The Effect of Intravenous Infusion of Magnesium Sulfate During Bimaxillary Orthognathic Surgery on Post-operative Pain: A Clinical Trial

Department of Craniomaxillofacial Surgery, School of Dentistry AND Health Policy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[3] *Department of Craniomaxillofacial Surgery, School of Dentistry AND Shahid Chamran Hospital, Shiraz University of Medical Sciences, Shiraz, Iran*

Received: **12 Nov. 2015*; Received in revised form:*** **26 Jul. 2016*; Accepted:*** **9 Jun. 2016**

Abstract

Background: This prospective randomized controlled clinical study aimed to investigate the effect of magnesium sulfate ($MgSO_4$) on pain management post orthognathic surgery.

Methods: In this study, 52 patients undergoing orthognatic surgery were randomly allocated to receive $MgSO_4$ or saline intravenously. The intervention group (n = 26) received intravenous $MgSO_4$ (30 mg/kg bolus for 15 minutes immediately before anesthesia induction followed by 10 mg/kg/h dissolved in saline via pump infusion) and the second group (n = 26) received the placebo in the same bolus volume as a normal saline in a 15 minute intravenous infusion which was continued until the end of the operation. A visual analog scale (VAS) was used to determine the intensity of pain. Invasive arterial blood pressure and valid and invalid analgesic demand were also recorded. Side effects were recorded, as well.

Results: This study was conducted on 52 patients, 26 per group. The results showed no statistically significant differences between the two groups with respect to demographics. During the post-operative period, the patients in the control group showed larger analgesic requirement 7 (26.9%) compared to those in the magnesium group 4 (15.4%) and the difference was not statistically significant (P = 0.308). The post-operative VAS scores evaluated serially from the recovery room also showed a significant difference between the intervention 3 (11.5%) and the control group 14 (53.8%) after the surgery (P = 0.001). However, no significant difference was found between the two groups regarding VAS scores in the surgical ward [7 (26.9%) vs. 8 (30.8%) P = 0.760].

Conclusions: Intra-operative administration of intravenous $MgSO_4$ reduced opioid consumption for pain after bimaxillary orthognathic operations.

Citation: Eftekharian HR, Hosseini SAA, Heydari ST. **The Effect of Intravenous Infusion of Magnesium Sulfate During Bimaxillary Orthognathic Surgery on Post-operative Pain: A Clinical Trial.** *Acad J Surg*, 2016; 3(1-2): 7-11.

Keywords: Infusions; Intravenous; Magnesium sulfate; Orthognathic surgery; Pain; Post-operative; Pain management

Introduction

A pain resulting from surgery is deleterious and can lead to post-operative complications if inadequately relieved (1). Magnesium sulfate ($MgSO_4$) has been used as an intravenous adjuvant to analgesics in the perioperative period (2). $MgSO_4$ acts as a physiologic calcium-channel blocker (3-5). Magnesium, which is a natural calcium antagonist, is an antagonist of the N-methyl-D-aspartate (NMDA) receptor that is a crucial element for enzymes function, neurotransmission, and cell signaling (6,7). NMDA receptor antagonists can prevent central sensitization because of peripheral nociceptive stimulation and abolish this hypersensitivity when it is established (7,8). Therefore, substances with calcium-channel blocker effect and NMDA antagonism can play a role in the prevention of pain, sensitization processes, and hyperalgesia in the early post-operative period (9,10). Magnesium is the fourth most common mineral salt in human body and contributes to muscle contraction, conduction of neuronal and pain impulses, and vascular tone regulation (4,5). Some studies have clearly shown that $MgSO_4$ reduces post-operative morphine requirement after remifentanil-based anesthesia (11). Similarly, it can reduce intra-operative and post-operative analgesic requirement in patients undergoing major lumbar orthopedic surgery (12). Opioid-induced hyperalgesia is defined as a state of nociceptive sensitization, which is characterized by a paradoxical response, whereby a

Corresponding Author: Seyed Ali Asghar Hosseini
Shahid Chamran Hospital, Shiraz University of Medical Sciences, Shiraz, Iran
Tel: +98 917 3061427/Fax: +98 713 6248980, E-mail: hoseiniaa@sums.ac.ir

patient receiving opioids for pain treatment might have an increased sensitivity to painful stimuli. However, concerns have been raised after reports indicated higher pain scores and exaggerated post-operative opioid consumption, suggesting the development of acute opioid tolerance and opioid-induced hyperalgesia in patients receiving a perioperative remifentanil infusion. Clinicians need to be cautious for the possibility of the development of opioid-induced hyperalgesia and opioid tolerance, which may impair treatment of pain or even aggravate preexisting pain (13).

