Pre-incisional epidural magnesium provides pre-emptive and preventive analgesia in patients undergoing abdominal hysterectomy

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Background. This prospective, randomized, double-blind study was designed to evaluate the pre-emptive and preventive analgesic efficacy of adding magnesium to a multimodal regimen of patient-controlled epidural analgesia (PCEA) in patients undergoing abdominal hysterectomy.

Methods. Ninety patients were randomly assigned to one of the three groups. Pre-magnesium patients received bolus of magnesium 50 mg epidurally before induction of anesthesia followed by infusion of 10 mg h⁻¹ until end of surgery. Post-magnesium patients received epidural saline during the same time periods plus bolus epidural magnesium 50 mg at the end of surgery. Patients in the control group received epidural saline during all three periods. Patients in the magnesium groups received PCEA with fentanyl 1 μg ml⁻¹, bupivacaine 0.08%, and magnesium 1 mg ml⁻¹ after operation. Patients in the control group received PCEA with fentanyl 1 μg ml⁻¹ and bupivacaine 0.08%. Data were recorded for three postoperative days.

Results. There were significantly lower pain scores on rest or movement in the pre-magnesium group compared with the post-magnesium and control groups (P<0.05). The daily analgesic consumption in the pre-magnesium group was significantly less than the other two groups (P<0.05) and the dose consumed in the post-magnesium group was significantly smaller than the control group (P<0.05). The groups were similar with respect to haemodynamic and respiratory variables, sedation, pruritus, nausea, and vomiting.

Conclusions. Continuous epidural magnesium started before anaesthesia provided pre-emptive, preventive analgesia, and an analgesic-sparing effect that improved postoperative analgesia without increasing the incidence of side-effects.

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Intraoperative and postoperative noxious inputs may cause central sensitization, but analgesic interventions given before the noxious stimulus may attenuate or block sensitization.¹ Pre-emptive analgesia is defined as an antinociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies postoperative pain.² The goals of pre-emptive analgesia are to decrease acute pain after tissue injury, to prevent pain-related pathologic modulation of the central nervous system, and to inhibit the persistence of postoperative pain and the development of chronic pain.³ A series of experimental data provide evidence that N-methyl-D-aspartate (NMDA) receptors play a significant role in neuronal plasticity and processes leading to central sensitization to pain.⁴ NMDA antagonists have been shown to be useful in the reduction of acute postoperative pain, analgesic consumption, or both.⁵ NMDA receptor is blocked by the presence of a centrally positioned magnesium ion.⁶ Magnesium can be considered as a physiological blocker of NMDA receptors.⁷ There are studies concerning different routes of magnesium administration, such as intrathecally or epidurally, that improve anaesthetic and analgesic quality.⁸–⁹
The current randomized, double-blind, prospective study was designed to evaluate the pre-emptive and preventive analgesic efficacy of adding magnesium to a multimodal regimen of patient-controlled epidural analgesia (PCEA) in patients undergoing abdominal hysterectomy.

**Methods**

After obtaining approval from the local ethics committee and written informed consent from the patients, we studied 90 healthy women, ASA I and II, undergoing elective total abdominal hysterectomy. Three surgeons performed most of the operations. The distribution of surgeons between the three groups was comparable. A prospective, randomized (sealed envelopes), double-blind design was used, with both patients and postoperative assessors blinded to intraoperative management. Exclusion criteria included hepatic, renal, or cardiovascular dysfunction, psychological disorders, history of chronic pain condition or regular ingestion of analgesic drugs, known allergy to magnesium sulphate or other study drugs, and any contraindication to epidural anaesthesia.

Before the operation, patients were instructed about the use of the visual analogue scale (VAS; 0, no pain; 10, worst possible pain) and the PCEA device. Before the induction of anaesthesia, an epidural catheter was placed at the L1–L2 intervertebral space under local anaesthesia with the use of a loss of resistance technique, and correct positioning was confirmed by an injection of lidocaine 2% (3 ml) with epinephrine 1:200 000. For the pre-magnesium patients, this was followed by an initial 10 ml bolus of magnesium 50 mg, infusion of magnesium 10 mg h\(^{-1}\) during surgery, and a 10 ml bolus of normal saline at the end of surgery. Patients in the post-magnesium group received normal saline 10 ml via epidural catheter before induction of general anaesthesia, infusion of normal saline during surgery, and a 50 mg bolus of magnesium epidurally at the end of surgery. Patients in the control group received epidural normal saline as placebo before induction of anaesthesia, during surgery, and at the end of the surgery.

