Res Cardiovasc Med. In Press(In Press):e59532. doi: 10.5812/cardiovascmed.59532.

Published online 2017 July 31. **Research Article**

The Effect of Magnesium Sulfate on Postoperative Pain Severity and Complications in Patients Undergoing Coronary Artery Bypass Grafting

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Received 2017 January 12; **Revised** 2017 March 17; **Accepted** 2017 April 29.

Abstract

Background: To determine the beneficial effect of magnesium as a supplement for postoperative pain relief, the present study aimed to assess this effect among patients undergoing coronary artery bypass grafting (CABG).

Methods: In a randomized double-blind controlled trial, 44 consecutive patients aged > 18 years with the American society of anesthesiologists physical status classification system (ASA) score II-III that were candidate for isolated CABG were randomly assigned to receive either magnesium sulfate (50 mg/kg bolus within 30 minutes followed by 10 mg/kg/h for 24 hours) as cases or 150 ml normal saline as controls.

Results: Both groups had a downward trend of pain severity; however, those who received magnesium sulfate had a significantly reduced mean pain score compared to the control group from 2 hours of ending operation to the time of extubation ($P < 0.001$). The prevalence of post-operative nausea and vomiting (PONV) (13% versus 66.7%, $P < 0.001$) and apnea within 24 hours of surgery (4.3% versus 33.3%, $P = 0.021$) was lower in the former group. Those who received magnesium sulfate had higher coconsciousness levels compared to the control group so that waking with severe painful stimuli was revealed in 17.4% and 42.9%, respectively ($P = 0.034$). With respect to the consumed dose of opioids, the dose of used morphine within 24 hours of surgery was 10.87 ± 6.83 mg in the magnesium sulfate group and 80.24 ± 31.56 mg in the control group ($P < 0.001$).

Conclusions: Infusion of magnesium sulfate in patients undergoing major surgeries such as CABG can reduce postoperative pain, PONV, postoperative apnea, required time for coconsciousness, and required analgesic dose.

Keywords: Magnesium Sulfate, Pain, Coronary Artery Bypasses Grafting, Post-Operative Nausea and Vomiting

1. Background

Magnesium is an essential cation in the body and its homeostasis plays an important role in body's normal function (1). Magnesium ions are involved as a cofactor in more than 300 enzymatic reactions known in the body; they also participate in many processes such as hormones bind to receptors, calcium channel structure, and effective ion transfer of cell membrane, regulation of adenylate cyclase, neuronal activity, vasomotor tone, heart muscle contraction, and release of neurotransmitters (2). Inhibition of N-methyl D-aspartate receptors such as magnesium and receivers leads to a painful stimuli-induced inhibition of central sensitivity of the environment (2, 3). These effects mainly relate to controlling the entry of calcium into the cells by applying agonistic role on calcium receptors or antagonistic action on NMDA receptors (4). Several studies indicate reduced levels of magnesium after induction of general anesthesia that returns to normal levels in 1 to 3 days after surgery (5-7). However, concentration of magnesium in cerebrospinal fluid remained unchanged during anesthesia and changes in plasma concentration of magnesium would not be consistent with the amount of cerebrospinal fluid (8). Accordingly, some of the studies have emphasized magnesium injection during surgery and general anesthesia for stabilizing magnesium levels (9). Effective treatment of pain before and after surgery is necessary to reduce the morbidity of surgery. This approach sometimes leads to the use of multiple medications and treatment because there is no specific treatment to improve pain control after surgery without drug side effects. In this regard, it is proven that magnesium inhibits calcium entry into the cell and inhibits NMDA channels, as well. These effects can lead us to use magnesium as a drug against pain during and after surgery. Indeed, the consumption of drugs such as morphine or fentanyl during surgery is significantly reduced (4). Some studies have focused on the role of magnesium as a neuromuscular blocker (10, 11). However, the results of studies are not always consistent; some studies have emphasized the ineffectiveness of magnesium sulfate in pain after the surgery (12) or lack of it effects on the sensory and motor block (13). However, there is useful evidence regarding magnesium sulfate effects on the relief of the pain caused by surgery due to anesthesia as well as sensory and motor block, but some studies also have not been able to prove these effects. In fact, factors such as dose, administration time, and quality of injection of drug could be effective on quality of its effect on postoperative analgesia. The study aimed to evaluate the effect of this drug on analgesia after open-heart surgery as a major surgery.

