

Attenuation of acute postoperative pain and opioid requirement with the use of magnesium sulfate in patients undergoing limb amputations

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Abstract

Objective: To compare the effects of magnesium sulphate on the total dose of intravenous morphine consumption postoperatively following limb amputations along with rescue analgesia requirement, pain scores and side effects.

Method: This prospective, triple-blinded, randomised controlled study was conducted from October 2021 to May 2022 at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised of patients scheduled for limb amputations. They were randomised into 2 equal groups. The anaesthesia protocol was uniform for all patients. Intervention group A was administered 30mg/kg loading dose and 10mg/kg/hr maintenance dose of magnesium sulphate intravenously, while patients in control group B received the same amount of plain isotonic saline. Morphine consumption, including that used for rescue analgesia and patient-controlled analgesia, was measured for 24 hours postoperatively. Numeric rating scale was used for the evaluation of postoperative pain in both groups at 15min, 1h, 2h, at discharge from the post-anaesthesia care unit and at 12h and 24h in the ward. Data was analysed using SPSS 23.

Results: Of the 24 patients enrolled, the study was completed by 20(83.33%). There were 10(50%) patients in group A; 8(40%) males and 2(20%) females with mean age 24.8 ± 14.14 years and mean surgery time 130.5 ± 47.86 minutes. There were 10(50%) patients in group B; 8(40%) males and 2(20%) females with mean age 23.2 ± 7.4 years and mean surgery time 117 ± 23.85 minutes ($p > 0.05$). Total morphine used over 24 hours in group A was 16 ± 3.1 mg compared to 29.6 ± 11.2 mg in group B ($p < 0.05$). The time for first use of patient-controlled analgesia after arriving in the post-anaesthesia care unit was significantly delayed in group A (72.2 ± 24.95 minutes) compared to that in group B (25 ± 26.68 minutes) ($p < 0.05$). Pain scores were significantly higher in the group B at 15min compared to group A ($p < 0.05$), but not at the rest of the time points ($p > 0.05$).

Conclusion: Intravenous magnesium sulphate proved to be effective in lowering postoperative opioid requirement following limb amputations.

Keywords: Postoperative pain, Analgesia, Amputation, Surgical amputation, N-methyl-D-aspartate receptors, Magnesium, Magnesium sulphate, Opioid analgesics, Morphine, Patient-controlled analgesia. (JPMA 74: 1046; 2024)

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Introduction

Whether for the management of dysvascular disease, trauma or cancer, millions of people undergo limb amputation annually. Early and effective perioperative management of limb amputation pain is a crucial element to address in a patient recovering from the surgery in order to avoid chronic pain,¹ thereby improving their quality of life (QOL) and circumventing the debilitating physical, mental and financial repercussions that come with chronic pain.²

The pain associated with amputations is multifactorial³ and its management is also multimodal. Various analgesic strategies include nerve blocks, pharmacological measures,

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like antidepressants, gabapentinoids and opioids, therapeutic modalities, such as mirror visual feedback and cognitive behavioural therapy (CBT), and surgical interventions, like trans-cutaneous electrical stimulation (TENS) and neuroma resection.⁴

Pain following limb amputations is thought to be mediated by the N-methyl-D-aspartate (NMDA) receptor and, hence, the use of NMDA receptor antagonists, like ketamine, have been shown to decrease opioid requirement, reverse opioid resistance⁵ and possibly even prevent the development of phantom limb pain.⁶ Therefore, these drugs have an emerging role in pain management.

Magnesium, though not an analgesic drug in itself, has a similar role in perioperative analgesia, and it acts by way of a voltage-dependent blockade of NMDA receptors.⁷ While it has shown favourable analgesic outcomes when given via the neuraxial route⁸⁻¹⁰ or as intravenous (IV) regional anaesthesia,¹¹ it has also shown beneficial effects in terms of better analgesia and/or reduced postoperative opioid

requirements when given as an IV adjunct in various surgeries.¹²⁻¹⁴

There exists abundant data establishing similar usefulness of magnesium sulphate (MgSO₄) in orthopaedic surgeries.¹⁵ However, there is lack of data addressing amputations per se. The current study was planned to compare the effects of MgSO₄ on the total dose of IV morphine consumption postoperatively following limb amputations along with rescue analgesia requirement, pain scores and side effects.

