Comparative clinical study of Intravenous Clonidine and Magnesium sulphate for attenuation haemodynamic response to Endotracheal Intubation

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Abstract

Background

Adrenergic reactions frequently occur in association with anaesthesia and surgery. Laryngoscopy and endotracheal intubation are stressful stimuli resulting in increased catecholamine levels in the blood which are deleterious for patients especially with hypertension, ischemic heart disease, raised intraocular and intracranial pressure. The objective of this study was to compare the efficacy of pretreatment with intravenous Clonidine and intravenous magnesium in attenuating the adverse haemodynamic responses to laryngoscopy and tracheal intubation.

Patients and Methods

This randomized controlled, prospective, double blinded study was undertaken on 90 American Society anesthesiologist Physical Status (ASA PS) grade-I and II patients posted for elective surgeries under general anaesthesia. These patients were divided into three groups of 30 each. Patients were randomly assigned to receive either IV Magnesium sulphate or IV Clonidine or IV normal saline (total volume of 100ml) 30 minutes before induction of anaesthesia over 15 minutes. The haemodynamic variables viz heart rate, systolic blood pressure and diastolic blood pressure were recorded at T0-Baseline (before infusion of drugs), T1-After infusion of the drugs -15 min beforeInduction,T2-Before induction of anaesthesia,T3-After injection of induction agents, T4-60 sec after end of laryngoscopy and T5-5 min after end of laryngoscopy. Analysis of variance (ANOVA) has been used to find the significance of study parameters and Post-Hoc Tukey test was used to find pairwise comparison.

Results

There was a significant rise in heart rate (13.6%) in control group (group C) at T2, T4 and T5 compared to baseline as compared to other groups which received IV Clonidine(group CL) or IV Magnesium sulphate(group M). Mean arterial blood pressure showed rise of 11% in control group as compared other groups. As compared to IV Magnesium sulphate IV Clonidine blunted the haemodynamic response better at T4 and T5.

Conclusion

We thus conclude that IV premedication with clonidine(3µg/kg) and magnesium sulphate(30mg/kg) when compared to placebo, effectively attenuates the haemodynamic response to laryngoscopy and intubation of trachea. The ease of administration and the haemodynamic stability it offers, projects both as useful and safe premedicants. IV magnesium sulphate though simple and cost-effective, it is less effective in blunting haemodynamic response to endotracheal intubation when compared to IV clonidine.
Key Words Clonidine, Magnesium sulphate, Endotracheal intubation, haemodynamic response.

ARTICLE FILE

It is a well known fact that laryngoscopy and endotracheal intubation is associated with haemodynamic response and a rise in plasma concentrations of catecholamines like noradrenaline, adrenaline and dopamine. Rise in sympathetic hormones during intubation is associated with complications in high risk patients which can increase morbidity as well as mortality. Various drugs like fentanyl, remifentanil, nalbuphine, esmolol, lignocaine, propofol, vasodilators etc have been tried to prevent haemodynamic response but each drug has its own limitations.

This prompted us to use and compare the efficacy of IV Clonidine and Magnesium sulphate to blunt the haemodynamic response to endotracheal intubation. Clonidine is an imidazole derivative with α2 adrenergic activity. It has intrinsic analgesic effect and produces preoperative sedation and anxiolysis. The potential advantage of using clonidine during anaesthesia are improved intraoperative haemodynamic stability, decreased requirement of anaesthetic drugs, attenuated sympathoadrenal response to laryngoscopy and tracheal intubation.

Parenteral magnesium sulphate (MgSO4) has been used for many years as an antiarrhythmic agent and for prophylaxis against seizures in pre-eclampsia. Recently the importance of magnesium in anaesthetic practice has been highlighted. MgSO4 inhibits the release of catecholamines from adrenal medulla and adrenergic nerve terminals. Thus both clonidine and magnesium are very useful adjuvants in balanced anaesthesia by virtue of their distinct properties.

PATIENTS AND METHODS

After getting approval from the hospital ethical committee and written informed consent, 90 ASA physical status grade I and II patients of either sex between 18-60 years of age, undergoing elective surgical procedures were included in the study and were randomly distributed to three groups (group C, group CL, group M, n=30). Exclusion criteria included anticipated difficult airway, allergy to the study drugs, hepatic or renal disease.

