Intraoperative Magnesium Sulfate Can Reduce Narcotic Requirement after Coronary Bypass Surgery

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Abstract

Background- **N**arcotics are the most common drugs used after cardiac surgery and their side effects, including respiratory depression, hemodynamic instability, nausea and vomiting, and itching are dose dependent. Magnesium is both an N Methyl D Aspartate (NMDA)–receptor and a calcium-receptor antagonist and can modify the important mechanisms of nociception. The purpose of this study was to investigate the effect of magnesium sulfate on the pain score and reducing narcotic requirement in coronary artery bypass grafting surgery (CABG) patients.

Methods- This randomized, double blinded, placebo-controlled trial recruited 185 patients (105 male and 80 female) undergoing elective CABG. Mean age was 58±11 years (range= 24 to 79 years). The patients were divided into two groups randomly: Group 1 received magnesium sulfate as an IV infusion (80 mg/kg) during a one-hour period post induction and Group 2 received the same volume of normal saline as a placebo. During the postoperative period, the patients' morphine requirement and pain score (visual analogue scale= scaled as 0 to 10, 0=no pain and 10= worst possible pain) at 6^{th}, 12^{th}, 18^{th}, and 24^{th} hours were recorded and documented.

Results- There were no significant differences between the two groups with respect to the baseline data. In the magnesium sulfate group, only 30 (32%) patients needed morphine sulfate, whereas 75 (83%) patients in the placebo group required some doses of morphine sulfate (p value < 0.001). The odds ratio showed that magnesium sulfate could strongly prevent the need for opioid analgesics for pain control.

Conclusion- The intraoperative use of magnesium sulfate can reduce the need for opioids post CABG ***(Iranian Heart Journal 2011; 12 (1):6 -11).***

Keywords: Magnesium Sulfate■ Coronary artery bypass■ Narcotics

Narcotics are the most common drugs used after cardiac surgery. Narcotics have been utilized as analgesics since 1853.

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nausea and vomiting, and itching are dose dependent.

Morphine in a dose of 2 mg/kg plus scopolamine was used as complete anesthesia in the 19th century.[1]
Magnesium sulfate is a commonly used drug in the field of anesthesiology, critical care, and pain control.
It is also drawn upon as a supplement in treating eclampsia, pre- eclampsia, hypokalemia, and premature labor, myocardial protection after ischemia, asthma crisis, postoperative pain control, and hemodynamic stability during intubation. [2,3,4]
The most important mechanisms of magnesium effects are its role in the N Methyl D Aspartate (NMDA) part of Gamma Amino Butyric Acid (CABG) receptors. These receptors are found in nerve endings and can modulate pain and inflammatory responses.[5,6,7] The present study is based on the theory that suppressing the inflammatory response induced by cardiopulmonary bypass and surgical stimulation in coronary artery bypass grafting surgery (CABG) patients could decrease the postoperative pain intensity and also help to extubate patients as soon as possible.[8] After surgery, pain may inhibit the effective coughing, deep inspiration, and early mobilization of patients. Thus, management of pain is an important part of postoperative care. Opening of the sternum and preparation of the internal mammary artery (IMA) graft may cause severe pain after surgery. Manipulation of the muscles, adjacent tissues of the chest, parietal pleura, and the periostium of the ribs and sternum is a common cause of pain. Analgesia after CABG is very important for both physicians and patients. There are numbers of adverse effects due to postoperative narcotic overuse, which affects the outcome of surgery.
This study was designed and executed to assess the effects of magnesium sulfate solution infusion on postoperative narcotic requirement in patients undergoing elective CABG.

