Acute Effect of Intravenous Administration of Magnesium Sulfate on Serum Levels of Interleukin-6 and Tumor Necrosis Factor-α in Patients Undergoing Elective Coronary Bypass Graft With Cardiopulmonary Bypass

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1. Background
Cardiovascular problems are among the most common health issues. A considerable number of cardiac patients undergo cardiac surgery, and coronary artery disease patients constitute about two-thirds of all these surgeries. The application of cardiopulmonary bypass (CBP) usually results in some untoward effects.

2. Objectives
Studies have suggested magnesium sulfate (MgSO4) as an anti-inflammatory agent in a coronary artery bypass graft (CABG). This study aimed to assess the effect of an IV MgSO4 infusion during elective CABG (with CBP) on the blood levels of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α).

Materials and Methods:
During a 12 month period, after review board approval and based on inclusion and exclusion criteria, 90 patients were selected and entered randomly into one of the two study groups (MgSO4, or placebo). Anesthesia, surgery and CBP were performed in exactly the same way, except for the use of MgSO4 or a placebo. Both preoperative and postoperative plasma levels of IL-6 and TNF-α were checked and compared between the two groups using an ELISA.

Results:
There was no difference found between the two groups with regard to; gender, basic variables, Ejection Fraction (EF), CBP time and aortic cross-clamp time. The preoperative levels of IL-6 and TNF-α were not different; however, their postoperative levels were significantly higher in the placebo group (P value = 0.01 for IL-6 and 0.005 for TNF-α).

Conclusions:
This study showed that MgSO4 infusion could suppress part of the inflammatory response after CABG with CBP. This was demonstrated by decreased levels of interleukin-6 and TNF-α in postoperative serum levels in elective CABG with CBP.

Keywords: Magnesium; Interleukin 6; Tumor Necrosis Factor Alpha
(MgSO$_4$) solution has anti-inflammatory properties in many conditions (3-6, 30-33). In addition, it has also been demonstrated in a number of studies that magnesium can ‘modulate cellular events involved in inflammation’ while ‘activation of leukocyte and macrophage and the release of inflammatory cytokines’ are the characteristic features of this inflammatory syndrome (34, 35). Among the main proposed mechanisms for the anti-inflammatory effects of MgSO$_4$, the ‘phosphoinositide 3-kinase/Akt pathway’ is one of the most important ones. Meanwhile, another main mechanism seems to be the suppressing role of magnesium throughout the inflammatory process by the ‘activation of N-methyl-D-aspartate (NMDA) receptors. Since, magnesium is a natural antagonist of calcium ion and MgSO$_4$, which acts through inhibition of ‘N-methyl-D-aspartate dependent cellular pathways’(3-6, 30, 35, 36). On the other hand, it has been demonstrated that decreased plasma levels of magnesium can activate inflammatory neuromediators via the activation of ‘neuroendocrinological pathways (37). At the same time, other studies have demonstrated that NF-kappaB activation with simultaneous suppression of endotoxin, induces an increase in inflammatory mediators due to magnesium infusion in animals; furthermore, these mechanisms possibly work in a similar way in coronary artery bypass graft (CABG) patients (3-6, 34, 38-43). A number of cytokines have been named as pro-inflammatory ones; interleukin-6 (IL-6) and tumor necrosis alpha (TNF-α) are among them (26, 38, 44, 45). This randomized clinical trial study was designed and implemented to assess the effect of an intravenous magnesium sulfate (IV MgSO$_4$) infusion compared with a placebo, during elective CABG (with CPB) on the blood levels of IL-6 and TNF-α.

3. Materials and Methods

The study started from October 2011 for a 12 month period, after review board approval from the Shahid Beheshti University of Medical Sciences Research Committee. The study complied with current ethical considerations. Authors declare that:
• Informed consent was obtained from each patient included in the study
• The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee.

All patients in the operating room of Shahid Modarres (a university hospital affiliated to Shahid Beheshti University of Medical Sciences), undergoing elective CABG surgery were the target population, and 90 patients were selected and entered the study. The patients were randomly allocated in either the control group (45 patients) or the case group (45 patients) the case group received a MgSO$_4$ infusion and the control group received a placebo (Figure 1). Except for this classification, there were no differences between the two groups regarding; anesthesia method, surgical procedure, surgeons and physicians, or medical treatment protocols. In addition, the volume of the magnesium infusion and the placebo as well as their syringes were similar (50 mL syringes). Sample size determination was done after a power analysis (power = 0.8, β = 0.2, α = 0.02) using sample size software: PASS 2005; NCSS, LLC; UT, USA.

Patient entry to the study was done after obtaining an informed written consent and they were allocated into the two groups based on a computer table of random numbers and after considering the inclusion and exclusion criteria.

