Magnesium sulphate attenuates arterial pressure increase during laparoscopic cholecystectomy†

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Background. Magnesium is well known to inhibit catecholamine release and attenuate vasopressin-stimulated vasoconstriction. We investigated whether i.v. magnesium sulphate attenuates the haemodynamic stress responses to pneumoperitoneum by changing neurohumoral responses during laparoscopic cholecystectomy.

Methods. Thirty-two patients undergoing laparoscopic cholecystectomy were randomly assigned to two groups; a control group was given saline, and a magnesium group received magnesium sulphate 50 mg kg\(^{-1}\) immediately before pneumoperitoneum. Arterial pressure, heart rate, serum magnesium, plasma renin activity (PRA), and catecholamine, cortisol, and vasopressin levels were measured.

Results. Systolic and diastolic arterial pressures were greater in the control group (\(P<0.05\)) than in the magnesium group at 10, 20, and 30 min post-pneumoperitoneum. Norepinephrine or epinephrine levels [pg ml\(^{-1}\), mean (SD)] were higher in the control group than in the magnesium group at 5 [211 (37) vs 138 (18)] or 10 min [59 (19) vs 39 (9)] post-pneumoperitoneum, respectively (\(P<0.05\)). In the control group, vasopressin levels [pg ml\(^{-1}\), mean (SD)] were higher compared with the magnesium group at 5 [64 (18) vs 35 (9), \(P<0.01\)] and 10 min [65 (18) vs 47 (11), \(P<0.05\)] post-pneumoperitoneum. There were no significant differences between the groups in PRA and cortisol levels.

Conclusions. I.V. magnesium sulphate before pneumoperitoneum attenuates arterial pressure increases during laparoscopic cholecystectomy. This attenuation is apparently related to reductions in the release of catecholamine, vasopressin, or both.

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directly on blood vessels, and high-dose magnesium attenuates vasopressin-stimulated vasoconstriction and normalizes sensitivity to vasopressin.

We therefore hypothesized that magnesium sulphate might attenuate the haemodynamic stress responses to pneumoperitoneum by changing neurohumoral responses. In this study, we investigated the ability of magnesium sulphate to modulate hypertension and neurohumoral responses in patients undergoing elective laparoscopic cholecystectomy with CO2 pneumoperitoneum.

Methods

After obtaining institutional review board approval and informed consent, 35 ASA physical status I subjects undergoing elective laparoscopic cholecystectomy with CO2 pneumoperitoneum were enrolled in this study. Patients with the following were excluded from the study: hypermagnesaemia, a known allergy to magnesium sulphate, any degree of heart block, hypertension, diabetes mellitus, cardiovascular or kidney disease, acute cholecystitis, or endocrine or metabolic disease.

Subjects were premedicated with glycopyrrolate 0.2 mg i.m. 1 h before surgery. The trachea was intubated after the induction of anaesthesia with midazolam 0.05 mg kg⁻¹, thiopental sodium 3–5 mg kg⁻¹, and vecuronium 0.1 mg kg⁻¹. Immediately before pneumoperitoneum, subjects were randomly divided into two groups using sealed envelopes chosen by the patients. The control group (n=17) received saline 0.5 ml kg⁻¹ i.v. and the magnesium group (n=18) received 0.5 ml kg⁻¹ of 10% magnesium sulphate (50 mg kg⁻¹) over 2–3 min.

Anaesthesia was maintained with 1.5–2.5% end-tidal sevoflurane and 1:1 O₂/N₂O at 4 litre min⁻¹. No opioids or other analgesics were used during surgery. Ventilation of the lungs was adjusted to maintain an end-tidal CO₂ of 4.6–5.3 kPa. During the anaesthesia, standard monitoring devices (Multi Channel Anaesthesia Monitor S/5™; Datex-Ohmeda, Beaverton, OR, USA) were applied. Bispectral index (BIS®) values, determined using an electroencephalograph (A-2000 BIS® Monitoring System; Aspect Medical Systems, Newton, MA, USA), were maintained at 40 (5). All patients were investigated in a head-up tilt of 15°. CO₂ pneumoperitoneum was established and maintained to a pressure of 14 mm Hg by an automatic insufflation unit throughout the laparoscopic surgery. The surgical technique used was identical in the two groups. During surgery, Ringer’s lactate solution was administered in accordance with fasting volumes, maintenance volumes, and blood losses.

