Original Article

Different doses of intravenous Magnesium sulfate on cardiovascular changes following the laryngoscopy and tracheal intubation: A double-blind randomized controlled trial

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ABSTRACT

Objective: Laryngoscopy and intratracheal intubation may cause acute hemodynamic instabilities due to catecholamine release. Magnesium sulfate ($MgSO_4$) prevents catecholamine release and results in bradycardia and vasodilatation, so can be used to diminish complications of laryngoscopy and intubation in doses > 50 mg/kg. The aim of this study was to compare the different doses of $MgSO_4$ used to improve cardiovascular instabilities due to laryngoscopy and intratracheal intubation.

Methods: In this double-blind randomized controlled trial, 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' hemodynamic status was recorded at baseline, before laryngoscopy and in 1, 3, 5, and 10 minutes after laryngoscopy. Bradycardia, tachycardia, hypertension, hypotension, ST-T changes, arrhythmias, and duration of extubation and laryngoscopy were also recorded.

Findings: There was no significant difference in heart rate between four groups ($P_{baseline} = 0.46$, $P_{preoperation} = 0.55$, $P_{1\ min} = 0.86$, $P_{3\ min} = 0.30$, $P_{5\ min} = 0.63$, $P_{10\ min} = 0.74$). Systolic, diastolic and mean arterial pressures were statistically significant less at 1, 3, and 5 minutes after intubation in comparison with other times of following-up in the three groups received $MgSO_4$ than the control group.

Conclusion: The use of $MgSO_4$ in doses less than 50 mg/kg can be effective to reduce cardiovascular instability related to laryngoscopy and tracheal intubation.

Keywords: Intra-tracheal; intubation; laryngoscopy; Magnesium sulfate

INTRODUCTION

Laryngoscopy and tracheal intubation cause catecholamine release due to the sympathoadrenal stimulation. This effect can cause acute hemodynamic instabilities such as increasing in blood pressure, heart rate (HR), pulmonary artery, and capillary wedge pressure.[1,2] Hemodynamic instability is defined as a state which requires for circulatory or mechanical support to maintain a normal blood pressure or cardiac output. The changes in hemodynamic parameters >20% of basal value for each patient is usually considered as abnormal.[1] These complications cause significant adverse effects especially in patients with heart diseases and pulmonary disorders.[3-6]

Various pharmacological agents have been used to prevent these effects consisting adrenoreceptor blockers,[7] narcotics,[8] calcium channel blockers,[9] sodium channel blockers,[10] vasodilators,[11-13] and paracetamol.[14]

Magnesium sulfate ($MgSO_4$) inhibits catecholamine release from adrenal glands.[15] It was shown that $MgSO_4$ reduces levels of serum epinephrine and cause a decrease in the atrial contraction, bradycardia,

and vasodilatation.[16,17] Puri *et al*.[18] showed that MgSO$_4$ 50 mg/kg administered before laryngoscopy could attenuated the pressor response to tracheal intubation better than lidocaine. However, the effects of the other doses of magnesium on the hemodynamic responses to laryngoscopy were not investigated before. We designed the present study to compare the effects of different doses of MgSO$_4$ on suppression of cardiovascular responses to the laryngoscopy and endotracheal intubation.

METHODS

After obtaining institutional approval from the Ethic Committee of Isfahan University of Medical Sciences (Isfahan, Iran), this double-blinded randomized controlled study was performed from September 2012 to July 2013.

We obtained written informed consent from 120 patients aged 18–65 years with America Society of Anesthesiologists physical status grades I–II, who underwent elective surgery under general anesthesia with endotracheal intubation.

Patients were not included in our study if they had previous history of renal disease, cardiovascular, gastrointestinal or neurological disorders, use of anticoagulant drugs, calcium channel blockers, known allergies to the study drug, and airway malformation. No pregnant patient was included into the study. Furthermore, if there was any change in technique of anesthesia or duration of laryngoscopy for >30 s, the patient was excluded from the study.

