Effect of Diclofenac Alone in Comparison with Diclofenac plus Paracetamol on Renal Colic in Emergency Department

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Summary
Background: Renal colic is one of the most prevalent diagnoses made in emergency unit, consequently, the use of effective pain killers like; non-steroidal anti-inflammatory drugs, or a combination of medications, play important roles in the treatment of these patients.
Objective: To compare effectiveness of paracetamol plus diclofenac vs diclofenac alone in treatment of renal colic. Patients and Methods: A single center double blinded-randomized clinical trial that conducted between the first of January and the first of March of 2022 among patients attending the emergency department of AL-Hilla teaching hospital at babil governorate. A total of 160 patients with definite diagnosis of renal colic with documented renal stone were asked to participate in this study, and excluded all asthmatic patient or peptic ulcer or duodenal ulcer and hypertensive patients. The patients were blindly and randomly divided into two equal groups, the first group received intravenous paracetamol (1g/100ml) plus intramuscular diclofenac (75mg/3ml) and second group received intramuscular diclofenac (75mg/ml) alone, the intensity of pain was measured after 10, 30, 60, 120 minute after administration of medication by numerical rating scale. Results: A total of 160 patients with renal colic were enrolled in this study. The two group were identical in term of age, gender. The difference in the mean numerical rating scale between two groups shown no significant difference before treatment, after 10, 30, 60 minutes (p=0.966, 0.097, 0.38 and 0.59 respectively), while there was a significant difference in the mean NRS after 120 minute (p=0.01) where the mean numerical rating scale was lower at diclofenac plus paracetamol group (mean 0.77) vs diclofenac only group (mean 1.51), Failure to relieve pain in renal colic, after 120 minute was found among 6.25% of diclofenac only group and among 3.75% of patients with diclofenac pulse paracetamol. Conclusion: The mean numerical rating scale was lower at diclofenac plus paracetamol group vs diclofenac only group after 120 minute only and the percentage of failure to relieve pain was lower in diclofenac plus paracetamol group.
Keywords: Renal colic, diclofenac, paracetamol, numerical rating scale.

1. Introduction

Acute renal colic is a severe form of sudden flank pain that typically originates over the costovertebral angle and extends anteriorly and inferiorly towards the groin or testicle(1). It is often caused by acute obstruction of the urinary tract by a calculus and is frequently associated with nausea and vomiting. This obstruction results in proximal ureteral and renal pelvic dilation which is the immediate cause of the intense pain known as renal colic. The degree of pain is related to the degree of obstruction and not the size of the stone (2-4). Renal colic incidence varies depending on the region, and its prevalence varies according to age and environmental conditions in the same region (5). Analgesics selection in different medical conditions are made based on analgesics effectiveness while trying to decrease side effects (6, 7). Diclofenac is NSAIDs that used alone or in combination with opioids have been used to treat renal colic pain for a long time (8). Analgesic effects of these medications are due to the inhibition of prostaglandin synthesis. As a result, NSAIDs prevent afferent arterial vasodilation and increase vascular permeability, which cause diuresis and increased pressure within the renal pelvis (9). The effect of NSAIDs on relieving pain in acute renal colic is similar to opiates. Peak plasma concentrations amounted to 2.15 micrograms/ml, 20-30 min following an intramuscular injection of 75 mg. Diclofenac sodium was excreted with an average half-life of 1.15 hour (10). Where Paracetamol (acetaminophen) is a safe and effective analgesic with fewer side effects than NSAIDs and opiates. The drug can be administered orally, rectally or intravenously (11). Acetaminophen acts by inhibiting prostaglandin synthesis (which are free of inflammatory response) (12), After therapeutic doses the half-life is 90 min to 2 h (13). As a Therapeutic approach for the treatment of renal colic in the emergency department were introduced in the studies. This study was focused on a common drug for treatment for renal colic in the emergency department and effectiveness on the rapid and complete control of renal colic pain and reason for chosen this two drugs was because they are the most frequently used agents for the treatment of acute pain. This study aimed to compare effectiveness of paracetamol plus diclofenac vs diclofenac alone in treatment of acute renal colic.

2. Patients and Methods

A single center double blinded-randomized clinical trial. The data collection was conducted between the first of January and the first of March of 2022 among

doi.org/10.31838/hiv22.02.367 Received: 10.05.22, Revised: 21.06.22, Accepted: 02.08.22

