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COMPARATIVE STUDY ON DEXMEDETOMIDINE AND MAGNESIUM SULPHATE ON ATTENUATION OF STRESS RESPONSE OF LARYNGOSCOPY AND INTUBATION IN PATIENTS UNDERGOING GENERAL ANAESTHESIA

Anaesthesiology

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ABSTRACT

Background: Laryngoscopy and intubation cause catecholamine release due to sympatho-adrenal stimulation. This can cause acute hemodynamic instabilities like increase in blood pressure and heart rate. These responses are well tolerated in healthy individuals, but may increase perioperative morbidity and mortality in those patients with comorbid condition. The aim of the study was to compare the efficacy of Dexmedetomidine and Magnesium sulphate along with saline used as control. **Methods:** After ethical committee approval and written informed consent, 90 patients belonging to ASA – I and II, 18-60 years of either sex were enrolled and randomized into 3 groups (n=30), Group D received Dexmedetomidine 0.5µg/kg (made 10 ml volume) , Group M received MgSO4 20mg/kg (made 10ml volume) and Group S received normal saline 10ml intravenously over 10 minutes before induction. Following laryngoscopy and intubation, the parameters like HR, SBP, DBP and MAP was recorded just after intubation at various time after intubation and side effects were noted. **Results:** Both dexmedetomidine and magnesium sulphate was effective in controlling the hemodynamic responses compared to the control group. However, Dexmedetomidine 0.5ug/kg was far more effective in achieving hemodynamic stability in terms of heart rate which was well observed till 5 mins as compared to Magnesium sulphate. **Conclusion:** Dexmedetomidine and Magnesium sulphate both were effective in controlling the stress response but Dexmedetomidine was better in achieving stability in terms of heart rate.

KEYWORDS

Laryngoscopy, Intubation, Stress response, Dexmedetomidine, Magnesium Sulphate

INTRODUCTION

The introduction of a foreign body into the trachea is almost always associated with cardiovascular disturbances.[1] Laryngoscopy and tracheal intubation cause catecholamine release due to sympatho-adrenal stimulation. This effect can cause acute hemodynamic instabilities such as increase in blood pressure, heart rate, pulmonary artery pressure and capillary wedge pressure.[2] These responses are well tolerated in healthy individuals, but it may increase perioperative morbidity and mortality in those patients with coronary artery disease, vascular anomalies or intracranial diseases.[3]

Several agents like intravenous (IV) Lignocaine, beta blockers, alpha 2 receptor agonists like clonidine, dexmedetomidine, opiods like (fentanyl, sufentanyl, alfentanyl etc) calcium channel blockers, nitroglycerine, were tried to obtund the pressor response.[4]

Magnesium (Mg) is one of the most common cations in the intracellular fluid space that inhibits calcium entry into cell via blockade of N-methyl-D-aspartate (NMDA) receptor. Mg has analgesic, anaesthetic and muscle relaxant effects. NMDA receptor and Mg play an important role in control of pain pathway.[5] Mg attenuates stress response to laryngoscopy and intubation by blocking catecholamines from adrenergic nerve terminals and adrenal gland.[4] NMDA receptors channels contain ligand-gated ion currents at glutamatergic synapses. Noxious stimulation leads to the release of glutamate and aspartate neurotransmitters, which bind to the NMDA receptor. Activation of these receptors leads to calcium entry into the cell and initiates a series of central sensitization, wind-up and long term potentiation in the spinal cord, in the response of the cells to prolonged stimuli. The addition of magnesium reduces the activation of C- fibres by inhibiting the slow excitatory post-synaptic currents produced by NMDA receptor 3activation. NMDA receptor signaling may be important in determining the duration of acute pain.[6]

Dexmedetomidine, a congener of clonidine, is a highly selective alpha 2 adrenoreceptor agonist.[7] Dexmedetomidine is known to attenuate hypertensive responses associated with intubation, surgical stimulation and emergence.[8] Dexmedetomidine has been shown to decrease induction doses of intravenous anesthetics and to decrease intraoperative opioid and volatile anesthetic requirements for maintenance of anaesthesia. In addition, it has been shown to decrease perioperative catecholamine concentrations and promote perioperative hemodynamic and adrenergic stability.

At present there are very few studies comparing intravenous dexmedetomidine and magnesium sulphate premedication for attenuation of hemodynamic responses following laryngoscopy and intubation. We therefore designed this study to get an ideal drug to obtund the stress response of laryngoscopy and intubation, as previously many studies have been done to attenuate the stress response of laryngoscopy and intubation but no ideal drug has been found.