The study population was be sub-divided into three groups with 30 patients in each group. Group-MS: receiving intravenous magnesium sulphate 30 mg/kg in 100 ml normal saline, Group-CL: receiving intravenous clonidine 3µg/kg in 100 ml normal saline and Group C: receiving normal saline 100 ml 15 min before induction respectively.

Preanaesthesia checkup and preparation

Preanaesthesia checkup was done a day prior to surgery. Patients were evaluated for systemic diseases and routine laboratory investigations recorded. The procedure of general anaesthesia was explained to the patient. Preparation included overnight fasting, premedication with Tab. Alprazolam 0.25-0.5mg and Tab Ranitidine 150mg night before surgery. Patients were randomised using computer generated tables.
ANAESTHETIC TECHNIQUE

Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Blood Pressure (MBP) were recorded before administering the study drug. An intravenous access was secured with 18G Vaso-fix. IV Mgso₄, IV clonidine or IV normal saline (total volume of 100 ml) was administered in the recovery room given over 15 minutes by an anaesthesiologist who was totally blinded to the nature of the study.

All patients were pre-oxygenated with 100% oxygen for 3 minutes prior to induction with a tight fitting face mask and baseline heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure were recorded before inducing the patients. After premedicating with Inj. Glycopyrrolate 0.2 mg IV, Inj. Ondansetron 4mg iv and 2µg/kg of Inj. Fentanyl citrate IV, anaesthesia was induced with Inj.Propofol 1.5-3mg/kg administered at a rate of 20mg/5 sec until verbal contact is lost and Injatracurium 0.5mg/kg IV. Laryngoscopy was done by an experienced anaesthesiologist with standard Macintosh blade 3 minutes after administering neuromuscular blocker. Intubation was carried out with an appropriate sized disposable, high volume low pressure cuffed endotracheal tube. Cases where more than one attempt at laryngoscopy was made were excluded from the study. Anaesthesia was maintained with 60% nitrous oxide, 40% oxygen and Isoflurane 0.8-1% with a tidal volume of 10-12 ml/kg and a respiratory rate of 12-14 breaths/min. SBP, DBP, and HR were monitored as follows.

To-Baseline (before infusion of drugs) - i.e., 30 min before induction,
T1-After infusion of the drugs - 15 min before induction,
T2-Before induction of anaesthesia,
T3-After injection of induction agents,
T4-60 sec after end of laryngoscopy,
T5-5 min after end of laryngoscopy.

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD Analysis of variance (ANOVA) has been used to find the significance of study parameters between the three groups of patients and Post-Hoc Tukey test has been used to find pairwise (Group wise) comparison.

RESULTS

Patients age, weight, gender, baseline heart rate and mean blood pressure were similar in all the three groups under study. In our study the difference in heart rate and systolic blood pressure was higher in control group as compared with IV Magnesium and IV Clonidine groups and was statistically significant before the induction of anaesthesia (after infusion of drug), one minute after laryngoscopy. The effect of intravenous clonidine and IV Magnesium persisted until 5 minutes post laryngoscopy (p<0.001). However Clonidine blunted the haemodynamic response better and a statistically significant difference in heart rates and systolic blood pressure was observed at 1 minute and 5 minutes post laryngoscopy when Clonidine and Magnesium groups were compared. The SBP showed a maximum rise by 1 minute in control, IV magnesium and IV Clonidine groups, but the rise was clinically significant with the control group. The drop in SBP noted immediate post induction can be attributed to the use of Propofol and Isoflurane.

Attenuation of diastolic blood pressure by IV Magnesium and IV Clonidine as compared to Control was highly significant statistically at the 1 and 5 minute (p<0.001) post laryngoscopy. IV Magnesium produced lower diastolic blood pressure as compared with IV Clonidine and a statistically significant difference in diastolic blood pressure was seen minute post laryngoscopy, though clinically significant difference was observed even before induction of anaesthesia. A maximum rise in diastolic blood pressure was 12% above the baseline for IV Clonidine groups and IV Magnesium groups, seen at 1 minute post laryngoscopy. In our study the mean diastolic blood pressure was less in magnesium and
Clonidine groups compared to control group and this was highly significant statistically (p<0.001) throughout the post laryngoscopy period. Also diastolic blood pressure was less in magnesium group compared to clonidine group at minute post laryngoscopy. Maximum rise in mean blood pressure above the baseline, was 14% for Control group, and 9% for IV Magnesium and IV Clonidine group, again at 1 minute post laryngoscopy.

