A prospective randomised study comparing intravenous magnesium sulphate and sublingual nitroglycerine spray in attenuating haemodynamic responses to laryngoscopy and intubation

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ABSTRACT

Background: Laryngoscopy and tracheal Intubation are invariably associated with certain stress responses due to the sympatho-adrenal stimulation. These cardiovascular and neurohumoral alterations may directly affect the physiology and increase the risk. So far, various drugs have been tried but none has been considered ideal for blunting this presser response. We therefore, planned this comparative study to evaluate and compare the efficacy of intravenous magnesium sulphate (30 mg/kg) versus sublingual nitroglycerine spray (0.4 mg/spray) in attenuating the presser response to Laryngoscopy and Tracheal Intubation.

Methods: Fifty patients, aged 15–50 years, scheduled for elective surgery under general anaesthesia, were randomly assigned to one of the two groups of 25 each, Group A (magnesium group) and Group B (nitroglycerine group). Study drug was given 90-120 seconds before tracheal intubation. Heart rate, Systolic blood pressure and Rate pressure product were recorded at different intervals after administering the study drug till 3 minutes after intubation.

Results: Mean heart rate was significantly higher from the baseline at all times after administering the study drug in both the groups. Increase in systolic blood pressure as a presser response was limited to 7.25% in Group A and 5.83% in Group B from the baseline after tracheal intubation. There was relative hypotension after administration of the study drug in both the groups.

Conclusions: Intravenous magnesium or sublingual nitroglycerine pre-treatment is found to be effective in attenuating the pressor response to laryngoscopy and intubation. These drugs may lead to rise in HR but it is transient and dose dependent. However, both the drugs can significantly control the hypertensive response after laryngoscopy and intubation.

Keywords: Laryngoscopy, Intubation, Magnesium sulphate, Nitroglycerine spray

INTRODUCTION

Tracheal intubation is a mandatory in most surgical patients requiring general anaesthesia and critically ill patients needing mechanical ventilation. Like all interventional procedures, laryngoscopy and tracheal intubation are invariably associated with certain stress responses in the human body by causing catecholamine release due to the sympatho-adrenal stimulation.¹,² These changes in cardio-vascular and neuro-humoral systems may directly affect the physiology of patients and increase the risk.³ The magnitude of these responses if smaller, is better tolerated in healthy normo-tensive individuals with no systemic illness.⁴ But such effects can be detrimental in susceptible individuals, with limited cardiovascular reserve specially in geriatric and elderly population.⁵,⁶
So far, various techniques like topical and intravenous lignocaine; sympatholytic drugs like phentolamine, narcotic agents like nalbuphine; fentanyl and alfentanil; Beta Blockers like intravenous labetalol, metoprolol and esmolol; alpha adrenergic blocking drugs like oral and intravenous clonidine; vasodilators like nitroglycerine and hydralazine; calcium channel blockers like diltiazem; deep general anaesthesia and various other drugs have been tried.\(^{1,3,7,15}\) However, none of the agents has been considered ideal.

Magnesium sulphate which is an established agent as an anti-convulsant in eclampsia, have recently been under trial for its utility in reducing cardiovascular effects and attenuating the stress responses associated with laryngoscopy and tracheal intubation, when used in relatively small doses.\(^{17-20}\) Nitroglycerine lingual spray as a premedication has also been recently studied to attenuate the hypertensive effect of laryngoscopy and intubation. We therefore, planned this comparative, prospective study to evaluate and compare the efficacy of intravenous magnesium sulphate (30 mg/kg) versus sublingual nitroglycerine spray (0.4 mg per spray) in attenuating the cardiovascular response to laryngoscopy and tracheal Intubation.

