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Effectiveness of Intravenous Ketorolac versus Intravenous Morphine Sulfate on Pain Control in Patients with Acute Renal Colic: A Phase 3 Randomized Clinical Trial

Maryam Masaeli [1], Ahmadreza Khazaee [2], Masoud Shahabian [1,*]

[1] *Department of Emergency Medicine, AJA University of Medical Sciences, Tehran, Iran*
[2] *Department of Emergency Medicine, Golestan Navy Hospital, Gorgan, Iran*
[3] *Department of Emergency Medicine, AJA University of Medical Sciences, Tehran, Iran*

* *Corresponding author: Masoud Shahabian, Department of Emergency Medicine, AJA University of Medical Sciences, Tehran, Iran. E-mail: elmpajooh@yahoo.com*

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Abstract

Introduction: Renal colic is an acute syndrome for which relieving the pain is known to be the best treatment. The aim of this randomized clinical trial was comparing the efficacy of intravenous ketorolac with intravenous morphine sulfate in relieving the acute pain of renal colic in patients referred to the emergency department of a tertiary care teaching hospital.

Methods: 98 cases were selected via convenience sampling method from patients with a presumptive diagnosis of renal colic admitted in the emergency department of Besat Nahaja hospital of Tehran, Iran from March to May 2014 and randomly divided into two groups of equal size, ketorolac, and morphine sulfate. The patients' vital signs and pain intensity were observed at baseline of the study and after 10, 30, 60, 120 and 180 minutes of drug administration. Patients were also followed for side effects. The area-under-the-curve (AUC) was used for pain assessment. Data were analyzed in SPSS 19 using T- test, Chi-square test, and Mann-Whitney test at significance level < 0.05.

Results: Demographic and clinical characteristics of the two groups were similar before drug administration. Both drugs were equally effective in reducing pain over time (P-value = 0.17). Side effects of treatment with ketorolac, were significantly less than using morphine sulfate. The most common adverse effects caused by morphine sulfate, were dizziness and vomiting while nausea and vomiting were the most frequent side effects of using ketorolac.

Conclusions: Findings of this study indicated that ketorolac and morphine sulfate were equally effective in relieving the pain of renal colic, but given the severity of side effects, ketorolac is the preferred drug.

INTRODUCTION

Urinary tract stones cause a wide number of patients referring to emergency departments all over the world [1]. They are responsible for a common and recurrent urological disease [2], and the pain caused by them is known as renal colic [3]. Actually, the acute obstruction of the urinary tract because of the presence of these stones causes dilation, stretching, and spasm [4]. Renal colic usually appears suddenly by pain onset radiating from the flank to the groin [5]. It should be noted that any other factor that causes dilation and inflammation of the pyelocaliceal system such as pyelonephritis, calyces tumors or pressure from outside the system can cause symptoms similar to those induced by renal colic [6]. 5 to 12 percent of people at least experience renal colic once in their lifetime [7]. The approximate number of patients that annually refer to hospitals because of the renal colic pain is estimated 1.2 million people which almost accounts for 1% of all hospital admissions [4]. Considering that 90 percent of stones are excreted spontaneously, relieving the patient's pain is in priority in renal colic treatment [8]. The treatment of pain includes immediate pain relief and prevent the patient from further pain [7]. So, emergency physicians must encounter the problem by rapid and effective treatment methods [9, 10]. Currently, various drugs such as opioids, non-steroidal anti-inflammatory drugs (NSAIDs) in the form of

suppository or intramuscular injection, serum aminophylline and anti-spasmodic are in use according to the physicians' experience and attitude.

