Changes in cerebrospinal fluid magnesium levels in patients undergoing spinal anaesthesia for hip arthroplasty: does intravenous infusion of magnesium sulphate make any difference? A prospective, randomized, controlled study

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Editor’s key points
- Magnesium (Mg) has several effects on the central nervous system, including analgesia and neuroprotection.
- In this study, cerebrospinal fluid Mg concentrations decreased after spinal anaesthesia, and did not increase with i.v. Mg infusion.
- These data suggest that any beneficial effects of i.v. Mg infusion are mediated peripherally.

Background. Most investigators have attributed the reduced postoperative pain or anaesthetic drug requirements in patients receiving i.v. magnesium sulphate (MgSO4) infusion during spinal or general anaesthesia to central N-methyl-D-aspartate (NMDA) receptor magnesium (Mg) activity. In this study, we investigated how cerebrospinal fluid (CSF) Mg concentrations change after spinal anaesthesia, and whether peripherally infusing MgSO4 influences central Mg levels.

Methods. Forty-five patients undergoing continuous spinal anaesthesia for hip arthroplasty were randomly assigned to receive either i.v. MgSO4 at a dose of 50 mg kg⁻¹ diluted in 100 ml 0.9% saline solution followed by 15 mg kg⁻¹ h⁻¹ for 6 h or saline at the same volume [mean (SD) 64 (10) ml]. The changes in CSF and serum total and ionized Mg concentrations were assessed at six time points before and after spinal anaesthesia. Secondary outcome variables included serum and CSF electrolytes and proteins.

Results. Thirty-five patients completed the study. We found that spinal anaesthesia reduced total and ionized Mg concentrations in CSF by about 10%. Increasing serum Mg concentration over 80% of the baseline value left CSF Mg levels unchanged.

Conclusions. Spinal anaesthesia unexpectedly reduced CSF total and ionized Mg concentrations in patients undergoing hip arthroplasty, although the mechanism is unclear. The dose used for peripheral MgSO4 infusion in this study had no influence on central Mg concentrations in neurologically healthy patients undergoing spinal anaesthesia. If CSF Mg concentration is a reliable marker of Mg brain bioavailability, peripherally infused MgSO4 during spinal anaesthesia is unlikely to influence central NMDA receptor activity.

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The role of magnesium (Mg) in several cerebral pathophysiological mechanisms is increasingly recognized. In particular, Mg inhibits N-methyl-D-aspartate (NMDA) receptors, thus reducing post-nociceptive central sensitization,1 anaesthetic requirements,2 and release of excitatory amino acids.3 4 The supposed benefits of Mg included antinociceptive, anaesthetic, and neuroprotective effects.

The factors that influence the central nervous system (CNS) Mg concentration are unclear. Because extracellular brain Mg concentration is difficult to measure directly in humans, some investigators suggested using cerebrospinal fluid (CSF) Mg concentrations as a surrogate marker of brain bioavailability.3-6 CSF Mg homeostasis is tightly controlled by active transport through the blood–brain barrier (BBB) and brain–CSF barrier (B-CSF), and maintained at a concentration greater than that in plasma.6 CSF Mg concentrations preferentially depend on active transport into the CNS through a specific ion channel.7 Even though local anaesthetics act on ion channels,8 whether local anaesthetics injected intrathecally alter CSF Mg level remains unknown.

Conversely, although most authors who found that peripherally infused MgSO4 reduces postoperative pain and
anaesthetic drug requirements attributed its analgesic or anaesthetic effects to its action on central NMDA receptors. \(^9\)–\(^{12}\) It is not clear whether peripherally infused MgSO\(_4\) reaches the CSF. The only previous study addressing changes in CSF Mg levels after i.v. infusion of MgSO\(_4\), found no changes in CSF Mg concentrations, in neurologically healthy women undergoing hysterectomy under general anaesthesia.

No study has, to our knowledge, investigated the changes in CSF Mg concentrations after spinal anaesthesia, nor whether MgSO\(_4\) injected i.v. during spinal anaesthesia reaches the CSF in neurologically healthy subjects. Having more information on factors influencing CSF Mg concentration would extend our current knowledge on the possible role of Mg in centrally mediated processing mechanisms.

In this prospective, randomized, controlled study, we investigated whether intrathecal injection of local anaesthetic (levobupivacaine) for spinal anaesthesia causes changes in the CSF Mg concentration. We then sought to find out whether increasing the serum Mg levels during spinal anaesthesia increases the CSF Mg concentration.

