

Original article

Comparative Study of Individual Pain relief Effect of Intravenous Ibuprofen Intravenous Morphine, Intravenous ketorolac Separately in renal colic Patient ED

Parivahs Yazdani^{1*}¹Emergency Medicine Department, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

*Corresponding author: Dr. Parivash Yazdani, Emergency Medicine Department, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. P.O.BOX: 6455134385. Email address: ; Tel: +98-612439152

Abstract

Background and objectives: Renal colic can be managed by preventing the contraction movements of ureter muscles. By reducing prostogelandin nonsteroidal anti-inflammatory drugs could be used as an effective analgesics drugs in renal colic. The aim of this study is to investigate the comparison of Ibuprofen, Ketorolac and morphin on acute renal colic pain relief. **Materials and methods:** The present study was a double-blind clinical trial in which the patients suffering from acute renal colic were randomly divided into 3 groups of who either received intravenous infusion of 30 mg of Ketorolac, IV Ibuprofen or morphine. Severity of patients' pain was measured by visual analogue scale (VAS) at baseline, 15,30,60 and 120 minutes after infusion. The collected data were analyzed using SPSS statistical software. **Results:** The three groups were similar in baseline pain score and demographic characteristics. At different time points, mean pain show statistically significant differences between the groups; patients received ibuprofen showed the least VAS. **Conclusion:** The results of this study showed that Ibuprofen can be superior to ketorolac and morphine in treatment of patients suffering from renal colic.

Key Words: Renal colic; Ketorolac; Morphine; Ibuprofen; Therapeutics.

1. Introduction

One of the most common reasons for emergency department(ED) attendance is acute pain. In fact, it has been reported that approximately 7 out of 10 attend to ED for seeking pain relief(1). Renal colic caused by nephrolithiasis, is one the most commonly reasons of acute pain. It has been affected around 11% of men and 7% of women. The patients admitted by acute unilateral flank pain radiating to the groin, nausea, vomiting, and urinary symptoms(2). The ureteric obstruction by stones lead to increase intraluminal pressure, stretching it, finally stimulate the nerves in lamina propria. Local synthesis of eicosanoids, such as prostaglandin E₂ and prostacyclin (PGI₂) and also nitric oxide production have also involved in the pathophysiology of renal colic pain(3). Therefore, the contraction in urethral smooth muscle, alteration in local blood flow rate and also Increasing the urinary tract pressure are the major etiologies of pain.

The management of Renal colic pain was done in ED because of the obstruction of the urinary flow, high pressure the urinary tract wall, spasm of ureter smooth muscle, edema and inflammation around the stone(4). Renal colic pain explained as the worst pain that could be experienced. Thus, very kinds of analgesic drugs have been suggested for controlling that. Non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics are the mainly therapeutic choices of acute renal colic(5). Although, the opioids have some benefits such as potency and familiarity, they indirectly effect on the pain causes. While, NSAIDs attenuate the production of prostaglandins and directly targeting the renal colic pain etiological factors. Moreover, there are a lots of clinical evidences that showed NSAIDs causing greater reduction of renal colic pain(6). It has been also reported in a Cochrane study that more incidence of adverse events were seen when opioids administrated for renal colic pain(7). Hence, NSAIDs must be prescribe as first line analgesic drug in controlling renal colic except that cases with a NSAIDs contraindication such as renal failure or history of peptic ulcers. But, the current studies fail to show the priority of different NSAIDs in controlling renal colic pain(7).

The most frequently used NSAIDs in the practical management of renal colin is Ketorolac(8). It is a non-selectively cyclooxygenase(COX) inhibitor that act as a dual COX-1/COX-2 inhibitor. Although, COX-1 constitutively expressed in wide range of cells, particularly platelets and gastrointestinal tract, COX-2 expression induced in the presence of inflammation(9). Hence, NSAIDs associated adverse events mainly caused by COX-1 inhibition. Ibuprofen is another dual COX-1/COX-2 inhibitor that inhibits COX-1 2.5 times less than COX-2. While,

Ketorolac has lower binding capacity to COX-2 than ibuprofen and theoretically provided more potential risk for causing adverse events(10). We have thought that Ibuprofen could be used in controlling renal colic pain with higher analgesic efficacy and lower incidence of adverse effects. Therefore, we have aimed to investigate the comparison of Ibuprofen, Ketorolac and morphin on acute renal colic pain relief.

