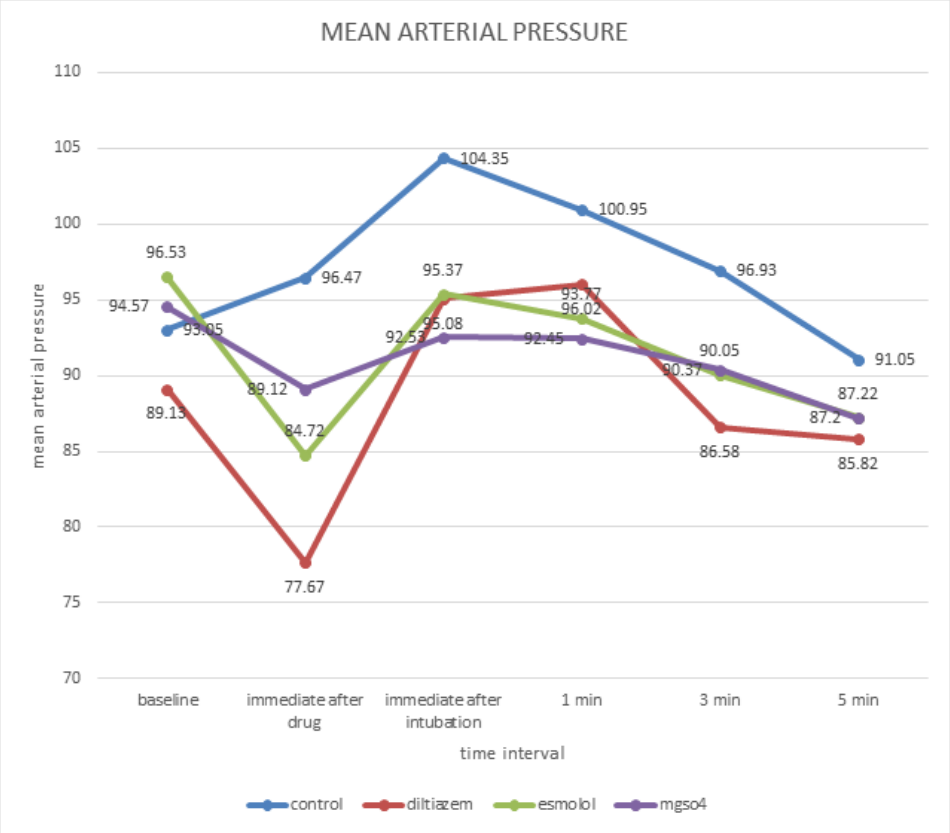
Time of follow up	p values					
	Ctrl Vs D	Ctrl Vs E	Ctrl Vs M	D Vs E	D Vs M	E Vs M
At Baseline	1	1	0.678	0.26	0.105	1
Immediately after drug	<0.0001	<0.0001	0.577	0.215	<0.0001	0.06
Immediately after intubation	0.071	0.015	0.015	1	1	1
After 1 min	1	0.063	0.477	0.108	0.723	1
After 3 min	0.008	0.151	0.471	1	0.76	1
After 5 min	0.041	0.357	0.307	1	1	1



Graph 3: diastolic blood pressure variation among different groups

Table 4: Comparison of mean diastolic blood pressure at various intervals between each of the four treatment groups using Bonferroni Post-hoc test for multiple comparison in oneway ANOVA

Time of follow up	P values					
	Ctrl Vs D	Ctrl Vs E	Ctrl Vs M	D Vs E	D Vs M	E Vs M
At Baseline	0.297	0.948	1	0.006	0.397	0.741
Immediately after drug	<0.0001	<0.0001	<0.0001	0.002	<0.0001	0.962
Immediately after intubation	<0.0001	<0.0001	<0.0001	1	1	1
After 1 min	0.004	0.002	<0.0001	1	1	0.829
After 3 min	<0.0001	0.001	0.001	0.251	0.282	1
After 5 min	0.078	0.342	0.362	1	1	1



Graph 4: Mean Arterial Pressure variation among different groups

Table 5: Comparison of mean arterial pressure at various intervals between each of the four treatment groups using Bonferroni Post-hoc test for multiple comparison in oneway ANOVA

