Effect of Magnesium Sulfate on Emergence Agitation in Patients Undergoing Radical Esophagectomy for Esophageal Cancer: A Postprint

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Abstract

Objective: To observe the efficacy and safety of magnesium sulfate for emergence agitation during the recovery period of general anesthesia in patients undergoing radical esophagectomy. Methods: A randomized, double-blind, controlled design was adopted. Patients scheduled for elective radical esophagectomy under general anesthesia from October 2015 to March 2016 were randomly divided into a magnesium sulfate group (experimental group) and a normal saline group (control group). All patients received total intravenous anesthesia. After induction, the magnesium sulfate group received a continuous infusion of magnesium sulfate at 0.1 mL/(kg · h) (2.5 g magnesium sulfate added to 50 mL normal saline, infusion rate 5 mg/(kg · h)), while the control group received an equivalent infusion of normal saline at the same rate until the end of surgery. The following parameters were recorded: patient agitation, pain, muscle tension scores, extubation time, post-anesthesia care unit (PACU) stay time, postoperative adverse reactions, and postoperative Mg^2 , Ca^2 , and K concentrations. Statistical analysis was performed using SPSS 17.0 software. Results: A total of 108 patients were enrolled, including 57 in the magnesium sulfate group and 51 in the control group. The magnesium sulfate group demonstrated significantly lower agitation, pain, and muscle tension scores in the PACU compared to the control group, while extubation time after drug discontinuation was significantly prolonged ($P<0.05$). Preoperative Ca^2 concentrations were significantly higher than postoperative levels in both groups, and preoperative Mg^2 concentrations in the control group were significantly higher than postoperative values; postoperative Mg^2 concentrations in the magnesium sulfate group were significantly higher than those in the control group postoperatively ($P<0.05$). No significant difference in Mg^2 concentrations was observed between preoperative and postoperative values within the magnesium sulfate group ($P>0.05$). No statistically significant differences were found between the two groups in PACU stay

time, immediate emergence agitation score upon PACU admission, or preoperative and postoperative K concentrations (P>0.05). Conclusion: Intraoperative infusion of magnesium sulfate at 5 mg/(kg·h) during radical esophagectomy significantly reduces the incidence of emergence agitation without causing delayed muscle strength recovery, electrolyte disturbances, or other complications.

Full Text

Preamble

Effect of Magnesium Sulphate Infusion on Emergence Agitation in Patients Undergoing Esophageal Carcinoma Surgery with General Anesthesia: A Randomized, Double-Blind, Controlled Trial

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Abstract

Objective: To evaluate the safety and effectiveness of magnesium sulphate for reducing the incidence of emergence agitation in patients undergoing surgery for esophageal carcinoma with general anesthesia.

Methods: This randomized, double-blind, controlled clinical trial was conducted in patients undergoing elective radical resection of esophageal carcinoma at Sichuan Provincial People' s Hospital between October 2015 and March 2016. All patients underwent surgery under total intravenous anesthesia. After anesthesia induction, patients were infused with magnesium sulphate at a rate of 0.1 mL/(kg·h) (2.5 g magnesium sulphate in 50 mL saline, pumped at 5 mg/(kg·h)) or saline (control group) at the same speed until the end of surgery. The Riker' s sedation-agitation scale, pain score, muscle tension score, extubation time, residence time in the postanesthesia care unit (PACU), and adverse reactions were recorded.

Results: A total of 108 patients were enrolled, including 57 in the magnesium sulphate group and 51 in the control group. The Riker' s sedation-agitation scale in the PACU, pain score, and muscle tension score were all significantly lower in the magnesium sulphate group compared to the control group, but the extubation time was significantly longer (P<0.05). In all patients, blood Ca^2 level was reduced significantly after the operation; blood Mg^2 level was significantly lowered postoperatively in the control group, and the postoperative Mg^2 level was significantly higher in the magnesium sulphate group than in the control group (P<0.05). Mg^2 level underwent no significant variations in the magnesium sulphate group after the operation (P>0.05). The residence time in

the PACU, postoperative Riker' s sedation-agitation scale score, and blood K level were all similar between the two groups (P>0.05).