Based on these studies, this randomized double-blind clinical trial aims to evaluate the analgesic effect of intra-operative $MgSO_4$ infusion administered intravenously on post-operative analgesic requirement, pain management, and side effects after orthognathic surgery. The investigators hypothesized that $MgSO_4$ could decrease morphine consumption and provide better pain relief after orthognathic surgery.

Materials and Methods

At first, the researchers gained the approval of the local Research Ethics Committee of Shiraz University of Medical Sciences and obtained written informed consents from the participants. Then, 52 patients with physical Status I according to the American Society of Anesthesiologists (ASA) undergoing bimaxillary orthognatic surgery were enrolled into this double-blinded, prospective, randomized trial [IRCT201307101674N7 (www.irct.ir)]. All the operations were performed by the same surgical team. The patients with hepatic, renal, or cardiovascular dysfunction, chronic obstructive pulmonary disease, asthma, heart block, myocardial damage, morbid obesity (body mass index $\geq$ 35), neuromuscular disease, history of neuropathy, history of using opioid or analgesics 3 days before the study, and history of using calcium channel blockers and those who were not willing to take part in the study were excluded. The study participants were required to fast for 6 hours before the surgery, and no premedication was given. The anesthetic method for surgery was similar for all the patients. Morphine 0.1 mg/kg was administered intravenously at induction of anesthesia which was achieved using 2-2.5 mg/kg propofol, 2-3 μ/kg fentanyl, and 0.5 mg/kg atracurum. Anesthesia was maintained using 6-12 mg/kg/h propofol and remifentanil by infusion. The patients were mechanically ventilated to keep $EtCO_2$ between 35 and 40 mm Hg and normothermia was maintained in the operation theater. The patients were selected through convenience sampling and were randomly divided into two groups via computer-generated table of random numbers. 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 another person was selected. The medications were prepared and randomly coded by nurses who were totally unaware of the nature of the study. The anesthesiologist and surgeon were also unaware of the content of injections. The patients in the intervention group received an intravenous $MgSO_4$ 30 mg/kg body weight bolus for 15 minutes followed by 10 mg/kg/h dissolved in saline via pump infusion. The control group, on the other hand, received the placebo in same bolus volume as normal saline in a 15-minutes intravenous infusion continued until the end of the operation. Intra-operative monitoring included invasive-arterial blood pressure, electrocardiograph, and peripheral oxygen saturation. A visual analog scale (VAS) was used to assess the intensity of pain (0 = no pain and 10 = worst pain imaginable) and the effectiveness of the administered analgesics. At the end of the surgical procedure, all the infusions were stopped, and the residual neuromuscular block was reversed using neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg). All the patients were monitored in the post-anesthesia recovery room for the first 6 hours. Post-operative monitoring included heart rate, non-invasive blood pressure, and pulse oximetry. During these 6 hours, the patients were kept in the recovery room and rescue analgesia was provided at VAS $\geq$ 3 in the form of intravenous morphine 0.1 mg/kg. In the surgical ward, administration of analgesics was recorded for 12 hours. Then, the patients' post-operative complications were recorded in a questionnaire. The incidence rates of bleeding, shivering, blood pressure changes, agitation and post-operative nausea and vomiting were also recorded after the surgery.

The data have been reported as mean ± standard deviations. Continuous variables, such as demographic data (age, height, and weight) and duration of surgeries, were analyzed using independent sample t-test. Besides, the effectiveness of blood-pressure lowering drugs was assessed by repeated measures ANOVA. In addition, chi-square and Fisher's exact tests were used to analyze VAS pain scores and morphine consumption. All the analyses were performed using the SPSS for Windows (version 10; SPSS Inc., Chicago, USA), and $P < 0.050$ was considered as statistically significant.

