Dose Response Study of Magnesium Sulphate for Attenuation of Haemodynamic Response to Intubation

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ABSTRACT

BACKGROUND

Effects of pretreatment with magnesium sulphate for attenuation of haemodynamic response to intubation have been studied previously but its effects on hypertensive patients are not much studied. This study was conducted primarily to find the minimal effective dose of magnesium sulphate to control the haemodynamic response to laryngoscopy and endotracheal intubation in controlled hypertensive patients.

METHODS

After institutional ethical committee clearance, a randomised, double blinded, clinical study was carried out among 90 American Society of Anaesthesiologists (ASA) physical status II, controlled hypertensive patients of age 30 - 60 years posted for elective surgery. Patients were randomly distributed into three equal groups as group I - received 30 mg / Kg magnesium sulfate and group II - received 40 mg / Kg magnesium sulfate before induction of anesthesia, while group III (control group) received 1.5 mg / Kg lidocaine bolus 90 seconds prior to intubation. The patients' haemodynamic responses were noted before, during, and after intubation for 10 minutes. Steps taken to manage haemodynamic instability along with serum magnesium levels were also noted. To calculate the sample size, mean value of serum magnesium was taken in three groups to find out effect size as 0.0387. Taking alpha error 0.05 and power required 90 %, the sample size in each group was 30.

RESULTS

Groups were properly matched for their demographic data. Among all the groups changes in heart rate were comparable ($P > 0.05$) throughout the study period. In group I there was no significant change in mean arterial pressure (MAP) while in group II and group III a significant decrease was noticed ($> 20\%$ of baseline value). Intervention was required to treat hypotension in significant number of patients in group II (nine patients) and group III (three patients).

CONCLUSIONS

In controlled hypertensive patients, magnesium in a dose of 30 mg / Kg intravenous is found optimal to attenuate the stress response following laryngoscopy and endotracheal intubation, as further increase in dose can lead to significant hypotension.

KEY WORDS

Hypertension, Laryngoscopy, Lignocaine, Magnesium Sulphate, Intubation

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DOI: 10.14260/jemds/2021/206

How to Cite This Article:

Nandal S, Chatrath V, Kaur H, et al. Dose response study of magnesium sulphate for attenuation of haemodynamic response to intubation. *J Evolution Med Dent Sci* 2021;10(13):956-961, DOI: 10.14260/jemds/2021/206

Submission 13-07-2020,
Peer Review 28-01-2021,
Acceptance 06-02-2021,
Published 29-03-2021.

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BACKGROUND

Laryngotracheal intubation is a noxious stimulus associated with a marked autonomic response which manifests as tachycardia and hypertension. The response is transient, occurring 30sec after intubation and lasting for less than 10 minutes.¹ Pressor response to laryngotracheal intubation is mediated by both sympathetic and parasympathetic nervous system. Sympathetic response to intubation results in tachycardia and hypertension. It is due to increased firing of cardio-acceleratory fibers resulting in release of catecholamines from adrenergic nerve endings and adrenal medulla. Parasympathetic response is more common in children but can occur in some adults.^{1,2}

Laryngoscopy and intubation leads to an average increase in blood pressure of 40 to 50 % and a 20 % increase in heart rate.³ Increase in blood pressure occurs after laryngoscopy with or without intubation but latter is associated with significant increase in heart rate.⁴ These haemodynamic changes are of little consequences in normal healthy patients but can be potentially deleterious in patients with hypertension, coronary heart disease, valvular heart disease, pre-eclampsia and patients with intracranial pathology.⁵

Hypertensive patients demonstrate an enhanced cardiovascular response to laryngoscopy and endotracheal intubation. They have marked pressure response to tracheal intubation, which may lead to life threatening complications such as myocardial ischemia, arrhythmias and intracranial haemorrhage.⁶ Arterial blood pressure response can vary from severe hypertension to hypotension in hypertensive patients, so it is important to be vigilant and precautions in such patients at the time of laryngoscopy and intubation.

Various pharmacological agents have been used to prevent the stress response like opioids,⁷ β blockers,⁸ α -adrenergic agonists,⁹ calcium channel blockers,¹⁰ vasodilators¹¹ and lignocaine¹² with varying results. Magnesium sulphate inhibits the catecholamine release from adrenal medulla and adrenergic nerve endings. It was also shown that magnesium sulphate decreases levels of serum epinephrine and causes decreased atrial contraction, bradycardia and vasodilation.^{13,14} Magnesium sulphate has been used in different doses for attenuating the haemodynamic response to laryngoscopy and endotracheal intubation.

