

Original article:

Intramuscular ketorolac versus diclofenac in acute renal colic: A comparative study of efficacy and safety

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ABSTRACT

Introduction: Acute renal colic is a common presenting clinical problem in the emergency departments. Nonsteroidal anti-inflammatory drugs and opioid analgesics remain the mainstay of treatment for acute renal colic. This study compares ketorolac and diclofenac which are the two most commonly used analgesics for their efficacy to relieve pain of renal colic.

Methods: Prospective, randomized, double blind clinical study including seventy patients with renal pain admitted in emergency department of a tertiary care teaching hospital. Parameters were observed at baseline and after 15, 30, 60, 180 and 300 minutes of drug treatment. The efficacy of the drug was measured by observing: Pain score, onset & duration of action, rescue drug use, patient's global impression on efficacy of drugs.

Results: The mean pain scores at 15, 30, 60, 180 and 300 minutes were 56.53 ± 15.27 , 30.14 ± 8.05 , 15.36 ± 6.68 , 7.03 ± 6.20 , 2.13 ± 1.05 respectively in the ketorolac group, whereas in the diclofenac group the same values were 65.91 ± 16.22 , 32.33 ± 7.59 , 16.13 ± 7.41 , 8.72 ± 6.55 and 2.36 ± 1.97 . Both drugs were effective in relieving pain of renal colic and maintaining it over time as well. When decrease in value of pain score was compared between the two groups at various intervals of time, there was statistically significant ($p < 0.05$) decrease in pain score only at 15 minutes favouring ketorolac group indicating that it was slightly more effective in early phase compared to diclofenac. In either group there is no statistically significant difference regarding onset of action, duration of action and side effect profile.

Conclusions: Both the drugs are equally effective and safe in renal colicky pain with added advantage of ketorolac being more effective in early period.

Key words: Ketorolac, Visual analog scale, Acute renal colic

INTRODUCTION

Acute renal colic is a common presenting clinical problem in the emergency departments.¹ Renal obstruction due to urolithiasis is the most frequent cause.^{2,3} The classic presentation of acute renal colic includes sudden pain onset radiating from the flank to the lower extremities which is usually accompanied by microscopic hematuria (85 % of cases), nausea and vomiting. Costovertebral angle tenderness is a common finding as well. It is more common in males at 6.1% than in females at 5.3%.⁴ Immediate initial

treatment besides proper diagnosis and consultations are among the duties of the emergency physicians.⁵

Opioid and nonsteroidal anti-inflammatory drugs (NSAIDs) remain the mainstay of treatment for acute renal colic.⁶ However, prolonged opioid use may cause dependence, tolerance and side-effects like nausea, vomiting, constipation and drowsiness. Larger doses even cause respiratory depression and hypotension. Moreover, recently in one study NSAIDs are proven to be more effective than opioids for the treatment of acute renal colic.⁷

Ketorolac, a pyrrolo pyrrole derivative and Diclofenac, an aryl acetic acid derivative are the two most extensively used NSAIDs and are still preferred first line drugs in renal colic pain. But surprisingly, there was no study which compared these two commonly used analgesic drugs for acute renal colic on Indian patients. Hence, the present study was conducted to compare the analgesic efficacy of intramuscular ketorolac and diclofenac in relieving renal colic pain on Indian population.

Administration of analgesics by the oral route in patients with renal colic is not the most recommended route, because these patients might have nausea and because of its slower analgesic effect. So the preferred route is parenteral, either intravenously or intramuscularly. The intramuscular route has theoretically the advantage of not requiring monitoring and thus can be administered quickly even in a crowded emergency department and hence we have selected this route of administration.

MATERIALS AND METHODS

The study was conducted in the emergency department of our institute, which is a tertiary care teaching hospital for a period of three months from January, 2013 to April, 2013 on 70 patients having pain of renal origin based on typical clinical history and relevant radiological investigations. The study protocol was approved by institutional ethical committee and the procedures followed in the present study were in accordance with the ethical standards of the by institutional ethical committee on human experimentation and with the 'Ethical Guidelines for Biomedical Research on Human Participants' provided by the Indian Council of Medical Research (ICMR), as revised in 2006 as well as the Helsinki Declaration of 1975, as revised in 2008. Patients aged 18-65 yrs of either sex willing to give informed

consent who should not have taken any analgesics at least within last two hours were included, patients with previous renal surgery, liver and renal failure, hypersensitivity to ketorolac or diclofenac, pregnant/lactating women, bronchospastic disease, urine examination showing more than 5 leukocytes suggestive of pyuria were excluded from the study.