After arriving to the operating room, patients were randomly allocated to one of the four groups (30 patients in each group). Randomization was performed using simple block method. Patients in Groups I, II, and III received intravenous (IV) MgSO$_4$ (30 mg/kg, 40 mg/kg and 50 mg/kg, respectively) over 1 min, while in control group, they received only the equal volume of IV saline 0.09% (Group S). General anesthesia was induced with IV propofol (2 mg/kg), IV fentanyl (3 μg/kg), and atracurium 0.6 mg/kg for facilitation of muscle relaxation. Tracheal intubation was performed after 2 min from injection of atracurium. Anesthesia was continued with 1.25% isoflurane in combination with 50% oxygen in nitric oxide. Morphine 0.1 mg/kg was used for intraoperative analgesia. Ventilation of the lungs was adjusted to maintain an end-tidal CO$_2$ of 35-40 mmHg. After surgery, IV neostigmine 0.04 mg/kg and atropine 0.02 mg/kg were used to reverse muscle relaxation. The serum level of MgSO$_4$ was not measured at any time throughout the study.

Anesthesia was performed by an anesthetist who was not involved in data collection. HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) and arterial oxygen saturation were recorded noninvasively before induction of anesthesia, just before laryngoscopy, and at 1, 3, 5, and 10 min after endotracheal intubation.

Grade of laryngoscopy was recorded by the use of Cromak–Lehane classification:[19] In Grade I, most of the glottic opening can be seen. In Grade II, only the posterior portion of the glottis or only arytenoid cartilages is visible. In Grade III, only the epiglottis but no portion of the glottis is visible and in Grade IV, neither the glottis nor the epiglottis can be seen.

Duration of laryngoscopy, extubation time, hypotension (SBP <20% of basal), hyper-tension (SBP >20% of basal), tachy-cardia (increased HR >20% of baseline), arrhythmias and changes in ST-T segments (>10 mm depression relative to baseline) were also recorded. Recordation of data was performed by a nurse who was unaware of the study group allocation.

For sample size estimation, we used MedCalc 9.0 statistical software and determined a sample population of 30 patients in each group needed to ensure 80% statistical power at α =0.05 to detect the 25% difference in MAP at maximum pressor response after intubation, with 0.3 difference in standard deviation (SD). Data are presented as mean ± SD or numbers (percentages). One-way analysis of variance and *post hoc* comparisons at various points in time using Bonferroni's type I error rate correction was used to compare differences in mean values between groups. Chi-square test was used for analysis of qualitative variables. The $P < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Totally, 120 patients were recruited to the study. No participant excluded from the study. No statistically significant difference was found in demographic characteristics between four groups [Table 1]. There was no significant difference in grading of laryngoscopy and duration of laryngoscopy among four groups [Table 1]. Furthermore, there was no statistically significant difference in HR values in different time intervals among four groups [Table 2].

The mean SBP, DBP, and MAP at 1, 3, and 5 min after laryngoscopy was significantly less in Group I, Group II, and Group III compared with Group S. These variables were not statistically significant at 10 min after laryngoscopy compared with the

control group. Furthermore, there was no significant difference among Group I, Group II, and Group III with respect to these variables [Tables 3-5]. As shown in Table 3, the percentage of patients with SBP changes <20% of basal value to percentage of patients with SBP changes >20% of basal value in Group III was significantly more than Group S (*P* < 0.05).

There was no significant difference in extubation time between four groups [Table 1]. The incidence of

Table 1: Demographic characteristic, grading and duration of laryngoscopy, and extubation time of the study patients in four groups

