Comparative study between Esmolol and Mgso4 for attenuation of Sympathomimetic response to laryngoscopy and intubation – a randomized control trial.

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.**ABSTRACT:**

Background & Aim: Direct laryngoscopy & Endotracheal intubation causes sympathetic response which is deleterious to patient. Various drugs are used to attenuate this response for better hemodynamic control. In this study, we aim to compare the efficacy of esmolol to that of mgso4 for attenuation of this response.

Methods: After obtaining approval from institution ethics committee and informed written consent from the patients, 60 patients coming for elective surgeries under general anesthesia were randomly allocated into 2 groups, Group E (Esmolol 1mg/kg) and Group M (Magnesium sulfate (MgSO4) 25mg /kg), with 30 patients in each group. Patients received drugs 5 min before intubation; HR, SBP, DBP and MAP were calculated at baseline, 0 min, 1 min, 3 min, 5 min and 10 min.

Results: Baseline parameters were compared between 2 groups, which were statistically not significant. HR at 1 min (p=0.034) and 3 min (p=0.025) was statistically significant in favor of Group M. SBP, DBP and MAP were reduced better with Group E than Group M, but statistically not significant.

Conclusion: MgSO4 reduces the sympathetic stimulation to laryngoscopy and intubation as effectively as Esmolol. MgSO4 also has the advantage of providing analgesia, reducing the dose of anesthetics, and provides better hemodynamic profile throughout intra-operative period.

Key words: Esmolol, Magnesium sulfate, Laryngoscopy

INTRODUCTION:

To establish and maintain a secure airway, endotracheal intubation is a very safe and life-saving procedure. Direct laryngoscopy and endotracheal intubation is commonly associated with pronounced sympathetic activity, which raises blood pressure, heart rate, and arrhythmias thus increases the risk of myocardial ischemia or infarction or stroke, particularly in the older age group.[1]The most common trigger of an increase in blood pressure and heart rate is reflex sympathetic discharge in response to laryngotracheal stimulation, which in turn

raises plasma norepinephrine levels.[2] The response begins in five seconds, reaches its peak effect in one to two minutes, and then returns to baseline in five minutes.

In a patient with hypertension, coronary artery disease, cerebrovascular disease, intracranial pathology, or overactive airways, the sympathoadrenal response can be dangerous but has little clinical importance in healthy patients. Sinus tachycardia, premature ventricular contractions with bigeminy or a trigeminal rhythm, lower voltage of T waves, sinus bradycardia, prolonged PR interval, ST depression, VT, and auricular fibrillation are the ECG alterations that occur immediately after intubation. Patients with heart illness cannot endure these modifications because of their damaged myocardium.[3] In these patients the stress response should be attenuated.

Various pharmacological agents are used to attenuate cardiovascular stress response to laryngoscopy and endotracheal intubation which includes local anaesthetics like lignocaine, opioids, vasodilators, beta blockers, calcium channel blockers, Magnesium and centrally acting sympatholytics.[4]

Esmolol is a cardio selective beta1 adrenergic receptor antagonist. It has rapid onset and a short duration of action. Its peak effect occurs between one and two minutes after a bolus injection and has a very brief diffusion and elimination half-life of nine minutes. These properties make esmolol an effective medication for preventing or treating unfavourable increase in systemic blood pressure and heart rate that happen during surgery in reaction to unpleasant stimuli, such as those that occur during laryngoscopy and intubation. [2]

Magnesium sulphate is a bivalent salt that reduces the sympathetic excitability of muscle cells, causing vasodilation and a decrease in blood pressure. It is commonly used to control blood pressure and treat preeclampsia.[4] In addition to preventing the adrenal medulla from releasing catecholamines, magnesium sulphate limits the calcium ion's ability to bind to calcium in vascular smooth muscle, which causes systemic and coronary vasodilation. It influences the potential of cell membranes by modifying sodium and potassium channels, and by antagonistically interacting with NMDA receptors, it also depresses the central nervous system.[5] As it prevents catecholamine release from adrenergic terminals and adrenal medulla during laryngoscopy and endotracheal intubation, it is used to reduce adverse cardiovascular effects.

