

Effect of Intervenus Magnesium Sulfate on Decreasing Opioid Requirement after Surgery of the Lower Limb Fracture by Spinal Anesthesia

Abstract

Background: Magnesium is the calcium natural physiological antagonist; it also antagonizes N-Methyl-D-aspartate receptors, therefore, providing antinociceptive properties. The reason for effective role of treatment with magnesium on decreasing opioid usage, less dissatisfaction, and good sleep quality is proposed theoretically yet. This study aimed to evaluate the effect of magnesium sulfate on decreasing opioids requirement after surgery of the lower limbs fracture by spinal anesthesia. **Methods:** A total of 60 patients aged from 45 to 75 years with the lower limb fractures (femur and hip) candidate for surgery by spinal anesthesia. In a randomized double-blind method, patients were divided into two groups as Magnesium Group (M) and Control Group (C). Group M received a bolus of 5 mg/kg magnesium sulfate plus (250 CC) normal saline and Group C received (250 CC) normal saline in the same condition. **Results:** Pain score and the physical dissatisfaction were reduced at 12, 24, and 48 h after surgery in Group M as compared with Group C ($P = 0.000$). Total opioid requirement at the end of 48 h and at the first 24 h after surgery were reduced in Group M as compared with Group C ($P = 0.001$). The endurance of spinal block was increased in Group M as compared with Group C ($P = 0.000$). **Conclusions:** A low dose of magnesium sulfate reduced the pain score, opioid requirement, and physical dissatisfaction while increased endurance of spinal block.

Keywords: Analgesia, anesthesia, lower extremity, magnesium sulfate, spine

Introduction

Postoperative pain may cause to an acute or chronic detrimental effects. Pathophysiology demoralization of pain before surgery can result to decrease pain complications through reducing the nociceptive receptors and also improve immediately after surgery and hospital discharge.

Postoperative pain is associated with a series of different pathophysiological responses. Although these responses may include beneficial purpose, they can have detrimental effects associated with surgery. Noncontrolled preoperative pain can reinforce pathophysiological responses. On the other hand, this may increase morbidity, mortality, and other complications. The purpose of postoperative anesthesia is reaching to patients' satisfactory and prevents nociceptive activity following trauma.^[1]

Ketamine and magnesium are two N-Methyl-D-aspartate (NMDA) receptor

antagonists that participate in neuroplasticity reactions in a non-compromised manner with a voltage-dependent mechanism. Increasing magnesium leads to reduced NMDA receptor-dependent neural conductivity and conversely, the reduction of magnesium results in the activation and transfer of the NMDA receptors.^[2]

Effect of intervenous magnesium sulfate on postoperative pain is evaluated recently in most studies such as in a study by Frassanito *et al.* about intervenous infusion of magnesium sulfate and postoperative analgesia in total knee arthroplasty;^[3] in a study by Kumar *et al.* about effect of intervenous magnesium sulfate on postoperative pain following spinal anesthesia;^[4] in a study by Kiran *et al.* about evaluation of a single dose of intervenous magnesium sulfate for prevention of postoperative pain after inguinal surgery;^[5] in a study by Akansha *et al.* about effect of continuous magnesium sulfate infusion on spinal block characteristic;^[6] in a study by Mustafa *et al.* about the

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effect of interavenous magnesium sulfate treatment on the spinal anesthesia produced by bupivacaine preeclamptic patients;^[7] and in a study by Shah and Dhengle about magnesium sulfate for postoperative analgesia after surgery under spinal anesthesia.^[8]

Regarding reasons such as antinociceptive and antagonist effects of magnesium, increased morbidity and mortality due to failure in pain management, and nociceptive stimulations in the activation of chronic or acute pain, we aimed to evaluate the effect of interavenous magnesium sulfate on pain severity, requirement to opioids, and patients' satisfactory after surgery of the lower limb fracture (femur and hip) by spinal anesthesia.

Methods

Patients and design

This study was done as a randomized double-blinded, clinical trial at Shahid Rajaei hospital during 1 year from 2016 to 2017. This study was approved by ethical committee of Qazvin University of Medical Sciences (IRCT code is IRCT2016022825676N3).

