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Original Research Article

Effects of magnesium sulphate on intraoperative neuromuscular blocking agent requirement: A prospective randomized double blind placebo controlled study

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Abstract

Introduction: Magnesium sulphate has been shown to decrease intraoperative anesthesia, analgesia and muscle relaxant requirements.

Aims: To study the effects of intraoperative magnesium sulphate on requirement of neuromuscular blocking agents.

Setting and Design: This prospective randomized double blind placebo controlled study was conducted in the department of Anaesthesiology and Critical Care of a tertiary care centre.

Materials and Methods: 50 patients of ASA physical status I and II were randomly allocated into two groups, magnesium group (Group M) received magnesium sulphate 50 $mg.kg^{-1}$ intravenously as a bolus in 100 ml of isotonic saline over 10 minutes before induction of anesthesia and 15 $mg.kg^{-1}h^{-1}$ by continuous infusion during the operation and the control group (Group S) received the same amount of isotonic saline over same time. Atracurium was administered 0.6 $mg.kg^{-1}$ before intubation and 0.1 $mg.kg^{-1}$ additionally when train-of-four counts were 2 or more intravenously. The consumption of atracurium was compared in both groups.

Statistical Analysis: The variables were analysed with independent t-test, Wilcoxon-Mann Whitney U- test and chi-square test. P-value<0.05 was considered significant.

Results: The mean consumption of atracurium in group M was 0.35±0.11 $mg.kg^{-1}h^{-1}$ and group S was 0.47±0.19 $mg.kg^{-1}h^{-1}$ with p-value<0.001 and comparison was statistically significant. The mean additional doses of intravenous fentanyl given in group M were 0.8±0.57 and group S were 1.5±1.29 with a p-value of 0.014 and the comparison was statistically significant. Hemodynamic variables were comparable between two groups.

Conclusion: Intravenous magnesium sulphate reduces atracurium requirements in patients undergoing abdominal surgeries under general anesthesia.

Introduction

Muscle relaxation is an important component in delivering of anesthesia. Non-depolarizing neuromuscular blocking agents are widely used in maintenance of the neuromuscular relaxation. The muscle relaxation is very important when working deep in abdominal compartments and near critical areas. Magnesium sulphate has been proven as a useful adjunct for administration of anesthesia and has been found to reduce intraoperative anesthetic and analgesic requirements.[1-5] These effects are primarily based on physiological calcium antagonism, that is voltage-dependent regulation of calcium influx into the cell, and non-competitive antagonism of N-methyl-D-aspartate (NMDA) receptors.[6,7] Thwaites and colleagues have found magnesium sulphate effective in treatment of tetanic muscle spasm and rigidity.[8] Magnesium sulphate has been suggested as a potential molecule for study in enhancing the effect of non-depolarizing neuromuscular blocking agents. The said effect is due to presynaptic inhibition of neurotransmitter release.[9] This is due to competition of magnesium ion with the calcium ion[9] which inhibits the release of acetylcholine from the presynaptic nerve terminal and enhance the effect of non-depolarizing neuromuscular blocking agents.[10,11] Our study was a randomized prospective placebo controlled study to evaluate the effect of administration of magnesium sulphate intravenously to find out the change in requirements of atracurium given as a primary muscle relaxant.

Materials and Methods

This prospective randomized double blind placebo controlled study was conducted on 50 patients of American society of Anesthesiologists physical status I and II, scheduled for elective abdominal surgeries in the age group

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of 18-65 years after written informed consent and approval from the departmental review board. This study was done for a period of two years from August 2013 to April 2015. Patients with allergy to magnesium salts, on antibiotics like aminoglycosides, patients with cardiovascular, hepatic, or renal dysfunction, atrio-ventricular conduction disturbance, neuromuscular diseases, opioid or analgesic abuse and patients on prior treatment with calcium channel blockers were excluded from study. Both the patient and the anaesthesiologist were blinded and drugs were prepared by a person not involved in the study. Patients were randomly divided into two groups of 25 each using computer generated randomized list, group M (magnesium group) and group S (saline group). Magnesium group (Group M) received magnesium sulphate 50 $mg.kg^{-1}$ intravenously as a bolus in 100 ml of isotonic saline over 10 minutes before induction of anesthesia and 15 $mg.kg^{-1}h^{-1}$ by continuous infusion during the operation and the control group (Group S) received the same amount of isotonic saline over same time.

After proper pre anaesthetic evaluation with necessary investigations patients were premedicated with tablet alprazolam 0.5 mg and tablet ranitidine 50 mg on night prior to surgery. Patients were shifted to operating room on a trolley and mandatory monitors like electrocardiogram (ECG), pulse oximetry, non invasive blood pressure, and temperature probe were connected to the patient after securing a 20 gauge intravenous line. A neuromuscular monitor (TOF watch) was also attached to see the ulnar nerve adduction response in thumb as needed by the nature of study. A blood sample for serum Mg levels was obtained while establishing an intravenous access. In addition patients urine output was also monitored.