MATERIALS AND METHODS

This study was a randomized double blinded controlled conducted in the Department of Anaesthesiology, a tertiary Care Centre in Imphal, over a period of two years. After obtaining approval from the institutional ethics committee, the present study enrolled 90 ASA I and II (American society of Anaesthesiologist physical status I and II) adult patients of either sex, aged 18-60 years scheduled for elective surgery under general anesthesia with endotracheal intubation.

They were randomized based on computer generated randomization and divided into three equal groups (n=30). Group D(n=30) received Dexmedetomidine 0.5µg/kg (diluted to 10ml with normal saline),

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Group M(n=30) received MgSO4 20mg/kg (diluted to 10ml with normal saline), and Group S(n=30) received normal saline 10ml, IV over 10 minutes before induction. The study was registered with the Clinical Trials Registry of India (CTRI/2021/06/034217).

A total of 90 participants were included in the trial and the flow of the study is shown in the Figure 1.

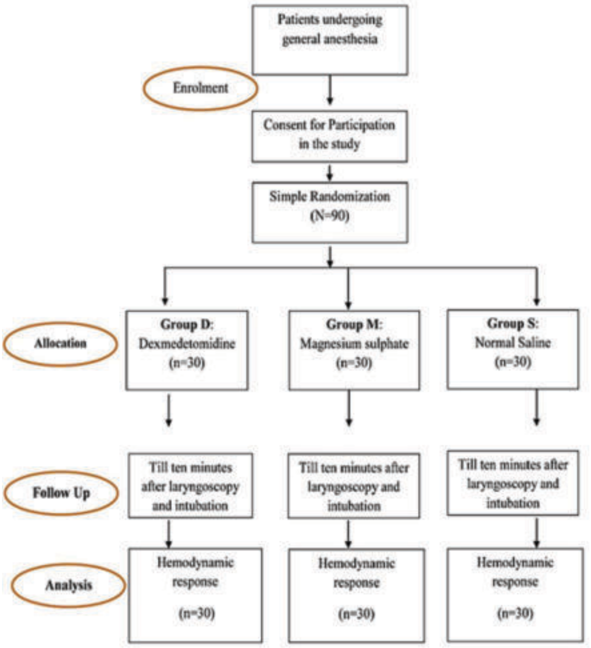

Figure 1. CONSORT diagram of the study participants

Patients with anticipated difficult airway [Mallampatti score > III, Thyromental distance <6.5 cm], patients with diabetes, hypertension, Pregnant, unwilling patients, patients with respiratory, cardiac, neurological, renal or liver disease with known allergy to study drugs, psychiatric patients were excluded from the study.

Pre-anaesthetic evaluation and relevant investigations were carried out in all patients. On the night before the surgery, informed consent was obtained and tablet alprazolam 0.5mg was given to all patients and were fasted for 6 h.

On arrival at the operation theatre, the patients were pre-medicated with injection glycopyrolate 0.2mg intramuscularly and injection ondansetron 4mg IV 30 min before induction.

In the operating room, patients were randomly allocated to one of the three groups. An intravenous line was secured and the patients were administered ringer lactate at a rate of 4-6ml/kg/hr. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and oxygen saturation (SpO2) were measured noninvasively and then study drug was given IV over 10 min. All the patients were pre-oxygenated for 3 min. General anaesthesia technique was standardised for all three groups. Pre-induction hemodynamic parametres like HR, SBP, DBP, and MAP was recorded.

Anaesthesia was induced with injection propofol 2mg/kg body wt, and intubation was facilitated by intravenous succinylcholine 2mg/kg body weight under direct laryngoscopy plus bolus doses of muscle relaxant . After endotracheal intubation, anaesthesia was maintained with 50% nitrous oxide in oxygen with a fresh-gas flow of 2L/min and sevoflurane 0.6 to 1.5% titrated to maintain a BIS value of 40 to 60. Ventilation was adjusted to keep end-tidal carbon dioxide (ETCO2) between 30-35 mmHg. Following laryngoscopy and endotracheal intubation, the parameters like HR, SBP, DBP and MAP was recorded just after intubation and also at 1, 3, 5 and 10 min after intubation. Anaesthesia was performed by an anaesthetist who is not involved in data collection.

