The neuroprotective effect of magnesium sulphate during iatrogenically-induced ventricular fibrillation

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Abstract. We studied the neuroprotective effect of magnesium sulphate (MgSO₄) administered before ventricular fibrillation was induced for internal cardioverter defibrillator threshold testing, and continued during reperfusion. Methods: with the intention of increasing serum magnesium (Mg) to >1.2 mmol/L, 15 patients received 16 mmol of MgSO₄, IV, followed by 5 mmol over two hours. Fifteen patients received placebo. Serum neuron-specific enolase (NSE) was assessed, as well as pre- and postoperative neurocognitive function. Results: NSE increased in all patients, reaching a peak at 24 hours. The target Mg level was maintained throughout surgery in only nine of the Mg patients, and mainly in those with low lean body mass (LBM). In these patients, increased Mg levels were related to altered NSE release (P<0.05). NSE increased when serum Mg dropped to <1.2 mmol/L, finally exceeding levels of inadequately or untreated patients. Neurocognitive function after surgery was similar between groups. Conclusions: insufficient dosing could account for our results, as NSE release could be inhibited by Mg >1.2 mmol/L. For neuroprotection, the Mg dosage should be adjusted according to LBM and infusion be extended to >2 hours.

Key words: magnesium sulphate, neuroprotection, global cerebral ischaemia, ventricular fibrillation, NSE, neurocognitive function

In clinical practice, iatrogenically-induced cardiac arrest with global cerebral hypoperfusion is frequently instigated. Surgical correction of congenital cardiac abnormalities or pathologies of the aortic arch, trans-femoral or trans-apical aortic valve insertion, and threshold testing during the course of implantation of internal cardioverter defibrillators (ICD), are situations that necessitate the induction of a more or less prolonged period of global ischaemia.

At our institution, threshold testing in conjunction with brief, repetitive, iatrogenically-induced periods of ventricular fibrillation used to be performed in patients undergoing elective ICD insertion. These short-lasting episodes of induced global brain ischaemia have been associated with a drop in regional cerebral saturation [1], as well as neuronal damage assessed by deteriorating neurocognitive function in conjunction with release of neuron-specific enolase (NSE) [2, 3].
NSE, which is also found in extracranial tissue, is predominantly localized in neuronal cytoplasm, and has become an established biomarker of brain injury [4]. ICD implantation with threshold testing appears therefore to be a suitable model for studying the neuroprotective properties of a pharmacological agent introduced before the induction of brief, but precisely monitored global cerebral ischaemia under well-controlled conditions.

Despite the benefits of moderate, therapeutic hypothermia, poor outcome after global brain ischaemia has driven research in pharmacological neuroprotection [5]. In this context, magnesium (Mg) salts have also been used. Mg is an N-methyl D-aspartate (NMDA) and calcium antagonist, and has vasodilatory properties. It may thus reduce the release of excitatory neurotransmitters, attenuate reperfusion injury by inhibiting cellular calcium influx, and improve cerebral blood flow during reperfusion. Despite the lack of data from randomised, controlled trials in humans [6], MgSO4 is still used during deep hypothermic cardiac arrest [7]. In addition, in the cardiac surgery field, where MgSO4 is frequently employed [8], Mg supplementation in patients undergoing coronary artery bypass surgery with cardiopulmonary bypass, dose-dependently decreased S100β and plasma matrix metalloproteinase-9 release, two biochemical markers of cerebral damage [9, 10]. MgSO4 administration in this setting, however, could not prevent a rise in serum glial fibrillary acidic protein concentration [10].

We hypothesised that MgSO4, when administered early enough, could mitigate the neuronal injury that was seen after repetitively-induced ventricular fibrillation in previous trials [2, 3]. Thus, the goal of this randomised, single-centre trial was to evaluate whether MgSO4 treatment, administered before global cerebral ischaemia and continued during early reperfusion, causes inhibition of NSE release in patients undergoing first-time ICD implantation with threshold testing. As a secondary outcome measure, we determined the impact of temporary hypermagnesaemia on neurocognitive function.

