Magnesium moderately decreases remifentanil dosage required for pain management after cardiac surgery†

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Background. Magnesium is a calcium and an NMDA-receptor antagonist and can modify important mechanisms of nociception. We evaluated the co-analgesic effect of magnesium in the postoperative setting after on-pump cardiac surgery.

Methods. Forty patients randomly received either magnesium gluconate as an i.v. bolus of 0.21 mmol kg⁻¹ (86.5 mg kg⁻¹) followed by a continuous infusion of 0.03 mmol kg⁻¹ h⁻¹ (13.8 mg kg⁻¹ h⁻¹) or placebo for 12 h after tracheal extubation. After surgery, remifentanil was decreased to 0.05 µg kg⁻¹ min⁻¹ and titrated according to a pain intensity score (PIS, range 1–6) in the intubated, awake patient and a VAS scale (range 1–100) after extubation. If PIS was >3 or VAS ≥30, the infusion was increased by 0.01 µg kg⁻¹ min⁻¹; if ventilatory frequency was ≤10 min⁻¹ it was decreased by the same magnitude.

Results. Magnesium lowered the cumulative remifentanil requirement after surgery (P<0.05). PIS >3 was more frequent in the placebo group (P<0.05). Despite increased remifentanil demand, VAS scores were also higher in the placebo group at 8 (2 vs 8) and 9 h after extubation (2 vs 7) (P<0.05). Dose reductions attributable to a ventilatory frequency ≤10 min⁻¹ occurred more often in the magnesium group (17 vs 6; P<0.05). However, time to tracheal extubation was not prolonged.

Conclusions. Magnesium gluconate moderately reduced the remifentanil consumption without serious side-effects. The opioid-sparing effect of magnesium may be greater at higher pain intensities and with increased dosages.

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Recently we have shown that remifentanil at a dose of 0.051 (0.01) µg kg⁻¹ min⁻¹ provides adequate postoperative analgesia in 73% of patients after cardiac surgery within 30 min after tracheal extubation.¹ Although initial rapid dose titrations are a disadvantage of remifentanil in this setting, it is, however, a good model to study the effects of co-analgesics, as remifentanil can be tightly titrated to effect.

Analgesic and anti-nociceptive properties of magnesium ions (Mg²⁺) have been investigated, based on their specified central and peripheral N-methyl-D-aspartate (NMDA) antagonism.²³ Mg²⁺ exerts a non-competitive voltage-dependent block of the NMDA receptor-operated ion channel, which prevents extracellular Ca²⁺ from entering the cell. The NMDA receptor is an excitatory amino acid receptor that mediates prolonged nociceptive behaviour and various chronic pain symptoms.⁴ Voltage-sensitivity of NMDA action is greatly reduced by lowering extracellular Mg²⁺.⁵⁶

Mg²⁺ preparations are usually well tolerated even when given at large dosages. In healthy patients plasma
concentrations in the range 2–3.5 mmol litre\(^{-1}\) are considered to be safe. The most common side-effects are heat sensation, pain at the injection site, myocardial conduction abnormalities and, more rarely, hypotension, sedation and neuromuscular depression.\(^7\) Muscle relaxation may be observed at serum \(\text{Mg}^{2+}\) concentrations above 2.5 mmol litre\(^{-1}\).\(^8\)

Results of clinical studies describe the systemic application of \(\text{Mg}^{2+}\) as an adjunct for postoperative pain management.\(^9\)\(^10\) However, the opioid-sparing effect of magnesium gluconate for postoperative pain relief after elective cardiac surgery with cardiopulmonary bypass, with potentially associated imbalances of electrolytes, has not been investigated.