Anaesthesia was induced in both the groups with propofol 2 $mg.kg^{-1}$, morphine 100μgkg^{-1} and fentanyl 2$\mu g.kg^{-1}$.Immediately after loss of consciousness, basal twitch response [at least three consecutive equal responses to 2 Hz train-of-four (TOF) stimulation every 12 s for 1–2 min] was established, and neuromuscular block was achieved with atracurium 0.6 $mg.kg^{-1}$, followed by tracheal intubation. Following induction, anaesthesia was maintained using oxygen in nitrous oxide along with isoflurane 0.6-1.2%, with atracurium 0.1 $mg.kg^{-1}$ i.v. top ups as indicated by the neuromuscular monitoring (a train of four count of 2 or more every 15 minutes after checking TOF response every 5 min). When there were clinical signs of recovery from muscle relaxation (notch of end tidal CO2 curve, body movement, hiccup), additional atracurium was administered, even though TOF count was 0 or 1. No additional atracurium was administered from 30 min before the end of the surgery and total atracurium doses were recorded.Ventilation was adjusted to maintain normocapnia. Fentanyl 25µg boluses were given intravenously for inadequate analgesia in both the groups. Inadequate analgesia was defined as an increase in mean arterial pressure or heart rate by more than 20% of preanaesthetic values. Heart rate, blood pressure, oxygen saturation and urine output were monitored in all patients intraoperatively and postoperatively at various intervals till 48 hours.

Hypotension defined as 20% decrease of systolic blood pressure compared with preoperative control levels was treated with rapid infusion of intravenous fluids and intravenous ephedrine administered in small increments of 6mg and to a maximum of 30mg. Intravenous atropine was given for bradycardia (heart rate less than 50beats/min). At the end of surgery neostigmine 60$\mu g.kg^{-1}$ and glycopyrolate 10$\mu g.kg^{-1}$ was used to reverse the residual neuromuscular block when TOF count $\geq$ 3 and time was also noted from the last dose of relaxant given. At the same time magnesium sulphate infusion was terminated and a blood sample sent for magnesium levels. Granisetron 40$\mu g.kg^{-1}$i.v. was given as an antiemetic. Postoperative analgesia was given by the nurse incharge PACU in form of boluses of fentanyl 25 µg. Subjects were observed for signs of hypermagnesaemia, including CNS depression, respiratory depression, cardiac arrhythmia, and any other adverse events. Parameters were evaluated by anaesthesiologist not involved in the study after 30 minutes in the post anesthesia care unit. Magnesium levels were checked at 24 hours also.

The primary outcome of the study was intraoperative atracurium consumption and the secondary outcomes monitored were analgesic consumption, effects on urine output, episodes of shivering, nausea and vomiting over a period of 48 hours postoperatively.

Statistical Analysis

The continuous variables were analysed with independent t-test and Wilcoxon-Mann Whitney U- test which belongs to the parametric and non-parametric categories of tests. The categorical variables were analysed with chi-square test. The required sample size is 25 for each group for the study, for 80% power of study and for moderate effect size. All the results were discussed on 5% level of significance i.e, P-value less than 0.05 was considered significant.

Results

The demographic variables like age, weight, height, gender and ASA physical status between two groups were comparable and statistically insignificant (table 1). The mean duration of surgery in group M was 153.8 ±33.33 min and group S was 156±32.14 min with a p-value of 0.813 and the comparison was statistically insignificant.

Comparing the magnesium levels preoperatively, immediate postoperative period and 24 hours postoperatively we found the levels were comparable at preoperative period and 24 hours post surgery. However there was statistically significant increase in magnesium level in group M as compared to group S in immediate postoperative period (Table 2) which returned to normal levels at 24 hours.

The mean consumption of atracurium in group M was 0.35±0.11 $mg.kg^{-1}h^{-1}$ and group S was 0.47±0.19 $mg.kg^{-1}h^{-1}$ with p-value<0.001 and comparison was statistically significant (table 3). The mean urine output in group M was 255.00±7.57 mL and group S was 244.92±7.57 mL with a

p-value of 0.352 and comparison was statistically insignificant. The mean additional doses of i.v. fentanyl given in group M were 0.8±0.57 and group S were 1.5±1.29 with a p-value of 0.014 and the comparison was statistically significant (Table 3).

The mean HR over a period of 48 hours intraoperatively and postoperatively in group M was 82.696±1.161 and group S was 80.012±1.161 with a p-value of 0.109 and the difference was statistically insignificant (Fig. 1). The mean SBP in group M was 119.028±1.068 and group S was 116.008±1.068 with a p-value of 0.051 and the comparison was statistically insignificant (Fig. 2). Similarly the mean DBP in group M was 77.360±0.456 and group S was 79.80±0.456 with a p-value of 0.558 and comparison was statistically insignificant (Fig. 3). The mean oxygen saturation in group M was 98.484±0.118 and group S was 98.632±0.118 with a p-value of 0.380 and the comparison was insignificant (Fig. 4). The mean time from last dose of atracurium to return of TOF to ≥3 in group M was 27±0.59 min and group S was 29±0.49 min and the comparison between two groups was statistically insignificant.

