MAGNESIUM SULFATE AS AN ADJUVANT TO ANESTHESIA IN PATIENTS WITH ARTERIAL HYPERTENSION*

Sanja Vicković¹,⁶, Miroslava Pjević¹,⁶, Arsen Uvelin²,⁶, Dragana Pap³, Dragan Nikolić⁴,⁶ and Ivica Lalić⁵,⁶

¹Department of Anesthesiology & Intensive Care, ²Emergency Centre, Clinical Centre of Vojvodina; ³Students Health Protection Institute, Department of Laboratory Diagnosis; ⁴Department of Vascular Surgery, ⁵Department of Orthopedic Surgery, Clinical Centre of Vojvodina; ⁶University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

SUMMARY – There is limited evidence showing that elevated arterial blood pressure in surgical patients may be associated with increased perioperative risk; however, cardiovascular instability frequently occurs during anesthesia. The most commonly used anesthetic agents, both intravenous and inhalation ones, produce a decrease in arterial blood pressure. Magnesium, acting as a natural calcium-channel blocker, induces direct and indirect vasodilatation, thus playing a role in the treatment of arterial hypertension. In this research, we assessed the effects of magnesium sulfate on cardiovascular stability in patients undergoing diverse planned surgical procedures (abdominal, orthopedic, urology) under general balanced anesthesia, who were diagnosed with arterial hypertension grade 1 and 2. The research encompassed 100 patients of both sexes, aged from 20 to 65. Immediately before induction of anesthesia with propofol, the patients in the experimental group (50 study subjects) received 30 mg/kg bolus dose and magnesium sulfate infusion at 10 mg/kg/h, whereas the subjects in the control group (50 patients) were administered normal saline. Anesthesia was achieved and maintained with sevoflurane, fentanyl and rocuronium. The hemodynamic variables of mean arterial pressure and heart rate were measured every five minutes, starting immediately before magnesium infusion. Statistical analysis of the categorized values of mean arterial pressure and heart rate revealed a statistically significant between-group difference at 60th and 90th minute of anesthesia. In conclusion, magnesium sulfate as an adjuvant to anesthesia in patients with arterial hypertension reduces hemodynamic changes during anesthesia.

Key words: Magnesium sulfate; Hypertension; Hemodynamics; Heart rate; Adjuvants, pharmaceutical; Anesthesia

Introduction

Although recent developments in technical and procedural aspects of anesthesiology have allowed substantial advancement of surgery, unavoidable anesthe-sia-related risks such as perioperative morbidity and mortality still remain a problem even in the 21st century. Accordingly, anesthesiologist plays an important role as a perioperative physician responsible for preoperative assessment, patient preparation, planning and selection of optimal anesthetic technique, and appropriate pharmacological agents.

*This article contains part of the research done for doctoral dissertation by Dr Sanja Vicković.
Preoperative indicators of cardiovascular risk in non-cardiac surgery include ischemic heart disease, congestive heart failure, cerebrovascular disease, preoperative insulin therapy, and preoperative serum creatinine levels above 150 μmol/L. Surgical factors affecting cardiac risks are strongly related to the urgency, extent, type and duration of the procedure itself.

It is believed that 15% of patients presenting for surgical procedures that require anesthesia suffer from arterial hypertension. Cardiovascular instability during anesthesia is more prevalent in these patients. Arterial hypertension associated with organ failure (ischemic heart disease, heart failure, renal failure) substantially increases the probability of perioperative cardiovascular complications. Establishing the type of hypertension, i.e. whether primary (essential) or secondary, is of great importance for further procedure. Conditions such as pheochromocytoma, hyperaldosteronism and renovascular hypertension require specific individual anesthesiologic approach.

According to the guidelines of the European Society of Hypertension (ESH) and European Society of Cardiology (ESC), blood pressure is defined and classified as follows: optimal (systolic <120 mm Hg, diastolic <80 mm Hg); normal (systolic 120-129 and/or diastolic 80-84); high normal (systolic 130-139 and/or diastolic 85-89); grade 1 hypertension (systolic 140-159 and/or diastolic 90-99); grade 2 hypertension (systolic 160-179 and/or diastolic 100-109); grade 3 hypertension (systolic >180 and/or diastolic >110); and isolated systolic hypertension (systolic >140, diastolic <90 mm Hg).