**Methods**

The study protocol was approved by the Ethics Committee of the Medical University of Vienna and follows the Helsinki Declaration. After written informed consent, 40 patients undergoing first-time elective cardiac surgery (aortic valve replacement, mitral valve replacement, coronary artery bypass grafting or atrial septal defect closure) were included in the study. Inclusion criteria were ASA physical status \(\leq IV\), age 18–80 yr and ability to speak and read German. Exclusion criteria were atroventricular block, previous \(\text{Mg}^{2+}\) intake, treatment with \(\text{Ca}^{2+}\) channel blockers, evidence of major organ system dysfunction, neurological deficit, congestive heart failure (ejection fraction <40%), BMI \(>35\) kg m\(^{-2}\), pregnancy or participation in another clinical trial.

**Protocol**

Patients were premedicated with midazolam 7.5 mg per os 1 h before surgery. Anaesthesia was induced with midazolam 0.05 mg kg\(^{-1}\) i.v. followed by etomidate 0.2–0.3 mg kg\(^{-1}\) and a continuous i.v. infusion of remifentanil (ULTIVA\(^\oplus\), GlaxoSmithKline Pharma GmbH, Vienna, Austria) at 0.25–0.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) until loss of consciousness. Tracheal intubation was facilitated with \(\text{cis-}\text{atracurium}\) 0.2 mg kg\(^{-1}\) when the bispectral index (A 2000, Aspect Medical Systems, Newton, MA, USA) reached a value <60; values between 40 and 60 were recorded throughout surgery.\(^11\) The lungs were ventilated using a mixture of oxygen (40%) in air. Anaesthesia was maintained by continuous administration of remifentanil at 0.15–0.5 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) and sevoflurane at 0.5–2.5 vol%.

Patients were allocated randomly to receive either magnesium gluconate (Magnesium gluconicum\(^\oplus\), Lannacher Heilmittel GmbH, Lannach, Austria) or saline (control) in a double blind fashion. After induction of anaesthesia, patients received either magnesium gluconate 0.21 mmol kg\(^{-1}\) (86.5 mg kg\(^{-1}\)) i.v. \((n=20)\) or the equivalent volume of saline \((n=20)\) over a 30 min period. The bolus injection was followed by a continuous infusion of magnesium gluconate at 0.03 mmol\(^{-1}\) kg\(^{-1}\) h\(^{-1}\) (13.8 mg kg\(^{-1}\) h\(^{-1}\)) or the same volume of saline for 12 h after extubation. This dosage was chosen as it has been shown to be effective in reducing perioperative pain in patients undergoing knee surgery.\(^10\) As the sensation of heat and pain during rapid peripheral venous injection of magnesium gluconate carries the risk of unblinding and observer bias, it was administered through the central venous line shortly after induction of anaesthesia. Serum \(\text{Mg}^{2+}\) concentrations were determined on the day before surgery, immediately after surgery and 12 h after operation. The investigators were blinded to the results.

At the end of surgery, patients received the first six-hourly administered paracetamol 1 g infusion (Perfalgan\(^\oplus\), Bristol-Myers Squibb GmbH, Munich, Germany). After arrival in the intensive care unit (ICU), continuous administration of propofol 1.5–3 mg kg\(^{-1}\) h\(^{-1}\) was started and the remifentanil infusion was decreased to 0.05 \(\mu\)g kg\(^{-1}\) min\(^{-1}\). Propofol was stopped after 90 min, when, in general, a skin surface gradient of 0°C (forearm minus fingertip temperature) was reached with forced-air warming (BairHugger, Augustine Medical Inc., Eden Prairie, MN, USA).\(^12\) In addition, patients had to meet the following extubation criteria: responsive, negative inspiratory force \(>–20\) mm Hg, core temperature \(>36.5^\circ\)C, arterial pH \(>7.3\), chest tube drainage \(<100\) ml h\(^{-1}\) and absence of uncontrolled dysrhythmia.\(^1\) After extubation patients received 6 litre min\(^{-1}\) oxygen via a face mask. Arterial blood gas analysis was performed every 2 h. Respiratory depression was defined as a ventilatory frequency \(<8\) min\(^{-1}\). Impaired consciousness [LOC=(level of consciousness) score 3–5 where 1=alert, awake; 2=lethargic, tends to drift off to sleep when not stimulated, spontaneous movements are decreased, awareness is limited; 3=obtunded, difficult to arouse, when aroused is confused; 4=stuporous, unresponsive, arousable only by vigorous and repeated stimuli; 5=comatose, unarousable and unresponsive]\(^13\) and postoperative nausea and vomiting were recorded during the study period.