Time of follow up	p values					
	Ctrl Vs D	Ctrl Vs E	Ctrl Vs M	D Vs E	D Vs M	E Vs M
At Baseline	0.582	0.835	1	0.013	0.134	1
Immediately after drug	<0.0001	<0.0001	0.003	0.005	<0.0001	0.196
Immediately after intubation	<0.0001	<0.0001	<0.0001	1	1	1
After 1 min	0.066	0.002	<0.0001	1	0.379	1
After 3 min	<0.0001	0.002	0.004	0.384	0.262	1
After 5 min	0.021	0.18	0.176	1	1	1

Discussion

Provision of general anesthesia by way of endotracheal intubation is one of the most performed and preferred choice of anesthesia technique. The hemodynamic responses to laryngoscopy and endotracheal intubation have beenthe topic of discussion since 1940 when Reid et al [25] found that stimulation of upper respiratory tract provoked an increase in vagal activity. A year later Burstein et al [26] totally contradicted Reid´s statement and found that the pressor response occurring at laryngoscopy and endotracheal intubation was due to augmented sympathetic response, provoked by stimulation of pharynx and larynx. These facts were further confirmed by Prys-Roberts et al [18] who stated that on stimulation, laryngoscopy within 5 sec activates sympathoadrenal reflex and propagates stress responses that suddenly cause a surge in catecholamine resulting in tachycardia and hypertension. Such changes unpleasantly result in myocardial ischemia, arrhythmias, raised intracranial pressure, raised intraocular pressure, laryngospasm and bronchospasm in patients of limited cardiac reserve due tothe disturbance of demand versus supply (oxygen) mismatch. The magnitude of response further escalates, peaks around 1-2 min, and return to pre- laryngoscopy level by 5-10 min. In early sixties, inhalation anesthetic agents were used to attenuate the laryngoscopic reactions. But inhalation anesthetic agents had their own demerits, for example myocardial depression and arrhythmogenicity with halothane, coronary steal with isoflurane. Among the pharmacological agents used for blunting the hemodynamic responses, opioids were found to be effective but they caused respiratory depression, chest wall rigidity and prolong the recovery time [27,28]. Plen-

ty of research has been going on for finding methods to decrease hemodynamic response to intubation.

Esmolol is a cardio selective beta blocker having an ultra-short durationof action and has been indicated for tachycardia and hypertension during tracheal intubation [29]. Diltiazem, a calcium channel blocker used as an antianginal and antiarrhythmic drug. Magnesium sulphate inhibits catecholamine release both from the adrenergic nerve terminals and the adrenal medulla. Our basis for choice of dose and method of administration to study these drugs to attenuate the pressor response to laryngoscopy and intubation was based on the study by Santosh Kumar et al [30]. and Singhal et al [31] who concluded that bolus dose of 1.5mg/kg esmolol, three minutes before intubation is safe and effective to attenuate hemodynamic changes.

In view of these investigations, the present clinical study was undertaken to study the mitigation of hemodynamic response to intubation with esmolol, diltiazem and magnesium sulphate.

The present study was carried out in 80 patients of both sex aged between 20 and 40years having ASA class I and II, requiring endotracheal intubation for maintenance of anaesthesia who were scheduled to undergo elective surgery. Demographic parameter of age of the subjects were comparable in all four groups ($p = 0.08$).

Analysis of variance showed that the heart rate immediately after drug administration and at 1,3 and 5 minutes after intubation when compared with the baseline rate before induction of anesthesia, changed significantly in all treatment groups except for group III (esmolol 2mg/kg) which showed most stable heart rate when compared with other groups ($p<0.0001$). Esmolol group showed minimum deviation of heart rate from mean which was 87.55±10.73, 76.9±7.76, 82.45±8.19, 82.65±8.31, 82.1±8.91 and 82.2±8.4 minutes respectively at baseline, immediately after study drug administration, immediately after intubation, at 1 minute, at 3 minute and at 5 minute after intubation. While the heart rate changes observed with diltiazem 0.2mg/kg (group II) were 90.25±10.88, 94.3±10.62, 102.8±14.36, 102.5±11.32, 101.35±7.39 and 92.95±9.14 minutes at specified time intervals and with magnesium sulphate 60mg/kg (group IV) 84.4±12.63, 87.05±12.8, 100.8±13.96, 96.9±16.85,

