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Intravenous magnesium sulfate *vs.* morphine sulfate in relieving renal colic: A randomized clinical trial

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ABSTRACT

Objective: Renal colic emerging from renal stone is virtually the most severe pain which is experienced. Intravenous infusion of morphine sulfate is known as a usual treatment for the disease. This study was designed to compare the efficacy of magnesium sulfate *vs* morphine sulfate in renal colic relief as for analgesic effect as well as lack of morphine sulfate side effects when using magnesium sulfate.
Methods: We conducted a double-blind randomized clinical trial in renal colic patients who had referred to the emergency department of Shahid Sadoughi Hospital in Yazd, Iran. A total of 80 eligible patients were selected and randomly assigned into two groups; patients in the case group received 50 mg/kg intravenous magnesium sulfate, and those in the control group 0.1 mg/kg intravenous morphine. The primary outcome was the pain score measured on a numerical rating scale at 0, 10 and 20 minutesmin after infusion. Data were analyzed using $SPSS_{16}$.
Results: The two groups were similar in terms of demographic features and pain intensity at the time of referral ($P < .0001$). Ten minutes after drug administration, the pain mean score in the morphine group leveled at 4.88, and in the magnesium group 5.70, which proved to be greater in the morphine group (P- = 0.06). However, the pain mean score turned out to be 3.65 in the morphine group and 3.20 in the magnesium group thus significantly indifferent ($P = .48$).
Conclusions: In this study, we concluded that administration of intravenous 50 mg/kg magnesium sulfate could be as effective as morphine in reducing renal colic without any further complications.

1. Introduction

Urinary and kidney stones are one of the most common clinical problems of urinary system which are manifested by sever renal colic pain arising from obstruction, inflammation and spasm of smooth muscles. The pattern of renal colic is related to the location of stone and obstruction, which can be detected in lumbar, flank and hypogastric region as well as the testes [1]. Renal colic is a serious painful condition that we frequently encounter in emergency departments and it generally recurs [2]. A wide variety of medications are available to treat the pain associated with acute renal colic; opioids and non-steroidal anti-inflammatories drugs (NSAIDs) are the main drugs used in treatment of renal colic [3-7].

Morphine Sulfate (MS) is one of the usual treatment protocols being employed frequently in order to relieve pain in patients [4]; however, there are two important clinical problems attributed to it. Drug dependency is the main complication that becomes more critical when considering the high number of patients who visit the emergency departments seeking to reduce their pain [7-12]. Dependency to M.S. as the common treatment for renal colic pain demands enormous efforts to find new and suitable substitutions for MS so as to eliminate its drug dependency and side effects [5,6,11,13,14]. Side effects can be regarded as the second challenge that appear in the form of apnea, cardiac and respiratory arrest, pressure and heart rate drop, shock, vomiting *etc.* [6,7,10,11,14-16]. Some studies have maintained the Magnesium Sulfate (MgSO4) analgesic effect (compared with placebo or standard drug) in reducing migraine pain, improvement of major-lumbar as well as laparoscopic cholecystectomy post-operative pain [17-20]. Jokar's et al. study revealed the effectiveness of magnesium sulfate as an adjunct to the treatment of renal colic patients [3]. Analgesic effects of magnesium can be ascribed to the regulation of calcium influx into the cell [21] and blockage of *N*-methyl-D-aspirate (NMDA) receptors in the central nervous system [22]. Magnesium deficiency produces hyperalgesia that can be reversed by NMDA antagonists and is associated with acute painful conditions [23,24]. In addition, Magnesium can block pain signals in dorsal nucleus of the hypothalamus to central nervous system [25].

Furthermore, magnesium sulfate's relaxant effect on the smooth muscles of urethra can reduce the severity of pain in patients through reducing ob-

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struction resulting from stone; this is in contrast to morphine which triggers smooth muscle spasms.

Features such as analgesic effect, lack of drug dependency, and few side effects are among the main reasons to select Mg·S. as an appropriate alternative to M.S. Therefore, the aim of current study was to investigate the efficacy of Mg.S. on lowering renal colic in comparison with M.S. in patients with urinary tract stone.

