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RESEARCH ARTICLE

EFFECTS OF MAGNESIUM SULPHATE ON HAEMODYNAMIC RESPONSE TO ENDOTRACHEAL INTUBATION, ANAESTHETIC REQUIREMENT AND POSTOPERATIVE OPIOID CONSUMPTION IN PATIENTS UNDERGOING SPINE SURGERY

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ABSTRACT

This randomized, placebo controlled, double blind study was designed to assess the effect of perioperative intravenous (i.v.) $MgSO_4$ administration on cardiovascular response to intubation, anaesthetic requirement and postoperative opioid consumption. Eighty patients undergoing spine surgery were randomly divided into two groups. Before induction of anaesthesia, group M received $MgSO_4$ 30 mg/kg^{-1} a bolus and 10 mg/kg^{-1h-1} iv by continuous infusion. Group C received the same volume of isotonic saline. Propofol, vecuronium and fentanyl was administered for anaesthesia maintenance. Heart rate (HR) and mean arterial pressure (MAP) before and after intubation and during perioperative period as well as total amount of anaesthetic required, pain scores and total opioids consumption in the postoperative period were evaluated

MAP and HR just after intubation were significantly lower in Group M ($p < 0.05$) and they also required less anesthetics ($p< 0.01$). Postoperative pain scores, cumulative analgesic consumptions and shivering were significantly lower in Group M ($p < 0.05$). Moreover, global satisfaction scores were significantly higher in Group M (0.05). No side effects were observed after magnesium administration. Perioperative iv $MgSO_4$ administration led to significant attenuation of cardiovascular responses to laryngoscopy and intubation, reduced anaesthetic requirement significantly and improved postoperative analgesia.

Key words: Anaesthetic techniques: iv infusion, ions, magnesium, neuromuscular block: vecuronium, pain: postoperative, surgery, spine

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INTRODUCTION

Magnesium sulphate ($MgSO_4$) is an inexpensive relatively harmless and readily available molecule[1]. It was first known for its efficacy in arrhythmia and preeclampsia[2]. Recently the importance of magnesium in anaesthetic practice has been highlighted.

Magnesium is a naturally occurring calcium antagonist and a non-competitive antagonist of N-methyl-D aspartate (NMDA) receptor[3]. It is involved in several processes like control of vasomotor tone, cardiac excitability, neurotransmitter release and modulation of pain. Magnesium competes with calcium for membrane channels. It can inhibit many calcium mediated responses like the release of catecholamine from both the adrenal gland and peripheral adrenergic nerve terminals in response to sympathetic stimulation[4] and has vasodilatation properties[5]. Magnesium also inhibits presynaptic release of acetylcholine at the neuromuscular junctions and may result in early onset time and unpredictable potentiation of neuromuscular blockade[6]. Moreover, as it antagonizes NMDA receptor in the central nervous system, magnesium decreases peripheral nociceptor sensitization and stress response to surgery[7] and thereby may reduce opioid requirement in the perioperative period.

Most studies suggest that perioperative magnesium controls cardiovascular response to tracheal intubation[5,8,9] reduces anaesthetic requirement[10-11] and has opioid sparing effect in perioperative period[12-14]. However, some studies reported limited or no effect[15,16] of magnesium sulphate. In this placebo controlled double blind study, we, therefore, decided to evaluate the effect of magnesium on cardiovascular response to tracheal intubation, anaesthetic requirement and postoperative opioid consumption in patients undergoing lumbar spinal instrumental fixation surgery.

METHODS

This prospective, randomized, double blind study was approved by the ethical committee of Calcutta National Medical College and written informed consent was obtained from all patients. 80 patients of both genders aged 18-40 years of ASA I or II who underwent lumbar spinal fixation surgery under general anaesthesia for an anticipated duration of 60-190 min were selected for the study. Patients with anticipated difficult tracheal intubation, renal, hepatic, cardiovascular, gastrointestinal disease, chronic obstructive pulmonary disease, hematological disorders, obesity, pregnancy, prior treatment with calcium channel blockers or opioids and known allergy to magnesium sulphate or any other drugs were excluded from the study.

The patients were randomly allocated into two equal groups by a computer generated randomization chart. The involved drugs were prepared and administered by different anesthesiologist who was not involved in the study. Thus anesthesiologists were blinded to the arranged group of patients. The magnesium group (Group M, n = 40) received MGSO4 30 mg/kg^{-1} in 100 ml isotonic saline intravenously for 10 mins immediately before induction of anaesthesia

followed by 10 mg/kg^{-1h-1} continuous iv infusion until the end of operation. Patients in the control group (Group C, n = 40) received the same volume of isotonic saline over the same period. All patients underwent the same type of surgery which was performed by the same group of surgeons.