Study design

It was a prospective, randomized comparative study where the drug solutions were administered intramuscularly to all patients in a double blind manner whereby neither the nurse who actually given the injections was not having any knowledge of the drugs she was giving nor the doctor who has done the observations of various parameters also has no knowledge of administered drugs. The patients were randomly allocated into two groups consisting of 35 patients each. The patients in the first group designated ketorolac group received 30 mg of ketorolac tromethamine and the patients in the second group designated as diclofenac group received 75 mg of diclofenac sodium, both the drugs being given as intramuscular injections.

Clinical assessment

Parameters were observed at baseline and after 15, 30, 60, 180 and 300 minutes (5 hrs) of drug treatment. The efficacy of the drug was measured by observing: pain score, onset & duration of action, rescue drug use, patient's global impression of efficacy of drugs.

Pain score

Pain was assessed in detail. As patients of renal colic coming to emergency room are in severe agony, pain assessing scale that is simple and sensitive was used. Pain was assessed by visual analog scale (VAS) measuring 0-10cm line. Where 0 stands for no pain and 10 for worst possible pain, measurements taken at 0, 15, 30, 60, 180 and 300 minutes (5 hrs). Patients

were asked to make a mark on this line that was measured and recorded in millimeters.

Hemodynamic Parameters :Just before starting treatment heart rate and blood pressure were recorded in each patient so that any fluctuations in the clinical parameters after giving the drug could be analyzed. These parameters were recorded subsequently at 15, 30, 60, 180 and 300 minutes.

Rescue drug use : Patients who were having no relief of pain with the drug in question after 30 minutes or VAS more than 40 mm were given intramuscular pethidine 50mg. Number of patients requiring rescue drug and time when required was noted in each group. More the number of patients requiring rescue drug, denote poor efficacy of drug used.

Onset and duration of action : Onset of action of drug was recorded as within 0-15 minutes and 15-30 minutes. The duration of action was taken as the time interval between the onset of action and first recurrence of pain or demand for analgesic.

Patient's global impression of efficacy: At the end of study period all patients were asked to rate the overall efficacy of drug used as good, very good or excellent.

Tolerability assessment : The tolerability of the drug was assessed on the basis of acceptance of the drug.

The parameters assessed were- nausea & vomiting, epigastric pain, headache, dizziness/faintness, vertigo, allergic manifestations and injection site pain. These parameters were observed after 15, 30, 60, 180 minutes and 5 hrs of drug administration

Statistical analysis : At the end of study, the data were compiled and pain score was evaluated by non parametric test (Mann Whitney test). Quantitative data was analyzed by using parametric test student's t-test and the value of $p < 0.05$ regarded as statistically significant.

RESULTS

The study was conducted on a total of 70 patients of which 35 patients who received ketorolac and another 35 who received diclofenac in a double blind fashion. The age of the participants ranged from 19–61 years in the ketorolac group and from 20–59 years in the diclofenac group. The percentage of females in ketorolac group was 37.1% and that in diclofenac group was 42.8% and both were comparable. Ultrasonography revealed hydronephrosis in 28(80%) cases and calculus in 24(68.6%) cases in ketorolac group whereas in diclofenac group, it has revealed hydronephrosis in 25(71.4%) cases and calculus in 20(57.1%) cases.

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Table 1 : Baseline demographics of patients in both the treatment groups

Parameter	Ketorolac Group	Diclofenac Group	P value
Total number of patients	35	35	
Number of Females	13	15	
Age (in years) (Mean ± SD)	36.32 ± 15.14	35.97 ± 14.06	0.92*
Weight (in Kg) (Mean ± SD)	63.46 ± 10.85	62.79 ± 12.10	0.80*
USG findings			
Hydronephrosis	28 (80.0%)	25 (71.4%)	
Calculus	24 (68.6%)	20 (57.1%)	

SD: standard deviation; Kg: kilogram; *P value not statistically significant; Values in parenthesis indicate respective percentages

The mean base line pain score was 87.39 ± 9.64 (71-100mm) in the ketorolac group and 85.72 ± 10.08 (65-100mm) in diclofenac group and was not statistically significant ($p=0.26$). Hence both groups were comparable regarding base line pain severity score. The mean pain score at fifteen minutes after ketorolac VAS15 was 56.53 ± 15.27 . When this reduction in pain score was compared with base line pain score

VAS0 it was highly significant ($p<0.001$) which suggest the effectiveness of ketorolac in providing pain relief after fifteen minutes. The mean pain score at 30, 60, 180 and 300 minutes were 30.14 ± 8.05 , 15.36 ± 6.68 , 7.03 ± 6.20 , 2.13 ± 1.05 respectively. These scores at different time interval were statistically highly significant compared to base line pain score ($p<0.001$) (**Table 2**). This proves that ketorolac is effective analgesic in renal colic.