We designed the present study to find the optimum dose of magnesium sulphate to reduce the haemodynamic response following laryngoscopy and intubation in controlled hypertensive patients.

METHODS

This study was conducted between November 2014 to September 2016. After taking institutional ethical committee clearance, a randomised and double blinded clinical study was conducted on 90 ASA physical status II, controlled hypertensive patients of both genders, in the age group 30 - 60 years scheduled for elective surgeries under general anaesthesia requiring endotracheal intubation after taking informed consent from each patient at Guru Nanak Dev Hospital, Amritsar. All the patients included in the study were subjected to detailed pre-anaesthetic checkup to rule out any

anatomical or systemic disorders. All the patients were having hypertension (BP < 160 / 90 mmHg) and taking medication from at least two weeks. Routine and relevant special investigations were carried out. To calculate the sample size mean value of serum magnesium was taken in three groups to find out effect size as 0.0387. Taking alpha error 0.05 and power required 90 % the sample size in each group was 30.

Patients were not included in our study if they had previous history of renal dysfunction, hepatic dysfunction, neuromuscular disease, cardiovascular disorder, cardiac arrhythmia, neurological disorder, respiratory problem, coagulation disorder, pregnancy, known allergies to the study drug, ASA physical status III or more and anticipated difficult airway. Furthermore, for patients requiring any change in technique of anaesthesia, inadequate jaw relaxation, any movement on laryngoscopy, Cromack-Lehane grade III or more or duration of laryngoscopy for > 30 sec, were not enrolled in the study. All patients were evaluated a day before surgery and were kept fasting for at least 6 hours prior to surgery. Patients were given Tab. alprazolam 0.50 mg and Tab. pantoprazole 40 mg along with their prescribed antihypertensive medications with sip of water in the morning on day of surgery. Patients were advised not to take morning dose of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB).

In this double blinded study, patients were randomised in to three groups using a computer-generated sequence of random numbers. Routine monitoring consisting of non-invasive blood pressure, pulse-oximeter oxygen saturation and electrocardiogram was started. Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), electrocardiograph (ECG) and oxygen saturation (SpO₂) were measured. After securing a peripheral intravenous line, 2 ml of venous blood was taken for baseline serum magnesium level. Infusion of Ringer Lactate was started and injection nalbuphine 10 mg was administered intravenously. Study drug was given in 100ml of normal saline over 10 minutes to Group I and II. Group III was given 100ml normal saline. Patients were looked after for any adverse effect like restlessness, confusion, agitation, hypotension and respiratory depression.

Ringer lactate 8 ml / Kg was given before induction. After three minutes of pre-oxygenation with 100 % oxygen, induction was done with 2.5 - 3.0 mg / Kg propofol till loss of eyelash reflex. To facilitate the endotracheal intubation injection vecuronium 0.1 mg / Kg was given intravenously. Oxygen and nitrous oxide were given in ratio 50:50 % with face mask. 90 seconds prior to laryngoscopy and intubation, the contents in the syringes (normal saline in Group I and II, and lignocaine in Group III) were injected. Laryngoscopy and endotracheal intubation were performed by an experienced anesthesiologist 4 minutes after administration of muscle relaxant. After confirmation of endotracheal tube position, anaesthesia was maintained using oxygen and nitrous oxide in ratio 50:50 % along with 1 % isoflurane with a closed circuit and positive pressure ventilation to maintain adequate oxygenation and normocapnia (state of normal arterial carbon dioxide pressure). Just after completion of laryngoscopy and intubation, 2 ml of venous blood was taken to check for serum magnesium level.

HR, SBP, DBP, MBP, SpO₂ and ECG were monitored and recorded at baseline, after giving infusion, prior to induction

of anaesthesia, at interval of 1 minute for 4 minutes after giving muscle relaxant, after laryngoscopy and intubation, at interval 1 minute for 5 minutes and at 7 minutes and 10 minutes post laryngoscopy and intubation.

During the study period, episodes of persistent hypotension (decrease in MAP > 20 % of baseline for > 60 sec) if not managed with decreasing the isoflurane, then increment doses of ephedrine 5mg was given and hypertension (rise in MAP > 20 % of baseline for > 60 sec) or tachycardia (HR > 100 beats / minute for > 60 sec) were treated with 0.5 mg / Kg esmolol. Atropine was used to manage bradycardia (HR < 40 beats / min) in increments of 300µg. Patients as well as the investigators present at the time of induction of anaesthesia and recording the data were blinded to the drug given to the patients.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 19.0 version. Comparison of

different groups was carried out with one-way analysis of variance (ANOVA) and post hoc Turkey test. P-value < 0.05 was considered statistically significant.

