Intraoperative Magnesium Sulfate can Reduce Narcotic Requirement after Coronary Bypass Surgery.

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Abstract:

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

Methods: In a randomized, double blinded, placebo-controlled trial One hundred and eighty five patients (105 male and 80 female) undergoing elective coronary artery bypass graft surgery were studied. Mean age were 58+_11 (from 24 to79 years).We enrolled them in two groups randomly. Group1 received magnesium sulfate as an IV infusion 80 mg/kg during one hour after induction and the second group received the same volume of normal saline as placebo. During the postoperative period, Morphine requirement and pain score (visual analogue scale: scaled as 0 to 10, 0=no pain and 10= worst possible pain) in 6, 12, 18, and 24 hours were recorded and documented.

Results: There were no significant differences between two groups with respect to baseline data. In MG group, only 30 patients (32%) needed to receive Morphine Sulfate , but in placebo group, 75 patients (83%) needs some doses of Morphine Sulfate (p value < 0.001); The odds ratio showed that MG could strongly prevent the needs for receiving opioid analgesics for controlling of the pain.

Conclusion: Intra operative use of magnesium sulfate can reduce receiving opioids after (CABG) operations.

Key words: Magnesium Sulfate, Coronary Artery Bypass, Narcotics.

Introduction

Narcotics are the most common drugs that have been used after cardiac surgery and they are used as analgesic from 1853. Everyone knows that their side effects including respiratory depression, hemodynamic instability, and nausea, vomiting and itching are dose dependent. Morphine in dose of 2 Mg/Kg plus scopolamine were used as complete anesthesia 1n the

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19th century (1). Magnesium – sulfate is a common used drug in the field of anesthesiology, critical care and pain control. It is also use as a supplement in treating eclampsia, pre – eclampsia, hypokalemia, 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 effect is 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). This theory is the basis for this study that suppressing the inflammatory response induced by cardiopulmonary bypass and surgical stimulation in CABG patients could decrease the postoperative pain intensity and also, can help to extubate the patients as soon as possible (8). After surgery, Pain may inhibit the effective coughing, deep inspiration, and early mobilization of the 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 the surgery. Manipulation of the muscles, adjacent tissues of the chest, parietal pleura, the periostium of the ribs and sternum are common causes of the pain. Analgesia after CABG operation is very important for both physicians and the patients. There are numbers of adverse effects due to post operative narcotic over usage that affect 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 coronary artery bypass graft surgery.

Methods

The study population selected from Rajaei Heart Center (RHC) patients, a tertiary center of cardiovascular diseases in Tehran that patients from all parts of IRAN are referred to. All the patients were between 18 to 65 years old who scheduled for an elective coronary artery bypass graft (CABG) surgery. Exclusion criteria in this study were:

Left ventricular ejection fraction (LVEF) less than 30%, peptic ulcer disease or history of gastrointestinal bleeding, liver or renal failure, history of sleep apnea, abused other substances or had any sign or history of denoting past or present neuropathy.

This study was approved by the RHC medical ethics committee. The objectives of the study were explained for all patients by the anesthesiologist and an inform consent was signed.

Using a random digits table, the patients were randomly assigned to intervention group (which received magnesium sulfate [MG]) and /or comparison group (which received normal saline as placebo). Randomization sequences had been prepared by one of the study collaborates, who was not participated in administration of drugs, data collection or data handling or analysis. The results of randomization had been put into sealed envelopes and these envelopes were sent to operating room. Patient's allocation was performed in the operating room, before surgery. When a patient enrolled in the study, another study collaborate, who wasn't involved in treatment process, data collection or analysis, opened an envelope according their serial numbers and was informed the grouping the related patient. Then, he prepared Magnesium Sulfate (80 mg per kilogram of body weight for intervention group) or normal saline (with the same volume for placebo group) in similar syringes. He also recorded the patients' group in their file by predefined codes. Nobody was aware of this coding system, except study designer and the mentioned participant. The medical staff who had no contribution in medical care or data collection were not aware of the actual group of the patients.

