Intravenous Magnesium Sulfate to Deliberate Hypotension and Bleeding after Bimaxillary Orthognathic Surgery; A Randomized Double-blind Controlled Trial

Hamed Modanlou Juibari 1, Hamid Reza Eftekharian 1, Hamid Reza Arabion 1

1Dept. of Craniomaxillofacial Surgery, School of Dentistry, Shiraz University of Medical Sciences, Shiraz, Iran.

ABSTRACT

Statement of the Problem: The preoperative or intraoperative administration of intravenous magnesium sulfate has been approved as an accepted medication for stabilizing hemodynamic indices during surgeries.

Purpose: Intraoperative blood loss during orthognathic surgery is frequently abundant and sometimes requires blood transfusion. The present trial addressed the efficacy of intravenous magnesium sulfate on deliberating hypotension and bleeding reduction in patients undergoing bimaxillary orthognathic surgery.

Materials and Method: This randomized double-blinded placebo controlled trial was conducted on 52 consecutive patients who underwent orthognathic surgery. The participants were randomly assigned to two groups receiving intravenous magnesium sulfate 30 mg/kg body weight bolus for 15 minutes immediately before anesthesia induction, followed by 10 mg/kg/hr dissolved in saline via pump infusion (n=26) and the second group received placebo as same bolus volume of normal saline in a 15-minute intravenous infusion which was continued until the end of operation (n=26). Both systolic and diastolic blood pressures were measured before anesthesia induction at baseline, during surgery, and at the end of the surgery. Intraoperative blood loss was also determined.

Results: Systolic and diastolic blood pressures did not differ between the two groups at baseline. Although a downward trend of both systolic and diastolic blood pressures was seen during the operation in both groups, the decrease in blood pressures occurred with greater gradient in the group administered magnesium sulfate. Assessing difference in the trend of the changes in systolic and diastolic blood pressures between the two study groups (adjusted for gender, age, mean body mass index, and time of surgery) showed different trends in the changes of blood pressures. No differences were observed in blood loss or blood product requirement between the two groups.

Conclusion: The administration of intravenous magnesium sulfate can attenuate both systolic and diastolic blood pressures during orthognathic surgery with no significant effect on the volume of blood loss or need for blood transfusion.

Introduction

Bimaxillary surgery results in a major volume of blood loss directly related to the operating time and the magnitude of the intervention. Recent studies have shown the deliberating effect of intravenous magnesium sulfate on hypotension. [1-2] The reducing effect of magnesium...
sulfate on blood pressure is related to intervening in the activation of Ca ATPase and Na–K ATPase presuppose in trans-membranous ion exchange resulting in the stabilization of the cell membrane and cytoplasm micro-organelles. [3-4] Another physiological role of magnesium sulfate is related to the inhibition of calcium channels leading to limited calcium outflow from sarcoplasmic reticulum. [5] Magnesium sulfate can induce production and secretion of prostacyclin as well as reduce the activity of angiotensin converting enzyme leading to vasodilatation. [6] Moreover, the depressant influence of magnesium sulfate on the myocardium results in reduced heart contractility. [7] The collection of studies on the physiological effects of intravenous magnesium sulfate on hemodynamic status emphasizes its practical value in different clinical settings. These beneficial effects are more important following surgeries that lead to undesirable and unexpected hemodynamic changes such as reflex tachycardia, systemic hypertension, pulmonary artery hypertension, and also arrhythmias. [8-9] In fact, the preoperative or intraoperative administration of intravenous magnesium sulfate has been approved as an accepted medication for stabilizing hemodynamic indices during surgery, especially through decreasing blood pressure and heart rate and also minimizing adverse hemodynamic responses. [10]

