Effects of magnesium sulphate and clonidine on propofol consumption, haemodynamics and postoperative recovery

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Background. This placebo-controlled, double-blind study was designed to assess the effects of magnesium sulphate and clonidine on peroperative haemodynamics, propofol consumption and postoperative recovery.

Methods. Sixty ASA I–II patients undergoing spinal surgery were randomized into three groups. Group M received magnesium sulphate 30 mg kg\(^{-1}\) as a bolus before induction and 10 mg kg\(^{-1}\) h\(^{-1}\) by infusion. Group CL received clonidine 3 μg kg\(^{-1}\) as a bolus before induction and 2 μg kg\(^{-1}\) h\(^{-1}\) by infusion during the operation period. The same volume of isotonic solution was administered to the control group (group CT). Anaesthesia was induced with propofol and was maintained with propofol infusion [dose according to the bispectral index (BIS)], fentanyl and cisatracurium. Analysis of variance and the Bonferroni test were used for statistical analysis.

Results. Induction of anaesthesia with propofol was rapid in the presence of magnesium sulphate and clonidine. The time for BIS to reach 60 was significantly shorter in group M and group CL (\(P<0.0001\)) but postoperative recovery was slower with magnesium sulphate compared with the clonidine and control groups (\(P<0.0001\)). There was no statistical difference in heart rate and arterial blood pressure between the groups. Propofol requirements for induction and maintenance of anaesthesia were significantly lower with magnesium and clonidine (\(P<0.0001\)).

Conclusion. Clonidine caused bradycardia and hypotension and magnesium sulphate caused delayed recovery, but can be used as adjuvant agents with careful management.

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\(\alpha_2\)-Adrenoreceptor agonists such as clonidine produce both preoperative sedation and anxiolysis. The potential advantages of using \(\alpha_2\) agonists during anaesthesia are improved intraoperative haemodynamic stability, attenuated sympathoadrenal responses to laryngoscopy, reduced intraoperative requirement for volatile and i.v. anaesthetics and less postoperative pain.\(^1\) However, depending on the dose selected, they can induce marked bradycardia and hypotension, and deep sedation can delay postoperative recovery.

Parenteral magnesium sulphate administration has been used for many years on an empirical basis as an anti-arrhythmic agent and for prophylaxis against seizures in pre-eclampsia. This placebo-controlled, double-blind study was designed to assess the effects of i.v. magnesium sulphate and i.v. clonidine on peroperative haemodynamics, propofol consumption and postoperative recovery when used as adjuvant agents.

Methods

After hospital ethics committee approval, informed consent was obtained from each patient. The study included 60 ASA I–II patients (37 female, 23 male) undergoing spinal surgery who were randomly assigned to one of three groups: group M (magnesium sulphate group), group CL (clonidine group) and group CT (control group). Exclusion criteria included hypertension, morbid obesity, drug or alcohol abuse, and severe hepatic, endocrine and cardiac dysfunction. Before the induction of anaesthesia, routine monitoring (ECG, pulse oximetry, oesophageal temperature) was started and an i.v. line was sited. The level of anaesthesia was monitored with the bispectral index (BIS\(^{TM}\)). The BIS electrodes were placed on the forehead and were connected to an A-2000 BIS monitoring system (Aspect Medical Systems, Framingham, MA, USA). A BIS of 40–60 was the target range for surgical anaesthesia. Group M patients received...
i.v. magnesium sulphate 30 mg kg\(^{-1}\) over a 15-min period before induction of anaesthesia and 10 mg kg\(^{-1}\) h\(^{-1}\) by continuous i.v. infusion during the operation. Group CL patients received clonidine 3 \(\mu g\) kg\(^{-1}\) i.v. at induction over a 15-min period and 2 \(\mu g\) kg\(^{-1}\) h\(^{-1}\) as maintenance. Group CT patients were given isotonic solution 0.9% in the same volume as the study drugs. Anaesthesia was induced i.v. with fentanyl 1.5 \(\mu g\) kg\(^{-1}\) and propofol was given 20 mg every 5 s until the BIS was below 60. After induction with propofol, cisatracurium was given and then the patient’s trachea was intubated. Anaesthesia was maintained with air 50% and oxygen 50%, and propofol infusion was adjusted to achieve a target BIS between 40 and 60. Propofol consumption was noted every hour. If hypertension or tachycardia developed during anaesthesia while BIS was between 40 and 60, it was assumed to be due to insufficient analgesia and a bolus dose of fentanyl 1 \(\mu g\) kg\(^{-1}\) was given. Adequacy of anaesthesia was assessed using a ‘pressure, rate, sweating and tears’ (PRST) scoring system (Table 4). Mean arterial pressure, heart rate, respiration and the presence of tears were recorded every 5 min and were scored. If the PRST score was higher than 2, an increased dose of anaesthetic and analgesic agent was given. After closure of the incision, propofol perfusion was stopped. Time for BIS to rise to 80 was recorded, and tracheal extubation was performed. At the end of the procedure all the infusions were stopped and the following times were recorded: (i) time to tracheal extubation; (ii) time to response to verbal commands (spontaneous eye opening); (iii) orientation time (for the patient to give their name, date of birth and location).

