J Nephropharmacol. 2022; 11(2): e10455.

http://www.jnephropharmacology.com DOI: 10.34172/npj.2022.10455

Journal of Nephropharmacology

A comparison of magnesium sulfate plus morphine with morphine alone for acute pain reduction in long-bone fractures; a double blind randomized clinical trial

Meisam Moezzi, Hassan Motamed, Javad Mozafari, Majid Fattah, Ali Delirrooyfard*

Department of Emergency Medicine, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

ARTICLE INFO

Article Type:
Original

Article History:
Received: 28 December 2021
Accepted: 27 February 2022
Published online: 28 June 2022

Keywords:
Bone fractures
Analgesia
Pain management
Magnesium sulfate
Emergency medicine

ABSTRACT

Introduction: Acute pain is a common symptom in patients with bone fractures referring to the emergency department (ED).

Objectives: The present study aimed at evaluating the efficacy of intravenous (IV) magnesium sulfate in controlling acute pain of long-bone fractures in EDs.

Patients and Methods: The present double-blind, randomized clinical trial was conducted on patients with isolated limb fractures referred to Golestan hospital of Ahvaz from 2019 to 2020. Patients in the intervention group were injected with 0.1 mg/kg morphine plus 30 mg/kg magnesium sulfate and 0.1 mg/kg morphine alone in the morphine group. The patient's pain scores were measured at 0, 15, 30, 45 and 60 minutes after injection. The patients' condition was monitored every 10 minutes, including respiratory and pulse rate, blood pressure, and knee reflex.

Results: The present study was conducted on 64 patients with long-bone fractures allocated to two groups of IV morphine plus magnesium sulfate and IV morphine alone (each of 32). The hemodynamic factors and mean body temperature did not significantly change after intervention and had a similar level in both groups. Before the intervention, the mean score of pain was measured in the morphine and magnesium sulfate plus morphine groups using a visual analogue scale. Results which were 8.87±0.83 and 8.93±0.94, respectively, showing no significant differences ($P=0.69$). After 60 minutes, the pain score reduced considerably in both groups.

Conclusion: In the study, magnesium sulfate plus morphine could better reduce pain than morphine alone without influencing the respiratory rate.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (IRCT20190617043913N1; https://en.irct.ir/trial/40370, ethical code# IR.AJUMS.REC.1398.143).

Implication for health policy/practice/research/medical education:
Acute pain is a common symptom in patients with bone fractures referring to the emergency department. The present study was conducted on patients with isolated limb fractures. Magnesium sulfate plus morphine could better reduce pain than morphine alone without influencing the respiratory rate.

Please cite this paper as: Moezzi M, Motamed M, Mozafari J, Fattah M, Delirrooyfard A. A comparison of magnesium sulfate plus morphine with morphine alone for acute pain reduction in long-bone fractures; a double blind randomized clinical trial. J Nephropharmacol. 2022;11(2):e10455. DOI: 10.34172/npj.2021.10455.

Original

Introduction

Acute pain is commonly seen in patients with bone fractures, referring to the emergency departments (EDs) (1). Reduction of pain is a priority for emergency physicians in ED. Pain management is often associated with delayed anesthesia, pain control, and patient satisfaction (2, 3). Medication is the main and common factor in pain management (4); however, prescriptions have significant side effects in the short and long term. For several years, the drug, called morphine sulfate, had been administered as a pain reliever. However, current guidelines support the intravenous (IV) administration of morphine sulfate for acute and chronic pain management (5). Morphine sulfate use is limited by several factors, including fear of side effects, physical disorder, and fear of addiction (6). Evidence shows that morphine sulfate is not considered an effective agent in patients admitted to ED (7). It was reported that within 15 minutes of injection, only 50% of patients had pain control (8). Combination drug therapy is proposed to improve pain control and reduce morphine consumption (9). Magnesium, an N-methyl-D-aspartate (NMDA) antagonist receptor, is an important mineral of

***Corresponding author**: Ali Delirrooyfard, Email: adelir2891@gmail.com, delirrooyfard-a@ajums.ac.ir

bones used to treat and prevent pain (10). Magnesium is used to treat eclampsia and preeclampsia, hypokalemia, asthma crisis, to prevent preterm birth, control acute postoperative pain, and to protect the heart after ischemia, and also hemodynamic stability during intubation. It has a synergistic effect with morphine (11,12). Kidney disorder is more prevalent in hypomagnesemic patients, magnesium supplementation protects against some kidney diseases. For example, magnesium sulfate administration before ischemia or following reperfusion significantly reduced renal Ischemia/reperfusion (I/R) injury in a diabetic rat model (13).

