Role of Magnesium Sulfate in Postoperative Analgesia

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Background: N-methyl-D-aspartate antagonists may play a role in the prevention of pain. An assessment was made of the effect of the physiologic N-methyl-D-aspartate antagonist magnesium on analgesic requirements, pain, comfort, and quality of sleep in the postoperative period.

Methods: In a randomized, double-blind study, 42 patients undergoing elective abdominal hysterectomy with general anesthesia received 20% magnesium sulfate or saline (control) 15 mL intravenously before start of surgery and 2.5 mL/h for the next 20 h. Postoperative morphine requirement was assessed for 48 h using patient-controlled analgesia. Maximum expiratory flow (peak flow), pain at rest and during peak flow, and discomfort were evaluated up to the 48th postoperative hour, and 1 week and 1 month after surgery. Insomnia was evaluated after the first and second postoperative nights.

Results: Compared to control subjects, magnesium-treated patients consumed less morphine during the first 48 h postoperatively (P < 0.05), which was most pronounced during the first 6 h (P < 0.001), and experienced less discomfort during the first and second postoperative days (P < 0.05–0.005). The magnesium-treated group revealed no change in postoperative sleeping patterns when compared to preoperative patterns. Control patients showed an increase in insomnia during the first and second postoperative nights (P < 0.002 and P < 0.005, respectively) compared to preoperative values.

Conclusions: This is the first clinical study showing that the perioperative application of magnesium sulfate is associated with smaller analgesic requirement, less discomfort, and a better quality of sleep in the postoperative period but not with adverse effects. Magnesium could be of interest as an adjuvant to postoperative analgesia. (Key words: Analgesics, postoperative; magnesium sulfate. Postoperative outcomes: comfort; insomnia; pain. Receptors: N-methyl-D-aspartate.)

Parenteral magnesium has been used for many years on an empirical basis as an antiarrhythmic and for prophylaxis against seizures in pre eclampsia. Because of its numerous physiologic activities, magnesium is called "nature's physiological calcium channel blocker." Calcium channel blockers have shown antinociceptive effects in animals and morphine potentiation in patients with chronic pain. Magnesium is also an antagonist of the N-methyl-D-aspartate (NMDA) receptor and its associated ion channels. N-methyl-D-aspartate receptor antagonists can prevent the induction of central sensitization due to peripheral noxious stimulation and abolish the hypersensitivity once it is established. In vitro data indicate that extracellular magnesium protects cerebellar neurons against the toxicity of the NMDA agonist glutamate. In animals, magnesium suppressed NMDA-induced adverse behavioral reactions and autotomy due to nerve injuries.

It has been suggested that substances with calcium channel blocking effects and NMDA antagonists could play a role in prevention of pain and treatment of established pain states. However, limited information is available on magnesium and pain interactions in humans. An inverse relationship has been demonstrated between the severity of pain with different painful medical and surgical conditions and the serum magnesium concentration. In women affected by premenstrual syndrome, oral magnesium supplementation showed more effectiveness in decreasing pain and relieving premenstrual mood changes and depression than placebo. In a nonblinded pilot study, intraperioperative magnesium supplementation was associated with lower postoperative analgesic requirement than with fentanyl.

Experimental and clinical data suggest that magnesium may exert an antinociceptive effect in humans. We conducted a randomized, double-blind, placebo-controlled trial to assess the effect of perioperative administered intravenous magnesium sulfate (MgSO4) on postoperative analgesic requirement, pain at rest and

Materials and Methods

Approval for this study was obtained from the institutional committee and written informed consent was obtained from the patients who gave informed consent for hysterectomy for benign gynecologic conditions. Forty-four women scheduled for elective abdominal hysterectomy for benign gynecologic conditions were enrolled. All subjects had no prior abdominal surgery, spinal anesthesia, or hormonal therapy. Patients were randomly assigned to receive physiologic saline (0.9% NaCl) or 10 mL/kg of intravenous MgSO4 administered over 10 min (loading dose) followed by 2 mL/kg/h for 24 h. The loading dose was followed by a maintenance dose of 2 mL/kg/h (0.2 mEq/kg/h). The safety of magnesium sulfate was assessed in all patients. Randomization and administration of the study drug were not performed under general anesthesia.