**Pain assessment**

The intensity of postoperative pain was assessed by the anaesthesiologist on call. It was started in the responsive but still intubated patient 10 min after stopping propofol, using a six point pain intensity scale (PIS), where 1=no pain, 2=mild pain, 3=moderate pain, 4=severe pain, 5=horrible and 6=worst possible pain. Pain intensity was evaluated in 10 min intervals until extubation. Moderate and severe pain (PIS=3) prompted a remifentanil dose increase of 0.01 \(\mu\)g kg\(^{-1}\) min\(^{-1}\).

After tracheal extubation, pain evaluation was performed with a visual analogue colour scale (VAS).\(^14\) The colour spectrum of the ruler had been explained to the patient the day before surgery. Pain intensity could be graded by moving from bright yellow on the far left of the scale (i.e. no pain) to dark red on the far right (i.e. worst pain imaginable).
On the back of the 10 cm scale, each colour was assigned a specific VAS grade from 0 mm (bright yellow) to 100 mm (dark red). Patients were only shown the coloured scale and the corresponding VAS grade in millimetres was recorded. Adequate pain relief was defined as VAS ratings <30 (mm). A VAS ≥30 in the extubated patient, similar to a PIS ≥3 in the intubated patient, induced a step increase of the remifentanil dose of 0.01 µg kg⁻¹ min⁻¹. During the first 6 h after extubation, pain was assessed every 30 min, then hourly up to 12 h after extubation.

A ventilatory frequency <10 min⁻¹ resulted in a 0.01 µg kg⁻¹ min⁻¹ reduction of the remifentanil dose. Thirty minutes before scheduled completion of the remifentanil infusion an i.v. bolus of piritramide 3 mg (Dipidolor®, JANSSEN–CILAG Pharma, Vienna, Austria), a synthetic opioid, was administered and the remifentanil infusion rate was decreased by 50%. In patients still reporting moderate or severe pain, a second dose of piritramide (4.5 mg) was given i.v. before termination of the infusion. Pain relief after discontinuation of remifentanil was managed by additional i.v. boluses of piritramide (4.5 mg) and paracetamol 1 g six-hourly according to a four point verbal rating scale (VRS) where 0=no, 1=mild, 2=moderate and 3=severe pain. The VRS score was determined by ICU nurses who were better acquainted with the VRS as compared with the VAS score.

**Statistical analysis**

The sample size calculation was based on detecting a 20% reduction in the mean remifentanil dosage between groups with a power of 80% and a significance level of \( P<0.05 \). In a previous investigation, the dosage for adequate analgesia after cardiac surgery was determined to be 0.05 (0.01) µg kg⁻¹ min⁻¹. For statistical analysis we used GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA). Categorical data were analysed with the \( \chi^2 \)-test, continuous data were compared with the Student’s \( t \)-test or, in the case of comparisons between groups over time, with ANOVA for repeated measurements. Values are given as means (SD) or means (SEM) or range as indicated.

**Results**

Of the 40 patients enrolled, 1 patient in the magnesium group was excluded from statistical analysis because of accidental extubation after only 60 min. Patient characteristics, intraoperative data and time to extubation are shown in Table 1. During surgery there were no differences between groups with respect to mean remifentanil dosage, arterial blood pressure and inotropic support, mainly noradrenaline.

Serum \( \text{Mg}^{2+} \) concentrations before surgery were not different between groups [0.79 (0.18) mmol litre⁻¹]. After surgery, this was 1.30 (0.25) mmol litre⁻¹ in the magnesium vs 0.80 (0.24) mmol litre⁻¹ in the placebo group (normal range: 0.70–1.0 mmol litre⁻¹) and 12 h later it was still elevated [1.20 (0.19) mmol litre⁻¹ vs 0.76 (0.12) mmol litre⁻¹] in the magnesium group (\( P<0.05 \), \( t \)-test). The highest postoperative \( \text{Mg}^{2+} \) concentration determined was 1.83 mmol litre⁻¹.