According to the guidelines of the European Association of Urology on ureteral calculi, NSAIDs and opioids are in front line of renal colic-treatment strategies [10]. Use of opioids is the primary and most powerful way of drug treatment which causes pain relief by inhibiting the pain center in the central nervous system [7]. Regardless of the low price of opioids, the addictive characteristic [3] and corresponding complications of these drugs such as inhibiting the respiratory center in the medulla and activating the vomiting center, have made their application such a double-edged sword [7]. However, opioids have advantages compared to NSAIDs which cause greater use of them. The lack of affordability and accessibility, the risk of gastrointestinal hemorrhage, and the acute renal insufficiency are the main drawbacks of use of NSAIDs [11]. In spite of these concerns, NSAIDs are attractive to alleviate the pain of renal colic because of their ability to prevent the release of prostaglandins which inhibits the cyclo-oxygenase enzyme, something that [12] consequently results in the pain relief by reducing renal pressure and diuresis [3]. NSAIDs are effective in reducing the frequency of hospitalizations, but have no effect on spontaneous stone passage. Although NSAIDs reduce pain, but they interfere with the spontaneous setting of kidneys which causes reduction in the blood flow of these organs [13]. Overall, it can be said that use of NSAIDs can be a logical choice for relieving the pain of renal colic because of the significant potential of them to reduce the intrarenal pressure and prevent spasm of the ureter [14]. According to evidence provided by some literatures, NSAIDs are more effective in the treatment of renal colic pain compared to opioids [5, 15]. Ketorolac is the most widely used of NSAIDs, has been suggested as the primary way of analgesia in the treatment of renal colic [10], does not require close patient monitoring, and is not accompanied by untoward sedation [16]. Ketorolac reduces renal blood flow and glomerular filtration and therefore is not recommended for patients with renal failure. The use of this drug is not justifiable in patients with history of bleeding diseases or current active hemorrhage and can increase bleeding. Ketorolac is not part of Iran pharmacopoeia, but it has been imported by pharmaceutical companies in recent years. According to our observations, there was no clinical trial conducted to compare the effect of intravenous ketorolac and intravenous opioid in Iranian patients with renal colic. Therefore, this study was undertaken to address the issue.

METHODS

Study Design and Participants

This double-blind randomized clinical trial study was carried out in the emergency department of the Besat Nahaja hospital, a tertiary teaching hospital, for a period of two months from March to May 2014. The study protocol was approved by the Medical Ethics Committee of the Aja University of Medical Sciences (number of ethics committee permission was 9306). The study subjects were selected via convenience sampling from patients referring to the emergency department of Besat hospital with respect to the inclusion and exclusion criteria of the study. Convenience sampling means that the researchers will only select the individuals who are conveniently available and also meet the requirements to begin with. The inclusion criteria were presumptive diagnosis of renal colic, age range of 16-65 years and patients' consent to participate in the study. Weight less than 50 kg, pain severity or in other words numeric rating scale (NRS) lower than 4, low blood pressure (systolic blood pressure < 90mmHg), prohibition for the consumption of opioids (allergy, pulmonary obstructive disease, etc.) and NSAIDs (sensitivity, history of gastrointestinal bleeding, acute coronary syndrome, etc.) and use of any analgesics prior to emergency department arrival were exclusion criteria of the study.

Intervention

Before the intervention, the sample size was calculated based on Piantadosi book [17] using the formula:

$n=(2\times(Z_{1-\alpha/2}+Z_{1-\beta})^2\times\sigma^2)/(\mu_1-\mu_2)^2$

Where $Z_{1-\alpha/2}=1.96$, $Z_{1-\beta}=0.84$, $\mu1=8$, $\mu2=4.6$, $\sigma=6$, $\alpha=0.05$, $\beta=0.2$.

In a double-blind manner, no information was given to the members of the medical team so that during the study period, neither the nurse who was responsible for injection nor the patients and physician were aware of the administered drugs. The only person who was aware of the study procedures was the main researcher. Dependent variables were measured by an assistant colleague. The patients were randomly assigned into two groups. Each group was consisted of 49 patients. The subjects of the first group received 30 mg of intravenous ketorolac while subjects of the second group received 0.05 mg/kg of intravenous morphine sulfate. The main researcher prepared medication. He sucked the medicine into the syringe. If the patient was belonged to the ketorolac group, 30 mg of this drug was sucked into the syringe and then, the volume of the contents of the syringe was equalized to 5 cc using distilled water. But, if the patient was belonged to the morphine group, 0.05 mg/kg of this drug was sucked into the syringe and then, the volume of the contents of the syringe was equalized to 5 cc using distilled water. There was no need for titration for none of drugs as both were used at the lowest effective dose. Drug was slowly infused over a period of 1 to 2 minutes by intravenous method. According to the protocol of current study, diclofenac suppository (100mg) and acetaminophen infusion (1 g IV/Inf) were used for the rescue treatment.

Clinical Assessment

Besides NRS values, information related to vital signs of participants including heart rate, blood pressure, and oxygen saturation were checked and recorded at baseline and after 10, 30, 60, 120 and 180 minutes (3 hours) of receiving drug. Patients were followed for adverse effects of drugs after treatment. Heart rate, blood pressure and oxygen saturation were recorded to simplify the analysis of fluctuations occurred in the clinical parameters after drug treatment. AUC was used for assessing pain and vital signs of heart rate and blood pressure. Respiratory changes were evaluated on the basis of peripheral oxygen saturation using pulse oximetry.

End Points

The primary outcome of this trial was pain relief based on changes occurred in the AUC values after the first injection. Secondary end point was reduction in the number of doses received by patients at 30, 60, 90, and 120 minutes after the first injection.

