J Med Sci 2024;44 (6):250-256
DOI: 10.4103/jmedsci.jmedsci_193_23

ORIGINAL ARTICLE

The Effect of Magnesium Sulfate plus Ketorolac versus Morphine plus Ketorolac on Pain Relief in Patients with Renal Colic: A Double-blind Randomized Clinical Trial

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Background: It seems that magnesium sulfate ($MgSO_4$) can be useful in reducing acute pain caused by stone passing through the ureter by reducing ureteral smooth muscle contractions. **Aim:** This study aimed to evaluate the effect of $MgSO_4$ plus ketorolac versus morphine plus ketorolac on pain relief in renal colic. **Methods:** The present double-blind randomized clinical trial was performed on 70 patients with renal colic divided into two groups. Patients in the first group received 30 mg intravenous ketorolac plus 5 mg intravenous morphine while patients in the second group received 30 mg/kg $MgSO_4$ plus 30 mg intravenous ketorolac. Then, patients' hemodynamic parameters and pain scores were evaluated before and 20, 40, and 60 min after the intervention. **Results:** Within 60 min of administration, systolic blood pressure was significantly reduced in the morphine plus ketorolac group ($P < 0.001$) while there was no significant change in the $MgSO_4$ plus ketorolac group in this regard ($P = 0.576$). In addition, the patients' mean pain scores were not significantly different between the two groups in any of the studied times ($P > 0.05$). **Conclusion:** Given that the addition of $MgSO_4$ to ketorolac, as compared with the addition of morphine (as a drug) to ketorolac, has been associated with fewer complications and greater stability of hemodynamic parameters, it can be stated that the use of $MgSO_4$ as an adjunct can be a good choice for further pain relief in patients with contraindications for drug administrations.

Key words: Renal colic, morphine, ketorolac, magnesium sulfate

INTRODUCTION

Renal colic is the most common clinical manifestation of urinary stones and one of the most prevalent urological emergencies such that its excruciating pain is one of the most prevailing reasons for patients' reference to emergency departments (EDs).[1,2] The mechanism of pain development in the urinary system is mainly due to inflammation and dilation. Pain relief by a proper selection of an effective medication with easy administration, lower complications, and rapid efficacy can be the best treatment action in the acute stage of the disease.[3]

Two main groups of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids are used as the main medications in the management of renal colic pain. The most regularly used opioid drug is morphine;[4] however, as morphine has the best effects on pain relief, a number of problems are associated with its administration due to its various complications, its unavailability in all medical centers, injection as its sole administration route, and its limited use in some diseases including asthma and pregnancy.[5,6] In addition, drug dependence as well as nausea, vomiting, constipation, drowsiness at higher doses, respiratory failure, and hypotension have led physicians to consider alternatives in this regard.[7] NSAIDs are other most prescribed medications that are less effective in the first 10 min but have similar effects to those of drugs in 20–30 min. The analgesic effects of these medications are due to the inhibition of prostaglandins, which in turn reduces vasodilation, increases their permeability, has a diuretic effect on kidneys, and increases the pressure of the renal pelvic and urinary collecting system.[6] Moreover, these medications reduce swelling, inflammation, and contractile

Received: July 20, 2023; Revised: October 03, 2023; Accepted: October 16, 2023; Published: October 16, 2024
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How to cite this article: Mardani H, Isfahani MN, Abootalebi A. The effect of magnesium sulfate plus ketorolac versus morphine plus ketorolac on pain relief in patients with renal colic: A double-blind randomized clinical trial. J Med Sci 2024;44:250-6.

activity of the ureteral muscles. The gastrointestinal and renal effects of NSAIDs have restricted their use.[6] However, their injectable generation such as ketorolac has minimized these complications, and researchers' attention has been drawn to the use of this medication in controlling and reducing pain.[8-10]

Furthermore, it seems that tocolytic agents such as magnesium sulfate ($MgSO_4$) can be useful in reducing pain caused by stone passing through the ureter by reducing ureteral smooth muscle contractions. By preventing the entry of calcium through the smooth muscle cell membrane, $MgSO_4$ can reduce the calcium needed for muscle contraction.[11] In addition, $MgSO_4$ can reduce muscle contractions by decreasing acetylcholine in the nerve terminals.[12] The role of $MgSO_4$ in reducing surgical pain has been confirmed in various studies.[13,14]

Many previous studies have evaluated the effect of morphine, ketorolac, and $MgSO_4$ on pain relief and have achieved different results. Some studies have not reported a significant difference between the effectiveness of these three medications[8,15,16] while another array of studies has considered a further reduction in pain following the administration of NSAIDs.[17] In addition, some studies have introduced $MgSO_4$ as an adjunct that is effective in reducing renal colic pain.[18] Therefore, considering the prevalence and significance of renal colic, various treatment options including opioids, NSAIDs, and N-methyl-D-aspartate (NMDA), the divergent effects and complications of these medications, and the limited number of studies addressing the combined effects of these medications in various medication categories, the present study aimed at evaluating the effect of $MgSO_4$ plus ketorolac versus morphine plus ketorolac on pain relief in patients with renal colic.