Göral et al. [11] demonstrated that magnesium sulfate significantly decreased the amount of surgical bleeding by inducing controlled hypotension leading to less need for blood transfusion following lumbar disectomy surgery and improved surgical exposure without marked hemodynamic effects. However, magnesium sulfate should be used with caution in patients with renal dysfunction and is even prohibited in patients with myocardial injury or cardiac blocks. [12] Furthermore, when using magnesium sulfate, its side effects should also be considered such as possible complication during anesthesia and poorer surgical outcome. The blood loss during orthognathic surgery can be considerable. The reason for the extensive blood loss is the extensive vascularization of the maxillofacial region and access difficulty in terms of cauterization or ligation of the vessels involved. This bleeding is caused by the palatal large vessels (sphenopalatine artery and descending palatine artery), the pterygoid plexus, and the internal maxillary artery and its collateral branches to the upper jaw in Le Fort I osteotomies. The maxillary artery and its branches are the most vulnerable to injury during pterygomaxillary dysjunction or maxillary down fracture, specifically, the descending palatine artery. It can also be damaged if the maxilla is advanced to a significant degree, intruded posteriorly, or retruded. [13] This study aimed to assess the efficacy of intravenous magnesium sulfate on deliberating hypotension and bleeding in patients undergoing bimaxillary orthognathic surgery.

Material and Method

Study population

This randomized double-blinded placebo controlled trial was conducted on 52 consecutive patients who underwent orthognathic surgery at Shahid Chamran Hospital affiliated to Shiraz University of Medical Sciences. The mean±SD age of the participants was 22.83±5.22 years (range: 15-36 years). All defined contraindications of magnesium sulfate injection including history of renal dysfunction, hypertension, diabetes mellitus, myocardial infarction, patients with heart block or myocardial damage, morbid obesity (BMI ≥35), neuromuscular disease, and history of neuropathy, asthma, and use of calcium channel blockers were considered as the exclusion criteria. Patients who did not sign the informed consent were also excluded. The participants were randomly assigned to two groups receiving intravenous magnesium sulfate at an initial dose of 30 mg/kg body weight during 15 minutes and then a dosage of magnesium sulfate 10 mg/kg/hr via pump infusion continuously until the end of operation (n=26) or normal saline as the placebo (n=26, Figure 1).

The same anesthetic protocol was followed for all subjects. Propofol (2.5mg/kg) and remifentanil (3micro/kg) were used for the induction. Propofol (100 micro/kg /min) and remifentanil (0.1 micro/kg /min) were infused for anesthetic maintenance during the operation. All subjects received N2O and O2 (50%) during the operation. The researcher physician and nurse who collected the data were unaware of the content of injected material (double blinded). The surgeon was also unaware of the types of administered drug. The randomization was performed by the random number generator and using permutation method. The sampling was also based on simple purposive method so if the selected person was not placed in the sample group, the other pe-
This clinical trial holds Iranian registry number IRCT201311051674N9 (www.irct.ir) and was approved by the local Research Ethics Committee of Shiraz University of Medical Sciences and all participants provided written informed consent before surgery.

**Study measurements**

Baseline characteristics including demographic characteristics, medical history, and anesthesia induction technique were collected by reviewing the recorded files. All patients received 6 ml/kg serum Ringer and their vital signs were monitored. Intraoperative monitoring included ECG, peripheral oxygen saturation, and continuous invasive intra-arterial blood pressure (typically measured at the radial artery) monitoring. Both systolic and diastolic blood pressures were measured before anesthesia induction (at baseline); during surgery, and also at the end of surgery. Each sample was constructed by selecting mean invasive arterial blood pressure sample from each of the selected patient trend records. Statistical significance of regression coefficients was determined based on 95% confidence intervals. Intraoperative blood loss was also determined by observing the volume of surgical suction bottles and all pieces of gauze were weighed at the end of the surgery and corrected by subtracting the amount of saline wash used during surgery. The incidence rates of bleeding, shivering, blood pressure changes, agitation and postoperative nausea and vomiting were also recorded after the surgery.