Grade 1 and 2 hypertension by itself is not considered a risk factor for the occurrence of perioperative cardiovascular complications. In patients with grade 3 hypertension associated with apparent heart or kidney failure, the surgery should be delayed until reestablishment of normal arterial blood pressure and etiologic examination. If the surgery must be performed without delay, invasive intraoperative monitoring of arterial blood pressure should be provided while limiting oscillations of the mean arterial blood pressure to 20% of baseline values.

An optimal strategy that would maximally reduce the risks of perioperative cardiovascular complications implicates comprehensive preoperative cardiac evaluation of the patient along with appropriate pharmacological treatment regimen. Patients suffering from arterial hypertension are frequently exposed to extreme hypotension after induction of anesthesia, as well as to hypertensive stress-response to laryngoscopy and intubation, surgical incision and extubation. Postoperatively, inadequate pain relief can induce hypertensive response in such patients. Hypertensive episodes are often associated with arrhythmia and myocardial ischemia. Hypo- as well as hypertension can result in cerebrovascular complications.

Magnesium is of vital importance for human body. The majority of magnesium is absorbed in the small intestine. Kidneys play an important role in maintaining magnesium balance within the body. Administration of diuretics substantially increases magnesium excretion. The metabolism of magnesium is regulated through the action of a variety of hormones. Parathyroid hormone upregulates renal excretion of magnesium and decreases its intestinal absorption. Mineralocorticoids (aldosterone), thyroid hormones and insulin are responsible for increased renal excretion of magnesium, whereas adrenaline is associated with elevation of plasma magnesium levels. Increased serum magnesium concentration (hypermagnesemia) can occur in chronic infectious diseases, diabetic ketoacidosis, Addison’s disease, atherosclerosis, and particularly in chronic renal insufficiency. Decreased serum magnesium level (hypomagnesemia) is often associated with enduring diarrhea, prolonged diuretic therapy, malabsorption syndrome, hyperaldosteronism and alcoholism. Hypomagnesemia is a common event in hypokalemic patients. Ionized free magnesium in serum is of crucial biological importance for mediating cellular ion channels and transport mechanisms. Magnesium plays a role in controlling calcium entry into the cells, thus affecting the cardiac smooth muscle tone, i.e. the tone of vascular smooth muscles.

Magnesium is considered the fourth most common cation within the whole of the human body and the second most important intracellular cation. It is a co-factor in the activation of a whole range of enzymes involved in biochemical reactions of protein synthesis. Magnesium manifests antinociceptive effects as a competitive antagonist of N-methyl-D-aspartate receptors. Competing with calcium ions, magnesium inhibits the release of presynaptic acetylcholine, thus enhancing the action of neuromuscular blocking agents. Magnesium sulfate depresses the central nervous system and reduces anesthetic requirements.
Magnesium is regarded as a natural physiologic calcium antagonist. Patients subjected to major surgical procedure without magnesium supplementation are exposed to an increased risk of hypomagnesemia during the early postoperative period. Magnesium is also used as an effective antiarrhythmic agent. Some in vitro studies demonstrated that magnesium prevented catecholamine release from the adrenal medulla and adrenergic terminals, and produced coronary vasodilatation. Ryu et al. demonstrated that the effects of magnesium sulfate in providing adequately controlled hypotension in patients undergoing ear surgery were the same as those of remifentanil.

Magnesium sulfate is applicable in therapy of hypokalemia, asthmatic attack and for protecting the heart muscle following ischemia. Some recent studies strongly suggest the anti-inflammatory effects of magnesium sulfate.

The concentration of total magnesium in the serum of an adult person ranges between 0.65 and 1.05 mmol/L. Magnesium preparations are usually well tolerated even if administered at large doses. In healthy individuals, plasma levels of magnesium ranging within the interval of 2-3.5 mmol/L are considered acceptable.

The aim of this research was to establish the effects of magnesium sulfate on cardiovascular stability in patients suffering from arterial hypertension, who were subjected to non-cardiac surgery (elective abdominal, orthopedic and urology surgical procedures) under general balanced anesthesia.