Variable	Group I (*n*=30)	Group II (*n*=30)	Group III (*n*=30)	Group S (*n*=30)	*P*
Age (year)	34.6±17.5	35.0±12.6	34.7±12.2	32.3±11.6	0.85
Sex (male/female)	19/11	20/10	26/4	18/12	0.10
BMI (kg/m^2)	26.4±4.4	24.5±3.9	25.9±2.4	26.6±2.8	0.097
ASA physical status grade (I/II)	26/4	29/1	27/3	29/1	0.35
Duration of laryngoscopy (min)	13.7±6.9	13.0±4.3	13.8±4.3	14.5±8.0	0.82
Extubation time (min)	16.9±2.9	18.2±2.9	16.4±3.3	17.8±2.4	0.08
Magnesium dose (mg)	2265.0±644.5	2725.3±418.5	3575.0±406.4	0	-
Grade of laryngoscopy					0.231
Grade I	22 (73.0)	23 (76.7)	20 (66.7)	28 (93.3)	
Grade II	8 (26.7)	6 (20)	9 (30.0)	2 (6.7)	
Grade III	0 (0.0)	1 (3.3)	1 (3.3)	0 (0.0)	
Grade IV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Data are presented as mean±SD or numbers (%) of patients, where applicable. Group I received magnesium sulfate 30 mg/kg, Group II received magnesium sulfate 40 mg/kg, Group III received magnesium sulfate 50 mg/kg, Group S received equal volume of normal saline. SD=Standard deviation, BMI=Body mass index, ASA=America Society of Anesthesiologists

Table 2: HR changes in different time intervals in four study groups

Time	Group I (*n*=30)	Group II (*n*=30)	Group III (*n*=30)	Group S (*n*=30)	*P*
Baseline	87.5±9.3	90.7±4.9	86.3±18.1	85.5±16.9	0.46
Before laryngoscopy	87.8±10.2	91.4±5.7	88.8±20.0	92.9±20.8	0.55
After laryngoscopy					
1 min	98.0±16.4	100.4±15.2	97.4±18.9	96.7±19.1	0.84
3 min	108.0±15.1	110.4±14.3	102.3±17.3	104.4±18.2	0.30
5 min	94.5±17.3	92.2±13.2	93.9±13.2	97.5±18.1	0.63
10 min	85.80±16.40	89.07±13.69	86.10±13.84	84.87±17.75	0.74

Data are presented as mean±SD. Group I received magnesium sulfate 30 mg/kg, Group II received magnesium sulfate 40 mg/kg, Group III received magnesium sulfate 50 mg/kg, Group S received equal volume of normal saline. SD=Standard deviation, HR=Heart rate

Table 3: SBP changes in different time intervals in four study groups

Time	Group I (*n*=30)	Group II (*n*=30)	Group III (*n*=30)	Group S (*n*=30)	*P*
Baseline	135.8±17.5	132.0±15.8	133.4±16.8	132.4±14.7	0.80
Before laryngoscopy	132.9±15.2	130.6±11.6	131.3±11.7	124.0±15.5	0.06
After laryngoscopy					
1 min					
Mean±SD	133.5±19.3**	131.8±19.7**	132.7±15.6**	148.4±20.4	0.002
Percentage*	66.7/33.3	70.0/30.0	86.7/13.3**	53.3/46.7	0.047
3 min					
Mean±SD	132.8±18.8**	132.3±23.5**	131.6±19.9**	149.6±23.8	0.003
Percentage*	73.3/26.7	76.7/23.3	76.7/23.3**	40/60	0.005
5 min					
Mean±SD	133.2±18.8**	132.3±19.4**	127.1±19.1**	146.7±14.9	0.001
Percentage*	73.3/26.7	53.3/46.7	90/10**	80/20	0.010
10 min					
Mean±SD	130.5±19.6	131.1±15.1	132.5±15.7	139.9±16.4	0.114
Percentage*	66.7/33.3	80/20	80/20**	86.7/13/3	0.292

*Data are presented as mean±SD or percentage of patients with SBP changes <20% of basal value to the percentage of patients with SBP changes >20% of basal value. **P<0.05 versus Group S. Group I received magnesium sulfate 30 mg/kg, Group II received magnesium sulfate 40 mg/kg, Group III received magnesium sulfate 50 mg/kg, Group S received equal volume of normal saline. SD=Standard deviation, SBP=Systolic blood pressure