Conclusion: Infusion of magnesium sulphate at 5 mg/(kg·h) can significantly reduce the incidence of emergence agitation in patients undergoing esophageal carcinoma surgery under general anesthesia without causing complications such as muscle recovery delay or electrolyte disorder.

Key words: magnesium sulphate; general anesthesia; emergence agitation; esophageal carcinoma; electrolyte

Introduction

Emergence agitation (EA) is an inappropriate behavior during the recovery period, characterized by excitement, restlessness, and consciousness disturbance [1]. In severe cases, EA can significantly compromise surgical outcomes and lead to respiratory and circulatory instability, causing substantial interference for medical staff. Currently, drugs used to alleviate EA are primarily sedatives and analgesics, such as dexmedetomidine, sufentanil, and parecoxib sodium [2-3]. Magnesium sulphate, commonly used for anticonvulsant purposes, has recently been found to possess adjunctive analgesic effects and to improve postoperative neurological function. Some scholars have applied magnesium sulphate for EA in children and found that it significantly reduces the incidence of agitation without obvious side effects [4]. However, there are no literature reports on the use of magnesium sulphate for EA in adults, and whether its use causes delayed muscle recovery, electrolyte disturbances, or other side effects requires further experimental investigation [5-6]. This study aims to explore the effect of magnesium sulphate on EA in patients undergoing thoracotomy.

1. Materials and Methods

1.1 Study Subjects

This study enrolled patients undergoing radical esophagectomy in the general thoracic surgery department of Sichuan Provincial People' s Hospital between October 2015 and March 2016. The trial was approved by the Ethics Committee of Sichuan Academy of Medical Sciences//Sichuan Provincial People' s Hospital, and all patients provided informed consent before enrollment.

Inclusion criteria: Patients admitted for radical esophagectomy, ASA grade I-II, BMI 18-30.

Exclusion criteria: Cardiovascular or cerebrovascular disease; abnormal mental behavior; use of opioids, sedatives, or anticonvulsants within 3 months; abnormal renal function (BUN>7.5 mmol/L; Scr>110 mol/L); abnormal liver function; myocardial damage, cardiac conduction block, or QT prolongation; abnormal preoperative magnesium, calcium, or potassium concentrations; use of

antibiotics including polymyxin B sulphate, streptomycin sulphate, calcium gluconate, dobutamine hydrochloride, procaine hydrochloride, tetracycline, penicillin, and nafcillin; refusal to sign informed consent.

Elimination criteria: Patients incorrectly enrolled who did not meet inclusion criteria; persistent intraoperative hypotension or hemorrhagic shock; intraoperative urine output <25-30 mL/h; surgery duration >10 h; total magnesium sulphate infusion >10 g.

1.2 Experimental Design

A randomized, double-blind, controlled trial design was employed. Random sequences were computer-generated and stored in sequentially numbered sealed envelopes. According to the order of enrollment, patients sequentially drew random numbers from the envelopes to determine group allocation. Sample size calculation using Ssize software determined that at least 46 patients per group were required.