**DISCUSSION**

Laryngoscopy and intubation causes a 40 to 50% rise in systolic blood pressure, 30% rise in diastolic blood pressure and 20% rise in HR. The rise in ABP and heart rate which accompany indicate that stress may be placed on the myocardium. 50% of the patients with coronary artery disease experience episodes of myocardial ischaemia during intubation if no specific measures are undertaken to attenuate the haemodynamic response.

Anaesthesiologists dedication their expertise to maintain milieuinterior and reduce the stress that anaesthesia has on human physiology, studied and followed many methods and drugs to attenuate or prevent the haemodynamic response that accompanies laryngoscopy and intubation.

It has been observed that typically blood pressure and heart rate elevations occur after about 15 seconds of laryngoscopy and become maximal after 30-45 seconds of direct laryngoscopy. This can be deleterious for patients especially with hypertension, ischemic heart disease or raised intracranial pressure.

Strategies to circumvent these changes have included minimizing the duration of laryngoscopy, IV Narcotics, IV and topical Lidocaine, Vasodilators, Beta-blockers, epidural analgesia etc. Although these drugs did obtund the cardiovascular response, they had their own limitations. Hence started the search for an ideal agent which was economical, safe and easily administrable.

Recently there has been considerable research in the α-2 adrenergic agonists and magnesium sulphate in this respect. These drugs act at α-2 receptor site in medulla oblongata and at NMDA receptors in the central nervous system respectively. In addition magnesium reduces the catecholamine release through sympathetic stimulation and decrease peripheral nociceptor sensitization. Premedication with these drugs attenuates potentially harmful cardiovascular responses like increased catecholamine levels, tachycardia and hypertension during laryngoscopy and intubation.

However, there are not many studies comparing intravenous magnesium with IV clonidine prior to induction of anaesthesia. In our study the intravenous clonidine administration prior to induction of anaesthesia was compared with IV magnesium sulphate and control group(normal saline administration) for alterations of heart rate, systolic blood pressure and diastolic blood pressure caused by endotracheal intubation.

Results of our study indicate that IV clonidine very effectively blunts the stress response due to endotracheal intubation in ASA physical status I and II patients compared to placebo (control) and IV magnesium sulphate. This was evidenced by a significantly lesser increase of heart rate and mean arterial pressure with IV clonidine. Dose(3µg/kg) and timing(15 minutes prior to anaesthesia) of IV clonidine were almost similar to previous studies. Larger doses(>4µg/kg) of IV clonidine are known to induce hypotension and bradycardia, which are maximal at 10-15 minutes after IV administration. Hence we preferred to use a 3µg/kg dose for this group.
Elsharnouby and Elsharnouby used MgSO4 40 mg/kg IV over a period of 15 min before induction of anaesthesia. They noticed more episodes of severe hypotension using this dose of MgSO4\(^4\),\(^6\). In our study we reduced the dose of MgSO4 to 30 mg/kg before induction of anaesthesia\(^7\),\(^8\),\(^9\). The dose selected by us resulted in a steady and smooth reduction of MAP and HR with no episodes of severe hypotension and bradycardia. Our finding was supported by previous study by Telci\(^20\).

Changes in heart rate were statistically significant in all the three groups at 1 minute and 5 minutes postlaryngoscopy (P<0.05). A statistical significance (P<0.05) in the SBP and DBP was noted in between the three groups at 1 minute postlaryngoscopy. The values started declining thereafter towards baseline values by 5 minutes postlaryngoscopy in the clonidine group whereas in the magnesium group the diastolic blood pressure was less than the baseline by 8%. These observations were similar to the previous study by Manjushree Ray, DhurgoticBattacharjee et al.\(^21\).