**METHODS**

After obtaining the approvals from the institutional review board, this double blind randomized prospective clinical study was designed and conducted in a tertiary care hospital from June 2016 to May 2017. A total of 50 ASA-Grade I and II patients of either sex in the age group of 15-50 years, posted for elective surgical procedures lasting for an hour or more and requiring general anaesthesia were enrolled for the study. Patients were thoroughly examined during pre-operative visit and patients below 15 years and above 50 years of age, belonging to ASA Grade III or more, with anticipated difficult airway, with de-compensated systemic co-morbidities or neuromuscular disease were excluded from the study. The selected patients were randomly divided into 2 Groups (25 patients each) depending upon the study drug administered. Group A - received intravenous MgSO4 (30 mg/kg) in 20 ml normal saline; Group B - received 2 puffs of sublingual nitroglycerine spray (0.4 mg/spray). Premedication was uniform for all the patients in the form of intravenous Glycopyrrolate 4 mcg/kg and Midazolam 0.03 mg/kg 10 minutes prior to induction. All patients received intravenous fentanyl (2 mcg/kg) as a routine opioid analgesic premedication. Study drug was given 3 minute before the induction of general anaesthesia. Rest of the general anaesthetic technique was same for all the patients. After preoxygenation with 100% oxygen general anaesthesia was induced with intravenous propofol (~3 mg/kg) till the fixation of eyeball, followed by intravenous suxamethonium 2 mg/kg to facilitate tracheal intubation. Patients were ventilated on mask using 100% oxygen until the disappearance of fasciculations. Laryngoscopy was carried out by an experienced anaesthesiologist and orotracheal intubation was achieved with appropriate sized cuffed endotracheal tube. Study included only those patients in whom intubation was achieved in single attempt within 30 seconds and by using conventional McIntosh curved blade laryngoscope. Surgical stimulation was not allowed until five minute after intubation. Maintenance of general anaesthesia, intraoperative monitoring and reversal of neuro-muscular blockade and/or extubation followed the standard practice. Parameters like Heart Rate (HR); systolic blood pressure (SBP); diastolic blood pressure (DBP) were recorded at following time intervals. Baseline; after administering the study drug; after induction of general anaesthesia; at laryngoscopy; just after intubation; at 2 minutes and at 5 minutes after intubation. Rate pressure product (RPP) defined as the product of HR and SBP was calculated at baseline and at different time intervals.

As magnesium is known to potentiate the action of both depolarizing and non-depolarizing muscle relaxants, the duration of suxamethonium (intubating dose) and time to 1st dose of non-depolarizing muscle relaxant decided on the basis of response to supramaximal twitch was also noted. Complications of magnesium and nitroglycerine, like hypotension, circulatory collapse, arrhythmias, nausea, flushing, sweating and hot sense etc. were also looked for.

Parametric data (age, HR, SBP and RPP) was reported as mean±SD and was analyzed by unpaired Student's t test. Categorical data was reported as number and percent and analysed using the Pearson's chi-square test/Fischer exact test. Percentage change from the baseline values of HR, SBP and RPP at different time intervals were calculated. The data were subjected to statistical analysis using t – test and Chi square. P value of 0.05 was considered as statistically significant.

**RESULTS**

Patients in both the groups were comparable with respect to age, gender or weight (Table 1). It was observed that the mean baseline parameters (HR, SBP and RPP) in the groups were comparable (p>0.1) (Table 1).

There was significant rise in the HR (p<0.001) from the baseline values after giving the study drug (magnesium sulphate in group A and Sublingual Nitroglycerine in group B)). Increase in HR was more in Group B (22.33%), than in Group A (17.96%). Mean HR values were significantly high from the baseline, in both the groups after laryngoscopy and intubation and at 2 and 5 minutes thereafter. On intergroup comparison (Table 3) it was observed that although the mean HR increased after administering the study drug in both the groups, there was no statistically significant difference in mean HR values at all points between the two groups.
# Table 1: Demographic data and baseline parameters.

| Demographic Data               | Group A (n=25) | Group B (n=25) | P value |
|-------------------------------|---------------|---------------|--------|
| Age in yrs (mean±SD)          | 30.4±9.896    | 30.1±11.661   | 0.856  |
| Weight in Kg (mean±SD)        | 54.3±10.575   | 53.5±9.435    | 0.705  |
| Sex (M:F)                     | 9: 16         | 8: 17         | 0.481  |
| Baseline HR (mean±SD)         | 84.3±9.673    | 89.9±11.76    | 0.110  |
| Baseline SBP (mean±SD)        | 117.6±9.292   | 122.4±9.018   | 0.297  |
| Baseline RPP (mean±SD)        | 9936.48±1532.868 | 10921.92±1832.951 | 0.064  |