MATERIALS AND METHODS

The present study was a double-blind clinical trial. The study population included all patients with renal colic who were referred to the ED of Al-Zahra Hospital in Isfahan during 2021–2022. Seventy patients (35 cases in each group) were selected as the sample according to the sample size formula for between-group comparison, 95% confidence interval, 80% test power, and the standard deviation (SD) of pain scores in the two groups receiving morphine and $MgSO_4$[18] to be, respectively, equal to 0.56 and 0.49, and the error level of 0.48 (mean 1 − mean 2 = 3.08 −2.60).

Inclusion criteria comprised the age of over 16 years, definitive diagnosis of renal colic (with renal colic symptoms and the presence of stones confirmed by computed tomography), pain intensity of equal to or more than 7, lack of drug addiction, and patients' consent to participate in this study. In addition, the patients were not included in the study in case of a history of allergy to morphine or ketorolac, pregnancy or suspicion of pregnancy, breastfeeding, the use of painkillers in the past 6 h, a history of diseases including asthma, the history of kidney failure (creatinine 1.08 and above), heart and liver failure, the history of gastric ulcer and gastrointestinal bleeding, the cerebral hemorrhage or the possibility of its occurrence, the vascular and cerebral lesions, the use of angiotensin-converting enzyme inhibitor or anticoagulants, or the history of coagulation disorders. They were also excluded from the study if there was a change in the patient's level of consciousness or the occurrence of severe complications. As no case encountered the mentioned issues in this study, the study sample did not decrease [Figure 1].

The research followed the tents of the Declaration of Helsinki. After obtaining the code of ethics from the Medical Ethics Committee of Isfahan University of Medical Sciences (approved code: IR.MUI.MED.REC.1398.665), the clinical trial code (IRCT20160130026253N4), and the written consent from eligible patients, the eligible patients were selected using the convenience sampling method. Then, these patients were divided into two groups of 35 using the random allocation software. At the beginning of the study, patients' demographic information such as age, sex, and body mass index (BMI) as well as patients' clinical information such as pain score (based on the Visual Analog Scale from 0 to 10), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiration rate (RR), and oxygen saturation (SpO_2) percentage were evaluated and recorded.

Patients in the first group received 30 mg intravenous ketorolac plus 5 mg intravenous morphine while patients in the second group received 30 mg/kg $MgSO_4$ plus 30 mg intravenous ketorolac within 15 min.

To observe the conditions of a double-blind study, the two medication combinations were prepared in advance by the emergency medicine specialist and were placed in ready-made packages with codes A and B. Thus, the patient, the intervener, and the person recording the patients' clinical and basic information were not aware of the type of intervention.

In addition, patients' hemodynamic parameters including SBP, DBP, HR, RR, and SpO_2 as well as their pain scores were recorded once more 20, 40, and 60 min after the intervention.

If the patients' pain score did not decrease to <5 within 30 min after the intervention, an additional drug (morphine 0.1 mg/kg) was used. In the mentioned cases, the additional dose of analgesic was recorded as well. Moreover, possible complications such as dizziness, loss of consciousness, nausea, vomiting, decreased SpO_2, and hypotension were also recorded.

Finally, the collected data were entered into Statistical Package for Social Sciences (SPSS) software for windows®, version 25, (SPSS Inc., Chicago, IL, USA).. Data were represented as means ± SD or *n* (%). According to the result of