Results

This study was conducted on 52 patients, 26 per group. The study results showed no statistically significant difference between the two groups regarding age, sex, weight, and height ($P > 0.050$). The surgery lasted for were 261.9 ± 56.0 and 234.0 ± 38.9 minutes in the $MgSO_4$ and control groups, respectively, the difference was statistically significant ($P = 0.044$) (Table 1).

Table 1. The demographic characteristics of the study patients

Characteristics	Control (n = 26)	Mg (n = 26)	P value
Age (years)	23.4 ± 5.3	22.3 ± 5.2	0.447
Sex (F/M)	11/15	9/17	0.569
Weight (kg)	61.4 ± 11.0	60.4 ± 9.1	0.742
Height (cm)	169.3 ± 9.2	167.0 ± 7.8	0.538
Duration of operation (min)	261.9 ± 56.0	234.0 ± 38.9	0.044

During the post-operative period, the patients in the control group showed larger analgesic requirement (7, 26.9%) compared to those in the magnesium group (4, 15.4%) and the difference was not statistically significant (P = 0.308). However, a significant difference was observed between the intervention and the control group regarding post-operative VAS scores evaluated serially from the recovery room (3, 11.5% vs. 14, 53.8%; P = 0.001). On the other hand, no significant difference was found between the two groups regarding VAS scores in the surgical ward (7, 26.9% vs. 8, 30.8%; P = 0.760).

In the $MgSO_4$ and control group, systolic and diastolic blood pressure decreased during operation significantly compared to the baseline. Besides, blood pressure increased after the operation. Furthermore, the mean of systolic blood pressure was lower in the magnesium group compared to the control group. However, the trend of changes in systolic and diastolic blood pressure was not statistically significant in $MgSO_4$ and control groups (Figures 1 and 2).

The results showed no significant difference between the two groups regarding the incidence of bleeding, shivering, blood pressure changes, agitation, nausea, and vomiting were 11.5%, 30.8%, 3.8%, 7.6%, and 3.8% in $MgSO_4$ group and 7.6%, 23.1%, 0.0%, 11.5%, and 3.8% in control group, respectively.