During the preoperative period, all patients were placed in a sitting position, and intravenous access was established with 20-gauge needles. A standardized, horizontal visual analog scale (VAS) was used to assess pain. The patient was asked, "How much worse?" The patient was also asked, "How well do you like it?" then asked to rate the pain (0 = no pain; 10 = severe pain). "0 = no pain; 10 = severe pain." Insomnia was assessed using the Sleep Diary, "How well did you sleep last night?" Patients received 75 mg ketamine intraperioperative premedication at the preanesthetic visit.
on movement, comfort, and quality of sleep. Because there is evidence from experimental studies, that post-injury neuroplasticity may lead to pain hypersensitivity and chronic pain, we assessed patients up to 1 month postoperatively to evaluate long-term effects of surgery and magnesium treatment.

Materials and Methods

Approval for this study was granted by the local ethical committee and written information was provided to the patients who gave written informed consent. Forty-four women scheduled for elective abdominal hysterectomy for benign disease and who were ASA physical status 1–2 were enrolled. Exclusion criteria were prior abdominal surgery, major organ system dysfunction, and treatment with calcium channel blockers. Patients were randomly assigned to receive either physiologic saline (control) or 20% MgSO4 (Dr. G. Bichsel AG, Interlaken, Switzerland) in a double-blind fashion. Randomization (with colored balls) and preparation of the study drugs in identical and numbered vials were done by the hospital pharmacy. Surgery was performed under general anesthesia and with a Pfannenstiel incision.

During the preoperative visit, the use of a patient-controlled analgesia (PCA) device was explained to each patient and baseline values of maximum expiratory flow (peak flow), pain at rest, pain during peak flow, discomfort, and insomnia were obtained. Maximum expiratory flow was measured with a peak flow meter (Vitalograph, Astra) with the patient in a 30 degree sitting position; the greatest value (l/min) of three attempts with maximal expiratory force was recorded. A standardized, horizontal 100-mm linear visual analog scale (VAS) was used to assess pain at rest and during peak flow (0 = no pain at all to 100 = worst pain imaginable). The same VAS was used to assess discomfort and insomnia. Discomfort was assessed using the question "How much discomfort do you feel right now?" The patient was then asked to rate her discomfort on the VAS (0 = no discomfort at all to 100 = extreme discomfort). Insomnia was assessed asking the patient "How well did you sleep last night?" The patient was then asked to rate the quality of her sleep on the VAS (0 = no insomnia—excellent quality of sleep to 100 = absolute insomnia).

Patients received 7.5 mg midazolam orally as a preoperative premedication 1 h before surgery. On arrival at the preanesthetic room, standard monitoring equipment consisting of electrocardiography, noninvasive blood pressure monitoring, finger pulse oximetry, and a neurostimulator with two electrodes attached on the ulnar side of the wrist was installed and a peripheral venous access was inserted.

A standardized general anesthetic was used. Induction was achieved with 5 mg/kg thiopental and 3 μg/kg fentanyl. After induction, patients received, intravenously, either 15 ml 20% MgSO4 (magnesium group) or 15 ml saline (control group) slowly. This bolus dose was given after induction to maintain the patients’ ignorance to the study design because of the frequent experience of internal heat after intravenous injection of magnesium sulfate. The bolus injection was followed by a continuous intravenous infusion of 2.5 ml/h of the study drug during 20 h with a syringe pump (P1000, Welmed). The total amount of magnesium sulfate infused in the magnesium group was 13 g. The bolus dose of our magnesium regimen (3 g) corresponded to 75% of a usual bolus dose in the treatment of preeclamptic women; the maintenance dose (0.5 g/h) corresponded to 25% of the normal amount given in these patients. An infusion duration of 20 h was chosen because this enabled us to give the maximal amount of 20% MgSO4, at the defined rate without changing the syringe. Vecuronium (0.1 mg/kg) was given to facilitate orotracheal intubation. Lungs were mechanically ventilated (end-tidal CO2 36–40 mmHg). Maintenance of anesthesia consisted of 0.5–1.5% isoflurane (end-tidal) and 60% nitrous oxide in oxygen. Fentanyl (1.5 μg/kg) was injected 5 min before start of surgery and repeated as bolus doses of 1 μg/kg every 30–45 min during surgery. Adequate muscle relaxation, defined as 0–2 responses of the train-of-four stimulation was maintained with vecuronium bolus doses until closure of the peritoneum. At the end of surgery, antagonism of neuromuscular blockade was achieved with 0.01 mg/kg intravenous atropine followed by 0.02 mg/kg Prostigmin if a 50 Hz tetanus stimulation was followed by a fading response. Total amount of fentanyl and vecuronium administered during surgery, time of last fentanyl dose before end of surgery, and need for reversal of neuromuscular blockade at the end of surgery were recorded.