# Table 2: Percent change in heart rate (HR) from baseline.

| Study group | Mean±SD | % Change | P value |
|-------------|---------|----------|--------|
| **Group A** |         |          |        |
| Baseline    | 84.32±9.673 | --      |        |
| After study drug | 99.08±10.606 | 17.96   | 0.000* |
| After Induction     | 100.08±10.512 | 19.09   | 0.000* |
| At laryngoscopy   | 101.04±10.490  | 20.22   | 0.000* |
| Just after Intubation | 103.52±14.734  | 22.78   | 0.000* |
| At 2 minutes      | 102.76±14.263   | 21.98   | 0.000* |
| At 5 minutes      | 95.76±12.614    | 13.75   | 0.000* |
| **Group B**     |         |          |        |
| Baseline        | 89.92±11.768   | --      |        |
| After study drug | 109.76±14.356  | 22.33   | 0.000* |
| After Induction  | 109.12±12.937   | 21.85   | 0.000* |
| At laryngoscopy  | 108.48±12.978   | 21.56   | 0.000* |
| Just after Intubation | 111.12±14.225  | 24.55   | 0.000* |
| At 2 minutes     | 107.52±13.911   | 20.82   | 0.000* |
| At 5 minutes     | 100.24±13.208   | 12.48   | 0.001* |

SD=standard deviation;* p<0.001 is highly significant.

# Table 3: Inter-group comparison of % change in HR.

| Point of time | Group A vs. B (p values) |
|---------------|--------------------------|
| Baseline      | 0.080                    |
| After study drug  | 0.004                  |
| After Induction        | 0.010                    |
| At laryngoscopy     | 0.054                    |
| After intubation   | 0.057                    |
| At 2 minutes      | 0.239                    |
| At 5 minutes      | 0.230                    |

There was fall in SBP after giving magnesium sulphate in group A (-6.02% from baseline) and group B (-7.69% from baseline). Mean SBP at all the points after laryngoscopy and intubation was higher than the baseline values (Table 4). But on intergroup comparison the mean SBP in both the groups was comparable and slight increase in SBP in response to laryngoscopy was observed in both the groups (Table 5).

RPP was increased by 10.75% and 14.36% from the baseline values after giving the study drug in group A and group B respectively. We observed significant increase in RPP (from the baseline) at laryngoscopy and intubation and later at 2 and 3 minutes in both the groups (Table 6).

However, on intergroup comparison it was seen that the rise in RPP was maximum after intubation and it was higher in group B (33.27% from baseline) than in group A (31.68% above baseline). However, the difference between the two groups was not statistically significant (p=0.810) (Table 7).

None of our patients had any complications of magnesium and nitroglycerine, like flushing and sense of warmth, tachyarrhythmias, nausea, sweating, etc, after intravenous administration. We did not observe any prolongation in duration of action of neuro-muscular blocking agents, with the doses (30 mg/kg) included in our study.
Table 4: Percent change in systolic blood pressure from baseline.

| Study group          | Mean±SD   | % Change | P value |
|----------------------|-----------|----------|---------|
| **Group A**          |           |          |         |
| Baseline             | 117.60±9.292 | -6.02    | 0.000*  |
| After study drug     | 110.24±6.790 | -7.69    | 0.000*  |
| After induction      | 108.08±7.884 | -0.89    | 0.524   |
| At laryngoscopy      | 116.32±11.101 | 7.25     | 0.001   |
| Just after intubation| 125.84±12.123 | 7.72     | 0.001   |
| At 2 minutes         | 126.48±13.245 | 1.211    | 0.568   |
| At 5 minutes         | 118.72±10.212 | 5.83     | 0.000*  |

**Group B**

| Mean±SD   | % Change | P value |
|-----------|----------|---------|
| Baseline  | 122.40±9.018 | -7.69   | 0.000** |
| After study drug | 114.24±16.816 | -4.48   | 0.001   |
| After induction | 129.28±10.163 | 5.83    | 0.017   |
| At 2 minutes | 120.16±8.204 | 1.52    | 0.238   |
| At 5 minutes | 112.96±6.611 | 7.32    | 0.000*  |

SD=standard Deviation; *P<0.001 is highly significant.

Table 5: Inter-group comparison of% change in SBP.

| Point of time | Group A vs. B (p value) |
|---------------|-------------------------|
| Baseline      | 0.137                   |
| After study drug | 0.411                 |
| After induction | 0.114                  |
| At laryngoscopy | 0.895                  |
| After intubation | 0.368                 |
| At 2 minutes  | 0.077                   |
| At 5 minutes  | 0.043                   |

Table 6: Percent change in rate pressure product from baseline.

| Study group          | Mean±SD   | % Change | P value |
|----------------------|-----------|----------|---------|
| **Group A**          |           |          |         |
| Baseline             | 9936.48±1532.86 | 10.75    | 0.000*  |
| After study drug     | 10916.08±1302.91 | 9.78     | 0.000*  |
| After induction      | 10830.08±1480.74 | 19.08    | 0.000*  |
| At laryngoscopy      | 11766.88±1731.79 | 31.68    | 0.000*  |
| Just after intubation| 13047.52±2317.33 | 31.37    | 0.000*  |
| At 2 minutes         | 13066.16±2696.42 | 15.21    | 0.000*  |
| At 5 minutes         | 11454.08±1807.25 | 5.74     | 0.342   |