Methods

The study population was selected from those hospitalized at Rajaei Cardiovascular, Medical and Research Center, a major tertiary center of cardiovascular diseases in Tehran, Iran. All the patients were between 18 to 65 years of age and were scheduled for elective CABG. The exclusion criteria comprised left ventricular ejection fraction < 30%, peptic ulcer disease or history of gastrointestinal bleeding, liver or renal failure, history of sleep apnea, abuse of other substances, and any sign or history of denoting past or present neuropathy. This study was approved by the institutional medical ethics committee. The objectives of the study were explained to all the patients by the anesthesiologists, and an informed written consent was obtained from all the patients.
Via a random digits table, the patients were randomly assigned to the intervention group, receiving magnesium sulfate, and the comparison group, receiving normal saline as a placebo. Randomization sequences were prepared by one of the study collaborates, who was not participated in the administration of the drugs, data collection, and data handling and analysis. The results of the randomization were put into sealed envelopes and these envelopes were sent to the operating room. Patient allocation was performed in the operating room before surgery. When a patient was enrolled in the study, another study collaborator, who was not involved in the treatment process, data collection, and data analysis opened an envelope according to its serial number before preparing magnesium sulfate (80 mg/kg) for the intervention group or normal saline (with the same volume) for the placebo group in similar syringes as well as recording the patients' group in the file through predefined codes. None of the medical staff was aware of this coding system, except for the study designer and the above-mentioned participant.

All the patients were visited the night before surgery by an anesthesiologist (amongst the authors) and were enrolled in the study according to the study protocol. In total, 185 were recruited in the study. The patients were premedicated intramuscularly with morphine sulfate (1mg/kg) and promethazine (1 mg/kg) one hour before transfer to the operating room. They were thereafter allocated to either of the study groups in the manner described above. Induction was achieved with an intravenous administration of thiopental (3 mg/kg), fentanyl (2.5 µg/kg), and atracurium (0.6 mg/kg). After tracheal intubation, the patients were mechanically ventilated to receive an initial tidal volume of 8 mL/kg, and a respiratory rate of 12 breaths/min. The ventilatory pattern was subsequently adjusted according to the arterial blood gases. General anesthesia was maintained with a continuous intravenous infusion of fentanyl (10 µg/kg/h), propofol, (4mg/kg) and atracurium (0.007 mg/kg/h). Further boluses of fentanyl (50-100µg) were administered if required at the skin incision and sternotomy field. Also, in the operating room, electrocardiography and radial artery pressure monitoring were commenced. Peripheral venous, central venous, and urethral catheters were inserted. Body temperature was monitored with rectal and esophageal probes. The patients were then positioned and were prepped and draped. After induction, the anesthesiologist started intravenous magnesium sulfate or normal saline infusion through a peripheral large bore catheter over a one-hour period. After surgery, the patients were transferred intubated to the postoperative intensive care unit, where they were extubated after full recovery of muscular forces and full awakening and with the establishment of hemodynamic stability. The cardiopulmonary bypass flow was started at a perfusion index of 2.4 L/min/m2. The mean arterial pressure was maintained at about 80 mmHg. Mild hypothermia was achieved and maintained during perfusion. The arterial pressure was controlled using a vasodilator (nitroglycerin [0.5_g/kg/min] or a vasoconstrictor (norepinephrine [0.05µg/kg/min]) to maintain the mean pressure value in a range of 40 to 100 mmHg. A diuretic (furosemide [20 mg]) was administered if urine output during cardiopulmonary bypass was < 0.5 mL/kg 30 minutes after the beginning of perfusion.

Statistical analysis was performed with the intention-to-treat approach. The data were classified as mean ± standard deviation for the interval and count (%) for the categorical variables. The comparison of the baseline data between the study groups was performed using the Student *t*-test or its non-parametric equivalent, Mann Whitney U test for the interval data, and Chi square test for the nominal data. Odds ratio (OR) with 95% confidence interval (CI 95%) was also computed to find the epidemiologic associations. P values < 0.05 were considered statistically significant.

The trend of pain severity and changes in the visual analogue scale results (across the time intervals and between the study groups) were investigated via a repeated measure analysis of variance (ANOVA) model. Survival analysis was performed using the Kaplan–Meier method to study the time of receiving the first dose of morphine sulfate, as a proxy of the time of intolerable pain by the patients. The Log rank test was used to compare the results between the study groups. SPSS 15 for Windows (SPSS Corporation, Chicago, Illinois) was employed for the statistical analyses.

Results

In total, 185 patients (F/M = 80/105; mean age = 58 ± 11.0 years, range= 24 to 79 years) were enrolled in the study. The mean left ventricular ejection fraction was 45 ± 8.4%. The average times of surgery and anesthesia were 3.8 ± 0.9 and 5 ± 0.9 hours, respectively. The patients stayed in the intensive care unit after surgery with a mean time of 2.2 ± 0.5 days (range= 2 to 4 days).

