Systemic magnesium to improve quality of post-surgical recovery in outpatient segmental mastectomy: a randomized, double-blind, placebo-controlled trial

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Abstract. Background: It remains to be determined if perioperative systemic magnesium can improve postoperative quality of recovery of patients undergoing ambulatory procedures. The main objective of the current investigation was to evaluate the effect of systemic magnesium on postoperative quality of recovery in patients undergoing outpatient segmental mastectomies. Methods: The study was a prospective randomized, double-blind, placebo-controlled, clinical trial. Female subjects were randomized to receive intravenous magnesium (MgSO₄ 50mg/kg in 100 mL of normal saline over 15 min before anesthesia induction, followed by an infusion of 15 mg/kg/hour) or the same volume of saline. The primary outcome was the Quality of Recovery 40 (QOR-40) questionnaire at 24 hours after surgery. Results: 50 subjects were recruited and 46 completed the study. Patients in the magnesium group had better global Quality of Recovery scores compared with the saline group, with a median difference of 24 (99% CI, 3 to 33), P<0.001. After discharge from hospital, subjects in the magnesium group required less oral opioids, median (IQR) of 10 (0 to 20) (oral milligrams of morphine equivalents) than the saline group, 30 (20 to 40) (P<0.001). The postoperative systemic magnesium concentrations were substantially higher in the magnesium group, 1.25 ± 0.28 mmol/L compared to control, 0.71 ± 0.11 mmol/L, P<0.0001. Simple linear regression demonstrated a direct linear relationship between the postoperative systemic magnesium concentrations and 24 hour postoperative quality of recovery scores (P = 0.004), and also an inverse relationship with pain burden in the postoperative care unit (P = 0.01). Conclusions: Systemic magnesium improves postoperative quality of recovery in patients undergoing outpatient segmental mastectomy. Systemic magnesium is a safe, inexpensive, efficacious strategy to improve quality of recovery after ambulatory surgery.

Key words: magnesium, quality of recovery, surgery

Ambulatory surgical procedures have become the most common surgical interventions as a result of the development of less invasive methods and the introduction of shorter acting anesthetics with fewer side effects [1-3]. Nonetheless, postoperative pain is frequently under-managed in the outpatient surgical setting, which can significantly jeopardize quality of recovery of surgical patients [4, 5]. The development and testing of multi-modal, opioid-sparing regimens appear to be a promising strategy for improving and speeding up overall recovery after ambulatory surgery [6, 7].

Magnesium has been utilized as an opioid-sparing agent in a variety of surgical procedures. Recently, our group has reported a substantial opioid-sparing effect of systemic magnesium across a wide variety of surgical procedures [8]. However, the only study performed in an ambulatory surgical setting did not detect any beneficial effect of systemic magnesium on postoperative analgesia outcomes [9].

In addition to opioid-sparing effects, systemic magnesium can also improve other aspects of surgical recovery by minimizing postoperative shivering, improving mood and decreasing postoperative airway morbidity after general anesthesia [9-11]. Nevertheless, it remains to be determined if perioperative systemic magnesium can improve overall postsurgical quality of recovery after ambulatory surgery.

The primary objective of the current investigation was to examine the effect of systemic magnesium on postoperative quality of recovery after ambulatory segmental mastectomy. We hypothesized that systemic magnesium would produce a large improvement in quality of postsurgical recovery compared to saline. In addition, we sought to investigate the analgesic effects of systemic magnesium in an ambulatory surgical setting.

