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Effects of Intravenous Injection of Magnesium Sulfate on Post Operative Analgesia in Patients Undergoing Lower Limb Orthopaedic Surgery Under Spinal Anaesthesia: A Randomised Double-Blind Indian Study

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ABSTRACT
Published evidence have shown the utility of magnesium (Mg) infusion during general anaesthesia, but the effects of magnesium sulphate (MgSO4) infusion during spinal anaesthesia have been seldom evaluated. Present study was undertaken to study the effectiveness of intravenous injection of MgSO4 on postoperative analgesia in patients undergoing lower limb orthopaedic surgery under spinal anaesthesia. A comparative, double-blind study was conducted by department of anaesthesiology at Vilasrao Deshmukh Government Medical College Hospital in Latur city (Maharashtra state of India). Patients undergoing lower limb orthopaedic surgery (ASA I and II) under spinal anaesthesia were screened for study inclusion between January 2021 and November 2022. Group A received injection MgSO4 8mg/kg/hour in 500 ml ringer lactate intravenously; and group B received same volume of placebo (0.9%Normal saline). Sensory block and motor block assessment was done along with post-operative pain evaluation. 30 patients were enrolled in each group. Majority patients in group A (56.67%) and group B (63.33%) were males, with comparable age and duration of surgery ($p>0.05$). Durations for anaesthesia, analgesia, sensory blockade and motor blockade were all significantly higher in Group A versus Group B ($p<0.05$). Mean VAS pain scores from 1-12 hours post-surgery were significantly lower in Group A versus Group B ($p<0.05$). Both, sensory and motor blockade were sustained to a significantly greater extent in group A between 4 hours to 8 hours post-surgery ($p<0.05$). Safety was comparable between study groups ($p>0.05$). Duration of sensory and motor blockade was significantly increased by intravenous MgSO4 in patients undergoing lower limb orthopaedic surgery under spinal anaesthesia. The requirement of rescue analgesia was also reduced with MgSO4, with comparable safety to placebo.

INTRODUCTION

Taxonomy Committee of International Association for the study of pain (IASP) defines pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage[1]. Severe acute pain causes sympathetic nervous system mediated increase in heart rate, blood pressure, systemic and coronary vascular resistances and cardiac output, which may lead to myocardial ischemia, infarction and cardiac failure[2]. These effects are even more deleterious in post-operative patients who are already in a compromised and vulnerable state. Thus, it not only prudent, but critical, to minimize post-operative pain.2 The fundamental of regional anesthesia is pharmacologically interrupting transmission of sensation in the specific nerve fiber. The sensory signals generated by tissue damage trigger a state of increased excitability, leading to prolonged post-operative pain or sensitization to such pain. The optimal pain treatment pre-empts the establishment of pain hypersensitivity during and after surgery by minimizing the patient discomfort while leaving physiologic nociceptive mechanisms intact so as to function as an early warning symptom[3,4].

Spinal anesthesia is an established mode of anesthesia for lower limb orthopedic surgeries because of its simplicity, ease of administration and absence of side-effects of general anesthesia. The limitations of the technique are short duration of action and limited postoperative analgesia. Additives to local anesthetic agent's solutions increases the duration of the spinal block and modulate post-operative analgesia[5]. Magnesium (Mg) is the fourth common cation in the body. Anti-nociceptive effects of Mg are due to regulation of calcium influx into the cell and antagonism of the N-methyl D-aspartate NMDA receptors. Numerous clinical investigations have demonstrated that Mg infusion during general anesthesia reduced anesthetic requirement and post-operative analgesic consumption[6,7]. The addition of intrathecal Mg to bupivacaine prolonged the time of two segment regression of spinal block height but did not affect maximum sensory level or the time to reach the highest level of sensory block[8,9].

Many clinical studies have demonstrated that intravenous Mg infusion during general anesthesia reduced anesthetic requirement and postoperative analgesic consumption[10-14]. Relatively few studies have been investigated on the effects of magnesium sulphate (MgSO4) infusion during spinal anesthesia[15,16]. Literature search revealed a lack of Indian published data evaluating the effect of Mg infusion during spinal anesthesia on postoperative analgesia and duration of spinal block. Hence, the present study was undertaken with the objective of studying the effectiveness of intravenous injection of MgSO4 on postoperative analgesia in patients undergoing lower limb orthopedic surgery under spinal anesthesia.