In this study we aim to compare the efficacy of Esmolol 1mg/kg to that of $MgSO_4$ 25mg/kg for attenuation of the sympathetic response to laryngoscopy and intubation.

METHODS:

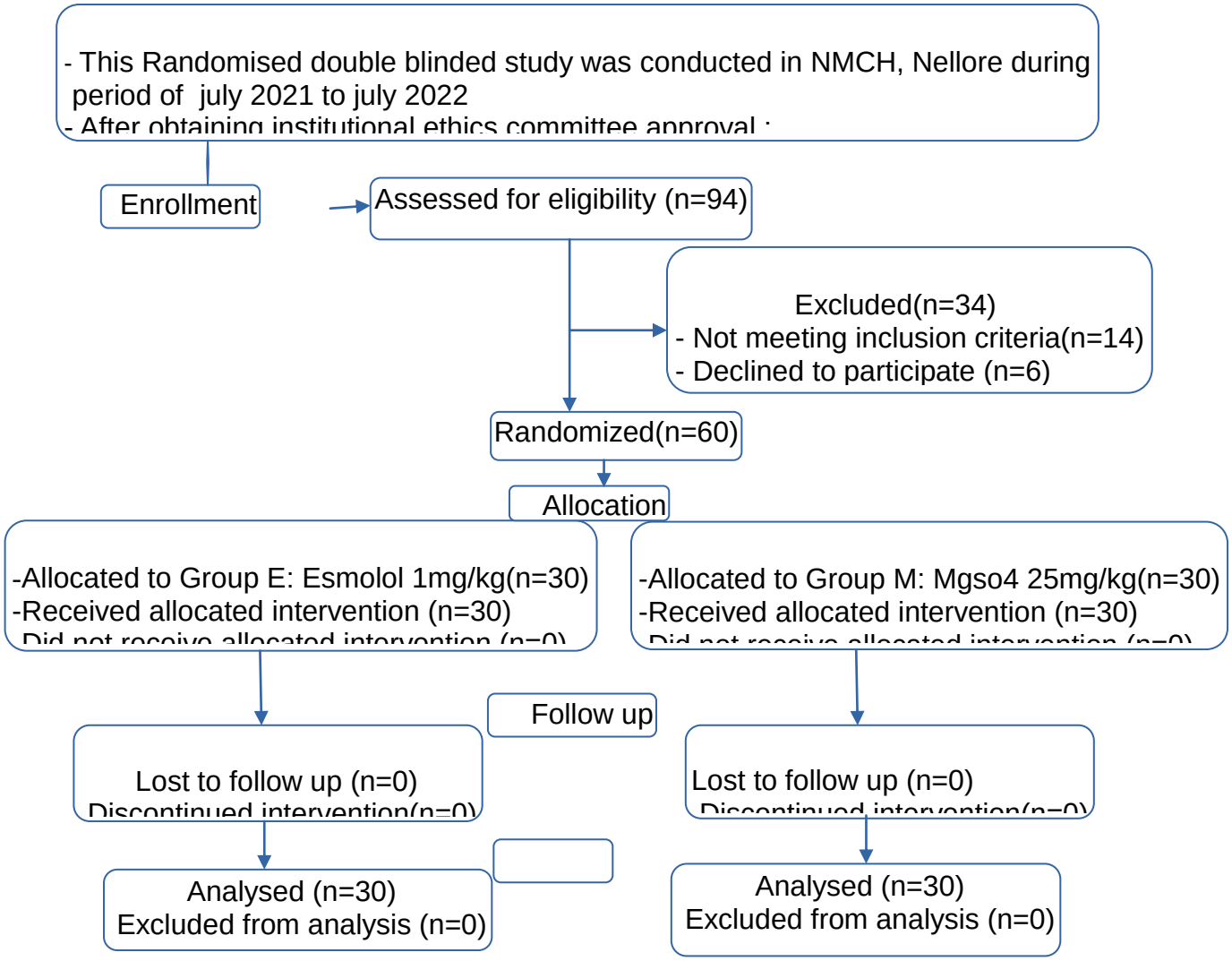
This prospective, double-blind, randomised control trial was performed at Narayana Medical College, Nellore, A.P., India, after obtaining approval from the institutional ethical committee with ref. no.IEC/NMC/15/02/2022_1, on sixty (60) patients posted for elective surgeries under General Anaesthesia. By randomization 60 patients satisfying the inclusion criteria were randomly assigned to two groups of 30 patients each. Group E received esmolol 1mg/kg IV and group M received magnesium sulphate 25 mg/kg IV 5 min before laryngoscopy and intubation.