patients attending the emergency department of AL-Hilla teaching hospital at babil governorate. The patients with definite diagnosis of renal colic with documented renal stone and attending emergency department were asked to participate in this study ,The Cochran formula was used for sample size determination as follow (15):n = (1.96) ² (0.05)(1-0.05)/(0.05) ², n=73 patients. A sample size of 73 was calculated throughout the study. Then, to increase the power of the study, 80 patients were designated as the population for each group. Therefore, in this study 160 patients were included, with excluded all asthmatic patient or patients with history of peptic ulcer. The required data was collected by using a self-constructed questionnaire form the participants regarding selected variables by direct interview with participants. the intensity of pain to all patient by using numerical rating scale (NRS), which is an 11-point scale comprising a number from 0 through 10; 0 indicates "no pain", and 10 indicates the "worst imaginable pain". Patients are instructed to choose a single number from the scale that best indicates their level of pain(16), the included patients were blindly and randomly divided by physician into two equal groups of intervention, than The first interventional group received intravenous paracetamol (1g/100ml) plus intramuscular diclofenac (75mg/3ml) and second interventional group received intramuscular diclofenac(75mg/ml) alone, then the intensity of pain measured after 10-30-60-120 minute after administration of medication. Data was analyzed using statistical package for the social sciences (SPSS version 23) computer software program.

3. Result

A total of 160 patients with renal colic were enrolled in this study, divided into two groups. There was no significant difference between two groups and they were identical in term of age and gender (p >0.05), table -1-.

Table -1- Sociodemographic character of both groups.

Sociodemographic character		Patients with renal colic		Total	P value
		Diclofenac only	Diclofenac plus paracetamol		
Age group	<40 years	46(57.5%)	44(55%)	90(56.3%)	0.107*
	41-60 years	29(36.3%)	28(35%)	57(35.6%)	
	>60 years	5(6.3%)	8(10%)	13(8.1%)	
	Mean ± SD	37.8± 11.3	38.6 ±14.6	38.2 ±13	
Gender	Female	31(38.8%)	20(25%)	51(31.9%)	0.062*
	Male	49(61.2%)	60(75%)	109(68.1%)	
Total		80	80	160	

*chi-square test, significant ≤0.05.

The difference in the mean numerical rating scale (NRS) between two interventional groups shown no significant difference before treatment, after 10 minutes, after 30 minutes and after 60-minute (p=0.966, 0.097, 0.38 and 0.59 respectively), while there was a significant difference in the mean NRS after 120 minute (p=0.01) where the mean NRS was lower at diclofenac plus paracetamol group (mean 0.77) vs diclofenac only group (mean 1.51), table -2.

Table -2- The difference in the mean NRS at each time between two groups.

NRS		Mean ±SD	P value
Before treatment	diclofenac only	7.68 ±1.6	0.966*
	diclofenac plus paracetamol	7.67 ±1.9	
After 10 minute	diclofenac only	5.2 ±2.4	0.097*
	diclofenac plus paracetamol	5.8 ±2.3	
After 30 minute	diclofenac only	4.2 ±2	0.38*
	diclofenac plus paracetamol	3.87 ±2.6	
After 60 minute	diclofenac only	2.5 ±2.3	0.59*
	diclofenac plus paracetamol	2.3 ±1.6	
After 120 minute	diclofenac only	1.51 ±1.9	0.01*
	diclofenac plus paracetamol	0.77 ±1.6	

** Student T test, significant ≤0.05.

The mean numerical rating scale (NRS) shown that: the pain score was not significantly differing according to age groups, only after 120 minutes where highest pain score was found among older age group in compare with other age group, table -3-.

Table -3- The difference in mean NRS according to age.

Age	Mean NRS at zero time	Mean NRS after 10 minute	Mean NRS after 30 minute	Mean NRS after 60 minute	Mean NRS after 120 minute
< 40 years	7.5 ±1.2	4.8 ±1.7	3.7 ±1.7	2.2 ±1.5	1 ±0.5
41-60 years	7.7± 2	5.8± 2.6	3.8 ±2.3	2.1 ±1.9	0.6± 0.5
>60 years	7.2 ±2.1	5.3± 1.9	3.8 ±2.9	3 ±2.4	2.2± 1.5
P value	0.66*	0.106*	0.22*	0.37*	0.011*

*ANOVA test, significant ≤0.05.

The mean numerical rating scale (NRS) shown that pain score was not significantly differ by gender, table -6-.

Table -4- The difference in mean NRS according to gender.					
Gender	Mean NRS at zero time	Mean NRS after 10 minute	Mean NRS after 30 minute	Mean NRS after 60 minute	Mean NRS after 120 minute
Male	7.5 ±1.7	5.6 ±1.9	4.2 ±2.1	2.1± 0.29	1 ±1.7
Female	7.8 ±2	5.3 ±3.1	3.4 ±2.5	2 ±0.19	1.3 ±1.9
P value	0.34*	0.47*	0.044*	0.45*	0.37*
* Student T test, significant ≤0.05.					

Failure to relieve pain in renal colic, after 2 hours was found among 6.25% of diclofenac only group and among 3.75% of patients with diclofenac plus paracetamol, figure -1-.