MATERIALS AND METHODS

A comparative, double blind study was conducted by department of anesthesiology at Vilasrao Deshmukh Government Medical College Hospital in Latur city (Maharashtra state of India). Patients undergoing lower limb orthopedic surgery (ASA I and II) under spinal anesthesia were screened for study inclusion between January 2021 and November 2022. Patients with history of bleeding disorders, patients who abused or illicitly used controlled drugs or substances, patients having severe systemic illness, or those allergic to magnesium sulphate were excluded from study. The enrolled patients were divided into two study groups by simple randomization technique: group A who received injection MgSO4 8mg/kg/hour in 500ml ringer lactate using syringe pump intravenously; and group B who received same volume of placebo (0.9%Normal saline) by same method. Patients received either MgSO4 or placebo after regional anesthesia but before incision and continued till the end of the surgery.

Outcome Assessment: A detailed pre-anesthetic checkup of patients selected for study was carried out a day before surgery and was recorded as per proforma. Relevant and required investigations were performed prior to surgery. The monitoring of patients included oxygen saturation, systolic and diastolic blood pressure (SBP, DBP), respiratory rate (RR), sensory and motor level of anesthesia and duration of analgesia. Data was collected every 3 mins for the first 15 mins, next every 5 mins for 15 mins and after completion of surgery sensory and motor blockade was assessed every 30 mins till complete recovery of blockade. Sensory block assessment was done by pin prick method, wherein patients who experienced sharp pin prick sensation were considered under grade 0 while those with no sensation under grade 2. Motor block assessment was determined by determined according to modified Bromage scale of lower extremity, wherein grade 0 indicated no paralysis while grade 3 indicated complete block. Time of onset of analgesia, time of onset sensory motor blockade, duration of sensory and motor blockade was also noted. The interpretation of post-operative pain was done by visual linear analogue scale, which was explained one day prior to surgery to the selected patient taken for study, to determine the analgesia in postoperative period.

Statistical Analysis: Sample size was calculated based on findings in study by Singhal *et al*[17]. The mean time

of first rescue analgesic requirement in Group I (cases) was 144.00±29.90 mins, while that in Group II (controls) was 246.00±88.22 mins. Considering power of study as 90% and alpha error as 1%, the minimum sample size calculated per study group was around[15]. Data was collected by using a structure proforma. Data was entered into the Microsoft excel sheet and analyzed by using Statistical Package for the Social Sciences (SPSS) 24.0 version IBM USA. Qualitative data was expressed in terms of proportions. Quantitative data was expressed in terms of Mean and Standard deviation. Association between two qualitative variables was seen by using Chi square/ Fischer's exact test. Comparison of mean and SD between two groups was done by using unpaired t test. Descriptive statistics of each variable were presented in terms of Mean, standard deviation, standard error of mean. A p<0.05 was considered as statistically significant.

RESULTS AND DISCUSSIONS

Demographic and baseline details A total of 60 patients (30 patients in each group) fulfilling inclusion criteria were enrolled. The age and gender distribution were comparable between group A and group B (p>0.05). Majority of patients in group A (56.67%) and group B (63.33%) were males. The mean height and weight were also statistically comparable between groups (p>0.05). Complete demographic and baseline patient details are mentioned in (Table 1). p>0.05 considered not significant using unpaired t-test. ^p>0.05 considered not significant using chi-square test. Duration of anaesthesia, analgesia, sensory and motor blockade The duration of surgery in both the study groups were statistically comparable (126.93±16.96 mins in Group A versus 119.00±10.62 mins in Group B, p = 0.09). The durations for anesthesia, analgesia, sensory blockade and motor blockade were all noted to be significantly higher in Group A versus Group B (p<0.05) (Table 2).

Comparison of pain VAS scores between groups: The mean VAS scores were comparable between the study groups from pre-operative time-point to 30 mins post-operatively (p>0.05). However, from 1-12 hours post-op, the mean VAS scores for pain were significantly lower in Group A versus Group B (p<0.05) (Table 3).

Comparison of Sensory Block and Motor Block Grades Between Study Groups: The mean grades for sensory blockade were comparable statistically between group A and group B till post-op 1 hour, however the sensory blockade was sustained to a significantly greater extent in group A between 4 hours to 8 hours post-surgery (p<0.05) (Table 4). A similar finding was noted in terms of motor blockade, with the blockade being sustained to a significantly greater extent in group A between 2 hours to 8 hours post-surgery (p<0.05) (Table 5). 6 patients in Group A (20%) while all patients in Group B (100%) required rescue analgesia which was a significant finding (p<0.05).