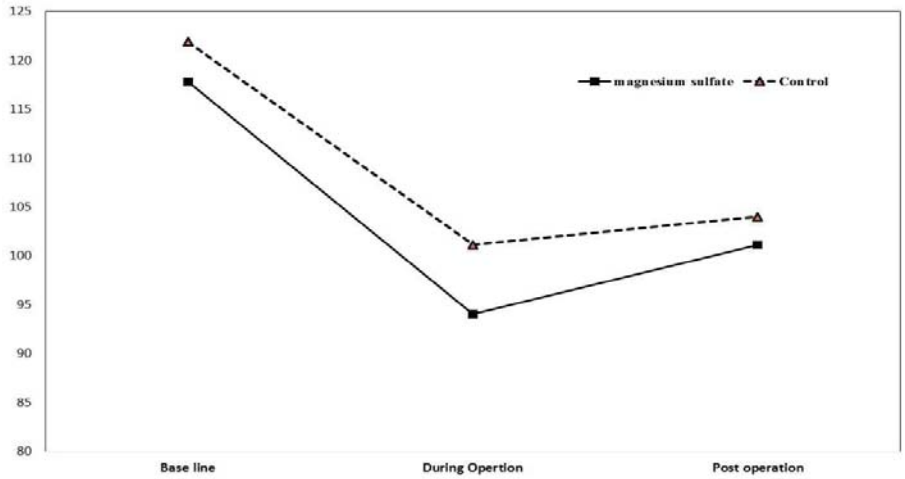

Figure 1. Trend of systolic blood pressure between two groups

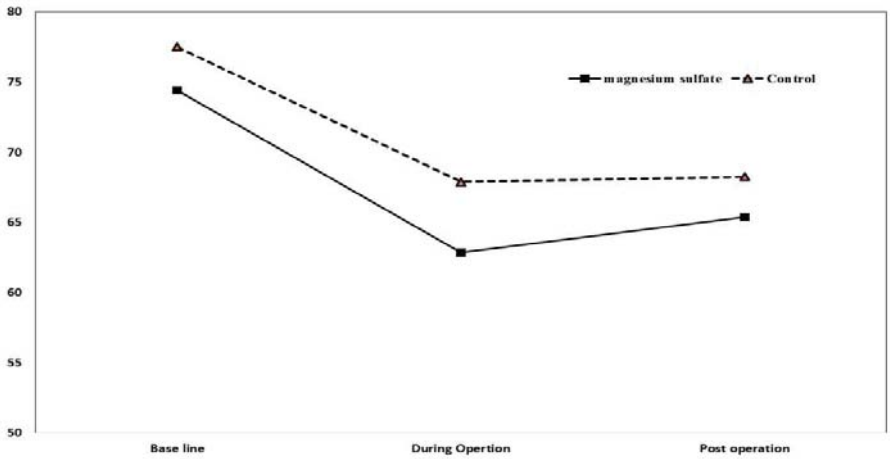

Figure 2. Trend of diastolic blood pressure between two groups

Nonetheless, no incidence of bradycardia, hypoxia or hypoventilation was recorded during the post-operative periods.

Discussion

This study assessed the possible effects of infusion of $MgSO_4$ started before induction of anesthesia and continued throughout the procedure on reducing the analgesic requirement and post-operative pain in the patients undergoing bimaxillary orthognatic surgery. In this study, 30 mg/kg $MgSO_4$ was administered as a bolus followed by 10 mg/kg/h infusion intra-operatively. No complications resulting from magnesium administration were evident at the used doses. Magnesium, which acts as the NMDA receptor antagonist, may play a role in prevention and treatment of perioperative pain. Some studies have indicated that $MgSO_4$ led to a reduction in analgesic consumption during the intra-operative (14,15) and post-operative periods (12,16,17). However, Ko et al. (18) reported that intravenous $MgSO_4$ had no analgesic efficacy and caused no reduction in post-operative analgesic requirement. In our study, on the other hand, administration of intra-operative $MgSO_4$ resulted in superior pain relief. Similar results were also obtained by Levaux et al. (12). Mentes and colleagues (16) also revealed the efficacy of $MgSO_4$ in reducing post-operative pain following major lumbar orthopedic surgery and laproscopic cholecystectomy. In addition, using $MgSO_4$ was associated with significantly less analgesic requirement in the patients undergoing lower limb operations (17) and abdominal hysterectomy (18) in the post-operative period (19,20).

The effect of magnesium on perioperative analgesic requirement was first evaluated by Koinig and colleagues (21) in patients with identical levels of surgical stimulation. Their results demonstrated that magnesium could be an adjuvant to per-operative analgesic management by lowering the fentanyl requirement. Tramer et al. (22) were the first to show that magnesium administration significantly reduced analgesic requirement. They found that the patients who had received magnesium required significantly less morphine compared to those in the control group during the post-operative period and this was most pronounced during the first 6 hours. Moreover, Kaur and Baghla (1) showed that administration of 30 mg/kg $MgSO_4$ bolus before induction followed by 10 mg/kg/h by infusion intra-operatively significantly reduced post-operative pain in the patients undergoing upper limb orthopedic surgery without any significant increase in the adverse effects. Furthermore, some researchers (11) believed that $MgSO_4$ in a 30 mg/kg bolus with 500 mg/h intra-operative continuous infusion significantly decreased post-operative morphine usage as well as early post-operative VAS scores. In contrast, Ko et al. (18) suggested that perioperative infusion of $MgSO_4$ neither increased the amount of $MgSO_4$ in the cerebrospinal fluid nor did it decrease the post-operative pain. However, we think that intra-operative $MgSO_4$ administration has a coanalgesic effect at least in patients receiving remifentanil during the intra-operative period and can reduce the analgesic requirement in patients undergoing bimaxillary orthognatic surgery.

