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EFFECTS OF DIFFERENT DOSES OF MAGNESIUM SULPHATE ON PNEUMOPERITONEUM-RELATED HEMODYNAMIC CHANGES IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY

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Abstract

Background: The infusion of magnesium sulfate is well known to reduce arterial pressure and attenuate hemodynamic response to pneumoperitoneum. This study aimed to investigate whether different doses of magnesium sulfate can effectively attenuate the pneumoperitoneum-related hemodynamic changes and the release of vasopressin in patients undergoing laparoscopic gastrointestinal surgery.

Methods" Sixty-nine patients undergoing laparoscopic partial gastrectomy were randomized into three groups: group L received magnesium sulfate 30 mg/kg loading dose and 15 mg/kg/h continuous maintenance infusion for 1 h; group H received magnesium sulfate 50 mg/kg followed by 30 mg/kg/h for 1 h; and group S (control group) received same volume 0.9% saline infusion, immediately before the induction of pneumoperitoneum. Systemic vascular resistance (SVR), cardiac output (CO), mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), serum vasopressin and magnesium concentrations were measured. The extubation time, visual analogue scale were also assessed. The primary outcome is the difference in SVR between different groups. The secondary outcome is the differences of other indicators between groups, such as CO, MAP, HR, CVP, vasopressin and postoperative pain score.

Results: Pneumoperitoneum instantly resulted in a significant reduction of cardiac output and an increase in mean arterial pressure, systemic vascular resistance, central venous pressure and heart rate in the control group ($P < 0.01$). The mean arterial pressure (T2 – T4), systemic vascular resistance (T2 – T3), central venous pressure(T3-T5) and the level of serum vasopressin were significantly lower ($P < 0.05$) and the cardiac output (T2 – T3) was significantly higher ($P < 0.05$) in group H than those in the control group. The mean arterial pressure (T4), systemic vascular resistance (T2), and central venous pressure(T3-T4) were significantly lower in group H than those in group L ($P < 0.05$). Furthermore, the visual analog scales at 5 min and 20 min, the level of vasopressin, and the dose of remifentanil were significantly decreased in group H compared to the control group and group L ($P < 0.01$).

Conclusion: Magnesium sulfate could safely and effectively attenuate the pneumoperitoneum-related hemodynamic instability during gastrointestinal laparoscopy and improve postoperative pain at serum magnesium concentrations above 2 mmol/L.

Keywords: magnesium sulfate, hemodynamics, laparoscopic cholecystectomy, propofol

Introduction

Although laparoscopic abdominal surgery has significant advantages, such as less trauma and faster recovery, the hemodynamic changes induced by pneumoperitoneum and the reverse Trendelenburg position are still challenges for anesthesia management during the surgery. The hemodynamic changes are characterized by abrupt elevations of arterial pressure and systemic vascular resistance. Besides the increase of intra-abdominal pressure, the increased levels of vasopressin, catecholamines, renin, and angiotensin are likely to be the reasons for these hemodynamic changes [1, 2]. These severe hemodynamic changes may have a significant impact on the perioperative status of the patient, especially in elderly patients with existing cardiovascular diseases. Therefore, it is crucial to use safe and effective drugs for maintaining hemodynamic stability during abdominal laparoscopy in such patients.

Magnesium sulfate is a well-known safe antihypertensive drug, which can be used during the perioperative period [3]. It can effectively attenuate the adverse hemodynamics fluctuations during laparoscopy, prevent the adverse cardiovascular events during laryngoscopy and tracheal intubation [4, 5], reduce the stress response, and strengthen the postoperative analgesia [6]. Furthermore, it was reported that high doses of intravenous magnesium sulfate could attenuate increased blood pressure and systemic vascular resistance [1, 4]. Although magnesium sulfate is believed to improve the cardiac output by reducing peripheral resistance, there is no available direct hemodynamic monitoring method to prove this effect.

