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ORIGINAL ARTICLE

The effect of intravenous magnesium sulfate on serum levels of N-terminal pro-brain natriuretic peptide (NT pro-BNP) in elective CABG with cardiopulmonary bypass

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Abstract
Introduction Nowadays, many patients undergo coronary artery bypass grafting (CABG) with a cardiopulmonary bypass (CPB); while a number of therapeutic agents have been used to suppress its related inflammatory process. Magnesium sulfate ($MgSO_4$) solution has been used as an anti-inflammatory agent. Among the cardiac biomarkers, N-terminal pro brain natriuretic peptide (NT Pro-BNP) is one of the most widely recognized. We performed this study to assess the effect of $MgSO_4$ solution on NT Pro-BNP levels in patients undergoing CABG with CPB.
Materials and methods In a double-blind clinical trial, after IRB approval for ethical considerations, during a 12-month period, 88 adult patients aged 40–70 years qualified for the study after inclusion and exclusion criteria were considered. After random allocation of the patients between the two groups, anesthesia, surgical procedure, cardiopulmonary bypass (CPB) methods, and postoperative care were made as similar as possible; however, one group received a $MgSO_4$ infusion (15 mg/kg/h) and the other group saline (placebo). Pre- and post-operative levels of NT Pro-BNP were assessed using an electrochemical luminescence immunoassay in an Elecsys 2010 (Roche, Indianapolis, IN, USA). The results were compared using a Student's *t*-test. A *P* value less than 5 % was considered significant.
Results The $MgSO_4$ group had shorter postoperative mechanical ventilation, lower postoperative morphine requirements and lower postoperative pain scores. Also, 24 h postoperative NT Pro-BNP levels were significantly lower in the $MgSO_4$ group.
Conclusion Administration of $MgSO_4$ in elective CABG with CPB can decrease the postoperative NT Pro-BNP levels; also, it decreases their time of postoperative mechanical ventilation.

Keywords Magnesium sulfate · CABG · Cardiopulmonary bypass · N-terminal pro-brain natriuretic peptide

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Introduction

Some of the most common health problems are cardiovascular system disorders which impose a great disease burden [1, 2]. A considerable number of cardiac patients undergo cardiac surgery, with coronary artery bypass grafting (CABG) being a leading procedure; usually with concomitant use of cardiopulmonary bypass (CBP). CPB has its own side effects, one of them being systemic inflammation [2–5], the occurrence and therapeutic interventions of which have been discussed in many studies [1, 5–7].

Nowadays, a number of therapeutic agents are used to suppress the inflammatory process. Magnesium sulfate solution has been used as an adjuvant drug in anesthesia for many different purposes [4, 5, 8–13]; it has been administered in surgical patients as an analgesic and in cardiac surgery patients as an anti-inflammatory agent [4, 5, 10].

Also, the administration of a magnesium sulfate ($MgSO_4$) infusion has been demonstrated to decrease the incidence of postoperative atrial fibrillation in cardiac surgery patients [9]. Cardiac biomarkers are currently popular in assessing cardiovascular function; among them, N-terminal pro-brain natriuretic peptide (NT Pro-BNP) is one of the most effective biomarkers used for such assessments [1]. Our hypothesis was that $MgSO_4$ could possibly suppress some degree of postoperative inflammation in patients undergoing cardiac surgery (mainly due to the stress of CPB and the surgery); this $MgSO_4$ effect might possibly prevent brisk rises in serum levels of NT Pro-BNP [1]. Possibly, the serum levels of NT Pro-BNP could be a sensitive index to prove our proposed hypothesis regarding the anti-inflammatory effects of $MgSO_4$ in adult cardiac surgery. So, we performed this study to assess the effect of $MgSO_4$ solution compared with a placebo, on the serum levels of NT Pro-BNP in adult patients undergoing elective CABG with CPB.