2. Methods

This study is a double blind randomized trial that was conducted in 2014 at Farshchian hospital in Hamadan. The study population included patients undergoing coronary bypass grafting and the study sample was selected by random sampling. Based on the inclusion criteria, patients aged over 18 years with ASA II-III undergoing isolated coronary artery bypass surgery were included in the study. Exclusion criteria included atrioventricular block, history of previous magnesium sulfate intake, treatment with calcium blockers, involving vital organs such as liver and kidney dysfunction, cerebral ischemic abnormalities, left ventricular ejection fraction less than 40%, obesity (body mass index$>$ 40 kg/m^2), and pregnancy. Patients were randomly assigned to two groups of 22 patients based on entry to the operating room and the blocks before and after using the software On Line. The magnesium sulfate group received magnesium infusion intravenously 50 mg/kg for 30 minutes and 10 mg/kg/h or at the speed of 0.5 mg/kg/h for 24 hours after induction of anesthesia. In the control group, patients received 150 cc saline with the same speed and period. All patients received morphine 50 mg/kg and promethazine 0.5 mg/kg intramuscularly one hour before surgery. Induction of anesthesia for all patients was performed with midazolam 0.1 mg/kg, sufentanil 1 μg/kg, and propofol 1.5 mg/kg. Intubation was done using atracurium 0.5 mg/kg and 100% oxygen delivery. Patient monitoring was performed by 5 leads ECG monitoring and critical parameters during operation.

At the end of the surgery and after termination of cardiopulmonary bypass, cardiac inotrope was used. Mechanical ventilation was performed with 100% oxygen delivery. Patients were transferred to the ICU and propofol infusion was used at the dose of 1 to 1.5 mg/kg/h until extubation. Monitoring of patients was continued. Patients received 1 g intravenous paracetamol for 6 hours and morphine 0.1 mg/kg as needed. If patient was hemodynamically stable with negative inspiratory pressure greater than 20 mmHg, core temperature greater than 36.5 degree, pH higher than 7.3, tube drainage less than 100 mL/hour, and without any arrhythmia, he/she was extubated and propofol injection would stop. After extubation, mouth mask at the rate of 6 liters oxygen per minute was applied. The parameters evaluated in this study were: 1) duration of ICU stay from admission to extubation, 2) impairment of consciousness, 3) serum magnesium levels before surgery, after surgery, and 24 hours later, 4) total dose of analgesic drug (morphine) over 24 hours of operation, 5) assessment of pain intensity based on visual analog pain scale system (VAS) (0 to 100), 6) extubation problem, 7) the need to restore muscle relaxant, 8) nausea and vomiting, 9) the need for inotropic drugs, 10) occurrence of respiratory depression (less than 8 /minute), 11) pain assessment based on personal informatics systems (PIS), with VAS = 1 - 6, ten minutes after discontinuing propofol infusion (1 painless, 2 mild pain, 3 moderate pain, 4 severe pain, 5 very severe pain, 6 worst possible pain). Pain intensity was recorded every half-hour until extubation. Moderate to severe pain and above this level needed to increase the dose of morphine at a rate of 0.05 to 0.1 mg/kg.

The results for quantitative variables are expressed as mean $\pm$ standard deviation (mean $\pm$ SD) and qualitative variables as percentages. Comparison of quantitative variables was conducted using t-test or Mann-Whitney test. For evaluating the index changes, the repeated measures ANOVA test was used. For statistical analysis of data, SAS version 1.9 and SPSS version 15 were used. $P < 0.05$ was considered significant.

3. Results

The case group (males: 78.3%, females: 21.7%) and the control group (males: 66.7%, females: 33.3%) did not differ in terms of age ($P = 0.338$). The average age of patients was not statistically different (57.12 ± 10.45 years and 56.42 ± 36.11 years, respectively) ($P = 0.224$)