All patients were visited the night before the surgery by an anesthesiologist (among the authors) and enrolled the study according to the study protocol. One hundred and eighty five patients were participated in the study. Patients were premedicated intramuscularly by Morphine Sulfate (1mg/kg) and Promethazine (1 mg/kg) one hour before coming to operating room. Then, they were allocated to the study groups (as mentioned before). Induction was achieved with intravenous administration of thiopental, 3 mg/kg; Fentanyl, 2.5 µg/kg; and Atracurium, 0.6 mg/kg. After tracheal intubation, patients were mechanically ventilated to give an initial tidal volume of 8 mL/kg, with inspiratory 100% oxygen 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 and Atracurioum 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 begun. Peripheral venous, central venous and urethral catheters were inserted. Body temperature was monitored with rectal and esophageal probes. The patients were then positioned and prep and drape was done for them. After induction, the anesthesiologist started intravenous Magnesium Sulfate or normal Saline infusion through a peripheral large bore catheter during one hour. Operated patients were transferred intubated to the post operative intensive care unit. The patients were extubated after full recovery of muscular forces and full awakening and with the establishment of hemodynamic stability.

CPB flow 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 (nor epinephrine, 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 CPB was less than 0.5 mL/kg 30 minutes after the beginning of perfusion.

Statistical analysis was performed with intention-to-treat approach. Data were classified as mean ± standard deviation for interval and count (%) for categorical variables. Comparison of baseline data between the groups of study was performed by student's test or its non-parametric equivalent, Mann Whitney U test for interval data and Chi square test for nominal data. Odds ratio (OR) with 95% confidence interval (CI 95%) also computed to find the epidemiologic associations. P value less than 0.05 considered as statistically significant.

The trend of pain severity and changes of VAS results (among time intervals and between study groups) were investigated by a repeated measure analysis of variance (ANOVA) model.

Survival analysis was performed by 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 patients. Log rank test was used to compare the results between the study groups.

SPSS 15 for windows (SPSS Corporation, Chicago, Illinois) was used for statistical analysis.

Results

One hundred and eighty five patients (F/M = 80/105; mean age = 58 ± 11.0 years, range 24 to 79 years) enrolled the study. Mean left ventricular ejection fraction (LVEF) was 45 ± 8.4 percent. The average time of surgery and anesthesia was 3.8 ± 0.9 and 5 ± 0.9 hours, respectively. Patients stayed in intensive care unit (ICU) after surgery with a mean time of 2.2 ± 0.5 days (range 2 to 4 days).

Ninety five patients received intravenous magnesium sul-

Table 1- 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 hours	5 ± 0.7	5 ± 1.1	0.43
Duration of Operation hours	4 ± 0.7	4 ± 1.0	0.57
Cardio-Pulmonary 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

fate (MG) and 90 patients received normal saline as placebo instead. Baseline data of the study groups are presented in Table 1. No important differences were observed between the groups.

Severity of pain was measured by a 10-point visual analogue scale (VAS) in different time intervals. The results are summarized in Table 2

Table 2 –Pain Score in 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 among time intervals (based on repeated measure ANOVA) < 0.001
* and †: Statistically significant difference in pairwise 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 less than 3. Immediately after surgery, 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 18th hour after surgery (figure 1). The significance of this trend was proved by repeated measure ANOVA in both MG and placebo groups (p value < 0.001).

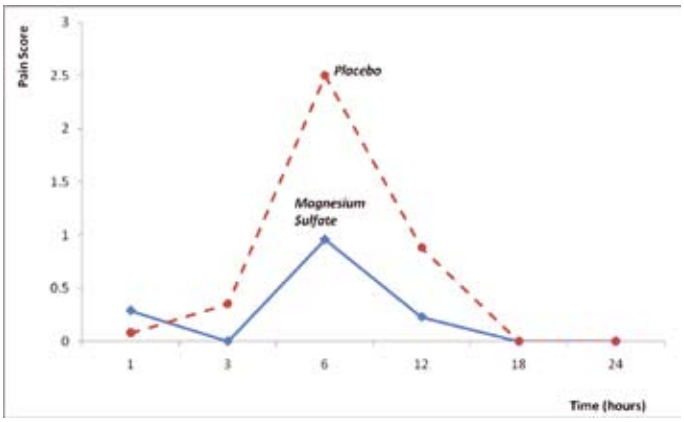

Figure 1- Changes of Pain Severity in the Study Groups.