All patients were also evaluated with the Aldrete post-anaesthesia recovery scoring system.\(^2\)

Statistical analysis was with analysis of variance and the Bonferroni test. The analysis was conducted on an intention-to-treat basis. A value of \(P<0.05\) was considered significant.

**Results**

The three groups were similar in terms of age, weight, height, ASA status and duration of surgery \((P>0.05)\) (Table 1).

The time for BIS to reach 60 was significantly shorter in group M and group CL \((P<0.0001)\) (Table 2). Significantly greater doses of propofol were required by group CT than by the M and CL groups, both for induction of anaesthesia [group CT, 2.22 (0.19) mg kg\(^{-1}\); group M, 1.69 (0.07) mg kg\(^{-1}\); group CL, 1.63 (0.06) mg kg\(^{-1}\), \(P<0.0001\)] and for maintenance [1 h, group CT, 6.59 (0.01) mg kg\(^{-1}\) h\(^{-1}\), group M, 5.64 (0.05) mg kg\(^{-1}\) h\(^{-1}\), group CL, 4.12 (0.02) mg kg\(^{-1}\) h\(^{-1}\); 2 h, group CT, 5.55 (0.01) mg kg\(^{-1}\) h\(^{-1}\), group M, 3.82 (0.07) mg kg\(^{-1}\) h\(^{-1}\), group CL, 3.22 (0.04) mg kg\(^{-1}\) h\(^{-1}\); 3 h, group CT, 5.31 (0.02) mg kg\(^{-1}\) h\(^{-1}\), group M, 3.48 (0.06) mg kg\(^{-1}\) h\(^{-1}\), group CL, 2.73 (0.05) mg kg\(^{-1}\) h\(^{-1}\)]. Fentanyl doses were significantly lower in group M and group CL \((P<0.001)\).

MAP values in group CT were significantly lower after induction \((P<0.001)\) and higher after intubation and incision compared with the preoperative value \((P<0.05)\) (Fig. 1). MAP in group M fell significantly after induction \((P<0.001)\). MAP in group CL fell significantly for all measurements with the exception of intubation and after infusion \((P<0.001)\) (Fig. 1). Heart rate in group CT increased significantly after intubation, incision and extubation \((P<0.01)\), and decreased significantly in the intraoperative period \((P<0.05)\) (Fig. 2). Heart rate in group CL decreased significantly in all periods with the exception of postintubation, postinfusion and extubation \((P<0.001)\). Heart rate in group M was significantly lower after induction \((P<0.05)\) and in the intraoperative period \((P<0.01, P<0.001\) respectively). At the end of anaesthesia, recovery time for BIS to reach 80 was significantly shorter for group CL with respect to group M and group CT \((P<0.0001)\) (Table 2). When the groups were compared for the parameters of recovery; extubation time; response to verbal commands and time for orientation were longer with group M \((P<0.001)\). There were no significant differences between the other two groups \((P>0.05)\) (Table 3).

**Discussion**

We studied the effects of magnesium sulphate and clonidine as adjuvants for general anaesthesia. When magnesium sulphate or clonidine was given peroperatively the dose of propofol for induction and maintenance was significantly reduced. In the magnesium sulphate group, no haemodynamic and cardiovascular effects were seen, but extubation time was longer and recovery was slower. Titrating propofol with BIS monitoring during balanced anaesthesia decreased propofol use and significantly improved recovery. These findings indicate that the use of BIS may be valuable in guiding the administration of propofol intraoperatively.\(^3\)-\(^6\)

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**Table 1** Patient characteristics. Mean (sd)

<table>
<thead>
<tr>
<th></th>
<th>Group CT</th>
<th>Group M</th>
<th>Group CL</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40.75 (29–51)</td>
<td>42.25 (33–51)</td>
<td>44.94 (36–54)</td>
<td>0.253</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>11/9</td>
<td>13/7</td>
<td>13/7</td>
<td>0.754</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.80 (10.18)</td>
<td>68.65 (10.0)</td>
<td>69.84 (10.34)</td>
<td>0.085</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.20 (8.77)</td>
<td>166.70 (7.08)</td>
<td>165.87 (7.53)</td>
<td>0.056</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>117.10 (30.98)</td>
<td>105.65 (27.46)</td>
<td>112.93 (34.41)</td>
<td>0.453</td>
</tr>
</tbody>
</table>

