Review Article

Analgesic Efficacy of Continuous Intravenous Magnesium Infusion as an Adjuvant to Morphine for Postoperative Analgesia: A Systematic Review and Meta-Analysis

Jamie D. Murphy*, Janaki Paskaradevan**, Lisa L. Eisler***, Jean-Pierre P. Ouanes****, Vicente A. Garcia Tomas***** Elizabeth A. Freck* and Christopher L. Wu******

Abstract

Background: The efficacy of perioperative intravenous magnesium administration on postoperative opioid use, opioid-related side effects (e.g., nausea and vomiting) and pain are uncertain, as randomized controlled trials on this topic have reported disparate results. The objective of this systematic review is to determine if perioperative magnesium reduces opioid use, opioid-related side effects, and postoperative pain.

Methods: An electronic search was conducted using the Library of Medicine’s PubMed and EMBASE databases. Included studies consisted of randomized controlled trials in an adult population with a clearly defined comparison of perioperative intravenous magnesium administration to a control with a documented assessment of opioid usage and postoperative pain. Relevant data was abstracted from included studies. Pooled estimates for weighted mean difference (WMD) with 95% confidence intervals (CI) were obtained for our primary outcome (opioid usage) using the Cochrane Collaboration’s RevMan version 4.2.7 (Cochrane Collaboration; Oxford, United Kingdom). WMD and odds ratios (OR) were calculated using a random effects model.

Results: The literature search ultimately yielded 22 trials, enrolling 1177 (599 magnesium, 578 control) patients, who were included in the analysis. A significant decrease in morphine usage by those patients who received magnesium was noted (WMD = -7.40; 95% CI: -9.40 to -5.41, p < 0.00001). Perioperative magnesium administration was not associated with a difference in postoperative nausea or vomiting (RR = 0.76; 95% CI: 0.52 to 1.09, p = 0.14). The pooled visual analog scores for pain at 4-6 hours after surgery were significantly less in those patients who received magnesium surgery (WMD = -0.67; 95% CI: -1.12 to -0.23, p = 0.003); however, there was no difference in pain scores at 20-24 hours after surgery (WMD = -0.25; 95% CI: -0.62 to 0.71, p = 0.17).

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Conclusion: Based on the results of this systematic review, perioperative intravenous magnesium may be a useful adjuvant for the management of postoperative pain providing analgesia through a different mechanism of action than that of opioids and would make a potential addition to a multimodal analgesic treatment plan; however, the decrease in opioid use with perioperative magnesium infusion does not appear to be associated with a decrease in opioid-related side effects.

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Introduction

Opioid-based analgesia plays a significant role in the control of postsurgical pain; however, use of opioid may lead to significant side effects (e.g., nausea and vomiting) and adverse events (e.g., respiratory depression), which may be associated with significantly longer hospital stays and higher hospital costs in the postsurgical setting. Since these adverse events occur more often in patients receiving higher doses of opioids, it is important to find ways to reduce opioid use in the postoperative period. Multimodal analgesia, using a non-opioid analgesic in addition to an opioid analgesic, has been suggested as a way to improve postoperative pain control and reduce opioid use.

Magnesium is a non-opioid analgesic that has been studied as an adjuvant to opioid analgesics. Magnesium sulfate has been found to have anesthetic, analgesic, and muscle relaxation effects and it has been suggested that magnesium may play a role in reducing analgesic requirements during the postoperative period. However, conflicting results have been found regarding the degree to which magnesium can reduce postoperative pain, postoperative analgesic requirements and postoperative side effects due to opioid use. As such, we have undertaken a systematic review and meta-analysis of published randomized control trials (RCTs) investigating perioperative intravenous magnesium infusion and postoperative outcomes to further examine these issues.