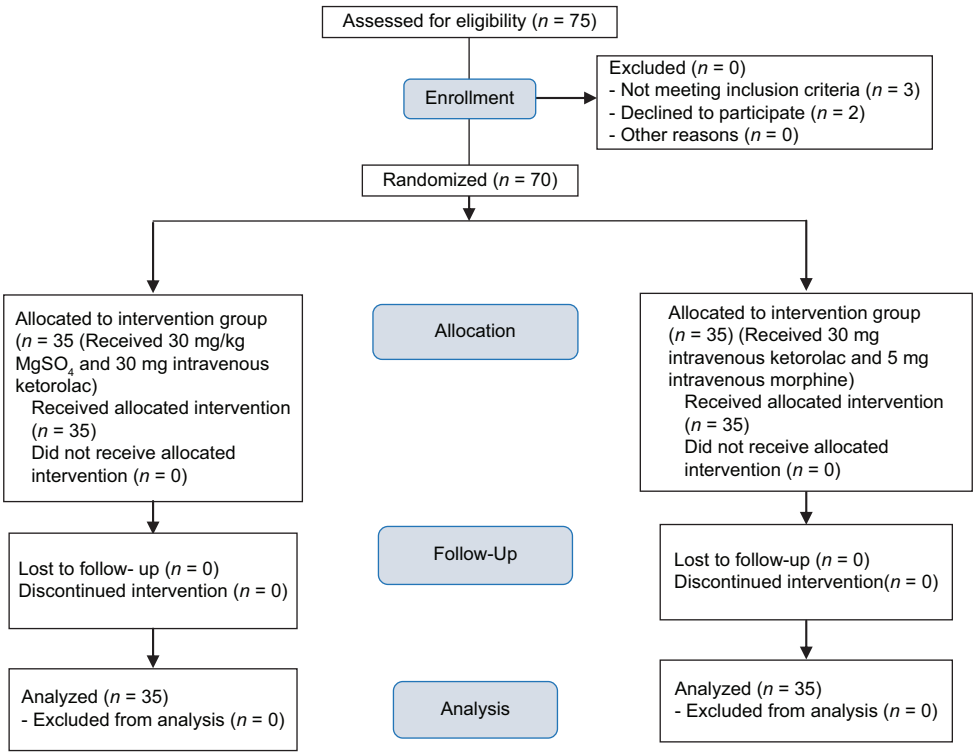

Figure 1: CONSORT flowchart of patients

the Kolmogorov–Smirnov test indicating the normal distribution of data, the Chi-squared test was used to compare the frequency distribution of qualitative variables between the two groups. Moreover, an independent samples *t*-test was run to compare the mean age and BMI between the two groups. In addition, the repeated measures ANOVA was used to compare changes in the mean pain scores and hemodynamic parameters in each of the two groups over time and also to compare the mean of these variables between the two groups at each study time. The significance level of $P < 0.05$ was considered in all analyses.

RESULTS

In the present study, of 35 patients receiving morphine plus ketorolac, 25 (71.4%) and 10 (28.6%) were, respectively, male and female with the mean age of 37.89 ± 9.83 years. Moreover, out of 35 patients receiving $MgSO_4$ plus ketorolac, 22 (62.9%) and 13 (37.1%) were, respectively, male and female with the mean age of 37.09 ± 10.89 years ($P > 0.05$) [Table 1].

Furthermore, the means of patients' hemodynamic parameters including SBP, DBP, HR, RR, and SpO_2 were not significantly different between the two groups at the beginning of the study and 20, 40, and 60 min after the intervention ($P > 0.05$). In contrast, patients' SBP decreased significantly in the morphine plus ketorolac group over 60 min ($P < 0.001$) while this parameter did not change significantly in the $MgSO_4$ plus ketorolac group ($P = 0.578$). Other changes in hemodynamic parameters were not significant in either group over 60 min ($P > 0.05$) [Table 2].

In addition, the patients' mean pain scores were not significantly different between the two groups at the beginning of the study ($P > 0.05$). Similarly, their mean pain scores after the intervention were not significantly different between the two groups 20, 40, and 60 min after the intervention ($P > 0.05$). In contrast, patients' pain scores significantly reduced in each of the two groups over time ($P < 0.001$) [Table 3].

Finally, 6 cases (17.1%) of nausea, 3 cases (8.6%) of dizziness, 1 case (2.8%) of decreased SpO_2, and 1 case (2.8%) of hypotension were observed in the morphine plus ketorolac group while only 2 cases (5.6%) of dizziness were reported in the $MgSO_4$ plus ketorolac group. Although the incidence of complications in the $MgSO_4$ plus ketorolac group was lower than that of the morphine plus ketorolac group, this difference was not significant between the two groups ($P > 0.05$) [Table 4].