Complications Noted in Study Groups: Seven patients (23.33%) in Group A and 8 patients (26.67%) in Group B experienced bradycardia. Nine patients (30%) in each study group experienced hypotension. Two patients (6.67%) in Group A complained of headache, while 3 patients (10%) experienced nausea or vomiting. Overall, the safety was comparable between study groups (p>0.05). The mean age in the MgSO4 group (group A) was noted to be 42.00±12.90 years, while it was 43.87±12.51 years in the control group. Overall, 56.67% cases in group A were males, while 43.33% were females. On the other hand, 63.33% cases in group B were males, while 36.67% were females. Overall, the demographic details were comparable between the study groups. In the similar study by Dabbagh *et al*.,[18] the mean age of cases in the MgSO4 group was noted to be 33.7±9.6 years, while the control group had a mean age of 35.1±7.7 years. Females were 70% in MgSO4 group and 80% in the control group. In the study by Abdulatif *et al*.[19] the mean age of cases in the intravenous MgSO4 group was noted to be 34.4±8.3 years, while the control group had a mean age of 35±10.4 years. Males were 76.92% in intravenous MgSO4 group and 74.07% in the control group. Just like our study, the baseline details were comparable between study groups in other identical studies.

In present study, the anaesthesia was more sustained in the group which received MgSO4, versus placebo. Similarly, sensory as well as motor blockade was sustained in the longer way by MgSO4. Sensory blockade was sustained to a significantly greater extent in group A between 4-8 hours post-surgery (p<0.05), while motor blockade was sustained to a significantly greater extent in group A between 2-8 hours post-surgery (p<0.05). In the study by Shal *et al*.20 no difference in the quality of sensory and motor block before and during surgery was noted between MgSO4 and control groups (the pneumatic tourniquet inflated after epidural anaesthesia when sensory level fixed at T10 and Bromage score of 3). There was no statistically significant difference between both groups for their mean time required to achieve complete sensory block up to the level of T-10 (10.59±2.87 min in Mg group versus 10.47±2.93 min in the control group) and time of motor block to Bromage Score-3 (19.39±2.87 min in Mg group versus 20.45±2.34 min in control group) (p>0.05). In our study, time to rescue analgesia was significantly greater in MgSO4 group and the mean VAS score was noted to be significantly lower in the

Table 1: Demographic and baseline details of study groups

	Group A	Group B	P-Value
Age details			
Mean Age (Years)	42.00±12.90	43.87±12.51	0.19*
Median Age with range (Years)	39 (22-62)	45.5 (20-64)	-
Gender distribution			
Number of Males	17 (56.67%)	19 (63.33%)	0.79^
Number of Female	13 (43.33%)	11 (36.67%)	
Height details			
Mean height (cm)	168.10±7.99	166.73±4.31	0.41*
Median height with range (cm)	169 (150-182)	168 (158-176)	-
Weight details			
Mean weight (kg)	65.97±7.83	66.90±6.96	0.62*
Median weight with range (kg)	68 (46-86)	68 (52-76)	-

Table 2: Comparison of durations of anaesthesia, analgesia, sensory and motor blockade between study groups

Characteristics	Group A	Group B	p-value
Mean duration of anaesthesia (mins)	181.40±6.30	143.5±4.18	<0.001*
Mean duration to rescue analgesia (hours)	5.73±0.64	1.63±0.85	<0.001*
Mean duration of sensory blockade (mins)	275.17±18.59	191.83±11.18	<0.001*
Mean duration of motor blockade (mins)	412.33±26.09	300.00±12.59	<0.001*

*P-Value <0.05 considered significant using unpaired t-test.

Table 3: Comparison of VAS scores for pain post-operatively

Characteristics	Group A	Group B	p-value
Pre-operative	0.00±0.00	0.00±0.00	1
Post-op (PO) 1 min	0.00±0.00	0.00±0.00	1
PO 5 min	0.00±0.00	0.00±0.00	1
PO 10 min	0.00±0.00	0.00±0.00	1
PO 15 min	0.00±0.00	0.00±0.00	1
PO 30 min	0.00±0.00	0.00±0.00	1
PO 1 hour	0.00±0.00	1.47±0.51	<0.001*
PO 2 hours	0.00±0.00	5.27±0.83	<0.001*
PO 4 hours	1.27±0.78	8.23±0.63	<0.001*
PO 8 hours	3.47±0.97	8.67±0.48	<0.001*
PO 12 hours	7.33±1.03	8.30±0.47	<0.001*

*P-Value <0.05 considered significant using unpaired t-test.

