Original Contribution

Minimal effective dose of magnesium sulfate for attenuation of intubation response in hypertensive patients☆,☆☆

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Abstract

Study Objective: To study the minimal effective dose of magnesium sulfate to control blood pressure (BP) during intubation in hypertensive patients.

Design: Prospective, randomized, double-blind study.

Setting: Operating room of an academic medical center.

Patients: 80 adult, ASA physical status 1 and 2, controlled hypertensive patients undergoing elective surgery under general anesthesia and requiring endotracheal intubation.

Interventions: Patients were randomized to 4 groups. Patients in study groups received a magnesium sulfate infusion at a dose of 30 (Group I), 40 (Group II), or 50 mg/kg (Group III) before induction of anesthesia, while patients in control group (Group IV) received a 1.5 mg/kg lidocaine bolus 90 seconds before intubation. Anesthesia was induced and maintained with a propofol infusion. Laryngoscopy and intubation were performed 4 minutes after administration of vecuronium.

Measurements: Heart rate (HR) and BP were recorded before, during, and after endotracheal intubation for 10 minutes. Measures to manage hemodynamic instability were recorded. Serum magnesium levels were also recorded.

Main Results: The changes in HR were comparable among groups. Mean arterial pressure (MAP) was maintained within normal limits in Group I patients while Groups II and III patients showed a significant decrease in MAP ($P$ = 0.01) compared with baseline. A total of 6 patients (30%) in Group II and 10 patients (50%) in Group III required interventions ($P$ = 0.001). No patient in Group I and only one patient (5%) in Group IV required intervention.

Conclusions: Magnesium 30 mg/kg is the optimum dose to control BP during intubation in hypertensive patients. A further increase in the dose of magnesium may cause significant hypotension.

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1. Introduction

Laryngoscopy and tracheal intubation stimulate somatic and visceral nociceptive afferents of the epiglottis, hypo- pharynx, peritracheal area, and vocal cords, which augment cervical sympathetic activity [1]. Hypertensive patients are more prone to exaggerated cardiovascular response to laryngoscopy and tracheal intubation than normotensive patients [2]. These transient hemodynamic changes are probably of no consequence in healthy individuals, but they may be dangerous in those with hypertension as they may lead to myocardial ischemia, arrhythmias, and intracranial hemorrhage [3]. Therefore, the prevention of cardiovascular stimulation following tracheal intubation is of particular importance in hypertensive patients.

Magnesium sulfate inhibits the release of catecholamines from the adrenal medulla and adrenergic nerve endings and is effective in attenuating the blood pressure (BP) response to tracheal intubation [4]. Different doses of the drug have been used by different authors to attenuate this response to endotracheal intubation [5–9], but the optimal dose of magnesium sulfate to control it in hypertensive patients has not been reported. This prospective, randomized, double-blind study was planned to determine the optimal dose of magnesium sulfate that prevents adverse hemodynamic response to tracheal intubation in hypertensive patients without producing significant hemodynamic compromise.

2. Materials and methods

After approval from Ethics Review Committee of PGIMER (no. MS/229/MD/4622) and written, informed consent, 80 adult hypertensive patients had included in the study. All patients had controlled hypertension (BP < 140/90 mmHg) and were receiving medication for a minimum of two weeks; they were posted for elective surgery under general anesthesia requiring endotracheal intubation. Patients with a history of coronary artery disease (CAD), cardiac arrhythmia, hypermagnesemia, neuromuscular disease, increased intracranial or intraocular pressure, hiatal hernia, or gastroesophageal reflux were excluded. Patients with anticipated difficult airway, morbid obesity, or ASA physical status 3 or higher also were excluded from the study. All patients were fasted for at least 6 hours before surgery. They received oral diazepam 0.1 mg/kg and ranitidine 150 mg along with their antihyper- tensive drugs on the morning of surgery except those receiving angiotensin-converting enzyme inhibitors (ACEIs), who were restricted from taking the morning dose.