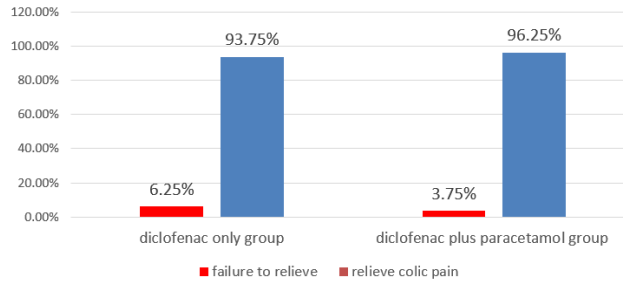

Figure -3- Percentage of failure to relive colic pain among both group.

4. Discussion

The current study depends on NRS, because it more reliable and appropriate for use in clinical practice and for general purposes the NRS was easier in generates data and also easy to analyzed for audit purposes. In compare to VAS that seems to be more difficult to understand and hence, more susceptible to misinterpretations.

The study shown that mean age of studied group was 38.2 years this in line to other studies that shown a peak onset of symptomatic renal stone in the third and fourth decades of life like Cupisti et al study; that shown The age distribution of patients admitted to emergency unit shows a higher rate among young adults (from 25 to 44 years of age)(17) and Serinken et al study in Turkey that shown mean age of patients with renal colic was 31.1 ± 7.0 years (9). The gender distribution among studied group was 68% male to 31.9% female, this distribution was similar to Hong et al, study that done among a total of 23,653 patients with renal colic and visited the 46 emergency departments in Korea and shown the male-to-female ratio was 2:1(18) and Serinken et al study in Turkey that shown male to female ratio was 3:1 (9). The initial NAS was elevated in both groups but the difference was not significant. Pain (measured as per NAS) decreased significantly in the diclofenac only group and it was not statistically difference with the diclofenac plus paracetamol group at 10, 30 and 60 minutes. The reduction in NAS with diclofenac plus paracetamol at 120 minute was marginally more than that of the diclofenac only group and the change was statistically differ. Also the evident of more pain relief was observed at 30th minute. This clinical observation of study was in line with the synergism between nonsteroidal anti-inflammatory drugs and paracetamol that demonstrated in in many study like Altman et al study; which demonstrated a reduction in moderate rheumatology pain when combination of both drug was used (19). Also among animal study Like Miranda study; that demonstrated, paracetamol combined with NSAIDs produces a supra-additive or synergic analgesic effect(20). And by Huuml et al study that shown a combination of oral acetaminophen and intramuscular diclofenac is more effective than oral acetaminophen alone or diclofenac alone in patients with renal colic(21), but the mechanism for synergy with paracetamol is not yet clear. Also may related to fact that; After therapeutic doses of paracetamol the half-life is 90 min to 2 h(13) . On the other hand, the systematic review conducted by Gu et al. revealed that in the most of the studies shown that combination therapy had significant priority compared to monotherapy in patients with uncontrollable renal colic pain regard all outcomes including pain variance at 30 min, rescue analgesic requirements and acute adverse effects(22).

The study shown that there was no difference in pain severity score according to age only after 2 hours, the pain score was high among older patients this similar to other studies like Kanda et al study that shown increasing age increase need for rescue drugs(23) also Shih, et al study shown no significant difference of pain score according to age (24). Also this study shown no significant difference in pain score according to gender. Consistent with current study, Hosseininejad et al. showed that gender and age had no significant difference among treatment groups of ketorolac, morphine, or the combination of both(25). also Forouzanfar et al. showed no significant difference between the treatment groups of ibuprofen and ketorolac in the category of gender, age, history of urolithiasis, and size or location of stone(26). But this not comparable with Naamany et al study that shown more men than women received analgesics (68.8% versus 62.1%, p = .04, respectively) and opioids were prescribed more often for men than for women (48.3 versus 35.7%, p = .001)(27). The difference may have related to the different sample size, the route and dose of drugs' administrations, and scales used for measuring the severity of pain. In general, Failure to relieve pain in renal colic, defined as requirement for rescue therapy, occurs in 7% to 39% with NSAIDs(28), this study shown a failure to relieve pain in diclofenac only group was 6.25% in Dash et al, study, the diclofenac therapy was effective in 88%

(44/50) with failure to relive was 12%(29). While in diclofenac pulse paracetamol the failure to relieve pain was 3.75%. this study had many limitation; Small sample size due to COVID 19 Outbreak and time frame, a Monocentric study with use of one pain scale to evaluate pain intensity and a short-term assessment done while early, long and late onset side effects were not inspected, therefore, designing clinical trials with longer periods of follow up may enrich the conclusion of the study.

5. In conclusion

There was no significant difference in pain severity before treatment, after 10, 30 minutes and after 1 hour with the mean NRS was significantly lower at diclofenac plus paracetamol group vs diclofenac only group after 2 hours. Failure to relieve pain in renal colic, after 2 hours was found among 6.25% of diclofenac only group and among 3.75% of patients with diclofenac pulse paracetamol.

Ethical Clearance: Taken from the Babylon collage of medicine.
Source of Funding: Self-funding.
Conflict of Interest: No conflict of interest.

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