The changes of pain intensity in patients differed in the two groups, so that a decrease in pain intensity was seen in both groups after operation from 2 hours after extubation, but the slope descending in the magnesium sulfate group was far more than that of the control group ($P < 0.001$). In terms of pain intensity between extubation time and 24 hours after extubation, in all periods of 1, 2, 3, 4, 5, 6, 12, and 24 hours after extubation, the mean VAS in the case group was far lower than that of the control group (Table 1). In fact, the decreasing trend for pain was seen in both groups, but the steep decline in the case group was far greater than that of the control group ($P < 0.001$). Incidence of difficult extubation in the two groups was similar (8.7% vs. 28.6%, P = 0.088) (Table 1). The frequency of the need to restore muscle relaxation was similar in the two groups (13% vs. 19%, P = 0.587). In terms of inotropic support, there was no difference between the two groups (3.4% vs. 19%, P = 0.176). Occurrence of nausea and vomiting was significantly lower in the case group (13% vs. 66.7%, $P < 0.001$). Moreover, the level of consciousness in patients receiving magnesium was higher than that of the control group so that waking up with severe stimulation was seen in 17.4% and 42.9% in the magnesium sulfate group and the control group, respectively (P = 0.034). On the other hand, the occurrence of apnea within 24 hours after surgery was significantly lower in the treatment group than the control group (4.3% vs. 33.3%, P = 0.021). Although average levels of magnesium in the day before surgery were similar in both groups (1.51 ± 0.19 to 1.71 ± 0.11 mg/dL, P = 0.35), serum magnesium levels after the operation (2.26 ± 0.19 vs. 1.63 ± 0.11 mg/dL, $P < 0.001$) and 24 hours after surgery (2.11 ± 0.15 to 1.58 ± 0.36 mg/dL, $P < 0.001$) were higher in the intervention group than the control group. The average dose of analgesic drug (morphine) 24 hours after surgery was 10.87 $\pm$ 6.83 mg in the treatment group and 80.24 $\pm$ 31.56 mg in the control group, indicating a significantly lower dose in the magnesium group ($P < 0.001$).

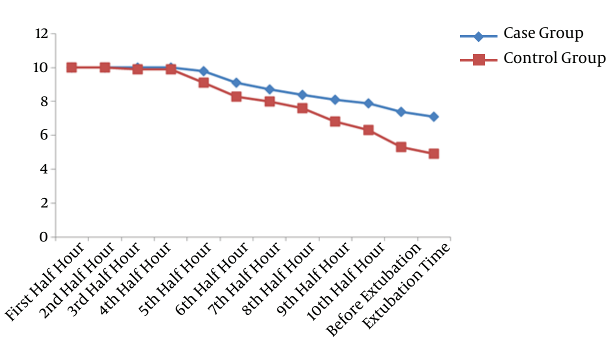

Figure 1. Postoperative Pain Intensity till Extubation Time

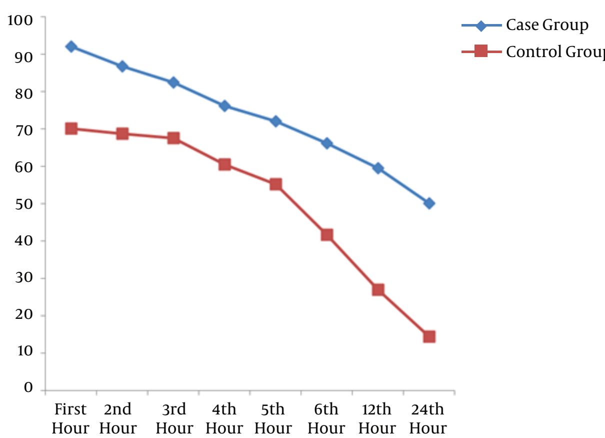

Figure 2. Pain Intensity between Extubation time and 24 Hours after Extubation

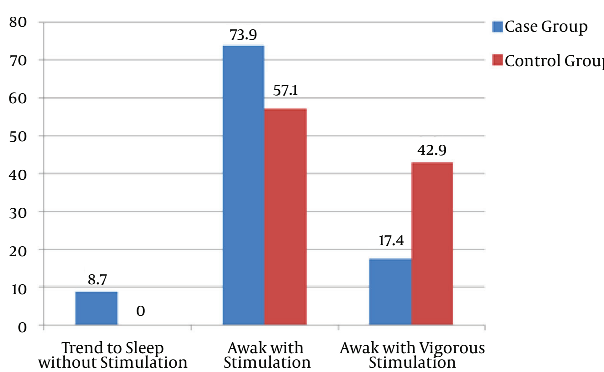

Figure 3. Levels of Consciousness After Operation

4. Discussion

The aim of the present study, in line with previous studies, was to assess the effects of magnesium sulfate on reducing pain associated with coronary artery bypass grafting (CABG) as a major surgery. In fact, as mentioned in most studies, many cases of morbidity in open-heart surgery are due to complications of anesthesia and pain caused by surgery; therefore, with management of anesthesia effects and pain relief, postoperative morbidity can reduce considerably. As found in this study, the beneficial effects of this drug on reducing pain intensity and side effects of surgery and anesthesia was considerable. First, we found that injection of magnesium sulfate considerably reduced the pain before extubation and within the first 24 hours after extubation although this reduction occurred in the control patients with a slight downward trend. On the other hand, the use of magnesium sulfate could reduce the time required for consciousness, the dose of analgesic

Table 1. Results

Comparison of Groups	Case Group (%)	Control Group (%)	P Value
Difficult extubation	8.7	28.6	0.088
Need to restore muscle relaxant	13	19	0.587
Need for inotropic drugs	4.3	19	0.176
Nausea and vomiting	13	66.7	< 0.001
Incidence of apnea	4.3	33.3	0.021
Consciousness level			
Trend to sleep without stimulation	8.7	0.0	
Awake with stimulation	73.9	57.1	
Awake with severe stimulation	17.4	57.1	

drugs after surgery, and postoperative nausea and vomiting.