1.3 Intervention Measures

All patients received total intravenous anesthesia without preoperative medication. Lidocaine cream was used to lubricate the urinary catheter to reduce postoperative irritation and restlessness. Anesthesia was induced with sufentanil 0.4 g/kg (sufentanil citrate injection, Yichang Renfu Pharmaceutical, batch 1150308 A1), midazolam 0.04 mg/kg (midazolam injection, Jiangsu Enhua Pharmaceutical, batch 20150208), propofol 1-1.5 mg/kg (propofol injection, AstraZeneca, batch MF165), and cisatracurium 0.2 mg/kg (cisatracurium besylate for injection, Shanghai Pharmaceutical Dongying, batch A11150801). After induction, a double-lumen endotracheal tube was inserted and mechanical ventilation was initiated (parameters: tidal volume 8-10 mL/kg, respiratory rate 12-14 breaths/min, I:E ratio = 1:2). Anesthesia was maintained with continuous intravenous infusion of remifentanil 0.1-0.2 g/(kg·min) (remifentanil hydrochloride for injection, Yichang Renfu Pharmaceutical, batch 6150209), propofol 4-10 mg/(kg·h), and intermittent intravenous injection of cisatracurium as needed. After induction, the magnesium sulphate group received magnesium sulphate 2.5 g diluted in 50 mL (magnesium sulphate injection, Sinopharm Rongsheng Pharmaceutical, batch 1503305-D42), while the control group received 50 mL saline, both infused at 0.1 mL/(kg·h) [7-9] until the end of surgery. Intraoperative blood pressure was maintained within 20% of baseline, and cerebral state index (CSI) was maintained at 40-60. Before the end of surgery, 5-10 g sufentanil was administered and a patient-controlled analgesia pump was connected (sufentanil 2 g/kg, tropisetron hydrochloride 5 mg (tropisetron hydrochloride injection, Southwest Pharmaceutical, batch 140707 215) in 100 mL total volume).

1.4 Observation Indicators

After enrollment, patient demographics including sex, age, weight, and height were collected to calculate body mass index (BMI) and ASA score. Preoperative venous blood samples were sent for biochemical and electrolyte analysis. During surgery, ECG, SpO , HR, ETCO , BP, cerebral state index (CSI), body temperature, and arterial blood gas analysis were monitored. Anesthesia duration, surgery duration, and extubation time were recorded. Upon arrival in the postanesthesia care unit (PACU), nurses assessed patients using the Riker sedation-agitation scale (SAS). At discharge from PACU, postoperative pain was evaluated using the Prince-Henry pain scale for thoracoabdominal surgery (which assesses pain during coughing, deep breathing, and rest states, particularly relevant for thoracic surgery where intercostal incisions affect respiration but postoperative coughing is required to promote respiratory recovery). Muscle tension was also scored.

Prince-Henry scoring: 0 = no pain with coughing; 1 = pain only with coughing; 2 = no pain at rest but pain with deep breathing; 3 = mild pain at rest that is tolerable; 4 = severe pain at rest that is intolerable.

Muscle tension was assessed using the Ashworth scale: Grade 0 = normal muscle tone; Grade 1 = slight increase in muscle tone with minimal resistance at the end of range of motion or sudden catch/release; Grade 2 = more marked increase in muscle tone through most of range of motion but limb can still be moved relatively easily; Grade 3 = severe increase in muscle tone with difficult passive movement; Grade 4 = rigidity with inability to move the limb during passive flexion/extension. Within 48 hours after surgery, venous blood samples were sent for biochemical analysis and electrolyte measurement (Mg^2 , Ca^2 , K).

1.5 Statistical Analysis

SPSS 17.0 software was used for statistical analysis. Measurement data were expressed as mean ± standard deviation. Within-group comparisons used one-way ANOVA, while between-group comparisons used t-tests. Count data were analyzed using ^{2} tests, and various scores were analyzed using rank-sum tests. $P<0.05$ was considered statistically significant.

A total of 111 patients diagnosed with esophageal carcinoma requiring thoracotomy for radical esophagectomy were initially enrolled. One patient in each group was eliminated due to hemorrhagic shock during surgery, and one patient in the magnesium sulphate group was eliminated because surgery duration exceeded 10 hours. Ultimately, 108 patients were included in the analysis.

2. Results

2.1 Comparison of Baseline Characteristics

There were no statistically significant differences between groups in sex, age, weight, ASA grade, BMI, or surgery duration, indicating comparable baseline characteristics (Table 1).