General anaesthesia was induced with thiopental 5 mg kg\(^{-1}\) i.v. and fentanyl 1 μg kg\(^{-1}\) i.v. Vecuronium 0.1 mg kg\(^{-1}\) i.v. was given to facilitate tracheal intubation. Anaesthesia was maintained with oxygen 50% in air and isoflurane 1–2%. Supplemental boluses of vecuronium 0.05 mg kg\(^{-1}\) i.v. were administered as required to maintain muscle relaxation during surgery. End-tidal CO\(_2\) concentration was maintained at 4.6–5.3 kPa. At the end of surgery, muscle relaxation was reversed by i.v. neostigmine 0.05 mg kg\(^{-1}\) and glycopyrrolate 0.01 mg kg\(^{-1}\). Intraoperative monitoring included ECG, arterial pressure, pulse oximetry, nasopharyngeal temperature, neuromuscular block, end-tidal CO\(_2\) concentration, and urine output. Haemodynamic variables such as mean arterial pressure (MAP) and heart rate (HR) were recorded as baseline (values on arrival at the operating theatre), preinduction (values at 5 min before induction of anaesthesia), after induction of anaesthesia, tracheal intubation, and during maintenance of anaesthesia (average values during anaesthesia). At the end of surgery, patients in the pre-magnesium and post-magnesium groups received a PCEA regimen containing fentanyl 1 μg ml\(^{-1}\), bupivacaine 0.08% (0.8 mg ml\(^{-1}\)), and magnesium (1 mg ml\(^{-1}\)); the patients in the control group received a PCEA regimen containing fentanyl 1 μg ml\(^{-1}\) and bupivacaine 0.08% (0.8 mg ml\(^{-1}\)). The PCEA device was initially programmed to administer a continuous infusion of 2.5 ml h\(^{-1}\) with a bolus dose of 2.5 ml on demand. The lockout time between boluses was 5 min. The PCEA infusion rate and bolus volume were titrated according to analgesic effect or occurrence of side-effects. If pain relief was unsatisfactory, the background infusion rate and bolus volume were each increased by 0.5 ml. If a patient experienced satisfactory pain relief, the background infusion rate and bolus volume were decreased daily by 0.5 ml. When systolic arterial pressure decreased to <90 mm Hg, background infusion and bolus were decreased to 2 ml h\(^{-1}\) and 2 ml, respectively, the patient received 500 ml hydroxyethyl starch, and if that did not correct the hypotension, the patient received incremental 3 mg doses of ephedrine. If a patient could not tolerate the pain (VAS >4), we rechecked the epidural insertion site to see whether the epidural catheter migrated and administered lidocaine 1.0% (7 ml) epidurally to ensure that the surgical area was covered by the analgesia field. If this did not result in satisfactory analgesia, we excluded the patient from the study and replaced PCEA with i.v. PCA. Severe nausea or vomiting was treated with dexamethasone 5 mg, and severe pruritus was treated with chlorpheniramine maleate 10 mg i.v. every 8 h as required. If any of the patients developed respiratory depression, continuous infusion of PCEA was stopped and intermittent doses of naloxone 40 μg i.v. were administered. The analgesic regimen was prepared by the anaesthesiologist managing the patient, who was not subsequently involved in data collection. This regimen was continued for 3 days.

MAP, HR, and arterial oxygen saturation were recorded every 5 min during surgery, every 20 min during early recovery, and thereafter every 2 h for 3 days. Pain intensity at rest (VAS-R) and after movement (changing sides in the supine position on the operation day, the morning of the first postoperative day and walking on other days) (VAS-M) were recorded by trained nurses at 2, 4, 6, 8, 10, and 12 h after the operation, on the first and second post-operative days at 8 a.m. and 4 p.m., and on the third post-operative day at 8 a.m. Nursing staff was blinded to the study medication. To ensure patient safety, a sealed opaque envelope containing the randomized treatment assignment was kept with each patient during the whole study period to permit immediate unmasking if any emergency made this step necessary.
Patients were assessed with a sedation scale (wide awake, 0; mildly sleepy and responsive to verbal command, 1; moderately sleepy, 2; and extremely sleepy and unresponsive to nociceptive stimulation, 3). Daily analgesic consumption and side-effects such as nausea, emesis, pruritus, respiratory depression, sleep deprivation, or motor block were recorded along with pain intensity assessments. Respiratory depression was defined as ventilatory frequency <10 bpm. Motor block was evaluated in terms of a modified four-grade Bromage scale: 10, 0, no weakness; 1, inability to raise extended leg (just able to move knee and feet); 2, inability to flex knee (able to move feet or first digit only); and 3, inability to move any joint in legs. Patient satisfaction with the quality of analgesia during PCEA treatment using the VAS score was also recorded on discharge from the hospital.