**Statistical analysis**

Results were presented as mean ± Standard deviation for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Continuous variables were compared using t, and one-way ANOVA tests, or non-parametric Mann-Whitney U or Kruskal-Wallis tests whenever the data did not appear to have a normal distribution or when the assumption of equal variances was violated across the groups. Repeated-measure ANOVA test was also used to assess the difference in trend of the changes in systolic and diastolic blood pressures between the study groups adjusted for baseline variables including gender, age, body mass index and duration of surgery.

Data were analyzed using SPSS software version 20.0 (SPSS Inc., Chicago, IL). P values of 0.05 or less.
### Table 1: Comparing baseline characteristics between the case and control groups presented as frequency (%) or mean±SD

| Variables                  | Magnesium Sulfate Group (n=26) | Placebo Group (n=26) | P value |
|---------------------------|--------------------------------|----------------------|---------|
| Gender                    |                                |                      |         |
| Male                       | 11 (42.3)                      | 9 (34.6)             | 0.569   |
| Female                     | 15 (57.7)                      | 17 (65.4)            |         |
| Age                        | 23.38±5.27                     | 22.27±5.21           | 0.447   |
| Weight, kg                 | 61.35±10.99                    | 59.62±8.04           | 0.520   |
| Height, cm                 | 169.27±9.17                    | 167.27±7.65          | 0.397   |
| Body mass index, kg/m²     | 21.33±2.71                     | 21.27±2.22           | 0.936   |
| Time of surgery, hour      | 4.37±0.93                      | 3.87±0.59            | 0.026   |

### Table 2: Intraoperative and postoperative events in case and control groups

| Variables                  | Magnesium Sulfate Group (n=26) | Placebo Group (n=26) | P value |
|---------------------------|--------------------------------|----------------------|---------|
| Blood loss (ml)            | 667.31±433.58                  | 667.31±294.26        | 0.999   |
| Blood packed cell          | 1 (3.8)                        | 1 (3.8)              | 1.000   |
| Fresh frozen plasma        | 2 (7.7)                        | 2 (7.7)              | 1.000   |
| Both                       | 1 (3.8)                        | 4 (15.4)             | 0.356   |
| Urine volume (ml)          | 1065.38±564.76                 | 1163.46±425.34       | 0.483   |
| Complication in recovery   |                                |                      |         |
| Bleeding                   | 3 (11.5)                       | 2 (7.6)              | 0.999   |
| Shivering                  | 8 (30.8)                       | 6 (23.1)             | 0.635   |
| Blood pressure changes     | 1 (3.8)                        | 0 (0.0)              | 0.999   |
| Agitation                  | 2 (7.6)                        | 3 (11.5)             | 0.999   |
| Nausea and vomiting        | 1 (3.8)                        | 1 (3.8)              | 1.000   |

Results

We found no significant difference between the group receiving intravenous magnesium sulfate and the group receiving placebo, regarding the baseline variables such as gender distribution, mean age, and mean body mass index (Table 1). However, in the magnesium sulfate group, there was a longer surgical time compared with the placebo group. Regarding intraoperative and postoperative events (Table 2), the volume of intraoperative blood loss and also blood products used for transfusion were similar in the two groups.

The total early sequela rate after surgery in the group receiving magnesium sulfate was 57.7% as compared with 46.2% in the placebo group (p= 0.737). The most common complication in the post anesthesia care unit was shivering (30.8% versus 23.1%), followed by bleeding (11.5% versus 7.6%) and agitation (7.6% versus 11.5%).

Systolic and diastolic blood pressures did not differ between the two groups at baseline. Compared to baseline assessment, intraoperative systolic blood pressure was reduced to 20.17% in the group receiving magnesium sulfate and to 17.04% in placebo group with no significant difference (p= 0.772). Also, postoperative systolic blood pressure was reduced to 14.14% in the magnesium sulfate group and to 14.66% in the placebo when compared with baseline measures (p= 0.957), regarding changes in diastolic blood pressure, intraoperative diastolic blood pressure decreased by 15.51% in the group receiving magnesium sulfate and by 12.90% in placebo group with no significant difference (p= 0.788). Furthermore, postoperative diastolic blood pressure decreased by 12.19% in the magnesium sulfate group and by 12.41% in the placebo when compared with baseline measures (p= 0.981). (Table 3)