2. Material and methods

2.1. Study design, setting, and selection of participant

This double-blind randomized clinical trial was conducted from November 2015 to September 2016 in Shahid Sadoughi and Shahid Rahnemoon Training Hospitals of Yazd, Iran. This study was approved by Ethics Committee of Yazd University of Medical Sciences (Code: 235385) and was registered in the Australian New Zealand Clinical Trial Registry at www.anzctr.org.au/(registrationcode:ACTRN12615001372572).

In this study, we hypothesized that intravenous morphine could replace magnesium sulfate in reducing renal colic pain without any complications.

The patients aged between 18 and 55 years with kidney stones who had been identified through sonographic approach and feeling renal pain (one sided flank pain to hypogastria, testis or major labia) were found to be eligible candidates for the study. The exclusion criteria consisted of any history of opium addiction, cardiac or renal failure, respiratory rate of lower than 12 per minute, systolic blood pressure lower than 100 mmHg, unwillingness to participate in the study, known hypersensitivity to morphine or Mg S, inability to understand the concept of VAS, use of painkillers during 4 h prior to admission, renal failure, pregnancy as well as lactation (Fig. 1).

Once the informed consent was obtained, the patients were randomly allocated to two different groups by block randomization, with the block sizes of 4, 6 and 8. Randomization was conducted using online software [26]. One group received magnesium sulfate and the other morphine sulfate both intravenously.

2.2. Sample size

Using repeated measures design sample size formula [27], we identified a sample of 40 participants per group as required for the study which proved 80% power and at least 3-unit reduction in pain score over MS, with a standard deviation of 4, and the correlation between observations on the same subject as 0.500, based on a two-sided type 1 error of 5%.

2.3. Study protocol

The baseline data and demographic characteristics of the patients and also data obtained during the study were recorded by the assistant emergency medicine (who was unaware of the treatment process) in predesigned checklists. Before injecting drug by the nurse in the emergency ward, one of the researchers assessed the initial pain severity using the numerical rating scale (NRS). The patients were randomly categorized into two groups: the control group each receiving 0.1 mg/kg IV morphine sulfate (maximum of 5 mgs) diluted with distilled water and brought to a volume of 10 cc that was slowly injected by 10 mL syringe over 60 s, plus 100 cc infusion of normal saline during 20 min, and the case group each receiving IV infusion of 50 mg/kg (maximum 2 g) Mg.S. plus 100 cc normal saline during 20 min, and simultaneous injection of 10 mL distilled water by 10 cc syringe (patients and assessing individual were all blinded to the study).

