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Research Article

Effect of IV Infusion of Magnesium Sulfate on Postoperative Pain after Spinal Anesthesia: A Prospective Randomized Trial

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ABSTRACT

Background: The current study attempts to evaluate the effect of intravenous (IV) infusion of magnesium sulfate during spinal anesthesia on postoperative pain and postoperative analgesic requirements in lower limb surgeries.
Methods: In this double blind, randomized controlled study, 60 patients undergoing elective lower limb surgeries, were selected and randomly divided into two groups. Group I received isotonic saline and group II was administered magnesium sulfate 50 mg Kg-1 IV for 15 min and then 15 mg Kg-1 h-1 by continuous IV infusion till the end of surgery or 2 hours, whichever was earlier. Ramsay sedation scores, visual analog scale (VAS) scores for pain, time of first administration of rescue analgesic and total analgesic requirement were noted in both the groups.
Results: Statistically significant difference was observed in the VAS score between the two groups at 1st, 2nd, 3rd, 6th, 9th and 12th hour intervals; with VAS scores being lower in the magnesium group ($p<0.05$). The mean time of first rescue analgesic requirement in control group was 144.00 mins, while in magnesium group was 246.00 mins ($p<0.05$). The total rescue analgesic requirement was found to be 251.67 mg and 181.67 mg at the end of 24 hours, in control and magnesium groups, respectively ($p<0.05$).
Conclusion: This study demonstrates statistically significant lowering of postoperative VAS scores, delayed need of postoperative analgesia and reduced total postoperative analgesic requirement in patients receiving intraoperative IV magnesium sulfate compared to the control group. Magnesium sulfate did not cause sedation or any other significant adverse effect in the doses used in the study.

The 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's not only prudent, but critical, to minimize post-operative pain.

Neuraxial blockade is the preferred mode of anesthesia for lower limb surgeries because of its rapid onset, superior blockade, excellent pain control, less failure rates and cost effectiveness. However, this pain relief is usually short-lived because of the relatively brief duration of action of currently available local anesthetics (LA) [3], resulting in resolution of block before the period of worst postoperative pain [4]. Increasing the volume (dose) of LAs prolongs the duration of analgesia [5], but also increases the risk of systemic LA toxicity [6]. Continuous catheter-based nerve blocks can extend postoperative analgesia, but their placement requires additional time, cost, and skill.

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Intrathecal adjuvants, like opioids, may be used to extend the duration of LA mediated blocks. However, the use of opioids is associated with increased incidence of postoperative complications such as respiratory depression, sedation, postoperative nausea & vomiting, ileus and urinary retention [7]. These adverse effects can delay recovery and discharge from hospital. Thus, the advent of day care surgeries has led to renewed interest in non-opioid adjuvants, like magnesium.

Numerous clinical studies have demonstrated that magnesium infusion during general anesthesia reduces anesthetic requirement and post-operative analgesic consumption [8-11], whereas others suggest that magnesium has no effect on postoperative pain [12-13]. Relatively few studies have tried to explore the effects of intravenous (IV) magnesium sulfate during spinal anesthesia. Hence, aim of the current study is to evaluate the effect of IV infusion of magnesium sulfate during spinal anesthesia on postoperative pain and postoperative analgesic requirements in lower limb surgeries.

Methods

This double-blind, randomized controlled comparative study was conducted at our institute in sixty adult patients of either sex, undergoing elective lower limb surgeries under spinal anesthesia. The study was planned in accordance with the Declaration of Helsinki. Ethical clearance for conducting the study was obtained from the institutional academics & ethical research committee. A written, informed consent was obtained from all the selected patients.

Postoperative rescue analgesic consumption was used to calculate the statistical power. With reference to a previous study conducted by Dabbagh et al [14], it was found that the mean analgesic consumption in control group was 9.8 ± 2.1 mg of IV morphine sulfate. Assuming the same estimated sample size, it was indicated that 30 patients per group will give a β risk of 90% at an α level of 0.05 for detecting a reduction of 20% in analgesic consumption for patients in the study group.

American society of anesthesiologists (ASA) grade I and II patients, in age group of 18 - 60 years, undergoing elective lower limb surgery under spinal anesthesia were included in the study. Exclusion criteria included patients with renal, hepatic, neuromuscular or cardiovascular dysfunction, those on angiotensin receptor or calcium channel blockers, body mass index (BMI) > 40 Kg m-2, any contraindication for spinal anesthesia, known allergy to the study drug, history of opioid or analgesic abuse, pregnant and lactating females and failure of spinal block.

