

A Comparative Study on the Efficacy of Intravenous Magnesium Sulfate and Tramadol Infusions on Controlling Acute Renal Colic as Adjuvants, Post Administration of Ketorolac

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Abstract

Objectives: The objectives were to compare the efficacy of intravenous magnesium sulfate and tramadol infusions on controlling acute renal colic as adjuvants, post administration of ketorolac.

Methods: This was a hospital based comparative study conducted in the Department of Emergency Medicine of a tertiary care teaching hospital, India between June 2021 and March 2022. The study included all patients more than 18 years of age presenting to the Department of Emergency Medicine with complaints of acute renal colic – a known case of renal calculi confirmed by either USG or NCCT or X-ray KUB.

Results: The study included a total of 80 patients – 40 each in the magnesium sulphate and tramadol groups. We found that 10.0% of the patients in magnesium sulfate group required rescue analgesia and 30.0% of the patients in the tramadol group required rescue analgesia. A significantly ($p < 0.05$) higher number of patients in the tramadol group required rescue analgesia in comparison with magnesium sulfate group. In other words, patients in the tramadol group were at four times increased risk of requiring rescue analgesia (Odds ratio (OR) 3.86, 95% CI 1.12 to 13.26; $p = 0.025$). At baseline, the severity of pain did not vary significantly between the magnesium sulfate and tramadol groups ($p > 0.05$). At 15, 30 and 45 minutes the severity of pain declined gradually in both the study groups. However, the decline was significantly higher among magnesium sulfate group in comparison with tramadol group ($p < 0.05$).

Conclusion: Patients treated with magnesium sulfate as adjunct to ketorolac had greater reduction in pain severity scores at 15, 30 and 45 minutes compared to patients treated with tramadol as adjunct to ketorolac.

Keywords: Pain, Magnesium sulfate, Tramadol, Acute renal colic, Ketorolac.

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Introduction

Nephrolithiasis, also known as kidney stones, are a common urological disease often symptomized through twinges localized to the sides or a radicular pain towards groins and genitalia. This is referred to as renal colic. Due to the obstruction of urine flow and thereby increased ureteral wall traction, renal colic is formed above the point of obstruction.[1] This increased pressure surges the production and local release of prostaglandins which brings about dilation of blood vessels and diuresis, resulting in a further increase in the pressure inside the kidney. High levels of prostaglandins, also play a role in development of

oedema around the stones.[2] In addition, long isotonic contractions above the point of obstruction increase the production of lactic acid, contributing to slow type A and fast type C nerve fibres stimulation and introduction of more pain.[3] A wide variety of medications are available to treat the pain associated with acute renal colic, each of which affect different parts of the mechanisms causing the pain.[4] Currently, opioids and nonsteroidal anti-inflammatories drugs (NSAIDs) are the main drugs in treatment of renal colic. Opioids are cheap and measurable drugs; nevertheless, they are addictive and may have side

effects such as nausea, vomiting, constipation, and drowsiness. In higher doses, they can even cause respiratory depression. Furthermore, opioids have no effect on the cause of pain while they may have contractile effects on the ureteral tone.[5] NSAIDs, on the other hand, having a direct effect on prostaglandins release, can bring about pain relief through reducing renal pressure and diuresis.[6,7] they may also reduce the oedema of ureter around the stones.

Despite all these advantages, however, these drugs may induce some secondary regulatory responses in the kidney leading to some obstructions.[8] Considering that renal colic can be caused by peristalsis movements above the point of obstruction, it is hypothesized that it is possible to control the patients' pain by preventing the contraction movements in the ureters – tocolytic drugs such as magnesium sulfate can be effective in this regard. It prevents calcium from entering the smooth muscle cell membrane, activates adenylate cyclase and cyclic AMP, and increases the uptake of calcium by sarcoplasmic network.[9] Moreover, reducing acetylcholine in the nerve terminals, magnesium sulfate can also decrease muscle contractions. Against this background, the aim of the present study was to investigate the effect of magnesium sulfate on acute renal colic pain relief. The specific objectives were to compare the efficacy of intravenous magnesium sulfate and tramadol infusions on controlling acute renal colic as adjuvants, post administration of ketorolac.

Methods

This was a hospital based comparative study that assessed the efficacy of intravenous magnesium sulfate and tramadol infusions on controlling acute renal colic as adjuvants, post administration of ketorolac – conducted in the Department of Emergency Medicine of a tertiary care teaching hospital, India between June 2021 and March 2022. The study was approved by the Institute Human Ethics Committee (IHEC).

