Use of magnesium sulfate in anesthesiology

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Key words: *anesthesia, magnesium, N-methyl-D–aspartate receptors, cardiovascular system, neuromuscular block.*

Summary. *The objective of this study was to evaluate usage possibilities of magnesium sulfate in anesthesiology.*

Methodology. In Clinic of Cardiac Surgery, Kaunas University of Medicine magnesium sulfate was started for use as an adjuvant to anesthetics. For anesthesia it was used in 20 cases. This review article presents the methodology based on which the magnesium sulfate anesthesia was given. Methodology was created using the data of international clinical trials. After anesthesia induction with thiopental (5 mg/kg) and fentanyl (2 mg/kg), patients were given shock-dose injection (30–50 mg/kg) of $MgSO_4$; also continual infusion through syringe pump at 500 mg/h was given for total duration of 20 hours. The state of patients during anesthesia was evaluated based on hemodynamic readings: arterial blood pressure, heart rate and functional oxygen saturation in the arterial blood (SpO_2).

Results. Data on importance of magnesium sulfate for anesthesia is currently in process, however it was determined that when magnesium sulfate is used for anesthesia, the smaller doses of fentanyl and myorelaxants are needed. The last dose of fentanyl before the end of anesthesia is injected at the similar interval as in cases when magnesium is not used.

Conclusions. Even though the precise data is not available yet, we can conclude that when magnesium sulfate is used as an adjuvant for anesthesia, the reduced doses of pain-killer medicines are needed and their action is strengthened. In addition, magnesium does not prolong the activity of painkiller substances.

Introduction

Magnesium is the fourth most plentiful cation in the body and the second most plentiful intracellular cation after potassium. Approximately one half of total body magnesium is present in bone and 20% in skeletal muscle. Magnesium is necessary for the presynaptic release of acetylcholine from nerve endings and may produce effects similar to calcium-entry-blocking drugs (1). Magnesium ions are involved as a cofactor in about 300 known enzymatic reactions in the body and in several important processes such as hormone receptor binding, gating of calcium channels, transmembrane ion flux, regulation of the adenylcyclase system, neuronal activity, vasomotor tone, cardiac excitability and neurotransmitter release (2). As magnesium blocks the N-methyl-D-aspartate receptor and its associated ion channels, it can prevent central sensitization caused by peripheral nociceptive stimulation (2-5). Magnesium also has antinociceptive effects in animal and human models of pain (6). These effects are primarily based on the regulation of calcium influx into the cell, i.e., ‘natural physiological calcium antagonism’ and antagonism of the NMDA receptor (2-6). An inverse relationship has been demonstrated between the severity of pain with different painful medical and surgical conditions and the serum magnesium concentration (2).

There will be data on several studies about the use of magnesium sulfate reviewed in this article. We will introduce positive clinical effects on use of magnesium sulfate in anesthesiology.

Changes of Mg^{2+} concentration in blood serum during anesthesia

The changes of serum magnesium concentration were investigated during several clinical studies. It was noticed that it was lowering during anesthesia and became normomagnesemic on the 1-3 day after surgery (2,7-12). The serum concentration of magnesium ions after administration of $MgSO_4$ was

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significantly higher in patients pretreated with $MgSO_4$ according to a dosage (12). The incidence of both postoperative arrhythmias and postoperative low cardiac index (<2.5 l/m^2) was statistically significantly more frequent in hypomagnesemic patients ($p<0.05$) after cardiopulmonary bypass (8). Cerebrospinal fluid (CSF) magnesium level remains unchanged during anesthesia ($p<0.001$) and magnesium plasma concentration is not parallel with CSF magnesium concentration (13). Sasaki R et al. in their study have concluded that the Mg^{2+} supplementation is required during anesthesia when a large amount of fluid is infused (14).