Methods

This study was a prospective, randomized, double-blind, placebo-controlled trial. Clinical trial registration for this study can be found at Clinical-Trial.gov; url: http://www.clinicaltrials.gov; registration identified: NCT01433081. Study approval was obtained from the Northwestern University Institutional Review Board, and written, informed consent was obtained from all of the study participants. Eligible subjects were females undergoing outpatient segmental mastectomy for breast cancer at Prentice Women’s Hospital. Patients with a history of chronic use of an opioid analgesic, corticosteroids and/or pregnant subjects were not enrolled. Reasons for exclusion from the study following study drug administration included inability to follow the study protocol or patient request. Subjects were randomized, using a computer-generated table of random numbers, into two groups, one to receive intravenous magnesium (MgSO4 50 mg/kg in 100 mL of normal saline over 15 min before anesthesia induction, followed by an infusion of 15 mg/kg/hour), or the same volume of saline until the end of the surgical procedure. The magnesium dose chosen is consistent with prior studies evaluating the analgesic properties of magnesium in the perioperative setting. [8]. Group assignments were sealed in sequentially numbered, opaque envelopes that were opened by a research nurse not involved with the patient care or data collection after the subject provided written, informed consent. The same nurse prepared syringes labeled with the study drug: subjects enrolled in the study, anesthesia providers and investigators collecting the data were all blinded.

All subjects were premedicated with 0.04 mg/kg iv midazolam, and provided blood samples for assessment of preoperative concentrations of serum magnesium. Propofol 1-2 mg/kg was administered for anesthesia induction, a remifentanil 0.1 μg/kg/min IV infusion was begun and succinylcholine 1-2 mg/kg iv was administered to induce muscle paralysis. Tracheal intubation was initially attempted by an anesthesia resident physician or a certified registered nurse anesthetist under the supervision of an attending anesthesiologist. Anesthesia was maintained using remifentanil, titrated to maintain the mean arterial pressure within 20% of baseline, and sevoflurane titrated to a BIS index (Aspect Medical System Inc, Norwood, MA) of between 40 and 60. At the end of the procedure, the remifentanil infusion was discontinued and the subjects received intravenous ondansetron 4 mg.

In the post-anesthesia care unit (PACU), subjects were asked to rate their pain at rest upon arrival and at regular intervals, on a 0 to 10 pain numeric rating scale (NRS), where 0 means no pain and 10 is the worst pain imaginable. A postoperative serum magnesium concentration
was collected on arrival at the PACU. A Ramsey sedation score was also recorded on arrival at the PACU (1 = anxious/agitated; 2 = cooperative/tranquil; 3 = drowsy/responds to command only; 4 = brisk response to shaking/loud sound; 5 = sluggish response to shaking/loud sound; 6 = no response). The area under the NRS pain scale versus time curve was calculated using the trapezoidal method as an indicator of pain burden during early recovery (Graph Pad Prism version 5.03, Graph Pad Software, Inc., La Jolla, CA, USA). Hydromorphone 0.4 mg was administered iv every five minutes to maintain an NRS pain score lower than 4 out of 10. In cases of postoperative nausea or vomiting, subjects received 10 mg iv metoclopramide, followed by 5 mg iv prochlorperazine, if necessary. Discharge readiness was assessed using the Modified Post Anesthesia Discharge Scoring System (PADSS) [12] score every 15 min until subjects met discharge criteria. The PADSS system assesses five criteria: vital signs, ambulation, pain, nausea and/or vomiting and surgical bleeding. Each criterion is scored on a 0 to 2 scale with higher scores representing a more acceptable condition. A score of ≥9 is considered to mean ready for discharge. At discharge, subjects were instructed to take hydrocodone 10 mg plus acetaminophen 325 mg for pain greater than 3 out of 10. Postoperative opioid consumption was converted to equivalent doses of intravenous (PACU) or oral morphine (after hospital discharge) [13].

Subjects were contacted by telephone 24 hours after the procedure by an investigator unaware of group allocation, and were questioned regarding analgesic consumption, pain score; the QoR-40 questionnaire was also administered [14]. The questionnaire consisted of 40 questions that examined five domains of patient recovery using a 5-point Likert scale: none of the time, some of the time, usually, most of the time and all of the time. The five domains include physical comfort, pain, physical independence, psychological support and emotional state [15, 16]. Other perioperative data collected included subject’s age, height, weight, American Society of Anesthesiologist physical status, duration of surgery, intraoperative remifentanil use, total intravenous fluids and total amount of hydromorphone in the PACU.