Methods

After approval by the local institutional review board and having obtained informed consent, 30 patients undergoing elective, transvenous ICD implantation were included in our investigation. Patients were allocated to either the Mg or control group by computerised randomisation. Left ventricular ejection fraction was determined by transthoracic echocardiography prior to surgery. Patients with second or third degree atrioventricular block, those with severe kidney disease defined as serum creatinine > 2.5 mmol/L, or neuromuscular disease, as well as pregnant women, were excluded from the trial.

In accordance with studies by Muir and Fuchs-Buder et al. [11, 12] and a subsequent multicentre trial in stroke patients [13], patients in the Mg group received a 16 mmol (4 g), intravenous bolus of MgSO4 over 30 minutes immediately before draping. At our institution, this is the average time it takes for proper placement of the electrodes in order to commence threshold testing. As we aimed at a target serum level of 1.2 mmol/L, ventricular fibrillation was not induced before complete administration of the loading dose. Following the loading dose, a continuous IV infusion of 5 mmol (1.25 g) MgSO4 over two hours was started to maintain the increased serum Mg level. Infusion covered the entire duration of implantation with threshold testing and early reperfusion (i.e. until wound closure at approximately 2 hours after the start of surgery). Such a dosage has been well tolerated and should guarantee achieving the desired serum Mg levels without delay [11, 12]. This serum level has been associated with the best neuroprotective results in a rat study conducted by Miles and colleagues [14], while lower and higher serum concentrations showed little benefit or even harm. Patients in the control group received saline solution from identical-looking syringes. This was a double blind study; the medication was prepared by the hospital dispensary.

Surgery was performed under local anaesthesia. Intraoperative monitoring consisted of ECG, pulse oximetry, arterial blood pressure monitoring, and capnography. Apart from 0.1 mg/kg etomidate IV, given immediately before induction of ventricular fibrillation, no further anaesthetics were administered. Ventricular fibrillation was induced either by rapid pacing or by an internal low energy shock during the T wave. Where the ICD failed to detect or terminate ventricular fibrillation, another internal shock at a higher energy level was applied, which, when unsuccessful, was followed by an external shock. After administration
of etomidate, which was chosen because of its haemodynamic stability, ventilation was assisted manually to maintain normoventilation, controlled by PETCO₂ until the patient awoke. The cumulative arrest time for each patient was determined as the added duration of total episodes in ventricular fibrillation. Blood samples were taken before the intervention at baseline, after wound closure (i.e. approximately 2 hours after skin incision), as well as two, six, and 24 hours after ICD insertion. In addition to blood gas parameters, haemoglobin, sodium, potassium, lactate and blood glucose (ABL700 Series®, Radiometer; Drott Medizintechnik GmbH, Wiener Neudorf, Austria), serum levels of NSE (Cobas Core NSE EIA II®, Hoffmann-La Roche Ltd, Basel, Switzerland), Mg (Magnesium reagent OSR6189, Olympus AU5400 Chemistry System® photometric unit, Beckman Coulter GmbH, Vienna, Austria), and free haemoglobin (In-house reagent, Olympus AU5400 Chemistry System® photometric unit, Beckman Coulter GmbH, Vienna, Austria) were also determined. Our laboratory does not process NSE measurements in haemolysed samples as this may provide falsely elevated results. Therefore, special care was taken to avoid haemolysis while drawing blood from the arterial line. Apart from gross neurological evaluation, the following psychometric tests were employed perioperatively (i.e. one day before implantation, as well as two days and three months after ICD insertion) in a quiet atmosphere: the Mini-Mental State Exam, the Forward and Backward Digit Span Tests, and the Trail Making A Test. Additionally, acoustic-evoked potentials (peak P300 latencies) were assessed during the same visit by two colleagues familiar with neurocognitive assessments. Differences in patients’ characteristics were evaluated using either the unpaired t-test or, in the case of categorical data, the Chi-squared test. To compare the change in NSE and serum Mg levels in each group and between groups over time, a two-way, repeated measures ANOVA model was employed. Because of multiple testing, the Bonferroni test was used for post hoc analysis. P-values less than 0.05 were considered to be statistically significant. Sigma Stat (Systat Software Inc. Chicago, IL, USA) was used for all computations. After unblinding of the test results at completion of the trial, we saw that IV Mg treatment in many cases failed to increase to or maintain serum Mg levels at the desired target level of >1.2 mmol/L over the entire duration of surgery. We therefore also performed a post hoc per protocol analysis comparing patients demonstrating intended Mg target level against patients in whom the target level was not reached, in addition to the intention-to-treat analysis. For the per protocol analysis we assumed that the projected, ideal serum Mg target level would be >1.2 mmol/L before and throughout the time of ischaemic neuronal damage. Control patients were thus analysed together with patients of the Mg group with insufficient substitution.