The effect of changes of Mg^{2+} concentration on cardiovascular system

After cardiac surgery, magnesium is often administered for prophylaxis and treatment of cardiac arrhythmias. Magnesium, however, inhibits platelet function in vitro and in healthy volunteers (15). Gries A et al. performed a randomized, blinded, and placebo-controlled study to investigate the effect of magnesium on platelet function in patients after cardiac surgery. They concluded that in a randomized, blinded, placebo-controlled study of patients 24 h after coronary artery bypass grafting, IV administered magnesium inhibited platelet function in vitro and in vivo (15). Akazawa S et al. have studied the effects of magnesium on atrioventricular (AV) conduction times and surface electrocardiogram during both sinus rhythm and atrial pacing in seven dogs anaesthetized with 1 MAC of sevoflurane. A bolus dose of magnesium sulfate ($MgSO_4$) 30, 60 and 90 mg kg^{-1} significantly increased plasma magnesium concentrations. $MgSO_4$ significantly prolonged AV nodal conduction time during sinus rhythm and QTc interval remained unchanged during sinus rhythm. This finding suggests that $MgSO_4$ in high doses was safe and may be indicated for cardiac arrhythmia and hypertension during sevoflurane anesthesia. However, further study is required to apply these findings to clinical anesthesia (16). The pharmacological effects of magnesium sulfate heptahydrate ($MgSO_4 \cdot 7H_2O$) on hypertensive patients during the perioperative period were used in Nastou H double-blind study, to control critical rises of blood pressure. The results indicated that parenteral administration of $MgSO_4 \cdot 7H_2O$ in hypertensive patients before surgery stabilized blood pressure fluctuations outside the critical range, without causing the pressure to fall to a level that might risk undesirable side effects during eye surgery under local anesthesia (17). Nakaigawa Y et al. have studied the effects of i.v. bolus doses of magnesium sulfate ($MgSO_4$) 60, 90 and 120 mg kg^{-1} on hemodynamic state, the coronary circulation and myocardial metabolism in nine dogs anaesthetized with pentobarbitone and fentanyl. This study indicated that the depressant effect of $MgSO_4$ on cardiac function was offset by lowering of peripheral vascular resistance, so that cardiac pump function remained effective, and the almost constant coronary sinus blood flow resulted from the decrease in coronary vascular resistance even at higher doses (18).

Role of Mg^{2+} in anesthesia

Effective treatment of peri- and post-operative pain represents an important component of postoperative recovery as it serves to blunt autonomic, somatic and endocrine reflexes with a resultant potential decrease in perioperative morbidity. It has become common practice to employ a polypharmacological approach to the treatment of postoperative pain, because no agent has yet been identified that specifically inhibits nociception without associated side effects. Magnesium can block calcium influx and non-competitively antagonize NMDA receptor channels. These effects have prompted the investigation of magnesium as an adjuvant agent for intra- and post-operative analgesia (6). Clinically relevant concentrations of volatile anesthetics inhibit functioning of N-methyl-D-aspartate receptors. This inhibition is reversible, concentration-dependent and voltage-insensitive, and results from noncompetitive antagonism of glutamate/glycine signaling. In addition, these effects can be potentiated significantly by co-application of either Mg^{2+}, S (+)-ketamine, or most profoundly- both. Mg^{2+} and ketamine interact super additively at N- methyl-D-aspartate (NMDA) receptors, which may explain the clinical efficacy of the combination (4).

S. Schulz- Stubner et al. study has shown that usage of $MgSO_4$ as a supplement during remifentanil or propofol and mivacurium anesthesia has reduced amounts of anesthetic and relaxant drugs needed (2). Similar results were achieved at Kara H. Et al. study. The mean intraoperative fentanyl consumption was significantly higher in the control group than in magnesium group ($p<0.05$). Postoperative morphine doses decreased significantly in magnesium group ($p<0.05$) (6).

Mizutani A et al studied the analgesic effect of iontophoresis with magnesium sulfate in fourteen healthy adult volunteers. The pain recognition time was significantly extended and lasted for 60 min. These results support the view that the iontophoresis with magnesium sulfate has analgesic effect and produces a good pain relief clinically (19).