The primary outcome was the global QoR-40 score. Global QoR-40 scores range from 40 to 200 representing very poor to outstanding quality of recovery respectively. A sample size of 23 subjects per group was estimated to achieve 80% power to detect a 15 point difference in the aggregated QoR-40 score for the two study groups to be compared, assuming an overall standard deviation of 18, similar to what was observed in a previous investigation [17]. We expected a large effect on quality of recovery due to the large opioid-sparing properties of systemic magnesium across different surgical procedures [8]. In anticipation of drop-outs, 50 subjects were recruited and randomized. The sample size calculation was made using PASS version 8.0.15 release date January 14, 2010 (NCSS, LLC, Kaysville, UT, USA).

The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to test the hypothesis of normal distribution. Normally distributed interval data are reported as mean (SD), and were evaluated with Student’s T test for equal variances. Non-normally distributed interval and ordinal data are reported as median (range or Interquartile range (IRQ)), and compared among groups using the Mann Whitney U test [18]. Median differences and 99% confidence intervals of the differences in global QoR-40 scores were calculated using a 10,000 sample bootstrapping method. A bivariate analysis with simple linear regression was used to detect an association between global quality of recovery and postoperative serum concentrations of magnesium, with the change in r² evaluated for significance. Estimates of exact P-values were determined for the χ² and the Kruskal-Wallis test using a Monte Carlo method with 10,000 samples and confidence limits of 95%. All reported P values are two-tailed. To avoid the chance of a type I error, the criterion for rejection of the null hypothesis was a two-tailed P<0.01 for comparisons involving the primary outcome variable. A value of P<0.05 was used for all other comparisons.

Statistical analysis was performed using NCSS 8, release date 5/15/2013 (NCSS, LLC, Kaysville, UT) and R version 3.0.1, release date 5/16/2011 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

The details of the study are shown in figure 1. Fifty subjects were randomly selected, with forty six completing the study. Patients were enrolled.
Figure 1. Consort flow study diagram.

Consecutively from February 2011 through April 2013. Patients’ baseline characteristics and surgical factors were not different between the groups (table 1). The preoperative baseline systemic magnesium concentrations were not different between the magnesium group, 0.77 ± 0.11 mmol/L and the control group, 0.75 ± 0.19 mg/100 mL (P = 0.61). In contrast, the postoperative systemic magnesium concentrations were substantially higher in the magnesium group, 1.25 ± 0.28 mmol/L compared to the control group, 0.71 ± 0.11 mmol/L, P<0.0001 (figure 2).

The median difference (99% CI) in global QoR-40 scores, 24 hours after surgery was 24 (3 to 33) (P<0.001) between the magnesium and the saline groups. Subjects in the systemic magnesium group also had better scores in the subcomponents of the quality of recovery score that specifically examined pain, physical comfort and physical independence (table 2).

Patients in the magnesium group had lower area under the pain scores versus time and lower opioid consumption in the PACU compared to the saline group (table 3). The time taken to meet
Table 1. Baseline subject and surgical procedure characteristics

<table>
<thead>
<tr>
<th></th>
<th>Magnesium (n = 23)</th>
<th>Saline (n = 23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>53 (45 to 57)</td>
<td>52 (48 to 57)</td>
<td>0.79</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 (21.7 to 29.7)</td>
<td>25.3 (23.1 to 28.3)</td>
<td>0.33</td>
</tr>
<tr>
<td>ASA Class I</td>
<td>10</td>
<td>6</td>
<td>0.35</td>
</tr>
<tr>
<td>ASA Class II</td>
<td>13</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segmental mastectomy/lymph node biopsy</td>
<td>21</td>
<td>20</td>
<td>1.0</td>
</tr>
<tr>
<td>Segmental mastectomy/lymph node dissection</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Surgical duration (minutes)</td>
<td>106 (91 to 128)</td>
<td>98 (83 to 134)</td>
<td>0.76</td>
</tr>
<tr>
<td>Remifentanil (µg)</td>
<td>413 (354 to 475)</td>
<td>442 (355 to 697)</td>
<td>0.39</td>
</tr>
<tr>
<td>Intravenous fluid (mL)</td>
<td>1,100 (1,000 to 1,600)</td>
<td>1100 (1,000 to 1,700)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD), median (IQR) or counts (n).