After surgery, patients stayed in the recovery room for 24 h and were then discharged to the ward. On arrival at the recovery room, a PCA device (Lifecare 4200, Abbott) containing 2 mg/dose morphine, with an 8-min lockout interval and no background infusion, was connected to the patient’s intravenous catheter and
the patient was able to start using the device. If necessary, 1–2 mg morphine, administered in intravenous bolus doses at 5–10 min intervals, were administered until the patient was pain-free. Only PCA-morphine was used for analgesia during the first 48 h postoperatively. Sedative drugs such as benzodiazepines were not allowed during this period. Morphine requirements were assessed 6, 12, 24, and 48 h after surgery. Sedation with a four-point rating scale\(^{19}\) (table 1), need for nasal oxygen (1/min) to maintain capillary oxygen saturation above 95%, heart rate, and noninvasive diastolic and systolic blood pressure were monitored continuously and recorded every 6 h during the first 24 h postoperatively. Peak flow, pain at rest and during peak flow, and discomfort were evaluated after 6, 12, 18, 24, and 48 h, and after 1 week and 1 month. Quality of sleep was evaluated in the morning after the first and second postoperative nights. One week and 1 month after surgery, patients completed a 12-point pain score established in our institution (table 1).

Any postoperative side effects, time for return of bowel function (first sounds, flatus, intake of oral fluids and diet, evacuation), and days until discharge were recorded. Blood samples for determination of serum magnesium concentration were obtained before start of the intravenous study drug treatment and immediately after the end of the infusion. The normal range was between 0.65 and 1.05 mmol/L.

### Statistical Analysis

Continuous variables such as demographic data and morphine consumption were analyzed using Student’s \(t\) test. Ordinal data (peak flow values, VAS values, pain rating score, and sedation score) were analyzed using the Mann-Whitney \(U\) test for independent samples and the Wilcoxon rank sum test for dependent samples. Comparisons of the mean levels among groups was by a one-way analysis of variance. Chi-square testing was used to analyze dichotomous data. A sample size of 20 patients per group was needed to detect a difference of at least 25% in morphine consumption with a power of 80%.\(^{20}\) A \(P\) value of \(< 0.05\) was considered statistically significant. Data are reported as median (and ranges), or mean values ± SD (tables) and mean values ± SEM (figures).

### Results

Forty-four women were enrolled in the study. Data from two patients were not included in the analysis. One patient experienced an exacerbation of a chronic low back and leg pain in the postoperative period and treated this episode with the PCA-morphine. In the other patient, surgery was complicated and an unforeseen median incision lead to exclusion of this patient from our trial. The two groups with the remaining 42 patients were similar with respect to demographic data, duration of surgery, intraoperative doses of fentanyl and vecuronium, and time from the last fentanyl administration until the end of surgery (table 2).

Cumulative mean morphine doses after 48 h were 65 mg in the magnesium group and 91 mg in the control group \(\left(P < 0.03\right);\) fig. 1). Analysis of morphine consumption during four different time intervals revealed that patients in the magnesium group consumed significantly \(\left(P < 0.004\right)\) less morphine than those in the control group during the first 6 h postoperatively but not thereafter (fig 1). Pain values at rest and during peak flow were similar in both groups throughout the study period (fig. 2). Postoperatively, pain during peak flow was significantly lower in both groups compared to preoperative levels (fig. 2).