The study drugs included magnesium sulfate 30, 40, and 50 mg/kg added to 100 mL of normal saline and lidocaine 1.5 mg/ kg (diluted to 5 mL) or saline in a 5 mL syringe. All the drugs were prepared by an anesthesiologist who was not involved in patient management or data collection. Patients were allocated randomly to one of the 4 groups by sealed envelope assignment and a computer-generated sequence of random numbers, opened just before the start of the study. Patients in Groups I, II, and III received a magnesium sulfate infusion at a dose of 30 mg/kg, 40 mg/kg, or 50 mg/kg, respectively, in 100 mL of normal saline over 10 minutes; patients in Group IV (control group) received 100 mL of normal saline without magnesium before induction of anesthesia. Before admin- istration of the study drug infusion, routine monitoring consisting of electrocardiography, BP, and pulse oximetry was started. During the magnesium infusion, patients were monitored for any adverse effects such as hypotension, restlessness, agitation, confusion, and respiratory depression.

Anesthesia was induced with propofol until loss of verbal contact, then maintained with propofol infusion at the rate of 6 mg/kg/hr. The rate of propofol was increased to 8 mg/kg/hr on an increase of mean arterial pressure (MAP) > 20% of baseline and decreased to 4 mg/kg/hr if the patient developed hypotension (MAP < 20% of baseline). Vecuronium 0.1 mg/kg was administered to facilitate endotracheal intubation. Patients were ventilated by face mask using 33% oxygen and 66% nitrous oxide to maintain adequate oxygenation and normocapnia. Contents of the test syringe (saline in Groups I, II, and III and lidocaine in Group IV) were injected approximately 90 seconds before laryngoscopy and intuba- tion. Laryngoscopy and intubation were carried out 4 minutes after administration of muscle relaxant once the train-of-four count became zero. Laryngoscopy and intuba- tion were performed by an anesthesiologist having at least three years’ experience in anesthesia. If laryngoscopy time exceeded 30 seconds or multiple attempts were required for intubation, patients were excluded from the study.

Heart rate (HR), noninvasive BP, and oxygen saturation (SpO₂) were recorded at baseline, ie, before starting the infusion of normal saline with or without magnesium sulfate, at the end of the infusion, just before induction of anesthesia, at 1-minute intervals for 4 minutes after injection of muscle relaxant, immediately after laryngoscopy and intubation, at 1-minute intervals for 5 minutes after endotracheal intubation, and at the seventh and tenth minute after endotracheal intubation. The episodes of persistent hypotension (MAP < 20% of baseline for > 60 sec) were treated with incremental doses of mephentermine 3 mg and hypertension (MAP > 20% of baseline for > 60 sec) was treated with an infusion of nitroglycerine, if not controlled with an adjustment of propofol infusion. In case of tachycardia (HR > 100 bpm lasting for > 60 sec) esmolol was given in a loading dose of 0.5 mg/kg. Bradycardia (HR < 40 bpm) was treated with incremental doses of 300 μg of atropine. Patients and the anesthesiologist present during induction of anesthesia and collection of data were blinded to the study drug.

Serum magnesium levels were measured twice during the study period, just before starting the study drug infusion and just after completion of laryngoscopy and endotracheal intubation.
3. Results

Patients in the 4 groups were comparable in age, weight, and duration of hypertension before surgery (Table 1). Beta blockers, calcium channel blockers, angiotensin receptor blockers, ACEIs, and diuretics were the drugs used for the treatment of hypertension. There was no significant difference between the groups with respect to the distribution of patients consuming different antihypertensive agents or their combinations. All patients were intubated on the first attempt and no patient was excluded from the study. Laryngoscopy time was comparable in the 4 groups (Table 1).

Baseline HR and BP were comparable among groups. Heart rate tended to decrease after induction, with a brief increase after intubation in all the groups. The difference in HR was not statistically significant between the groups throughout the study period (Fig. 1). No patient required rescue medication to treat tachycardia or bradycardia. Systolic, diastolic, and MAP decreased after induction of anesthesia ($P < 0.001$), with an increase towards baseline immediately after intubation in all groups. There was no significant increase in BP after laryngoscopy and intubation in any group of patients when compared with baseline.

Mean arterial pressure was well maintained in Group I (magnesium 30 mg/kg) after intubation throughout the study period. Patients in Groups II (magnesium 40 mg/kg) and IV (control group) showed a significant decrease in MAP as compared with baseline 3 and 4 minutes after intubation, which continued until the end of study period. In Group III patients (magnesium 50 mg/kg), MAP decreased after induction and remained lower after tracheal intubation compared with the baseline and other groups (Fig. 2).