The selected patients were randomly divided into 2 groups of 30 patients each using computer generated randomization. Group I received isotonic saline by continuous IV infusion till the end of surgery or 2 hours, whichever was earlier. While group II was administered magnesium sulfate 50 mg Kg-1 IV for 15 min and then 15 mg Kg-1 h-1 by continuous IV infusion till the end of surgery or 2 hours, whichever was earlier.

On the morning of surgery, the patients were evaluated, nil by mouth status was confirmed and a written, informed consent was taken. At this point, one of the researchers allocated the patient to one of the two groups after matching the serial number of that patient with the computer-generated random numbers. Based on the allocated group, the researcher then prepared magnesium or saline solution and labelled the same with only the name of the patient. These syringes containing drug/saline solutions were then handed over to the other researcher who was involved with the intraoperative proceedings and subsequent data collection. The first researcher was blind towards the collected data, while the second researcher was blind towards the contents of the syringes.

In the previous studies, it was seen that the patients receiving magnesium sulfate intraoperatively had higher serum magnesium levels than those receiving isotonic saline but no adverse effects were noted [15-16].

Likewise, the dose of IV magnesium sulfate to be given in this study was unlikely to cause any adverse effects. Thus, it was safely assumed that there will be no need for serum magnesium monitoring in the patients involved in this study.

Inside the operation theatre, two dedicated IV lines were secured, one for bolus and continuous infusion of magnesium sulfate or isotonic saline and second for IV replacement fluids and administration of all other drugs. The monitors; including pulse oximetry, ECG and noninvasive blood pressure, were connected to the patient. After preloading with 10 ml Kg-1 of Ringer's Lactate solution IV over 15 min and with the patient in sitting position, lumbar puncture was performed at L3-4 or L4-5 level, through midline approach, using a 25-gauge Quincke's spinal needle. After the dural puncture, hyperbaric Bupivacaine 0.5% solution with Fentanyl 20 mcg was injected intrathecally. The dose of Bupivacaine was determined based on the height of the patient (height<155 cm = 12 mg; 155 – 170 cm = 13 mg; 170 – 180 cm= 14 mg; ≥180 cm = 15 mg). Intraoperative sedation scores (Ramsay Sedation Scale) were recorded just before the initiation of surgery and thereafter every 15 minutes during the surgery.

After completion of the procedure, patients were shifted to the post anaesthetic care unit (PACU) and the intensity of postoperative pain was assessed using visual analogue scale (VAS). The assessment was done after 1, 2, 3, 6, 9, 12, 18 and 24 hours. If VAS was > 3 on assessment or if the patient complained of pain at any point of time, injection Tramadol 50 mg in 9 cc normal

saline (slow IV) along with injection Ondansetron 4 mg IV was given. Time of administration of rescue analgesia and total tramadol requirement was recorded for both the groups. Any incidence of postoperative nausea, vomiting, or any other adverse effects was also recorded.

The collected data is presented using mean (with standard deviation) for quantitative variables. Categorical variables are presented in frequencies along with respective percentages. The statistical comparisons for quantitative variables are done by using Student's 't' test for two independent groups. For categorical variables Chi-square test is used. Data was entered and coded in MS Excel (Version, 2013) and all statistical analyses were performed by using SPSS software (Version 22, SPSS Inc, Chicago, IL, USA). P value less than 0.05 is considered statistically significant.

Results

Sixty-four patients were assessed for eligibility during the study. Four of them did not meet the inclusion criteria and were excluded. Rest of the 60 patients were randomized into two groups of 30 patients each. The consolidated standards of reporting trials (CONSORT) flow diagram is depicted in (Figure 1).

There was no statistically significant difference between the two groups with respect to ASA classification, sex distribution, age, weight, height, BMI or duration of surgery (Table 1), rendering the two groups comparable.

No statistically significant difference was observed in the Ramsay sedation scores between the two groups (Figure 2) indicating that magnesium sulfate did not cause any statistically significant sedation at the doses used in the study. Statistically significant difference was observed in the VAS scoring between the two groups at 1st, 2nd, 3rd, 6th, 9th and 12th hour intervals; with VAS scores being lower in the Group II (Figure 3). The mean time of first rescue analgesic requirement in Group I was 144.00 ± 29.90 mins, while that in Group II was 246.00± 88.22 mins. The difference between the two groups was found to be statistically significant with p value < 0.05 (Figure 4). The requirement of rescue analgesic between the two groups was calculated and was found to be lower in Group II. The result was statistically significant at the end of 2^{nd}, 3^{rd}, 6^{th}, 9^{th}, 12^{th}, 18^{th} and 24^{th} hour. The total rescue analgesic requirement was found to be 251.67 ± 20.69 mg and 181.67 ± 24.51 mg at the end of 24 hours, Group I and Group II, respectively. The difference was statistically significant with p value < 0.05 (Figure 5).