Inclusion Criteria:

1. Patients posted for elective surgery under GA.
2. American Society of Anaesthesiologists (ASA) grade 1 & 2.
3. Laryngoscopy time <30 sec.
4. Age group 18 to 60 years.
5. Weight 50 to 80 kg.

Exclusion criteria:

1. Patients own refusal for participation.
2. Emergency surgery.
3. ASA grade 3 and 4.
4. Age <18yrs and >60yrs.
5. SBP <90 mmHg and HR <60 bpm.
6. Laryngoscopy time >30 sec.
7. CAD, COPD, Morbid Obesity, Renal compromise.
8. Pregnant and lactating women.
9. H/O allergy to the study drugs



CONSORT FLOW DIAGRAM

All the patients were pre-medicated with oral tab. Rantidine 150 mg and oral tab. Alprazolam 0.25 mg on the night before surgery. All the patients were remain fasting for solids 6 hours and for liquids 2 hrs prior to surgery.

On arrival in the operation theatre, ASA standard monitors in the form of ECG, NIBP and SPO2 were connected. Intravenous access was established with 18G intravenous cannula on the dorsum of the non -dominant hand and balanced crystalloid solution was started. Baseline values of the systolic and diastolic blood pressure (SBP and DBP) and HR were recorded.

Patients were preoxygenated with 100% oxygen for 3 min. Standard General Anaesthesia technique was instituted with inj.Glycopyrrolate 0.2mg, inj.Midaz 0.05mg/kg ,

inj.Fentanyl 2mcg/kg. The study drugs were administered intravenously 5 minutes prior to laryngoscopy.

Anaesthesia was induced with inj.Propofol 2 mg/kg & titrated upto the loss of verbal response. Hemodynamic variables were recorded again following which endotracheal intubation was performed facilitated by inj.Vecronium(0.1mg/kg). The laryngoscopy and intubation time were noted. Hemodynamic parameters (HR, SBP, DBP and MAP) were recorded at baseline, 0 min, 1 min, 3 min, 5 min and 10 min after intubation and compared. Anaesthesia was maintained with 50% O2 , Air , Sevoflurane and inj. Vecuronium(0.01mg/kg) top ups. At the end of surgery anaesthesia was reversed with inj.Neostigmine 0.05 mg/kg and inj. Glycopyrrolate 0.01mg/kg intravenously.when adequate spontaneous ventilation was established, patients were extubated.

Statistical analysis:

Statistical analysis was done using Jamovi version 1.6.23 software. Results were presented as means ± standard deviation.

P-value was calculated by using Student's-T-test; p-value <0.05 is considered to be statistically significant.

SAMPLE SIZE ESTIMATION:

Sample size was calculated keeping two-sided alpha error at 5 % and a power @ 80% by using formula $N = 2(Z\alpha+Z\beta)\sigma 2/(\mu 1-\mu 2)\ 2$

N=Sample size

$Z\alpha$ =Level of significance

$Z\beta$ =Required power

Σ= Anticipated standard deviation

$\mu 1-\mu 2$= Meaningful difference between two means.

Minimum of 23 patients were required in each group. For better validation 30 patients in each group were selected.

RESULTS:

Ninty four (94) patients were assessed for eligibility, of these 60 patients were enrolled and randomized to 2 groups of 30 patients in each group.