Table II : VAS pain scores at different intervals in both the treatment groups.

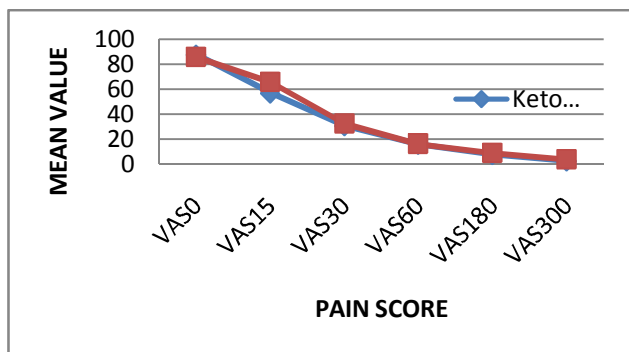
	GROUP	TIME INTERVAL					
		0 min	15 min	30 min	60 min	180 min	300 min
VAS pain score*	Ketorolac group (n=35)	87.39 ± 9.64	56.53 ± 15.27	30.14 ± 8.05	15.36 ± 6.68	7.03 ± 6.20	2.13 ± 1.05
	Diclofenac group (n=35)	85.72 ± 10.08	65.91 ± 16.22	32.33 ± 7.59	16.13 ± 7.41	8.72 ± 6.55	2.36 ± 1.97
P value		0.26	0.02 [†]	0.24	0.65	0.27	0.54

VAS: visual analogue scale; *Values are given as Mean ± SD; [†]P value statistically significant

Similarly in the diclofenac group the mean pain score at fifteen minutes was 65.91 ± 16.22 and compared with base line pain score, it was highly statistically significant ($p < 0.001$). The pain score at 30, 60, 180 and 300 minutes were 32.33 ± 7.59, 16.13 ± 7.41, 8.72 ± 6.55 and 2.36 ± 1.97. These scores compared to base line pain score are highly significantly decreased ($p < 0.001$). This proves that diclofenac is also an effective analgesic in renal colic.

Pain intensity decreased significantly over time in both groups, but the ketorolac group had significantly lower pain scores than the diclofenac group at 15 minutes ($p = 0.02$). Thus ketorolac was slightly more effective in pain relief at 15 minutes. After this interval, both drugs were equally potent in relieving pain and maintaining its efficacy over observation period (**Figure 1**).

Figure 1: Mean pain scores at different intervals in the two groups.



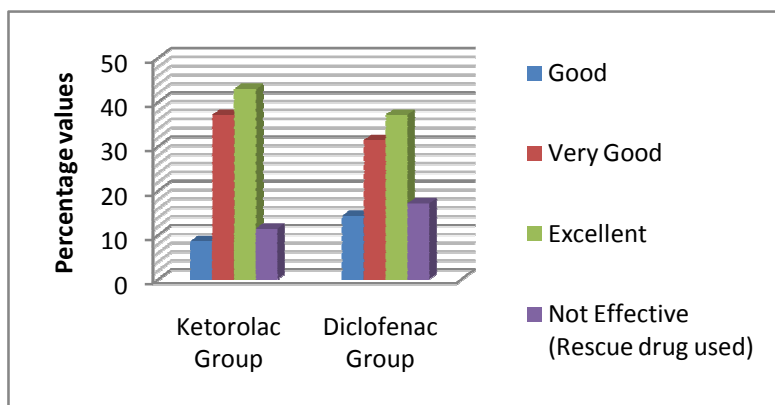
The mean onset of action was 23.83 ± 8.26 min (range 15-30 minutes) in ketorolac group and 28.37 ± 11.61 min (range 15-60 minutes) in diclofenac group. Mean onset of action in either group was comparable ($p>0.05$) and did not show any significant difference statistically. Hence both drugs are equally effective regarding onset of action. None of the patient in either group required repeat dose of same or different drug, provided the drug was effective in initial period, during observation period. Hence both drugs are equally effective regarding duration of action. Four (11.4%) patients in ketorolac group and six (17.1%) patients in diclofenac group required rescue drug as the drug in question was not effective (VAS more than 4 at 30 minutes). Thus two

more patients in diclofenac group required rescue drug which is not statistically significant ($p>0.05$). So both groups were similar as far as rescue drug requirement is concerned.