Patients pretreated with magnesium 40 and 50 mg/kg required significantly more interventions to manage hypertensive episodes when compared with patients pretreated with magnesium 30 mg/kg (Table 2). A total of 6 patients (30%) in Group II and 16 patients (80%) in Group III required intervention. No patient in Group I and only one patient (5%) in Group IV required intervention. No interventions were required to treat hypertension in any group of patients. None of the patients developed arrhythmia or significant ST changes.

Baseline serum magnesium levels were within normal limits in the 4 groups (Table 3). Groups I, II, and III showed a significant increase in serum magnesium levels postintubation compared with the control group ($P = 0.001$), but always remained within therapeutic range (2 - 4 mmol/L). There was no statistical difference in serum magnesium levels between Groups I, II, and III.

4. Discussion

Hypertensive patients show an enhanced hemodynamic response to laryngoscopy and tracheal intubation. There are exaggerated swings in BP in these patients that vary from severe hypertension to hypotension. Therefore, it is necessary to be cautious in such patients to attenuate hemodynamic responses during intubation. Many adjuvant drugs, including opioids, vasodilators, calcium channel blockers, and adrenoceptor blockers have been used with variable success to blunt the hemodynamic response to intubation in hypertensive patients [10–14]. All of these techniques have disadvantages related to either cardiovascular or respiratory depression; none directly inhibits the release of catecholamines. Among the therapeutic regimens useful in suppressing the hormonal stress response to tracheal intubation,

### Table 1  Patient characteristics and duration of laryngoscopy

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>49.1 ± 9.3</td>
<td>50.6 ± 10.6</td>
<td>54.1 ± 9.1</td>
<td>51.8 ± 6.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.0 ± 12.0</td>
<td>63.4 ± 11.9</td>
<td>59.8 ± 7.4</td>
<td>61.5 ± 7.4</td>
</tr>
<tr>
<td>Duration of hypertension (yrs)</td>
<td>2.0 ± 2.2</td>
<td>2.2 ± 3.2</td>
<td>1.6 ± 0.9</td>
<td>3.5 ± 2.2</td>
</tr>
<tr>
<td>Duration of laryngoscopy (sec)</td>
<td>15.0 ± 3.8</td>
<td>13.8 ± 2.9</td>
<td>14.2 ± 2.0</td>
<td>13.6 ± 0.8</td>
</tr>
</tbody>
</table>

Data are means ± SD.

Study patients received a magnesium sulfate infusion at a dose of 30 mg/kg (Group I), 40 mg/kg (Group II), or 50 mg/kg (Group III) before induction of anesthesia. Group IV received a 1.5 mg/kg lidocaine bolus 90 seconds before intubation.
magnesium may be a forerunner as it not only has direct vasodilator properties [15], it also significantly suppresses the release of catecholamines [4].

In the present study, magnesium sulfate attenuated the pressor response to laryngoscopy and intubation in all three doses (30, 40, and 50 mg/kg) administered before induction of anesthesia. There was no significant increase in HR or BP as compared with baseline values, after laryngoscopy, and intubation in any group of patients. However, patients who received magnesium in doses of 40 and 50 mg/kg developed significant hypotension at various time points requiring intervention.

Magnesium pretreatment is associated with a good control of adrenergic response during intubation. Allen et al [5] compared magnesium sulfate 40 mg/kg with lidocaine and alfentanil in moderate to severely hypertensive, proteinuric parturients and observed optimal control of BP in the magnesium group. Puri et al [7] compared 50 mg/kg of

![Fig. 1](image1.png)
Fig. 1  Median heart rate in each group from baseline to 10 minutes after intubation (postintub). MR=muscle relaxant.

![Fig. 2](image2.png)
Fig. 2  Mean arterial pressure (MAP) in each group from baseline to 10 minutes after intubation (postintub). MR=muscle relaxant. *P < 0.05 between groups.
magnesium sulfate with lidocaine in CAD patients and concluded that magnesium was significantly better than lidocaine in attenuating the cardiovascular response during endotracheal intubation. In another study, 30 mg/kg of magnesium sulfate with alfentanil was superior to 40 mg/kg of magnesium sulfate alone in hypertensive, proteinuric patients undergoing cesarean section [6]. In all of these studies, magnesium was given as a bolus at the time of induction of anesthesia with thiopental sodium. The authors reported an initial increase in HR after induction of anesthesia in patients receiving magnesium sulfate, which we did not observe. This finding may be due to the use of propofol for induction and maintenance of anesthesia in the present study, which might have prevented the early tachycardia observed by others. Altan et al [8] reported that magnesium sulfate 30 mg/kg infused over 15 minutes, before induction of anesthesia with propofol, attenuated the pressor response to intubation in normotensive patients. There was no increase in HR, and BP was better maintained in patients receiving magnesium sulfate than those given clonidine 3 μg/kg (more hypotension).