**Methods**

In this randomized, controlled study, we prospectively enrolled consecutive patients, aged \(\geq 18\) yr, undergoing spinal anaesthesia for hip arthroplasty in our university hospital. To avoid possible confounding effects of fluid therapy, we excluded patients who had received i.v. fluids the week before surgery. We also excluded patients of ASA class \(\geq III\), those with coagulation disorders, severe cardiovascular dysfunction (in particular atrio-ventricular block), contraindications to spinal catheter insertion, diabetes mellitus, need for catecholamines, blood loss \(>400\) ml during surgery, anticipated use of diuretics, and preoperative serum total Mg concentration outside the normal range (1.6–2.6 mg dl\(^{-1}\)). The study protocol was approved by the institutional review board at Sant’Andrea Hospital, and each patient gave written informed consent.

Patients arrived in the operating theatre 90 min before surgery, and monitoring (ECC, non invasive arterial pressure, and peripheral oxygen saturation) was started immediately. Before spinal anaesthesia, patients were randomly assigned, with a computer-generated random number, to one of the two groups, to receive i.v. MgSO\(_4\) or saline (control) as an adjunct to spinal anaesthesia.

Spinal anaesthesia was administered through a spinal catheter positioned to treat postoperative pain. The spinal catheter was inserted using an IntraLong Set for continuous spinal anaesthesia (Pajunk\(^\circ\), Geisingen, Germany). An expert anaesthetist inserted the catheter through a paramedian approach at the L3–4 or L4–5 level through a 22 G Sparrte needle. The catheter, not previously filled, was inserted 3 cm into the subarachnoid space.

Because under physiological conditions, only the ionized Mg (Mg\(^{2+}\)) is actively transported into the CNS, as primary outcome variables, we assessed changes in serum and CSF total and ionized Mg concentrations over time. Secondary outcome variables were changes in proteins and electrolytes concentrations in serum and CSF: sodium (Na\(^{+}\)), chloride (Cl\(^{-}\)), calcium (total and ionized), and phosphate over time. Samples were collected and stored in heparin-free tubes to avoid heparin chelation of ionized electrolytes. Ionized electrolytes concentrations were immediately quantitated using a Nova 8 electrolyte analyzer (Nova Biomedical, Waltham, MA, USA). To account for changes in sample pH that could alter ionized electrolyte concentration in vitro, all values were normalized to pH 7.4. Because red blood cells have a three times higher Mg concentration than serum, CSF samples contaminated with blood were discarded.

To determine values of the studied outcome variables, a 3 ml blood sample was obtained from a 14 G indwelling antecubital vein catheter positioned in the arm opposite to the i.v. injection site and, after clear CSF flowed from the spinal catheter, a 0.5 ml CSF sample was collected at six time points (Fig. 1): T0 baseline, on arrival in the operating theatre; T1, when an i.v. MgSO\(_4\) bolus at a dose of 50 mg kg\(^{-1}\) (2.1 mmol kg\(^{-1}\) of body weight, diluted in 100 ml normal saline solution (0.9% NaCl) and infused over 15 min in the Mg group patients, or the same volume and rate of saline in controls, ended; T2, 1 h after continuous 6 h i.v. infusion of 10% MgSO\(_4\) started at the dose of 15 mg kg\(^{-1}\) h\(^{-1}\) (0.6 mmol kg\(^{-1}\) h\(^{-1}\)), or the same volume in saline with a syringe pump. After T2 sampling, anaesthesia was induced in both groups with 20 mg of 0.5% levobupivacaine (Chirocaine\(^\circ\), Abbott, Abbott Park, IL, USA) injected through the spinal catheter, and at T3 (1 h after T2), T4 (3 h after T2), and T5 (5 h after T2), further blood and CSF samples were collected. The Mg regimen corresponded to 50–70% of that used in patients with preeclampsia and has already been used in works studying the effectiveness of Mg in postoperative pain.\(^{13}\) All the patients received 24 h fluid replacement with a continuous infusion of normal saline at 1.5 ml kg\(^{-1}\) h\(^{-1}\) starting from T0. After T5, patients received for postoperative analgesia a continuous infusion of levobupivacaine 0.5% through a spinal pump. No more CSF samples were collected.

During surgery, systolic, mean, and diastolic arterial pressures (SAP, MAP, and DAP), respiratory rate (RR), and peripheral oxygen saturation (Sp\(_{O_2}\)) were recorded every 5 min.