Materials and methods

We performed a double-blind clinical trial to assess the effects of a $MgSO_4$ infusion on serum levels of NT Pro-BNP in patients undergoing elective CABG with CPB. This study was performed after Institutional Review Board approval (Research Deputy, Shahid Beheshti University of Medical Sciences), regarding ethical considerations. The study started in January 2010 and lasted 12 months. The clinical trial was registered at the Iranian Registry of Clinical Trials website which is available at this link irct.ir. Also, the study registration code at IRCT is "IRCT201205069650N1".

Eighty-eight study patients were admitted to the cardiac operating room of a university hospital (Tehran, Iran) to undergo elective CABG surgery. We did a sample size calculation after power analysis (with a power = 0.8, $\beta = 0.2$, and $\alpha = 0.02$); using the power analysis and sample size software PASS 2005.

Patients entered the study after an informed written consent and consideration of inclusion and exclusion criteria. Then they were randomly allocated into two groups.

The inclusion criteria were elective CABG with CPB, and age 40–70 years. The exclusion criteria were prolonged QT syndrome, current or previous history of neuromuscular junction disorders, current or previous history of bundle branch block, current or previous history of atrial fibrillation, history of diabetes mellitus, emergency operation, current unstable angina, current or previous history of chronic renal failure, redo operations, operations (including CABG) with any other disorders (like CABG with valvular disease or CABG with carotid endarterectomy, etc.), and any history of drug abuse or opium abuse.

Then the patients were allocated into one of the two groups based on a computer random numbers table. There were 44 patients in the control group and 44 patients were allocated to the case group, all selected randomly. The case group received a magnesium sulfate infusion (hence the $MgSO_4$ group); while a placebo was administered for the control group (i.e. the placebo group).

Then, for the $MgSO_4$ group, we started a $MgSO_4$ infusion through a peripheral large-bore IV catheter; the dose was 15 mg/kg/h (per kg of body weight) and was administered via a 50 ml syringe. The same volume of normal saline was administered as a placebo via a 50 ml syringe intravenously. The dose (15 mg/kg/h) was chosen based on previous studies, and also the outcome for this study (i.e. NT pro-BNP) would be measurable. In other words, the effects of different doses of $MgSO_4$ infusion on postoperative extubation time, postoperative pain and postoperative bleeding has been assessed in previous studies [4, 5, 14]; however, in the current study, a dose of 15 mg/kg/h was calculated and started after anesthesia induction and continued up to the time of skin closure.

Except for administration of $MgSO_4$ or placebo, the anesthesia methods and protocols for the two patient groups were exactly the same. Also, we performed the same surgery procedures, the same cardiopulmonary bypass details and the same postoperative care protocols. For these purposes, the anesthesiologists, the surgeons, and the medical team were the same.

The patients entered the operating room and standard monitoring was used. This included electrocardiography (ECG), pulse oxymetry and invasive blood pressure monitoring. For monitoring invasive blood pressure, first an Allen test was done in the non-dominant radial artery, then a small wheal of local anesthetics was injected, and finally an indwelling arterial catheter was introduced into the radial artery of the non-dominant hand.

After installation of the monitoring equipment, we anesthetized the patients using a titrated intravenous dose of sufentanil (1 μg/kg), cisatracurium (0.2 mg/kg) and sodium thiopental (1 mg/kg). Then, after 3 min, we intubated the patients. We inserted a central venous catheter through the right internal jugular vein. Anesthesia was continued using a combination of intravenous and inhalational anesthetics. The intravenous maintenance cocktail included 150 μg sufentanil, 150 mg atracurium, and 15 mg midazolam; this cocktail was supplemented with normal saline to 50 ml to be administered over 4 h. Isoflurane (0.2–1 %) was also administered by an inhalational route, in order to keep the anesthesia level between 40 and 60; the depth of anesthesia was monitored using a bispectral index. We anesthetized all the patients using the same method,

while the same surgeons operated on the patients, applying the same surgical techniques as much as possible. For applying inotropic support during weaning from CPB in the cases where this was necessary, we used the following protocol:

1. Dopamine: with a dose of 2–5 μg/kg/min
2. Low dose epinephrine infusion: starting dose of 0.01–0.03 μg/kg/min
3. Incremental increase in epinephrine dose: up to 0.5 μg/kg/min
4. Milrinone: loading dose of 0.5 μg/kg and infusion dose of 0.05 μg/kg/min.