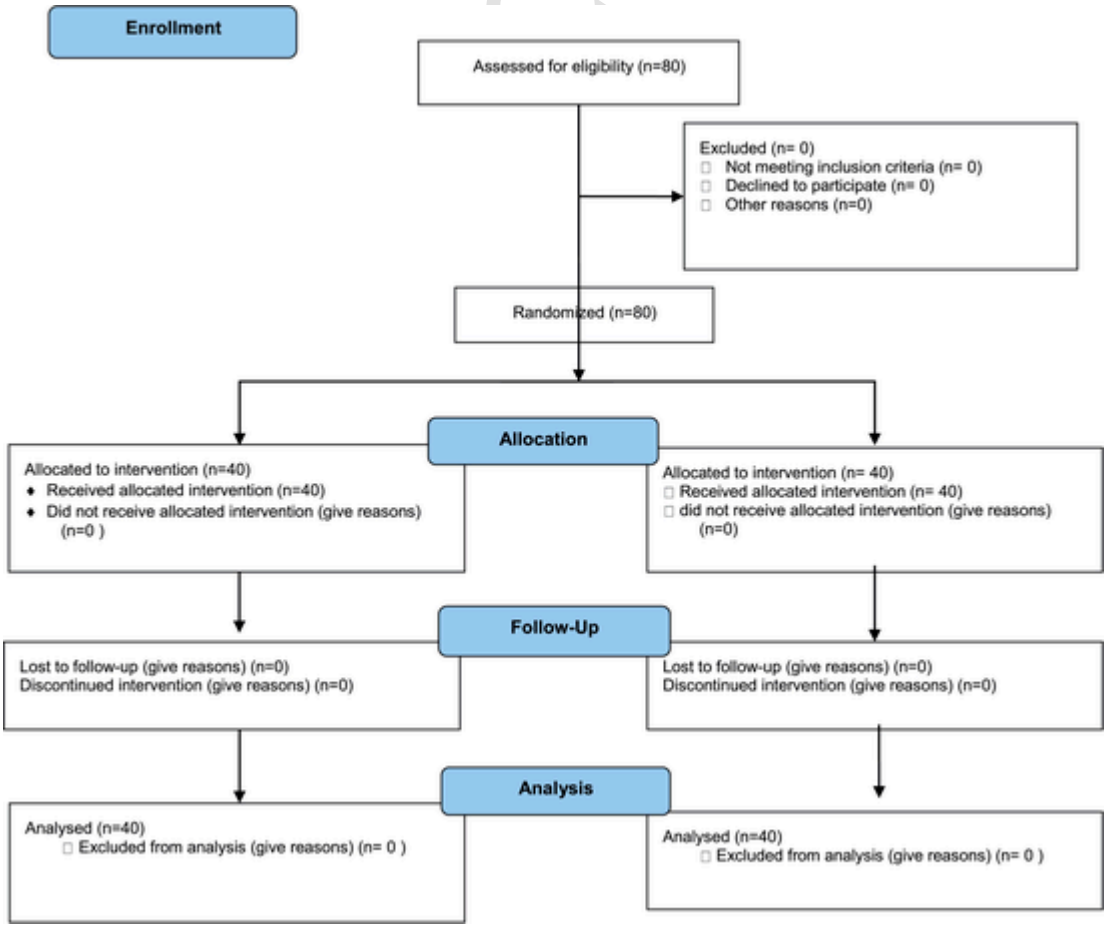

Fig. 1. The flow diagram of study.

The primary outcome was severity of patients' pain measured by numerical rating scale (NRS). The pain score was measured at 10 and 20 min after the drugs administration in each group. Three or more scores of pain reduction were considered as positive response to the drugs. In case the reduction of pain after 20 min was less than 3 scores, the response to drug was registered as negative and 30 mg ketorolac IV was administered to the patients for rescue analgesia. One hour after administration of the drugs and thus to assess the effects of recurrent symptoms, all the patients were monitored at the emergency room and the satisfaction level of all the recipients was recorded. The secondary outcome was related to side effects of M.S. and Mg.S. including vomiting, nausea, hypotension (systolic blood pressure less than 100 mmhg), apnea, flushing, dizziness and lightheadedness. The drug injection was discontinued in case any side effect was observed.

2.4. Data analysis

All the data collected were analyzed by SPSS v.16 (IBM, Chicago, Illinois, USA). Mean (SD) or frequency (percent) was used to describe the variables. A repeated-measures model was used to obtain the absolute reduction in pain scores between the 2 groups. Estimates of between-group mean differences were adjusted for baseline values. All reported *P*-values were two-sided and P-value less than 0.05 was considered as significant.

3. Results

3.1. Patient characteristics

Each group included 40 patients; 27 men and 13 women in the magnesium group, and 30 men and 10 women in the morphine group. The mean age of the participants in the magnesium and morphine groups turned out to be 34.65 (8.47) and 34.97 (9.71) respectively. Baseline characteristics were similar between the two groups (Table 1).

3.2. Primary outcome

Prior to intervention, the pain mean score in the morphine group was 7.88 (SD = 1.48) and in the magnesium group 7.93 (SD = 1.42). There was no significant difference between NRS scores of the two groups at the beginning of the study ($P = .88$). Mauchly's Test of Sphericity indicated assumption of sphericity being violated, $\chi 2\ (2) = 25.82$, $p < .0001$, and therefore, Greenhouse-Geisser correction was used. A repeated measures ANOVA with a Greenhouse-Geisser correction indicted NRS mean scores being statistically significant between the time points ($F\ (1.56, 121.41) = 188.65$, $P < .0001$).