**Statistical analysis**

In a pilot study of patients undergoing spinal anaesthesia using identical settings and anaesthetic solution concentration, conducted because no previous studies have verified CSF changes after spinal anaesthesia, a power analysis showed that a sample size of 16 patients would have 80% power to detect at least 10% variation in CSF Mg concentration at T3 at \(\alpha=0.05\). All data are expressed as mean (sd). Continuous variables were tested for significance using repeated-measures analysis of variance (ANOVA) followed by Dunnett’s *post hoc* test for significant *F* statistic (\(P<0.05\)) for comparisons with baseline values. Patient characteristic
and dichotomous data were tested using the $\chi^2$ and Student's t-test.

**Results**

A total of 45 patients entered the study (24 women and 21 men); 22 were randomized to the control group and 23 to the Mg group (Fig. 2). Ten patients (six control group and four Mg group) stopped the study either because they had a blood loss of $>$400 ml during surgery (three control group and two Mg group) or because CSF samples were blood tinged (three control group and two Mg group). Therefore, a total of 35 patients (77%) successfully completed the study, 16 in the control group and 19 in the Mg group. No differences were found in the patient characteristic, duration of surgery, or preoperative serum and CSF total and ionized Mg levels between the groups (Table 1).

No differences were found in the cardiorespiratory variables (MAP, SAP, DAP, HR, RR, and $S_pO_2$) between the groups during surgery. No major intraoperative or postoperative complications developed during the study period.

Baseline ionized/total serum Mg ratios were 0.7 in CSF and 0.64 in serum in the Mg group and 0.69 in CSF and 0.65 in serum in the control group. Ionized and total Mg concentrations underwent similar changes over time (Fig. 3A and B).

In patients from the Mg group, serum total Mg concentration (mg dl$^{-1}$) increased from T0 to T5 ($P<0.001$ by ANOVA) and peaked at T4 (82% increase from baseline). The ionized Mg level (mg dl$^{-1}$) followed the same trend increasing from T0 to T5 and also peaked at T4 (79% increase from baseline).
In controls, serum Mg concentration slowly decreased and became significant at T5 ($P<0.05$) with a $\pm 10\%$ variation from baseline.

In patients from both groups, 1 h after spinal anaesthesia (T3), CSF total and ionized Mg levels decreased significantly from baseline ($P<0.001$), whereas in the Mg group, at T3, CSF Mg level (mg dl$^{-1}$) decreased by about 9% ($P<0.001$). The ionized CSF Mg concentration (mg dl$^{-1}$) followed a similar trend of decreasing at T3 in the control group by about 10% and in the Mg group from baseline by about 8.5% ($P<0.05$). No significant differences were found in CSF total and ionized Mg concentration at each time point between the groups.

During the study period, serum calcium significantly decreased by about 13% in both groups (T5), whereas CSF calcium remained unchanged (Table 2). No other CSF or serum variables changed significantly over time.

**Discussion**

In this study, increasing the serum Mg concentration (by 80% over baseline value) and maintaining it stable by i.v. infusion of MgSO$_4$ for 6 h in patients undergoing hip arthroplasty did not compensate for the unexpectedly reduced CSF total and ionized Mg concentration after spinal anaesthesia. The lack of significant changes in CSF Mg levels after MgSO$_4$ i.v. infusion is in line with the only previous study by Ko and colleagues, addressing postoperative pain and serum to CSF Mg transfer after i.v. MgSO$_4$ supplementation. A strength of our study is that we measured total and ionized CSF Mg levels at six time points before and after inducing spinal anaesthesia, whereas Ko and colleagues measured total Mg concentration only once, when surgery ended.

The finding that increasing serum Mg concentration leaves CSF Mg levels unchanged, during spinal anaesthesia in neurologically healthy subjects, provides an insight into the supposed roles of peripherally infused MgSO$_4$ on several pathophysiological mechanisms. For example, most studies of the adjuvant effects of Mg on postoperative pain and during general anaesthesia have found reduced postoperative pain or anaesthetic drug requirements after i.v. MgSO$_4$ infusion, and the analgesic or anaesthetic effects have been attributed to its actions on central NMDA receptors. Mg binds to NMDA receptors and can theoretically modulate pain transmission. Drugs acting at a central level nevertheless have to reach their site of action. Accordingly, in a previous randomized controlled trial, we have already shown that centrally injected MgSO$_4$ effectively reduces postoperative pain. The more MgSO$_4$ reaches a central site, the more its anti-nociceptive effect increases, in particular: MgSO$_4$ given through a combined spinal–epidural route is more effective than MgSO$_4$ given by an intrathecal route alone, and intrathecal MgSO$_4$ is more effective than epidural MgSO$_4$ alone.