All patients were taught to interpret the visual analogue scale (VAS) before operation. Oral diazepam 0.1 mg/kg^{-1} 2 hr before induction of anaesthesia was used for premedication. Upon arrival in the operating room, ECG, non invasive arterial pressure and pulse oxymeter monitors were attached. IV line and urinary catheterization were done. Train of four (TOF) Neuromuscular block and bispectral index (BIS, Aspect 2000) monitoring were also performed. Preoperative serum magnesium levels were determined from all patients before infusion of magnesium sulphate.

Anesthetic management of patients was similar in both groups. After pre-oxygenation of at least 3 min with 100% oxygen, anaesthesia was induced with fentanyl 1.5 µg/kg^{-1} and propofol in increments of 20 mg every 5 seconds until BIS reached a predetermined value of 50. After induction of anaesthesia supramaximal train of four (TOF) response was measured at 20s interval when a stable twitch response (at least three successive equal responses to TOF stimulation) had been established, vecuronium 0.1 mg/kg^{-1} was administered. The time from the start of anaesthesia induction to reach as BIS of 50, the amount of propofol needed for induction of anaesthesia and the time to achieve 80% (T_1 = 20%) single twitch depression after administering vecuronium were recorded. Orotracheal intubation was facilitated after complete (T_1 = 0%) single twitch depression than a further set of recordings were made. All intubations were performed by the same anaesthesiologist.

Anaesthesia was maintained with 33% O_2 in N_2O and propofol infusion. The propofol infusion was started at the rate of 6 mg/kg^{-1h-1} and titrated to maintain BIS between 40 and 50. The hourly consumption of propofol was recorded as mg/kg^{-1h-1} . Dose adjustment of fentanyl infusion (0.5µg/kg^{-1}) were based on standard clinical signs and hemodynamic measurements. Inadequate analgesia was defined as an increase in mean arterial pressure (MAP) or heart rate (HR) by more than 20% of pre-anaesthetic values. If inadequate analgesia or hypotension (systolic arterial pressure SAP < 90 mmHg) occurred when BIS was 50, fentanyl infusion was increased or decreased respectively. Propofol infusion was stopped until blood pressure rises. Muscle relaxation was achieved with an infusion of vecuronium adjusted to provide complete depression of the first twitch after TOF stimulation. The TOF was measured every 10 min. Lungs of all patients were ventilated to maintain $EtCO_2$ between 35-40 mmHg.

The study drug magnesium sulphate / isotonic saline and propofol infusion were discontinued at skin closure. Ondansetron (4 mg) were administered iv at the end of surgery. The patients were allowed to recover spontaneously until the return of T_1 = 25%. Then a combination of neostigmine

0.05 mg/kg^{-1} and glycopyrrolate 0.01 mg/kg^{-1} were used to reverse neuromuscular block and trachea was extubated when the patient fulfilled the criteria of extubation. Times from anesthetic discontinuation to a BIS value 70 and to tracheal extubation were noted.

After the operation the patients were transferred to the recovery room and the sedation score was evaluated every 5 min using the modified Aldrete score until ready for discharge from the recovery room (0 = not responding; 1 = arousable with minimal stimulation and 2 = fully awake).

An iv continuous infusion of morphine 50 mg in normal saline in a total volume of 50 ml at the rate of 1 ml/hr set to deliver initially for postoperative analgesia and was titrated to maintain VAS pain score ≤ 30(using 0- 100mm VAS scale) . If necessary, rescue analgesic (diclofenac sodium injection 75 mg IM) was administered in the recovery room.

Data collected by independent observers blinded to the nature of the experimental treatment. HR and MAP at 5 minute before giving any drug as basal rest status (time = 0), just before laryngoscopy and at 1, 2,3,4,5, min after intubation and at 10, 15,30,60,90,120 min vecuronium administered were recorded,

The VAS pain score was recorded at emergence from anaesthesia and at 30 min, 4hr, 24hr and 48 hr after surgery. Pain score at rest and during movement were recorded using 0-100 mm VAS scale (0 – no pain to 100 = worst imaginable pain). Postoperative PCA analgesic solution consumption at 30 min and at 4hr, 24hr and 48 hr after operation were recorded.

Episodes of shivering, postoperative nausea and vomiting (PONV) were monitored and recorded at emergence and throughout the remainder of the study period. Blood samples for serum magnesium concentration determination were obtained before and immediately after surgery (the normal range used at our institution is 0.7-1.3 mmol/liter).