1) **HEART RATE (HR):**

There were no significant changes seen in baseline HR, at 0 min, 5 min and 10 min in both Group E and Group M. Patients in Group M had significantly lower HR at 1 min (P- 0.034) and 3 min (P- 0.025) after intubation when compared to group E.

Table 1: Mean heart rate at various time intervals

HEART RATE						
PARAMETER	MINUTE	ESMOLOL (N=30)		MGSO4(N=30)		P - VALUE
		MEAN	SD	MEAN	SD	
HR	Baseline	86.8	13.4	83.1	16.8	0.341
	0	91.8	17.2	85.1	16.9	0.132
	1	92	17	83	15.1	0.034
	3	90.7	17.3	81	15.1	0.025
	5	81.6	13.5	80.7	13.7	0.813
	10	80.7	15.6	84	15.3	0.402

Figure 1: Mean Heart Rate at various time intervals.

2) SYSTOLIC BLOOD PRESSURE (SBP):

SBP of patients at different interval was compared with student t test. Baseline SBP in group E was 131 ± 26.2 & in group M 137 ± 14.7 without any significant difference p value = 0.276 as shown in table 2. After study drug administration SBP was decreased in both the groups as shown in figure 2, which was statistically not significant (p value > 0.05)

Table 2: Mean SBP at various time intervals

SBP						
PARAMETER	MINUTE	ESMOLOL (N=30)		MGSO4(N=30)		P- VALUE
		MEAN	SD	MEAN	SD	
SBP	Baseline	131	26.2	137	14.7	0.276
	0	127	26.5	133	27.3	0.384
	1	122	20.1	118	14.4	0.438
	3	114	21.3	116	10.3	0.748
	5	116	22	124	13.8	0.115
	10	117	14.8	125	17.8	0.061

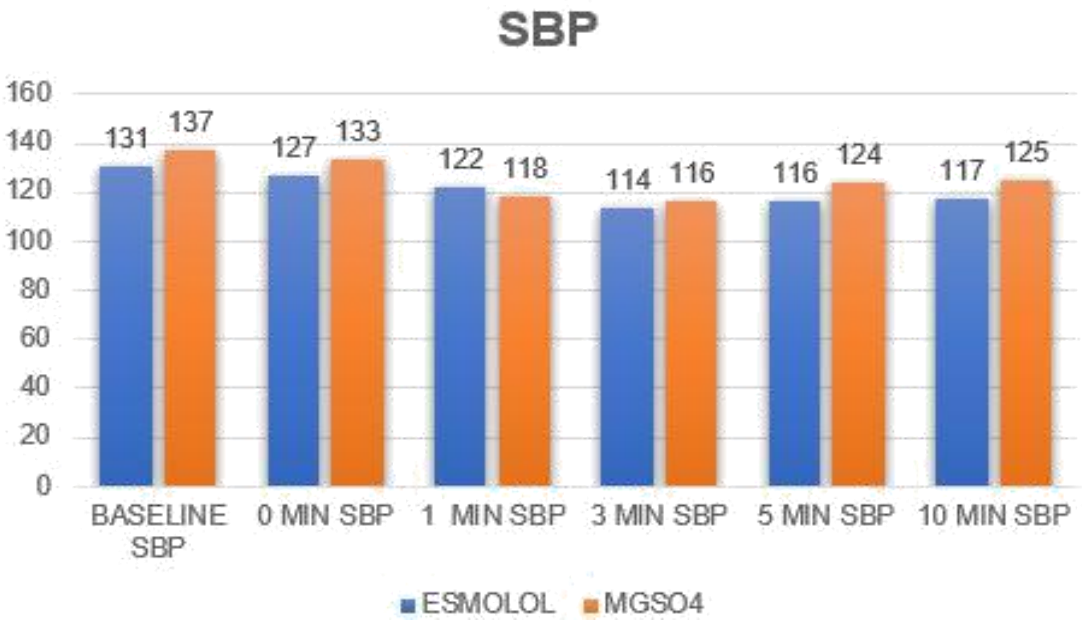


Figure 2: Mean SBP at various time intervals

3) DIASTOLIC BLOOD PRESSURE:

DBP of patients at different interval was compared with student t test. Baseline DBP in group E was 79.9 ± 12.1 & in group M was 81.6 ± 12.3 without any significant difference p value = 0.578 as shown in table 3. After study drug administration DBP was decreased in both the groups as shown in figure 3, which was statistically not significant (p value > 0.05) except at 0 min where mean DBP was increased in both groups without any significant difference (p value-0.92).

Table 3: Mean DBP at various time intervals.

DBP						
PARAMETER	MINUTE	ESMOLOL (N=30)		MGSO4(N=30)		P- VALUE
		MEAN	SD	MEAN	SD	
DBP	Baseline	79.9	12.1	81.6	12.3	0.578
	0	85.1	8.25	84.7	20	0.92
	1	74	15.3	74.5	12.2	0.897
	3	70.7	15.9	74	11.4	0.359
	5	74.9	14.3	80.5	16.1	0.163
	10	72.7	11.1	82.8	16.2	0.062

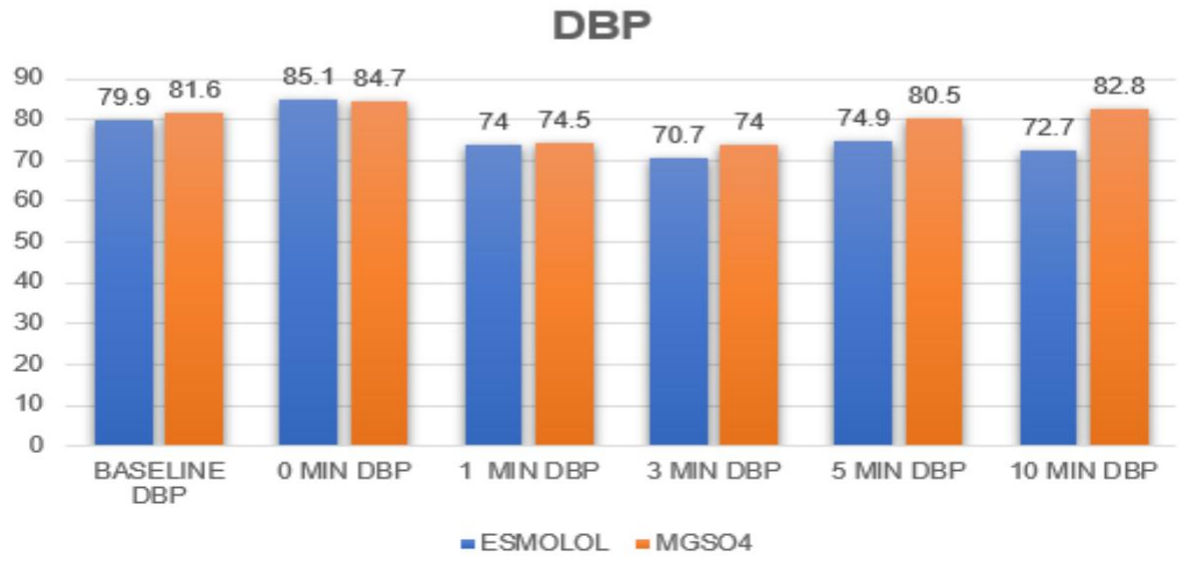


Figure 3: Mean DBP at various time intervals

4) MEAN ARTERIAL PRESSURE (MAP):

MAP of patients at different interval was compared with student t test. Baseline MAP in group E was 95.2 ± 12.5 & in group M was 98.9 ± 12.7 without any significant difference p value = 0.264 as shown in table 4. After study drug administration MAP was decreased in both the groups as shown in figure 4, which

was statistically not significant (p value > 0.05) except at 0 min where mean MAP was increased in both groups without any significant difference (p value-0.685)