**Group B**

| Mean±SD   | % Change | P value |
|-----------|----------|---------|
| Baseline  | 10921.92±1832.95 | 14.36   | 0.000*  |
| After study drug | 12519.04±2713.49 | 15.33   | 0.001   |
| After induction | 12693.12±2078.08 | 17.65   | 0.000*  |
| At laryngoscopy | 14413.28±2436.52 | 33.27   | 0.000*  |
| Just after intubation | 12926.40±1671.86 | 20.72   | 0.000*  |
| At 2 minutes  | 11346.72±1807.25 | 5.74    | 0.342   |
| At 5 minutes  | 11346.72±1807.25 | 5.74    | 0.342   |

SD=standard deviation; *p<0.001 is highly significant.
**DISCUSSION**

Laryngoscopy and intubation, like any other procedure, can evoke sympathetic response in the body. This is well established and there have been number of ways to control or reduce the stress response evoked by such stimuli. Magnesium is already studied and has been proved to attenuate the sympathetic outburst during stress. We planned this study, to compare intravenous magnesium sulphate (30 mg/kg) versus sublingual nitroglycerine spray (2 puffs of 0.4 mg/spray) in attenuating the cardiovascular effects of the stress response during Laryngoscopy and intubation.

**Heart rate**

Our results and observations, pertaining to heart rate were comparable to James et al in their double blind study. They assessed the effects of pre-treatment with intravenous magnesium sulphate 60 mg/kg on cardiovascular responses and the release of catecholamines associated with tracheal intubation in otherwise normal subjects compared to normal saline pre-treated controls. They found that induction of anesthesia produced no changes in HR in either Group, but magnesium pre-treatment produced initial increase in HR by 13±3.9 beats/minute. HR increased by 30.9 beats/minute in the control Group 2 minutes after intubation, whereas in the magnesium Group, HR remained virtually unchanged from the post-magnesium values. Puri et al studied 36 patients with coronary artery disease to evaluate the hemodynamic effects of magnesium and its efficacy in attenuating the response to intubation. Magnesium Group received 50 mg/kg magnesium sulphate and the control group received normal saline solution before the induction of anesthesia. They found that there was initial insignificant (p>0.05) rise in the HR from 65.2±12.7 to 70.5±15.6 after administering the study drug and no further significant rise in HR in the magnesium Group after intubation. But in control group though there was no initial rise in HR after the study drug, HR increased significantly (p<0.001) from 64.2±8.8 to 72.9±8.8 after intubation. This study also supports our findings.

Similarly, the initial increase in the HR after giving nitroglycerine was also observed by Singh et al and Channaiah et al in their study.

The changes in the Heart Rate observed in our study as well as the studies quoted above are particularly interesting. It might be expected that magnesium would slow the HR by inhibiting the calcium mediated depolarizing current in the pacemaker tissue, the effect that has been demonstrated in the isolated animal hearts. However, in the intact animal the ability of magnesium to inhibit the release of acetylcholine from the vagus nerve predominates and, therefore, the overall effect is mild increase in the heart rate as seen in this study.

Also, the tachycardia observed in all these studies who used nitroglycerine maybe due to the fact that in patients with normal left ventricular end diastolic pressure, a decrease in blood pressure following nitroglycerine results in reflex tachycardia.

**Blood pressure**

James et al reported significant increase in SBP (from 106.4±3.1 to 145.1±5.6 mmHg) after intubation in control group but not significantly (p>0.05) in magnesium group (from 106.8±3.1 to 110.0±4.4 mmHg). Puri et al also reported similar observation with the changes in mean arterial pressure (MAP). They reported that MAP decreased significantly (p<0.001) from after administering the study drug in the magnesium Group as compared to control group though MAP increased after intubation in both the Groups, it was significantly (p<0.001) higher than the base line in control Group as compared to magnesium group where the levels were just near baseline after intubation.

The similar observations in the blood pressure values were made by Singh et al and Channaiah et al in their study.