2.2 Comparison of Postoperative Extubation Time, PACU Stay, Emergence Agitation Scores, and Pain Scores

Extubation was performed when patients had recovered spontaneous breathing with stable circulation, normal tidal volume, minute ventilation, and pulse oxygen saturation, normal cough and swallowing reflexes, responsive to calling with eye opening, and able to follow commands. The time from PACU admission to tracheal extubation was recorded as extubation time. There were no statistically significant differences between groups in PACU residence time or immediate postoperative agitation scores upon PACU admission ($P>0.05$). However, agitation scores, pain scores, and muscle tension scores at PACU discharge were significantly lower in the magnesium sulphate group ($P<0.05$), while extubation time was significantly longer in the magnesium sulphate group ($P<0.05$, Table 2).

2.3 Comparison of Postoperative Adverse Reactions

The incidence of adverse reactions in the PACU is shown in Table 3 . No severe adverse reactions were observed in either group.

2.4 Changes in Mg^2 , Ca^2 , and K Concentrations

Preoperative Ca^2 concentrations were significantly higher than postoperative values in both groups. Preoperative Mg^2 concentrations were significantly higher than postoperative values in the control group, while postoperative Mg^2 concentrations were significantly higher in the magnesium sulphate group compared to the control group ($P<0.05$). There was no significant difference between preoperative and postoperative Mg^2 concentrations within the magnesium sulphate group. K concentrations showed no significant differences pre- and postoperatively between groups ($P>0.05$, Table 4).

3. Discussion

Current clinical factors considered to contribute to EA include: (1) Patient-related factors: preoperative anxiety, history of alcohol or opioid addiction; EA is more common in children, young adults, and males, with an incidence of 5.3% in adults and approximately 12-13% in children; patients carrying the ApoE 4 gene are more susceptible [10]. (2) Surgery-related factors: thoracic and ENT surgeries, prolonged procedures, and noxious stimuli such as postoperative pain and indwelling catheters. (3) Anesthesia-related factors: anesthetic agents

such as sevoflurane, postoperative awakening drugs like doxapram, as well as suctioning, tracheal tube stimulation, and carbon dioxide retention may also cause emergence agitation.

Some scholars propose that the physiological mechanism of EA involves anesthetic drugs inhibiting the central nervous system, leading to imbalance of neurotransmitters (serotonin, dopamine, acetylcholine, etc.) [11], resulting in patients whose sensations have recovered but consciousness has not, manifesting as unconscious behavioral disturbances.

Thoracic surgery patients have a high incidence of EA, possibly due to extensive surgical fields, multiple intercostal muscle fiber transections, prolonged special positioning, postoperative closed thoracic drainage tubes stimulating intercostal nerves, and incomplete postoperative analgesia.

The results of this study demonstrate that patients receiving magnesium sulphate infusion had significantly reduced agitation scores in the PACU. Magnesium ion serves as a cofactor for over 300 enzymatic activities in metabolism [12-13], maintaining nucleic acid structural stability and participating in various physiological processes including protein and nucleic acid synthesis and muscle contraction. Mg^{2} can also reduce the release of acetylcholine and calcium from presynaptic membranes. Therefore, magnesium sulphate may reduce EA incidence by decreasing acetylcholine release, thereby maintaining M-cholinergic receptor excitation, which is crucial for maintaining normal human consciousness [14]. Magnesium sulphate may maintain this balance and consequently reduce EA occurrence.

Mg^{2} is also a non-anesthetic N-methyl-D-aspartate (NMDA) receptor antagonist. Wu et al. [15] demonstrated that NMDA receptor antagonists can reduce postoperative pain intensity and improve patient satisfaction, consistent with our experimental results.