### Patients and Methods

In this double blind, prospective, randomized and controlled clinical trial, we assessed the effects of magnesium sulfate on cardiovascular stability in patients undergoing diverse planned surgical procedures (abdominal, orthopedic, urology) under general balanced anesthesia, who were diagnosed with grade 1 and 2 arterial hypertension. The research encompassed 100 patients of both sexes, aged from 20 to 65. Immediately before the induction of anesthesia with propofol (2 mg/kg intravenously), the patients received 30 mg/kg bolus dose and magnesium sulfate infusion at 10 mg/kg/h (M group, n=50 patients) or saline placebo (K group, n=50 patients). Anesthesia was achieved and maintained with sevoflurane (1-3 vol%), fentanyl (5 μg/kg) and rocuronium (0.15 mg/kg every 30 minutes).

Pregnant women, patients with organ failure, patients with elevated potassium and magnesium levels, patients on calcium channel blocker therapy, and patients with AV block, myasthenia gravis or porphyria were not included in the research. Furthermore, patients suffering massive intraoperative blood loss and those treated intraoperatively with antihypertensive drugs, antiarrhythmics or diuretics were excluded from the study.

The hemodynamic parameters of the mean arterial pressure (MAP) and heart rate (HR) were monitored and recorded every five minutes. Baseline MAP had been measured before magnesium intravenous bolus was administered to the patient. Arterial blood pressure was measured noninvasively (Datex-Ohmeda S/5 2008).

All subjects gave their informed consent for participation in this study, approved by the local Ethics Committee.

Differences between the investigated groups were evaluated using Pearson χ²-test, Fisher exact test, and Wilcoxon rank sum test (Mann-Whitney). All hypotheses were tested at the level of statistical significance of 0.05.

### Results

The study encompassed 100 patients, 49 males and 51 females. Pearson χ²-test found no statistically significant gender-related differences between the groups (χ²=0.04, df=1, p=0.84145, p>0.05). The mean age of the group K and M patients was 57.1±7.96 and 56.32±7.89 years, respectively. Mann-Whitney test demonstrated no statistically significant age differences (W=1303, p=0.71671, p>0.05). Out of 100 patients included in the study, 53 were categorized as American Society of Anesthesiologists (ASA) class II, whereas 47 were classified as ASA III. Pearson χ²-test demonstrated no statistically significant differences according to ASA status (χ²=1.004, df=1, p=0.31644, p>0.05). All patients included in this study suffered from arterial hypertension. Out of 100 participating patients, 47 had grade I hypertension, whereas 53 patients had grade II hypertension. Pearson χ²-test yielded no statistically significant between-group differences according to the grade of arterial hypertension (χ²=0.04, df=1, p=0.8412, p>0.05). The groups of participants were homogeneous, thus statistical analysis is considered representative.
Preoperative serum levels of magnesium ranged from 0.42 to 0.99 mmol/L in group K and from 0.56 to 1.06 mmol/L in group M (Table 1). Postoperative serum magnesium values ranged from 0.4 to 0.9 mmol/L and from 0.75 to 3.51 mmol/L in group K and M, respectively (Table 2).

Intravenous administration of magnesium sulfate bolus dose (30 mg/kg) resulted in MAP decrease in the majority of participants. After induction in anesthesia, patients from both groups manifested MAP decrease; however, differences between the groups were not statistically significant. An increase in MAP values was recorded after endotracheal intubation in both groups, at a rate of 21% in group K and 18% in group M. In the majority of our patients, endotracheal intubation resulted in HR increase. Median HR increase as related to baseline values was 33% and 26% in groups K and M, respectively. Statistical analysis of categorized values of MAP and HR yielded a statistically significant between-group difference at 60th and 90th minute of anesthesia. MAP values were within the range of hemodynamic stability (-20% to 20% decline from baseline values) in 21 (42%) group K patients and 38 (76%) group M patients (Fig. 1). HR values were within the interval from -30% to 30% decline from baseline values in 26 (52%) group K patients and 37 (74%) group M patients (Fig. 2).