Table 1- Comparison of baseline characteristics between the groups

Variable	**Group I**		**Group II**		**P value**
	Mean	**SD**	**Mean**	**SD**	
Age (Years)	39.93	12.14	36.73	13.26	0.334
Weight (kg)	65.80	3.63	68.53	5.48	0.067
Height (cm)	161.97	6.52	162.40	5.86	0.788
BMI (Kgm^2)	25.12	1.40	26.06	2.69	0.094
Duration of Surgery (min)	89.60	21.43	89.87	21.13	0.961
	n	**%**	**n**	**%**	
ASA Class					
Class I	16	53.30	19	63.30	0.432
Class II	14	46.70	11	36.70	
Sex					
Female	13	43.30	11	36.70	0.598
Male	17	56.70	19	63.30	

(SD: Standard deviation, min: Minutes, n: Frequency, %: Percentage)

Figure 1- Demographic information of patients

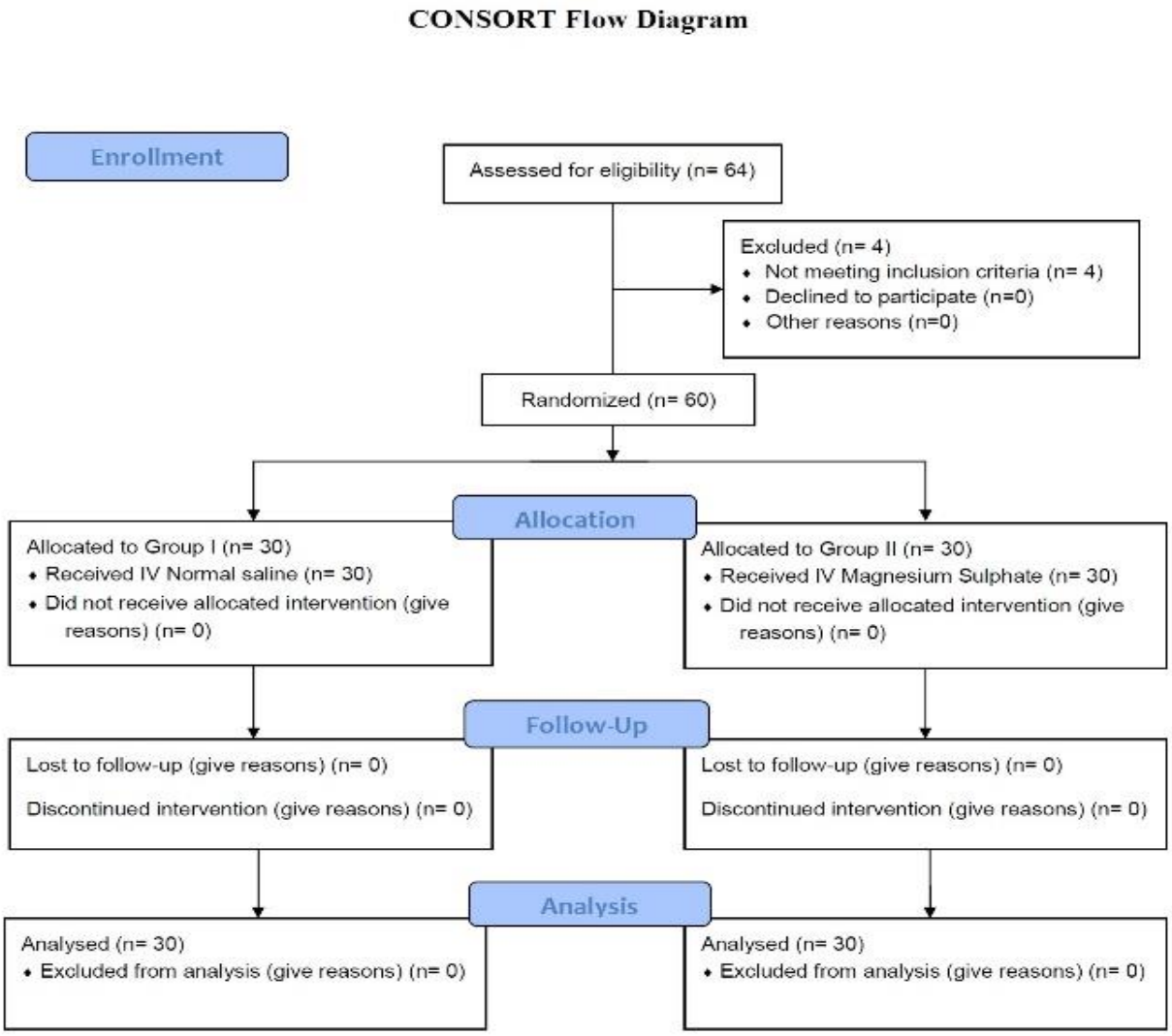
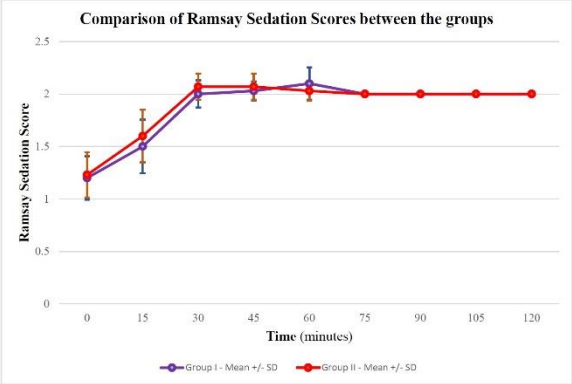
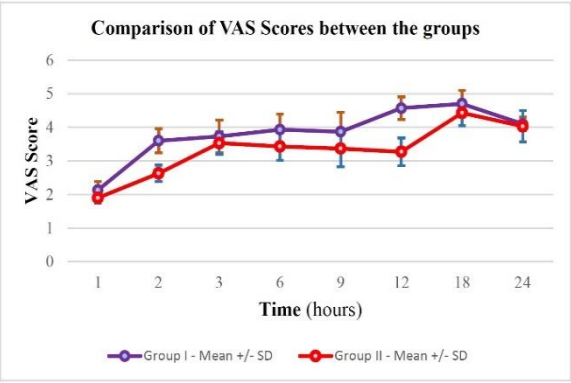