Inadequate pain control (PIS≥3) before extubation was more common in the placebo group (9 vs 23, \( P<0.05 \), \( \chi^2 \)-test). Consequently, more dose increases were necessary in intubated patients of this group (Fig. 1). In contrast, dose reductions attributable to a ventilatory frequency <10 min⁻¹ occurred more frequently in patients in the magnesium group (7 patients on 17 occasions vs 4 patients on 6 occasions, \( P<0.05 \), \( \chi^2 \)-test). However, these reductions did not result in a PIS >2. The lowest ventilatory frequency (6 min⁻¹) was recorded once in an intubated patient in the magnesium group with the ventilator being in a pressure support mode. As a result, the remifentanil rate in this particular patient was decreased, producing

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Magnesium group (n=19)</th>
<th>Placebo group (n=20)</th>
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<tbody>
<tr>
<td>Gender (female/male)</td>
<td>4/15</td>
<td>4/16</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 (23–79)</td>
<td>61 (33–77)</td>
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<tr>
<td>Weight (kg)</td>
<td>80 (16)</td>
<td>82 (13)</td>
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<tr>
<td>Height (cm)</td>
<td>175 (9)</td>
<td>169 (8)</td>
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<tr>
<td>BMI (kg m⁻²)</td>
<td>26 (4)</td>
<td>28 (4)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>51 (3)</td>
<td>52 (2)</td>
</tr>
<tr>
<td>AVR/MVR/CABG/CABG+/AVR/ASDC</td>
<td>8/2/8/0/1</td>
<td>4/0/12/2/2</td>
</tr>
<tr>
<td>Duration of CPB (min)</td>
<td>86 (23)</td>
<td>90 (35)</td>
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<tr>
<td>Duration of aortic cross-clamping (min)</td>
<td>58 (20)</td>
<td>57 (24)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>294 (53)</td>
<td>291 (58)</td>
</tr>
<tr>
<td>Time to extubation (min)</td>
<td>137 (23)</td>
<td>134 (21)</td>
</tr>
<tr>
<td>Mean remifentanil dosage (µg kg⁻¹ min⁻¹)</td>
<td>0.23 (0.08)</td>
<td>0.23 (0.05)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>71 (6)</td>
<td>73 (6)</td>
</tr>
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</table>

**Fig 1** The number of patients requiring a dose increase based on PIS ≥3 at the defined time points after termination of propofol while still intubated (\( P<0.05 \) magnesium vs control group, \( \chi^2 \)-test).
an increase in ventilatory frequency. After propofol was stopped, the respirator mode could be switched from controlled to pressure support ventilation in 7 (4) min in the placebo group compared with 8 (4) min (P>0.05, t-test) in the treatment group but time to extubation was not delayed in Mg²⁺ treated patients.

After extubation, VAS ≥ 30 induced seven dose increases in the magnesium group and 18 in the placebo group. The last dose increase in the placebo group occurred 10 h after extubation. In contrast, no patient in the magnesium group had a VAS ≥ 30 more than 3 h after extubation. (Fig. 2A) The differences in the individual VAS score between groups ranged between 0 (i.e. the lowest VAS score in both groups was the same over the 12 h post-extubation period) and 30, which was the greatest difference determined in the maximal VAS score between groups. VAS rating significantly decreased over time in both groups with higher values in the control group at 8 and 9 h after extubation (P<0.05, two-way repeated measures ANOVA). Mean remifentanil dose within 12 h after extubation was 0.04 (0.02) µg kg⁻¹ min⁻¹ (range: 0.01–0.08) in the magnesium group compared with 0.06 (0.02) µg kg⁻¹ min⁻¹ (range: 0.03–0.1) in the placebo group (P=0.008, two-way repeated measures ANOVA, Fig. 2B). The mean cumulative remifentanil consumption after surgery was also significantly lower in the magnesium group (P=0.014, t-test, Fig. 3).