Ko et al. (18) used magnesium during abdominal hysterectomy. After induction of anesthesia, they used a 50 mg/kg bolus dose followed by intravenous infusion of 15 mg/kg/h for 6 hours. Cerebrospinal fluid magnesium concentration was measured at the end of the surgery, indicating an inverse relationship between cumulative post-operative analgesic consumption and cerebrospinal fluid magnesium concentration. It was also realized that magnesium had no effects on post-operative pain. Our data with pre- and intra-operative administration of $MgSO_4$ at 30 mg/kg bolus and maintenance of 10 mg/kg/h demonstrated a significant reduction in the post-operative analgesic consumption without any notable side effects. Ozcan et al. (23) also concluded that $MgSO_4$ (30 mg/kg bolus and10 mg/kg/h infusion for 48 hours) was associated with a decrease in intravenous morphine requirement during the first 48 hours after thoracotomies. In this study, morphine consumption was lower in the magnesium group after 6 and 12 hours. In a meta-analysis in 2013, the effect of perioperative administration of $MgSO_4$ on post-operative pain was evaluated in 25 trials comparing magnesium with placebo were identified. Independent of the mode of administration (bolus or continuous infusion), perioperative magnesium reduced cumulative intravenous morphine consumption by 24.4% at 24 hours postoperatively (24). In our study, similar to the previous reports, intravenous $MgSO_4$ infusion reduced post-operative pain and analgesic consumption in the patients undergoing bimaxillary orthognatic surgery without any notable complications. Furthermore, no hemodynamic alterations, such as hypotension or bradycardia, occurred in this study. Therefore, the $MgSO_4$ bolus and maintenance doses used in our study appear to be safe in the post-operative period.

This study had some limitations. For example, $MgSO_4$ potentiates the effect of neuromuscular blocking agents (25,26). However, we could not monitor neuromuscular block. Yet, atracurium prolonged the duration of neuromuscular blockade although it could not be measured in our study. One other limitation of this study was that we did not measure serum magnesium concentration because of lack of the required facilities at our institute.

Conclusion

In summary, intravenous $MgSO_4$ following general

anesthesia reduced post-operative pain and consumption of opioids after bimaxillary orthognathic procedures. Thus, administration of 30 mg/kg $MgSO_4$ before induction as bolus followed by 10 mg/kg/h by intra-operative infusion significantly reduced post-operative pain in the patients undergoing bimaxillary orthognathic surgery without any significant increase in the adverse effects.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

This study was financially supported by the Research Vice-chancellor of Shiraz University of Medical Sciences, Shiraz, Iran (Grant No. 92-01-03-6010). This manuscript was extracted from the thesis written by Seyed Ali AsgharHosseini. Hereby, the authors would like to thank Ms. A. Keivan Shekouh at the Research Improvement Center of Shiraz University of Medical Sciences for improving the use of English in the manuscript. They are also grateful for the maxillofacial nursing staff in Shahid Chamran Hospital for their cooperation.