Patients and Methods

This prospective, triple-blinded, randomised controlled study was conducted from October 2021 to May 2022 at the Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan.

After approval from the institutional ethics review board, the sample was raised from among cancer patients with American Society of Anaesthesiologists physical status I-II,¹⁶ aged 12-70 years, weighing >30kg who were scheduled to undergo elective limb amputation surgery. Those with ASA status III-IV, with pre-existing pain in the affected limb, known hypersensitivity to the study drugs, any major organ system dysfunction, any psychiatric illness that could interfere with perception and assessment of pain, history of magnesium, calcium channel blocker or long-term opioid use, any event that interrupted routine surgical procedure and led to non-routine interventions, and those refusing to participate were excluded.

Using an online randomiser,¹⁷ a list of numbers was generated and divided into two equal groups, A and B. Each patient was numbered in the sequence in which they appeared for surgery, such that the first person enrolled was given the number 1, the second person number 2 and so on. In the event of exclusion of a patient, their originally assigned random number was to be passed on to the next patient. This process ensured the elimination of any bias in the recruitment process.

After taking informed consent, the patients were explained how to rate their pain using the Numeric Pain Rating Scale (NPRS).¹⁸ They were also educated about demanding rescue analgesia for breakthrough pain (NPRS >3) in the post-anaesthesia care unit (PACU) and about the use of patient-controlled analgesia (PCA) device.

All the patients, surgeons, attending anaesthetists, nursing staff and data collectors were blinded to the identity of the study drug being used in a particular patient. Infusions were prepared preoperatively in identical syringes by the investigators who were not involved in the data-collection process. The syringe was then handed over to the

attending anaesthetist blinded to the contents for administration as per the study protocol. The same surgeon operated on all the patients.

The general anaesthesia (GA) protocol was kept uniform for all the patients. After transfer to the operation theatre, routine monitoring, including electrocardiogram (ECG), heart rate (HR), non-invasive blood pressure (NIBP), pulse oximetry and capnography, was attached. No anxiolytic was given. Ringer lactate was used as the maintenance fluid. Blood transfusions or fluid boluses were provided as per clinical requirement. GA induction was done with IV 0.1 mg/kg morphine, 2 mg/kg propofol, and 0.5 mg/kg atracurium to facilitate intubation. GA was maintained with sevoflurane in 50% oxygen/air mixture. Atracurium boluses were repeated as required.

After induction, group A was administered a 30mg/kg loading dose of MgSO₄ diluted in 100ml of normal saline IV over 10 min, or 10 ml/min, followed by a maintenance dose of 10 mg/kg/hr diluted in 150ml normal saline for 90min, or 100 ml/hr. Patients in group B received the same amount of plain normal saline. These doses were calculated keeping in view the IV dosage regimens employed in a previous study; 30-50 mg/kg loading dose (administered slowly over >10 minutes to avoid any cardiovascular side effects), followed by a continuous infusion (maintenance) at 6-20 mg/kg/hr until the end of the surgery.¹⁹

The anaesthetist recorded if the patient experienced any side-effects, like nausea, vomiting, shivering or delayed recovery (no response to stimulation for >60 minutes). Hypotension (mean arterial pressure [MAP] <65) and bradycardia (>20% decrease in baseline HR) was treated according to standard protocol. In case of arrhythmia, it was treated appropriately and the patient was excluded from the study.

Before the end of the procedure, 1 g paracetamol and 4 mg ondansetron were given to all the patients. Neuromuscular blockade was reversed with neostigmine/glycopyrrolate 0.5/2.5 mg prior to extubation. No additional medication was given that could affect analgesic medication.

After transferring the patient to PACU with standard monitoring, the presence and severity of pain was assessed by the registered nurse (RN) attending the patient, using NPRS and at 15 min, 1 h, 2 h and at the time of discharge from PACU. The RN was not involved in intraoperative care of the patient, and was blinded to the patient's group. Patients with complaint of pain >8 on NPRS were given 2 mg morphine IV every 10min until the score was <7, following which, 1 mg morphine was given every 10 min until the score reached <3.