Arterial pressures and heart rates were measured before induction (baseline); before pneumoperitoneum (P0); at 5 (P5), 10 (P10), 20 (P20), and 30 (P30) min after pneumoperitoneum commencement (post-pneumoperitoneum); and after surgery. The anaesthetist who measured arterial pressures and heart rates was unaware of the study protocol. Blood samples for serum magnesium, plasma renin activity (PRA), and plasma epinephrine, norepinephrine, cortisol, and vasopressin concentrations were collected from an antecubital vein. The samples were obtained on the evening before surgery (baseline), before pneumoperitoneum (P0), at 5 (P5) and 10 (P10) min post-pneumoperitoneum, and after surgery. Plasma epinephrine and norepinephrine were measured by high-performance liquid chromatography equipped with an electrochemical detector. Intra-assay coefficients of variation were ~9% and 3%, respectively. PRA, cortisol, and vasopressin were determined by radioimmunoassay, and their intra-assay coefficients of variation were 5.6%, 3.7%, and 7.4%, respectively.

After surgery, glycopyrrolate and pyridostigmine were administered i.v. to reverse muscle relaxation and tracheal tubes were removed. Data from subjects in whom pneumoperitoneum was terminated within 30 min or who needed i.v. antihypertensive drug or opioid during surgery were excluded.

Power calculations suggested that a minimum of 12 subjects per group would detect a 15% difference in arterial pressure between the groups after the administration of magnesium sulphate (α=0.05, β=0.80). Intra-group differences were evaluated by two-way analysis of variance (ANOVA), and inter-group differences using the unpaired t-test. P-values of <0.05 were considered significant. Statistical analysis was performed using SPSS® 14.0. software (SPSS Inc., Chicago, IL, USA). Data are expressed as mean (SD).

Results

Three subjects were excluded from the analysis because pneumoperitoneum duration was <30 min (one in the control group and one in the magnesium group) or because of an exaggerated hypertensive response during surgery (one in the control group). Statistical analyses were performed with the remaining data.

No statistically significant differences were found between the two study groups with respect to patient characteristic data, end-tidal sevoflurane concentration, BIS® values, times of operation, anaesthesia and extubation, or baseline haemodynamic data (Table 1).

Serum magnesium concentrations at the different sampling times are presented in Table 2. Serum magnesium levels were significantly higher in the magnesium group (P<0.001) than in the control group at 5 [2.2 (0.71) vs 0.87 (0.16) mmol litre⁻¹] and 10 min [2.0 (0.44) vs 0.90 (0.12) mmol litre⁻¹] post-pneumoperitoneum and after surgery [1.5 (0.43) vs 0.85 (0.30) mmol litre⁻¹]. Compared with baseline levels, serum magnesium levels were higher at 5 and 10 min post-pneumoperitoneum and after surgery in the magnesium group (P<0.001), but remained unchanged in the control group.
Baseline arterial pressures and heart rates were similar in the two groups (Table 1). However, systolic and diastolic arterial pressures were significantly higher in the control group (P<0.05) than in the magnesium group at 10 [144 (12)/103 (16) vs 130 (9)/89 (13) mm Hg], 20 [140 (7.0)/96 (9) vs 126 (10)/87 (10) mm Hg], and 30 min [135 (13)/94 (9) vs 123 (10)/84 (7) mm Hg] post-pneumoperitoneum. Compared with baseline values, systolic arterial pressures were higher at 5, 10, 20, and 30 min post-pneumoperitoneum and after surgery in the control group (P<0.01), but were only higher at 10 min post-pneumoperitoneum in the magnesium group (P<0.05). On the other hand, diastolic arterial pressure was higher at 5, 10, 20, and 30 min post-pneumoperitoneum and after surgery in both groups (P<0.05). Heart rates were similar in the two groups (Fig. 1).

Changes in plasma catecholamine and vasopressin levels are presented in Figure 2. Baseline catecholamine and vasopressin levels were similar in both groups. In the magnesium group, epinephrine and norepinephrine levels were unchanged during the study period, but in the control group, epinephrine levels were elevated at 10 min post-pneumoperitoneum (P<0.05) and norepinephrine levels at 5 min post-pneumoperitoneum (P<0.05). Norepinephrine or epinephrine levels were significantly higher in the control group than in the magnesium group at 5 [211 (37) vs 138 (18) pg ml\(^{-1}\)] or 10 min [59 (19) vs 39 (9) pg ml\(^{-1}\)] post-pneumoperitoneum, respectively (P<0.05). When compared with the baseline values, vasopressin levels were higher at 5