We designed a double blinded, randomized, placebo-controlled clinical trial to investigate the possible association between the effects of magnesium sulfate and hemodynamic changes by using a FloTrac/Vigileo Monitoring System (Edwards Lifesciences, Irvine, CA, USA), which can monitor the cardiac output (CO), systemic vascular resistance (SVR), mean arterial pressure (MAP), central venous pressure (CVP) and heart rate (HR), and to determine the relationship between magnesium sulfate and vasopressin.

Methods:

Sixty-nine American Society of Anesthesiologists grade I and II patients, aged 30–65 years, undergoing laparoscopic partial gastrectomy with carbon dioxide pneumoperitoneum, were enrolled in this study. Patients with hypermagnesemia, with known allergy to magnesium sulfate, unstable blood pressure (hypertension or hypotension), cardiac dysfunction (NYHA grade III and IV), morbid obesity, and severe hepatic, renal or endocrine were excluded from the study. Peripheral, central venous, and arterial cannulations were performed on the patients, under local anesthesia on arrival at the operation theatre. Electrocardiogram, oximetry, intra-arterial blood pressure, and central venous pressure were monitored. The participants were premedicated with midazolam, 1–2 mg intravenously, 10 min before the induction of anesthesia. The anesthesia was induced intravenously using etomidate 0.25 mg/kg and sufentanil 0.5 μg/kg. Endotracheal intubation was facilitated by administering the muscle relaxant cisatracurium 0.3 mg/kg intravenously. The initial tidal volume was 8–10 ml/kg at a respiratory rate of 12 breaths per minute. Ventilation was adjusted to maintain the end-tidal carbon dioxide at 35 to 45 mmHg. After 10 min of stable cardiovascular variables, HR, MAP, CO, CVP and SVR were measured using the FloTrac/Vigileo Monitoring System. The persons who dispensed the drugs and generated random sequence grouping did not participate in the monitoring of hemodynamic parameters and recruiting subjects. Immediately before the pneumoperitoneum, the participants were assigned (using a computer derived random number sequence) to one of the three groups. Group L received magnesium sulfate 30 mg/kg in 20 ml of normal saline over 5 min intravenously as a bolus dose followed by 15 mg/kg/h in 20 ml of normal saline as continuous maintenance infusion for 1 h; group H received magnesium sulfate 50 mg/kg in 20 ml of normal saline over 5 min as a bolus dose followed by 30 mg/kg/h in 20 ml of normal saline as continuous maintenance infusion for 1 h; and group S (control group) received 20 ml 0.9% saline infusion as bolus dose followed by 20 ml/h continuous maintenance infusion for 1 h, immediately before the induction of pneumoperitoneum.

Anesthesia in all the groups was maintained by propofol (4–6 mg/kg/h), remifentanil (0.25–0.35 μg/kg/min) and cisatracurium (0.1–0.12 mg/kg/h) administered intravenously. During the maintenance, bispectral index (BIS) values, determined by Conview™ Depth of Anesthesia Monitor (Pearlcare Medical, Zhejiang, China), were maintained at 45–60. During the surgery, we adjusted the pumping rate of propofol and remifentanil based on BIS, heart rate, and blood pressure, our study controlled according to the BIS value, When the BIS value was above 60 or below 45, propofol infusion rate would be adjusted by 0.5 mg/ kg/h each time. If the BIS value was maintained between 45 and 60, but the blood pressure fluctuates more than 20% of the basal level, remifentanil infusion rate would be adjusted by 0.02μg/kg/min each time. In addition, the degree of muscle relaxation was monitored with the TOF-GUARD muscle relaxometer (Organon Teknika, Turnhout, Belgium). Esophageal temperature was maintained using a heated blanket. Stopped pumping cisatracurium at the beginning of suture. The propofol and remifentanil infusions were stopped at the end of surgery. Patients were routinely sent to the PACU followed by intravenous administration of atropine sulfate 0.02 mg/kg and neostigmine 0.04 mg/kg for reversal of muscle relaxation, and the staffs worked in PACU monitored and removed the tracheal tube when the TOF ratio > 90%.