Table 4: Comparison of mean grades for sensory block post-operatively between groups

Characteristics	Group A	Group B	p-value
Pre-operative	0.00±0.00	0.00±0.00	1
PO 1 min	2.00±0.00	2.00±0.00	1
PO 5 min	2.00±0.00	2.00±0.00	1
PO 10 min	2.00±0.00	2.00±0.00	1
PO 15 min	2.00±0.00	2.00±0.00	1
PO 30 min	2.00±0.00	2.00±0.00	1
PO 1 hour	0.00±0.00	0.10±0.31	0.08
PO 2 hours	0.13±0.35	0.67±0.48	<0.001*
PO 4 hours	1.77±0.43	0.10±0.31	<0.001*
PO 8 hours	0.60±0.97	0.00±0.00	<0.001*
PO 12 hours	0.00±0.00	0.00±0.00	1

*p-value <0.05 considered significant using unpaired t-test.

Table 5: Comparison of mean grades for motor block post-operatively between groups

Characteristics	Group A	Group B	p-value
Pre-operative	0.00±0.00	0.00±0.00	1
PO 1 min	3.00±0.00	3.00±0.00	1
PO 5 min	3.00±0.00	3.00±0.00	1
PO 10 min	3.00±0.00	3.00±0.00	1
PO 15 min	3.00±0.00	3.00±0.00	1
PO 30 min	3.00±0.00	3.00±0.00	1
PO 1 hour	2.87±0.35	2.80±0.41	0.49
PO 2 hours	2.60±0.50	2.07±0.25	<0.001*
PO 4 hours	1.77±0.43	0.20±0.41	<0.001*
PO 8 hours	0.10±0.97	0.00±0.00	0.08
PO 12 hours	0.00±0.00	0.00±0.00	1

*p-value <0.05 considered significant using unpaired t-test.

magnesium sulphate group at post-operative 1 hour to post-operative 12 hours versus placebo group (p<0.05). Significantly lower patients in MgSO4 group required rescue analgesia versus placebo (p<0.05). In the study by Dabaggh *et al*.,[18] pain reported by the first group that received MgSO4 was significantly less at the 1st, 3rd, 6th and 12th hours after the operation in comparison with the group that received placebo. The findings of the study demonstrated a beneficial effect for MgSO4 in patients undergoing spinal anaesthesia with bupivacaine, which had a complementary effect over the analgesic effects of residual intrathecal bupivacaine in the early post-operative period. The same study also mentioned that the N-methyl

D-aspartate (NMDA) receptor is a major affecting site for the effects of Mg. Mg is an antagonist of the NMDA receptor, acting as a non-competitive antagonist, blocking ion channels in a voltage-dependent fashion. In the study by Abdul-atif *et al*.,[19] pain scores were significantly greater in the control group starting from 6 hours to 24 hours in comparison to the intravenous MgSO4 group. The use of intravenous MgSO4 was associated with significant ($p<0.01$) prolongation of the time to first request to postoperative rescue analgesic [11.6 (4.5) hours] and [7.5 (3.6) hours] respectively as compared to [5.2 (2.3) hours] in the placebo group. In the study by Shal *et al*.,[20] in the post-operative period, Mg group patients had significantly lower VAS scores after 1, 2, 4, 8, and 12 h ($p< 0.001$). After 18 and 24 h VAS scores were comparable. Time to first request of postoperative analgesia was significantly longer in Mg group compared to control group (243±20 min vs 150±22 min) ($p<0.001$).

In our study, MgSO4 showed statistically comparable adverse effects versus placebo group, indicating adequate safety profile. None of the patients in either of the study groups developed pruritis or reduction in oxygen saturation. The findings have been echoed previously in other similar studies by Dabaggh *et al*., Abdul atif *et al*. and Shal *et al*[18,20]. The study had a few limitations. The sample size was less and the study was conducted at only one hospital. Hence, the generalisation of the findings to Indian population needs to be done with caution. Additionally, the long-term outcomes or effects of MgSO4 in patients were not evaluated.

CONCLUSIONS

The total duration of anaesthesia, duration of sensory as well as motor blockades were significantly increased by Intravenous MgSO4 in patients undergoing lower limb orthopaedic surgery under spinal anaesthesia. Only one-fifth of the patients administered MgSO4 required rescue analgesia, compared to the other group wherein all patients required rescue analgesia. MgSO4 administration was also found to have comparable safety to placebo.

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