Methods

This study was exempt from the Johns Hopkins Institutional Review Board. The aim of this study was to review all relevant randomized controlled trials (RCTs) assessing the role of magnesium as an adjuvant to opioid based postoperative analgesia. In conducting this study, we followed the recommended checklist provided by the PRISMA statement. An electronic literature search of the Library of Medicine’s PubMed and EMBASE databases was conducted in July, 2011. Searches were limited to RCTs and the search terms used were “magnesium” and “pain”. Abstracts were screened based on the following criteria for inclusion: 1) adult study population; 2) surgical population; 3) clear comparison of perioperative (with or without bolus) intravenous magnesium infusion (≥ 15 min) vs. control; 4) assessment of magnesium as an analgesic adjuvant to opioids; 5) measurement of pain score that could be converted to visual analogue scale (VAS) pain score. Studies that did not meet these criteria were excluded. There were no language restrictions for study inclusion.

Data extraction was completed by two independent reviewers who were given full text versions of each article. Data were extracted from all trials that met inclusion criteria including first author, publication year, study location, patient demographics, study size, exclusion criteria, region of surgery, perioperative opioid analgesic used, perioperative magnesium technique used, control, postoperative opioid consumption, postoperative pain scores (visual analogue or numerical rating scale), and minor complications and side effects. Study quality was assessed for all articles by scoring each trial for both a Cochrane Collaboration for assessing risk of bias and Jadad score. The primary outcome variable was postoperative opioid consumption in the 24 hours after surgery and opioid related postoperative side effects. Secondary outcomes were VAS or numerical rating scale (NRS) pain scores 4 to 6 and 20 to 24 hours after surgery. A random effects model was used. The level of significance for all tests was set at an alpha level of 0.05. All statistical analyses were performed with RevMan 4.2.7 (The Cochrane Collaboration, 2004; Oxford, United Kingdom).
Results

The search resulted in 243 abstracts (Figure 1). After duplicates were removed, 236 abstracts remained from which the original articles were obtained. A total of 22 studies (Table 1) met all inclusion criteria. A total of 210 articles were rejected upon abstract screening for the following reasons: 38 did not compare perioperative intravenous magnesium versus control, 43 did not assess magnesium as an adjuvant to opioids, 14 did not study an adult population, 105 did not study a surgical population, 8 did not have a pain score that could be converted to VAS, and 2 were not RCTs. An additional 4 articles were excluded after full text screening for the following reasons: 2 did not use a continuous infusion of magnesium, 1 was not described as a RCT and 1 where the full text could not be located. A summary of the 22 articles used for the meta-analysis is shown in Table 1. There were 599 subjects who received perioperative intravenous magnesium and 578 subjects who received a control.

Fig. 1
PRISMA Flow Diagram: Literature Search Results

This figure shows the PRISMA flow diagram showing literature search results. A total of 23 randomized controlled trials were ultimately used for the analysis.
### Table 1
Characteristics of Studies Included in Meta-analysis