No patient in either group had bradycardia, arrhythmias or respiratory depression. Eight patients in group M and 10 patients in group S had episodes of post operative nausea and vomiting and were comparable. Two patients in group M and 12 patients in group S had episodes of shivering with a p-value of 0.042 and the comparison was statistically significant. Six patients in group M and four patients in group S had episodes of hypotension and were comparable (Table 4).

Discussion

Magnesium has a definitive role in many enzymatic reactions and is involved in regulation of ion channels. It has many applications in anesthesia because of its actions as a NMDA receptor antagonist and a calcium channel blocker.[12] Magnesium has been used in both acute and chronic pain as the involvement of NMDA receptors in pain became evident.[13,14] Studies have shown magnesium to enhance the activity of non-depolarizing neuromuscular blocking agents.[8,9] Our study had the main result that intravenous administration of magnesium sulphate decreased the requirement of atracurium intraoperatively. Secondarily the intraoperative consumption of fentanyl also decreased in the magnesium group. There was no much difference in the hemodynamics and side effects in two groups.

The demographic characteristics and ASA status between two groups were comparable. The duration of surgeries between two groups were comparable and statistically insignificant and hence the duration of magnesium infusion between the two groups was comparable.

The hemodynamic parameters (HR, SBP, DBP) and oxygen saturation (SpO_2) between two groups were comparable at various study intervals and difference was statistically insignificant. Six patients in magnesium group and four patients in saline group had hypotension and were managed as per study protocol (statistically insignificant). No patient in both the groups had cardiac arrhythmias or bradycardia. Tramer Martin R et al[1] also observed non-significant association in the haemodynamic parameters between the two groups. Our study was also in concordance with Hwang JY et al[15] and Hala El-Kerdawy[16] who also found a non-significant association in the hemodynamic parameters between the two groups.

The magnesium levels in the magnesium group were comparable preoperatively and 24 hours postoperatively with the saline group. However in immediate postoperative period the magnesium levels were higher in magnesium group than saline group and were statistically significant but the mean levels were 2.83±0.33 $mg.dL^{-1}$ which were much less than the toxic level of 7 $mg.dL^{-1}$. Our study corresponded with H.S. Na et al[17] and Seyhan et al[2] who also found that the dosage required to decrease anesthetic, analgesic and muscle requirement was much less than the toxic dosage and returned to normal levels in 24 hours postoperatively. A study by Lysakowski C et al[18] found that perioperative magnesium supplementation prevents postoperative hypomagnesaemia.

The mean atracurium consumption in magnesium group is 0.35±0.11 $mg.kg^{-1}h^{-1}$ and saline group is 0.47±0.19 $mg.kg^{-1}h^{-1}$ with a p-value of <0.001 and the difference is statistically significant. The average requirement of atracurium in saline group is more than the magnesium group which shows that intraoperative administration of magnesium sulphate decreases intraoperative atracurium requirement. Magnesium sulphate has been found to increase the speed of onset and potentiates the action of non depolarizing neuromuscular blocking agents.[10,19] Our study corresponds with Seyhan TO et al,[2] Fuchs Buder T et al,[10] H S Na et al[17] and Pinard AM et al[19] who also concluded that intraoperative administration of magnesium sulphate decreased requirement and the total dose of non-depolarizing neuromuscular blocking agents.

The number of average doses of fentanyl required as additional analgesia was 0.8±0.57 in magnesium group and 1.5±1.29 in saline group with a p-value of 0.014 and the difference was statistically significant. This shows magnesium sulphate reduces intraoperative analgesic requirement. This finding was in concordance with studies done by Tramer Martin R et al,[1] Seyhan TO et al,[2] Hwang J Y[15] and Herbert Koinig et al.[20]

The urine output in both the groups was comparable which shows magnesium sulphate at the study protocol dose doesn't affect the renal output. But it should be used with caution in patients with renal disease. Postoperative nausea and vomiting was comparable in both the groups. Postoperative shivering was less in magnesium group as compared to saline group and the difference was statistically significant. Our study was in concordance with Lysakowski C et al[18] who found that intraoperative magnesium supplementation decreased postoperative shivering. H S Na et al[17] found no shivering in their patients.

Limitations

Magnesium sulphate has been also found to decrease anesthetic and analgesic requirements but we maintained anesthesia with isoflurane similarly for both the groups and we didn't studied that narrative. Apart from TOF count of two or more we also administered muscle relaxant for hiccups, capnography notches and patient movement which was not monitored with respect to anesthetic depth by bispectral index (BIS) monitoring which may have added to bias. Different types of abdominal surgeries were included in the study which might have different muscle relaxant requirements.

Conclusion

Magnesium sulphate 50 $mg.kg^{-1}$ bolus and $15mg.kg^{-1}h^{-1}$ by continuous infusion given intravenously reduces the intraoperative atracurium requirements in abdominal surgeries under general anesthesia. It is also found to decrease intraoperative fentanyl consumption and postoperative shivering.

Conflicts of Interest: There are no conflicts of interest.

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