2. Material and Methods

Study design

The double blind randomized clinical trial study was carried out on patients suspicious to renal colic admitted to emergency department, Ahvaz, Iran. Inclusion criteria were confirmed acute renal colic by computed tomography scan or urinary tract ultrasound and age of 18 to 65 years. While, patients with history of renal or hepatic disease, blood systolic pressure lower than 90 mmHg, fever, pregnancy, Peritonitis, absence of stone were excluded from the study. The study was confirmed by Jundishapour university of medical sciences ethical committee(IR.AJUMS.REC.1395.554). The study process was explained for the patients and informed consent were given. Moreover, the study has been registered to Iranian randomized clinical trial (IRCT code: IRCT2016050125027N2)

Therapeutic intervention

The demographic information of the included patients were collected by a questionnaire. Then, the patients were divided into three group randomly, using block randomization procedure. Group A received 800 mg I.V Ibuprofen during 5 minutes, Group B received standard protocol; 30 mg I.V Ketorolac and Group C treated by 5 mg Morphine sulphate. To measure to pain severity changes during the study follow up, Visual analog scale (VAS) was used at baseline, 15, 30, 60 and 120 minutes after intervention. The VAS scale is an eleven point method to quantified pain severity in adults.

Statistically analysis

The statistical analysis were performed by IBM SPSS statistics Ver.22. ANOVA repeated measure was used to determine the pain alteration during the study. Chi-square test was used to compare the categorical variables. Tukey's Honest Significant Difference test was used to multiple comparison between the groups. P value less than 0.05 considered significant (11-14).

3. Results

One-hundred and ninety patients were meet the inclusion criteria that 7 out of them were excluded and finally 183 subjects were included in our study (Figure1).

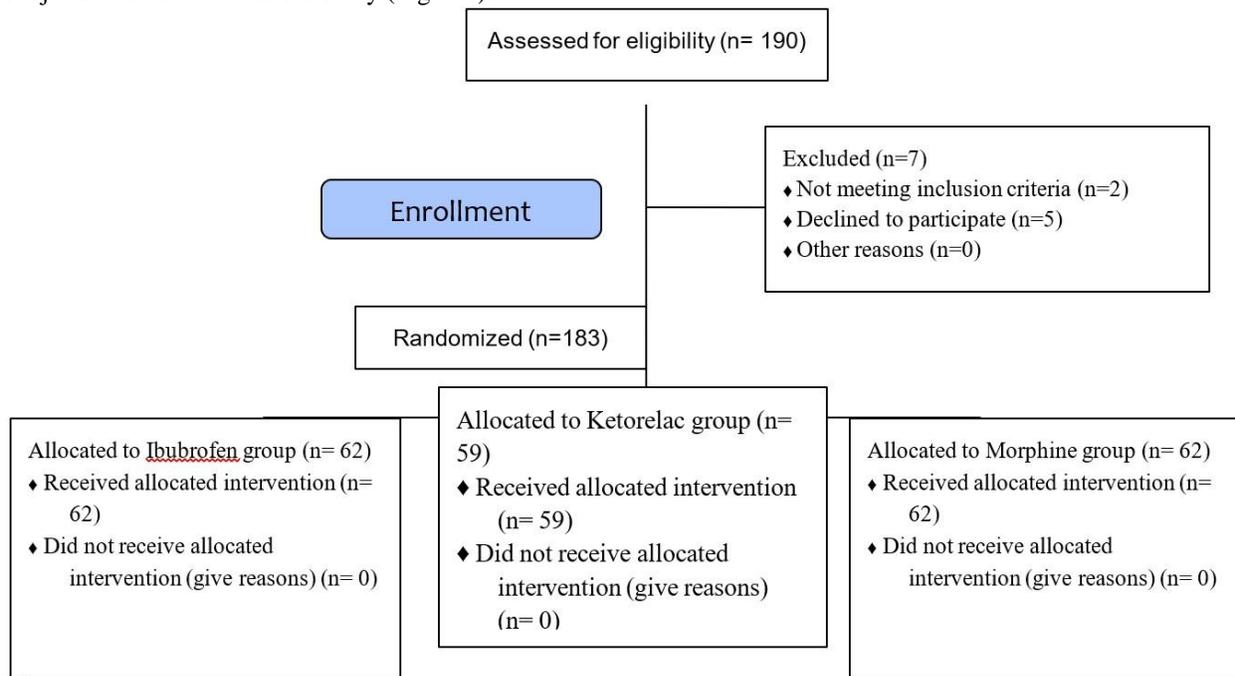


Figure1. Study flowchart.