In cases of acute and severe hemodynamic fluctuations, the following medical interventions were performed: during the operation, we maintained the BIS value between 45 and 60 and excluded the effects of insufficient analgesia, for hypotension (MAP < 60 mmHg), an intravenous bolus dose of 50 μg phenylephrine was administered; and for hypertension (MAP > 110 mmHg) an intravenous bolus dose of 5 mg urapidil was administered. The data from the subjects who required vasoactive drugs during the surgery were excluded from the subsequent analysis.

Results:

The distribution of patients in the three study groups . All groups were comparable with respect to age, body weight, height, duration of surgery and pneumoperitoneum (h). The baseline MAP, HR, CO, SVR, CVP, vasopressin and preoperative medication were similar in all groups . Three patients in the control group and two patients in group L required pharmacological management for hypertension. In addition, patients with pneumoperitoneum duration of < 2 h (one in magnesium group L and two in group H) were excluded. None of the patients in our study had bradycardia, while only one participant in group H had transient hypotension and improved after treatment with phenylephrine.

There was no significant difference in serum magnesium concentrations among the three groups at baseline. The average serum magnesium concentration level of group H was slightly higher than 2 mmol/l. Serum magnesium concentration level in group H rapidly increased to 2.01 ± 0.13 mmol/l ($P < 0.01$, compared with baseline value) at T3, then dropped to 1.38 ± 0.13 mmol/l at T7. In contrast, in group L, the level of serum magnesium concentration was 1.50 ± 0.11 mmol/l at T3, and it dropped to the same level as baseline at T7. Compared to group L, the serum magnesium concentration level was significantly ($P < 0.01$) higher at T3 and T7 in group H.

Pneumoperitoneum instantly resulted in a significant reduction of CO and an increase in MAP, SVR, CVP, and HR in the control group ($P < 0.01$). Patients in group H showed stable levels of CO, SVR, CVP, and MAP. Compared to the control group, MAP (T2-T4), CVP(T3-T5) and SVR (T2-T3) were significantly lower in group H ($P < 0.05$), while the CO (T2-T3) was higher ($P < 0.05$). Compared to group L patients, MAP (T4), CVP(T3-T4) and SVR (T2) were significantly lower in group H ($P < 0.05$). There was no significant difference in HR between the three groups at each time point.

Compared with the baseline values, the level of vasopressin increased significantly in the control group and group L at T3 ($P < 0.01$). The level of vasopressin was significantly lower at T3 ($P < 0.01$) in group H compared to the control group and group L.

The postoperative extubation time and the dosage of fentanil were not statistically significant between the groups. VAS (5 min), VAS (20 min), and the dosage of remifentanil were significantly decreased in group H compared to group L and the control group ($P < 0.01$). In addition, no

postoperative muscle weakness and significant episodes of hypotension were found in any of the groups.

Discussion:

By using the FloTrac / Vigileo Monitoring System, our study demonstrated that pneumoperitoneum decreased CO, which was observed in previous studies [7]. Our results also showed that intravenous magnesium sulfate at a dose of 50 mg/kg could effectively alleviate the reduction in CO, by dilating the peripheral blood vessels and reducing the vascular tone.