SPSS statistical software package was used for data analysis. Data are expressed as mean (SD) for quantitative measures, and n and % for categorized measures. Student’s t-test was used for comparison between two groups for parametric or dispersed data and Z-test was used to compare independent groups for proportions. VAS pain intensity scores were analysed between the groups across time using repeated-measures analysis of variance with post hoc testing performed using Tukey’s test. A P-value of <0.05 was considered significant. From preliminary data, the VAS-M at 2 h after operation was 4.9 ± 1.9, power analysis indicated that a sample size of 20 patients per group would yield 80% chance (at P=0.05) of detecting 30% reduction in pain intensity at movement.

### Results

Of the 90 patients enrolled in this study, three were excluded because of deviations in protocol standard or incomplete data collection. Eighty-seven patients completed the study, 29 patients in each one of the three groups. There were no significant differences among the three groups with regards to age, weight, height, duration of anaesthesia, and ASA physical status (Table 1). Intraoperative haemodynamic data such as MAP and HR are shown in Table 2; there were no significant differences among the groups regarding baseline, pre-induction, tracheal intubation, or maintenance data. All patients were fully awake during postoperative visits and sedation scores were evaluated to be zero with no differences among the groups.

There were significantly lower VAS-R for the pre-magnesium group at 2, 4, 6, 8, 10, and 12 h after operation, and on the first (1 a.m., 1 p.m.), second (2 a.m., 2 p.m.), and third (3 a.m.) postoperative days compared with the post-magnesium and control groups (P<0.05). There were significantly lower VAS-M for the pre-magnesium group compared with the post-magnesium group at 8, 10, and 12 h after operation, and on the first, second, and third postoperative days; and when compared with the control group at 2, 4, 6, 8, 10, and 12 h after operation, and on the first, second, and third postoperative days (P<0.05). VAS-M at 2, 4, and 6 h after operation were lower for the pre-magnesium group compared with the post-magnesium group, but did not reach statistical significance. There were no significant differences in VAS-R and VAS-M pain scores for the post-magnesium group compared with the control group (Tables 3 and 4). During movement, the incidence of mild pain (VAS 30–69 mm) was significantly higher in the pre-magnesium group when compared with the post-magnesium and control groups, whereas the incidence of moderate pain (VAS 31–69 mm) was significantly higher in the post-magnesium group when compared with the pre-magnesium and control groups, when compared with the pre-magnesium group on the first, second, and third postoperative days (P<0.05). Pain intensity scores at rest for all patients were <4, which indicate adequate postoperative pain management. The daily postoperative analgesic regimen consumption (ml) among the three groups is shown in Table 5. In the pre-magnesium group, the daily analgesic regimen consumption for

### Table 1 Patient characteristics and duration of surgery. Data are mean (range), mean (so), or the numbers of patients. n=29 in each of the three groups. There were no significant differences between the groups.

<table>
<thead>
<tr>
<th></th>
<th>Pre-magnesium group</th>
<th>Post-magnesium group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51.3 (45–58)</td>
<td>49.4 (44–59)</td>
<td>50.7 (44–58)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.4 (9.8)</td>
<td>59.7 (11.4)</td>
<td>61.5 (10.2)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.4 (6.5)</td>
<td>160.2 (7.5)</td>
<td>159.3 (5.4)</td>
</tr>
<tr>
<td>ASA physical status (I/II)</td>
<td>10/19</td>
<td>9/20</td>
<td>11/18</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>91.5 (10.2)</td>
<td>89.3 (11.4)</td>
<td>93.1 (12.6)</td>
</tr>
</tbody>
</table>

### Table 2 Intraoperative haemodynamic variables. MAP, mean arterial pressure; HR, heart rate. Data are presented as mean (so). There were no significant differences between the groups.