### Table 2. Demographic Data for the Two Treatment Groups

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Saline</th>
<th>MgSO₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47 ± 7</td>
<td>49 ± 6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66 ± 11</td>
<td>63 ± 11</td>
</tr>
<tr>
<td>Intraoperative fentanyl (µg/kg)</td>
<td>6.3 ± 1.1</td>
<td>5.8 ± 0.8</td>
</tr>
<tr>
<td>Last fentanyl dose before end of surgery (min)</td>
<td>45 ± 19</td>
<td>40 ± 13</td>
</tr>
<tr>
<td>Intraoperative vecuronium (mg/kg)</td>
<td>0.15 ± 0.04</td>
<td>0.13 ± 0.02</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>108 ± 34</td>
<td>88 ± 21</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
POSTOPERATIVE ANALGESIA WITH MAGNESIUM SULFATE

Fig. 1. Hourly morphine consumption with patient-controlled analgesia device. Dotted bars represent the control (saline) group; solid bars represent the magnesium group. Data are mean ± SEM. *P < 0.05 from control. **P < 0.005 from control.

Flow was significantly higher than pain at rest in both groups except for the 1 month assessment. Peak flow values of both groups showed a significant (P < 0.0001) change during the study period. Pain during peak flow was inversely related to peak flow values and the change over time was significant (P < 0.0001) for both groups (fig. 2).

Preoperative discomfort and insomnia levels were similar in both groups (fig. 2). Discomfort at the 6 h postoperatively was significantly increased (P < 0.007) in both groups compared to preoperative values. Analysis of variance revealed no significant change of discomfort levels during the study period in control patients but a significant (P = 0.0002) change in magnesium-treated patients. From 18 to 48 h, distress was significantly less in magnesium-treated patients compared to patients in the control group (fig. 2). Compared to preoperative values, there was no significant change in postoperative insomnia in magnesium-treated patients but a significant increase in control patients during the first and second night (P < 0.002 and P < 0.005, respectively). During the second postoperative night, magnesium-treated patients reported significantly lower insomnia values (P < 0.005) than control patients (fig. 2).

One patient in the magnesium group had a hypotensive episode at induction (systolic blood pressure 80 mmHg) that was treated with 10 mg intravenous ephedrine. Three patients, two in the control and one in the magnesium group, had bradycardic episodes during surgery (HR < 40/min) that were treated with 0.5 mg intravenous atropine. These were the only cases of hemodynamic instability during anesthesia. Reversal of neuromuscular blockade at the end of surgery was needed in five control patients and ten magnesium-treated patients (NS).

Diastolic and systolic blood pressure, heart rate, sedation scores, and oxygen requirements were similar in both groups during the first 24 h postoperatively (table 3). At the end of the 20-h treatment, patients from the control group had significantly lower magnesium serum concentrations (P < 0.002) compared to pretreatment values (table 4). Fifteen patients in this group had a lower serum magnesium concentration at the end of the infusion compared to pretreatment values and in seven patients the value was less than 0.65 mmol/l. Magnesium-treated patients had significantly greater serum magnesium concentrations (P < 0.0001) after termination of the infusion compared to both pretreatment values and control posttreatment values (table 4). All patients in this group showed an increase in serum magnesium and all had a value above the upper limit of the normal range at the end of the

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*P < 0.05 from control. **P < 0.005 from control.

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Anesthesiology. V 84, No 2. Feb 1996
infusion. Delay until return of bowel function, time of discharge, and postoperative controls at 1 week and 1 month were similar in both groups (Fig. 2 and Table 4). Postoperative vomiting occurred in ten patients of the control group and six of the magnesium sulfate group (NS). One patient from each group complained of pruritus and one patient from the control group had shivering that resolved spontaneously.

One patient in the control group had a respiratory rate of 8/min 5 h after surgery and the PCA morphine bolus was therefore reduced to 1 mg with a lockout interval of 12 min. One hour later, the cumulative morphine dose was 32 mg and the respiratory frequency was 4 per min. This patient then received intravenous naloxone (total dose 80 μg). She recovered completely and had no further postoperative complications. Data from this patient were included in the analyses up to the 6th postoperative hour. One patient from each group underwent a second laparotomy because of a suspected ureter ligation in one case and surgery-related intraabdominal bleeding in the other. Data of these patients were not considered from the 48th h and 1 week onward, respectively. In one patient from the control group, an unexpected carcinoma of the endometrium was histologically diagnosed, which was treated with chemotherapy. A vesicovalvular fistula developed in another patient in the control group. Both patients were excluded from the control at 1 month. Two patients from the control group did not attend the postoperative 1-month assessment for unknown reasons.