Results

Of the 30 patients we included in the trial, one patient assigned to the control group had to be excluded from statistical analysis because of withdrawal of consent. Patients’ characteristics are given in table 1. No significant group differences were noted. In addition, the number of shocks applied as well as the energy level of the internal shocks and the cumulative arrest time were similar in both groups. The mean time between shocks was greater than five minutes. The prevalence of atrial fibrillation on the day of surgery was insignificantly higher in patients from the Mg group. The target serum Mg level of >1.2 mmol/L during ischaemia and early reperfusion could only be achieved and maintained in nine out of 15 patients in the Mg group. The percentage of male patients within the group where the Mg target level could not be reached or maintained was significantly higher (P<0.05). In addition, the lean body mass (LBM) of these patients was also significantly higher (P<0.05). There was a statistically significant relationship (P = 0.025) between LBM and peak serum Mg concentration ([Mg]ₚₑᵃᵏ) that was reached after bolus administration in patients from the Mg group. The corresponding correlation coefficient R was 0.62. The linear relationship between the two variables can be described as:

\[ [\text{Mg}]_{\text{peak}} = 2.446 - (0.0192 \times \text{LBM}) \]

No appreciable increase in serum lactate levels, as a consequence of the induced, brief, global hypoperfusion, was seen in either group, and no adverse events occurred perioperatively. Moderate hypotension was observed in one female
Table 1. Patient characteristics and intra-operative data.

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 14)</th>
<th>Mg (n = 15)</th>
<th>Target serum Mg level &gt;1.2 mmol/L reached</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (yrs)</td>
<td>63 ± 14</td>
<td>60 ± 9 P = ns</td>
</tr>
<tr>
<td></td>
<td>Gender (male/female)</td>
<td>10/4</td>
<td>10/5 P = ns</td>
</tr>
<tr>
<td></td>
<td>BMI (kg/m²)</td>
<td>25 ± 3</td>
<td>25 ± 5 P = ns</td>
</tr>
<tr>
<td></td>
<td>Lean body mass (kg)</td>
<td>58 ± 8</td>
<td>55 ± 11 P = ns</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine (mg/dL)</td>
<td>1.4 ± 0.5</td>
<td>1.2 ± 0.3 P = ns</td>
</tr>
<tr>
<td></td>
<td>EF (%)</td>
<td>34 ± 4</td>
<td>34 ± 13 P = ns</td>
</tr>
<tr>
<td>Sinus rhythm on the day of surgery (n)</td>
<td>14/14</td>
<td>12/15 P = ns</td>
<td>19/20</td>
</tr>
<tr>
<td>Number of shocks (n)</td>
<td>3 ± 1</td>
<td>2 ± 1 P = ns</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Mean energy level of internal shocks (J)</td>
<td>21 ± 5</td>
<td>21 ± 2 P = ns</td>
<td>21 ± 4</td>
</tr>
<tr>
<td>Cumulative arrest time (s)</td>
<td>36 ± 32</td>
<td>30 ± 17 P = ns</td>
<td>35 ± 29</td>
</tr>
</tbody>
</table>

Mean ± SD or absolute value

Patient from the Mg group whose serum Mg concentration could be raised and maintained at target level. The hypotension in this case was easily reversed by the administration of neosynephrine, and did not affect her overall well-being. No further side-effects of the Mg substitution were observed.