Ten minutes after drug administration, the pain mean score in the morphine group reached 4.88 and in the magnesium group 5.70 hence showing lower in the morphine group; the difference was statistically significant although being at the borderline ($P = .06$), However, in 20 min, the pain score showed to be 3.65 and 3.20 in the morphine and magnesium groups respectively thus revealing no significant difference between the two groups ($P > .05$) (Table 2 and Fig. 2).

Table 1
Baseline demographic characteristics of study participants

Groups	Magnesium sulfate [a] (*N* = 40)	Morphine sulfate [a] (N = 40)
Age (year)	34.65(8.47)	34.97 (9.71)
Male	27 (67.5)	30 (75)
Female	13 (32.5)	10 (25)
Pain score	7.88 (1.48)	7.93 (1.42)

[a] Mean (SD) or frequency (percent).

Table 2
Comparison of the pain severity between two groups in baseline, 10, and 20 min after drug administration

Time	Magnesium sulfate	Morphine sulfate	P-value
0	7.93 (SD = 1.42) [a]	7.88 (SD = 1.48)	0.88
10	5.70 (SD = 1.62)	4.88 (SD = 2.18)	0.06
20	3.20 (SD = 2.48)	3.65 (SD = 3.11)	0.48

[a] Mean numerical rating score (SD) at baseline, after 10 and 20 min.

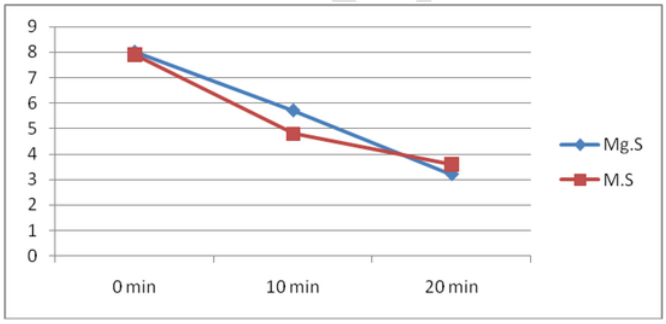

Fig. 2. Comparison of the pain severity between two groups in baseline, 10, and 20 min after drug administration.

It should be noted that 8 participants (20%) in the magnesium group and 10 (25%) in the morphine group failed to respond to treatment in 20 min, and were thus given 30 mg ketorolac IV as rescue therapy.

3.3. Secondary outcome

The most common side effects in the two groups were non-specific symptoms. Minor nausea, vomiting, flushing and dizziness events occurred in the two groups. Because none of the participants experienced life-threatening complications, treatment did not stop in any of the patients. There was also no significant difference between the study groups regarding patients' vital signs after administration of the medications ($P > .05$). In general, 11(27%) patients in magnesium group and 9 (22.5%) patients in morphine group showed several complications. There was no significant difference between the two groups regarding the occurrence of nausea, vomiting, flushing and dizziness ($P > .05$) Moreover, none of the patients suffered from hemodynamic abnormalities or respiratory depression. (Table 3).

4. Discussion

This study was performed to compare magnesium sulfate *vs.* morphine in acute pain management of patients with renal colic. In designing this study, we did not consider placebo to be compared with Mg.S because it is unethical refusing to give painkillers to a group of patients who have been hospitalized with severe and annoying renal colic. The main objective of this study was to compare the analgesic effect of Mg.S. *vs.* M.S. which is one of the main and, at the same time, most complicated medications for reducing renal colic pain. This appears to be in line with the findings of researchers like Olapour et al. who compared the effect of intravenous magnesium sul-

Table 3
Side effects of the two groups.

Groups	Non-specific symptoms	Nausea/ vomiting	Flushing	Dizziness
Magnesium sulfate	29 (72.5)	3 (7.5)	5 (12.5)	3 (7.5)
Morphine sulfate	31 (77.5)	5 (12.5)	0 (0)	4 (10)

fate *vs* intravenous sufentanil on the duration of analgesia and postoperative pain in patients with tibia fracture [28].