A total of 60 patients aged from 45 to 75 years entered into the study who were candidates for surgery of the lower limb fracture (femur and hip) by spinal anesthesia and were in Class of I and II based on American Society of Anesthesiologists classification. Patients with diabetic disease, liver dysfunction, kidney dysfunction, cardiac blocks, high blood pressure (BP), neurological disorders, myopathy, opioid or alcohol usage, pregnancy, magnesium supplement usage, blocker calcium usage, and surgery duration with more than 2 h along with back pain were excluded from the study. In preparation for surgery, patients were randomly, by colorful cards, assigned into two groups as magnesium group (M, $n = 30$) and control group (C, $n = 30$) by a nurse that educated for how to prepare drugs. Besides, anesthesiologist was not informed about how groups are assigned. Group M received a low dose of magnesium (5 mg/kg) plus 250 cc normal saline during 15 min after block, in the case of stable vital signs and hypotension <20%. Group C received only a dose of 250 cc normal saline.

Anesthesia technique

In the operation room, the patients' pulse oximetry and electrocardiography, pulse rate, BP, and rate pressure were monitored. In continuation, a dose of 0.02 mg/kg midazolam and 50 mg/kg microfantanyl were prescribed as premedication. Before anesthesia onset, all patients were received 500 cc normal saline. The anesthesia was done by spinal method on L3–L4 or L4–L5 vertebrals and using N23 or N22 Quincke needles by an anesthesiologist. Besides, 4 ml bupivacaine 0.5% was injected in subarachnoid block.

Sensory block level was assessed through pinprick sensor by using hypothermia needle number 20. Furthermore, motor

block was assessed by adjusted Bromage score (zero = the lack of motor block; 1 = an inability to raising straight leg; 2 = ability to bend the knee or inability to bend but having ability to flex the ankle). Patients were prepared for surgery when their motor block was appropriate (Bromage score ≥ 2), and anesthesia was assessed by pinprick. At the end, BP assessed per 3 min for 15 min, and then per 5 min until the end of surgery. None of the patients experienced complications during surgery. In the recovery room, pump patient-controlled analgesia (PCA) was embedded for postoperative analgesia immediately after surgery. The setting of PCA considered as 1 ml bolus with a 10 min block period. Pumps were embedded with 20 mg morphine in 100 ml normal saline, 2 gr apotel, 8 mg dexamethasone, and 4 gr ondansetron for the first 24 h; and also 10 mg morphine plus 1 g apotel, 4 mg dexamethasone, and 4 mg ondansetron for the second 24 h.

Pumps usage was educated to patients by recovery nurse and was asked from patients to use that immediately after pain onset. The pain onset time was considered as zero time.

Outcome assessment

Primary outcomes

Pain severity and the requirement to opioids were measured as primary outcomes. Pain severity was assessed by using visual analog scale (VAS) with score from zero (complete analgesia) to 10 (extremely pain). The VAS scale was educated to patients before surgery. Pain severity was assessed at 4, 6, 12, 24, and 48 h after surgery. The requirement to morphine or other opioids was recorded through patients' medical document during 24 and 48 h after surgery.

Secondary outcomes

The day after surgery, patients were asked to rate the quality of their first night's sleep, which is the inverse VAS scored from zero = absolute insomnia to 10 = no insomnia, excellent quality of sleep as described by Kara *et al.*^[9]

The patient's global satisfaction regarding comfort scored from zero = worst discomfort ever experienced in their life to 10 = totally satisfied by comfort provided during the immediate postoperative period as described by Tramer *et al.*^[10] Physical dissatisfaction as inversely score was assessed at 4, 6, 12, 24, and 48 h after surgery.

Besides, awaking at the first night after surgery and continuity of analgesia block were evaluated.

Sample size and statistical analysis

G-power software was used for estimating sample size. Under power 80%, alpha 0.05, effect size 0.68, the required sample size was estimated at least 29 cases in each group. The sample size can be estimated using the following formula.

At first, normality test was checked by Kolmogorov–Smirnov and Shapiro–Wilk testes which did not confirm normality of data in our study. Results are reported as median and interquartile range (IQR). Data analysis was done by Mann–Whitney test. Significant level was considered as $P < 0.05$.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2}$$

Results

In this study, data from 60 patients in two groups (30 cases per group) were analyzed. Groups were homogenate regarding age ($P = 0.761$) and gender ($P = 0.184$). Descriptive information of patients is reported in Table 1.