Figure 1 depicts the change in serum Mg concentrations over time. Panel A shows the corresponding changes in the Mg and the control groups, whereas panel B depicts the changes in patients who either reached and maintained the targeted serum Mg levels or whose serum levels was measured as below 1.2 mmol/L at wound closure and/or 2 hours after surgery. Serum Mg levels increased significantly at these two time-points in the Mg group (P < 0.05) and were still elevated six hours after surgery. Serum Mg levels increased significantly at these two time-points in the Mg group (P < 0.05) and were still elevated six hours after surgery. In relation to the control patients, values were significantly higher at these three time-points (P < 0.05). This also applied to patients with target serum levels >1.2 mmol/L when compared with patients whose serum Mg concentrations remained below target level (P < 0.05).

Release kinetics of serum NSE are shown in figure 2; again, level A depicts the changes in control and Mg-treated patients, whereas panel B reflects changes in patients with and without target Mg levels >1.2 mmol/L at wound closure and at 2 hours after threshold testing. NSE levels at six and 24 hours after surgery were elevated in the Mg and the control group when compared with equivalent baseline values (P < 0.05). This was also the case in patients with adequate target serum Mg levels, while only the NSE value at six hours was significantly different from baseline in patients whose serum Mg levels was below 1.2 mmol/L. In relation to these patients, the NSE values in the group with adequate target levels were significantly lower at wound closure, but higher at 24 hours after surgery (P < 0.05).

Figure 3 displays the temporal relationship between serum Mg and concomitant serum NSE levels for the control and the Mg groups (panel A), as well as for patients with and without adequate Mg target levels (panel B). It shows that delayed increases in NSE were closely associated with declining Mg serum levels in patients treated with MgSO4. The insert in panel B further depicts the relationship between serum Mg concentration and log-transformed NSE values (correlation coefficient R = 0.525, P = 0.008) in patients with sufficient Mg supplementation.

The corresponding pre- and postoperative neurocognitive test results for all patients who completed all three assessments are given in table 2. Postoperative tests showed similar results in both groups. Interestingly, P300 latencies were increased significantly in all patients who were available for the third assessment at three months after surgery (P < 0.05), independent of group assignment.
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Figure 1. Time-course of intra- and postoperative serum Mg levels in patients in the control (n = 14) and the Mg group (n = 15; panel A). Panel B shows serum Mg concentrations in patients whose serum Mg levels reached the desired target (i.e. >1.2 mmol/L) in grey (n = 9), and patients with serum Mg levels below target (n = 20) in white. * = P<0.05 versus corresponding baseline, # P<0.05 versus control patients (Panel A) or versus patients whose serum Mg level remained below target (Panel B), respectively. BL = baseline, WC = wound closure. Boxplots depict median and 10th, 25th, 75th, and 90th percentiles; dots are outliers.

Discussion

To our knowledge this is the first study that has investigated the neuroprotective effect of MgSO₄ in a controlled setting of brief, iatrogenically-induced, global brain ischaemia when administered before the ischaemic insult and with administration continued throughout early reperfusion. Unfortunately, the results of this trial do not show a clear benefit of Mg treatment.
Figure 2. Release of NSE over time in the control (white boxplots) and the Mg group (grey boxplots, Panel A), whereas panel B depicts the corresponding serum NSE concentrations in patients whose serum Mg levels were below target (white boxplots), and in patients whose target level was reached (grey boxplots). * P < 0.05 versus corresponding baseline, # P < 0.05 versus patients whose serum Mg levels were below target, respectively. BL = baseline, WC = wound closure. Boxplots depict median and 10th, 25th, 75th, and 90th percentiles.

in this setting and the reason might be inadequate dosing. In the post hoc per protocol analysis, it appears that NSE release could actually be suppressed as long as serum Mg levels were > 1.2 mmol/L (i.e. almost double baseline levels). These serum levels have previously been reported to increase significantly cerebrospinal Mg levels [12] and confer neuroprotection in the setting of global brain ischaemia in rats [14]. Recently, targeting similar serum levels in pregnant patients with a potential risk of preterm delivery has been advocated in order to minimise brain injury in the newborn [15].