Statistical Analyses

Data from the study were analyzed using both descriptive (mean, standard deviation, median and IQR) and inferential (t-test, X^2 and Mann-Whitney) statistics in the Statistical Package for Social Science version19 (SPSS Inc., Chicago, IL, USA). Moreover, quantitative and qualitative variables, were reported in the form of Mean±SEM and Mean ± [IQR]/ percent, respectively. P value less than 0.05 was considered statistically significant.

RESULTS

Before Intervention

Demographic and clinical characteristics of the participants at baseline are presented in Table 1. Accordingly, the mean age of the patients for whom morphine sulfate was injected was 31.91 ± 6.06 (range: 19 to 49) years, while this parameter for the patients receiving ketorolac was 32.52 ± 5.23 (range: 21 to 46) years. Based on the results of t-test, the difference between the groups in terms of the mean age of patients was not significant (P = 0.616). As can be seen in Table 1, 57% of patients in group opioid and 51% of patients in group ketorolac were men. With respect to the chi-square test there was no statistically significant difference between groups regarding gender (P = 0.548). In Table 1, pre-intervention NRS and vital signs are also compared between the two groups. Accordingly, interquartile range of pain severity in opioid group compared with ketorolac group before taking the drug was similar. As Fig 1 also indicates, no significant difference was observed between the two groups in terms of pain intensity (P = 0.597). Although, in the group receiving the ketorolac, heart rate was slightly better than morphine group before treatment, but this difference was not statistically significant (P = 0.405). Distribution of heart rate in both groups are presented in Fig 2. The lowest systolic blood pressure was recorded for the patients in the morphine group equal to 92 mmHg and the highest blood pressure of 157 mmHg was observed in the ketorolac group. But, based on the statistical analysis the difference was not significant (P = 0.071). As shown in Table 1, peripheral oxygen saturation equal to an average of 95% and 96% in the morphine and ketorolac groups, respectively was normal and acceptable. Consequently, the two groups were similar regarding the baseline characteristics.

Table 1: Baseline Characteristics of Patients

Variable	Morphine Sulfate Group (n = 49)	Ketorolac Group (n = 49)	P-value
Age, Mean ± SD	6.06 ± 31.91	5.23 ± 32.52	0.616
(%) Gender, n			0.548
Male	(28) 57	(25) 51	
Female	(21) 43	(24) 49	
Pain intensity, Median± IQR	1 ± 9	1 ± 9	0.597
Heartbeat, Mean ± SEM	3.8 ± 100	4.1 ± 99	0.405
Blood pressure(mmHg), Mean ± SEM	5.2 ± 145	4.7 ± 148	0.071
Oxygen saturation, Mean ± SEM	1.6 ± 95	2.1 ± 96	0.062

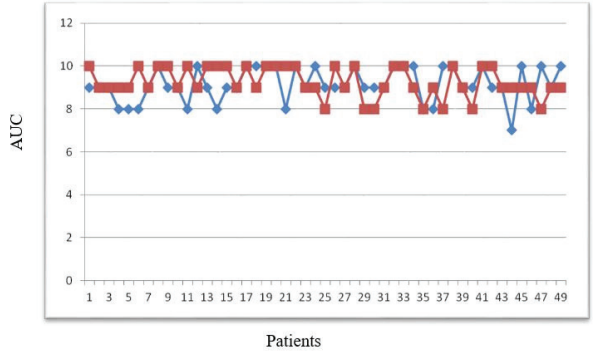

Figure 1: The Scattering of Pain Intensity in the Two Groups before Treatment, Blue-Color Curve: Morphine Sulfate & Red-Color Curve: Ketorolac

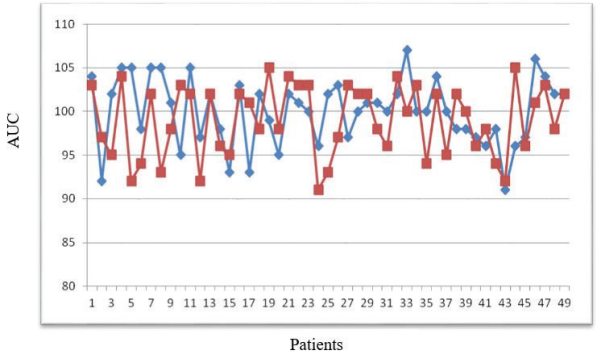

Figure 2: The Scattering of Heartbeat in the Two Groups Before Treatment, Blue-Color Curve: Morphine Sulfate & Red-Color Curve: Ketorolac

After Intervention

According to Table 2, there is no considerable difference between the two treatment groups regarding heart rate, pulse oximetry and pain severity. Systolic blood pressure was the only parameter which showed a dramatic difference between the patients of groups ketorolac and morphine sulfate. Figure 3 provides a better view on the difference of parameters between the two categories of treatment. In both groups, the pain was disappeared after intervention and there was no significant difference between the two groups in this regard (p-value=0.17).