Table 1 Characteristics of patients. Values were expressed as mean (range), mean (SD) or numbers. \(\varepsilon_{\text{ex}}\), end-tidal sevoflurane concentration; BIS\(^b\), bispectral index; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=15)</th>
<th>Magnesium group (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46.6 (28–56)</td>
<td>48.2 (31–54)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/7</td>
<td>10/7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.5 (9.8)</td>
<td>166.2 (8.3)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.2 (8.1)</td>
<td>64.4 (10.4)</td>
</tr>
<tr>
<td>(\varepsilon_{\text{ex}}) (%)</td>
<td>2.3 (0.2)</td>
<td>2.1 (0.3)</td>
</tr>
<tr>
<td>BIS(^b)</td>
<td>42.6 (5.1)</td>
<td>41.4 (9.7)</td>
</tr>
<tr>
<td>Operating time (min)</td>
<td>54.3 (10.7)</td>
<td>51.9 (14.2)</td>
</tr>
<tr>
<td>Anaesthesia time (min)</td>
<td>81.1 (13.9)</td>
<td>79.3 (15.2)</td>
</tr>
<tr>
<td>Extubation time (min)</td>
<td>5.7 (2.8)</td>
<td>7.2 (3.7)</td>
</tr>
<tr>
<td>Baseline haemodynamics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>124.8 (10.9)</td>
<td>121.3 (11.5)</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>76.2 (10.4)</td>
<td>74.5 (9.8)</td>
</tr>
<tr>
<td>HR (beats min(^{-1}))</td>
<td>75.5 (9.7)</td>
<td>80.1 (8.8)</td>
</tr>
</tbody>
</table>

Table 2 Serum magnesium concentrations (mmol litre\(^{-1}\)) in groups. Values were expressed as mean (SD). \(*P<0.001\) when compared with baseline and \(\dagger P<0.001\) when compared with the control group

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>P0</th>
<th>P5</th>
<th>P10</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>0.91 (0.16)</td>
<td>0.89 (0.12)</td>
<td>0.87 (0.16)</td>
<td>0.90 (0.12)</td>
<td>0.85 (0.30)</td>
</tr>
<tr>
<td>Magnesium group</td>
<td>0.93 (0.21)</td>
<td>0.97 (0.61)</td>
<td>2.24 (0.71)(\dagger)</td>
<td>2.02 (0.44)(\dagger)</td>
<td>1.53 (0.43)(\dagger)</td>
</tr>
</tbody>
</table>

Fig 1 Haemodynamic changes during laparoscopic cholecystectomy. Values were expressed as mean (SD). \(*P<0.05\), \(\dagger P<0.01\) when compared with baseline and \(\ddagger P<0.005\) when compared with the magnesium group. There was no significant difference in the heart rate between the groups. SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate.
and 10 min post-pneumoperitoneum and after surgery in both groups (P<0.01). However, vasopressin levels were significantly higher in the control group than in the magnesium group at 5 [64 (18) vs 35 (9) pg ml⁻¹, P<0.01] and 10 min [65 (18) vs 47 (11) pg ml⁻¹, P<0.05] post-pneumoperitoneum.

Baseline PRA levels were similar in the two groups. PRA levels were higher at 5 and 10 min post-pneumoperitoneum and after surgery than at baseline in both groups (P<0.01), and no significant inter-group difference was observed (Fig. 3).

Baseline cortisol levels were similar in the two groups. In the control group, cortisol levels were elevated at 5 (P<0.05) and 10 min (P<0.01) post-pneumoperitoneum and after surgery (P<0.01) vs baseline, and in the magnesium group, cortisol levels were elevated at 5 (P<0.05) and 10 min (P<0.05) post-pneumoperitoneum and after surgery (P<0.01). There was no significant difference between the groups (Fig. 4).

**Discussion**

This is the first randomized, double-blind, placebo-controlled study to investigate the effects of magnesium during laparoscopic cholecystectomy. Our results show that the administration of magnesium sulphate before pneumoperitoneum attenuates increases in arterial pressure during CO₂ pneumoperitoneum in patients under general anaesthesia. We also demonstrated that immediately after pneumoperitoneum, plasma levels of catecholamines and vasopressin increased significantly in the control group but not in the magnesium group.

The majority of studies on laparoscopic surgery have focused on haemodynamic changes during pneumoperitoneum. In the present study, we observed that systolic and diastolic arterial pressures increased abruptly after pneumoperitoneum commencement, and increases in arterial pressure were sustained during the entire pneumoperitoneum period in the control group as reported in previous observations. However, in the magnesium group, haemodynamic responses to the onset of pneumoperitoneum were effectively blunted, and in particular, arterial pressures remained at a significantly lower level when compared with the control group. Prolonged intraoperative increases of 20 mm Hg or more in mean arterial pressure
are known to significantly increase the incidence of myocardial ischaemia, infarction, and death. In the present study, pre-pneumoperitoneum i.v. magnesium sulphate effectively attenuated this adverse haemodynamic stress response, and thus, might be beneficial in patients with hypertension or cardiac diseases during laparoscopic procedures. Similar to other studies, no increase in heart rate was observed after pneumoperitoneum commencement in the present study.