Male to female ratio was 2.38. The patients did not show any significant differences in terms of age and gender. Moreover the hemodynamic factors including body temperature, blood pressure, plus and respiratory rate were similar in different groups. The baseline VAS scores has also non-significant differences (Table1).

Table1. Baseline characteristics of patients.

Variables	Group a (Ibuprofen) n=62	Group b(Ketorolac) n=59	Group c (Morphine) n=62	p-value
Age	35.2±7.63	35.29±6.66	37.4±8.31	p=0.244
Female n(%)	15(24.2%)	19(32.2%)	20(32.3%)	p=0.529
Male%	47(75.8%)	40(67.8%)	42(67.7%)	
Systolic pressure	140.08±10.81	135.87±12.04	137.71±10.49	p=0.116
Diastolic pressure	83.11±5.64	82.77±6.28	83.49±5.82	p=0.798
O2 saturation	93.93±1.65	93.92±1.56	93.76±1.53	p=0.125
Puls rate	96.72±4.76	96.15±4.02	95.62±4.2	p=0.787
Respiratory rate	17.25±1.21	17.42±1.7	17.27±1.24	p=0.371
Baseline VAS	8.93±0.38	9.06±0.46	8.9±0.50	p=0.105

The pain score was significantly decreased from 8.93 (at baseline) to 2.14 (120 minutes after treatment) in patients received Ibuprofen (p<0.0001). The similar pattern was also seen in the patients treated by ketorolac and morphine, VAS score decreased from 9.6 to 3.64 and 8.9 to 4.99, respectively (Table2, Figure2).

Table2. VAS score changes during study follow up.

Time point	Ibuprophen	Ketorolac	Morphine	P-vlaue
VASI	8.93±0.384	9.06±0.468	8.90±0.507	p=0.105
VASII	4.57±0.911	4.97±0.605	6.62±1.526	p<0.0001
VASIII	2.12±0.934	3.64±0.711	4.99±1.73	p<0.0001
VAS IV	2.02±0.713	3.37±0.828	4.74±1.59	p<0.0001
VAS V	2.14±0.920	3.61±0.708	4.35±1.73	p<0.0001
Repeated measure analysis	p<0.0001	p<0.0001	p<0.0001	

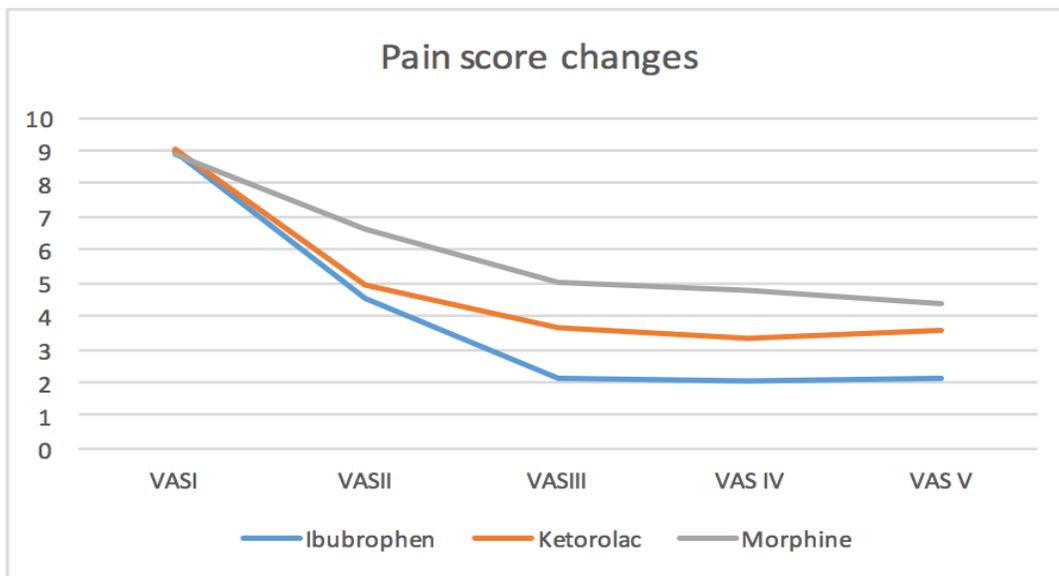


Figure2. The trend of pain score in different groups.