Objectives

Magnesium sulfate is a naturally occurring mineral prevalent product, which its efficacy was evaluated by several studies on anesthesia (14). Hence, the present study aimed at evaluating the efficacy of magnesium sulfate plus morphine compared with morphine alone for acute pain management of long-bone fractures in ED.

Patients and Methods

Trial design

The present double-blind, randomized clinical trial was conducted on patients with isolated limb fractures (those with long-bone fractures) referred to Golestan hospital in Ahvaz.

Participants

Inclusion criteria of the study were age 18-65 years and having a bone fracture. Exclusion criteria were a history of allergy to drugs or benzodiazepine, cardiac arrhythmia, prehospital use of drugs, chronic respiratory failure, drug treatment, pregnancy, a history of chronic pain, concurrent trauma that led to shock, multiple trauma simultaneously with numerous fractures, evidence of intracranial hemorrhage or free pelvic, abdominal fluid, and having a disease that is a contraindication for magnesium sulfate injection (eg, severe renal failure, Addison's disease, or hepatitis).

Interventions

At the time of admission, the patients' pain level was scored using a visual analog scale (VAS) from 0 to 10 (15). Patients in the magnesium sulfate plus morphine group were injected with 0.1 mg/kg morphine and 30 mg/kg magnesium sulfate. In the morphine group, patients were injected with 0.1 mg/kg morphine alone. Doses were chosen based on previous studies as well as their efficacy and safety. Patient pain scores were measured at 0, 15, 30, 45, and 60 minutes of injection.

Outcomes

During the study, the patients' condition was monitored every 10 minutes by a pulse oximeter, including respiratory and pulse rate, blood pressure, and knee reflex. Oxygen was administered if the pulse oximeter showed less than 95%. Normal saline was injected for systolic blood pressure less than 100 mmHg, pulse oximeter less than 95% after oxygen uptake, and systolic blood pressure less than 100 mmHg after saline bolus administration. Patients were excluded from the study if they had any unwanted side effects. After 60 minutes, if the VAS score was above 3, the rescue dose of fentanyl was prescribed at 1.5 µg/kg.

Sample size

According to the Cohen d formula and literature review, the minimum sample size was 30 for each group (16).

Randomization

The random allocation software performed simple randomization with the block method, and patients were randomly allocated to two equal groups of morphine and morphine/magnesium sulfate.

Blinding

The present double-blind study was conducted to eliminate errors caused by patient or physician awareness, assessment of drug delivery results, and the possible impact on the investigation outcomes.

Statistical methods

Data were analyzed using SPSS software. The normality of data was examined using the Kolmogorov-Smirnov test, confirming the normality of parametric methods, such as the student test; if not normal, the Mann-Whitney U test was used. The chi-square test was used to analyze data with a nominal scale, and the Fisher's exact test was employed if more than 20% of the expected counts were less than 5 (Cochran). Linear models were conducted to evaluate the results, and the significance level of the tests was less than 5%.