The study included all patients more than 18 years of age presenting to the Department of Emergency Medicine with complaints of acute renal colic – a known case of renal calculi confirmed by either USG or NCCT or X-ray KUB. However, we excluded patients with previous history of allergy to NSAID, opioids and/or magnesium sulphate; patients with loin pain, suspected to have some other diagnosis; pregnant and breast-feeding women; and patients who got analgesics up to six hours before admission. Patients with known Arrhythmia or heart blocks, Cardiac failure, those having underlying bradycardia (fewer than 60 heart beats per minute) and QRS interval prolongation (>0.12 second), QTC interval prolongation (>0.44 second), hepatic disease, renal failure and

neuromuscular disease were also excluded from the present study. We estimated the sample size based on the analgesic efficacy of magnesium sulphate in comparison with ketorolac (Mean 3.43 (SD 3.31) and Mean 1.67 (SD 0.81) respectively) reported in a study done by Verki MM et al. Taking 95% confidence interval, 80% power and 1:1 ratio between comparison groups the sample size was estimated using Open Epi open-source online resource (SSMean) version 3. Considering a 20% non-response rate the final sample size was adjusted to 72 and rounded off to 80 (40 each in the magnesium sulphate and tramadol groups).

The study population of the present study was specific and rare – we resorted to purposive sampling. All accessible renal colic patients satisfying the inclusion criteria were included in the study. However, the allocation of patients to the intervention groups were done using block randomization technique. Patients were first given ketorolac injection as primary analgesic. They were then administered with adjuvants if their pain doesn't subside within 15 minutes. The allocation of selected intervention adjuvants (tramadol and magnesium sulphate) was done randomly using block randomization method in a ratio of 1:1 and results of the analgesia with adjuvants was noted using visual analogue scale (VAS scores ranging between 1 and 10). The severity of pain was assessed first before administration of intervention adjuvants. If pain score was over six, then group A received injection tramadol 100 mg in 100 ml normal saline over 20 minutes and group B received injection magnesium sulfate 50 mg/kg – maximum 2gm, diluted in 100ml NS over 20 minutes. Fifteen minutes after the infusion gets over, the first measurement of pain severity was done and there after measured every 15 minutes till 45 minutes after infusion (that is at 15, 30 and 45 minutes). The baseline, 15-, 30- and 45-minutes values of VAS was compared for both groups (tramadol and magnesium sulphate). Three or more points drop in the pain score based on VAS was considered as treatment success, if pain reduction is not achieved (less than 50% reduction in VAS score) after 45 minutes, then those patients received rescue analgesia with intravenous morphine of 0.1 mg/kg. They were excluded from the study but included in statistical analysis.

The data collected was entered manually in Microsoft Excel format and analysed using Stata v16. Frequency and proportions were calculated for categorical variables. Mean (standard deviation) and median (interquartile range) were estimated for continuous variables. Appropriate tables and graphs were made. To assess the association between intervention and pain (continuous variable), paired sample t test was used to compare mean pain score values. Mean differences along with 95%

confidence intervals were presented. On the other hand, tests of association for categorical variables was done using Chi square test. Statistical significance was considered at $p < 0.05$.

Results

In the present study, the mean (SD) age of the study population in magnesium sulfate group and tramadol group was 31.9 years (8.1) and 32.0 years (8.3) respectively. Age (in years) did not vary significantly between the two study groups ($p > 0.05$). Majority of the patients included in the present study were males – 57.5% in the magnesium sulfate group and 62.5% in the tramadol group. The proportion of females in the magnesium sulfate and tramadol group were 42.5% and 37.5% respectively. Both the study groups did not vary significantly by gender ($p > 0.05$). The mean (SD) weight of the patients included in the present study was 69.8 kilograms (12.9) and 68.4 kilograms (11.5) in the magnesium sulfate and tramadol groups respectively. The mean (SD) height of the patients included in the present study was 162.6 centimetres (6.8) and 161.3 centimetres (6.0) in the magnesium sulfate and tramadol groups respectively. The weight (in kilograms) and height (in centimetres) did not vary significantly between the two groups ($p > 0.05$). Based on body mass index categorization, majority of the patients

(73.2%) were normal, 14.9% patients were overweight, and 11.9% patients were obese, in that order. The mean (SD) body mass index of the patients was 26.4 kg/m² (4.7) and 26.7 kg/m² (5.2) in the magnesium sulfate and tramadol groups respectively. Importantly, the body mass index (in kg/m²) did not vary significantly between the two groups ($p > 0.05$).