<table>
<thead>
<tr>
<th>Haemodynamic variables</th>
<th>Baseline</th>
<th>Pre-induction</th>
<th>Induction</th>
<th>Intubation</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>83 (3.7)</td>
<td>81 (5.1)</td>
<td>78 (4.6)</td>
<td>90 (5.2)</td>
<td>75 (4.6)</td>
</tr>
<tr>
<td>Pre-magnesium group</td>
<td>85 (5.6)</td>
<td>83 (6.7)</td>
<td>80 (4.4)</td>
<td>92 (6.1)</td>
<td>77 (5.1)</td>
</tr>
<tr>
<td>Post-magnesium group</td>
<td>85 (5.2)</td>
<td>83 (5.2)</td>
<td>80 (5.0)</td>
<td>92 (5.8)</td>
<td>76 (4.8)</td>
</tr>
<tr>
<td>Control group</td>
<td>79 (5.5)</td>
<td>76 (4.2)</td>
<td>70 (4.7)</td>
<td>87 (4.8)</td>
<td>66 (3.9)</td>
</tr>
<tr>
<td>HR (beats min⁻¹)</td>
<td>78 (4.7)</td>
<td>76 (5.7)</td>
<td>70 (5.1)</td>
<td>88 (5.0)</td>
<td>66 (3.3)</td>
</tr>
<tr>
<td>Pre-magnesium group</td>
<td>80 (5.1)</td>
<td>78 (4.8)</td>
<td>72 (5.5)</td>
<td>89 (6.6)</td>
<td>68 (5.6)</td>
</tr>
</tbody>
</table>
The results of the present study demonstrate that continuous epidural magnesium infusion started before induction of anaesthesia and extended into the postoperative period (pre-magnesium group) provided pre-emptive and preventative analgesia and decreased pain intensity during the postoperative period compared with postoperative epidural magnesium infusion and saline placebo infusion. Postoperative epidural magnesium infusion via PCEA decreased postoperative daily analgesic consumption with similar pain intensity compared with the control group.

Noxious stimulation leads to the release of glutamate and aspartate neurotransmitters, which bind to various subclasses of excitatory amino acid receptors, including the NMDA receptor. Activation of NMDA receptors leads to calcium and sodium influx into the cell with an efflux of potassium and initiation of central sensitization and wind-up. Magnesium blocks NMDA channels in a voltage-dependent way (depolarization removes magnesium block), and the addition of magnesium produces a dramatic reduction of NMDA-induced currents. A limitation to the parenteral application of magnesium for modulation of antinociception via NMDA channel antagonism is insufficient blood–brain barrier penetration to achieve effective cerebrospinal fluid concentrations. Asokumar and colleagues conducted the first human study to evaluate whether intrathecal magnesium could prolong spinal opioid analgesia and concluded that the non-competitive NMDA antagonist magnesium, intrathecally administered, prolongs the duration of spinal opioid analgesia in humans.

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Discussion

The results of the present study indicate that continuous epidural magnesium infusion started before induction of anaesthesia and extended into the postoperative period (pre-magnesium group) provided pre-emptive and preventative analgesia and decreased pain intensity during the postoperative period compared with postoperative epidural magnesium infusion and saline placebo infusion. Postoperative epidural magnesium infusion via PCEA decreased postoperative daily analgesic consumption with similar pain intensity compared with the control group.

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induction of anaesthesia and extended into the postoperative period decreased postoperative pain and daily analgesic consumption during the first three postoperative days after abdominal hysterectomy. Bilir and colleagues reported that the administration of epidural magnesium 50 mg as an initial bolus dose followed by a continuous infusion of 100 mg day $^{-1}$ for patients undergoing hip surgery resulted in the reduction in postoperative fentanyl consumption without any side-effects. A study examined the effect of combined intrathecal 94.5 mg and epidural 100 mg h$^{-1}$ magnesium sulphate supplementation of spinal anaesthesia on postoperative analgesic requirements in patients undergoing major orthopaedic surgery and reported that supplementation of spinal anaesthesia with combined intrathecal and epidural magnesium significantly reduces patient’s postoperative analgesic requirements. Doses of continuous epidural magnesium significantly reduces patient’s postoperative analgesic requirements. Doses of continuous epidural magnesium significantly reduces patient’s postoperative analgesic requirements.