Results

The study was carried out on 64 patients with long-bone fractures (the morphine plus magnesium sulfate and morphine groups, each of 32) (Figure 1). The mean age of the patients was 29.76 ± 13.18 years; 48 (75%) were males (Table 1). The hemodynamic factors (i e, means of heart rate, systolic and diastolic blood pressure and number of breaths) and mean body temperature did not significantly change after intervention in both groups (Figures 2-7). Before the intervention, VAS scores in the morphine alone and magnesium sulfate plus morphine groups were 8.87 ± 0.83 and 8.93 ± 0.94, respectively, which did not significantly differ ($P=0.69$). After 60 minutes, pain score significantly reduced in both groups (Figure 2). However, 15 and 30 minutes after the injection, VAS scores showed significant differences between the groups (Table 2). Moreover, 45 minutes after the intervention, the pain score was not significantly different between the groups (Table 2). The frequency of side effects in both groups was

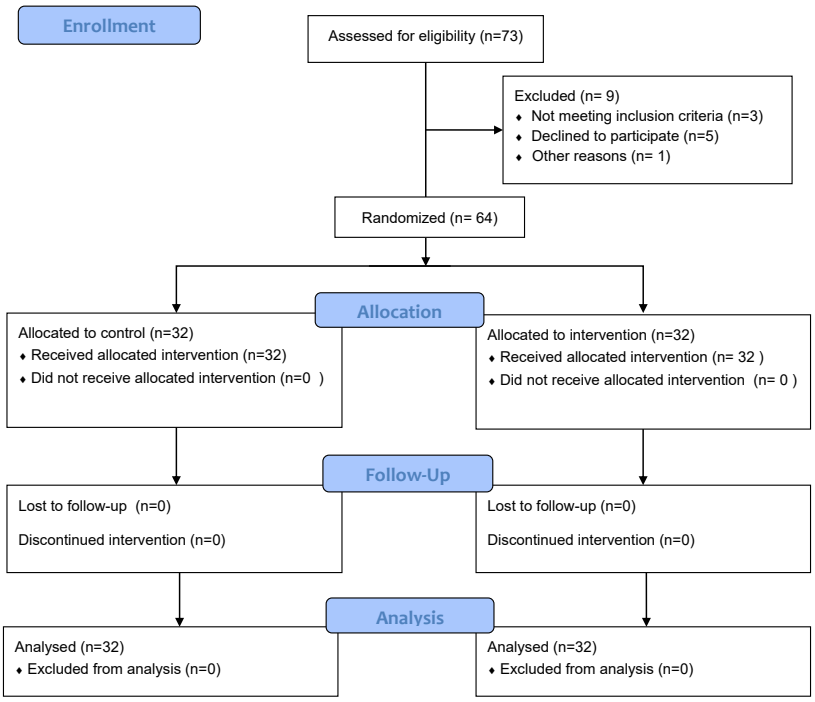

Figure 1. The Flowchart of the study.

not statistically significant. A few patients needed rescue medication; however, there was no significant difference between the two groups (Table 2).

Discussion

Magnesium is an important mineral of the body, especially for nerves and muscles. Magnesium sulfate is administered to control certain types of seizures and meet the body's need for magnesium. Our findings showed that the pain score was significantly lower in the magnesium sulfate plus morphine group than the morphine group at 15 and 30 minutes of intervention. Likewise, there were no statistically significant differences at 45 and 60 minutes of intervention. Regarding other variables like hemodynamic changes, the incidence of complications was not significantly different between the two groups after 60 minutes. Jebali et al, showed that magnesium sulfate should be considered an effective and safe adjuvant for lidocaine in prehospital femoral nerve block (17). Magnesium sulfate significantly reduced pain in the first minutes compared to morphine alone. There was no significant difference in the incidence of side effects between the groups, and magnesium sulfate can be used as a suitable adjuvant in combination with morphine to reduce pain. Results of a previous meta-analysis showed that perioperative IV magnesium reduces opioid consumption, and to a lesser extent, pain scores, in the first 24 hours postoperatively, without any reported serious (18). Acosta-Olivo et al, also showed that 1 mg of magnesium sulfate and 1.5 mg of bupivacaine helped reduce distal radius bone fracture (19). In another study,

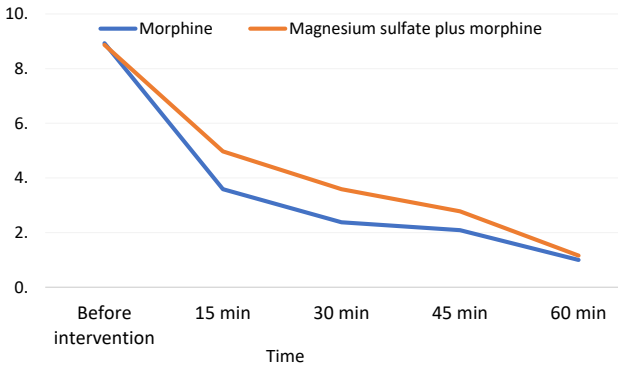

Figure 2. Pain score trend during the study follow-up.