Table 3 provides the mean, standard deviation, and p values of changes occurred in pain score at different points of time after intervention. Table 4 shows number of doses received by patients in different time intervals after intervention. Drop-out rates at study time points can be seen in Table 4.

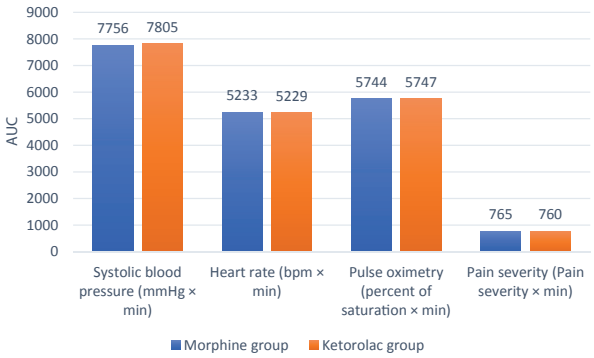

Figure 3: Displaying the Difference between the Two Treatment Groups Regarding Vital Signs and Pain Intensity after Drug Administration

Table 2: Comparing the Effects of Treatment in the Two Groups

Assessment method		Statistics	Recipients of Morphine	Recipients of Ketorolac	P-value
AUC of Changes in systolic blood pressure	MmHg × min	Mean ± SEM	7756 ± 11	7805 ± 10	< 0.001
AUC of Changes in heart rate	Bpm × min	Mean ± SEM	5233 ± 9	5229 ± 11	0.804
AUC of Changes in pulse oximetry	Saturation percentage × min	Mean ± SEM	5744 ± 5	5747 ± 8	0.810
AUC of Changes in pain severity	Pain severity × min	Median± IQR	765 ± 95	760 ± 112	0.212

Table 3: The Mean Changes in Pain Score at Different Time Intervals after Treatment

Time intervals (min)					
Group	**N**	**Mean**	**Std. Deviation**	**Std. Error mean**	**P-value**
0					0.51
MS	49	9.0816	.27664	.03952	
K	49	9.1224	.33120	.04731	
30					0.40
MS	49	7.9388	.42857	.06122	
K	49	8.0000	.28868	.04124	
60					0.06
MS	49	6.0408	.28571	.04082	
K	49	6.1837	.44128	.06304	
90					0.65
MS	49	3.0408	.19991	.02856	
K	49	3.0612	.24223	.03460	
120					0.21
MS	49	2.1224	.33120	.04731	
K	49	2.2245	.46839	.06691	
180					0.76
MS	49	1.1429	.35355	.05051	
K	49	1.1224	.33120	.04731	

MS: morphine sulfate, K: ketorolac

Table 4: Number of Doses Received by Patients in Different Time Intervals and Drop-Out Rates

Time intervals	All patients	Morphine sulfate	Ketorolac
First dose (baseline)	98 (100%)	49 (100%)	49 (100%)
Second dose (30 min)	79 (80.61%)	37 (75.5%)	40 (81.63%)
Third dose (60 min)	19 (19.38%)	10 (20.40%)	9 (18.36%)
Fourth dose (90 min)	9 (9.18%)	4 (8.16%)	5 (10.20%)
Fifth dose (120 min)	1 (1.02%)	0	1 (2.04%)

Chi-square: p-value: 0.17

Table 5: Comparing the Adverse Events of Drugs in the Two Treatment Groups

Variable	Nausea	Vomiting	Headache	Dizziness	Hypotension
Morphine	(16.3%)8	(20.4%)10	(16.3%)8	(24.4%)12	(6.1%)3
Ketorolac	(10.2%)5	(12.2%)6	(10.2%)5	(6.1%)3	0
P-value	0.04	0.05	0.05	0.001	0.01

Adverse Events

The side effects in the two groups are compared in Table 5. There were 12 (24.4%) patients in the morphine group and 3 (6.1%) patients in the ketorolac group who experienced dizziness (P = 0.001). The percentage of patients who experienced vomiting was 20.4% (10 patients) in the morphine group and 12.2% (6 patients) in the ketorolac group (P = 0.05). 16.3% of patients in the group receiving morphine (8 patients) developed nausea and headaches, while these outcomes were recorded for 10.2% (5 patients) of patients treated by ketorolac. 3 out of those who received morphine showed hypotension while no cases of hypotension were reported in the other group (P = 0.01). Clearly seen that the frequency of adverse events has a great difference between the two groups and treatment using ketorolac has fewer complications.