### Table 3: Measures of blood pressure at different time points

| Variables                  | Magnesium Sulfate Group (n=26) | Placebo Group (n=26) |
|---------------------------|--------------------------------|----------------------|
| Preoperative (mmHg)        | 117.81±12.07                   | 121.92±6.49          |
| Intraoperative (mmHg)      | 94.04±4.69                     | 101.15±6.53          |
| Postoperative (mmHg)       | 101.15±8.87                    | 104.04±6.00          |
| Preoperative (mmHg)        | 74.42±6.53                     | 77.50±7.52           |
| Intraoperative (mmHg)      | 62.88±2.52                     | 67.50±4.06           |
| Postoperative (mmHg)       | 65.38±4.22                     | 67.88±4.51           |

Discussion

The present study aimed to address the changes in blood pressure and blood loss following administration of intravenous magnesium sulfate in patients who underwent bimaxillary orthognathic surgery. Although previous studies evaluated similar effects of magnesium sulfate in different surgical groups, to the best of our knowledge, our study was the first in patients who were...
candidate for orthognathic surgery. In this study, magnesium sulfate was administered as 30 mg/kg body weight intravenously during 15 minutes and then 10 mg/kg/hr continuously during the operation. The pointed regimen reduced both systolic and diastolic blood pressure within operation without any significant changes in the volume of blood loss or required blood products; however, similar changes in both systolic and diastolic blood pressures were revealed in the placebo group. On the other hand, the change in both blood pressures was shown to be similar in both groups and also blood pressures were similarly compensated post-operatively in both groups. In total, administrating magnesium sulfate could not result in more reduction in both systolic and diastolic blood pressures compared with the control group within operation with no effect on the total amount of blood loss.

Reviewing the literature, we found contradictory results especially in terms of magnesium sulfate effect on blood loss or bleeding time. In a study by Elsharnouby et al., [14] a significant reduction of blood loss as well as mean arterial blood pressure was found in the group receiving magnesium sulfate. Sanders and Sim [15] reported increase in prothrombin time, and decrease in partial thromboplastin time after administering magnesium sulfate. Prielipp and colleagues [16] reported that magnesium sulfate could blunt epinephrine's hypertensive action and prevent increase in mean arterial pressure during administration. Dabbagh et al. [9] also showed that the magnesium group had less postoperative bleeding and less packed cell use compared with the placebo group, which is inconsistent with our findings. Furthermore, Nastou et al. [17] observed that systolic and diastolic blood pressures fluctuated outside the critical range when magnesium sulfate was administered, whereas in the control group an increase of blood pressure was noted which was treated with other types of anti-hypertensive drugs. In total, it seems that the use of intravenous magnesium sulfate cannot stabilize blood pressure during different types of operations without useful reduction in systolic and diastolic blood pressures. In addition, its effects on intraoperative or postoperative bleeding or on blood transfusion requirement may differ regarding the type of surgery (major or minor surgery), anesthesia technique (drug-based protocol of general anesthesia for different operation), surgical time, or even definition of bleeding in the studies. Type of surgery on soft tissue or bone tissue could have various effects on the amount of bleeding.

Considering the impact of intravenous magnesium sulfate on reducing blood pressure or even its probable effect on surgical-related bleeding in some observations, various physiological theories were proposed. First, it has been demonstrated that magnesium sulfate may act as a vasodilator with a minimal myocardial depression that could lower cardiac contractility as well as peripheral vascular resistance. [7, 18] The ability of this agent to inhibit the release of catecholamines has also been revealed. [19-21] Jee et al. [22] reported that norepinephrine, epinephrine, and vasopressin levels were lower in the magnesium group than in the control group. However, these effects could not be revealed in our survey.