During pneumoperitoneum for operative laparoscopy, impairment of hemodynamic status occurs mainly at the beginning of peritoneal insufflation [2]. It is well known that elevated intrapleural pressure significantly reduces the venous return and the circulating blood volume, which induces the elevated levels of vasopressin [1, 2, 9, 10]. Adrenergic receptor blockers, calcium channel blockers, opioids, and vasodilators are routinely used to attenuate the pneumoperitoneum-related hemodynamic instability, but they are all accompanied with varying degrees of reduction in CO. In contrast, magnesium sulfate produces rapid and transient vasodilation by a direct action without causing a reduction in CO, and by indirectly blocking the sympathetic pathway and inhibiting the catecholamine and vasopressin release [1, 3]. Adjuvant analgesia with magnesium sulfate can significantly reduce the dose of remifentanil. Consistent with these findings, in the present study, at the initiation of pneumoperitoneum, and 5, 10 min post-pneumoperitoneum are the most severe periods of hemodynamic fluctuations, and it was also the most effective time period for magnesium sulfate to inhibit pneumoperitoneum associated hypertension. Moreover, hemodynamic fluctuations at 30 and 60 min post-pneumoperitoneum were less pronounced, indicating that magnesium sulfate only reduced abnormally elevated blood pressure and had no effect on normal blood pressure. Jee D found that intravenous magnesium sulfate could improve the increased arterial pressure and inhibit the release of vasopressin caused by pneumoperitoneum at 5 and 10 min post-pneumoperitoneum [1]. Similarly, we found that magnesium sulfate at a dose of 50 mg/kg could effectively attenuate the release of vasopressin.

A minimum therapeutic level of 2 mmol/L magnesium sulfate has been proposed in the clinical management of eclampsia patients [11]. If the magnesium serum concentration is more than 3 mmol/L, the patients may develop tendinous reflexes [3]. Therefore, it is essential to select a safe and effective minimum dose of magnesium sulfate to ensure the safety of patients. Besides, taking into account the effect of magnesium sulfate on intraoperative muscle relaxation, the magnesium ion concentration was measured again before extubation to ensure patients' safety. In the present study, the average serum concentration of magnesium sulfate in group H was between 2 and 3 mmol/L. In group L, the level of serum magnesium concentration was lower than 2 mmol/L at T3. Further, there were no statistically significant differences in the extubation time between the three groups, did not observed any reported serious adverse effects and the potentiation effect of magnesium on neuromuscular blockade as reported in other observations [12], which could be related to the surgery time and the metabolic duration of magnesium sulfate. These results indicate that 50 mg/kg magnesium sulfate may be a safe dose for attenuating the pneumoperitoneum-related hemodynamic changes during laparoscopic gastrointestinal surgery.

The analgesic effect of magnesium sulfate at a dose of 50 mg/kg was relatively obvious, which may be related to the higher concentration of magnesium ions after surgery (Serum magnesium concentration level in group H was1.38 ± 0.13 mmol/l after surgery). In contrast, the reason why the postoperative pain score in group L was higher was that the magnesium ion concentration was lower after surgery, so it did not play an analgesic role. (The level of serum magnesium concentration was 1.07 ± 0.11 mmol/l after surgery). Perioperative intravenous magnesium reduced opioid consumption and pain scores, which was believed to be caused by a physiological block of the ion channel on the N-methyl-D-aspartate receptor and inhibition of the intracellular Ca^{2+} mobility [6, 10, 13]. This analgesic effect may also contribute to the hemodynamic stability in the patient during

surgery. However, further research is needed to determine the exact mechanisms causing the analgesia.

Conclusions

Magnesium sulfate is a safe, inexpensive, and old drug for treating hypertension. In recent years, it has been found to have many other effects during perioperative applications, such as its role in alleviating post-operative pain and treating intubation induced hypertension. In the present study, by comparing different dose of magnesium sulfate, we found that the application of 50 mg/kg magnesium sulfate not only can suppress stress response and hypertension significantly caused by laparoscopic surgery, but also has analgesia effect after surgery. Another advantage of this trial is that, we firstly provided the direct evidence for the role of magnesium sulfate in suppressing the increased SVR induced by pneumoperitoneum. There are several limitations of this study. First, it is a single-center study. Second, we did not monitor the release of catecholamines during the surgery. Other studies have showed that perioperative administration of magnesium sulfate could reduce the release of catecholamines induced by intubation [4].

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