DISCUSSION

The results of the present study revealed that the patients' mean pain scores were not significantly different between the two groups before and 20, 40, and 60 min after the injection

Table 1: Patients' basic information in two groups

Variables	Morphine + Ketorolac group	$MgSO_4$ + Ketorolac group	*P*
Sex, *n* (%)			
Male	25 (71.4)	22 (62.9)	0.445
Female	10 (28.6)	13 (37.1)	
Age (year)	37.89±9.83	37.09±10.89	0.748
BMI (kg/m^2)	24.09±3.60	24.21±3.14	0.721
Morphine dose (mg/kg)	0.62±0.51	0.25±0.03	<0.001

$MgSO_4$=Magnesium sulfate; BMI=Body mass index

Table 2: Determination and comparison of patients' mean hemodynamic parameters in two groups

Variables	Morphine + Ketorolac group	$MgSO_4$ + Ketorolac group	*P*[a]
SBP (mmHg)			
Baseline	11.81±0.69	11.76±0.84	0.758
20th min	11.58±0.71	11.71±0.81	0.482
40th min	11.51±0.69	11.73±0.76	0.222
60th min	11.46±0.57	11.74±0.72	0.071
P[b]	<0.001	0.578	
DBP (mmHg)			
Baseline	7.16±0.58	7.09±0.65	0.671
20th min	7.13±0.55	7.06±0.62	0.655
40th min	7.10±0.57	7.08±0.61	0.888
60th min	7.13±0.52	7.08±0.61	0.722
P[b]	0.226	0.499	
HR (bpm)			
Baseline	69.31±5.50	67.23±3.93	0.072
20th min	69.31±5.88	67.37±4.26	0.118
40th min	68.97±6.10	66.91±3.85	0.096
60th min	68.83±5.68	66.91±3.85	0.104
P[b]	0.450	0.101	
RR (bpm)			
Baseline	16.37±1.63	15.83±1.42	0.142
20th min	16.43±1.70	15.83±1.42	0.114
40th min	16.23±1.75	15.83±1.42	0.298
60th min	16.20±1.73	15.80±1.45	0.373
P[b]	0.078	0.396	
SpO_2 (%)			
Baseline	95.06±0.97	95.14±1.14	0.736
20th min	94.94±1.13	95.12±1.14	0.465
40th min	95.01±1.15	95.18±1.11	0.406
60th min	95.10±1.16	95.63±1.10	0.401
P[b]	0.117	0.324	

[a]Significance level obtained from comparing the mean of the variable between the two groups in each of the studied times; [b]Significance level obtained from comparing the mean of variable changes over time in each of the two groups. SBP=Systolic blood pressure; DBP=Diastolic blood pressure; HR=Heart rate; RR=Respiration rate; SpO_2=Oxygen saturation; $MgSO_4$=Magnesium sulfate

of the studied medications. In fact, the role of the combination of medications was obvious in reducing patients' pain in both groups, and it was not possible to distinguish between the effectiveness of these two combinations of medications.

Consistent with the findings of the present study, the results of the study conducted by Maleki Verki *et al*. indicated that there was no significant difference between the effectiveness of the combination of ketorolac plus $MgSO_4$ versus ketorolac alone in reducing renal colic pain.[19] Although our study used a lower dose of $MgSO_4$ (30 mg/kg) plus ketorolac, the mentioned study used a higher dose of $MgSO_4$ (50 mg/kg) plus ketorolac. However, the administration of $MgSO_4$ plus ketorolac did not play a significant role in reducing patients' pain.

Another study examined the severity of pain after total knee arthroplasty and stated that the intravenous infusion of $MgSO_4$ after surgery could not affect postoperative pain.[20]

In contrast to the findings of the present study, Jokar *et al*. conducted a clinical trial and showed that $MgSO_4$, as compared with morphine plus ketorolac, could play a significant role in relieving pain caused by renal colic. In addition, they revealed that the administration of $MgSO_4$ reduced the need for additional doses of morphine. Moreover, there was no significant difference between the two groups in terms of hemodynamic parameters.[16]

Sun *et al*. evaluated the analgesic effects of perineural $MgSO_4$ for diabetic toe amputation and figured out that $MgSO_4$, as an adjunct medication, in addition to relieving pain, also reduces the need for additional analgesia.[20]

The presented findings confirm the results of the present study, which indicated the analgesic effects of $MgSO_4$ on patients with renal colic. The findings can be justified considering that $MgSO_4$ exerts relaxation effects on smooth muscles.

In fact, $MgSO_4$ is an NMDA receptor antagonist binding to ion channels and has analgesic effects. Intravenous magnesium reduces the need for anesthetics and opioids.[11] By inhibiting calcium channels, $MgSO_4$ partially explains the analgesic effects, muscle relaxation, and reduction of laryngospasm.[21] NMDA receptors are amino acid receptors that transmit excitatory synapses, which are involved in inducing and maintaining central sensitization processes in pain situations. Therefore, the analgesic mechanism of NMDA antagonists can prevent nociceptive sensitization. Another mechanism may involve a reduced release of catecholamines, thus reducing peripheral nociceptors or stress responses.[22]

Another array of studies has examined the effects of ketorolac and morphine alone or in combination with