Once the patient was fully conscious and oriented, PCA morphine 1 mg/ml was attached (B. Braun Perfusor® Space® USA syringe pump; 50 ml; bolus dose: 1 ml; lockout time: 5 min; no background infusion). The time of first use of PCA was recorded in all cases.

Furthermore, the presence of side effects was observed throughout the PACU stay, and appropriate medication was given as required.

Total morphine consumption was recorded by noting the residual volume in the PCA 24 hours after the surgery plus rescue analgesia, if requested by the patient in the PACU. Pain scores were also recorded after discharge to the ward at 12h and 24h by a resident from the acute pain management team who was blinded to the patient's group.

All data was maintained on a predesigned proforma. Data was analysed using SPSS 23. At the outset of the study, the sample size was calculated on the basis of literature²⁰ having total postoperative IV morphine consumption of 0.59 ± 0.04 mg and 0.7 ± 0.08 mg/kg in the MgSO₄ and control groups, respectively. The estimation was done with 95% power and two-sided confidence interval (CI) of 95%. The sample was inflated by 10% to compensate for any dropouts. Categorical data was presented as frequencies and percentages, and analysed using chi-square or Fisher's exact test, as appropriate. Continuous variables were presented as means \pm standard deviation, and compared using independent t-test. Comparison of pain scores was done using Mann-Whitney U test after establishing data non-normality through Shapiro-Wilk test. Data analysis was done by a researcher blinded to the randomisation. $P \leq 0.05$ was considered statistically significant.

Results

Of the 24 patients enrolled, the study was completed by 20 (83.33%). There were 10(50%) patients in group A; 8 (40%) males and 2(20%) females with mean age 24.8 ± 14.14 years and mean surgery time 130.5 ± 47.86 minutes. There were 10 (50%) patients in group B; 8 (40%) males and 2 (20%) females with mean age 23.2 ± 7.4 years and mean surgery time 117 ± 23.85 minutes ($p > 0.05$) (Table 1).

Total morphine used over 24 hours in group A was 16 ± 3.1 mg compared to 29.6 ± 11.2 mg in group B ($p < 0.05$). The time for first use of PCA after arriving in PACU was significantly delayed in group A (72.2 ± 24.95 minutes) compared to that in group B (25 ± 26.68 minutes) ($p < 0.05$) (Table 2).

Pain scores were significantly higher in the group B at 15min compared to group A ($p < 0.05$), but not at the rest of the time points ($p > 0.05$) (Table 3).

Table-1: Descriptive data.

| Parameters | Group A n (%) | Group B n (%) | p-value |
|-----------------------------|-------------------|------------------|---------|
| Mean Age (years) | 24.8 \pm 14.14 | 23.2 \pm 7.4 | 0.75 |
| ASA Grade-II | 10 (50) | 10 (50) | - |
| Gender | | | |
| Male | 8 (40) | 8 (40) | 1.0 |
| Female | 2 (10) | 2 (10) | |
| Amputation Side | | | |
| Right | 4 (20) | 7 (35) | 0.37 |
| Left | 6 (30) | 3 (15) | |
| Amputation Limb | | | |
| Upper | 3 (15) | 2 (10) | 1.0 |
| Lower | 7 (35) | 8 (40) | |
| Mean Surgery Duration (min) | 130.5 \pm 47.86 | 117 \pm 23.85 | 0.43 |

ASA: American Society of Anaesthesiologists.

Table-2: Snaalgesia requirement.

| Parameters | Group A n (%) | Group B n (%) | p-value |
|---|-------------------|------------------|---------|
| Request for rescue analgesia | | | |
| Yes | 1 (5) | 3 (15) | 0.26 |
| No | 9 (45) | 7 (35) | |
| Mean Time for first PCA use (min after arrival in the PACU) | 72.2 \pm 24.95* | 25 \pm 26.68* | 0.001 |
| Mean Total dose of morphine consumed in 24 hours (mg) | 16 \pm 3.1* | 29.6 \pm 11.2* | 0.002 |

PCA: Patient-controlled analgesia, PACU: Post-anaesthesia care unit, * Statistically significant

Table-3: Pain scores at various time points.

| | Mean Pain Score (NRS) | | | | | |
|---------|-----------------------|--------|---------|------------------------|----------|----------|
| | 15 min | 1 hour | 2 hours | Discharge from PACU | 12 hours | 24 hours |
| Group A | 0.6 | 1.6 | 1.8 | 0.5 | 1.5 | 1 |
| Group B | 3.5 | 3.2 | 2.3 | 1.3 | 1.4 | 1.5 |
| p-value | 0.006* | 0.09 | 0.39 | 0.46 | 0.93 | 0.15 |

NRS: Numeric rating scale, PACU: Post-anaesthesia care unit. * Statistically significant.