Two patients in the control group had the PCA morphine bolus reduced to 1 mg with an interval of 12 min because of respiratory rates between 6 and 8 breaths/min and excessive sedation (score 4) 6 h after surgery. In one of these patients, arterial pH was 7.29 and pCO₂ 51 mmHg before change of the PCA program. One patient in the magnesium group had the morphine bolus reduced to 1 mg 30 h after surgery because of a flush sensation after each bolus. No other changes in the PCA regimen were required.

**Discussion**

This is the first clinical trial showing that the perioperative administration of magnesium sulfate is associated with lower analgesic requirement, less discomfort, and a better quality of sleep in the postoperative period but no adverse effects.
Cumulative morphine consumption after 48 h was 30% less in magnesium-treated patients compared to control patients. Postoperative pain scores were similar in both groups, indicating that patients from both groups titrated themselves to a subjectively comfortable level of analgesia with the PCA-morphine. Intraoperative fentanyl dose and time of last administration of fentanyl were also similar in both groups. These data suggest that magnesium induced the morphine-sparing effect. Three patients in the control group were seen with respiratory depression, of whom one required naloxone administration. There was no respiratory depression in patients treated with magnesium (P > 0.05). The respiratory depression in control patients may be explained by our PCA program; it has been shown that a 2-mg bolus dose of morphine may increase the risk of adverse effects compared to smaller boluses. Ten control patients experienced postoperative vomiting compared to six magnesium-treated patients (P > 0.05). This may suggest an antiemetic effect of magnesium or an indirect effect via decreased consumption of morphine in magnesium-treated patients. Although the differences between groups in both the incidence of postoperative respiratory depression and vomiting were statistically nonsignificant, they are of clinical interest and suggest the need for further study.

Control patients experienced significant discomfort during the first two postoperative days and their quality of sleep had not returned to baseline after the second postoperative night. The aim of postoperative pain relief is to provide subjective comfort in addition to inhibiting trauma-induced nociceptive impulses. Magnesium-treated patients showed no deterioration of sleep quality and level of discomfort returned faster to baseline than in control patients suggesting an enhanced general well-being.

There seemed to be a discrepancy between magnesium's apparent short-lived effect on morphine consumption and its rather late beneficial effect on comfort and quality of sleep. Patients with postoperative PCA tend to demand more analgesics in the immediate postoperative period to achieve a steady state. Then the demand decreases to maintain the steady state. Magnesium-treated patients consumed significantly less morphine within the first 6 h, suggesting that they either experienced less pain or that they needed less morphine to reach this steady state. Magnesium treatment showed a beneficial effect on quality of sleep and comfort. There was no way to evaluate quality of sleep earlier than after the first night. Discomfort values became significantly less in magnesium-treated patients compared to control patients from the 18th postoperative hour onward. This may reflect the problem of assessing discomfort with a VAS in the early postoperative period when vigilance is still impaired. These results suggest that our magnesium regimen does have an effect on comfort and quality of sleep up to the 48th postoperative hour despite subtherapeutic anticonvulsive serum concentrations at the end of the infusion. We did not measure magnesium serum concentrations in the immediate postoperative period when the morphine-sparing effect was most pronounced and we did not measure cerebrospinal fluid magnesium either. We therefore were unable to correlate clinical outcome with magnesium concentrations in serum or cerebrospinal fluid. It has been shown that only a small amount of magnesium crosses the blood-brain barrier in patients with preeclampsia undergoing magnesium therapy. However, the increment in cerebrospinal fluid magnesium was found to be highly statistically significant and correlated with serum magnesium concentrations. It has to be stressed that a dose-response of magnesium and its potential antinociceptive effect has yet to be established.