Ninety-five patients received intravenous magnesium sulfate and 90 patients received normal saline as a placebo instead. The baseline data of the study groups are presented in Table I. No important difference was observed between the groups.

Table I. Comparison of the baseline data between magnesium sulfate and placebo groups

	Magnesium sulfate (n = 95)	Placebo (n = 90)	P value
Age *years*	57 ± 11.5	59 ± 10.4	0.19
Sex			0.54
Female	39 (41%)	41 (46%)	
Male	56 (59%)	49 (54%)	
Left Ventricular Ejection Fraction *percent*	44 ± 7.3	44 ± 9.5	0.64
Duration of Anesthesia	5 ± 0.7	5 ± 1.1	0.43

hours			
Duration of Operation *hours*	4 ± 0.7	4 ± 1.0	0.57
CardioPulmonary Pump Time *minutes*	103 ± 58.3	104 ± 41.5	0.63
ICU Stay *days*	2 ± 0.4	2 ± 0.5	0.52
Number of the Grafts	3 ± 0.4	3 ± 0.3	0.19
Intubation Time *hours*	14.1 ± 4.3	16.5 ± 14.9	0.32

Severity of pain was measured using a 10-point visual analogue scale at different time intervals. The results are summarized in Table II.

Table II. Pain score at different time intervals after cardiac surgery in magnesium sulfate and placebo groups

	Mean Score ± Standard Deviation					
	1st Hour	3rd Hour	6th Hour	12th Hour	18th Hour	24th Hour
MG	0.29 ± 1.17	0.0 ± 0.0*	0.97 ± 2.02*	0.23 ± 1.0*	0.0 ± 0.0*	0.0 ± 0.0
Placebo	0.09 ± 0.59†	0.36 ± 1.26†	2.53 ± 2.43†	0.89 ± 1.83†	0.0 ± 0.0†	0.0 ± 0.0

MG: Magnesium Sulfate
P value for comparison between MG and Placebo (based on repeated measure ANOVA) < 0.001
P value for comparison across time intervals (based on repeated measure ANOVA) < 0.001
* and †: Statistically significant difference in pair-wise comparisons (based on Bonferroni post-hoc test). P values range <0.001 to 0.006.

Note that the most severe pain had a point, which was < 3. Immediately after surgery, the patients experienced a period of analgesia. The pain appeared gradually and became more severe by the 6th hour after finishing the operation. Then, the severity of pain decreased until it disappeared at the 18th postoperative hour (Figure 1). The significance of this trend was proved by a repeated measure ANOVA in both magnesium sulfate and placebo groups (p value < 0.001).

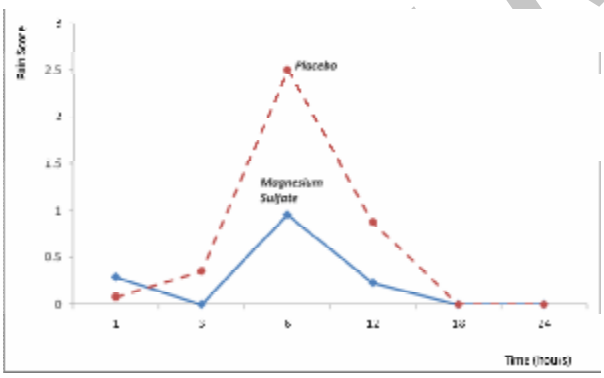

Fig. 1. Changes in pain severity in study groups

The severity of pain was equal in the two groups in the first postoperative hour. The period of analgesia continued in the patients who received magnesium sulfate until the 3rd postoperative hour, while in the placebo group, the severity of pain was rising. It was observed that at any time interval, the patients in the magnesium sulfate group experienced less severe pain compared to the placebo group. This difference was statistically significant (p value < 0.001).

According to the protocol of the study, the patients could receive morphine sulfate as an analgesic agent for controlling the pain, if indicated. In the magnesium sulfate group, only 30 (32%) patients needed to receive any dose of morphine sulfate, but in the placebo group, 75 (83%) patients received some doses of it (p value < 0.001; OR = 0.09, CI 95: [0.05 – 0.19]). The odds ratio showed that magnesium sulfate could strongly prevent the need for receiving opioid analgesic for pain control.