We found that 10.0% of the patients in magnesium sulfate group required rescue analgesia and 30.0% of the patients in the tramadol group required rescue analgesia. A significantly ($p < 0.05$) higher number of patients in the tramadol group required rescue analgesia in comparison with magnesium sulfate group. In other words, patients in the tramadol group were at four times increased risk of requiring rescue analgesia (Odds ratio (OR) 3.86, 95% CI 1.12 to 13.26; $p = 0.025$).

The severity of pain estimated using visual analogue scale (VAS) at baseline, 15, 30 and 45 minutes are shown in Table and Figure. At baseline, the severity of pain did not vary significantly between the magnesium sulfate and tramadol groups ($p > 0.05$). At 15, 30 and 45 minutes the severity of pain declined gradually in both the study groups. However, the decline was significantly higher among magnesium sulfate group in comparison with tramadol group ($p < 0.05$).

Table 1: Distribution of study population

		Magnesium sulfate group N = 40 n (%)	Tramadol group N = 40 n (%)	p value
Age (in years) Mean (SD)		31.9 (8.1)	32.0 (8.3)	0.991
Gender	Male	23 (57.5)	25 (62.5)	0.648
	Female	17 (42.5)	15 (37.5)	
Weight (in kilograms) Mean (SD)		69.8 (12.9)	68.4 (11.5)	0.572
Height (in centimetres) Mean (SD)		162.6 (6.8)	161.3 (6.0)	0.320
BMI (in kg/m ²) Mean (SD)		26.4 (4.7)	26.7 (5.2)	0.787
Rescue analgesia	Given	4 (10.0)	12 (30.0)	0.025*
	Not given	36 (90.0)	28 (70.0)	

SD, Standard deviation *Statistically significant at $p < 0.05$

Table 2: Severity of pain, by study group

	Magnesium sulfate group N = 40	Tramadol group N = 40	p value
At baseline Mean (SD)	8.8 (0.7)	8.6 (0.9)	0.271
At 15 minutes Mean (SD)	6.4 (0.4)	6.9 (0.5)	<0.001*
At 30 minutes Mean (SD)	4.9 (0.7)	5.4 (0.3)	0.001*
At 45 minutes Mean (SD)	3.1 (0.6)	3.4 (0.7)	0.041*