Patients satisfaction levels regarding comfort and quality of pain control were assessed using a five point scale (1 – very unsatisfactory, 5 = excellent).
After transfer to the recovery room, patients were assessed neurologically for any sign of hypermagnesemia. Any adverse events were recorded during the perioperative periods.

Statistical analysis

On the basis of unpublished pilot data on anaesthetic requirement and opioid consumption in 24 h, power analysis revealed a sample size of 30 patients per group was sufficient to achieve a power of 80% and an α error of 0.05 to detect a mean difference of 30% reduction in total anaesthetic requirement or opioid consumption. Statistical analysis was performed using students 't' test, X^2 test and ANOVA as appropriate. A value of $P < 0.05$ was considered statistically significant.

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RESULTS

80 patients completed the study protocol. Patient characteristics including duration of surgery were comparable between the two groups. Induction of anaesthesia with propofol was much earlier in Group M ($p < 0.01$) [Table 1]. There was significant reduction of propofol fentanyl and vecuronium requirement for maintenance of anaesthesia in patients receiving magnesium sulphate ($p < 0.001$) [Table 1]. Duration of neuromuscular block after incremental dose of vecuronium was prolonged in group M compared with control group [25.19 (3.3) vs. 15.32 (3.1) min, $p = 0.023$]. Moreover the times from infusion of vecuronium to $T_1 = 25\%$ [48.2 (2.1) vs 38.9 (1.1) min, $p < 0.001$] were significantly longer in group M compared with control group. However, there was no statistically significant difference in the conscious score (table I) immediately after recovery from anaesthesia. Time from discontinuation of study drug infusion to BIS 70 was 5.2 (2.3) min in group C vs 6.9 (2.1) min in group M ($p = 0.38$) and to tracheal extubation was 9.0 (2.4) min in group C vs 10.5 (1.9) min in group M ($p = 0.70$).

MAP and HR were comparable in both groups immediately before study solution infusion and endotracheal intubation ($p > 0.05$) [Table II and III). In response to laryngoscopy and intubation MAP and HR increased significantly in the control group ($p < 0.001$) while increases were significantly less in the group treated with $MgSO_4$ ($p < 0.05$) in comparison to baseline values. However, these variables returned to baseline level in 4-6 min in group M and 7 to 10 min in group C [Table II and III]. Hypotension (SAP < 90 mmHg) or bradycardia (HR < 60 beats min^{-1}) did not occur during bolus injection of study medication in either group. During this study, no patient in group M developed hypotension or bradycardia severe enough to require pressure or sympathomimetric agents. At 30 min after operation, MAP and HR were significantly more in control group than group M ($p < 0.05$). However, in rest of the postoperative period these variables were comparable in both groups ($p > 0.05$) [Table II and III).

The patients receiving $MgSO_4$ had significantly less shivering in the postoperative period [group M 2 vs. 15 patients in group C out of 40 patients each), $p < 0.001$]. Incidence of PONV was similar in both groups (group M 10 vs. 14 patients group C, $p > 0.05$).

The time of first postoperative analgesic requirement was significantly longer in group M than group C ($p < 0.05$). Cumulative postoperative opioid consumption was significantly less in group M at 24 and 48 hr after operation ($p < 0.024$, $p < 0.007$) [Table IV]. The postoperative VAS score for pain were less in group M at 24 and 48 hr ($p = 0.01$, $p = 0.012$). [Table V].

Serum total magnesium before infusion of study medication was comparable in both groups ($p > 0.05$). However, it was significantly increased in group M after the end of surgery ($p < 0.01$).

Global satisfaction score were significantly higher in group M [4.3 (1) in group M vs. 3.6 (1.9) in group C ($p<0.01$].

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Table I: Patients characteristics, anaesthetic requirement and postanaesthetic consciousness score, Group C (control group), group M (Magnesium group).