The multiple comparison test showed that in time point of 15 minutes pain score was significantly higher in group C than other groups. While in time points of 30,60 and 120 minutes Group A shows the lowest pain score in compared with other two groups (Table3).

Table3. Multiple comparison of pain score in different groups.

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
VASI	Ibuprofen	Ketorolac	-0.138	0.291	-0.34	0.06
		Morphine	0.028	1.000	-0.17	0.23
	Ketorolac	Morphine	0.166	0.140	-0.03	0.37
VASII	Ibuprofen	Ketorolac	-0.403	0.131	-0.88	0.08
		Morphine	-2.049*	0.000	-2.52	-1.58
	Ketorolac	Morphine	-1.646*	0.000	-2.13	-1.17
VASIII	Ibuprofen	Ketorolac	-1.517*	0.000	-2.05	-0.98
		Morphine	-2.876*	0.000	-3.40	-2.35
	Ketorolac	Morphine	-1.359*	0.000	-1.89	-0.83

VASIV	Ibuprofen	Ketorolac	-1.357*	0.000	-1.85	-0.86
		Morphine	-2.728*	0.000	-3.21	-2.24
	Ketorolac	Morphine	-1.371*	0.000	-1.86	-0.88
VASV	Ibuprofen	Ketorolac	-1.498*	0.000	-2.03	-0.97
		Morphine	-2.206*	0.000	-2.73	-1.68
	Ketorolac	Morphine	-.708*	0.005	-1.24	-0.18

4. Discussion

In the current study we have shown that Ketorolac, Morphine and ibuprofen separately could be significantly decreased the pain score during 120 minutes after treatment. The findings were in line with previous studies. Holdgate et al. in the systematic review study reported that either NSAIDs or opioids could be successfully provided pain relief in patients with renal colic (5). Similarly, Cenker et al. in RCT study evaluated the ibuprofen efficacy in treatment of patients with renal colic, they showed that I.V ibuprofen caused pain relief during 30 minutes after treatment. We have also showed that, Ibuprofen provide analgesic effects during 30 minutes after treatment that persisted till end of the study follow up (120 minutes) (15).

Thereafter, we have compared the analgesic effects of different medications to control renal colic pain score. Our results showed that, although the effects of Ibuprofen and Ketorolac were approximately comparable, Morphine provided the least analgesic effects. Several studies indicated the priority of NSAIDs compared with opioids in management of renal colic pain (5, 7). The opioids target the pain indirectly to the root cause of the diseases and it could be the main cause of their lower potency than NSAIDs in management of the renal colic patients. Hosseini-nejad et al. in a RCT study that compared the effects of Morphine and Ketorolac in controlling renal colic pain showed that the drug's efficacy were comparable 40 minutes after treatment (16). They administrate 10 mg morphine for the patients, while we used 5 mg. The differences in the treatment dose could be explain the controversy between our findings and Hosseini-nejad's study (16).

Moreover, we have found that after the 30 minutes time point, VAS scores in Group A are significantly lower than other two groups. Meanwhile, the ibuprofen causes the most effective analgesia in the patients. Mahon et al in a study compared the post-operative analgesic effects of I.V ketorolac and I.V ibuprofen, they showed both of the medications provided similar effects. Procedure of the pain measurement in the study did not explained well and so its difficult to compared with our results. Moreover, they studied patients under cesarean section that the pain etiology is completely different with renal colic pain (17).

Although the several studies evaluated the adverse effects of I.V ibuprofen, because of short follow up period, we have failed to figure out of them. But in some other RCT studies done by Singla et al., Soutworth et al., and Kroll et al have reported that GI and renal complications are comparable with placebo when we administrate ibuprofen (18-20).

5. Conclusion

Our findings indicated that Ibuprofen provided the most analgesic effects compared with ketorolac and morphine in patients suffered from renal colic pain. Moreover, we have found that NSAIDs showed significantly higher potency in controlling renal colic pain than opioids. To the best of our knowledge we have for the first time compared the Ibuprofen, ketorolac and morphine in the management of renal colic patients.

Acknowledgements

We wish to thank all our colleagues in Golestan Hospital, Ahvaz, Iran.

Conflict of interest

The authors declared no conflict of interest.

Ethical standards

All procedures have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent

Informed consent was signed prior to participation in the study.