Pneumoperitoneum using CO₂ causes a rapid and immediate increase in plasma catecholamines, possibly due to an increase in intraperitoneal pressure and stimulation of the peritoneum by CO₂. Studies have suggested that magnesium can inhibit catecholamine release in vitro and in vivo, and others have reported that serum magnesium concentrations of 2–4 mmol litre⁻¹ are required to exert these effects. We observed that a magnesium sulphate bolus of 50 mg kg⁻¹ before pneumoperitoneum increased serum magnesium concentrations to this range. The unchanged catecholamine concentrations observed in the magnesium group indicate that magnesium sulphate effectively prevents sympathoadrenal haemodynamic stress responses during pneumoperitoneum. In addition to catecholamines, vasopressin is a major contributor to the haemodynamic changes induced by pneumoperitoneum. The high concentrations of vasopressin measured during pneumoperitoneum have been shown to be sufficient to have significant cardiovascular effects. Our results show that the induction of pneumoperitoneum significantly increased vasopressin plasma concentrations in both groups, although the mean increase was significantly greater in the control group. In addition, linear correlations have been reported between changes in arterial pressure and increases in the plasma concentrations of catecholamines and vasopressin during pneumoperitoneum. In the present study, the timings of the releases of catecholamines and vasopressin and their magnitudes in the control group coincided with observed increases in arterial pressure. However, in the magnesium group, pneumoperitoneum was only associated with an initial insignificant increase in arterial pressure and no further increase, which could be because magnesium sulphate reduces catecholamine and vasopressin levels, and thus attenuates haemodynamic responses during pneumoperitoneum.

It has been shown that acute magnesium administration induces rapid vasodilation and attenuates agonist-induced vasoconstriction, whereas magnesium withdrawal increases peripheral vascular resistance. Moreover, in a previous study, i.v. magnesium sulphate (50 mg kg⁻¹) significantly decreased mean arterial pressure and systemic vascular resistance over the 9 min after administration during cardiopulmonary bypass. The authors suggested that this decrease in mean arterial pressure was attributed to the relaxing effect of magnesium sulphate on vascular smooth muscle because pump flow was constant after injection. Taken together, we are not able to exclude the possibility that the vasodilatory effects of magnesium sulphate were responsible for the improved arterial pressure control observed in the magnesium group.

It is interesting that plasma vasopressin concentrations were significantly lower in the magnesium group than in the control group. To the best of our knowledge, the mechanism whereby magnesium sulphate inhibits vasopressin secretion has not been studied. However, vasopressin concentrations have been reported to increase when intra-abdominal pressure is elevated. Furthermore, some studies have shown that increases or decreases in intrathoracic blood volume associated with pneumoperitoneum have been suggested to compress abdominal capacitance vessels, diminish intrathoracic blood volume, and ultimately reduce venous return. Furthermore, some studies have shown that increases or decreases in intrathoracic blood volume inhibit or stimulate vasopressin release, respectively. These findings suggest that the vasodilatory effect of magnesium sulphate increases intrathoracic blood volume by relieving abdominal vessels from compression, and thus increased intrathoracic blood volume in the magnesium group would have prevented vasopressin release. However, further studies are needed to determine the precise mechanism.

PRA concentrations increased in both groups post-pneumoperitoneum vs baseline, which concurs with the results of previous studies. The mechanism by which acutely elevated intra-abdominal pressure stimulates PRA is unclear, although an elevation of renal venous pressure secondary to acutely elevated intra-abdominal pressure is possible. In some studies, a positive correlation was found between PRA and arterial pressure, but this was not observed in the present study. Furthermore, we found that cortisol levels increased in both study groups. This is in accord with previous studies, which found that the hypothalamic–pituitary–adrenal axis is still stimulated during pneumoperitoneum under general anaesthesia. In addition, no significant inter-group differences were observed in terms of PRA or cortisol responses, indicating that magnesium sulphate has no apparent effect on PRA or cortisol release.

In conclusion, our results show that a close relationship exists between increases in plasma levels of catecholamines and vasopressin and arterial pressure during pneumoperitoneum. Furthermore, the administration of magnesium sulphate before pneumoperitoneum effectively attenuated arterial pressure increases in subjects undergoing laparoscopic cholecystectomy. We suggest that this attenuation results from reductions in the release of catecholamines and vasopressin caused by magnesium sulphate. Moreover, the possibility remains that vasodilatory effects of magnesium sulphate could provide haemodynamic stability during pneumoperitoneum. Magnesium sulphate can be recommended to avoid pressor response during the induction and maintenance of pneumoperitoneum.
Magnesium sulphate during laparoscopic cholecystectomy

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

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