RESULTS

Patients in the three groups were well matched for their demographic data and duration of hypertension (Table 2). Intubation was done in first attempt in all patients and none of the patients were excluded. Duration of laryngoscopy and intubation was comparable in all the three groups (Table 2).

Baseline serum magnesium levels were comparable and within normal limits in all three groups (Table 3). Serum magnesium level after laryngoscopy and intubation was found to be increased significantly in group I and II, but that was within the therapeutic range (2 - 4 mmol / L).

Time Interval	Group I	Group II	Group III	P-Value
Baseline	84.07 ± 11.519	84.30 ± 15.957	82.37 ± 15.446	I / II: 0.998 I / III: 0.892 II / III: 0.863
End of infusion	80.87 ± 11.079	81.10 ± 13.066	81.40 ± 14.903	I / II: 0.997 I / III: 0.986 II / III: 0.996
Beginning of induction	78.53 ± 11.881	78.53 ± 13.480	80.73 ± 15.213	I / II: 1.000 I / III: 0.806 II / III: 0.998
At the time of administration of MR	77.63 ± 12.007	77.87 ± 13.788	79.70 ± 15.488	I / II: 0.998 I / III: 0.838 II / III: 0.865
1 min after MR*	76.93 ± 11.918	76.93 ± 14.586	79.47 ± 15.106	I / II: 1.000 I / III: 0.768 II / III: 0.768
2 min after MR*	76.23 ± 11.948	76.47 ± 14.256	78.87 ± 15.085	I / II: 0.998 I / III: 0.741 II / III: 0.779
3 min after MR*	75.10 ± 11.887	75.60 ± 14.217	78.70 ± 14.814	I / II: 0.989 I / III: 0.560 II / III: 0.650
4 min after MR*	78.63 ± 10.794	74.87 ± 14.512	78.17 ± 15.541	I / II: 0.805 I / III: 0.270 II / III: 0.624
Immediately after intubation	85.63 ± 11.690	81.87 ± 14.236	79.97 ± 15.366	I / II: 0.546 I / III: 0.258 II / III: 0.856
1 min after intubation	82.13 ± 12.139	81.07 ± 14.741	80.20 ± 15.341	I / II: 0.954 I / III: 0.857 II / III: 0.969
2 min after intubation	79.77 ± 12.588	78.70 ± 13.417	79.30 ± 14.716	I / II: 0.950 I / III: 0.990 II / III: 0.984
3 min after intubation	78.77 ± 13.088	76.63 ± 13.459	78.03 ± 14.330	I / II: 0.817 I / III: 0.976 II / III: 0.917
4 min after intubation	78.27 ± 12.275	75.60 ± 13.027	77.40 ± 14.202	I / II: 0.714 I / III: 0.965 II / III: 0.858
5 min after intubation	76.63 ± 12.378	74.63 ± 12.778	76.37 ± 14.041	I / II: 0.825 I / III: 0.997 II / III: 0.865
7 min after intubation	74.07 ± 11.832	73.47 ± 12.643	75.50 ± 13.592	I / II: 0.982 I / III: 0.900 II / III: 0.810
10 min after intubation	73.10 ± 11.487	72.63 ± 12.568	74.43 ± 13.096	I / II: 0.988 I / III: 0.909 II / III: 0.841

Table 3. HR (Mean ± SD) Beats / Min

P-value: > 0.05 (not significant); < 0.05 (significant)

*MR - Muscle Relaxant

Variables	Group I	Group II	Group III	P-Value
Age (years)	49.23 ± 8.61	51.33 ± 8.49	49.97 ± 6.98	0.594
Weight (Kg)	61.13 ± 11.92	64.57 ± 12.10	64.13 ± 9.91	0.447
Duration of hypertension (years)	2.01 ± 2.15	2.20 ± 3.16	2.50 ± 2.16	0.452
Duration of laryngoscopy and intubation (secs)	15.03 ± 3.95	13.67 ± 2.56	13.70 ± 0.79	0.097
Table 2. Patients Characteristics and Duration of Laryngoscopy and Intubation				
Data is comparable in three groups (P > 0.05)				

	Group I	Group II	Group III	P-Value
Serum Mg (baseline)	1.86 ± 0.22	1.87 ± 0.14	1.83 ± 0.10	0.605
Serum Mg (after intubation)	2.68 ± 0.48	2.96 ± 0.34	1.83 ± 0.09	0.000
Table 3. Serum Magnesium Levels (Mmol / L)				

There was no statistically significant difference in HR

values at different time intervals among three groups [Table 1, Fig 1].