	Group C (n = 40)	Group M (n = 40)
Age	34.8 (28-47)	35.2 (30-45)
Body weight	57.2 (6)	57.5 (3.9)
Height (cm)	149.4 (4.2)	149.7 (3.2)
Duration of surgery (min)	160.6 (32.5)	162.2 (3.2)
Induction time with propofol (sec)	80.2 (10.8)	58.4 (10.6)
Total propofol requirement (mg/kg^{-1h-1})	5.4 (2.1)	3.6 (2.6)
Total vecuronium requirement (mg/kg^{-1h-1})	0.035 (5.4)	0.021(4.4)
Total fentanyl requirement ($\mu g/kg^{-1h-1}$)	1.14 (0.26)	0.45 (0.11)
Consciousness score after surgery		
0 (n)	0	0
1 (n)	6	9
2 (n)	34	31
Time to first postoperative analgesic requirement (min)	50.5 (7.9)	68.1 (5.1)
Total magnesium (mg/l^{-1})		
Preop		
Postop	1.80 (0.54)	1.81 (0.48)
	1.71 (0.55)	1.86 (0.47)

Values are expressed as mean (range) for age, mean (SD) or number of patients (n)
*** p < 0.05 compared with Group C**

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Table II: Perioperative changes in mean arterial pressure (mmHg). Values are mean (SD). Group C (control group), Group M (magnesium group)

	Group C (n = 40)	Group M (n = 40)
Preinduction	92.5 (5.7)	93.6 (5.2)
Preintubation	80.7 (10.2)	75.7 (1.5)
Postintubation		
At 1 min	122.9 (10.2)	94.9 (9.1)
2 min	120.1 (4.5)	93.8 (7.5)
3 min	112.2 (3.2)	92.4 (5.7)
4 min	107.3 (2.1)	92.1 (2.9)
5 min	98.5 (7.2)	79.3 (7.8)
15 min	77.2 (10.1)	66.2 (8.1)
30 min	73.9 (8.3)	69.1 (5.1)
45 min	94.1 (10.1)	74.9 (8.2)
90 min	91.5 (11)	79.5 (4.9)
120 min	88.9 (5.1)	77.2 (10)
End of surgery (min)	86.2 (4.9)	83.1 (7.9)
Postoperative 30 min	107.4 (3.1)	84.6 (1.5)
4 hour	94.9 (9.2)	92.9 (7.1)
24 hour	93.8 (7.5)	93.9 (10.1)
48 hour	92.1 (5.5)	94.1 (5.9)

*** p < 0.05 compared with Group C, ** p < 0.001 compared with baseline in group C, $^{\#}$p < 0.01 compared with baseline in Group M**

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Table III: Perioperative changes in heart rate (beats / min^{-1}). Values are mean (SD). Group C (control group), Group M (magnesium group)

	Group C (n = 40)	Group M (n = 40)
Preinduction	85.2 (6.9)	83.9 (8.9)
Preintubation	83.7 (5.1)	80.1 (5.4)
Postintubation		
At 1 min	145.9 (10.2)	102.5 (8.1)
2 min	135.1 (5.4)	89.1 (2.1)
3 min	126.5 (9.2)	85.4 (5.8)
4 min	114.1 (7.4)	80.5 (6.7)
5 min	109.5 (6.9)	74.1 (8.7)
15 min	75.9 (5.1)	70.2 (6.9)
30 min	78.1 (6.5)	75.5 (9.1)
60 min	75.9 (8.4)	76.2 (9.1)
120 min	75.4 (7.1)	74.1 (4.5)
End of surgery (min)	89.5 (10)	85.9 (9.1)
Postoperative 30 min	102.3 (8.1)	85.2 (10)
4 hour	85.2 (5.4)	86.1 (4.1)
24 hour	86.1 (4.5)	85 (6.7)
48 hour	84.5 (9.5)	85.5 (9.1)

*** p < 0.05 compared with preinduction value in Group C, #p < 0.05 compared with preinduction value in Group M, ** p < 0.05 at 30 min postoperative when compared between Group C and Group M,**

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Table IV: Mean cumulative injected volume (ml) of iv patient controlled analgesic solution in two groups. Values are mean (SD). Group C (control group). Group M (magnesium group)

	Group C (n = 40)	Group M (n = 40)
Postoperative at		
30 min	2.85 (0.28)	2.78 (0.38)*
6 hr	23.15 (2.17)	20.51 (2.55)*
12 hr	41.9 (3.9)	36.5 (1.89)*
24 hr	65.1 (3.24)	60.77 (1.89)*
48 hr	90.19 (3.79)	85.79 (2.61)*

*** p < 0.05 compared with Group C**

DISCUSSION

In this placebo controlled randomized study, we have found that administration of magnesium sulphate immediately before induction of general anaesthesia and during intraoperative period reduced the induction time with propofol, hemodynamic response to laryngoscopy and intubation, consumption of propofol, fentanyl and vecuronium as well as opioid consumption and pain intensity during first postoperative day. Moreover, patients receiving magnesium sulphate had less PONV and shivering compared to control group.