Mean ventilatory frequency immediately after extubation was 18 (6) vs 16 (6) bpm in the magnesium and the placebo group, respectively. Dose reductions in the extubated patient because of a ventilatory frequency < 10 min⁻¹ were necessary in 8 patients of the magnesium group at 12 occasions as compared with 10 patients of the control group at 15 occasions (P>0.05, t-test). Mean arterial PCO₂ after extubation in the magnesium group was 5.73 (0.13) kPa (range: 3.99–7.07) and 5.47 (0.27) kPa (range: 3.60–8.40) in the placebo group. Mean arterial PO₂ in the placebo group was 16.80 (4.53) kPa (range: 9.20–25.20) and 14.53 (4.67) kPa (range: 9.60–28.13) in the magnesium group. Arterial saturation after extubation determined by pulse oximetry with the patients breathing supplemental oxygen via a face mask never decreased below 93% in either group and mean SaO₂ did not differ between groups (i.e. 98%; P>0.05, t-test).

After remifentanil and magnesium gluconate were stopped, patients were given piritramide, depending on VRS. The cumulative piritramide consumption over 8 h was 14 (8) mg (range: 6–33) in the magnesium as opposed to 14 (6) mg (range: 6–32) in the placebo group (P>0.05, t-test).

Ten minutes after termination of propofol four patients in the magnesium group but none in the placebo group showed a LOC of 3. After extubation, a LOC ≥ 3 was not seen in either group. Extubation after 120 min was feasible in

**Fig 2** (A) VAS rating up to 12 h after extubation [mean (SEM); *P<0.05 magnesium vs control group, two-way repeated measures ANOVA].

(B) Mean remifentanil dosage required in both groups to control pain after extubation [mean (SEM), P<0.05 magnesium vs control group, two-way repeated measures ANOVA].

**Fig 3** Cumulative remifentanil consumption of each patient from arrival in the ICU to the end of the study period (19 patients in the magnesium vs 20 patients in the control group, *P=0.014, t-test).
12 patients in the magnesium group and in 11 patients in the placebo group. After 150 min another four patients in the magnesium group and seven patients in the placebo group were extubated. Three patients in the magnesium group and two in the placebo group met our extubation criteria only after 180 min.

Heart rate and mean arterial pressure were stable throughout the study period in both groups, although eight patients in the magnesium group and seven patients in the placebo group required pacemaker stimulation via external pacemaker. Postoperative nausea and vomiting was documented in two patients in each group. Shivering occurred in two patients of the placebo group, which was successfully treated with i.v. clonidine. Magnesium related side-effects were not observed in any patient in the treatment group.

**Discussion**

Our study showed that a continuous infusion of magnesium gluconate moderately reduced overall remifentanil consumption after cardiac surgery without severe side-effects. A fentanyl-sparing effect of magnesium sulphate during surgery has already been observed by Koinig and colleagues in patients undergoing knee surgery. Based on this, we gave an equivalent dose of magnesium gluconate and achieved similar postoperative serum Mg2+ levels, about twice the baseline level, in our treatment group. In another study, serum Mg2+ levels above the upper limit of normal and approximately double the pre-treatment level, reduced the total consumption of morphine by 30%. The greatest reductions in morphine dose associated with magnesium sulphate (40 mg kg⁻¹ bolus followed by 15 mg kg⁻¹ h⁻¹) after gynaecological surgery were consistently well below 40%. The reduction of total mean remifentanil consumption in our treatment group was even smaller (i.e. 25%). In our study, the most pronounced impact of Mg2+ was seen immediately after surgery when propofol was stopped. Patients in the treatment group reported lower PIS values and required less remifentanil. At slightly lower VAS scores, significantly lower mean remifentanil dosages were necessary to adequately control pain in the magnesium group, after extubation. Interestingly, the difference between groups in the remifentanil dose remained almost constant throughout the 12 h observation period. This may be explained, in part, by our study protocol that allowed remifentanil dose increases but no decreases unless hypoventilation occurred. Yet, it was our intention to ensure that patients felt comfortable at rest. The fact that only a few dose adjustments were necessary, mainly in control patients, furthermore emphasizes the efficacy of the set remifentanil dosage for pain control after cardiac surgery. Maintenance of low pain scores, however, may have limited the marginal benefit of magnesium.