In the present study, BP was well maintained in patients receiving 30 mg/kg of magnesium sulfate. None of the patients in this group developed significant hypotension while 30% of patients receiving magnesium sulfate 40 mg/kg and 80% of patients who received magnesium sulfate 50 mg/kg developed significant hypotension requiring rescue management. Magnesium is an α-adrenergic antagonist and may lead to a transient decrease in BP associated with peripheral vasodilatation [15]. However, despite its vasodilator properties, magnesium does not generally produce significant hypotension in normotensive patients because of a concomitant increase in cardiac output [16]. When this increase does not occur, marked hypotension may result. Puri et al [7] reported that administration of magnesium was associated with a significant decrease in MAP (P < 0.001) and systemic vascular resistance (P < 0.001) in patients with CAD. They also observed that in spite of a significant decrease in MAP, none of the patients in the magnesium group (n=19) developed significant ST changes while three lidocaine group (n=17) patients had significant ST depression. The absence of significant ST segment changes in the magnesium group may have been the result of a decrease in afterload and coronary vasodilatation produced by magnesium. Allen et al [4] found that the rate pressure products were significantly worse in the lidocaine group than the magnesium group for the first 4 minutes after intubation in moderate to severely hypertensive parturients. We also observed cardiac instability after intubation in the patients who received intravenous lidocaine.

Ashton et al [6] reported that a serum magnesium level of 2.19 ± 0.50 mmol/L at the time of endotracheal intubation was effective in reducing catecholamine levels and intubation response in hypertensive pregnant patients. In the present study, serum magnesium values were more than 2.2 in Groups I, II, and III immediately after intubation, which were adequate to control the pressor response to tracheal intubation.

We observed that 30 mg/kg is the optimum dose of magnesium to prevent a hypertensive response to laryngoscopy and tracheal intubation in hypertensive patients. It maintains cardiac stability better than pretreatment with lidocaine 1.5 mg/kg. Increasing the dose of magnesium may cause a decrease in BP requiring intervention. The limitation of this study was that the propofol infusion for maintenance of anesthesia was titrated according to hemodynamic parameters. Measurement of depth of anesthesia by Bispectral Index may have helped in better titration of propofol infusion. We included only controlled hypertensive patients in our study. Further studies are needed to observe the effect of magnesium sulfate in uncontrolled hypertensive patients with associated cardiac disease.

### Table 2

<table>
<thead>
<tr>
<th>Hypotension, n (%)</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>nil</td>
<td></td>
<td>6 (30)</td>
<td>16 (80)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol decreased</td>
<td>-</td>
<td>4 (20)</td>
<td>10 (50)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Mephentermine</td>
<td>-</td>
<td>2 (10)</td>
<td>6 (30)</td>
<td></td>
</tr>
</tbody>
</table>

Study patients received a magnesium sulfate infusion at a dose of 30 mg/kg (Group I), 40 mg/kg (Group II), or 50 mg/kg (Group III) before induction of anesthesia. Group IV received a 1.5 mg/kg lidocaine bolus 90 seconds before intubation.

### Table 3

<table>
<thead>
<tr>
<th>Serum magnesium (mmol/L)</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.15 ± 0.2</td>
<td>1.12 ± 0.1</td>
<td>1.18 ± 0.2</td>
<td>1.22 ± 0.1</td>
<td>0.078</td>
</tr>
<tr>
<td>After intubation</td>
<td>2.63 ± 0.5</td>
<td>2.88 ± 0.4</td>
<td>3.19 ± 0.3</td>
<td>1.79 ± 0.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are means ± SD.

Study patients received a magnesium sulfate infusion at a dose of 30 mg/kg (Group I), 40 mg/kg (Group II), or 50 mg/kg (Group III) before induction of anesthesia. Group IV received a 1.5 mg/kg lidocaine bolus 90 seconds before intubation.
References