Many authors have studied role of magnesium sulfate for postoperative analgesia (6,20,28). Tramer MR et al. have performed a randomized, double blind study; an assessment was made of the effect of the physiologic N-methyl-D-aspartate antagonist magnesium on analgesic requirements, pain, comfort, and quality of sleep in the postoperative period. 42 patients undergoing elective abdominal hysterectomy with general anesthesia received 20% magnesium sulfate or saline (control) 15 ml intravenously before start of surgery and 2.5 ml/h for the next 20 h. Postoperative morphine requirement was assessed for 48 h using patient-controlled analgesia. Compared to control subjects, magnesium-treated patients consumed less morphine during the first 48h ($P<0.03$), which was most pronounced during the first 6 h ($P<0.004$), and experienced less discomfort during the first and second postoperative days ($P<0.05$-0.005). The magnesium-treated group revealed no change in postoperative sleeping patterns when compared to preoperative patterns. This clinical study showed that the perioperative application of magnesium sulfate is associated with smaller analgesic requirement, less discomfort, and a better quality of sleep in the postoperative period but not with adverse effects. Magnesium could be of interest as an adjuvant to postoperative analgesia (20). Many authors have paid attention to the role of magnesium sulfate on neuromuscular block (2,12,21-26). The effect of magnesium as muscle relaxant has been known since the 1950s (2). T. Fuchs-Buder et al, T. Okuda et al and H. Hino et al have investigated the interaction between magnesium sulfate 40 mg kg-1 i.v. and vecuronium in their studies and ascertained that the neuromuscular potency of vecuronium was increased by pretreatment with magnesium sulfate, in addition to modifying the time course of its neuromuscular block (12,21,22,25). Okuda T. et al also concluded that pretreatment with $MgSO_4$ 40 mg/kg but not 20 mg/kg enhances vecuronium-induced neuromuscular block (12). Sloan PA and Rasul M. have reported a prolonged neuromuscular block with the nondepolarizing muscle relaxant rapacuronium in the presence of clindamycin and magnesium (23). Ahn EK et al. in their study concluded that among women undergoing a cesarean section who were given magnesium pretreatment, the infusion rate of mivacurium required to obtain relaxation was lower than that among women who did not receive pretreatment (24). Ross RM and Baker T determined that clinically relevant infusions of magnesium sulfate produced significant changes in neuromuscular transmission as manifested by diminished 'test of four' (TOF) response to ulnar nerve stimulation (26).

Discussion

We can see in this article that many authors say that magnesium has a positive effect to anesthesia and postoperative pain reduction. But also there is a different opinion that magnesium is not that effective in anesthesia (3,27) and does not have a positive effect on neuromuscular block (28).

Ko SH et al tried to evaluate whether perioperative intravenous magnesium sulfate infusion affects postoperative pain. They say that perioperative intravenous administration of magnesium sulfate did not increase CSF magnesium concentration and had no effects on postoperative pain. However, an inverse relation between cumulative postoperative analgesic consumption and the CSF magnesium concentration was observed (3). Mikkelsen S. et al have investigated the effects of i.v. magnesium on secondary hyperalgesia following heat/capsaicin stimulation in human volunteers no analgesic or antihyperalgesic effect could be demonstrated in sensitized skin during infusion of magnesium (27).

Zarauza R. et al. in a randomized, double-blinded study examined the effects of nifedipine, nimodipine, and magnesium sulfate in postoperative analgesia after colorectal surgery and found no differences in morphine consumption with the administration of each drug alone (28). Wilder-Smith OH et al. have studied the effects on postsurgical sensory processing of general anesthesia supplemented by drugs affecting opioid or N-methyl-D-aspartate receptors using sensory thresholds. Generalized central sensory inhibition, differently affected by the drugs, predominated after surgery. Fentanyl showed the most, and magnesium the least, central sensory inhibition up to 5 days postoperatively, with different patterns of inhibition directly post-surgery versus later (29).

S. Schulz- Stubner et al. have concluded in their drug cost analysis scenario, that a 2-h anesthetic without magnesium would cost 21–35% more than in magnesium group (2). In 1992 Wilder-Smith et al. used magnesium only intraoperatively and suggested that it had a better intraoperative antinociceptive efficacy than fentanyl (6).

Conclusions

1. The serum concentration of magnesium ions after administration of $MgSO_4$ remains significantly higher in patients pretreated with $MgSO_4$ according to a dosage (12). The incidence of both postoperative arrhythmias and postoperative low cardiac index (<2.5 l/m^2) was statistically significantly more frequent in hypomagnesemic patients ($p<0.05$) after cardiopulmonary bypass (8).

2. Magnesium has a positive effect on platelet function.

3. Magnesium premeditations has a positive effects on neuromuscular block, provides a better quality of anesthesia while hastening functional recovery.

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