**Table 1** Patient characteristics. Data expressed as mean (sd), mean (range), or number (%)

<table>
<thead>
<tr>
<th></th>
<th>Controls ($n=16$)</th>
<th>I.V. MgSO$_4$ ($n=19$)</th>
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<tbody>
<tr>
<td>Males [n (%)]</td>
<td>7 (43)</td>
<td>9 (47)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>68.6 (27–85)</td>
<td>66.3 (46–83)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.5 (12.5)</td>
<td>71.2 (12.5)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165 (9)</td>
<td>166 (8)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>111 (18)</td>
<td>108 (22)</td>
</tr>
<tr>
<td>Total serum Mg (mg dl$^{-1}$)</td>
<td>2.05 (0.2)</td>
<td>2.14 (0.8)</td>
</tr>
<tr>
<td>Ionized serum Mg (mg dl$^{-1}$)</td>
<td>1.30 (0.18)</td>
<td>1.37 (0.5)</td>
</tr>
<tr>
<td>Total CSF Mg (mg dl$^{-1}$)</td>
<td>2.9 (0.1)</td>
<td>2.85 (0.3)</td>
</tr>
<tr>
<td>Ionized CSF Mg (mg dl$^{-1}$)</td>
<td>2.01 (0.13)</td>
<td>2.0 (0.21)</td>
</tr>
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and its serum concentration is increased up to 80% more than baseline, it leaves CSF Mg levels unchanged and does not compensate for the slight reduction induced by spinal anaesthesia. This finding strongly suggests that peripherally infused MgSO₄ exerts its possible anti-nociceptive effects through peripheral rather than central NMDA-receptor mechanisms.¹⁷–¹⁹

Further data favouring our finding that CSF Mg concentration seems almost uninfluenced by increases in serum Mg come from patients with neurological disorders.⁷ Although patients with potential BBB disruption may respond differently to increased serum Mg concentration, most studies on patients with acute neurological disorders receiving prolonged MgSO₄ infusions found only marginal (11–19%) or no increase in CSF Mg.⁴ ⁵ ¹⁰ Even though the CSF Mg increment necessary for possible neuroprotection remains unestablished, large clinical trials found i.v. MgSO₄ ineffective.²¹ Our finding that peripherally infused MgSO₄ fails to reach the CSF may support those who conclude that increasing serum Mg concentration gives only limited, if any, neuroprotection in humans with acute brain injury,⁷ and others who underlined a more important role of Mg in the periphery than in the CNS.²² Even its anticonvulsant effect in patients with eclampsia raised concerns that by acting at the neuromuscular junction, Mg might mask seizure manifestations without treating the CNS cause.²³

In the patients, we studied, undergoing hip arthroplasty, CSF Mg unexpectedly decreased by about 10% 1 h after we induced spinal anaesthesia with levobupivacaine and returned to normal after about 5 h, approximately matching the duration of action of the local anaesthetic.²⁴ This finding means that as soon as ion channels regain their function, CSF Mg concentration rapidly returns to baseline values. It is uncertain whether the decrease in CSF Mg is clinically, rather than statistically, significant.

It is difficult to explain how an intrathecal injection at the lumbar level of local anaesthetic reduces CSF Mg concentration. One possible explanation is that the decrease in CSF Mg is simply due to an Mg ion shift from CSF to the intracellular compartment. Intrathecally injected anaesthetic molecules

![Figure 3](https://academic.oup.com/bja/article-abstract/109/2/208/253573)

**Fig 3** (a) Changes in serum total [Mg] and ionized [Mg²⁺] Mg concentrations in both groups. In the Mg group, serum [Mg] peaked at T4 and increased by 80% from baseline. Ionized Mg levels underwent the same changes over time. In the control group, serum total [Mg] slowly decreased and the change became significant at T5, when the 6 h MgSO₄ infusion ended. (a) The changes in total and ionized CSF Mg levels in both groups. After spinal anaesthesia, total and ionized CSF Mg concentrations decreased by about 10% from baseline and at T5 returned to baseline in both groups. Ionized and total Mg concentrations underwent similar changes over time, in both serum and CSF, confirming that total Mg concentration accurately reflects concomitant changes in the ionized fraction.⁴  *P<0.05, **P<0.001. No significant differences were found at each time point between the groups, except for serum Mg in the Mg group with respect to the control group.
I.V. magnesium infusion and changes in CSF magnesium levels