SD, Standard deviation *Statistically significant at $p < 0.05$

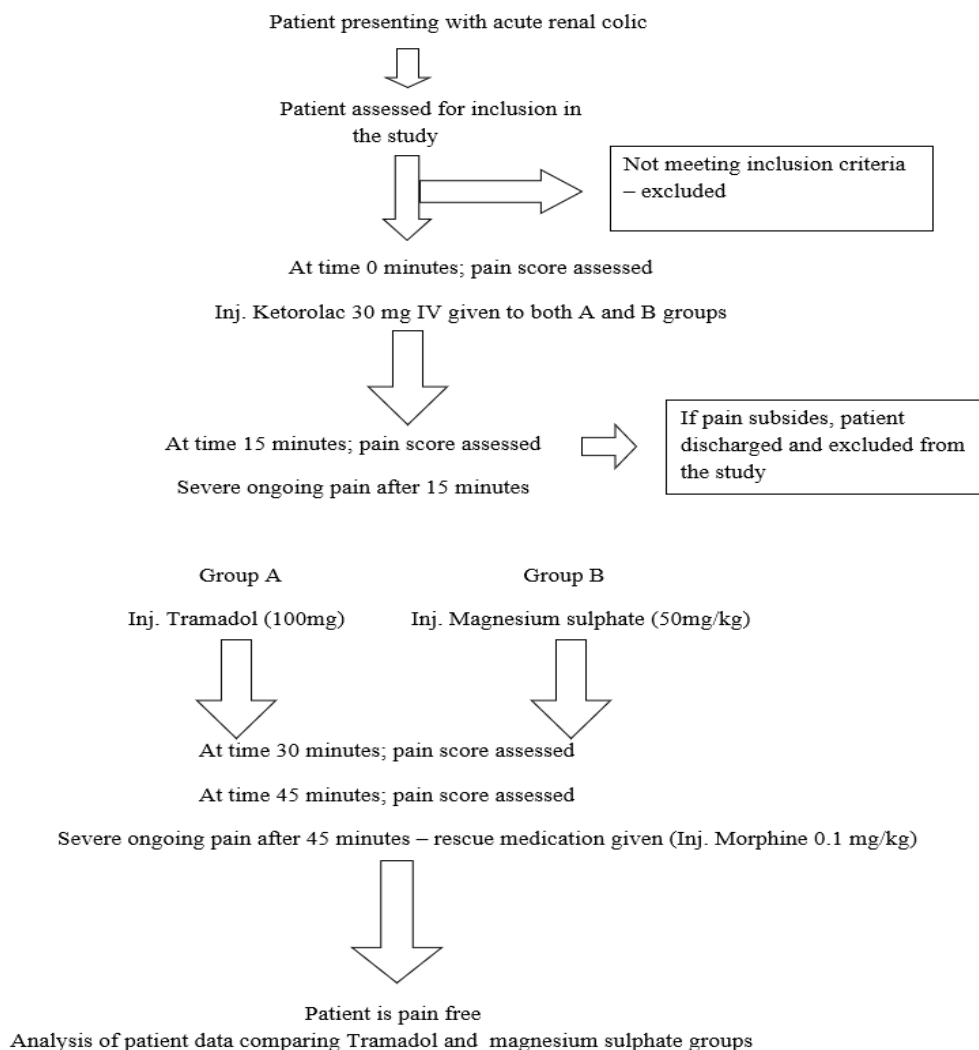


Figure 1: Study flowchart

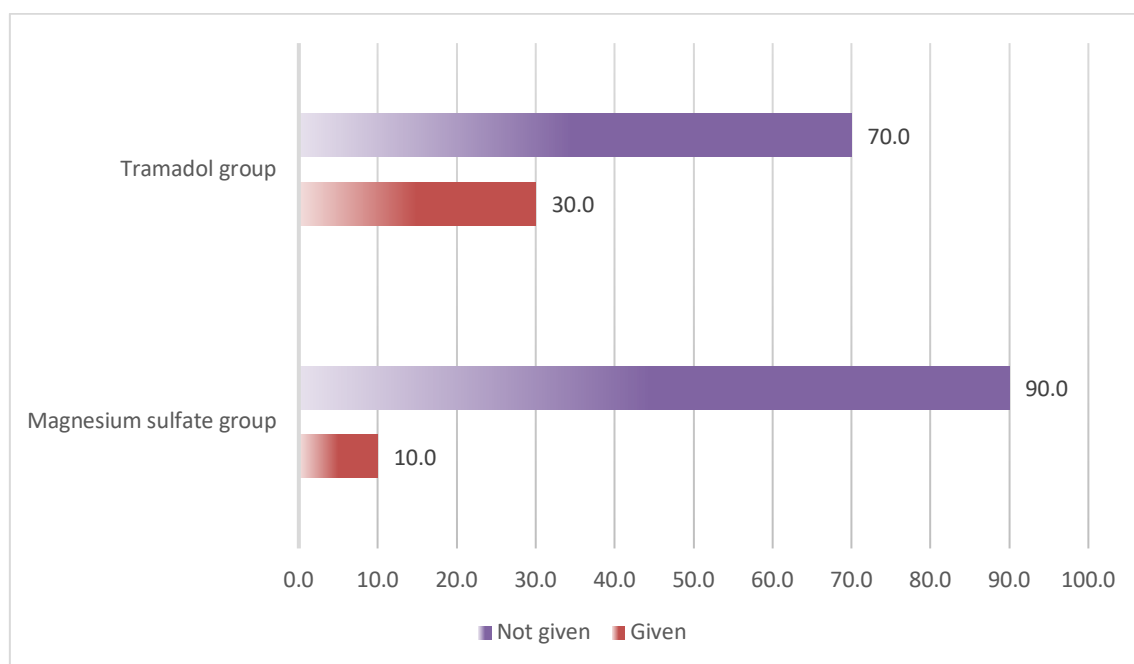


Figure 2: Proportion receiving rescue analgesia, by study group

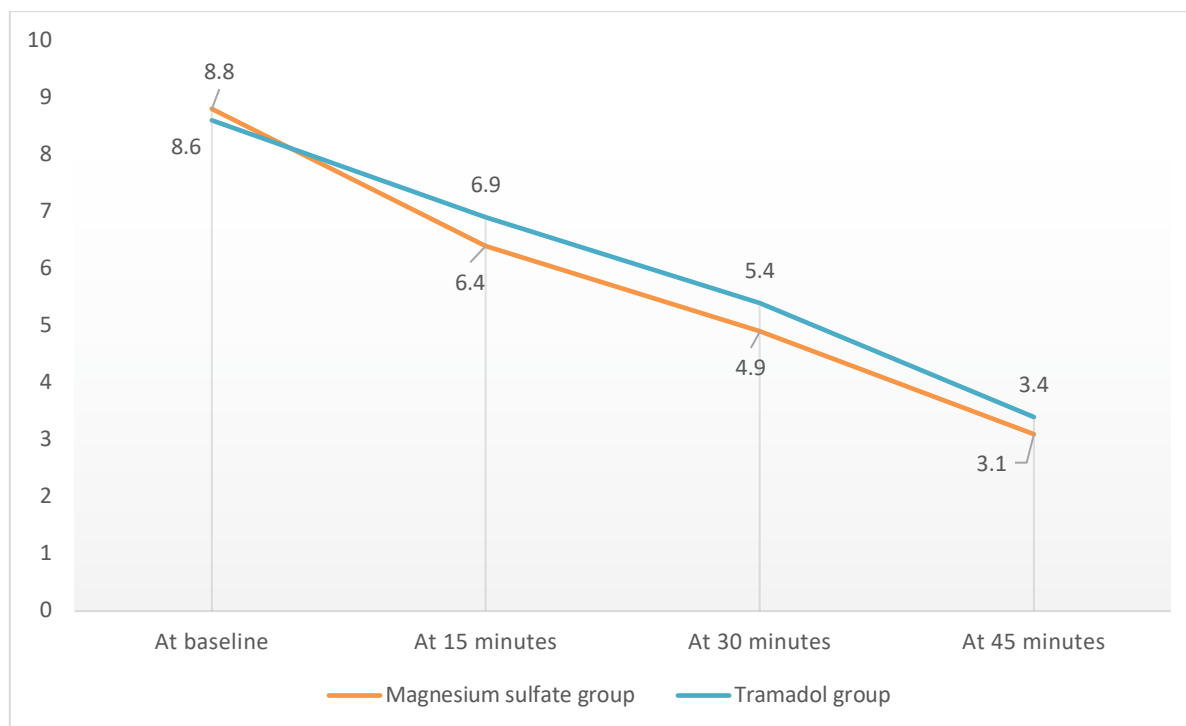


Figure 3: Severity of pain, by study group

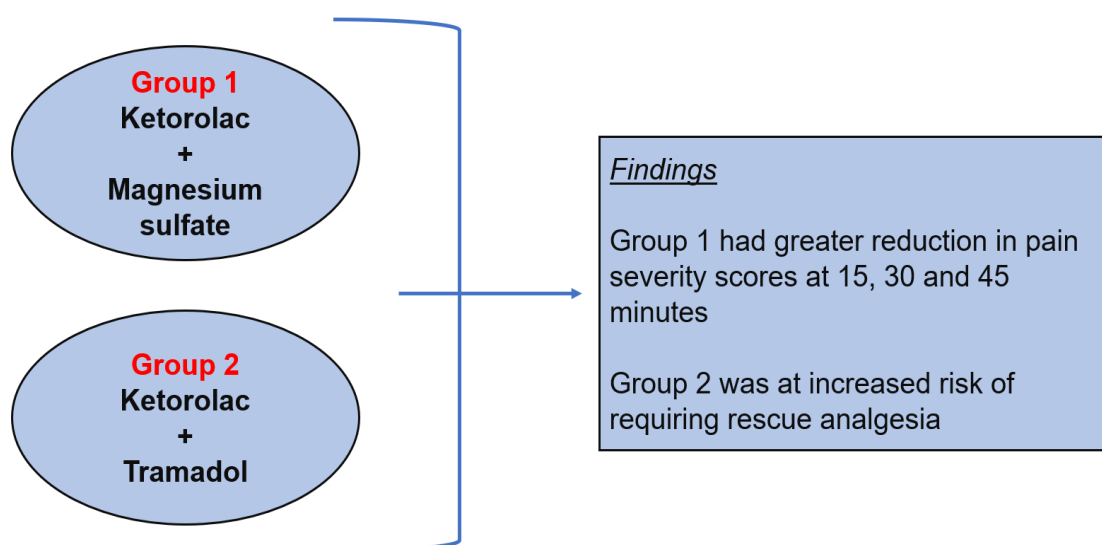


Figure 4: Summary of findings

Discussion

The present study found that a higher number of patients treated with tramadol as adjunct to ketorolac for complaints of acute renal colic required rescue analgesia (intravenous morphine of 0.1 mg/kg) in comparison with patients given magnesium sulfate as adjunct to ketorolac. The study found that acute renal colic patients treated with tramadol as adjunct to ketorolac were at four times increased risk of requiring rescue analgesia (OR 3.86, 95% CI 1.12 to 13.26; $p = 0.025$) in comparison with patients given magnesium sulfate