Our results are in line with those published by Levaux and colleagues where patients undergoing lumbar surgery received a single i.v. bolus of magnesium sulphate 50 mg kg⁻¹ before induction of anaesthesia. Intra- and early postoperative analgesia was also achieved with remifentanil and piritramide 0.15 mg kg⁻¹, given 15 min before the end of surgery. After operation, Mg2+ treated patients had significantly lower pain scores and lower piritramide requirements over the 24 h study period. These results were explained by the inhibition of central sensitization by the Mg2+ bolus given before the start of nociceptive stimulation.

As already mentioned, Mg2+ blocks NMDA Ca2+ ionophores, in a voltage-dependent way. The central and peripheral receptors of the excitatory amino acid NMDA play an important role in determining the intensity and duration of postoperative pain. Unlugenc and colleagues focused exclusively on the postoperative additive analgesic effect of magnesium sulphate and ketamine, another NMDA antagonist, in addition to i.v. patient controlled analgesia with tramadol. Either combination of drugs significantly reduced the tramadol consumption during the first 24 h, which makes an NMDA-mediated mechanism of action likely.

In contrast to the studies that showed a benefit from single dose applications, O’Flaherty and Lin failed to demonstrate any significant benefit from a single bolus dose (30 mg kg⁻¹) of magnesium sulphate, in addition to fentanyl after tonsillectomy in children. The average time from anaesthesia induction with Mg2+ application until pain evaluation at the postanaesthesia care unit was about 1 h. Possibly, this single bolus of magnesium sulphate used in this study was insufficient. These results suggest that either a continuous infusion or repeated bolus doses should be used. Therefore, we decided to administer magnesium gluconate continuously, both during and after operation, after an initial bolus dose.

As Mg2+ does not easily cross the blood–brain barrier, Buvanendran and colleagues gave magnesium sulphate (50 mg) intrathecally, in addition to fentanyl 25 μg. They demonstrated that this bolus significantly prolonged mean duration of spinal analgesia compared with fentanyl alone but cautioned that effective cerebrospinal fluid Mg2+ concentrations for modulation of antinociception via central NMDA channel antagonism cannot be achieved by the i.v. route. In line with these results, Ko and colleagues failed to show a benefit of i.v. Mg2+ (50 mg kg⁻¹ bolus followed by 15 mg kg⁻¹ h⁻¹ for 6 h) in patients undergoing hysterectomy. Higher postoperative serum Mg2+ levels in the Mg2+ group did not cause a significant increase in the cerebrospinal fluid Mg2+ concentration. Although higher Mg2+ dosages were given in our study, the increase in cerebrospinal fluid Mg2+ levels can be assumed to be small. However, Mg2+ pharmacokinetics and pharmacodynamics may change after cardiopulmonary bypass in the presence of hypomagnesaemia. Furthermore, it is still unclear what the effective Mg2+ concentration in the cerebrospinal fluid needs to be for antagonism of central NMDA receptors. Nevertheless, the predominant mechanism should rather be a peripheral analgesic effect that
has been demonstrated by Tramer and Glynn and Turanam colleagues. In conclusion, we demonstrated a moderate reduction of overall remifentanil consumption after cardiac surgery by co-administered i.v. magnesium gluconate. As magnesium does not easily penetrate the blood–brain barrier this anti-nociceptive action should have been modulated by peripheral mechanisms. A more pronounced opioid-sparing effect might be found with higher pain scores or with a larger dose of magnesium. No major side-effects were seen in the treatment group where serum magnesium levels that were slightly above normal.

References

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