The findings of previous studies are largely consistent with our results although many studies have examined different doses of the drug.

In a study by Mirdu and colleagues to assess the effects of magnesium sulfate on intrathecal analgesia after hysterectomy, it was found that magnesium sulfate led to longer duration of analgesia after surgery and reduced postoperative analgesic requirement (14). Farasatkish and colleagues also studied the effects of magnesium sulfate on postoperative pain scores and extubation time in patients undergoing coronary artery bypass surgery. The results showed that extubation time was shorter in the group receiving magnesium than the placebo group. In addition, the average pain scores at 6, 12, 18, and 24 hours postoperatively in the group receiving magnesium sulfate were less than those of the placebo group were, and the need for morphine was also lower (15).

On the other hand, Dabbagh and colleagues studied the effects of intravenous magnesium sulfate removal on postoperative orthopedic pain. The first group received intravenous magnesium 80 mg/kg during surgery and the second group received the same dose of placebo. The group receiving magnesium had a lower pain scores (VAS) at 1, 3, 6, and 12 hours compared to the control group. The amount of analgesic consumption within 24 hours in the group receiving magnesium was lower than that of the control group (16). Levaux and colleagues studied the effects of intravenous magnesium infusion on pain due to major surgery in 24 patients. The case group received about 50 mg/kg intravenous magnesium sulphate. The results showed that in the group receiving magnesium, postoperative pain scores, and consumption of analgesics during surgery were lower than those of the patients in the control group were. In addition, recovery of neuromuscular block was longer than magnesium sulfate group (17). The mechanism of analgesic effect of magnesium is not entirely clear; however, it seems interfering with calcium channels and NMDA receptors play an important role in this regard. Studies have shown that calcium channel blockers, opioids, increase pain relief in patients with cancer treated with morphine. Since the entry of calcium into the cells releases neurotransmitters and other painful and inflammatory symptoms, analgesic effect of calcium channel blockers can increase the pain threshold due to the interference caused by calcium entry into the cell (18). NMDA receptor is an amino acid receptor that is also responsible for the transmission of stimuli through synapses, excitatory amino acids such as glutamate, and has a binding site for molecules that weaken and like ketamine and magnesium, can be an ion channel permeable to potassium and calcium. Magnesium inhibits these receptor influxes through the voltage-dependent channels (19). Based on this information, we can conclude that magnesium stimuli before surgery can have a preventive effect (preventive analgesia) on pain. However, a few studies have obtained contrary results. Ozcan and colleagues conducted a study to evaluate the effect of magnesium sulfate on pain management in patients after thoracotomy in open-heart surgery. There was no difference in pain score between the two groups (the recipient of magnesium and control groups). However, the total dose of morphine in the control group during 4, 8, and 48 hours after surgery was higher (20). Moreover, in Koing and colleagues study, postoperative pain scores were similar in both groups (less than 4) (21). Therefore, the majority of studies emphasize the analgesic effect of magnesium sulfate as well as its impact on reducing the need for narcotic use.

A decrease in pain and a reduction in opioid consumption after surgery significantly reduce the postoperative complications and increase patient satisfaction with surgery.

4.1. Conclusion

In total, it can be concluded that the infusion of magnesium sulfate in patients undergoing major surgeries such as coronary artery bypass grafting (CABG) is accompanied with pain relief during and after extubation, reduced incidence of nausea and vomiting after surgery, reduced incidence of apnea, reduced dose of analgesic drugs after surgery, and shorten the time required for consciousness after open-heart surgery. However, in spite of considerable results, this study had potential limitations as follows: first, the sample size of our study was limited that could adversely affect the power of the study; second due to possible influence of various factors on sedation after surgery, it is recommended to evaluate the effects of other factors such as type of surgical techniques.

Footnotes

Authors' Contribution: All authors contributed to this project and article equally; all authors read and approved the final manuscript.

Conflict of Interest: There is no conflict of interest to be declared.

Funding/Support: This study was supported financially by the Medical Faculty of Hamadan University of Medical Sciences. This manuscript was extracted from Mr Ehsan Baghbani Jam MD thesis.

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