as adjunct to ketorolac. Also, the study found that the patients treated with magnesium sulfate as adjunct to ketorolac had greater reduction in pain severity scores at 15, 30 and 45 minutes compared to patients treated with tramadol as adjunct to ketorolac.

These findings align with previous research suggesting that magnesium sulfate may be more effective than tramadol in managing acute renal colic. Magnesium sulfate has been recognized for its potential analgesic properties and its ability to reduce pain in various clinical conditions, including

renal colic. Magnesium sulfate is believed to act by blocking calcium channels and reducing intracellular calcium levels, leading to smooth muscle relaxation and pain relief. On the other hand, tramadol is a centrally acting analgesic that exerts its effects by binding to opioid receptors and inhibiting the reuptake of norepinephrine and serotonin. While tramadol has demonstrated efficacy in managing pain, its role in acute renal colic remains controversial. Some studies have reported beneficial effects of tramadol in renal colic pain management, while others have suggested potential limitations and the need for caution due to its side effects and limited analgesic potency.

The observed higher risk of requiring rescue analgesia in the tramadol group could be attributed to several factors. Firstly, the analgesic potency of tramadol may be insufficient to adequately control the severe pain associated with acute renal colic. Secondly, tramadol's mechanisms of action, particularly its weak opioid receptor binding affinity, may not be optimal for managing the specific pain pathways involved in renal colic. Thirdly, individual patient factors and variations in drug metabolism and response might contribute to differential treatment outcomes.

Magnesium plays key roles in several physiological processes. It has been stated to potentiate lidocaine,[10] induce analgesia during spinal anaesthesia, [11, 12] improve morphine analgesia, [13, 14] and reduce consumption of postoperative morphine.[15] Numerous studies with diverse doses, routes, and methods of administration of magnesium have been conducted with contradictory results.[16-18] examining the impact of low dose magnesium sulfate infusions on pain after laparoscopic cholecystectomy surgery, Kocman et al.[18] Found that magnesium sulfate significantly reduces post-operative pain. In 2006, Safdar et al.[19] Study showed that a combination of morphine and ketorolac relief pain better to either drug alone. Rezae et al. examined the effect of magnesium sulfate infusion on pain relief after caesarean section and declared that infusion of 50 mg/kg magnesium sulfate reduces the pain and diminishes the need for other pain medications as well.[20] Studying the bronchodilating effect of intravenous magnesium sulfate in bronchial asthma, Okayama et al. also found that magnesium sulfate infusion can bring about rapid and significant dilation of the bronchi in both mild and severe asthma. Their study showed that magnesium sulfate relaxes the smooth muscles of the bronchial wall and dilates the ducts. In our study, adding magnesium sulfate to the standard treatment of patients with renal colic reduced the severity of pain and decreased the need for additional morphine (rescue analgesia).[21] Considering that no side effects have been reported for using

magnesium sulfate, as well as its easy application, this drug can be used as an adjunct drug in treatment of patients suffering from renal colic. Simultaneous use of magnesium sulfate with other drugs can also reduce their dosage and possible side effects.

It is important to acknowledge the limitations of this study. The sample size was relatively small, and the study design was observational, which may introduce biases and confounding factors. Furthermore, other variables, such as baseline pain severity, stone size, and patient characteristics, were not fully controlled for in the analysis, which might influence the results. Future randomized controlled trials with larger sample sizes and rigorous study designs are needed to confirm these findings and provide more robust evidence.

To conclude, the present study found that magnesium sulfate as adjunct to ketorolac had greater reduction in pain severity scores at 15, 30 and 45 minutes. Also, tramadol as adjunct to ketorolac increased the chances of requiring rescue analgesia. Overall, magnesium sulfate can indicated as an adjunct drug in treatment of patients suffering from renal colic. It can reduce the pain and diminish the need for additional doses of morphine sulfate without disturbing hemodynamic measures.

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