According to minimum MAP values, it is apparent that the highest average drop was recorded among participants from group K with arterial hypertension grade 2. Differences between the group K arterial hypertension grade 2 and group M arterial hypertension grade 2 subgroups (K HTA 2 and M HTA 2) were

---

**Table 1. Preoperative serum magnesium levels**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (mmol/L) ±SD</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K (n=50)</td>
<td>0.82 ±0.12</td>
<td>0.86 (0.42 to 0.99)</td>
</tr>
<tr>
<td>M (n=50)</td>
<td>0.86 ±0.12</td>
<td>0.88 (0.56 to 1.06)</td>
</tr>
</tbody>
</table>

Group K = patients received saline placebo; group M = patients received 30 mg/kg bolus dose and magnesium sulfate infusion at 10 mg/kg/h.

**Table 2. Postoperative serum magnesium levels**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median (mmol/L) ±SD</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K (n=50)</td>
<td>0.79 ±0.07</td>
<td>0.775 (0.4 to 0.9)</td>
</tr>
<tr>
<td>M (n=50)</td>
<td>1.36 ±0.74</td>
<td>1.14 (0.75 to 3.51)</td>
</tr>
</tbody>
</table>

Group K = patients received saline placebo; group M = patients received 30 mg/kg bolus dose and magnesium sulfate infusion at 10 mg/kg/h.

**Fig. 1. Mean arterial pressure (MAP) in 60th minute of anesthesia.**

**Fig. 2. Heart rate (HR) in 90th minute of anesthesia.**
statistically significant (Mann-Whitney pair test, $W=221, p=0.02033, p<0.05$). The participants suffering from grade 2 arterial hypertension who were administered magnesium sulfate manifested a significantly lower MAP drop (Fig. 3).

K HTA 1 = patients with arterial hypertension grade 1 receiving saline placebo; K HTA 2 = patients with arterial hypertension grade 2 receiving saline placebo; M HTA 1 = patients with arterial hypertension grade 1 receiving 30 mg/kg bolus dose and magnesium sulfate infusion at 10 mg/kg/h; M HTA 2 = patients with arterial hypertension grade 2 receiving 30 mg/kg bolus dose and magnesium sulfate infusion at 10 mg/kg/h.

Fig. 3. Lowest mean arterial pressure (MAP) compared to baseline MAP (percent change).

The median extubation time after cessation of inhalation anesthetic was 7.8±3.33 minutes in group K and 7.1±2.96 minutes in group M. This extubation time difference was not statistically significant (Mann-Whitney test, $W=1395, p=0.31108, p>0.05$). The mean pain intensity during the immediate postoperative period was assessed using the numerical point scale, which yielded 5.58±2.89 points in group K and 5.02±2.35 in group M. With respect to this parameter, there were no statistically significant differences between the groups (Mann-Whitney test, $W=1401.5, p=0.28882, p>0.05$).

Discussion

In our research, statistical analysis of categorized MAP values at different time intervals revealed a statistically significant difference between the groups in the 60th minute of anesthesia. At 60th minute of anesthesia, there were no patients with hypertension (patients manifesting MAP increase by more than 20% as compared with baseline values) in group M. The data obtained data clearly showed that group M patients manifested better hemodynamic stability than those from group K at 60th minute of anesthesia. The HR values at 90th minute of anesthesia ranged from -30% to +30% from baseline values in 52% of group K patients and 74% of group M patients.

So far, the dosage of magnesium sulfate has been highly variable. Usmani et al. administered magnesium sulfate bolus 50 mg/kg along with continuous infusion at 15 mg/kg/h for pain control$^{16}$. In the study by Seyhan et al., continuous infusion of magnesium sulfate at a dose of 10 mg/kg/h was sufficient to substantially reduce the doses of intraoperative anesthetics and neuromuscular blockers, as well as postoperative analgesics$^{17}$. Niruthisard et al. administered magnesium sulfate infusion to attenuate hypertensive crisis during pheochromocytoma resection in a patient with multiple endocrine neoplasia type IIa$^{18}$.

A number of studies demonstrated that the administration of magnesium sulfate during anesthesia substantially affected the hemodynamic parameters. Elsharnouby and Elsharnouby applied magnesium sulfate (bolus dose 40 mg/kg, along with i.v. infusion at 15 mg/kg/h) as a technique of hypotensive anesthesia in endoscopic sinus surgery. The authors report statistically significantly lower MAP values in patients having received magnesium$^{19}$.