At conclusion of study period all patients were asked to rate the overall efficacy of drug used as good, very good or excellent. In ketorolac group, fifteen patients rated the drug used as excellent, thirteen patients as very good while three patients rated it as just good. In four patients drug was not effective and they required rescue drug. In ketorolac group, thirteen patients rated the drug used as excellent, eleven patients as very good while five patients rated it as just good.

Figure 2 shows the patients global impression of efficacy of both the drugs in percentage values.

Figure 2 : Patients global impression of efficacy in both the treatment groups



Two patients in ketorolac group and four in diclofenac group had nausea and vomiting while in addition one patient in diclofenac group complained of epigastric pain. None of the patients in any of the group reported other events like dizziness, headache, mental confusion, bleeding, allergy, pruritus, pain at injection site etc. There were no fluctuations in the hemodynamic parameters like blood pressure and heart rate during various time intervals measured. Therefore both the drugs were fairly well tolerated.

DISCUSSION

Renal colic is an important and frequent occurrence in clinical practice. It affects 1-5% of the population in industrialised countries, with a lifetime risk of 20% in white men and 5-10% in women.⁸ In our study majority of the patients were males in their 3rd to 4th decade with mean age of 36.14 years. Similar observation was made in a study in which majority of patients were male upto 85% with maximum incidence in 3rd to 4th decade of life.⁹ Ketorolac and

diclofenac are the two most commonly used NSAIDs for the treatment of acute pain of renal colic and in this study both these drugs were compared head to head.

In the present study, good pain relief was seen with both ketorolac and diclofenac as seen by a significant decrease in pain score over time in both the groups and this effect has lasted over the total duration of study period of 5 hrs. So both the drugs are effective in relieving pain of renal origin and maintaining it over time as well. When the decrease in value of pain score was compared between the two groups at various intervals, then there is a statistically significant difference observed in pain score only at 15 minutes favouring ketorolac group showing that ketorolac is slightly more effective in early phase as compared to diclofenac within 30 minutes. The analgesic effect of ketorolac is similar to that of diclofenac at therapeutic doses in terms of onset, degree and duration of analgesia. The results of our study are in line with a previous study done in Israel, who did a double-blind, randomized clinical trial on 57 patients admitted to the emergency room for renal colic and found that there was no significant difference between ketorolac and diclofenac, with respect to pain level over time, the number of patients requiring rescue medicine, or the level of adverse effects.¹⁰ Many studies have proven that both ketorolac^{11,12,13} and diclofenac^{14,15,16,17,18} are very good analgesics for relief of pain due to acute renal colic. In a previous study done on 106 patients which compared intravenous ketorolac, meperidine, and both (balanced analgesia) for renal colic in which they found that by 30 minutes, 75% of the ketorolac group and 74% of the combination group had a 50% reduction in pain scores, compared with 23% of the meperidine group ($P < .001$). IV ketorolac, alone or

in combination with meperidine, was superior to IV meperidine alone in moderate and severe renal colic.¹⁹

In relation to the assessment of the global impression by patients about the efficacy of drugs given to them, both groups were fairly comparable. In the ketorolac group, 8.6% patients rated it as good, 37.1% patients as very good and 42.9% patients as excellent whereas in diclofenac group 14.3% patients rated it as good, 31.4% patients as very good and 37.1% as excellent [Figure 2].

As far as the need of rescue drugs was concerned four (11.4%) patients in ketorolac group and six (17.1%) patients in diclofenac group needed the rescue medication as their pain was not subsided by the given drug after 30 minutes or VAS more than 40 mm and were given intramuscular pethidine 50mg.

In our study tolerability profile of ketorolac was found to be excellent. Only two patients in ketorolac group had nausea and vomiting while four patients in diclofenac group complained of nausea and vomiting. None of the patient in ketorolac group had serious side effects i.e. mental confusion, dizziness, bleeding or allergy etc.

Our study was based on the "intention to treat" and thus included all patients, except for the exclusion criteria in whom the initial diagnosis on presentation, by the attending physician, was renal colic. Thus, confirmation of the diagnosis was not required for inclusion in the study. This more accurately reflects the emergency clinical setting where analgesia is required before diagnostic tests are completed.