Figure 2- Comparison of Ramsay sedation scores between the groups



(SD: Standard deviation)

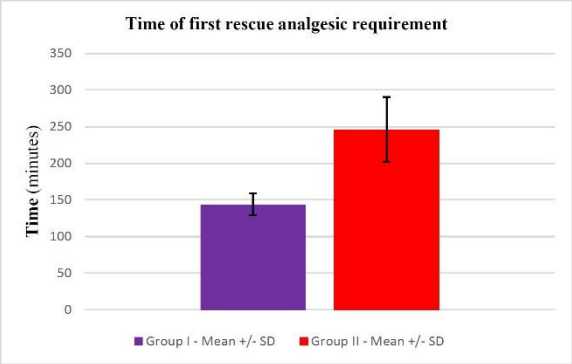
Figure 3- Comparison of VAS score between the groups



(SD: Standard deviation)

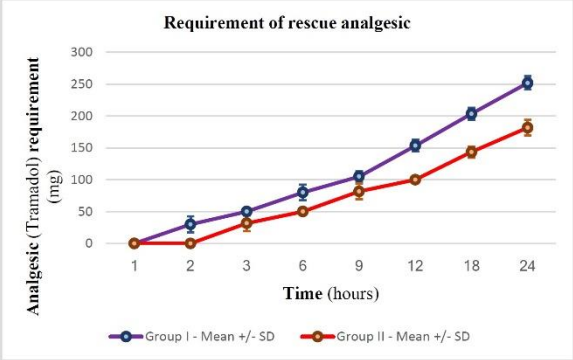
No adverse effects were seen in either of the groups.

Figure 4- Time of administration of first rescue analgesic in the groups



(SD: Standard deviation)

Figure 5- Comparison of requirement of rescue analgesics between the groups



(SD: Standard deviation)

Discussion

Multimodal or "balanced" analgesia regimes that use non-opioid analgesics (viz. local anesthetics, non-steroidal anti-inflammatory drugs, acetaminophen, ketamine, N-methyl-D-Aspartate receptor antagonists etc.) to supplement opioid analgesics have become a part of modern anesthesia practice. The opioid-sparing effect of these compounds reduces nausea, vomiting, constipation, urinary retention, respiratory depression and sedation leading to an improved quality of recovery for surgical patients [17].