None of the patients experienced hypotension, bradycardia or any other side effects requiring any intervention.

Discussion

The current study investigated the analgesic effects of IV MgSO₄ in patients undergoing limb amputations compared to a control group, and found extended time to postoperative rescue analgesia requests, reduced total morphine consumption in 24 hours post-surgery and lower immediate postoperative pain scores.

Pain following limb amputations is thought to be mediated by the NMDA receptor, which is one of the primary excitatory neurotransmitters that carry pain signals from the dorsal horn to the brain.^{21,22} The activation of this receptor causes neuronal sensitisation, leading to hyperalgesia, neuropathic pain and reduced opioid

receptor sensitivity. This eventually results in the patient requiring opioids in more doses than normal to achieve a certain analgesic effect.²³

Regional anaesthesia and systemic opioids remain the mainstay for managing pain after amputations. However, it is imperative to mind the possible side effects that may be caused by excessive doses of opioids, such as sedation, respiratory depression, physical dependence, tolerance and even delayed discharge from hospital. Moreover, pain in these patients, if not treated as a key priority and optimised inadequately, will go on to cause phantom pain, and eventually poor functional recovery and psychological stress to the patient.

The precise mechanism by which magnesium acts as an analgesic is still ambiguous, but it is suggested that NMDA receptor antagonism and calcium channel blockade are involved.^{7,24,25}

Numerous researchers²⁶⁻²⁸ have investigated the effect of MgSO₄ in various orthopaedic surgeries, but, to our knowledge, the current study is the first involving limb amputations. Among the more recent ones, 2 studies found significant reduction in pain scores and prolonged time to first analgesia request in patients undergoing arthroscopic knee surgeries under GA and epidural anaesthesia (EA), respectively.^{26,27} In addition, El Shal et al. also reported significantly reduced tourniquet pain during surgery extended.²⁷ Shin HJ et al. had similar results in total knee arthroplasty (TKA) under lumbar subarachnoid block, whereby the patients in the magnesium group had significantly lower pain scores in both TKAs as well as lower amount of postoperative rescue analgesics and opioids. Moreover, these patients also received continuous femoral nerve block in addition to PCA as part of their postoperative analgesia plan.²⁸ The current results are mostly in line the published data cited above.

The disparity in the findings of Ghaffaripour S et al.²⁰ could be attributed to a difference in the cohort of patients being observed. Patients undergoing laminectomy for disc herniation predominantly suffer from radicular pain compared to the pain from tissue trauma and direct neural injury caused by limb amputations.

The strength of the current study is the triple-blind methodology it used. On top of that, it excluded patients with pre-existing pain in the affected limb, hence minimising discrepancy in the findings.

Our study had limitations as it did not measure pre- and post-operative MgSO₄ levels, and, hence, did not assess the association between magnesium concentration and pain scores. Further, MgSO₄ is a known central nervous system

(CNS) depressant in high doses, and although none of the patients experienced side effects requiring intervention while being monitored routinely for postoperative sedation in PACU, the study did not record the sedation scores for analysis. Lastly, the generalisability of the findings may be limited since the entire study population consisted of patients with cancer, which in itself could alter the perception of pain.

Though the sample size was calculated with 95% power, a study with a larger and more diverse population is recommended for making definitive inference about the intervention.

Conclusion

Intraoperative use of intravenous MgSO₄ in limb amputations significantly reduced immediate postoperative pain score, delayed the time to first use of PCA, and lowered postoperative morphine requirement over 24 hours. It could, therefore, prove to be a useful adjuvant in multimodal analgesic plan in such surgeries.

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Conflict of Interest: None.

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Author Contribution:

RSQ: Study concept, design, data analysis, interpretation, drafting.

TA: Study concept, design, questionnaire design, data collection.

AWK: Supervision.

MBS: Data analysis and interpretation.