Table 1. Patient's characteristics

Variable	Magnesium sulfate plus morphine (n = 32)	Morphine (n = 32)	*P* value
Age (y), mean ± SD	29.41 ± 13.23	30.12 ± 13.33	0.89
Gender/Female, No. (%)	9 (28.1)	7 (21.9)	0.43
Limb fracture, No. (%)			
Upper	18 (35.4)	20 (27.4)	0.61
Lower	14 (64.6)	12 (72.6)	

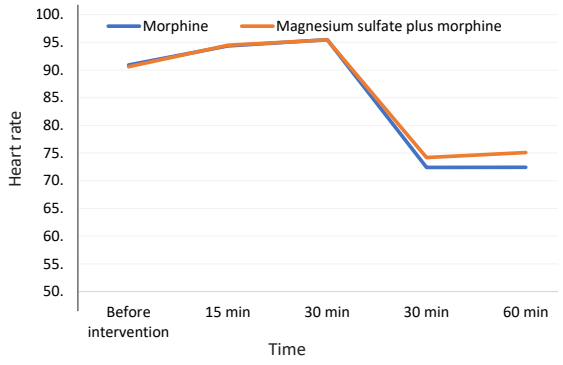

Figure 3. The trend in heart rate during the study follow-up.

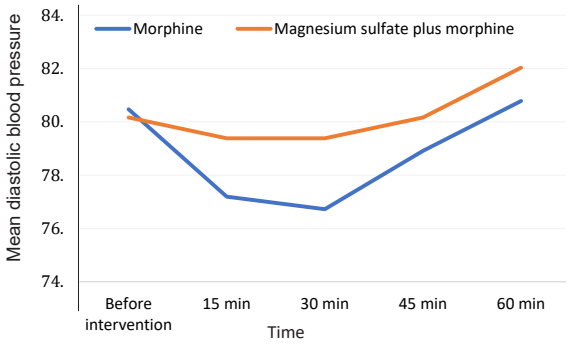

Figure 5. The trend in mean diastolic blood pressure during the study follow-up.

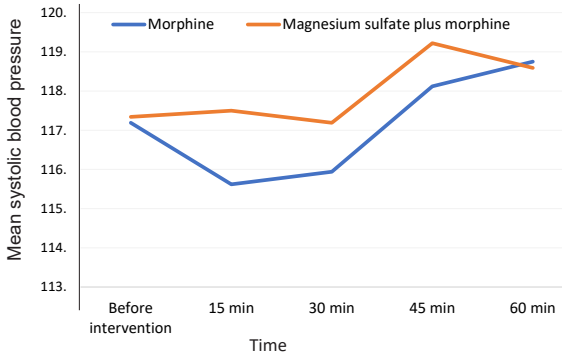

Figure 4. The trend in mean systolic blood pressure during the study follow-up.

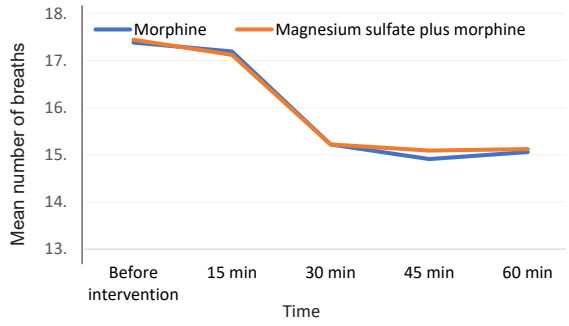

Figure 6. The trend in mean number of breaths during the study follow-up.