Table 4: DBP changes in different time intervals in four study groups

Time	Group I (*n*=30)	Group II (*n*=30)	Group III (*n*=30)	Group S (*n*=30)	*P*
Baseline	79.7±11.5	83.5±15.4	80.9±12.2	81.4±13.7	0.720
Before laryngoscopy	77.2±10.8	80.6±13.6	78.3±12.0	72.8±10.6	0.070
After laryngoscopy					
1 min	81.8±22.1*	85.5±14.4*	82.2±12.6*	97.3±13.4	0.001
3 min	166.6±37.3*	172.2±32.7*	160.7±28.7*	198.3±37.4	0.001
5 min	165.3±22.9*	171.8±35.2*	159.4±31.9*	194.5±29.0	0.001
10 min	78.8±15.0	82.0±13.5	81.2±11.8	80.8±16.2	0.830

Data are presented as mean±SD. *$P<0.05$ versus Group S. Group I received magnesium sulfate 30 mg/kg, Group II received magnesium sulfate 40 mg/kg, Group III received magnesium sulfate 50 mg/kg, Group S received equal volume of normal saline. SD=Standard deviation, DBP=Diastolic blood pressure

Table 5: MAP changes in different time intervals in four study groups

Time	Group I (*n*=30)	Group II (*n*=30)	Group III (*n*=30)	Group S (*n*=30)	*P*
Baseline	98.4±11.5	99.7±12.0	98.4±12.1	100.4±13.4	0.900
Before laryngoscopy	97.4±10.7	97.2±10.9	97.7±9.4	92.6±11.7	0.200
After laryngoscopy					
1 min	99.1±17.3*	100.9±15.1*	99.0±12.7*	114.3±15.1	0.001
3 min	99.8±17.8*	101.5±17.9*	97.4±15.5*	114.6±19.6	0.001
5 min	99.5±12.9*	101.4±16.5*	95.5±16.5*	112.7±14.1	0.010
10 min	96.0±15.8	98.4±12.9	98.3±12.4	100.6±15.9	0.680

Data are presented as mean±SD. *$P<0.05$ versus Group S. Group I received magnesium sulfate 30 mg/kg, Group II received magnesium sulfate 40 mg/kg, Group III received magnesium sulfate 50 mg/kg, Group S received equal volume of normal saline. SD=Standard deviation, MAP=Mean arterial (blood) pressure

Table 6: The incidence of cardiovascular complications in four study groups

Variable	Group I (*n*=30)	Group II (*n*=30)	Group III (*n*=30)	Group S (*n*=30)	*P*
Hypertension	3 (10)	2 (6.7)	1 (3.3)	5 (16.7)	0.32
Hypotension	2 (6.7)	2 (6.7)	3 (10)	2 (6.7)	0.94
Tachycardia	4 (13.3)	4 (13.3)	5 (16.7)	3 (10)	0.90
Bradycardia	2 (6.7)	0 (0.0)	0 (0.0)	3 (10)	0.13
Arrhythmia	1 (3.3)	0 (0.0)	0 (0.0)	3 (10)	0.10

Data are presented as numbers (%) of the patients. Group I received magnesium sulfate 30 mg/kg, Group II received magnesium sulfate 40 mg/kg, Group III received magnesium sulfate 50 mg/kg, Group S received equal volume of normal saline

hypertension, hypotension, tachycardia, bradycardia, and arrhythmias was not significantly different among the four groups [Table 6].

DISCUSSION

To the best of our knowledge, the present study is the first one investigated the effect of administering MgSO₄ with doses of <50 mg/kg (30 mg/kg and 40 mg/kg) for prevention of cardiovascular changes after laryngoscopy in normotensive patients.

Our results showed that using lower doses of MgSO₄ (30 mg/kg or 40 mg/kg, IV) comparable with using 50 mg/kg IV could significantly decrease the SBP, DBP, and MBP changes till 5 min after laryngoscopy in comparison with control group.