The recent finding that sensory signals generated by cellular injury during surgery can trigger a prolonged state of hyperexcitability in the central nervous system has led to a renewed interest in N-methyl-D-Aspartate (NMDA) receptor antagonists [18]. These agents not only prevent the development of central sensitization but also eliminate hypersensitivity after its onset [19]. Magnesium, an NMDA receptor antagonist, also has antinociceptive effects in animal and human models of chronic pain [20]. These effects are primarily based on regulation of calcium influx into the cell, i.e., natural physiological calcium antagonism [21] and antagonism of NMDA receptor [22].

In a study conducted by Agrawal A et al [23], need for first analgesic requirement presented after 262.88 ± 21.11 min in Group M (Magnesium) and 193.25 ± 17.74 min in Group S (Saline) ($p < 0.001$). In the present study similar results are obtained, with the time of first rescue analgesic requirement in Group II (Magnesium) being 246 ± 88.2 mins, while that in Group I (control) being 144 ± 29.90 mins. Agrawal A et al also reported that the mean dosage of tramadol needed in first 24 hours was less in group M compared to group S (190 ± 30.38 mg versus 265 ± 48.30 mg, $P = 0.000$). Likewise, in the current study the total rescue analgesic requirement is found to be 251.67± 20.69 mg and 181.67 ± 24.51 mg at the end of 24 hours, in Control and Magnesium groups, respectively (p value< 0.000).

Hwang et al [15] reported markedly lower postoperative VAS scores in group M (Magnesium) at 4th, 24th and 48th hour after surgery whereas in the current study statistically significant lowering of VAS scores in magnesium group is seen at 1st, 2nd, 3rd, 6th, 9th and 12th hour intervals. This difference could be explained by the fact that the time intervals for observation of parameters chosen by Hwang et al were 30 min, 4, 24 and 48 hours. Had they observed VAS scores in between the set intervals, they might have found significant differences, as were found in the current study. The total rescue analgesic requirement was significantly lower in the magnesium group in both the studies.

The results of the current study are consistent with that conducted by Dabbagh A et al [14]. Their study concluded that pain in the magnesium sulfate group was significantly less at the first, third, sixth and twelfth hours after the surgery, in comparison with the control group. The IV morphine consumption in the first 24 hours after the procedure was also less in the magnesium group (4.2± 1.6 mg) than in the Control group (9.8 ± 2.1 mg).

Kumar M et al. [24] concluded that the first rescue analgesic was required after 334 ± 202 min in Magnesium group and after 233 ± 141 min in Control group. Whereas in the current study the mean time of first rescue analgesic requirement in Group I is 144 ± 29.90 mins and in Group II is 246 ± 88.2 mins. This disparity could be due to difference in the duration of magnesium infusion. The magnesium sulfate infusion was continued for 12 hours in the said study compared to 2 hours or the end of surgery (whichever was earlier) in the present study. Kumar M et al also reported reduced morphine requirement over 24 hours in the Magnesium group (3.99± 1.25 mg) compared to Control group (7.13 ± 2.68 mg) ($P < 0.000$). This observation is consistent with the current study.

Olapour A et al [25], in their study concluded that the postoperative pain scores were significantly lower in Magnesium group at 2nd, 3rd, 4th and 6th hour interval after surgery (P< 0.05). Total postoperative meperidine consumption after 24 hours was also significantly lower in Magnesium group (17.6 ± 8.09 mg) than in Control group (37.5 ± 7.3 mg) (P< 0.05). Both of these observations agree with the current study.

In a study conducted by Tramer and Glynn [26], 200 patients posted for ilioinguinal hernia repair or varicose vein procedure under general anesthesia were randomized to either receive magnesium sulfate 4 g IV or normal saline after induction. These patients were administered diclofenac 100 mg rectally in the preoperative period. And patients undergoing hernia repairs were also administered ilioinguinal-iliohypogastric nerve block after completion of the procedure. A questionnaire was used to assess pain, analgesic consumption and adverse effects in the postoperative period. It was concluded that pre-treatment with IV magnesium sulfate 4 g had no effect on postoperative pain and analgesic consumption. This is in contrast to the results of the current study. A possible explanation could be that in their study Tramer and Glynn, used only a single bolus dose of magnesium sulfate and not a continuous I.V infusion.

Conclusion

The current study demonstrates significantly lower postoperative VAS scores, delayed need of postoperative analgesia and reduced total postoperative analgesic requirement in patients receiving intraoperative IV magnesium sulfate compared to the control group. Magnesium sulfate did not cause sedation or any other significant adverse effect in the doses used in the current study.

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