Those patients who received triple inotropic agent therapy for CPB weaning were excluded from the study. The number of patients excluded from the study in each group was registered.

Then we transferred the patients at the end of the surgery to the cardiac ICU for the postoperative recovery period. We monitored them using standard monitoring, the patients were extubated after they fulfilled the criteria for extubation:

- Normal consciousness state: the patient being alert, awake and cooperative, without any agitation or over-activation
- Normal hemodynamic status: systolic blood pressure >100 mmHg; no or minimal inotropic infusion, no considerable or lethal arrhythmia, no significant hemodynamic derangement
- Normal respiratory status, no pain in inspiration and expiration; no tachypnea or bradypnea; tolerating the process of weaning, leading to a minimum of PEEP = 5 cm H_2O and CPAP = 8 cm H_2O
- No active bleeding from mediastinal tubes or chest tubes with normal coagulation profile
- No acute fall of hematocrit
- Full reversal of neuromuscular blocking drugs by administration of pharmacologic reversing agents with full muscle recovery
- No abnormalities in blood gas parameters, electrolyte status or metabolic parameters
- Normal chest X-ray with normal costophrenic angle, clear lung fields without any mediastinal widening.

Postoperative pain scores were assessed using a scale of 10 VAS scoring system. If the VAS score was more than 3, 0.1 mg/kg intravenous morphine sulfate was administered slowly and in a dilute solution. Postoperative pain scores at 1, 6 and 24 h after ICU entry and total postoperative morphine consumption were measured and compared between the two groups.

If there was unacceptable chest tube drainage or unstable hemodynamics mandating any surgical intervention, the extubation process was delayed until the problem was resolved. After 2 days of ICU care, the patients were transferred to the postoperative cardiac surgery ward.

We took 10 ml of non-heparinized arterial samples from the arterial lines of the patients before anesthesia and 24 h after patient arrival at the ICU; the samples were kept in bottles containing EDTA. Then, we performed blood centrifugation at 2,500×*g* for 10 min at 4 °C; then samples were frozen at −18 °C inside the Stat-lab of the ICU and then transferred in an ice box to storage at −70 °C. Sampling temperature, centrifugation and refrigeration were kept consistent throughout the study.

Measurement of NT pro-BNP was performed using an electrochemical luminescence immunoassay in an Elecsys 2010 (Roche, Indianapolis, IN, USA). This method is based on two polyclonal antibodies (against the epitopes of NT-proBNP). This method has a coefficient of variation of 2.2–3.2 %, with a detection range of 5–35,000 pg/ml. Also, we measured CPK-MB levels the day before surgery and at the 6th and 12th hours after surgery.

We extracted the study data from each patient's data sheet, then we performed statistical analysis using SPSS (version 11.5; SPSS Inc, Chicago, IL, USA). For statistical data analysis, Student's *t*-test and Chi-square test were used. We considered a value less than 0.05 significant.

Results

A total of 88 patients were enrolled in the study. There was no difference between the two groups regarding age, body surface area (BSA), Euroscore, weight, baseline ejection fraction (EF), erythrocyte sedimentation rate before operation (pre CPB ESR), baseline hematocrit values (pre CPB hematocrit), preoperative blood levels of magnesium and ionized calcium and baseline creatinine values (pre CPB Cr); (Table 1).

Also, cardiopulmonary bypass pump time (CPB time), aortic cross clamp time (ACC time), and the total number of coronary grafts were not statistically different between the two groups (Table 1).