As an NMDA-inhibitor and a calcium-antagonist, Mg is likely to confer its neuroprotective action together with its vascular effects at an early stage of ischaemia-reperfusion [16]. Treatment with MgCl₂, for example, was associated with a reduction of cortical infarct volume after middle cerebral artery occlusion in rats when applied intraperitoneally during and after simulated focal ischaemia [17]. A similar neuroprotective effect of MgSO₄ was also found in this species after global brain ischaemia [14]. In contrast, the IMAGES trial, published in 2004, did not confirm a significant difference
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**Figure 3.**

[Graph showing serum NSE concentration against serum magnesium concentration with data points and regression line.]
Figure 3. Continued.

Changes over time in the relationship between serum Mg levels and corresponding serum NSE concentration. Numbers reflect time-points as given in figure 1. Blue dots in panel A depict control patients; in panel B, patients whose serum Mg level remained below target level. Red dots in panel A represent the Mg-treated patients, and in panel B, patients in whom serum Mg levels could be raised above 1.2 mmol/L at wound closure, as well as two hours post-surgery, respectively. The insert in panel B shows the correlation between declining serum Mg levels after supplementation and concomitantly rising log-transformed serum NSE concentrations with the corresponding equation of the regression line.

regarding death or disability between human stroke patients treated with or without Mg. The lack of effect was explained by the delay in the Mg treatment. Because of administrative difficulties, the median duration until treatment could begin was seven hours after the onset of stroke [13]. Focal brain injury however, is a different entity that is distinct from global brain injury. In the latter, neuroprotection by MgSO4 has mostly been demonstrated in animals when the MgSO4 was administered either preemptively or soon after the initiation of ischaemia. This can be explained by the inhibition of excitatory amino acid release that occurs soon after hypoxic injury of the brain [16]. Following the initial intravenously administered loading dose of 16 mmol MgSO4, increased Mg levels in the cerebrospinal fluid ought to be achieved after 30 min [12]. Accordingly, potentially neuroprotective Mg concentrations should have been reached at the time of skin incision, as only minor increments in brain Mg content are sufficient to interfere with neuronal transmission [18]. Greater changes in the cerebral Mg levels will occur when the blood-brain barrier is compromised as is the case when NSE liberated from dying neurons becomes detectable in the blood, which already occurs as early as 2 hours after threshold testing [2]. It was exactly at this time-point (i.e. at wound closure)

Table 2. Results of the neurocognitive evaluation of all patients who completed all three assessments.

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Two days after surgery</th>
<th>Three months after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>DST forward</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target not reached</td>
<td></td>
<td>42 ± 11</td>
<td>44 ± 8</td>
</tr>
<tr>
<td>Target reached</td>
<td></td>
<td>40 ± 11</td>
<td>41 ± 8</td>
</tr>
<tr>
<td>DST backward</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target not reached</td>
<td></td>
<td>29 ± 11</td>
<td>30 ± 10</td>
</tr>
<tr>
<td>Target reached</td>
<td></td>
<td>26 ± 12</td>
<td>22 ± 12</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target not reached</td>
<td></td>
<td>29 ± 2</td>
<td>29 ± 2</td>
</tr>
<tr>
<td>Target reached</td>
<td></td>
<td>28 ± 1</td>
<td>29 ± 1</td>
</tr>
<tr>
<td>Trail-making test A (s)</td>
<td>71 ± 76</td>
<td>71 ± 76</td>
<td>66 ± 76</td>
</tr>
<tr>
<td>Target not reached</td>
<td></td>
<td>50 ± 9</td>
<td>51 ± 19</td>
</tr>
<tr>
<td>Target reached</td>
<td></td>
<td>382 ± 51</td>
<td>382 ± 35</td>
</tr>
<tr>
<td>P300 latencies (ms)</td>
<td>411 ± 118</td>
<td>441 ± 65</td>
<td>459 ± 120*</td>
</tr>
</tbody>
</table>