Two groups were compared for main outcomes of pain severity and requirement to opioid. According to the results of our study in Table 2, pain score based on VAS scale was significant between two groups during 4 h (median [IQR]: Group M, 8 [1] vs. group C 8 [0.25], $P = 0.048$), 12 h (Group M, 5 [2] vs. group C 6 [1], $P = 0.000$), 24 h (Group M, 4 [1] vs. Group C 5 [1], $P = 0.000$), and 48 h (Group M, 2 [1] vs. Group C 4 [1], $P = 0.000$) after surgery.

Furthermore, rate of requirement to opioid at 24 h after surgery (median [IQR]: Group M, 20 mg [3] vs. Group C, 25 mg [3], $P = 0.001$) and total of opioid usage during 48 h after surgery (Group M, 30 mg [5] vs. Group C, 35 mg [5], $P = 0.001$) were significant between two groups, while that was not significant between two groups at the second

24 h after surgery (Group M, 10 mg vs. Group C, 10 mg, $P = 0.116$).

In this study also, physical dissatisfaction, sleep quality, and block endurance were compared between groups by using Mann–Whitney test. Score of physical dissatisfaction was significant between two groups during 12 h (median [IQR]: Group M, 5 [2] vs. Group C 6 [1], $P = 0.006$), 24 h (Group M, 4 [1] vs. Group C 5 [2], $P = 0.000$), and 48 h (Group M, 2 [1] vs. Group C 4 [1], $P = 0.000$) after surgery.

In another result of this study, score of sleep quality was not significant between two groups at the first night after surgery (median [IQR]: Group M, 7 [3] vs. Group C, 6 [2], $P = 0.05$).

Besides, results of the present study showed that the spinal block endurance is significantly increased in magnesium group than that of control group (median [IQR]: 2.3 h [0.5] vs. 1.3 h [0.38], $P < 0.0001$).

Discussion

This study aimed to evaluate the effect of magnesium sulfate on pain severity, opioid requirement, and patients' satisfactory and sleep quality after surgery. Pain severity was reduced at 12, 24, and 48 h after surgery in Group M as compared with Group C. Total opioid requirement at the end of 48 h and also at the first 24 h after surgery were reduced in Group M as compared with Group C. Endurance of spinal block was increased in Group M as compared with Group C. Besides, physical dissatisfaction was reduced at 12, 24, and 48 h after surgery in Group M.

In a study by Frassanito *et al.* on patients under surgery of knee replacement, a dose of 40 mg/kg bolus was used and continued with 10 mg/kg/h infusion. Their results showed that magnesium had no effect on postoperative pain and decreasing requirement to opioid in the early hours after the surgery.^[3] Their finding was in accordance with results of our study, in which magnesium had decreased postoperative pain and requirement to opioid. One difference is maybe type of opioid used in their study as paracetamol, ketorolac for case group, and morphine for control group.

In a study by Apan *et al.*, the requirement to opioid and analgesia consumption after surgery was significantly decreased with infusion of 5 mg/kg of magnesium sulfate bolus plus 5000 mg/h for 24 h.^[11] In a study by Kumar *et al.*, after to receive 50 mg/kg magnesium sulfate bolus with 10 mg/kg/h infusion which had continued for 12 h, analgesia after surgery was increased in magnesium group at the first 24 h.^[4] In a study by Kiran *et al.* on patients under inguinal surgery, results showed that the requirement to opioid and pain severity in magnesium group who received 50 mg/kg/ns bolus were lower than control group at 2, 4, 6, 12, and 24 h after surgery.^[5] In a study by Martin *et al.*, 15 ml of magnesium sulfate 20% bolus with 2.5 ml/h of the same drug was injected during surgery. Patients were

Table 1: Demographic characteristics of patients (n=60)

Variable	Category	M group (n=30)	C group (n=30)	P
Age (year), mean±SD	-	60.23±10.5	61.06±10.4	0.761
Gender, n (%)	Male	16 (53.3)	21 (70)	0.184
	Female	14 (46.7)	9 (30)	