References

1. Kaur S, Baghla N. Evaluation of intravenous magnesium sulphate for postoperative analgesia in upper limb orthopaedic surgery under general anaesthesia: A comparative study. Internet J Anaesth. 2012; 30(2): 248-52.
2. Byrd RP Jr., Roy TM. Magnesium: its proven and potential clinical significance. South Med J. 2003; 96(1): 104.
3. Seo JW, Park TJ. Magnesium metabolism. Electrolyte Blood Press. 2008; 6(2): 86-95.
4. Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. Am Heart J. 1984; 108(1): 188-93.
5. Dube L, Granry JC. The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review. Can J Anaesth. 2003; 50(7): 732-46.
6. Konrad M, Schlingmann KP, Gudermann T. Insights into the molecular nature of magnesium homeostasis. Am J Physiol Renal Physiol. 2004; 286(4): F599-F605.
7. Alexander RT, Hoenderop JG, Bindels RJ. Molecular determinants of magnesium homeostasis: insights from human disease. J Am Soc Nephrol. 2008; 19(8): 1451-8.
8. Omote K, Sonoda H, Kawamata M, Iwasaki H, Namiki A. Potentiation of antinociceptive effects of morphine by calcium-channel blockers at the level of the spinal cord. Anesthesiology. 1993; 79(4): 746-52.
9. Lee DH, Kwon IC. Magnesium sulphate has beneficial effects as an adjuvant during general anaesthesia for Caesarean section. Br J Anaesth. 2009; 103(6): 861-6.
10. Ismail Y, Ismail AA, Ismail AA. The underestimated problem of using serum magnesium measurements to exclude magnesium deficiency in adults; a health warning is needed for "normal" results. Clin Chem Lab Med. 2010; 48(3): 323-7.
11. Kaya S, Kararmaz A, Gedik R, Turhanoglu S. Magnesium sulfate reduces postoperative morphine requirement after remifentanil-based anesthesia. Med Sci Monit. 2009; 15(2): I5-I9.
12. Levaux C, Bonhomme V, Dewandre PY, Brichant JF, Hans P. Effect of intra-operative magnesium sulphate on pain relief and patient comfort after major lumbar orthopaedic surgery. Anaesthesia. 2003; 58(2): 131-5.
13. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth. 2014; 112(6): 991-1004.
14. Telci L, Esen F, Akcora D, Erden T, Canbolat AT, Akpir K. Evaluation of effects of magnesium sulphate in reducing intraoperative anaesthetic requirements. Br J Anaesth. 2002; 89(4): 594-8.
15. Lee C, Song YK, Jeong HM, Park SN. The effects of magnesium sulfate infiltration on perioperative opioid consumption and opioid-induced hyperalgesia in patients undergoing robot-assisted laparoscopic prostatectomy with remifentanil-based anesthesia. Korean J Anesthesiol. 2011; 61(3): 244-50.
16. Mentes O, Harlak A, Yigit T, Balkan A, Balkan M, Cosar A, et al. Effect of intraoperative magnesium sulphate infusion on pain relief after laparoscopic cholecystectomy. Acta Anaesthesiol Scand. 2008; 52(10): 1353-9.
17. Dabbagh A, Elyasi H, Razavi SS, Fathi M, Rajaei S. Intravenous magnesium sulfate for post-operative pain in patients undergoing lower limb orthopedic surgery. Acta Anaesthesiol Scand. 2009; 53(8): 1088-91.
18. Ko SH, Lim HR, Kim DC, Han YJ, Choe H, Song HS. Magnesium sulfate does not reduce postoperative analgesic requirements. Anesthesiology. 2001; 95(3): 640-6.
19. Bhatia A, Kashyap L, Pawar DK, Trikha A. Effect of intraoperative magnesium infusion on perioperative analgesia in open cholecystectomy. J Clin Anesth. 2004; 16(4): 262-5.
20. Kiran S, Gupta R, Verma D. Evaluation of a single-dose of intravenous magnesium sulphate for prevention of postoperative pain after inguinal surgery. Indian J Anaesth. 2011; 55(1): 31-5.
21. Koinig H, Wallner T, Marhofer P, Andel H, Horauf K, Mayer N. Magnesium sulfate reduces intra- and postoperative analgesic requirements. Anesth Analg. 1998; 87(1): 206-10.
22. Tramer MR, Schneider J, Marti RA, Rifat K. Role of magnesium sulfate in postoperative analgesia. Anesthesiology. 1996; 84(2): 340-7.
23. Ozcan PE, Tugrul S, Senturk NM, Uludag E, Cakar N, Telci L, et al. Role of magnesium sulfate in postoperative pain management for patients undergoing thoracotomy. J Cardiothorac Vasc Anesth. 2007; 21(6): 827-31.
24. Albrecht E, Kirkham KR, Liu SS, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. Anaesthesia. 2013; 68(1): 79-90.
25. Fawcett WJ, Stone JP. Recurarization in the recovery room following the use of magnesium sulphate. Br J Anaesth. 2003; 91(3): 435-8.
26. Na HS, Lee JH, Hwang JY, Ryu JH, Han SH, Jeon YT, et al. Effects of magnesium sulphate on intraoperative neuromuscular blocking agent requirements and postoperative analgesia in children with cerebral palsy. Br J Anaesth. 2010; 104(3): 344-50.