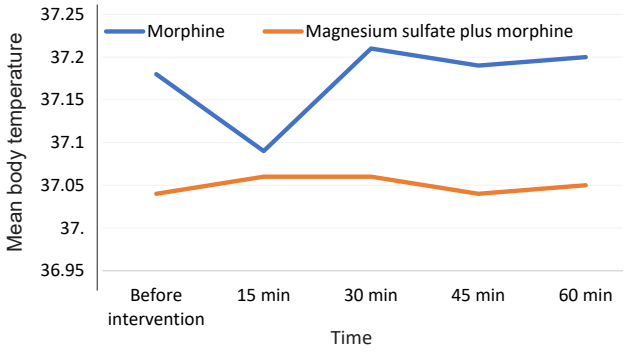

Figure 7. The trend in mean body temperature during the study follow-up.

the effects of magnesium sulfate administration on the reduction of chronic postoperative pain in rats were investigated. Results showed that a single magnesium sulfate injection mitigated skin/muscle incision and retraction (SMIR)-induced mechanical hyperalgesia possibly by modulating Grin1 expression. Preoperative magnesium sulfate administration could prove to be a simple and safe chronic postsurgical pain treatment (20). The findings of the study were in line with those of the present research.

Conclusion

In the present study, magnesium sulfate in combination with morphine could better reduce pain than morphine alone without influencing the respiratory rate. It is suggested that the interaction mechanism of magnesium sulfate and morphine is independent of each other as magnesium sulfate also helps with ketamine and local anesthetics. Magnesium sulfate led to a reduction in arterial pressure, heart rate and blood loss. Magnesium sulfate affects the activity of the kidneys and causes

Table 2. Comparison of drug efficacy between the study groups

Variable		Magnesium sulfate plus morphine (n=32)	Morphine (n=32)	*P* value
Pain score	Before intervention	8.93 ± 0.94	8.87 ± 0.83	0.69
	15 min	3.59 ± 1.4	4.97± 1.09	<0.001
	30 min	2.38 ± 0.7	3.59 ± 2.1	<0.001
	45 min	2.09 ± 0.85	2.78 ± 2.1	0.19
	60 min	1.0 ± 0.95	1.16 ± 0.88	<0.001
Rescue medication needed, N (%)	Yes	3 (9.4)	5 (5.6)	0.74
	No	29 (90.6)	27 (84.4)	
Side effects, N (%)	Nausea	15 (46.9)	14 (43.8)	0.80
	Vomiting	12 (37.5)	11 (34.4)	0.79
	Drowsiness	2 (6.2)	0 (0)	0.49

hypotension, so it should be administered with caution.

Limitations of the study

The present study had some limitations; for instance, the patients were not followed up for a long time to determine adverse effects. The research design method did not allow us to repeat the drug administration. Therefore, we examined the effects of repeated drug administration on pain relief.

Authors' contribution

MM, MF and ADF were the principal investigators of the study. HM, JM, MF and MM were included in preparing the concept and design. MM and ADF revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research was conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences approved this study. The institutional ethical committee at Ahvaz Jundishapur University of Medical Sciences accepted all study protocols (IR.AJUMS.REC.1398.143). Accordingly, written informed consent was taken from all participants before any intervention. This study was part of the emergency medicine residential thesis of Majid Fattah at this university. The trial protocol was approved by the Iranian Registry of Clinical Trials (#IRCT201.906.17043913N1; https://en.irct.ir/trial/40370).

Funding/Support

This project was funded by Ahvaz Jundishapur University of Medical Sciences (Grant # U-98032).