**Table 2** Induction and recovery periods for BIS. Mean (sd). \(P\)-values were determined by comparing control (CT), magnesium (M) and clonidine (CL) groups. *Significant difference within groups \((P<0.0001)\)

<table>
<thead>
<tr>
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<th>Group CL</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction period</td>
<td>81.75 (9.40)</td>
<td>60.25 (7.12)*</td>
<td>53.28 (6.61)*</td>
<td>0.0000</td>
</tr>
<tr>
<td>Recovery period</td>
<td>6.52 (1.26)*</td>
<td>8.71 (1.06)</td>
<td>5.35 (1.28)*</td>
<td>0.0000</td>
</tr>
</tbody>
</table>
Magnesium sulphate has been reported to produce general anaesthesia and enhance the activity of local anaesthetic agents. In these studies, depressant effects on the CNS of animals injected with magnesium sulphate salts were reported. However, Aldrete and Vazeery\(^7\) suggested that this was actually a sleep-like state caused by cerebral hypoxia from progressive respiratory and cardiac depression. When ventilation was maintained, even very high levels of serum magnesium sulphate produced no CNS depression. However, increasing the magnesium sulphate dose was found to be associated with a reduction in halothane MAC in rats.\(^8\) Magnesium sulphate antagonizes NMDA receptors in the CNS and may reduce catecholamine release, thus decreasing peripheral nociceptor sensitization or the stress response to surgery. In our study, fentanyl requirements were lower in the magnesium sulphate group. Van Den Berg and colleagues found that magnesium sulphate attenuated the haemodynamic response to tracheal intubation.\(^9\)

![Figure 1](image1.png) Mean arterial blood pressure (mm Hg). Mean and SD. *P<0.05; **P<0.01; *P<0.001 compared with preoperative period.

![Figure 2](image2.png) Heart rate (beats min\(^{-1}\)). Mean and SD. *P<0.05; **P<0.01; *P<0.001 compared with preoperative period.

**Table 3** Recovery time (min). Mean (sd). \(P\) values were determined by comparing control, magnesium and clonidine groups. ***Significant difference within groups \((P<0.001)\)

<table>
<thead>
<tr>
<th></th>
<th>Group CT</th>
<th>Group M</th>
<th>Group CL</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extubation time</td>
<td>6.52 (1.26)</td>
<td>8.71 (10.6) ***</td>
<td>5.37 (1.06)</td>
<td>0.000</td>
</tr>
<tr>
<td>Response to verbal commands</td>
<td>7.82 (1.27)</td>
<td>9.97 (1.04) ***</td>
<td>7.88 (1.24)</td>
<td>0.000</td>
</tr>
<tr>
<td>Time for orientation</td>
<td>8.96 (1.44)</td>
<td>10.70 (1.08) ***</td>
<td>9.26 (1.731)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Magnesium sulphate has been reported to produce general anaesthesia and enhance the activity of local anaesthetic agents. In these studies, depressant effects on the CNS of animals injected with magnesium sulphate salts were reported. However, Aldrete and Vazeery\(^7\) suggested that this was actually a sleep-like state caused by cerebral hypoxia from progressive respiratory and cardiac depression. When ventilation was maintained, even very high levels of serum magnesium sulphate produced no CNS depression. However, increasing the magnesium sulphate dose was found to be associated with a reduction in halothane MAC in rats.\(^8\) Magnesium sulphate antagonizes NMDA receptors in the CNS and may reduce catecholamine release, thus decreasing peripheral nociceptor sensitization or the stress response to surgery. In our study, fentanyl requirements were lower in the magnesium sulphate group. Van Den Berg and colleagues found that magnesium sulphate attenuated the haemodynamic response to tracheal intubation.\(^9\)
In our study, both magnesium sulphate and clonidine lowered the haemodynamic response to intubation but clonidine was more effective in attenuating the sympathetic response.

Taittoven and colleagues compared clonidine and midazolam as premedication agents and observed no difference in oxygen consumption, anxiolysis, energy expenditure and carbon dioxide production. Preoperative oral clonidine protects against the pressor response to intubation, and hypotension and bradycardia may be encountered with clonidine, and in our study we found more bradycardia and hypotension in the clonidine group than in the other groups. Clonidine has been shown to decrease propofol requirements during anaesthesia and our study confirms this. Preoperative administration of clonidine, in addition to careful anaesthetic management, results in improved perioperative haemodynamic stability in patients with mild or moderate arterial hypertension and a reduction of the anaesthetic requirement, but further studies are necessary to investigate whether this approach may be safely extended to hypertensive patients.

In conclusion, both clonidine and magnesium sulphate lowered propofol consumption and attenuated the haemodynamic response to tracheal intubation. Clonidine was associated with bradycardia and hypotension and magnesium sulphate caused a delay in recovery.

References