Although we could not demonstrate the effect of magnesium sulfate on the total amount of blood loss, reduced bleeding in some previous reports might be attributed to vasodilation or the systemic hypotensive effects of this drug. Also, the effects of the drug on coagulation system and platelet function, which leads to changes in bleeding time, has also been pointed. [23-24] a finding which was not observed in our study. Since the effects of magnesium sulfate are dose-dependent, it seems that our employed dosage of this drug was not sufficient to lead to changes in bleeding or required blood products. In this context, the effects of the different dosages of magnesium sulfate on volume of blood loss and need for intraoperative blood transfusion should be further assessed in future studies.

One of the interesting points in our results is that despite the long duration of surgery in the magnesium sulfate group, the total amount of perioperative bleeding was similar in both groups. In fact, considering probable increasing intraoperative bleeding in prolonged operations, the use of magnesium sulfate may prevent perioperative bleeding appropriately. In some clinical studies on patients who underwent major surgeries, administrating intravenous magnesium sulfate lowered both perioperative and postoperative bleeding and packed cell use. [9] In total, it seems that in order to achieve correct results about the impact of intravenous magnesium sulfate on perioperative bleeding or needing blood transfusion, different time points of surgery duration in future
studies should be considered. As magnesium is a natural physiological calcium antagonist and regulates calcium influx into cells, it may affect the coagulation cascade. [24-25] It is recommended that in future studies coagulation profile tests should be determined in these patients.

**Conclusion**

The administration of intravenous magnesium sulfate can attenuate both systolic and diastolic blood pressures during bimaxillary orthognathic surgery with no significant effect on blood loss or needing blood products. Despite the long duration of surgery in the magnesium sulfate group, the total amount of perioperative bleeding was similar in both groups. Because of the nature of dose-dependent effects of magnesium sulfate, its effects on hemodynamic parameter may be different in different used dosages and prescribed protocols.

**Conflict of Interest**

The authors of this manuscript certify no financial or other competing interest regarding this article.

**References**

[1] Somani M, Mathur V, Sachdev S, Jethava D, Jethava DD. Role of Intravenous Magnesium Sulphate in Spine Surgery for Hypotensive Anesthesia; A Randomized Control Trial. International. J Contemp Med Res. 2015; 2: 818-821.

[2] Carlos E, Monnazzi MS, Castiglia YM, Gabrielli MF, Passeri LA, Guimarães NC. Orthognathic surgery with or without induced hypotension. Int J Oral Maxillofac Surg. 2014; 43: 577-580.

[3] Koinig H, Wallner T, Marhofer P, Andel H, Höräuf K, Mayer N. Magnesium sulfate reduces intra- and postoperative analgesic requirements. Anesth Analg. 1998; 87: 206-210.

[4] Cunha AR, Umbelino B, Correia ML, Neves MF. Magnesium and vascular changes in hypertension. Int J Hypertens. 2012; 2012: 754250.

[5] Sharma N, Prasad Bhattarai J, Han Hwang P, Kyu Han S, Yang YS. Inhibition of L-type calcium currents by magnesium sulfate on the rat basilar artery smooth muscle cells. Neurology Asia. 2014; 19: 301-307.

[6] Mesbah Kiae M, Safari S, Movaseghi GR, Mohaghegh Dolatabadi MR, Ghorbani M, Etemadi M, et al. The effect of intravenous magnesium sulfate and lidocaine in hemodynamic responses to endotracheal intubation in elective coronary artery bypass grafting: a randomized controlled clinical trial. Anesth Pain Med. 2014;4: e15905.

[7] Massy ZA, Driëcke TB. Magnesium and cardiovascular complications of chronic kidney disease. Nat Rev Nephrol. 2015; 11: 432-342.

[8] Kiziltepe U, Eyyleton ZB, Sirlak M, Tasoz R, Aral A, Eren NT, et al. Antiarrhythmic effect of magnesium sulfate after open heart surgery: effect of blood levels. Int J Cardiol. 2003; 89: 153-158.