Amongst the patients who needed the analgesics, the mean dose of morphine sulfate was 1.0 ± 1.5 mg in the magnesium group and 2.8 ± 1.4 mg in the placebo group (p value < 0.001); it means that magnesium may reduce the average dose of morphine sulfate needed for controlling pain.

The time of the prescription of the first dose of morphine sulfate could be considered a proxy for the beginning of intolerable pain (pain score between 4 and 5); this was investigated using the Kaplan-Meyer method (Figure 2). The results indicated that in most of the patients who needed extra analgesia, the pain became relatively intolerable six hours after finishing the surgery. The Log-rank test showed no significant difference between the two groups (p value = 0.09); as a result, the pattern of receiving the first dose of morphine sulfate could be deemed similar in both magnesium and placebo groups.

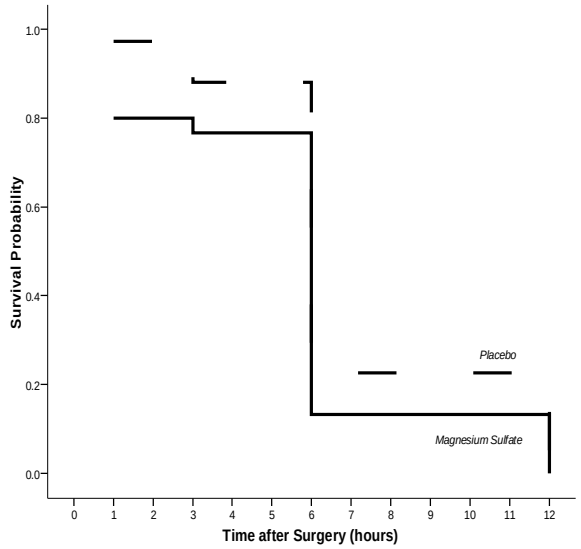

Fig II. Kaplan– Meier curve for estimation of the time-to-receive the first dose of opioid analgesics

Discussion

We demonstrated in this study that a continuous infusion of magnesium sulfate in doses of 80 mg/kg during elective CABG can reduce acute postoperative pain scores; this is in concordance with other similar studies on acute postoperative pain in other surgical procedures.[9] The mechanism of this analgesic effect of magnesium is not clear, but interference with calcium channels and NMDA receptors can play an important role in the reduction of inflammatory response and can show its effect on pain control through the central and peripheral nervous system.[10]

Magnesium also has a vasodilator effect on both the cardiac epicardium and resistance coronary arteries in humans. Furthermore, the coronary arterial response to magnesium is dose dependent.[11] This vasodilator effect can be useful in CABG, especially in patients who need arterial grafts .The preventive effect of magnesium on arterial graft vasospasm is also useful. After on-pump CABG, the inflammatory responses of the extracorporeal circulation are common. The effects of magnesium sulfate in decreasing the general inflammatory response in these patients, both intraoperatively and postoperatively, can lead to a more rapid recovery of them. We should also take into consideration the effects of decreased postoperative pain scores, which and can reduce the need for narcotics and intubation time.[12]

It seems that one of the most potent proposed mechanisms involved in the effects of magnesium in decreasing the postoperative pain scores is its role in affecting the N Methyl D Aspartate (NMDA) part of Gamma Amino Butyric Acid (GABA) receptors all over the body.[13] In one study in gynecological surgical patients, a loading dose of 50 mg/kg of magnesium sulfate maintained with a continuous dose of 15 mg/kg/h caused a 40% decrease in the postoperative use of morphine. This amount of magnesium sulfate (maximum dose up to 5 gr) cannot produce any side effect in patients.[14]

Conclusion

The results of the present study showed that the prescription of magnesium sulfate could prolong the analgesic time of patients, reduce the severity of pain after cardiac surgery, the need for receiving opioid agents, and the total dose of

morphine sulfate by comparison with the placebo group. The time of the prescription of the first dose of morphine sulfate did not differ between our two study groups.

Conflict of Interest

No conflicts of interest have been claimed by the authors.

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