3.1. Inclusion and Exclusion Criteria Were as Follows

3.1.1. Inclusion Criteria
• Elective CABG using CPB
• Age 30-65 years

3.1.2. Exclusion Criteria
• Underlying heart failure (right sided or left sided, including low left ventricular ejection fraction, ie. preoperative LVEF < 25%)
• Underlying renal disease
• Underlying diabetes mellitus
• Underlying uncontrolled hypertension
• Underlying thyroid problems (hypo/hyperthyroidism, active or controlled)
• Underlying malabsorption (active or controlled)
• Underlying untreated arrhythmias
• Underlying inflammatory disease (active or controlled)
• Underlying uncorrected magnesium or calcium abnormalities
• Emergent or urgent CABG
• Patient refusal to enter or continue study

Figure 1: A Summary of Study Stages Are Presented in the Following Diagram
Table 1. Basic Variables in the Two Groups

|                | MgSO₄ group | Placebo group | P value |
|----------------|-------------|---------------|---------|
| Gender         |             |               |         |
| Male           | 28          | 30            | > 0.05  |
| Female         | 17          | 15            | -       |
| Age, y         | 64 ± 8      | 62 ± 10       | > 0.05  |
| Weight, kg     | 73 ± 12     | 77 ± 6        | > 0.05  |
| LVEF, %        | 44 ± 12     | 47 ± 10       | > 0.05  |
| CPB time       | 96 ± 8      | 92 ± 12       | > 0.05  |
| ACC time       | 54 ± 6      | 57 ± 7        | > 0.05  |

Abbreviations: MgSO₄, magnesium sulfate; CPB, cardiopulmonary bypass pump; LVEF, Left Ventricle Ejection Fraction; ACC, aortic cross-clamp.

Chi square.

There was no difference between the two groups regarding demographic variables including: gender, age, weight, ejection fraction (EF), cardiopulmonary bypass pump time, and aortic cross-clamp time (Table 1).

In the MgSO₄ group, the post-operative level of IL-6 was 67.6 ± 22.3 pg/ml; while in the placebo group, the post-operative level of IL-6 was 102.1 ± 33.7 pg/ml (P value = 0.01). Also, the postoperative level of TNF-α in the MgSO₄ group was 27.4 ± 4.2 pg/ml; while in the placebo group, the post-operative level of TNF-α was 44.7 ± 6.1 pg/ml (P value = 0.005).
5. Discussion
The results of this study demonstrated that administration of MgSO₄ solution in adult patients undergoing elective CABG could suppress part of the inflammatory response after CABG with CPB. This was demonstrated as decreased levels of IL-6 and TNF-α in postoperative serum. However, the two groups had no difference in regard to cardiopulmonary bypass items, surgical variables, or anesthetic parameters; this indicated that the underlying clinical situations for the study were largely identical in the two groups. Magnesium may ‘modulate cellular inflammation’ while ‘suppressing the inflammatory role of inflammatory cells and cytokines’ (34, 35) through the ‘activation of N-methyl-D-aspartate (NMDA) receptors’, ‘phosphoinositide 3-kinase/Akt pathway’ and suppression of inflammatory neuromediators through the activation of ‘neuro-endocrinological pathways’ as the main mechanisms; since, magnesium is a natural antagonist of calcium ion (3-6, 30, 35-37, 42). The inflammatory response after CPB is one of the most significant side effects of this surgical intervention, and a number of compensatory mechanisms and approaches have been proposed, though many remain equivocal (1, 2, 10, 12, 27, 45-49). Magnesium infusion is an easy and routine therapeutic agent, and its anti-inflammatory effects are an important effect of the drug (4, 31, 35, 39, 50, 51). There are many studies denoting the therapeutic effects of magnesium infusion on many other systems, including its positive effects on the cardiovascular and respiratory system, as well as its analgesic effects (30). Since the usage of magnesium infusion could lead to improved inflammatory status, according to this study, it can be recommended that a magnesium infusion is used to suppress some of the inflammation in a cost effective way.

5.1. Limitations
Among the study methods, the limited assessment epistodes of IL-6 and TNF-α assessments are among the main limitations of the study. Moreover, other interleukins could be helpful for making more exact assessments. The sample size was also limited.

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Authors’ Contributions
Parastou Aryana: study concept and design, acquisition of data, drafting of the manuscript, technical, and material support, and study supervision; Samira Rajaei: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content and study supervision; Abdolhamid Bagheri: study concept and design, interpretation of data, and drafting of the manuscript; Forouzan Karimi: study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript; Ali Dabbagh: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, administrative, technical and material support, and study supervision.

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