[9] Dabbagh A, Rajaei S, Shamsolahrar MH. The effect of intravenous magnesium sulfate on acute postoperative bleeding in elective coronary artery bypass surgery. J Perianesth Nurs. 2010; 25: 290-295.

[10] Nooraei N, Dekhordi ME, Radpay B, Teimoorian H, Mohajerani SA. Effects of intravenous magnesium sulfate and lidocaine on hemodynamic variables following direct laryngoscopy and intubation in elective surgery patients. Tanaffos. 2013; 12: 57-63.

[11] Görul N, Ergil J, Alptekin A, Ozkan D, Güner B, Dolgun H, et al. Effect of magnesium sulphate on bleeding during lumbar discectomy. Anaesthesia. 2011; 66: 1140-1145.

[12] Gröber U, Schmidt J, Kisters K. Magnesium in Prevention and Therapy. Nutrients. 2015; 7: 8199-8226.

[13] Lanigan DT, Hey JH, West RA. Major vascular complications of orthognathic surgery: hemorrhage associated with Le Fort I osteotomies. J Oral Maxillofac Surg. 1990; 48: 561-573.

[14] Elsharnouby NM, Elsharnouby MM. Magnesium sulphate as a technique of hypotensive anaesthesia. Br J Anaesth. 2006; 96: 727-731.

[15] Sanders GM, Sim KM. Is it feasible to use magnesium sulphate as a hypotensive agent in oral and maxillofacial surgery? Ann Acad Med Singapore. 1998; 27: 780-785.

[16] Prilipp RC, Zaloga GP, Butterworth JF 4th, Robertie PG, Dudas LM, Black KW, et al. Magnesium inhibits the hypertensive but not the cardiotonic actions of low-dose epinephrine. Anesthesiology. 1991; 74: 973-979.

[17] Nastou H, Sarros G, Nastos A, Sarrou V, Anastassopoulou J. Prophylactic effects of intravenous magnesium on hypertensive emergencies after cataract surgery. A new contribution to the pharmacological use of magnesium in anaesthesiology. Magnes Res. 1995; 8: 271-276.

[18] Czocher TA, Radke J, Weyland A, Sydow M, Seyde W, Markakis E, et al. Haemodynamic and endocrine effects
of deliberate hypotension with magnesium sulphate for cerebral-aneurysm surgery. Eur J Anaesthesiol. 1991; 8: 115-121.

[19] Min JH, Chai HS, Kim YH, Chae YK, Choi SS, Lee A, et al. Attenuation of hemodynamic responses to laryngoscopy and tracheal intubation during rapid sequence induction: remifentanil vs. lidocaine with esmolol. Minerva Anestesiol. 2010; 76: 188-192.

[20] Massy ZA, Drüeke TB. Magnesium and cardiovascular complications of chronic kidney disease. Nat Rev Nephrol. 2015; 11: 432-442.

[21] James MF, Beer RE, Esser JD. Intravenous magnesium sulfate inhibits catecholamine release associated with tracheal intubation. Anesth Analg. 1989; 68: 772-776.

[22] Jee D, Lee D, Yun S, Lee C. Magnesium sulphate attenuates arterial pressure increase during laparoscopic cholecystectomy. Br J Anaesth. 2009; 103: 484-489.

[23] Héman LM, Van Der Linden PJ. Does magnesium sulfate increase the incidence of postpartum hemorrhage? A systematic review. Open Journal of Obstetrics and Gynecology. 2011; 1: 168-173.

[24] Guzin K, Goynumer G, Gokdagli F, Turkgeldi E, Gunduz G, Kayabasoglu F. The effect of magnesium sulfate treatment on blood biochemistry and bleeding time in patients with severe preeclampsia. J Matern Fetal Neonatal Med. 2010; 23: 399-402.

[25] Gries A, Bode C, Gross S, Peter K, Böhrer H, Martin E. The effect of intravenously administered magnesium on platelet function in patients after cardiac surgery. Anesth Analg. 1999; 88: 1213-1219.