Patients were monitored for any adverse effects like bradycardia, and hypotension during intraoperative period.

Muscle relaxation was maintained with loading dose of IV atracurium besylate 0.5mg/kg and maintenance dose of 0.1mg/kg. After surgery, reversal was achieved with IV neostigmine 0.05 mg/kg and IV glycopyrolate 0.01mg/kg. The data collected were entered in a computer and statistical analysis was performed using IBM SPSS statistics version 21 for windows, descriptive summary was summarised in mean, standard deviation, frequency and percentage, for continuous variable; ANOVA, independent t-test, paired t-test were used and p value of <0.05 was considered statistically significant.

RESULTS:

Table 1

Demographic characteristics of patients in three groups

Characteristics	Group D (Mean +/-SD)	Group M (Mean +/- SD)	Group S (Mean +/- SD)	p Value
AGE(years)	39.6+/- 13.1	41.6+/- 12.9	41.4+/- 14.1	0.824
WEIGHT(kgs)	60.0+/- 7.2	57.7+/- 8.6	59.9+/- 8.2	0.458
GENDER(M:F)	14:16	10:20	17:13	0.191
ASA(I:II)	22:8	27:3	27:3	0.121

ASA- American Society of Anaesthesiologists

Baseline haemodynamic parameters were comparable among three groups [Table 1].

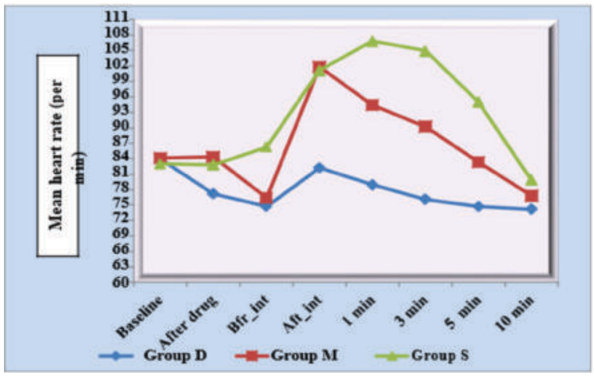

Figure 2

Comparison of mean heart rate at various time intervals among three groups.

The intragroup comparison of HR in three groups compared to pre-drug values showed a statistically highly significant (p <0.001) fall in group D followed by group M which was well observed till 5 minutes, whereas a significant rise was seen in group S (p <0.001) post intubation. The HR reached the baseline level and attained its stability by 5 mins. On intergroup comparison, both group D and M had a significant (p<0.001) fall in HR compared to group S after study drug, but group D showed a statistically highly significant attenuation of HR compared to group M upto 5 min [Figure 2].

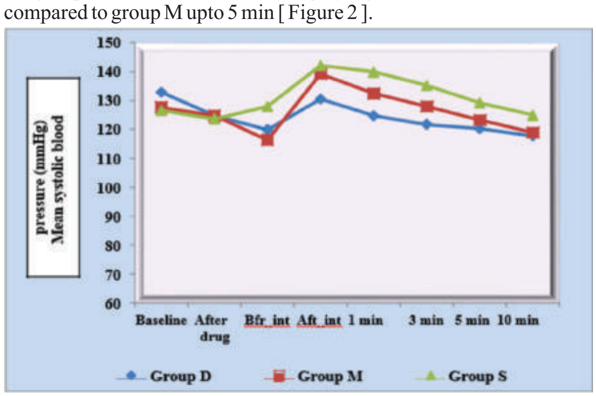

Figure 3

Comparison of mean systolic blood pressure (SBP) among three groups

Before intubation, a significant reduction in the mean SBP values was seen after the study drug was given in group D from 132.8 to 124.7 and group M from 127.6 to 124.7 ($p<0.001$), but not is group S. In group S, SBP increased significantly ($p<0.001$) at intubation from 127.9 to 142.1. However SBP remained significantly lower in other two groups ($p<0.001$) till 5 min post-intubation as compared to pre-drug values. Compared to group S, both group D and group M showed a significant ($p<0.05$) decrease in SBP. However, there was no significant difference in SBP between group D and group M [Figure 3].