The severity of pain was equal in two groups in the first hour after operation. The period of analgesia continued in patients who received MG until the 3rd hour after surgery, while in placebo group, the severity of pain was rising. It was observed that in any time interval, the patients in MG group experienced a less severe pain, compared to placebo group. This difference was statistically significant (p value < 0.001). According to the protocol of the study, patients could receive morphine sulfate (MS) as analgesic agent for controlling the pain, if they needed.

In MG group, only 30 patients (32%) needed to receive any dose of MS, but in placebo group, 75 patients (83%) got some doses of it (p value < 0.001; OR = 0.09, CI 95: [0.05 – 0.19]). The odds ratio showed that MG could strongly prevent the need for receiving opioid analgesic for pain controlling. Among the patients who needed the analgesics, the mean dose of Morphin Sulfate was 1.0±1.5 mg in magnesium group and 2.8±1.4 mg in placebo group (p value < 0.001). It means that magnesium may reduce the average dose of Morphin Sulfate needed for controlling the pain.

The time of prescription the first dose of morphine sulfate could be considered as a proxy for the beginning of intolerable pain (pain score between 4 and 5). This was investigated using Kaplan-Meyer method (figure 2). The results proposed that in most of the patients who needed extra analgesia, the pain became relatively intolerable 6 hours after finishing the surgery. Log-rank test showed no significant difference between two groups (p value = 0.09); then, the pattern of receiving the first dose of Morphin Sulfate could be considered similar in both magnesium and placebo groups.

Discussion

In this study, we demonstrated that the continuous infusion of magnesium sulfate in dose of 80 Mg/Kg during elective CABG surgery can reduce acute postoperative pain scores that is in concordance with the other similar studies performed on acute postoperative pain in other surgi-

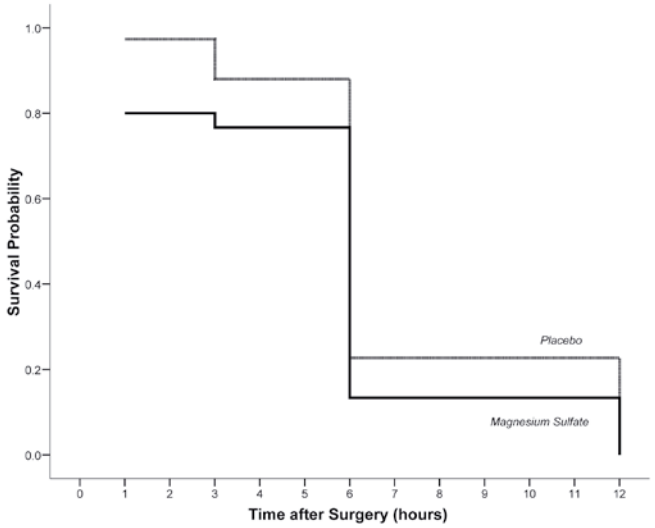

Figure 2 – Kaplan – Meier Curve for Estimation of the Time to Receive the First Dose of Opioid Analgesics.

cal 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 by the way of 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 operations especially patients that needs arterial grafts .The preventive effect of magnesium on arterial graft vasospasm is also useful. After on pump CABG the inflammatory responses of extracorporeal circulation are common. The effects of magnesium sulfate in decreasing the general inflammatory response in these patients, both intra-operatively and postoperatively can lead to a more rapid recovery of them. This rapid recovery also takes in to consideration the effects of decreased postoperative pain scores and can lead to reducing 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 gynecologic surgical patients loading dose of 50 Mg/Kg of Magnesium Sulfate maintained with continuous dose of 15 Mg/Kg/h after awhile can cause 40% decrease in post operative use of Morphine. This amount of magnesium sulfate (maximum dose up to 5 gr) can't produce any side effect in patients (14).

Conclusion: We concluded that prescription of magnesium sulfate could prolong the analgesic time of patients and reduce the severity of pain after cardiac surgery, the need for receiving opioid agents and the total dose of Morphine Sulfate, compared to the placebo group. The time of prescription of the first dose of Morphine Sulfate didn't differ between two groups.

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