M=Magnesium group, C=Control group, SD=Standard deviation

Table 2: Comparing pain score and physical dissatisfaction between magnesium group (M, n=30) and control group (C, n=30) in patients under surgery of the lower limb fracture by spinal anesthesia

Time after surgery (h)	Pain score			Physical dissatisfaction		
	M	C	P	M	C	P
4	8 (1)	8 (0.25)	0.048*	7 (3.7)	7 (1)	0.184
6	7 (2)	7 (1)	0.191	6 (3)	7 (1)	0.352
12	5 (2)	6 (1)	0.000*	5 (2)	6 (1)	0.006*
24	4 (1)	5 (1)	0.000*	4 (1)	5 (2)	<0.0001
48	2 (1)	4 (1)	0.000*	2 (1)	4 (1)	<0.0001

*Is significant at level of 0.05, Data are represented as median (IQR). M=Magnesium group, C=Control group, IQR=Interquartile range

followed up to 24 h, 1 week, and 1 month after surgery for their required opioid and their finding indicated that requirement to morphine was lower in magnesium group than control group. Furthermore, patients' dissatisfactory was lower in magnesium group at first and 2 days after surgery.^[12] In a study by Levaux *et al.*, 50 mg/kg of magnesium sulfate as bolus was injected in patients under general anesthesia of lumbar surgery. Their results showed that pain severity and required opioid after surgery were lower in magnesium group, while their sleep quality and total physical satisfaction were more.^[10] All of the above findings are accordance with the results of our study.

In a study by Bhatia *et al.*, although using 50 mg/kg magnesium sulfate in 100 ml of normal saline during open cholecystectomy surgery caused to pain reducing, more feeling comfortable at the first time and good sleep quality on the first night after surgery, it clearly did not reduce the need for morphine.^[13] According to results of our study also, pain severity and need to opioid were significantly reduced in magnesium group but was not obtained significant finding in sleep quality. One difference is maybe using a low dose of magnesium sulfate (5 mg/kg) in 250 cc normal saline.

In a study by Akansha *et al.*, magnesium sulfate 15 mg/kg/h until the end of surgery was injected and their results indicated that magnesium sulfate can affect block features and activity length of internal bupivacaine.^[6] According to the study by Mustafa *et al.* in Turkish, receiving magnesium sulfate 50 mg/kg in 100 ml dextrose caused to elongate the sensory block onset. Besides, block duration was shortened that led to increasing the need for initial analgesia.^[7] In another study by Shah and Dhengle, results showed that sensory and motor block were, respectively, shorter about 34 min and 25 min in the control group. Postoperative requirement to analgesia in magnesium group was lower than control group (33% vs. 53.7%).^[8] In comparison with the results of our study, sensory block in magnesium group was significantly more than control group. This difference in results probably is related to drug dosage and adopting a bolus doses with a maintenance dose. Furthermore, it seems that more dosage of magnesium sulfate is required at the first time after surgery due to more pain severity and also to reach the better and acceptable results as reduced pain severity at the next times after surgery.

Conclusions

According to the results of the present study, a dose 5 mg/kg/intravenous magnesium sulfate has no effect on the decreasing pain score and reducing physical dissatisfaction at the first time (4 and 6 h) after surgery. These factors had significantly better results in the magnesium group at 12, 24, and 48 h after surgery. Regarding a low dose of magnesium was noticeable effect on increasing the block, thus evaluating blood magnesium and cerebrospinal fluid (CSF) fluid with more studies is recommended to

evaluate the effect of low-dose magnesium on the analgesia after surgery.

In comparison with the results of other studies, two prominence differences are given such as a low dose of magnesium sulfate (5 mg/kg) as infusion during 30 min without maintenance dose and pain assessing only at 12 and 24 h after surgery. Although pain severity on the first time was almost reduced in case group (M), no significant differences was observed. In the present study, patients were followed up to 48 h after surgery due to pain severity. Besides, acute complications related to magnesium sulfate was not observed in none of the patients during the study.

On the other hand, one limit of the present study is failure to measure of magnesium in the blood and cerebrospinal fluid for evaluating the effect of low-dose magnesium on postoperative analgesia.

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Conflicts of interest

There are no conflicts of interest.

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