*P<0.05 versus corresponding baseline value.
Mean ± SD or absolute value
when NSE values in patients with serum Mg levels >1.2 mmol/L were significantly below corresponding levels in patients with serum Mg concentrations <1.2 mmol/L. NSE values were also numerically, but not significantly, lower in these patients two hours after ICD implantation. Additionally, they were below those of an historic group of patients undergoing the same implantation procedure [2]. However, the suppression of NSE release was only temporary, which can be interpreted as limited protection against neuronal death. The NSE values in all groups determined at 24 hours after ICD insertion, were similar to those reported after successful resuscitation of patients with good neurological outcome [19]. As stated by Reisinger and colleagues, we too did not observe any gross neurological abnormalities in our patients after ICD insertion with threshold testing.

The delayed, medium increase in serum NSE levels that we found in patients with adequately raised serum Mg levels, which was greater than twice the corresponding baseline value, might explain why we could find neither improved neurocognitive function nor shorter P300 latencies in MgSO4-treated patients [20]. In addition, small group size may have precluded detection of differences in cognitive function, particularly in the three-month assessment when some patients had been lost to follow-up. Even if NSE values could have been suppressed permanently by the administration of MgSO4, it may not necessarily have translated into improved neurocognitive function, as it is not known which neurons were salvaged and which succumbed to ischaemia-reperfusion injury. Reduced NSE release after cardiac surgery has however, been linked to improved neurocognitive outcome [20]. The significant, and comparable prolongation in P300 latencies seen at three months after ICD insertion in both groups, regardless of whether target levels had been achieved, may reflect a natural, cognitive decline in patients with impaired left ventricular pump function and intermittent cardiac arrhythmia [21].

Following the loading dose of 16 mmol of MgSO4, we achieved similar serum Mg concentrations as those reported by Muir and Fuchs-Buder et al. [11, 12]. Even though Mg administration has a broad therapeutic range, care has to be taken not to increase serum Mg levels >3 mmol/L, which results in declining arterial blood pressure and cardiac output that can compromise the efficacy of the Mg treatment [14, 22]. Accordingly, we restricted the subsequent, steady-state dose to 5 mmol over 2 hours, which has been shown to be well tolerated [11]. The downside of this cautious treatment regimen may have been that the continuous infusion was insufficient to keep up the intended target level in a good number of Mg patients.

This is also the major limitation of our investigation, which might have obscured an actual treatment benefit. A dosing regimen adjusted to the patients’ LBM would have resulted in larger doses being given to predominantly male patients with greater LBM. Higher dosages, i.e. a 6 g MgSO4 bolus followed by constant infusion of 2 g per hour administered to women at imminent risk of preterm delivery have been well tolerated and mitigated the incidence of moderate and severe cerebral palsy in newborns [23]. In this context, continuous MgSO4 infusion of up to 24 hours had also been given without harmful side-effects [15].

As body temperature was not measured in our patients, we cannot rule out that the short-lasting benefit of MgSO4 is actually a combined effect of increased serum Mg levels and moderate hypothermia, which can occur in the course of surgery when patients are pharmacologically vasodilated. Such a synergistic effect could be substantiated in animal studies, and has been postulated for humans [24-26].

**Conclusions**

Treatment with MgSO4 in this study did not show a clear, neuroprotective effect in the chosen setting. The lack of effect may be due to inadequate serum Mg concentrations. Serum Mg levels >1.2 mmol/L, before global cerebral ischaemia and early reperfusion however, were associated with temporarily-suppressed NSE release. It remains to be elucidated whether either higher doses or prolonged increases in serum Mg levels (potentially in combination with hypothermia or prevention of hyperthermia), have a longer lasting effect, with permanent neuronal salvage [27]. This approach has been efficacious in other settings [15, 25, 28]. Our results further demonstrate that the Mg dosage, intended to increase serum Mg levels beyond 1.2 mmol/L, should ideally be adjusted to LBM.
Disclosure

Financial support: this study received institutional support only. Conflict of interest: none.

References