However, the duration of postoperative mechanical ventilation was significantly lower in the magnesium sulfate group, while the duration of ICU stay and the amount of blood loss was not different between the two groups (Table 2). Also, postoperative pain scores at 6 and 24 h after the operation, and total postoperative morphine requirements were lower in the $MgSO_4$ group compared with the placebo group.

Baseline serum levels of CKMB (i.e., MB isoenzyme of creatine phosphokinase) (pre CPB CKMB), serum levels of CKMB at 6 h after surgery (6th CKMB), CKMB at 12 h after surgery (12th CKMB), and baseline serum levels of

Table 1 Baseline and intra-operative study variables

Variable	Results in the study groups				*P* value
	$MgSO_4$ group ($n = 44$)		Placebo group ($n = 44$)		
	Mean	±SD	Mean	±SD	
Age (year)	60	9.8	59	8.1	0.518
BSA (m^2)	1.78	0.12	1.8	0.17	0.445
Euroscore	2.9	1.5	2.7	1.6	0.406
Weight (kg)	68	5.4	71	3.3	0.318
Pre CPB EF (%)	44.5	1.5	45.2	2.4	0.211
Pre CPB ESR	19.3	19	21	20.1	0.742
Pre CPB Hct (%)	41.3	3.7	40.5	4.1	0.395
Pre CPB Cr (mg/dl)	1.05	0.24	1.13	0.2	0.173
ACC time (min)	59.97	16.883	64.90	15.732	0.238
CPB time (min)	102.90	29.841	104.13	21.880	0.854
Graft number	3.13	0.619	3.00	0.816	0.486
Preoperative blood magnesium level (mmol/l)	0.89	0.2	0.93	0.1	0.332
Preoperative blood level of ionized calcium (mmol/l)	1.3	0.4	1.4	0.4	0.281

BSA body surface area, *Pre CPB EF* baseline ejection fraction, *Pre CPB ESR* erythrocyte sedimentation rate before operation, *Pre CPB Hct* baseline hematocrit values, *Pre CPB Cr* baseline creatinine values, *ACC time* aortic cross clamp time, *CPB time* cardiopulmonary bypass pump time, *Graft number* the total number of coronary grafts

Table 2 Postoperative clinical variables

Variable	Results in the study groups				*P* value
	$MgSO_4$ group ($n = 44$)		Placebo group ($n = 44$)		
	Mean	±SD	Mean	±SD	
Ventilation duration (h)	1.7	0.6	2.4	0.6	0.001
ICU stay (day)	4.3	0.7	4.5	0.8	0.3
Blood loss (ml)	355	142	369	376	0.8
Post op pain (6th hour)	2.2	0.5	2.3	0.4	0.2
Post op pain (12th hour)	1.8	0.3	2.5	0.3	0.01
Post op pain (24th hour)	1.6	0.1	2.2	0.4	0.01
Post op (24 h) morphine requirement	11.3	3.4	18.8	5.3	0.01

NT pro-BNP (pre CPB BNP) were not statistically different between the two groups (Table 3).

However, regarding the main study end point, i.e. serum levels of NT pro-BNP after the operation, the levels 24 h after patient arrival at the ICU (i.e. postoperative NT pro-BNP) were significantly lower in the magnesium sulfate group (Table 3).

Table 3 Laboratory data of the study groups

Variable	Results in the study groups				*P* value
	$MgSO_4$ group ($n = 44$)		Placebo group ($n = 44$)		
	Mean	±SEM	Mean	±SEM	
Pre CPB CKMB	19.3	10.3	19.1	12.9	0.940
6th CKMB	48.2	28.2	50.9	29.9	0.263
12th CKMB	49.7	28.1	48.5	26.5	0.861
Pre CPB BNP	1179.7	57.4	1164.7	39.3	0.690
Postoperative BNP	1566.4	15.9	2632.1	29.2	0.002

Pre CPB BNP baseline serum levels of BNP, *Postoperative BNP* serum levels of BNP after the operation (2 h after patient arrival at the ICU)

Discussion

This study suggests that in patients undergoing elective CABG with coronary bypass cardiopulmonary bypass, administration of intravenous magnesium sulfate may decrease the duration of postoperative mechanical ventilation, and also postoperative NT pro-BNP levels (i.e. serum levels of beta natriuretic peptide in patients undergoing CABG). However, the infusion did not affect the length of ICU stay or the amount of postoperative blood loss.