According to the results, administration of 50 mg/kg Mg.S. can remarkably reduce pain in patients with renal colic. The reduction of pain associated with Mg.S. is the same as that of M.S. After 20 min; however, Mg.S. infusion fails to be as effective as M.S. used in 10 min. In recent years, Magnesium sulfate has been the subject of many investigations used through different doses and methods for reducing pain [20,28-30]. Previous studies have examined the effect of magnesium on postoperative pain relief, but the results have not been similar. In 2017, Olapour et al. designed a study to compare effectiveness of infusion of 8 mg/kg magnesium sulfate with sufentanil in postoperative pain management as a pretreatment protocol before anesthetizing for tibia fracture surgery. Their findings revealed that magnesium fails to be effective in reducing pain; this could be due to employing much lower doses of the drug compared with our study [28] whereas Arman Taheri et al. in 2015 reported that a single dose of magnesium at a dose similar to that of our study for postoperative pain relief is effective [20].

Additionally, in 2011 Shashi Kiran et al. found that administering a dose of 50 mg/kg magnesium before inguinal surgery clearly reduces postoperative pain in patients without complications such as hypotension or bradycardia [30]. Moreover, Sedighinejad et al. (2014) reported that combination of Mg.S. and Sufentanil can act as an effective approach to reduce pain in patients with orthopedic surgery; the combination protocol showed fewer side effects [31].

Also Dabbagh et al. (2009) identified that Mg.S. can be used as a supplementary analgesic to reduce morphine consumption in postoperative period for patients undergoing orthopedic surgery [32]. A crucial reason for altering the results of Mg.S. is the stronger pain relief effect of nerve block or epidural analgesia in some studies; epidural analgesia can dominate the efficacy of Mg.S. As for Mg.S., this point is critical because it suggests that other factors can influence the Mg.S. efficiency.

Compared to M.S., the reason for delayed response to Mg.S. can be pertinent to the time of Mg.S. effect. As noted in some studies, the effect of magnesium on pain management has been assessed at least one hour after administration [20,28,30].

However, it is possible that the use of Mg.s. adjunct to other drugs such as ketorolac can improve the time of response because time has a critical role in the crowded emergency departments, an example being our hospitals, so drugs with lower time response prove to be more efficient.

To the best of our knowledge, as the single-drug treatment of renal colic this is the first study on Mg.S. efficiency. In 2017 Jokar et al. designed a study in which Mg.S. (15 mg/Kg of intravenous) was used as an adjunct drug to standard protocol (intravenous infusion of 0.1 mg/Kg M.S. plus 30 mg of Ketorolac) in patients suffering from renal colic. Finally, they reported that Mg.S. without disturbing hemodynamic values, can be effective in reducing pain while diminishing the need for M.S. [3]

Our results demonstrated that Mg.S. can induce the same side effects as M.S. and no peculiarity can thus be attributed to Mg.S. However, 50 mg/kg IV administration of Mg.S. has been reported to be safe for postoperative pain without any adverse effects [20].

In terms of renal colic, the combination of Mg.S. and other agents can be more beneficial than Mg.S. alone to alleviate the pain. Further investigations, however, are needed to test and confirm the hypothesis.

It should be noted that this study may have some limitations. First, a criterion which was excluded from our investigation was opium addiction and accordingly the effectiveness of Mg.S. did not touch upon the addicted patients so that it is unlikely to extrapolate the results to such patients; we suggest that future studies include opiate addicts for their study populations as well.

Second, given the increasing efficiency of Mg.S. over time (after 20 min), the effect of Mg.S. needs to be tested in longer periods of time and to identify whether it can be prescribed in combination with other non-opioid analgesics.

Third, in the present study, the aim was not only to assess Mg.S. as an analgesic agent but also to understand whether it could be taken as an alternative to M.S. (because of its side effects specially the possibility of morphine dependency in renal colic patients).

Therefore, we suggest that the effect of magnesium sulfate be assessed independently and only in comparison with placebo in reducing renal colic.

5. Conclusion

In this study, we concluded that intravenous administration of 50 mg/kg magnesium sulfate could be as effective as morphine in reducing renal colic without any further complications.

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Authors' contributions

All the authors contributed to designing the study and editing the manuscript, reading and approving the final manuscript.

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