Following the induction of anaesthesia, there was a significant decrease in SBP, DBP and MAP, but immediately after laryngoscopy and endotracheal intubation the blood pressure increased toward the baseline. In all the three groups BP was comparable to the baseline and there was no significant rise after intubation. MAP was nicely maintained in group I during entire study time. In group II and III MAP decreased significantly at 3- and 4-min post intubation, which persisted throughout the study time.

Intervention was required to treat hypotension in significant number of patients in group II (nine patients) and group III (three patients). No intervention was required to treat hypertension in any patient. No any arrhythmia or significant change in ST segment was noticed in any of the patients.

Time Interval	Group I	Group II	Group III	P-Value	P-Value
Baseline	99.63 ± 12.311	98.47 ± 7.371	96.60 ± 6.981	0.441	I / II: 0.876 I / III: 0.413 II / III: 0.713
End of infusion	94.33 ± 10.643	95.77 ± 8.224	93.33 ± 6.593	0.551	I / II: 0.797 I / III: 0.895 II / III: 0.523
Beginning of induction	90.03 ± 11.012	90.27 ± 9.277	90.17 ± 6.968	0.995	I / II: 0.995 I / III: 0.998 II / III: 0.999
At the time of administration of MR*	85.70 ± 13.118	85.63 ± 9.510	87.17 ± 5.331	0.793	I / II: 1.000 I / III: 0.833 II / III: 0.819
1 min after MR*	82.10 ± 11.748	78.20 ± 15.482	84.20 ± 6.008	0.139	I / II: 0.407 I / III: 0.768 II / III: 0.124
2 min after MR*	79.93 ± 11.611	75.20 ± 9.430	81.27 ± 9.815	0.063	I / II: 0.184 I / III: 0.872 II / III: 0.065
3 min after MR*	78.93 ± 12.117	72.87 ± 11.840	76.20 ± 8.442	0.104	I / II: 0.086 I / III: 0.599 II / III: 0.467
4 min after MR*	77.30 ± 11.244	72.30 ± 10.326	76.23 ± 9.069	0.144	I / II: 0.148 I / III: 0.914 II / III: 0.303
Immediately after intubation	99.10 ± 12.653	96.93 ± 14.408	87.07 ± 6.253	0.000	I / II: 0.752 I / III: 0.000 II / III: 0.004
1 min after intubation	96.57 ± 10.972	91.27 ± 13.493	83.40 ± 8.286	0.000	I / II: 0.161 I / III: 0.000 II / III: 0.020
2 min after intubation	93.93 ± 14.074	85.47 ± 12.522	80.33 ± 7.058	0.000	I / II: 0.016 I / III: 0.000 II / III: 0.207
3 min after intubation	91.50 ± 13.858	81.53 ± 10.821	75.83 ± 7.382	0.000	I / II: 0.002 I / III: 0.000 II / III: 0.117
4 min after intubation	91.50 ± 15.122	76.60 ± 10.763	72.43 ± 7.718	0.000	I / II: 0.000 I / III: 0.000 II / III: 0.350
5 min after intubation	88.77 ± 15.190	74.00 ± 12.143	71.47 ± 8.815	0.000	I / II: 0.000 I / III: 0.000 II / III: 0.707
7 min after intubation	86.23 ± 12.286	73.67 ± 10.646	72.50 ± 4.988	0.000	I / II: 0.000 I / III: 0.000 II / III: 0.890
10 min after intubation	86.40 ± 13.952	72.60 ± 8.585	72.20 ± 6.718	0.000	I / II: 0.000 I / III: 0.000 II / III: 0.987
Table 4. Mean Arterial Pressure (mmHg) Values in Mean ± SD					
P-Value: > 0.05 (not significant); < 0.05 (significant)					
*MR- Muscle relaxant					

DISCUSSION

Laryngoscopy and intubation cause sympathetic stimulation leading to pressor response characterised by approximately 20 % rise in HR and 40 - 50 % rise in BP,³ which can be tolerated well by normal patients but may cause life threatening complications such as myocardial ischemia, arrhythmias and intracranial haemorrhage in hypertensive patients.⁶

Many adjuvant drugs, including opioids,⁷ β blockers,⁸ α -adrenergic agonists,⁹ calcium channel blockers,¹⁰ vasodilators¹¹ and lignocaine¹² have been tried with variable results to attenuate the haemodynamic stress response to endotracheal intubation. But all of them have been found to be associated with either cardiovascular or respiratory complications.