penetrate deeply into the spinal cord tissue. Local anaesthetics, including lidocaine, mepivacaine, and bupivacaine, when applied on snail dorsal ganglion neurones increased intracellular sodium ions in a concentration-dependent manner. The increased intracellular sodium interferes with the Na\textsuperscript{+}–Mg\textsuperscript{2+} exchanger, thus reversing the Na\textsuperscript{+}–Mg\textsuperscript{2+} antiport. Accordingly, incubating Mg\textsuperscript{2+}-loaded rat pancreatic acinar cells in a local anaesthetic (lidocaine) strongly reduced the Mg\textsuperscript{2+} efflux with respect to controls. The Na\textsuperscript{+} CSF concentration remained unchanged because hydrated Na\textsuperscript{+}, the main osmolyte in the organism, shifts between compartments retaining water, thus without altering its concentration.

Alternatively, and less likely, considering that local anaesthetics inhibit not only Na\textsuperscript{+} channels but also various K\textsuperscript{+} channels and Ca\textsuperscript{2+} channels, we found no concentration gradient between CSF low doses might have inhibited Mg\textsuperscript{2+} active transport at the choroid plexus. At the lumbar level, a regurgitant CSF fraction (i.e. the ratio of caudal to cranial CSF flow per single CSF volume moving caudally in systole and cephalically during diastole) normally displaces about 30% of CSF, and injectate currents may displace further CSF. One millilitre of radioisotope intrathecally injected at the lumbar level results in cisterna magna activity within 1 h, suggesting a rapid rostral distribution. Hence, physiological CSF and injectate flows might have carried the drug towards the rostral region, where the local anaesthetic at low doses reached the choroid plexus inhibiting Mg\textsuperscript{2+} active transport, and fostering the other two types of CSF Mg\textsuperscript{2+}/serum Mg\textsuperscript{2+} interchange: diffusion and ion bulk flow.

When we studied secondary outcome variables (Na\textsuperscript{+}, Cl\textsuperscript{-}, Ca\textsuperscript{2+}, K\textsuperscript{+}), we found no concentration gradient between CSF...
and serum and no significant differences in CSF and serum Na\(^+\), Cl\(^-\) concentrations at any of the six time points studied, before or after inducing spinal anaesthesia, whereas serum Ca\(^{2+}\) progressively decreased. A progressive serum Ca\(^{2+}\) decrease has already been described associated with induced hypermagnesemia and speculatively related to impaired release of parathyroid hormone.\(^7\) The Ca\(^{2+}\)-free Mg solution we infused in patients or saline solution we infused in controls might also have diluted serum Ca\(^{2+}\). Possibly through the same mechanism, infusing saline also reduced serum Mg levels in the control group as reported in other controlled studies.\(^13\)\(^14\)

Our study has several limitations. Apart from the small sample size of the study groups, because we enrolled patients undergoing spinal anaesthesia, we do not know whether increasing serum Mg without inducing spinal anaesthesia would have had a larger influence on CSF Mg concentrations. This hypothesis seems, however, unlikely considering that BBB and B-CSF barriers tightly limit its CNS penetration and MgSO\(_4\) infused i.v. at high doses for prolonged times even in patients with BBB or B-CSF disruption reaches limited brain bioavailability.\(^5\)\(^20\) Nor can we state whether a larger increase in serum Mg concentration would have had a greater influence on CSF Mg levels. An unavoidable limitation is that we measured CSF Mg concentration, an indirect marker of extracellular brain Mg availability. Finally, because it was beyond the scope of our study, we did not consider postoperative pain among the outcome variables. Because postoperative pain was controlled through local anaesthetic intrathecal infusion, the possible Mg adjuvant effect on pain would have been hard to interpret and we needed a far larger sample size to assess postoperative analgesic consumption to draw definitive conclusions.

In conclusion, the local anaesthetic, levobupivacaine, intrathecally injected for spinal anaesthesia in patients undergoing hip arthroplasty, reduced serum Mg concentrations. MgSO\(_4\) peripherally infused at doses that almost double its serum concentration has no influence on CSF Mg levels in humans with acute brain injury undergoing prolonged induced hypermagnesemia. Crit Care Med 2005; 33: 661–6.


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