References

1. Woolf CJ. What is this thing called pain? J Clin Invest. 2010;120:3742-4. doi: 10.1172/JCI45178.
2. Mitchell SAT, Majuta LA, Mantyh PW. New Insights in Understanding and Treating Bone Fracture Pain. Curr Osteoporos Rep. 2018;16:325-332. doi: 10.1007/s11914.018.0446-8.
3. Majuta LA, Longo G, Fealk MN, McCaffrey G, Mantyh PW. Orthopedic surgery and bone fracture pain are both significantly attenuated by sustained blockade of nerve growth factor. Pain. 2015;156:157-165. doi: 10.1016/j.pain.000.000.0000000017.
4. Bach AM, Forman A, Seibaek L. Postoperative Pain Management: A Bedside Perspective. Pain Manag Nurs. 2018;19:608-618. doi: 10.1016/j.pmn.2018.05.005.
5. Howard PK, Gisness CM. Is Subdissociative Ketamine As Safe and Effective As Morphine for Pain Management in the Emergency Department? Adv Emerg Nurs J. 2017;39:81-85. doi: 10.1097/TME.000.000.0000000145.
6. Gehling M, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. Anaesthesia. 2009;64:643-51. doi: 10.1111/j.1365-2044.2008.05817.x.
7. iscusi ER, Gambling DR, Hughes TL, Manvelian GZ. Pharmacokinetics of extended-release epidural morphine sulfate: pooled analysis of six clinical studies. Am J Health Syst Pharm. 2009;66:1020-30. doi: 10.2146/ajhp080154.
8. Rasmussen NA, Farr LA. Effects of morphine and time of day on pain and beta-endorphin. Biol Res Nurs. 2003;5:105-16. doi: 10.1177/109.980.0403257166.
9. Arkinstall WW, Goughnour BR, White JA, Stewart JH. Control of severe pain with sustained-release morphine tablets v. oral morphine solution. CMAJ. 1989;140:653-7, 661.
10. Gröber U, Schmidt J, Kisters K. Magnesium in Prevention and Therapy. Nutrients. 2015;7:8199-226. doi: 10.3390/nu7095388.
11. Shin HJ, Na HS, Do SH. Magnesium and Pain. Nutrients.

2020;12:2184. doi: 10.3390/nu12082184.
12. Paula-Garcia WN, Oliveira-Paula GH, de Boer HD, Garcia LV. Lidocaine combined with magnesium sulfate preserved hemodynamic stability during general anesthesia without prolonging neuromuscular blockade: a randomized, double-blind, controlled trial. BMC Anesthesiol. 2021;21:91. doi: 10.1186/s12871.021.01311-y.
13. Akan M, Ozbilgin S, Boztas N, Celik A, Ozkardesler S, Ergur BU, et al. Effect of magnesium sulfate on renal ischemia-reperfusion injury in streptozotocin-induced diabetic rats. Eur Rev Med Pharmacol Sci. 2016; 20:1642-55. PMID: 27160141.
14. Albrecht E, Kirkham KR, Liu SS, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. Anaesthesia. 2013;68:79-90. doi: 10.1111/j.1365-2044.2012.07335.x.
15. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14:798-804. doi: 10.1111/j.1365-2702.2005.01121.x.
16. Cohen BH, Lea RB. Essentials of Statistics for the Social and Behavioral Sciences. John Wiley & Sons; 2004.
17. Jebali C, Kahloul M, Hassine N, Jaouadi MA, Ferhi F, Naija W et al. Magnesium Sulfate as Adjuvant in Prehospital Femoral Nerve Block for a Patient with Diaphysial Femoral Fracture: A Randomized Controlled Trial. Pain Res Manag. 2018;2018:2926404. doi: 10.1155/2018/2926404.
18. Albrecht E, Kirkham KR, Liu SS, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. Anaesthesia. 2013;68:79-90. doi: 10.1111/j.1365-2044.2012.07335.x.
19. Acosta-Olivo C, Tamez-Mata Y, Murillo-Rodríguez J, Peña-Martínez V, Villa-Chavarría J. Infiltración intraarticular con sulfato de magnesio y bupivacaína en fracturas de radio distal. Estudio piloto [Intrarticular infiltration of bupivacaine and magnesium sulfate in distal radius fractures. A pilot study]. Acta Ortop Mex. 2017;31:217-221.
20. Kido K, Katagiri N, Kawana H, Sugino S, Konno D, Suzuki J, et al. Effects of magnesium sulfate administration in attenuating chronic postsurgical pain in rats. Biochem Biophys Res Commun. 2021;534:395-400. doi: 10.1016/j.bbrc.2020.11.069.