Magnesium sulphate has been shown to inhibit catecholamine release and pressor response to tracheal intubation.¹⁵ The mechanism of action of magnesium in limiting the pressor response to intubation is multifactorial. It has been demonstrated that magnesium being a physiological calcium antagonist inhibits the release of catecholamine in vivo at the time of intubation. In addition, magnesium is an α -adrenergic antagonist and has direct vasodilator properties. Magnesium produces vasodilatation by a direct action, as well as indirectly by sympathetic blockade and inhibition of catecholamine release.¹⁶

Magnesium sulfate is utilised in conditions with catecholamine excess such as tetanus,¹⁷ pheochromocytoma¹⁸ and ST elevation anterior myocardial infarction.¹⁹ Magnesium sulfate (MgSO_4) also directly reduces smooth muscle tonicity and subsequently vascular contraction.^{20,21} Therefore, MgSO_4 is useful to decrease systemic hypertension, as used for treatment of pregnancy induced hypertension.²²

James et al. evaluated the effect of intravenous MgSO_4 on catecholamine release related to tracheal intubation. They compared intravenous MgSO_4 60 mg / Kg with an equal volume of intravenous normal saline both given before laryngoscopy. They recorded plasma concentration of catecholamine immediately before, during and after intubation, and also 2 and 5 min after intubation. They concluded that MgSO_4 attenuates the catecholamine mediated response to tracheal intubation.²³

Puri et al. compared 50 mg / Kg of magnesium sulfate with lidocaine in coronary artery diseases patients and concluded that magnesium was significantly better than lidocaine in attenuating the cardiovascular response during endotracheal intubation.²⁴

In a double-blinded randomised controlled trial, done by Azim et al., 120 patients undergoing elective surgery were divided equally into four groups (N = 30) and received different doses of MgSO_4 as case groups (Group I: 30 mg / Kg, Group II: 40 mg / Kg, Group III: 50 mg / Kg) or the equal volume of normal saline as a control group. The patients' haemodynamic status was recorded at baseline, before laryngoscopy and in 1, 3, 5, and 10 minutes after laryngoscopy. They concluded that use of MgSO_4 in doses less than 50 mg / Kg can be effective to reduce cardiovascular instability related to laryngoscopy and tracheal intubation.²⁵

In our study, magnesium sulphate was found to suppress the haemodynamic response to laryngoscopy and

endotracheal intubation in 30 mg / Kg as well as 40 mg / Kg when given slow intravenously prior to induction of anaesthesia. As compared with the baseline values, no significant rise in HR and BP was noticed following the laryngoscopy and intubation in all the three groups. However, none of the patients receiving 30 mg / Kg magnesium sulphate developed significant hypotension while 30 % of patients who received 40 mg / Kg magnesium sulphate developed significant hypotension requiring rescue medication.

Magnesium prolongs sinus node recovery time by indirect and direct inhibition of the sinoatrial node. It was shown that magnesium slows HR at rest by blockade of the nictitating membrane of the sympathetic ganglia.²⁶ Magnesium has a negative chronotropic effect after administration of atropine.²⁷ Due to its parasympathetic effects on the sinoatrial node at dosage used in our study, magnesium prevented the increase in HR in response to laryngoscopy and intubation.

Magnesium caused vasodilation by sympathetic blockade and inhibition of catecholamine release. Intravenous magnesium administration resulted in decrease in systemic vascular resistance.²⁸ Due to these effects, magnesium inhibited the increase in arterial pressure after laryngoscopy and tracheal intubation.

Magnesium causes decrease in afterload and coronary vasodilation.²⁹ Due to this there were no ST segment changes during induction and tracheal intubation. The effect of magnesium on the coronary and systemic arteries is probably due to its calcium antagonist effect.³⁰ The plasma levels of magnesium during the study period have been in the therapeutic range.

CONCLUSIONS

Magnesium administered at doses of 30 mg / Kg, and 40 mg / Kg attenuated the rise in arterial pressure and heart rate changes following laryngoscopy and endotracheal intubation. Magnesium sulphate in the dosage 30 mg / Kg is found optimal to control the haemodynamic response during intubation in controlled hypertensive patients as significant hypotension may be caused by further increase in the dosage.

Limitations

We did not measure the depth of anaesthesia and plasma level of catecholamine during the study period. These are the limitations of our study. We recommend future studies considering such limitations.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.

Financial or other competing interests: None.

Disclosure forms provided by the authors are available with the full text of this article at jemds.com.

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