Prior studies have documented the effectiveness of magnesium sulfate infusion in improving postoperative pain scores and therefore reducing morphine requirements [5] in patients undergoing elective CABG and some other surgeries [4]; similar results are seen in this study.

Also, the results of this study were in concordance with another study which demonstrated the role of magnesium accompanied with *N*-acetylcysteine in "prevention of CPB-induced oxidative stress" [9]. In another study, it was demonstrated that adding magnesium to warm-blood cardioplegia may decrease the chance of cardiac injury [11]; this study may support our finding regarding the decreased level of postoperative NT pro-BNP in the $MgSO_4$ group.

Using magnesium solutions for organ protection has been mentioned in many studies [4, 5, 8–13]; a considerable number of these studies deal with the patients undergoing cardiac surgery with a cardiopulmonary bypass. Also, cardiac biomarkers have been demonstrated to be effective in assessing the protective magnesium effects; with an infusion of 10 mg per min which could "reduce the serum S100β concentrations" [12]. However, it has been demonstrated that perioperative glucose–insulin–potassium administration could decrease the plasma levels of postoperative N-terminal pro-brain natriuretic peptide in patients undergoing CABG [1]. Until now, however, there have been no studies demonstrating the effects of

magnesium infusion on postoperative N-terminal pro-brain natriuretic peptide levels in patients undergoing CABG with CPB.

The results of our study also demonstrated a lower duration of postoperative mechanical ventilation in the $MgSO_4$ group; this finding could be compatible with the possible anti-inflammatory or analgesic effects of $MgSO_4$ infusion; in other words, decreased pain and/or inflammation could improve spontaneous ventilation through decreasing the postoperative pain level, especially in the chest wall, leading to inspiration and expiration [1, 5, 8].

Although there are studies that have mentioned impaired coagulation after magnesium infusion in CABG due to the effects of magnesium on platelet function [15], our study demonstrated no difference between the two groups regarding postoperative blood loss. However, there are a number of studies supporting the effect of magnesium sulfate in decreasing postoperative bleeding after cardiac surgery [14, 16]. One of these [14] demonstrated less postoperative bleeding and decreased use of packed cell after administration of intravenous magnesium sulfate in CABG, possibly due to the anti-inflammatory effects of magnesium infusion in patients undergoing CPB for CABG; a process overtly increasing the inflammatory process after cardiac surgery. So, the results of the current study might support the anti-inflammatory effects of magnesium sulfate, operating by decreasing the severity of impairment in the coagulation cascade which is affected by the inflammatory cascade. There are many proteins in common between the two protein cascades, supporting the hypothesis that magnesium sulfate administration might be effective in "decreasing the activation of pro-coagulant and inflammatory proteins" [15, 17].

Limitations

There are a number of limitations in this study. First of all, the inflammatory cytokine levels were not assessed before and after the surgical procedures. Also, the patients were not evaluated regarding their underlying diseases including their inflammatory disease states. Another major limitation of our study was that we just assessed two points of the serum levels of NT pro-BNP; while the trend of the marker or the "area under curve" (AUC) was not measured.

Also, C-reactive protein (CRP) is a sensitive and important marker of inflammation [17]; however, we did not check it before and after surgery in our study; this could be one of our limitations in the study.

Final conclusion: this study demonstrated that administration of magnesium sulfate infusion in patients undergoing elective CABG with CBP can decrease postoperative pain, postoperative morphine requirements, and serum levels of N-terminal beta pro natriuretic peptide (pro-BNP) compared with a placebo. Also, $MgSO_4$ solution could decrease the duration of postoperative mechanical ventilation.

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