References

1. Keating L, Smith S. Acute pain in the emergency department: the challenges. *Reviews in pain*. 2011;5(3):13-7.
2. Wang RC. Managing urolithiasis. *Annals of emergency medicine*. 2016;67(4):449-54.
3. Shokeir AA. Renal colic: pathophysiology, diagnosis and treatment. *European urology*. 2001;39(3):241-9.
4. Golzari SE, Soleimanpour H, Rahmani F, Mehr NZ, Safari S, Heshmat Y, Bakhtavar HE. Therapeutic approaches for renal colic in the emergency department: a review article. *Anesthesiology and pain medicine*. 2014;4(1).
5. Holdgate A, 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;328(7453):1401.
6. Bultitude M, Rees J. Management of renal colic. *BMj*. 2012;345(5499):129.
7. Holdgate A, Pollock T. Nonsteroidal anti-inflammatory drugs (NSAIDS) versus opioids for acute renal colic. *The Cochrane Library*. 2004
8. Brown J. Diagnostic and treatment patterns for renal colic in US emergency departments. *International urology and nephrology*. 2006;38(1):87-92.
9. Jackson LM, Wu KC, Mahida YR, Jenkins D, Hawkey CJ. Cyclooxygenase (COX) 1 and 2 in normal, inflamed, and ulcerated human gastric mucosa. *Gut*. 2000;47(6):762-70.
10. Veronica Mahon DO, Dmitri Chamchad MD, Jay CH. A Randomized Double-Blind Comparison of IV Ibuprofen vs. IV Ketorolac to Prevent Postoperative Pain after Scheduled Cesarean Section. *International Journal of Health Sciences*. 2016;4(3):1-6.
11. Dehkordi FS, Valizadeh Y, Birgani TA, Dehkordi KG. Prevalence study of *Brucella melitensis* and *Brucella abortus* in cow's milk using dot enzyme linked immuno sorbent assay and duplex polymerase chain reaction. *Journal of Pure and Applied Microbiology*. 2014;8(2):1065-9.
12. Mirzaie A, Halaji M, Dehkordi FS, Ranjbar R, Noorbazargan H. A narrative literature review on traditional medicine options for treatment of corona virus disease 2019 (COVID-19). *Complementary Therapies in Clinical Practice*. 2020:101214.
13. Abdolmaleki Z, Mashak Z, Dehkordi FS. Phenotypic and genotypic characterization of antibiotic resistance in the methicillin-resistant *Staphylococcus aureus* strains isolated from hospital cockroaches. *Antimicrobial Resistance & Infection Control*. 2019;8(1):1-4.
14. Ranjbar R, Farsani FY, Dehkordi FS. Phenotypic analysis of antibiotic resistance and genotypic study of the *vacA*, *cagA*, *iceA*, *oipA* and *babA* genotypes of the *Helicobacter pylori* strains isolated from raw milk. *Antimicrobial Resistance & Infection Control*. 2018;7(1):1-4.
15. Cenker E, Serinken M, Uyanik E. Intravenous paracetamol vs ibuprofen in renal colic: a randomised, double-blind, controlled clinical trial. *Urolithiasis*. 2018;46(4):369-73.
16. Hosseininejad SM, Ahidashti HA, Bozorgi F, Khatir IG, Montazar SH, Jahanian F, Khanabbasi MA. Efficacy and Safety of Combination Therapy with Ketorolac and Morphine in Patient with Acute Renal Colic; A Triple-Blind Randomized Controlled Clinical Trial. *Bulletin of Emergency & Trauma*. 2017;5(3):165.
17. Veronica Mahon DO, Dmitri Chamchad MD, Jay CH. A Randomized Double-Blind Comparison of IV Ibuprofen vs. IV Ketorolac to Prevent Postoperative Pain after Scheduled Cesarean Section. *International Journal of Health Sciences*. 2016;4(3):1-6.
18. Singla N, Rock A, Pavliv L. A Multi-Center, Randomized, Double-Blind Placebo-Controlled Trial of Intravenous-Ibuprofen (IV-Ibuprofen) for Treatment of Pain in Post-Operative Orthopedic Adult Patients. *Pain Medicine*. 2010;11(8):1284-93.
19. Southworth S, Peters J, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. *Clinical*

- therapeutics. 2009;31(9):1922-35.
20. Kroll PB, Meadows L, Rock A, Pavliv L. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Intravenous Ibuprofen (IV-Ibuprofen) in the Management of Postoperative Pain Following Abdominal Hysterectomy. *Pain Practice*. 2011;11(1):23-32.