DISCUSSION

Literature review showed a number of studies in which therapeutic effects of various NSAIDs and narcotics were evaluated. Various outcomes were reported in the comparisons conducted by these researches between NSAIDs and narcotics. Holdgate and Pollock [18] carried out a systematic review to compare the relative efficacy of NSAIDs and opioids in the treatment of acute renal colic. They attributed a slightly better effect to the NSAIDs in relieving pain compared to narcotics, but they considered no clinical significance for this difference. This report is in conformity with the results of present research that indicated no significant difference between impacts of morphine and ketorolac in pain relief. Wood et al. compared the efficacy of intravenous ketorolac and intravenous meperidine for the relief of acute renal colic and expressed that these two drug are equally effective in pain treatment [16]. Kolasani and Juturu conducted a comparative study between therapeutic effects of ketorolac and diclofenac and showed that drugs were equally effective in relief of renal colicky pain [5]. According to the results, patients in the group receiving morphine indicated a considerable difference with ketorolac group regarding systolic blood pressure. It arises from the nature and properties of morphine sulfate which causes hypotension. In this study those who received morphine experienced more adverse effects than ketorolac receivers. It may be because of administrating high dose of morphine to achieve a proper pain relief, because patients who suffer renal colic often require doses of opioid more than what health care providers administrate, something that its administration leads to the increase of side effects [16]. Current research showed significantly lower number of vomiting cases in group treated with ketorolac than patients of morphine group. This finding is consistent with related report in study conducted by Holdgate and Pollock [18]. The maximum difference between the two groups in terms of adverse events in this trial was related to the dizziness that showed the highest frequency among various side effects reported for morphine-treated patients. Like present research, a big difference was observed between meperidine-treated patients and ketorolac-treated patients regarding incidence of dizziness in the study done by Wood et al. [16] in which administration of meperidine unlike ketorolac was led to 19% dizziness while just 1% of ketorolac receivers experienced the event. In a study two drugs, diclofenac and ketorolac, were examined in terms of effectiveness and side effects in the treatment of renal colic. The results showed no difference in terms of complications, pain relief and analgesic requirements between the two groups and both drugs have equal and appropriate efficacy in the treatment of renal colic [19]. In a study to assess the efficacy of single-dose ketorolac versus intravenous meperidine in the treatment of renal colic on 70 patients, it was shown that in times of 40, 60 and 90 after injection, intramuscular ketorolac was more effective than meperidine in reducing pain [15]. Bektas that assessed in his study morphine and intravenous paracetamol in patients with renal colic, finally, suggested the latter as an effective and harmless treatment for renal colic patients admitted to the emergency department [20]. Axelsson that examined a composition of ropivacaine, morphine, and ketorolac in reducing patients pain after shoulder surgery, showed that subjects who had received more ketorolac than morphine were more satisfied [21].

Although both kinds of drugs used in current study were titratable, but as previously expressed in the section "intervention" there was no need for titration in present work. In this study, the lowest dose of drugs that were effective in the treatment of renal colic pain were selected and used. For example, because ketorolac was effective in dose: 30 mg, there was not any need for dose: 60 mg of that. In addition to previous experiences of researchers regarding the use of such dose, literature review also confirmed the effectiveness of selected dose. According to one case series conducted by Larsen et al [22] 30 mg of intravenous ketorolac relieved the pain of renal colic remarkably in 10-20 minutes. Overall, this study showed that ketorolac was as effective as morphine sulfate for acute pain relief and it can be suggested as an effective treatment with minor adverse events for relieving the acute pain in the patients with renal colic.

Limitations & Suggestions for Further Studies

The risk of error in measuring variables such as blood pressure, heart rate and oxygen saturation because of the dependence of measurements to the individuals and instruments, unfamiliarity of patients to the correct way of pain expression on the basis of numerical criteria of NRS, and early leaving of hospital or emergency department by patients were limitations of current study. Due to the fact that young children, pregnant women and elderly people were not studied in our

research, we recommend that future studies evaluate the impacts of ketorolac and morphine sulfate on these populations. Given that only short-term effects of ketorolac and morphine sulfate were evaluated on patients with renal colic pain in this research, further researches are needed to determine the long-term effects of them on patients.

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CONFLICTS OF INTEREST

There is no conflict of interest to be reported by authors.

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AUTHOR S' CONTRIBUTIONS

All the authors participated in all the stages of this study including preparing the research proposal, conducting the research, analyzing the data, and drafting and approving the manuscript.

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