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.[16,17,20-22]

Laurant *et al.*[23] showed that IV MgSO₄ attenuated the release both catecholamine and vasopressin in mesenteric resistance arteries of spontaneously hypertensive rats.[23]

Magnesium sulfate is utilized in conditions with catecholamine excess such as tetanus,[24] pheochromocytoma,[25] and ST elevation anterior myocardial infarction.[26] MgSO₄ also directly reduces smooth muscle tonicity and subsequently vascular contraction.[27,28] Therefore, MgSO₄ is useful to decrease systemic hypertension, as using for treatment of pregnancy induced hypertension.[29]

Laryngoscopy and endotracheal intubation, two daily common procedures with catecholamine release,

are usually performed for general anesthesia[11] and cardiopulmonary resuscitation.[30] In one study, the authors believed IV use of lidocaine 1.5 mg/kg or $MgSO_4$ 60 mg/kg before anesthetic induction reduced mean arterial and systolic pressures in the first 2 min after intubation better than lidocaine while the effect of these drugs on HR was not significantly different.[11]

James *et al.*[15] evaluated the effect of IV $MgSO_4$ on catecholamine release related to tracheal intubation. They compared IV $MgSO_4$ 60 mg/kg with an equal volume of IV 0.09% sodium chloride both IV over 1 min before laryngoscopy. They recorded plasma concentration of magnesium and catecholamine immediately before, during and after intubation, and also 2 and 5 min after intubation. They demonstrated induction of general anesthesia induced no significant changes in HR while it caused a decrease in SBP and DBP, arterial blood pressure.

In a similar randomized control trial study, Puri and Batra[31] appraised the effect of IV $MgSO_4$ 50 mg/kg on hemodynamics changes after tracheal intubation in patients suffering coronary artery disease scheduled for coronary artery bypass graft. They used $MgSO_4$ for 19 sedated patients and normal saline 0.05 mL/kg for 17 patients. They showed $MgSO_4$ effectively prevented the rise in arterial blood pressure associated with endotracheal intubation. In addition, this drug could decrease ST segment changes during laryngoscopy.

In our study, magnesium attenuated the increase in blood pressure till 5 min after laryngoscopy. The ineffectiveness of magnesium administration for prevention of the rise in blood pressure 10 min after laryngoscopy was probably due to decrease in catecholamine release in this time. After laryngoscopy and tracheal intubation, the catecholamines rises maximally till 5 min and after that its release gradually decrease.[15]

Stanbury[32] showed that $MgSO_4$ prolongs sinus node recovery time by indirect and direct inhibition on the sinoatrial node. It was shown that magnesium slows HR at rest by blockade of the nictitating membrane of the sympathetic ganglia. Magnesium has a negative chronotropic effect after administration of atropine.[33] It was probable that stress of laryngoscopy and consequently stimulation of sympathetic nervous system was so large that could not be attenuated by the parasympathetic effect of magnesium on the sinoatrial node at dosage used in our study. It is recommended that future studies with higher dosage of $MgSO_4$ designs to investigate this issue.

Magnesium caused vasodilation by sympathetic blockade and inhibition of catecholamine release. IV magnesium administration results in a decrease in systemic vascular resistance. Due to these effects,

magnesium inhibited the increase in arterial pressure after laryngoscopy and tracheal intubation.[34]

In our study, there were no significant ST segment changes during induction and tracheal intubation. This could be due to decrease in afterload and coronary vasodilation produced by magnesium administration.[35] The effect of magnesium on the coronary and systemic arteries is probably due to its calcium antagonist effect.[36]

We did not measure the plasma level of $MgSO_4$ during the study periods. This is a limitation of our study. We recommend future study in this issue with considering such limitation.

In conclusion, magnesium administered at dosages of 30 mg/kg, 40 mg/kg, and 50 mg/kg comparably attenuated the increase in arterial pressure changes after laryngoscopy and endotracheal intubation without significant effect on the HR changes.

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AUTHORS' CONTRIBUTION

MRS has planned the study and finalized it; SB, AH, ND and MRS did the statistical analysis and prepared the first version of manuscript for publish. All authors read and approved the final manuscript.

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