89.65±16.98 and 86.55±13.42 minutes at specified time intervals. Santosh Kumar et al30, who compared esmolol (2mg/kg), diltiazem (0.2mg/kg) and magnesium sulphate (60mg/kg) in their study, observed that esmolol given 3 minute before intubation, when compared with pre operative values shows insignificant rise ($p<0.05$) in heart rate immediately intubation and at 1 and 3 minutes after intubation, and at 5 minutes it was even less than the pre operative value ($p>0.05$). Hence it was more efficacious in attenuating the heart rate response to intubation. Menkhaus et al [32] studied the cardiovascular effects of esmolol in anesthetized human. Esmolol was given by continuous infusion in cumulative doses of 1100mcg/kg (group 1), 2000mcg/kg (group 2) and 2700mcg/kg (group 3), 3 minute prior to intubation, and found that all three doses of esmolol given by continuous infusion attenuated heart rate responses at 1,3 and 4 minutes after laryngoscopy and intubation. Mikawa et al [33] conducted a study to evaluate the effect of diltiazem (0.2 or 0.3mg/kg) on cardiovascular response to tracheal intubation, given 60 seconds before start of laryngoscopy and found diltiazem failed to attenuate rise in heart rate after laryngoscopy. Singh et al [34] concluded that prophylactic treatment with esmolol (2mg/kg) is most effective in blunting responses to laryngoscopy and intubation. Study conducted by Fernandez Galinski et at [35], comparing effects of alfentanil (3mcg/kg), esmolol (1mg/kg) and clonidine (3mcg/kg) in attenuating cardiovascular responses to endotracheal intubation, found esmolol to be effective in blunting the heart rate response at 1mg/kg. Michael F M et al [36] studied the effects of pretreatment with 60mg/kg magnesium sulphate intravenous on cardiovascular responses and observed a unique effect that pre-treatment caused an increase in heart rate but after intubation heart rate was unchanged. The results of above studies are in corroboration with the results of present study.

Analysis of variance showed that systolic blood pressure, immediately after drug administration, immediately after intubation, and at 1,3 and 5 minutes after intubation, when compared from baseline, changed significantly in all treatment groups except for group I (control/normal saline). Group III (esmolol) values observed were 127.6±8.92, 114.85±6.71, 127.3±7.09, 125.1±7.38, 121.65±8.6 and 119.25±7.24 mmHg respectively at baseline, immediately after drug administration, immediately after intubation, and at 1 minute, at 3 minute and at 5 minute after intubation while the values of systolic blood pressure observed in group IV (magnesium sulphate) were 128.8±8.93, 122.45±9.77, 127.3±9.28, 127.15±8.62, 122.8±6.78 and 119.1±6.45 mmHg at specified time interval showed the least variance in systolic blood pressure over group II (diltiazem) which showed the values 121±11.88, 108.7±9.72, 128.65±7.69, 130.95±6.32, 119.25±6.86 and 117.35±7.83 mmHg of mean systolic blood pressure at specified time interval ($p<0.0001$).

Analysis of variance showed that diastolic blood pressure, immediately after drug administration, immediately after intubation, and at 1, 3 and 5 minutes after intubation, when compared from

baseline, changed significantly in all treatment groups except control. Group III (esmolol) values observed were 81.6±6.96, 69.65±5.21, 79.4±8.16, 78.1±7.45, 74.25±6.37 and 71.2±5.61 mm Hg respectively at baseline, immediately after drug administration, immediately after intubation, and at 1 minute, at 3 minute and at 5 minute after intubation while the values of diastolic blood pressure observed in group IV (magnesium sulphate) were 77.45±5.12, 72.45±43, 75.15±6.34, 75.1±6.23, 74.15±6.37 and 71.25±5.86 mmHg at specified time interval showed the least variance in diastolic blood pressure over group II (diltiazem) whose observed parameters were 73.2±7.55, 62.15±6.52, 78.3±6.1, 78.55±5.31, 70.25±4.9 and 70.05±5.56 mmHg at specified time interval ($p<0.0001$).