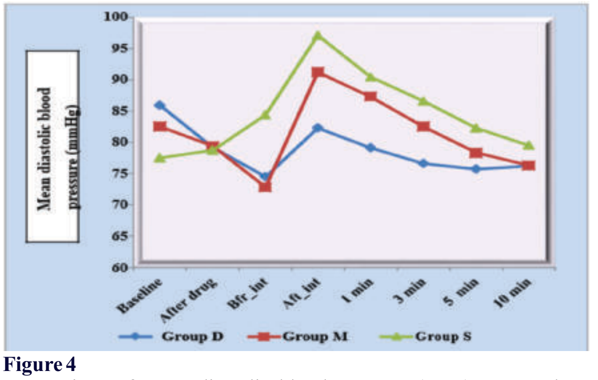

Figure 4
Comparison of mean diastolic blood pressure (DBP) among three groups

Similarly, there was a greater rise in mean DBP for patients in group S immediately following intubation followed by the patients in group M. The patients in group D were relatively stable in terms of DBP after intubation and the stability could be well observed till 5 min after intubation. Significant difference was noted in mean DBP for group S with group D and group M ($p<0.05$). However, no significant difference in DBP between group D and group M [Figure 4].

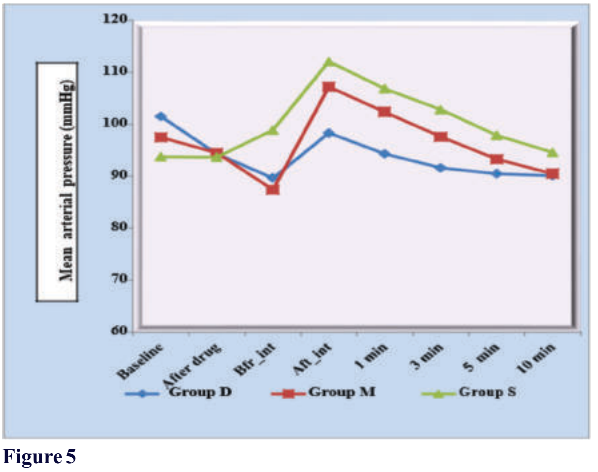

Figure 5
Comparison of mean arterial pressure (MAP) among three groups

Figure 5 shows that there was a greater rise in MAP for patients in group S immediately following intubation followed by the patients in group M. The patients in group D were relatively stable in terms of MAP after intubation and the stability could be well observed till 5 min after intubation. Significant difference in MAP was noted for group S with group D and group M ($p<0.05$). However, there was no significant difference in MAP between group D and group M.

DISCUSSION

Laryngoscopy and intubation can cause hemodynamic instabilities like increase in heart rate and blood pressure. The three groups were comparable as regards to the demographic profile

The demographic profile of the study in terms of age, gender, weight and ASA status was found to be statistically not significant between the study groups, showing that patients were comparable by the gender distribution ($p=0.191$), age ($p=0.834$), weight ($p=0.458$), ASA ($p=0.121$).

The present study evaluated and compared the efficacy of dexmedetomidine and magnesium sulphate in attenuating stress response of laryngoscopy and intubation in patients undergoing general anaesthesia. This particular combination being compared for the same was unprecedented, making this study unique.

Dexmedetomidine, alpha-2 adrenergic agonists have been introduced to clinical anaesthesia for their sympatholytic, sedative, anaesthetic sparing and haemodynamic stabilizing properties. Others claimed advantages include minimal respiratory depression with cardioprotection, neuroprotection and renoprotection, thus making it useful at various situations including offsite procedures.[9,10]

Similarly, magnesium inhibits catecholamine release from the adrenergic nerve endings and from the adrenal medulla, thereby controlling the vasomotor tone, cardiac excitability and neurotransmitter release. In many of its actions, it is likened to a physiological calcium antagonist.[11] Administration of magnesium sulphate preoperatively has also been proven to reduce the haemodynamic response to endotracheal intubation.[12,13]

α-2 agonists such as clonidine and dexmedetomidine have been used by some researchers for attenuation of the stress response to laryngoscopy and intubation with varied dosages.[14,15,16] Although they found promising results, the higher dose of 1 µg/kg was associated with increased incidence of cardiovascular compromise in the form of hypotension and bradycardia.[15,16]

Our study showed that the heart rate was comparable between the groups at baseline ($p>0.05$). There was a greater rise in mean heart rate for patients administered with normal saline immediately following intubation followed by the patients in the MgSO4 group and Dexmedetomidine group. The heart rate was relatively stable in Dexmedetomidine group and the stability could be well observed till five minutes after intubation. The heart rate in the normal saline group reached the baseline level and became stable after five minutes of intubation. There was significant difference in the mean heart rate for the normal saline group with the Dexmedetomidine group and MgSO4 group ($p<0.05$). There was also a significant difference between the Dexmedetomidine group and MgSO4 group which clearly implies that the Dexmedetomidine group was the better drug in achieving hemodynamic stability following intubation in terms of heart rate because of activation of alpha 2 adrenoceptors in the CNS causing dose dependent reduction in level of plasma catecholamine and sympathetic inhibition of medullary vasomotor centre.