Table 3: Determination and comparison of patients' pain scores in the two groups

Variables Pain	Morphine + Ketorolac group	$MgSO_4$ + Ketorolac group	P^a
Baseline	9.06±2.33	9.00±2.36	0.919
20th min	7.01±1.94	6.93±1.97	0.855
40th min	4.99±1.77	4.93±1.78	0.877
60th min	1.54±1.31	1.74±1.74	0.589
P^b	<0.001	<0.001	

[a]Significant level obtained from comparing the mean pain scores between the two groups in each of the studied times; [b]Significance level obtained from comparing the mean changes of pain scores in each of the two groups over time. $MgSO_4$=Magnesium sulfate

Table 4: Determination and comparison of the frequency distribution of complications in two groups

Complications	Morphine + Ketorolac group, *n* (%)	$MgSO_4$ + Ketorolac group, *n* (%)	*P*
Nausea	6 (17.1)	0	0.833
Dizziness	3 (8.6)	2 (5.6)	
Decreased SpO_2	1 (2.8)	0	
Hypotension	1 (2.8)	0	

SpO_2=Oxygen saturation; $MgSO_4$=Magnesium sulfate

one another (excluding $MgSO_4$) and has shown that the administration of morphine or ketorolac alone was not significantly different in relieving patients' pain; however, their combination could significantly reduce the patients' pain. In addition, the administration of an additional dose of analgesia in the group receiving the combination of these two medications was lower than that of the two groups receiving morphine and ketorolac alone.[8,23] It is worth mentioning that only one case received an additional dose of painkillers (morphine) in our study while other patients did not receive an additional dose due to the administration of the combination of the medications, which was significant in this regard.

In this respect, it can be stated that although medications may cause spasms of the ureteral smooth muscles, their analgesic effects are due to their effect on the central nervous system. Morphine reduces the patient's discomfort by affecting the central nerve receptor; however, it does not affect the cause of the pain, which may lead to the repetition of medication administration.[7]

It is noteworthy that the parameters of SBP, DBP, HR, RR, and SpO_2 were not significantly different between the two groups in any of the studied times in our study. However, within 60 min following the medication injection, only SBP was significantly reduced in the morphine plus ketorolac group while changes in this parameter were not significant in the $MgSO_4$ plus ketorolac group. Other hemodynamic parameters did not change significantly 60 min after the intervention. In other words, although the stability of hemodynamic parameters was higher in the $MgSO_4$ plus ketorolac group, as compared with the morphine plus ketorolac group, this difference was only significant in terms of patients' SBP.

In line with the findings of the present study, a good number of studies have revealed that the group receiving $MgSO_4$ had higher stability of hemodynamic parameters or had no significant difference with the group receiving ketorolac and placebo.[16,24] In this regard, a meta-analysis study concluded that $MgSO_4$ may be used as an adjunct in patients who do not respond to initial analgesia, and its use has no effect on patients' hemodynamic parameters and respiratory status.[25]

In addition, the incidence of complications such as nausea, dizziness, decreased SpO_2, and hypotension in the morphine plus ketorolac group was higher than their incidence in $MgSO_4$ plus ketorolac group in this study although this difference was not significant.

Similar to this study, Holdgate and Pollock's study has reported opioids, especially morphine, as an effective and potent analgesic, which was unfortunately associated with complications such as vomiting. The mentioned study recommended minimizing the use of morphine as much as possible in the treatment of renal colic.[17] In another study conducted in the same year, they found that NSAIDs had fewer complications than opioids and reduced the need for analgesia over time. Moreover, opioids such as morphine increased the risk and complication of vomiting among patients.[9]

Although evaluating and comparing the effectiveness of $MgSO_4$ and the most commonly used opioids on pain relief along with the stability of hemodynamic parameters can be regarded as the strong and innovative aspects of this study, the main limitation of this study was its small sample size. Therefore, it is suggested to conduct further studies with a larger sample size and different doses of $MgSO_4$ so that the results can be generalized to the target population with more confidence.

CONCLUSION

According to the results of the present study, although complications and hypotension caused by administering morphine were more than those caused by $MgSO_4$, the addition of $MgSO_4$ to ketorolac, as compared with the addition of morphine to ketorolac, could not make a significant difference in relieving pain caused by renal colic.

Acknowledgments

The authors would like to express their special gratitude to Editgate English for translating and editing this study.

Data availability statement

The data that support the findings of this study are available

on request from the corresponding author, Alireza Abootalebi. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Financial support and sponsorship

This work was supported by deputy research and technology of Isfahan University of Medical Sciences (Grant #398687).

Conflicts of interest

There are no conflicts of interest.

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