Analysis of variance showed that mean arterial pressure (MAP) immediately after drug administration, immediately after intubation, and 1, 3 and 5 minutes after intubation, when compared from baseline, changed significantly in all treatment group except control. Group III (esmolol) values observed were 96.53±6.35, 84.72±4.56, 95.37±6.91, 93.77±6.12, 90.05±6.56 and 87.22±4.88 mmHg respectively at baseline, immediately after drug administration, immediately after intubation, at 1 minute, at 3 minute and at 5 minute after intubation and the values of mean arterial pressure observed in group IV (magnesium sulphate) were 94.57±5.5, 89.12±5.32, 92.53±6.74, 92.45±6.38, 90.37±5.77 and 87.2±5.5 mmHg at specified time interval both of which showed the least variance in mean arterial pressure over group II (diltiazem) whose observed parameters were 89.13±8.46, 77.67±7.01, 95.08±6.38, 96.02±5.32, 86.58±5.04 and 85.82±5.74 mmHg at specified time interval ($p<0.0001$). Esmolol and magnesium treatment group shows the fall in mean arterial pressure even below the baseline after the stressful procedure.

Parvez et al [37] conducted a comparative study to see the attenuation of pressure response to laryngoscopy and tracheal intubation with intravenous diltiazem (0.2mg/kg) and esmolol (1.5mg/kg) and found significant difference in pressures between diltiazem and esmolol groups at 1,3 and 5 minutes after intubation. Esmolol group revealed lower values at all time interval. Gogus et at [38] concluded in their study that esmolol at 2mg/kg was more competent in maintaining SBP, DBP and MAP response compared to dexmedetomidine 1mcg/kg and fentanyl 2mcg/kg during laryngoscopy and endotracheal intubation. Sarkar et al [39] reported that the increase in pressor was greater with esmolol (2mg/kg) than diltiazem (0.2mg/kg), indicating that diltiazem controls the myocardial oxygen demand more efficiently than esmolol, this was in contrast to the results of our study. Similar to our study Gupta et al [40] conducted study to compare esmolol (1.5mg/kg), lignocaine (1.5mg/kg) and diltiazem (0.2mg/kg) for suppression of laryngoscopy and intubation pressor response and concluded that esmolol was better than diltiazem and they both were better than lignocaine. Puri GD et al [41] observed that magnesium sulphate in dose of 50mg/kg effectively attenuate the pressor responses following laryngoscopy and intubation. Santosh kumar et al. [30] in their study demonstrated that esmolol group cause a significant fall in systolic blood pressure and diastolic blood pressure after giving the study drug and after intubation, and at 3 min. and 5 min after laryngoscopy and intubation. Diltiazem group shows highly significant fall after giving study drug but at 5 min. after intubation, blood pressure came to near normal or below normal values. Systolic and diastolic blood pressure in MgSo4 group when compared to the pre- operative values shows that after giving the study drug there is insignificant fall in systolic and diastolic blood pressure.

None of our cases in each study group demonstrated either any bradycardia or hypotensive episode.

Limitation of the Study

There were a few limitations to the present study. The first was the use of non-invasive blood pressure monitoring, as invasive monitoring gives time to time variability and exact readings while with former, there was a time lag present. Secondly, laryngoscopy and intubation both separately contribute to pressor response, but we did not study it separately and don´t know the drug effectiveness in hypertensive patients, as our study population included only ASA class I and II subjects. Preoperatively we have used injection glycopyrrolate as premedication. This drug owing to its anticholinergic effects might have mitigated the bradycardic or hypotensive response to the study medications. Probably this could be the plausible reason that we did not observe such episodes in our study.

Conclusion

Based on the results of our study, it can be concluded that Esmolol at a dose of 2mg/kg bolus 2 minute before intubation is more effective in attenuating the cardiovascular pressure response to laryngoscopy and intubation than Diltiazem 0.2mg/kg and Magnesium Sulphate 60mg/kg.

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