Bachofen M et al[17] had concluded that Dexmedetomidine and magnesium sulphate appeared to best meet the characteristics of a drug to prevent these sympathetic responses with Dexmedetomidine producing a better response which is comparable to our study.

Individual studies conducted by Puri GD et al[12] and Trivedi V et al[13] also have concluded that administration of magnesium sulphate preoperatively significantly reduces the hemodynamic response to intubation which is comparable to our study.

Even a study by Honarmand A et al[2] had concluded that lower doses of MgSO4 (30 mg/kg or 40 mg/kg, IV) by itself can significantly result in hemodynamic stability following intubation till five minutes after laryngoscopy in comparison with control group. The mechanism of action is considered to be through its calcium antagonistic properties. Calcium has a major role in the release of catecholamines from the adrenal medulla and adrenergic nerve terminals in response to the stimulation by sympathetic nervous system. Magnesium competes with calcium for binding to the membrane channels. Hence, magnesium acts as a calcium antagonist and can modify the responses that mediated by calcium. Hence, MgSO4 blocks release of catecholamine stores and decrease responses to adrenergic stimulations, which are proved by various other studies.[18,19,20]

Dexmedetomidine accounted for relatively better stability because of its sympatholytic and vagomimetic effects.[15] The fact that Dexmedetomidine produces better reduction and stability in heart rate has also been proved by a study conducted by Mahajan L et al.[8]

One another important observation in our study is that there was a steep increase in the heart rate immediately following intubation in the magnesium sulphate group and it could be attributed to the inhibition of action of acetylcholine on the heart, which are explained by various studies.[21,22]

With regards to systolic blood pressure, diastolic blood pressure and mean arterial pressure, there was a greater rise in mean pressure values for patients administered with normal saline immediately following intubation followed by the patients in the MgSO4 group. The patients in the Dexmedetomidine group were relatively stable in terms of blood pressure changes after intubation and the stability could be well observed till five minutes after intubation. There was significant difference in the mean blood pressure values for the normal saline group with the Dexmedetomidine group and MgSO4 group ($p<0.05$). However, there was no significant difference in blood pressure values between the Dexmedetomidine group and MgSO4 group. Our study findings are consistent with the results of the study conducted by Mahajan L et al.[8] There are not many studies comparing the use of dexmedetomidine and Magnesium sulphate in preventing the pressor response to laryngoscopy and intubation. Magnesium sulphate has inhibitory effect on catecholamine release as well as its vasodilatory properties and hence it also be noted in our study that there was not as much increase in blood pressure values after intubation in this group as it occurred with the heart rate values.[22] However, it is noteworthy to mention that these findings should be interpreted with caution owing to the smaller sample size of our study and always it is advisable to interpret based on the clinical correlation.

There were a few limitations of this study:

First is that the sample size was lesser and hence it could not be generalizable to the entire population. However, since the representative sample was taken for this study, it could be representative for the similar setting. It is therefore recommended that further studies with larger sample size would help in making our study findings more robust.

Second, we did not measure the plasma concentration of catecholamine. Therefore, we could not demonstrate the effectiveness of the dosage of dexmedetomidine and magnesium sulphate used in the study in decreasing the sympathetic nervous system activity.

Lastly, in this study, we could not confirm the anesthesia depth in all groups due to lack of facility. Inadequate depth of anesthesia can, to some extent, increase the hemodynamic responses to intubation.

CONCLUSION

It is concluded that pre-treatment with Dexmedetomidine and Magnesium sulphate is effective in controlling the hemodynamic response after laryngoscopy and intubation. However, Dexmedetomidine 0.5µg/kg body weight was far more effective in achieving hemodynamic stability in terms of heart rate which was well observed till 5 minutes after intubation as compared to Magnesium sulphate 20mg/kg body weight. Hence future studies using combination of these drugs with varying dosage is required to acquire more evidence with high quality data.

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