The insignificant rise systemic blood pressure during intubation in nitroglycerine pretreated patients was because of the pharmacological effect of the drug, which by virtue of its hypotensive property buffered the hypertensive response. The nitroglycerine has direct vasodilator effect, resulting in pooling of blood volume in the capacitance system and decreased venous return to the heart, leading to a fall in left ventricular end diastolic pressure. The insignificant rise systemic blood pressure during intubation in nitroglycerine pretreated patients was because of the pharmacological effect of the drug, which by virtue of its hypotensive property buffered the hypertensive response. The nitroglycerine has direct vasodilator effect, resulting in pooling of blood volume in the capacitance system and decreased venous return to the heart, leading to a fall in left ventricular end diastolic pressure. The insignificant rise systemic blood pressure during intubation in nitroglycerine pretreated patients was because of the pharmacological effect of the drug, which by virtue of its hypotensive property buffered the hypertensive response. The nitroglycerine has direct vasodilator effect, resulting in pooling of blood volume in the capacitance system and decreased venous return to the heart, leading to a fall in left ventricular end diastolic pressure.

**Table 7: Inter-group comparison % change in RPP.**

| Point of time     | Group A vs. B (p value) |
|-------------------|-------------------------|
| Baseline          | 0.043*                  |
| After study drug  | 0.007*                  |
| After induction   | 0.008*                  |
| At laryngoscopy   | 0.184                   |
| After intubation  | 0.081                   |
| At 2 minutes      | 0.856                   |
| At 5 minutes      | 0.865                   |
attributed to its direct vasodilating property as well as by its action on sympathetic nervous system and inhibition of catecholamine release. Magnesium also reduces responsiveness of vascular smooth muscles, to nor epinephrine. Parenteral magnesium administration results in rapid but transient decrease in systemic vascular resistance (SVR).²⁴

Therefore, arterial pressure did not show any appreciable increase after endotracheal intubation in magnesium and nitroglycerine pre-treated patients compared to those in control group.

**Rate pressure product**

Since RPP is the index of myocardial oxygen demand, rise in RPP, however transient, may be deleterious in patients with compromised medical status.

Our results of changes in RPP could be compared to the study of Berg et al who conducted a study in 100 middle-aged to elderly patients (52 healthy & 48 suffering from systemic diseases).³ They observed that magnesium sulphate did attenuate the responses to laryngoscopy and tracheal intubation, but were associated with increase in RPP. Their observations were similar to our study.

From the above discussion it is clear that both magnesium and nitroglycerine administration leads to tachycardia and hypotension, but by itself this effect is transient and can be attributed to the reflex tachycardia caused by vasodilator effect. At the doses (magnesium 30 mg/kg and sublingual nitroglycerine 0.8 mg), definitely attenuates the effect on SBP in response to laryngoscopy and intubation. When Group A was compared to Group B, it was seen that by virtue of their mechanism of action, both the drugs cause relative hypotension which is comparable in both the groups, thereby blunting the presser effect of laryngoscopy and intubation.

Montazeri et al in their study, compared five doses of magnesium (10, 20, 30, 40, 50 mg/kg) and concluded that Magnesium sulphate in 30 mg/kg dose was a better alternative as compared to other higher doses. More tachycardia and hypotension were seen with doses higher than 30 mg/kg.²³ ²⁴

Kumari et al also found similar observations in 90 adult ASA I and II patients using sublingual spray of NTG (one spray one minute before intubation) in attenuation of pressor response to intubation.²⁷

We also looked for complications of magnesium and nitroglycerine, like flushing and sense of warmth, arrhythmias, ST-T changes in ECG, nausea, sweating, etc, after intravenous administration. We did not come across such effects in the dose range used in our study. Although magnesium is known to prolong the action of neuro-muscular blocking agents, this was not seen with the dose used in our study.

**Limitations of our study**

Present study was done in a small group of 25 patients each in the groups. All patients were belonging to ASA I and II. Patients with comorbid conditions like coronary artery disease, hypertension and diabetes, etc. were excluded from the study. In addition, influence of age of patient on pressor response to laryngoscopy and intubation or role of preoperative antihypertensive medications were not evaluated in our study.

Also, we did not compare our results with the control group to know the extent to which the presser response to intubation is attenuated with magnesium and nitroglycerine.

**CONCLUSION**

Intravenous Magnesium or sublingual nitroglycerine spray as pre-treatment is found to be effective in attenuating the presser response to laryngoscopy and intubation. These drugs may lead to rise in HR but it is transient and dose dependent. However, both the drugs can significantly control the hypertensive response after laryngoscopy and intubation and the effect on SBP and RPP. Their observations were similar to our study.

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