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study Location</th>
<th>Sex</th>
<th>Region of Surgery</th>
<th>Subjects (n, Mg/C)</th>
<th>Method of magnesium administration</th>
<th>Rate of Magnesium Infusion</th>
<th>Control</th>
<th>Cochrane Quality Score</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramer8 (1996)</td>
<td>Europe</td>
<td>F</td>
<td>Abdominal</td>
<td>21 Mg/21 C</td>
<td>Bolus + continuous infusion</td>
<td>500 mg/h (I, P)</td>
<td>Saline</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Wilder-Smith8 (1997)</td>
<td>Europe</td>
<td>F</td>
<td>Abdominal</td>
<td>13 Mg/11 C</td>
<td>Bolus + continuous infusion</td>
<td>200 mg/h (I, P)</td>
<td>Placebo</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Zauraza10 (2000)</td>
<td>Europe</td>
<td>M/F</td>
<td>Multiple</td>
<td>23 Mg/24 C</td>
<td>Bolus + continuous infusion</td>
<td>10 mg/kg/h (I, P)</td>
<td>Placebo pill and saline</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Ko11 (2001)</td>
<td>Asia</td>
<td>F</td>
<td>Abdominal</td>
<td>29 Mg/29 C</td>
<td>Bolus + continuous infusion</td>
<td>15 mg/kg/h (I, P)</td>
<td>Saline</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Kara12 (2002)</td>
<td>Europe</td>
<td>F</td>
<td>Abdominal</td>
<td>12 Mg/12 C</td>
<td>Bolus + continuous infusion</td>
<td>500 mg/h (I, P)</td>
<td>Saline</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Levaux13 (2002)</td>
<td>Europe</td>
<td>M/F</td>
<td>Lumbar</td>
<td>12 Mg/12 C</td>
<td>Continuous infusion only</td>
<td>25 mg/kg/h (I)</td>
<td>Saline</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Unlugenc14 (2002)</td>
<td>Europe</td>
<td>M/F</td>
<td>Abdominal</td>
<td>23 Mg/21 C</td>
<td>Bolus + continuous infusion</td>
<td>Used in patient-controlled analgesia</td>
<td>No Mg</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Tan14 (2004)</td>
<td>Europe</td>
<td>M/F</td>
<td>Multiple</td>
<td>25 Mg/25 C</td>
<td>Bolus + continuous infusion</td>
<td>500 mg/h (I, P)</td>
<td>Saline</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Bhatia18 (2004)</td>
<td>Asia</td>
<td>M/F</td>
<td>Abdominal</td>
<td>25 Mg/25 C</td>
<td>Bolus + continuous infusion</td>
<td>15 mg/kg/h (I)</td>
<td>Saline</td>
<td>4</td>
<td>3</td>
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<tr>
<td>Ayoglu17 (2005)</td>
<td>Europe</td>
<td>M/F</td>
<td>Abdominal</td>
<td>20 Mg/20 C</td>
<td>Bolus + continuous infusion</td>
<td>8 mg/kg/h (I, P)</td>
<td>Saline</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Seyhan19 (2005)</td>
<td>USA</td>
<td>F</td>
<td>Abdominal</td>
<td>40 Mg/20 C</td>
<td>Bolus + continuous infusion</td>
<td>10-20 mg/kg/h (I, P)</td>
<td>Saline</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Steinelchner20 (2006)</td>
<td>Europe</td>
<td>M/F</td>
<td>Thoracic</td>
<td>19 Mg/20 C</td>
<td>Bolus + continuous infusion</td>
<td>13.8 mg/kg/h (I, P)</td>
<td>Saline</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Taugzen-Fin21 (2006)</td>
<td>Europe</td>
<td>M</td>
<td>Pelvic</td>
<td>15 Mg/15 C</td>
<td>Continuous infusion only</td>
<td>16.7 mg/kg/h (I)</td>
<td>Saline</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Ozcan22 (2007)</td>
<td>Europe</td>
<td>M/F</td>
<td>Thoracic</td>
<td>12 Mg/12 C</td>
<td>Bolus + continuous infusion</td>
<td>10 mg/kg/h (P)</td>
<td>Saline</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Ryu23 (2008)</td>
<td>Asia</td>
<td>F</td>
<td>Abdominal</td>
<td>25 Mg/25 C</td>
<td>Bolus + continuous infusion</td>
<td>15 mg/kg/h (I)</td>
<td>Saline</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Ferasatkish24 (2008)</td>
<td>Asia</td>
<td>M/F</td>
<td>Thoracic</td>
<td>109 Mg/109 C</td>
<td>Continuous infusion only</td>
<td>32 nmol/kg/h</td>
<td>Saline</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Mentess25 (2008)</td>
<td>Europe</td>
<td>M/F</td>
<td>Abdominal</td>
<td>41 Mg/42 C</td>
<td>Continuous infusion only</td>
<td>n/a (I)</td>
<td>Saline</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Oguzhan26 (2008)</td>
<td>Europe</td>
<td>M/F</td>
<td>Lumbar</td>
<td>25 Mg/25 C</td>
<td>Continuous infusion only</td>
<td>10 mg/kg/h (I)</td>
<td>Saline</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Dabbagh27 (2009)</td>
<td>Asia</td>
<td>M/F</td>
<td>Lower Extremity</td>
<td>30 Mg/30 C</td>
<td>Continuous infusion only</td>
<td>8 mg/kg/h (I)</td>
<td>Saline</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Hwang28 (2009)</td>
<td>Asia</td>
<td>M/F</td>
<td>Lower Extremity</td>
<td>20 Mg/20 C</td>
<td>Bolus + continuous infusion</td>
<td>15 mg/kg/h (I)</td>
<td>Saline</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Kaya29 (2009)</td>
<td>Europe</td>
<td>F</td>
<td>Abdominal</td>
<td>20 Mg/20 C</td>
<td>Bolus + continuous infusion</td>
<td>500 mg/h (I)</td>
<td>Saline</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Saadawy30 (2009)</td>
<td>Africa</td>
<td>M/F</td>
<td>Abdominal</td>
<td>40 Mg/40 C</td>
<td>Bolus + continuous infusion</td>
<td>25 mg/kg/h (I)</td>
<td>Saline</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: C: control, F: female, I: intraoperative; M: male, Mg: magnesium; n/a: not available; P: postoperative; USA: United States of America.