Table 4: Mean MAP at various time intervals

MAP						
PARAMETER	MINUTE	ESMOLOL (N=30)		MGSO4(N=30)		P- VALUE
		MEAN	SD	MEAN	SD	
MAP	Baseline	95.2	12.5	98.9	12.7	0.264
	0	98.4	10.5	100	21.3	0.685
	1	89	12.7	89.1	13	0.968
	3	84.3	15.1	88.5	9.71	0.204
	5	89	16.1	94.5	15.6	0.184
	10	86.5	10.8	96.2	14.2	0.064

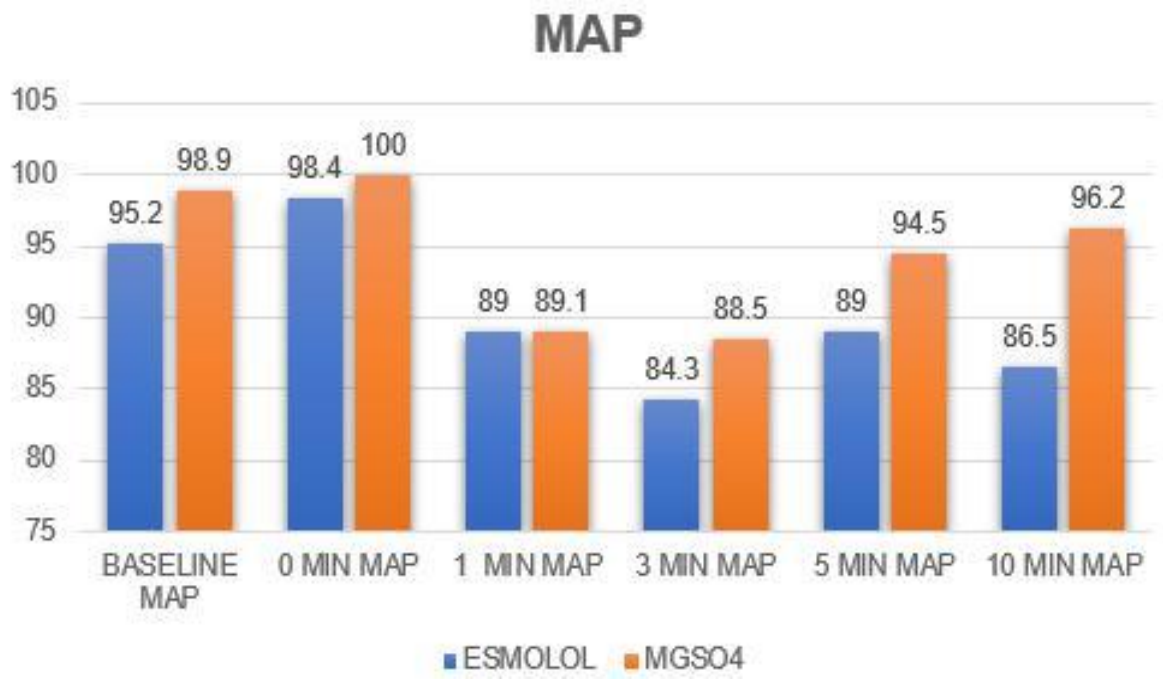


Figure 4: Mean MAP at various time intervals

Side Effect:

No episode of bradycardia, hypotension, nausea, vomiting, prolongation of neuromuscular blockade was obsereved in any patient.

DISCUSSION:

In many high-risk patients, the sequence of induction, laryngoscopy, and intubation is associated with significant haemodynamic changes and autonomic reflex activity, which may be cause for concern. In patients with cardiovascular or cerebral disease, the hemodynamic reaction to the stress of laryngoscopy and intubation is dangerous due to the increased risk of morbidity and mortality from tachycardia and hypertension resulting from the stress reflex caused by irritation of the respiratory tract. The cardiac strain and oxygen demand of the myocardium are raised in normal persons during intubation due to an increase in blood pressure and heart rate. This increased requirement is met by coronary vasodilation and increased coronary blood flow. A fresh episode of myocardial ischemia and infarction, however, is more likely to occur in patients with a history of ischemic heart disease due to stagnant coronary blood flow, a decline in cardiac index, and a loss of ejection fraction.[6]

Laryngoscopy and intubation cause hemodynamic responses that result in acute coronary events, arrhythmias, ventricular failure, and an increase in intracranial pressure.[7]Various methods have been tried to attenuate the hemodynamic response to laryngoscopy and intubation.