In our study there was a significant difference (p<0.05) in the mean blood pressure with all the three groups throughout the postlaryngoscopy period. Maximum rise in mean blood pressure above the baseline, was 11% for control group, and 9% for IV magnesium and IV clonidine group, again at 1 minute postlaryngoscopy. In a similar study, A Altan, NTurgut et al showed that the increase in mean arterial pressure was significantly less in IV clonidine group compared to the IV magnesium and control (placebo) group\(^12\). The results with respect to heart rate and mean blood pressure response to laryngoscopy and intubation in our study were consistent with the above mentioned study.

In addition to efficacy, both safety and applicability of IV pre-induction clonidine and IV magnesium sulphate administration are important for clinical practice. Since the drugs are administered intravenously in the operation theatre, the patients receiving IV clonidine and IV magnesium sulphate are monitored and under the control of anaesthesiologist in the operating room. This may be advantageous in patients with increased cardiac risk because undetected cardiovascular side effects of clonidine such as bradycardia and hypotension and magnesium such as hypotension and respiratory depression could be hazardous\(^6\). No such untoward effects were noted anyway in our study.

Though attenuation of pressor response was observed in both IV clonidine and IV magnesium groups, it was more significant with the IV clonidine group on inter-group comparison at 1\(^{st}\) and 5\(^{th}\) minute after laryngoscopy.

In view of the above findings, it can be summarized from this study that premedication with IV clonidine 3µ/kg and IV magnesium sulphate 30mg/kg in comparison to control, significantly attenuates the heart rate and blood pressure response to laryngoscopy and intubation to a clinically acceptable level and in our study we found IV clonidine to be more effective in doing the same compared to IV magnesium sulphate.

To conclude, IV premedication with clonidine and magnesium sulphate when compared to placebo, effectively attenuates the haemodynamic response to laryngoscopy and intubation to trachea. The ease of administration and the haemodynamic stability it offers, projects both as useful and safe premedicants. IV magnesium sulphate though simple and cost-effective, is it less effective in blunting haemodynamic response to endotracheal intubation when compared to IV clonidine. However more studies are required to assess the efficacy of these drugs in ASA PS III/IV patients with severe cardiovascular risk.
Authors disclosure
There is no conflict of interest and financial considerations.

REFERENCES

ANALYSIS OF HEART RATE

Table 1: Comparison of pulse rate in three groups of patients studied

<table>
<thead>
<tr>
<th>Pulse rate</th>
<th>Group MS</th>
<th>Group CL</th>
<th>Group C</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-MS</td>
</tr>
<tr>
<td>T0</td>
<td>82.80±13.55</td>
<td>86.23±3.46</td>
<td>82.46±8.17</td>
<td>0.990</td>
</tr>
<tr>
<td>T1</td>
<td>83.23±11.01</td>
<td>80.00±3.85</td>
<td>78.26±7.51</td>
<td>0.048*</td>
</tr>
<tr>
<td>T2</td>
<td>84.26±11.43</td>
<td>81.80±3.52</td>
<td>95.70±7.26</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>T3</td>
<td>87.40±10.08</td>
<td>83.56±6.04</td>
<td>100.73±7.09</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>T4</td>
<td>100.83±8.99</td>
<td>87.80±4.86</td>
<td>112.43±11.65</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>T5</td>
<td>97.20±8.66</td>
<td>89.96±10.66</td>
<td>101.20±10.00</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

Time Intervals

Table 1 and Fig 1 show the statistical analysis of changes in the heart rate (beats/min) at different time intervals pre and post induction between the three groups.
ANALYSIS OF SYSTOLIC BLOOD PRESSURE

Table 2: Comparison of Systolic blood pressure (SBP) mmHg in three groups of patients studied