Perioperative administration of magnesium was associated with a significant decrease in postoperative morphine usage postoperatively (weighted mean difference [WMD] = -7.40 mg; 95% CI: -9.40 to -5.41, p < 0.00001) (Figure 2); however, there were no differences in the incidence of nausea and vomiting in the postoperative period (relative risk [RR] = 0.76; 95% CI: 0.52 to 1.09, p = 0.14) (Figure 3). Figures 4 and 5 show the effect of perioperative intravenous magnesium on pain scores 4-6 and 20-24 hours after surgery, respectively. Perioperative administration of magnesium was associated with a decrease in postoperative pain at 4-6 hours (WMD = -0.67; 95% CI: -1.12 to -0.23, p = 0.003); however, there was no difference in pain scores at 20-24 hours after surgery (WMD = -0.25; 95% CI: -0.62 to 0.71, p = 0.17).
The weighted (pooled) estimate for the effect of perioperative intravenous magnesium on opioid consumption as measured by parenteral morphine equivalents (in milligrams). “N” represents the number of subjects in each experimental group. The entire diamond (pooled estimate) lies to the left of the WMD = 0 (which represents “no difference”), suggesting that magnesium administration is associated with lower postoperative opioid consumption (WMD = -7.40 mg; 95% CI: -9.40 to -5.41, p < 0.00001).

The weighted (pooled) estimate for the effect of perioperative intravenous magnesium on the incidence of nausea and vomiting. “n” represents the number of subjects within an experimental group who reported nausea or vomiting. “N” represents the number of subjects in each experimental group. The entire diamond (pooled estimate) overlies the RR = 1 (which represents “no difference”), suggesting that magnesium administration is not associated with the incidence of nausea or vomiting (RR = 0.76; 95% CI: 0.52 to 1.09, p = 0.14).
**Fig. 4**
Pooled estimates for pain at 4 to 6 hours after surgery: magnesium vs. control

The weighted (pooled) estimate for the effect of perioperative intravenous magnesium on pain as measured by VAS 4-6 hours after surgery. "N" represents the number of subjects in each experimental group. The entire diamond (pooled estimate) lies to the left of the WMD = 0 (which represents “no difference”), suggesting that magnesium administration is associated with lower pain scores (WMD = -0.67; 95% CI: -1.12 to -0.23, p = 0.003) at 4-6 hours after surgery.

**Fig. 5**
Pooled estimates for pain at 20 to 24 hours after surgery: magnesium vs. control

The weighted (pooled) estimate for the effect of perioperative intravenous magnesium on pain as measured by VAS 20-24 hours after surgery. “N” represents the number of subjects in each experimental group. The entire diamond (pooled estimate) crosses WMD = 0 (which represents “no difference”), suggesting that magnesium administration is not associated with lower pain scores (WMD = -0.25; 95% CI: -0.62 to 0.71, p = 0.17) at 20-24 hours after surgery.
Discussion

We found that perioperative infusion of magnesium was associated with a decrease in postoperative opioid consumption; however, the decrease in opioid consumption was not associated with a decrease in opioid-related side effects such as postoperative nausea and vomiting. In addition, we also found that perioperative magnesium infusion was associated with a decrease in VAS pain scores up to 4-6 hours after surgery but there was no benefit from magnesium infusion at 20-24 hours after surgery. Our results are similar to those from a previous systematic review although our analysis included more studies (22 versus 14), many of which were published after the previous systematic review.