Additionally, this study found that electrolytes Mg^{2} , Ca^{2} , and K , which participate in numerous intracellular physiological reactions, showed different changes during thoracic surgery. Although pre- and postoperative changes in Mg^{2} , Ca^{2} , and K concentrations remained within normal ranges in both groups, Mg^{2} concentrations showed no statistically significant difference between pre- and postoperative values in the magnesium sulphate group, whereas the control group showed significantly decreased Mg^{2} concentrations. Postoperative pain scores were also significantly lower in the magnesium sulphate group, suggesting a potential analgesic effect of Mg^{2} , consistent with findings from Gupta et al. [16-19]. Therefore, maintaining stable Mg^{2} concentrations before and after surgery may not only reduce emergence agitation but also decrease postoperative pain.

We also observed that PACU residence time was not prolonged in the magnesium sulphate group, but extubation time was extended. This may be because patients in the magnesium sulphate group remained quiet, cooperative, and tolerant of the tracheal tube in the PACU, leading nursing staff to delay extubation [20-21]. Postoperative Ca^{2} concentrations decreased significantly in both

groups; the cause of this Ca^2 reduction requires further investigation, but it is clear that although magnesium sulphate is a calcium channel blocker, Ca^2 concentrations were not affected by the 5 mg/(kg · h) magnesium sulphate infusion. K concentrations showed no significant changes pre- and postoperatively and were not influenced by this infusion rate of magnesium sulphate or surgical/anesthetic factors.

Regarding postoperative adverse reactions, the magnesium sulphate group showed significantly reduced muscle rigidity and lower incidence of hypertension [22-23], possibly due to magnesium sulphate directly dilating peripheral vascular smooth muscle, causing vasodilation and blood pressure reduction [24-25]. Additionally, Mg^2 directly reduces blood catecholamine concentrations, which may also contribute to reduced blood pressure elevation [26].

In conclusion, infusion of magnesium sulphate at 5 mg/(kg · h) during thoracic esophagectomy can significantly reduce the incidence of emergence agitation without causing delayed muscle recovery or electrolyte disturbances. However, whether postoperative pain relief is sustained requires further investigation.

References

[1] 鲍杨, 史东平, 封卫征. 全麻苏醒期患者躁动的研究进展 [J]. 临床麻醉学杂志, 2010, 26(2): 183-4.
[2] Ham SY, Kim JE, Park C, et al. Dexmedetomidine does not reduce emergence agitation in adults following orthognathic surgery[J]. Acta Anaesthesiol Scand, 2014, 58(8): 955-60.
[3] 李治贵, 麻伟青, 杨云丽, 等. 帕瑞昔布钠对开胸手术患者全麻苏醒期的影响 [J]. 昆明医学院学报, 2012, 33(8): 37-40.
[4] Abdulatif M, Ahmed A, Mukhtar A, et al. The effect of Magnesium sulphate infusion on the incidence and severity of emergence agitation in children undergoing adenotonsillectomy using sevoflurane anaesthesia[J]. Anaesthesia, 2013, 68(10): 1045-52.
[5] 张明瑜, 余艳丽, 方海滨, 等. 静脉应用硫酸镁对维库溴铵肌松作用的影响 [J]. 南京医科大学学报: 自然科学版, 2014, 34(6): 782-5.
[6] 陈巍, 胡永初, 田谋利, 等. 术中静脉注射硫酸镁对异丙酚和瑞芬太尼用量及术后不良事件的影响 [J]. 第二军医大学学报, 2014, 35(7):
[7] Choi JC, Yoon KB, Um DJ, et al. Intravenous magnesium sulfate administration reduces propofol infusion requirements during maintenance of propofol-N2O anesthesia: part I: comparing propofol requirements according to hemodynamic responses; part II: comparing bispectral index in control and magnesium groups[J]. Anesthesiology, 2002, 97(5): 1137-41.
[8] 阎玮, 王世端, 褚海辰, 等. 持续静脉输注硫酸镁对丙泊酚有效靶浓度及病人血流动力学相关参数的影响 [J]. 青岛大学医学院学报, 2007, 43(4): 353-6.
[9] 吴宏亮, 叶铁虎, 孙莉. 镁离子对阿曲库铵神经肌肉传递阻滞时间的影响 [J]. 中国医学科学院学报, 2009, 31(1): 73-6.
[10] 张双全, 王刚, 于卫, 等. ApoE 4 等位基因与全麻苏醒期躁动的关系 [J]. 南方医科大学学报, 2008, 28(9): 1652-3.