Altan et al. compared the effects of magnesium sulfate and clonidine on hemodynamic parameters during anesthesia and surgical procedure. MAP values recorded in patients receiving clonidine were significantly lower at all time intervals; however, the difference between the groups was not statistically significant$^{10}$.

Magnesium sulfate was used to prevent fluctuation in arterial blood pressure during surgery for catecholamine-active glomus tumors in two patients. In one patient, sodium nitroprusside failed to provide adequate hemodynamic stability, which was established after the administration of magnesium sulfate. In the second patient, hemodynamic stability was successfully managed using magnesium sulfate as a single agent$^{20}$.

Magnesium sulfate proved effective in patients with subarachnoid hemorrhage due to ruptured aneurysm of cerebral vessels$^{21}$.
In the present study, cortisol, vasopressin and catecholamine plasma levels were not analyzed, but the interaction of magnesium sulfate and vasopressin is well known because hypersecretion of antiuretic hormone (vasopressin) results in hypomagnesemia. High concentrations of antiuretic hormone also caused vasoconstriction and consequential increase of blood pressure. Application of magnesium sulfate reduces the effects of hormone stress response during anesthesia.

Ryu et al. demonstrated the effects of magnesium sulfate in providing adequately controlled hypotension to be the same as those of remifentanil. However, post-extubation MAP and HR values were higher in participants administered remifentanil.

The question, whether magnesium sulfate can actually provide hemodynamic stability during anesthesia and under which dosage regimen, requires further research in order to be answered.

In conclusion, magnesium sulfate as an adjuvant to anesthesia in patients with arterial hypertension reduces hemodynamic changes during anesthesia.

References


20. Goutcher CM, Cossar DF, Ratnasabapathy U, Burke AM. Magnesium in the management of catecholamine-secreting...


Sažetak

MAGNEZIJ SULFAT KAO ADJUVANS U ANESTEZIJI KOD BOLESNIKA S POVIŠENIM KRVNIHM TLAKOM

S. Vicković, M. Pjević, A. Uvelin, D. Pap, D. Nikolić i I. Lalić

Postoje određeni dokazi koji ukazuju na postojanje povišenog perioperacijskog rizika kod kirurških bolesnika s povišenim arterijskim tlakom, a kardiocirkulacijska nestabilnost je česta pojava tijekom anestezije. Najčešće upotrebljavani intravenski i inhalacijski anestetici izazivaju snižavanje arterijskog tlaka. Magnezij kao prirodni blokator kalcijevih kanala izaziva vazodilataciju te može imati ulogu u terapiji hipertenzije. U istraživanju su ispitani učinci magnezij sulfata na kardiocirkulacijsku stabilnost kod bolesnika s hipertenzijom prvog i drugog stupnja koji su podvrgnuti različitim elektivnim operacijskim zahvatima (abdominalna, ortopedska kirurgija, urologija) u općoj balansiranoj anesteziji. Studija je obuhvatila sto bolesnika oba spola u dobi od 20 do 65 godina. Neposredno prije intravenskog uvoda u opću anesteziju propofolom bolesnici u eksperimentalnoj skupini dobili su magnezij sulfat u dozi od 30 mg/kg intravenski, a zatim je infuzija magnezij sulfata nastavljena po stopi od 10 mg/kg/h, dok su bolesnici u kontrolnoj skupini dobili 0,9%-tnu otopinu natrij klorida. Anestezija se održavala primjenom sevoflurana i fentanila, a mišićna relaksacija primjenom rokuronija. Hemodinamski parametri, srednji arterijski tlak i srčana frekvencija mjereni su svakih 5 minuta, počevši neposredno prije infuzije magnezij sulfata. Statistička analiza pokazala je statistički značajnu razliku između eksperimentalne i kontrolne skupine u vrijednostima srednjeg arterijskog tlaka i srčane frekvencije u 60. i 90. minuti anestezije. Magnezij sulfat kao adjuvans kod bolesnika s hipertenzijom smanjuje hemodinamske promjene tijekom anestezije.

Ključne riječi: Magnezijev sulfat; Hipertenzija; Hemodinamika; Srčana frekvencija; Adjuvans, farmakološki; Anestezija