In this study, we compared the efficacy of a single pre intubation intravenous dose of esmolol (1 mg/kg) in attenuating these cardiovascular responses to that of magnesium sulphate(25 mg/kg).

Esmolol is a selective β1-receptor antagonist which has rapid onset of action and short duration of action.

MgSO4 is currently gaining popularity as it attenuates this sympathetic response as well as provide analgesia due to its Ca^{2+} blocking property. As it prevents catecholamine release from the adrenal medulla and adrenergic nerve terminals, it is also recommended for reducing the stress response during laryngoscopy and intubation.

Various studies have been done comparing the efficacy of both these drugs, in doses Esmolol 1.5 to 2 mg/kg and $MgSO_4$ 30 to 50 mg/kg.

In our study, we compared the efficacy of Esmolol 1mg/kg and $MgSO_4$ 25mg/kg in attenuation of the sympathetic response.

Kanhaiya Kumar et.al. (2022)[6] performed comparative study of the efficacy of intravenous esmolol 2mg/kg and intravenous magnesium sulphate 50mg/ kg in attenuating haemodynamic response to laryngoscopy and endotracheal intubation and concluded that HR was better controlled in Esmolol group which was statistically significant ($p<0.05$); SBP, DBP and MAP were comparable.

In our study we observed that after the trial drugs was given, there was a significant increase in heart rate from the basal values in both groups during direct laryngoscopy & intubation (at 0 min) compared to above study and the difference in increase in heart rate between the two groups were not statistically significant as we used lower concentration of drugs i.e., Esmolol 1mg/kg & Mgso4 25mg/kg in our study compared to the above study. But HR was better controlled in $MgSO_4$ group at 1min and 3 min, which was statistically significant. At 5 and 10 min after intubation in both the groups HR was decreased which was statistically not significant($p>0.05$). SBP, DBP and MAP were comparable in both the groups in our study similar to above study.

Norhuzaimah J et.al.(2018) [1] performed similar study and concluded that attenuation of haemodynamic response due to laryngoscopy and tracheal intubation by esmolol at 1.0 mg/kg was more pronounced compared to MgSO4 at 40 mg/kg in normotensive patients undergoing general anaesthesia for elective surgery.

In our study we observed that after the trial drugs was given, there was a significant increase in heart rate from the basal values in both groups during direct laryngoscopy & intubation (at 0 min) and the difference in increase in heart rate between the two groups were not significant statistically. HR was better controlled in Group M than Group E at 1min and 3 min, which was statistically significant. At 5 and 10 min after intubation in both the groups HR was decreased which was statistically not significant($p>0.05$).

The baseline systolic blood pressure values in both the groups were comparable ($p >0.05$). After the trial drug there was significant decrease in the SBP in both groups at 0 min, 1 min, 3 min, 5 min and 10 min which was statistically not significant($p>0.05$). Similarly, the baseline DBP and MAP in both the groups were comparable but there was

significant increase in DBP and MAP in both groups at 0 min ($p>0.05$) and there was significant decrease in the DBP and MAP in both groups at 1 min, 3 min, 5 min and 10 min which was statistically not significant($p>0.05$).

No side effects like bradycardia, hypotension, undue prolongation of neuromuscular blockade were observed.

$MgSO_4$ has the advantage of being cost effective, showing predilection for its use compared to Esmolol.

CONCLUSION:

We conclude that $MgSO_4$ 25 mg/kg is as efficacious as Esmolol 1 mg/kg in attenuating sympathetic response to laryngoscopy and intubation.

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