Figure 2. Box plot demonstrating differences in postoperative concentrations of systemic magnesium between the magnesium and control group (P<0.0001).

Hospital discharge criteria was shorter, but not statistically different in the magnesium group; median (IQR) of 90 (75 to 120) min compared to 120 (90 to 165) min in the saline group (P = 0.07). After hospital discharge, subjects in the magnesium group required less oral opioids, median (IQR) of 10 (0 to 20) (oral mg morphine equivalents) than the saline group, 30 (20 to 40) (P = 0.0002).

Simple linear regression demonstrated a direct linear relationship between the postoperative systemic magnesium concentrations and 24 hour postoperative quality of recovery scores (P = 0.004) (figure 3), and also an inverse relationship with pain burden in the postoperative care unit (slope of regression line (95%CI) = -50.4 (-92.0 to -8.88), goodness-of-fit r² (95%CI) = 0.12 (0.06 to 0.18), and slope significantly different from 0 (P = 0.01).

Discussion

The most important finding of the current investigation was the improvement in postoperative quality of recovery in patients who received intraoperative systemic magnesium compared to the ones who received only saline during ambulatory segmental mastectomy. In addition, magnesium specifically improved the pain, physical comfort and physical independence subcomponents of the quality-of-recovery score. We also detected a direct relationship between postoperative magnesium concentrations and global quality-of-recovery scores. Taken together, our results suggest that systemic magnesium should be considered to improve recovery of ambulatory patients undergoing segmental mastectomy surgery.

Another important finding of the current investigation was the detection of positive analgesic properties of systemic magnesium for patients undergoing ambulatory surgery. Patients in the systemic magnesium group had less postoperative pain in the PACU and hence opioid consumption than the saline group. Our findings are important since the only previous study investigating the analgesic role of systemic magnesium in ambulatory patients did not detect any opioid-sparing effects of magnesium compared to saline [9]. In contrast, our group and others have demonstrated...
Table 2. Quality of recovery (QOR-40) and subcomponent scores by study group

<table>
<thead>
<tr>
<th></th>
<th>Magnesium (n = 23)</th>
<th>Saline (n = 23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical comfort</td>
<td>57 (53 to 59)</td>
<td>49 (45 to 54)</td>
<td>0.002</td>
</tr>
<tr>
<td>Physical independence</td>
<td>22 (21 to 24)</td>
<td>18 (15 to 22)</td>
<td>0.004</td>
</tr>
<tr>
<td>Emotional</td>
<td>43 (41 to 44)</td>
<td>38 (35 to 41)</td>
<td>0.001</td>
</tr>
<tr>
<td>Support</td>
<td>29 (27 to 31)</td>
<td>28 (26 to 29)</td>
<td>0.07</td>
</tr>
<tr>
<td>Pain</td>
<td>33 (31 to 34)</td>
<td>29 (26 to 31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Overall score</td>
<td>183 (173 to 188)</td>
<td>159 (153 to 175)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as median (IQR)

Table 3. Post-anesthesia care unit data

<table>
<thead>
<tr>
<th></th>
<th>Magnesium (n = 23)</th>
<th>Saline (n = 23)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Area under the numeric rating scale for pain versus time curve in post-anesthesia care unit (score * min)</td>
<td>172 (90 to 270)</td>
<td>270 (225 to 360)</td>
<td>0.006</td>
</tr>
<tr>
<td>Ramsey Sedation score</td>
<td>2 (2 to 3)</td>
<td>2 (2 to 3)</td>
<td>0.41</td>
</tr>
<tr>
<td>Opioid (iv morphine equivalents)</td>
<td>2.5 (2 to 5)</td>
<td>6.0 (3.5 to 11)</td>
<td>0.008</td>
</tr>
<tr>
<td>Time-to-opioid request (min)</td>
<td>11 (5 to 43)</td>
<td>1 (1 to 15)</td>
<td>0.15</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>10</td>
<td>0.36</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>6</td>
<td>0.24</td>
</tr>
<tr>
<td>No</td>
<td>21</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as medians (IQR) or counts (n)

a large opioid-sparing effect of systemic magnesium, across a large variety of surgical procedures [8,19].