The present study had certain limitations, as no placebo control was used in the patients in view of the ethical problems, so a comparison was made using an active control only. The study measured the adverse effect of drugs for a short time only because

the study duration was only 5 hrs. Also number of patients in each group was relatively small. It was beyond the scope of the present study to observe limitations as the number of patients included in the groups were small in numbers and restriction of the period of study which prevented the extrapolation of the results to the general population where the numbers of cases are large.

CONCLUSION

In the treatment of acute renal colic, both ketorolac and diclofenac were equally effective and safe with added advantage of former being more effective in early period. Though we acknowledge the pitfalls in the subjective assessment of analgesic activity, we feel our rigorous methodology provided a true

comparison of the efficacy of ketorolac and diclofenac in renal colic pain.

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REFERENCES

1. Leslie SW. Nephrolithiasis: Acute Renal Colic. 2005. <http://www.emedicine.com/med/topic3437.html> (Updated : May 3,2007)
2. Pepe P, Motta L, Pennisi M, Aragona F. Functional evaluation of the urinary tract by color-Doppler ultrasonography (CDU) in 100 patients with renal colic. *Eur J Radiol.* 2005;53:131–135.
3. Geavlete P, Georgescu D, Cauni V, Nita G. Value of duplex Doppler ultrasonography in renal colic. *Eur Urol.* 2002;41:71–78.
4. Safarinejad MR. Adult urolithiasis in a population based study in Iran: prevalence, incidence and associated risk factors. *Urol Res.* 2007;35(2):73–82.
5. Curhan GC, Aronson MD, Preminger GM. Diagnosis and acute management of suspected nephrolithiasis in adults. 2009.
6. Holdgate A and Pollock T. Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. *BMJ* 2004 Jun 12; 328:1401-4.
7. Larkin GL, Peacock WF 4th, Pearl SM, Blair GA, D'Amico F. Efficacy of ketorolac tromethamine versus meperidine in the ED treatment of acuterrenal colic. *Am J Emerg Med.* 1999;17:6–10
8. Balaji KC, Menon M. Mechanism of stone formation. *Urol Clin North Am* 1997;24:1-11.
9. Pincus S, Macbean C, Taylor D. The effects of temperature, age and sex on presentations of renal colic. *Eur J Emerg Med* 2010;17:328-31.
10. Cohen E, Hafner R, Rotenberg Z, Fadilla M, Garty M. Comparison of ketorolac and diclofenac in the treatment of renal colic. *Eur J Clin Pharmacol.* 1998 Aug;54(6):455-8.
11. Yealy DM. Ketorolac in the treatment of acute pain: the pendulum swings. *Ann Emerg Med.*1992;21:985-986.

12. Larsen LS, Miller A, Allegra JR. The use of intravenous ketorolac for the treatment of renal colic in the emergency department. *Am J Emerg Med.* 1993 May;11(3):197-9.
13. Di Trolio RN, Sing RF, Bates GM. Use of ketorolac in renal colic. *J Am Osteopath Assoc.* 1999 Nov;99(11):589-90.
14. Hetherington JW, Philip NH. Diclofenac sodium versus pethidine in acute renal colic. *Br Med J* 1986; 292:-237-8.
15. Lundstam S, Wahlander L, Leissner KH, Karl JG. Prostaglandin-synthetase inhibition with diclofenac sodium in treatment of renal colic: comparison with use of a narcotic analgesic. *Lancet* 1982; 1: 1096-7.
16. Sanahuja J, Corbera G, Garau J, Pl R, Carmen Carre M. Intramuscular diclofenac sodium versus intravenous baralgin in the treatment of renal colic. *DICP, The Annals of Pharmacotherapy* 1990; 24:361-4.
17. Miralles R, Cami J, Torne J, Garces JM, Badenas JM. Diclofenac sodium versus dipyron in acute renal colic: A double-blind controlled trial. *Eur J Clin Pharmacol* 1987; 33:527-8.
18. Vignoni A, Fierro A, Moreschini G, Cau M, Agostino A, Daniele E, Foti G. Diclofenac sodium in ureteral colic: double-blind comparison trial with placebo. *J Int Med Res* 1983; 11:303-7.
19. Cordell WH, Wright SW, Wolfson AB, et al. Comparison of intravenous ketorolac, meperidine, and both (balanced analgesia) for renal colic. *Ann Emerg Med* 1996;28:151-158.

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