In comparing our results to the previous published systematic review, both studies demonstrated a decrease in opioid consumption with the perioperative use of magnesium. We noted a weighted mean difference of approximately 7.4 mg of morphine at 24 hours after surgery while the prior systematic review found that cumulative morphine consumption was decreased by a median of 28% (range of 12-47%). This decrease in morphine consumption in patients receiving perioperative magnesium infusion did not result in an apparent decrease in the presumed opioid-related side effect, postoperative nausea and vomiting. The lack of decreased in the incidence of opioid-related side effects despite the presence of an opioid sparing effect may not be surprising as use of other adjuvants (e.g., acetaminophen) may also not be associated with a decrease in opioid-related side effects.

Our study also noted a relatively brief period of analgesic benefit (<20-24 hours after surgery) for perioperative magnesium infusion. This finding may not be surprising as the previous systematic review concluded that the randomized studies investigating perioperative magnesium as an adjuvant did not provide convincing evidence for analgesic efficacy. Our findings suggest that if there is an analgesic benefit for perioperative magnesium infusion, it would be limited to the immediate postoperative period. Furthermore, it is uncertain whether the decreases in VAS pain scores for the time period where there was a benefit for magnesium (i.e., 4-6 after surgery) would actually be clinically meaningful. The mechanism of analgesia for magnesium is unclear; however, possible mechanisms include inhibition of calcium influx, antagonism of N-methyl-D-aspartate receptors, and attenuation of central sensitization.

Several points need to be made in interpreting our results. Not all studies used morphine for postoperative analgesia and not all assessed cumulative opioid consumption at 24 hours. Although equianalgesic tables are available for conversion of some of these opioids, we elected to exclude these studies from the 24 hour cumulative morphine analysis in an attempt to make this analysis more uniform. In addition, there was limited available data on opioid-related side effects other than postoperative nausea and vomiting. There was no or limited data on pruritus, sedation, urinary retention, and respiratory depression. Nevertheless, it is unlikely that perioperative magnesium infusion would have a significant effect on major adverse events such as respiratory depression, as prior studies indicate that perioperative administration of other adjuvants (e.g., acetaminophen, nonsteroidal anti-inflammatory agents, ketamine) do not significantly decrease opioid-related adverse events despite the presence of an opioid-sparing effect.

There are several limitations to our study. The sample size of the included studies was relatively small (typically < 50 subjects/study) and as a result, there may have been little data on less frequent outcomes of interest (such as respiratory depression). We included only studies that utilized infusions with or without a bolus (i.e., did not include those that used only a bolus dose) as we presumed that an infusion would have a prolonged effect on postoperative analgesia, our primary interest. There was heterogeneity present in several of the analyses; however, we attempted to minimize this effect by using a more conservative random effect model for our meta-analysis. We attempted to minimize publication bias by searching several databases and including non-English language papers. Finally, there are general limitations to the meta-analytic technique which have been discussed elsewhere.

In summary, we found a decrease in postoperative opioid consumption which was not associated with a decrease in opioid-related side effects such as
postoperative nausea and vomiting with the use of perioperative infusion of magnesium. Although perioperative magnesium infusion was associated with a decrease in VAS pain scores up to 4-6 hours after surgery, there was no benefit from magnesium infusion at 20-24 hours after surgery. The overall analgesic benefit of perioperative magnesium is uncertain; however, larger scale trials are probably needed to address some of the limitations of currently available randomized trials.
ORPHINE FOR POSTOPERATIVE ANALGESIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

ANALGESIC EFFICACY OF CONTINUOUS INTRAVENOUS MAGNESIUM INFUSION AS AN ADJUVANT TO MORPHINE FOR POSTOPERATIVE ANALGESIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

References