<table>
<thead>
<tr>
<th>SBP(mmHg)</th>
<th>Group MS</th>
<th>Group CL</th>
<th>Group C</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-MS</td>
</tr>
<tr>
<td>T0</td>
<td>131.60±13.47</td>
<td>129.80±5.21</td>
<td>127.73±11.37</td>
<td>0.343</td>
</tr>
<tr>
<td>T1</td>
<td>120.73±11.17</td>
<td>118.16±6.39</td>
<td>129.26±8.57</td>
<td>0.001**</td>
</tr>
<tr>
<td>T2</td>
<td>116.73±9.66</td>
<td>112.03±6.90</td>
<td>130.00±7.14</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>T3</td>
<td>104.06±9.40</td>
<td>103.90±8.35</td>
<td>91.56±6.37</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>T4</td>
<td>142.63±9.69</td>
<td>137.20±6.77</td>
<td>151.16±13.90</td>
<td>0.007**</td>
</tr>
<tr>
<td>T5</td>
<td>128.00±4.95</td>
<td>123.16±9.36</td>
<td>130.06±9.88</td>
<td>0.004**</td>
</tr>
</tbody>
</table>

Time Intervals

In Table 2 and Fig 2, the statistical analysis of changes in the systolic blood pressure at baseline and at different time intervals from before and after the onset of laryngoscopy and intubation in the three groups are presented.
**ANALYSIS OF DIASTOLIC BLOOD PRESSURE**

Table 3: Comparison of Diastolic blood pressure (mmHg) in three groups of patients studied

<table>
<thead>
<tr>
<th>DBP (mmHg)</th>
<th>Group MS</th>
<th>Group CL</th>
<th>Group C</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-MS</td>
</tr>
<tr>
<td>T0</td>
<td>78.60±6.42</td>
<td>79.43±6.70</td>
<td>82.63±6.88</td>
<td>0.056</td>
</tr>
<tr>
<td>T1</td>
<td>78.06±5.21</td>
<td>74.33±6.58</td>
<td>80.03±5.75</td>
<td>0.401</td>
</tr>
<tr>
<td>T2</td>
<td>78.73±5.07</td>
<td>70.43±6.76</td>
<td>80.53±4.89</td>
<td>0.436</td>
</tr>
<tr>
<td>T3</td>
<td>62.50±8.70</td>
<td>66.70±7.86</td>
<td>72.46±7.82</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>T4</td>
<td>75.93±5.11</td>
<td>82.37±7.54</td>
<td>90.43±13.63</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>T5</td>
<td>68.46±8.14</td>
<td>79.67±4.30</td>
<td>83.70±6.69</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

Time Intervals

In Table 3 and fig 3, the statistical analysis of changes in the diastolic blood pressure at baseline and at different time intervals before and after the onset of laryngoscopy and intubation between the three groups are presented.
ANALYSIS OF MEAN BLOOD PRESSURE:

Table 4: Comparison of patients in three groups of patients studied

<table>
<thead>
<tr>
<th>Time Intervals</th>
<th>MAP(mm Hg)</th>
<th>Group MS</th>
<th>Group CL</th>
<th>Group C</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Group MS</td>
<td>Group CL</td>
<td>Group C</td>
<td>C-MS</td>
</tr>
<tr>
<td>T0</td>
<td>94.97±6.45</td>
<td>93.33±5.19</td>
<td>98.95±7.17</td>
<td>0.044*</td>
<td>0.575</td>
</tr>
<tr>
<td>T1</td>
<td>95.13±5.25</td>
<td>88.94±5.42</td>
<td>93.60±5.30</td>
<td>0.508</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>T2</td>
<td>95.82±4.65</td>
<td>84.30±5.64</td>
<td>92.60±4.85</td>
<td>0.041*</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>T3</td>
<td>72.18±7.51</td>
<td>79.10±6.29</td>
<td>83.00±6.71</td>
<td>&lt;0.001**</td>
<td>0.001**</td>
</tr>
<tr>
<td>T4</td>
<td>101.13±6.92</td>
<td>100.74±5.38</td>
<td>107.83±9.97</td>
<td>0.035*</td>
<td>0.024*</td>
</tr>
<tr>
<td>T5</td>
<td>93.88±7.10</td>
<td>86.67±3.31</td>
<td>99.18±5.93</td>
<td>&lt;0.001**</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

Time Intervals
The statistical analysis of changes in the mean blood pressure at baseline and at different time intervals pre and post laryngoscopy and intubation in the three groups are presented in Table 4 and Fig 4.