The concept of pre-emptive analgesia was initially put forward by Crile$^{17}$ and then by Wall;$^{1}$ they suggested that the administration of opioids or local anaesthetics before surgery might reduce the C-fibre-induced injury barrage associated with incision and, thereby, the intensity of postoperative pain. The first definition of pre-emptive analgesia did not include the imperative to compare a preoperative intervention with a postoperative intervention.$^{18}$ Kissin$^{2, 19}$ introduced the term ‘preventive analgesia’ to emphasize the fact that central sensitization is induced by noxious preoperative and postoperative inputs. The aim of preventive analgesia is to reduce central sensitization that occurs from noxious inputs across the entire perioperative period when compared with placebo and not just from those initiated by incision.$^{20}$ These concepts suggest a possible study design; effective analgesia starts before incision and covers both the period of surgery and the postoperative period. The NMDA receptor antagonists would appear to be potentially useful drugs in this regard because of their effect in reducing central hypersensitivity and wind-up-like states in humans. The current study showed that antinociceptive treatment with continuous epidural magnesium started before noxious stimulation and extended into the postoperative period produced effective analgesia, resulted in better pain outcomes, and the effects were pre-emptive and preventive. The addition of magnesium 1 mg ml$^{-1}$ in the multimodal analgesic mixture also produced an analgesic-sparing effect, which reduced the analgesic mixture consumption between the post-magnesium and the control groups.

Wu and colleagues$^{21}$ investigated the benefits of pre-emptive analgesia for upper abdominal surgery, using pre-incisional epidural ketamine, an NMDA antagonist; morphine; and bupivacaine treatment for achieving postoperative pain relief and demonstrated that pre-incisional epidural ketamine, morphine, and bupivacaine treatment combined with continuous epidural analgesia and general anaesthesia provides an ideal pre-emptive analgesic therapy, exhibiting better postoperative pain relief than general anaesthesia and post-incisional ketamine, morphine, and bupivacaine treatment. A study$^{22}$ supported the role of pre-incisional i.m. dextromethorphan, an NMDA antagonist, as part of a multimodal analgesic regimen to enhance postoperative analgesia after colonic surgery, perhaps in a synergistic manner with local anaesthetics and opioids. However, Gottschalk and colleagues$^{23}$ evaluated the effect of pre-incisional epidural ropivacaine, sufentanil, clonidine, and S(+)-ketamine on postoperative pain in patients undergoing major pancreatic surgery and demonstrated that the pre-incisional epidural analgesic infusion did not provide pre-emptive analgesia compared with administration started at the end of surgery, but both groups had low pain scores. Another study$^{24}$ reported that preoperative administration of ketamine 0.15 mg kg$^{-1}$ in patients undergoing total mastectomy did not elicit a pre-emptive analgesic effect. Multiple factors interact to produce or prevent a pre-emptive analgesic effect. The nature and duration of the surgery, the type and extent of tissue damage, the timing and method of administration and the nature of agents used, interactions with other substances used intraoperatively, the afferent neuronal block produced, and the time course of central sensitization all interact with the emotional, physiological, and psychological state of the individual.$^{25, 26}$ Small differences in the initial state of the host and in the intensity, quality, and meaning of the nociceptive stimulus can produce major differences in the final perception of pain. Many of these factors are difficult to control in the clinical studies and may account for some of the discrepancies between the studies on pre-emptive analgesia.

This present study demonstrated that the pain intensity between the post-magnesium and the control groups was not statistically significant. This may suggest that continuous epidural magnesium started after surgery neither prevents nor decreases establishment of central hypersensitivity, thus failing to decrease postoperative pain intensity for the post-magnesium group compared with the control group, but it still provides an analgesic-sparing effect. In animal research, it has been suggested that block for a successful reversal of established hypersensitivity should be stronger in intensity and longer in duration than a pre-emptive effect to prevent establishment because the intensity of afferent input for re-initiation of central hypersensitivity is less than that for its initiation.$^{27}$

In conclusion, preoperative use of epidural magnesium for patients undergoing abdominal hysterectomy followed by continuous infusion during surgery with extension into the postoperative period provides pre-emptive and preventive analgesic effects on postoperative pain intensity and provides an analgesic-sparing effect on PCEA consumption without increasing the incidence of side-effects. Further studies are required in different surgical settings and for the possible long-term benefits.
References