Magnesium treatment had no effect on pain scores and peak flow values were similar between the two groups throughout the study period. It is interesting to note that for both groups pain during peak flow as a measurement of movement-related pain was significantly higher than pain at rest at all times except for the preoperative and the 1-month assessment. Pain during peak flow showed an inverse relationship to peak flow values and the change over time was significant for both parameters and both groups. The internal consistency of the three measurements indicated the sensitivity of our clinical model. Pain scores from our institutional 12-point score showed considerable handicap in patients from both groups 1 week and 1 month after surgery. Magnesium treatment did not decrease this score and had no effect on return of bowel function or discharge times.

The reason for the observed beneficial effects of magnesium treatment (i.e., decreased morphine consumption, less discomfort, better quality of sleep) remains speculative. The NMDA receptor channel complex is implicated in neuroplasticity. It contains binding sites for noncompetitive antagonists like ketamine and magnesium. Ketamine decreased postoperative pain, opioid requirement, wound hyperalgesia, and
Experimental ischemic pain. However, psychotomimetic adverse effects may limit its clinical use. Magnesium blocks the NMDA channels in a voltage-dependent way. Addition of magnesium produces a dramatic reduction of the NMDA-induced currents. Conversely, in the absence of extracellular magnesium, the effect of NMDA agonists is enhanced. Major surgery is followed by a significant decrease in serum magnesium concentrations as shown by others and confirmed in our study. For this reason, the prevention of hypomagnesemia during and after surgery appears to be important to prevent neuroplasticity. The results of our study suggest that magnesium may indeed exert a clinically significant specific antinociceptive effect via blockade of the NMDA receptor complex or a non-specific effect via prevention of hypomagnesemia.

The effect of magnesium on morphine consumption, comfort, and sleep pattern could have been related to magnesium-induced sedation although data from the literature in this regard are conflicting. In rats, intravenous MgSO4 produced a dose-dependent reduction in halothane MAC, measured by the tail-clamp technique and this has been interpreted by the authors as a significant anesthetic effect of magnesium. However, the method used is a simple spinal withdrawal reflex demonstrating analgesia rather than sedation. In healthy volunteers, intravenous MgSO4 failed to induce sleep even at magnesium serum concentrations ten times higher than normal. In our study, sedation and magnesium serum concentrations were not measured in the early postoperative period (i.e., before the 6th postoperative hour). It is therefore possible that we failed to document high serum magnesium concentrations and related sedation. It is also possible that increased sedation owing to the PCA prescription limited our ability to observe magnesium-induced sedation. However, sedation scores from the 6th up to the 24th postoperative hour were similar in both groups and serum magnesium concentrations at the end of the intravenous treatment were only slightly higher than pretreatment values. These results suggest that at least better quality of sleep and comfort in magnesium-treated patients did not result from sedation.

The aim of this study was to describe a clinical effect of magnesium on postoperative analgesia and we therefore wished to administer a dose that was most likely to achieve an effect without adverse effects. Two major problems may arise with the use of magnesium in patients undergoing general anesthesia. First, magnesium enhances the action of nondepolaryzing muscle relaxants. An increased serum concentration of magnesium per se may produce profound paralysis of skeletal muscles. However, in the presence of normal renal function renal elimination of magnesium is rapid. Second, magnesium may interact with calcium ions at vascular membranes and decrease peripheral vascular resistance. Our magnesium regimen was reduced compared to the doses used in the treatment of preeclamptic women. Patients with major organ diseases (i.e., renal impairment) were excluded. In addition, we routinely monitored neuromuscular blockade. Intraoperative vecuronium use was similar in both groups and only a tendency toward increased need for reversal of neuromuscular blockade at the end of surgery was noted in the magnesium group. Postoperative peak flow values as an indicator of muscle strength were similar in both groups. Hemodynamically, magnesium-treated patients did not show any difference compared to control patients, neither during nor after surgery.

In conclusion, patients undergoing lower abdominal surgery with magnesium supplementation consumed significantly less morphine and experienced significantly less disturbances in comfort and quality of sleep in the postoperative period compared to control patients. In this limited number of patients, we did not find any evidence of major adverse effects owing to magnesium. Further studies should address different dosages of magnesium, other surgical settings, and comparisons with established analgesic drugs. A dose-response relationship for magnesium's potential antinociceptive effect has to be established. If our findings should be confirmed, magnesium could become an useful adjuvant to postoperative analgesia.

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References