Several factors might have contributed to the differences between the positive analgesic properties of magnesium observed in the current investigation, and the lack of analgesic properties of systemic magnesium in the previous investigation [9]. Firstly, the previous investigation used a multi-modal analgesic technique that included a regional block (ilioinguinal-iliohypogastric nerve) and/or 100 mg of rectal diclofenac: the impact of this multimodal analgesic strategy could have masked the analgesic effect of magnesium. Secondly, in the aforementioned study the investigators used a single bolus injection of magnesium at the beginning of the study. It is therefore possible that the systemic concentrations of magnesium were lower than those achieved in the current study. Finally, the surgical procedure examined in the previous study was different from the current one, and differences in the types of surgical procedures have been shown to be an important confounding factor in studies evaluating postoperative pain interventions [20-22].

Other pharmacological strategies have been shown to improve postoperative quality-of-recovery in ambulatory surgical patients. Specifically, systemic dexamethasone has been shown to improve postoperative recovery in patients undergoing laparoscopic ambulatory gynecological surgery [23,24]. We normally avoid dexamethasone in breast cancer subjects to minimize perioperative immunosuppression and any potential effects on cancer outcomes [25-27]. Nevertheless, our group has recently demonstrated that a single dose of perioperative, systemic dexamethasone does not affect ovarian cancer outcomes [28]. It remains to be determined if systemic magnesium maintains its beneficial properties in postoperative recovery when given in combination with systemic dexamethasone.

We did not observe any adverse effects of systemic magnesium. It is important to note however that we examined only subjects with normal
kidney function that were at low risk for magnesium toxicity. It is possible that the current intervention regimen could have led to toxic concentrations in higher risk patients. Nevertheless, our group has previously examined higher risk cardiac patients and did not detect magnesium toxicity, even at dosage regimens greater than the one employed in the current study [29].

A variety of mechanisms of action for the analgesic properties of systemic magnesium have been proposed, but the modulation of calcium transport in the cellular membrane and the antagonism of N-methyl-D-aspartate (NMDA) receptors are the most commonly cited ones [30, 31]. Both mechanisms are well established in the field of acute and chronic pain [32-36]. The variations seen in the analgesic effects of systemic magnesium are likely due to limited movement of magnesium across the blood-brain barrier [37].

Although the postoperative opioid-sparing effects of magnesium have been recently demonstrated by independent quantitative analysis [8, 19], whether our results on quality-of-recovery could also be relevant to more painful surgical procedures such as colon and thoracic surgery [38, 39], remains to be established. In addition, the effect of systemic magnesium on pain outcomes might also be affected by the type of regional anesthesia technique [40, 41].

Our study should only be interpreted within the context of its limitations. We studied a relatively small number of patients, and we were underpowered to examine the beneficial properties of systemic magnesium in the individual items of the quality-of-recovery score. We did not implement a multimodal analgesic strategy, and it is possible that the use of a multimodal analgesic strategy could lead to different results. Ketorolac was the only parenteral, non-opioid analgesic approved for use in the United States at the time of the study, and ketorolac is avoided in breast surgery patients due to its possible association with postoperative hematomas [42, 43].

In summary, we detected an analgesic effect of systemic magnesium in patients undergoing outpatient breast surgery. More importantly, systemic magnesium improved postoperative quality-of-recovery in the same population. In addition, postoperative concentrations of systemic magnesium were also directly associated with better global quality-of-recovery scores. Systemic magnesium should be considered as an effective strategy for improving recovery in ambulatory surgical patients.

Disclosure

Funding provided by departmental sources. The authors attest that there is no conflict of interest.

References