[11] Mizuno J, Nakata Y, Morita S, et al. Predisposing factors and intubating condition for rapid-sequence intubation: a randomized controlled trial[J]. J Clin Anesth, 2015, 27(7): 595-601.
[12] Schulz-Stübner S, Wettmann G, Reyle-Hahn M, et al. Magnesium as part of balanced general anaesthesia with propofol, remifentanil and mivacurium: a double-blind, randomized prospective study in 50 patients[J]. Eur J Anaesthesiol, 2001, 18(11): 723-9.
[13] Guo L, Lin Y, Hu W, et al. Effects of systemic Magnesium on post-operative analgesia: is the current evidence strong enough?[J]. Pain Physician, 2015, 18(5): 405-18.
[14] Yu D, Chai W, Sun X, et al. Emergence agitation in adults: risk factors in 2,000 patients[J]. Can J Anaesth, 2010, 57(9): 843-8.
[15] Wu L, Huang X, Sun L. The efficacy of N-methyl-D-aspartate receptor antagonists on improving the postoperative pain intensity and satisfaction after remifentanil-based anesthesia in adults: a meta-analysis[J]. J Clin Anesth, 2015, 27(4): 311-24.
[16] Gupta K, Vohra V, Sood J. The role of Magnesium as an adjuvant during general anaesthesia[J]. Anaesthesia, 2006, 61(11): 1058-63.
[17] Shariat MR, Motalebi M, Najafi A, et al. Magnesium can decrease postoperative physiological ileus and postoperative pain in major nonlaparoscopic gastrointestinal surgeries: a randomized controlled trial[J]. Anesth Pain Med, 2013, 4(1): e12750.
[18] Benzon A, Shah D, Hansen J, et al. The effect of systemic Magnesium on postsurgical children undergoing tonsillectomies: a Double-Blinded, randomized, Placebo-Controlled trial[J]. Anesth Analg, 2015, 121(6): 1627-31.
[19] 段晓霞, 张官鹏, 欧册华. 硫酸镁联合芬太尼对老年患者冠脉搭桥术后镇痛的影响 [J]. 实用医学杂志, 2009, 25(23): 4039-40.
[20] Kim H, Oh Y, Han H, et al. The effect of Magnesium sulphate on prevention of emergence agitation[J]. Masui, 2011, 60(4): 425-35.
[21] 尹秀茹, 裴凌. 硫酸镁对全麻术后疼痛和并发症影响的 Meta 分析 [J]. 中国循证医学杂志, 2012, 12(3): 334-40.
[22] Panda B, Bharti N, Prasad S. Minimal effective dose of Magnesium sulfate for attenuation of intubation response in hypertensive patients[J]. J Clin Anesth, 2013, 25(2): 92-7.
[23] Mesbah KM, Safari S, Movaseghi GR, 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[J]. Anesth Pain Med, 2014, 4(3): e15905.
[24] Jee D, Lee D, Yun S, et al. Magnesium sulphate attenuates arterial pressure increase during laparoscopic cholecystectomy[J]. Br J Anaesth, 2009, 103(4): 484-9.
[25] Hatzakorzian R, Shan Li, Côté V, et al. The management of severe emergence agitation using droperidol[J]. Anaesthesia, 2006, 61(11):
[26] Srivastava VK, Mishra A, Agrawal S, et al. Comparative evaluation of dexmedetomidine and Magnesium sulphate on propofol consumption, haemodynamics and postoperative recovery in spine surgery: a prospective, randomized,

placebo controlled, double-blind study[J]. Advanced pharmaceutical bulletin, 2016, 6(1):

Note: Figure translations are in progress. See original paper for figures.