In the present study, we chose the bolus (30 mg/kg^{-1}) and continuous 10 $mg/kg^{-1}h^{-1}$) infusion doses of magnesium sulphate based on previous investigations[9,11]. When $MgSO_4$ is administered IV the onset of action is immediate and duration of action is about 30 min[7].

Consistent with previous reports[5,8,9,18] we have confirmed that $MgSO_4$ a calcium channel antagonist, attenuated hypertension associated with laryngoscopy and tracheal intubation.

There is a good correlation between the cardiovascular response to intubation and changes in plasma catecholamine concentration. Calcium ions exert a major role in the release of catecholamine from the adrenal gland and adrenergic nerve endings in response to sympathetic stimulation[4]. Animal experiments have shown that calcium channel stimulation[19]. In a study of healthy volunteers[21], calcium channel blockers inhibited the increase is plasma adrenaline induced by exercise. These observations suggest that the effect of $MgSO_4$ on heart rate and blood pressure is explained by the vasodilatation due to calcium channel blockade, analgesic effect

or consequent inhibition of catecholamine release after tracheal intubation.

We have shown that perioperative $MgSO_4$ infusion resulted in more rapid induction of anaesthesia and reduced consumption of propofol which was adjusted to maintain BIS between 40 and 50. We share the view of others[10-11]. Thomson and colleagues [21] suggested that anaesthetics should be titrated carefully in patients receiving magnesium. However, some studies[22-23] contradict our views and reported no effect on propofol requirement is not definitely known. The possible mechanisms for reduction of anaesthetic requirements may be anatagonism of NMDA receptors in the CNS and reduction of catecholamine release by sympathetic stimulation, thus decreasing peripheral nociceptor sensitization and stress response to surgery.

It is reported that use of parenteral $MgSO_4$ may result in severe and unpredictable potentiation of neuromuscular block[6, 24]. In our study, we monitored neuromuscular block throughout the intraoperative period and additional doses of vecuronium were administered when the count was > 2. For this reason, at the end of surgery probably we did not observe prolonged effect of magnesium on emergence from anaesthesia. As vecuronium was administered under guidance of TOF, our data documented significant reduction of vecuronium consumption with magnesium. Our observations are supported by other authors[11, 22, 24]. It is well known that action of magnesium at the neuromuscular junction include a reduction of acetylcholine release from the motor nerve terminals, a decrease in the depolarization action of acetylcholine at the end plate and depression of muscle fiber excitability by membrane stabilization action. It has been suggested that NMDA receptor antagonists are best administered before generation of noxious stimuli to prevent central sensitization[25] and may substantially reduce analgesic requirement after surgery. Therefore, giving magnesium postoperatively minimizes the initiation of pain and enhances its effectiveness as analgesic and reduces postoperative analgesic requirement; this may explain the hemodynamic stability during the perioperative period, reduction in opioid consumption and better pain relief after lumbar spine surgery in magnesium group which corroborates with studies[12-14] done after earlier. However, two reports contradict our views[15-16].

Magnesium is the second most abundant intracellular action and is involved in the regulation of many ion channels and enzymatic reactions. Hypomagensemia is the most under diagnosed electrolyte deficiency in the preoperative and critically ill patient[26, 27]. This decrease is probably due to large loss of fluids and fluid movement between body compartments. Perioperative magnesium supplementation may prevent postoperative hypomagnesaemia and also have a beneficial effect on postoperative pain. After surgery, patients in magnesium group showed higher serum magnesium concentrations than patients in the saline group. However, no clinical symptoms of hypo or hypermagnesemia were observed in any of the patients of group C and group M. Magnesium toxicity begins at serum concentration of 2.5-5 $mmol/l^{-1}$ [28], and cardiac arrest occurs at 12.5 $mmol/l^{-1}$ 28. We observed that in group M serum magnesium never reached the toxic level (2.5-5 $mmol/l^{-1}$) after giving magnesium both in bolus and in infusion. Our observation is supported by other studies[28].

Shivering causes discomfort and aggravated postoperative pain. Therefore, prevention of shivering may attenuate postoperative pain

and enhance patient satisfaction. Intravenous $MgSO_4$ has been reported previously to suppress post anaesthetic shivering[29]. In the present study also, patient in group M showed less postoperative shivering.

CONCLUSION

In conclusion, perioperative administration of magnesium sulphate (30 mg/kg^{-1} bolus followed by 10 mg/kg^{-1} continuous infusion) in patients undergoing lumbar spine surgery significantly reduced stress response to endotracheal intubation, anesthetic requirement along with significant reduction of postoperative shivering without any major adverse effects. Therefore, we conclude that IV magnesium sulphate may be a useful for spine surgery.

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