Randomized Double Blinded Placebo Controlled Trial Comparing Diclofenac and Piroxicam in Management of Acute Renal Colic and Its Clinical Implications

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Purpose: To compare the efficacy of sublingual piroxicam 40 mg with intramuscular diclofenac 75 mg in treatment of acute renal colic. The secondary objective was to look for factors that can affect the severity of the pain and pain relief in acute renal colic.

Materials and Methods: One hundred patients with acute renal colic were randomized into two groups. Group A (n = 50) received intramuscular diclofenac and sublingual methylcobalamin. Group B (n = 50) received sublingual piroxicam 40 mg and intramuscular distilled water. Pain severity was measured using Visual Analog Scale (VAS) and verbal and facial response scales. They were followed up for 3 h. Intramuscular injection of pentazocine 30 mg with promethazine 25 mg were used as rescue drugs.

Results: Both groups were comparable for age, sex distribution, body mass index (BMI), and pain duration before presentation. Significant pain relief was noticed in both groups. Sixteen percent in group A and 18% in group B had complete pain relief within 30 min (P = .75). Fifteen patients in group A and 13 patients in group B needed rescue drugs, 84% of group A and 76% of group B had complete pain relief at the end of 3 hours (P = .25). Decrease in pain by each scoring method was also comparable (P = .75). In multiple regression analysis, increasing age, positively affects the severity of pain and pain relief while increasing BMI negatively affect the initial pain relief. Acute renal colic seems to affect men more commonly than women, 81% of the study population were men. Patients with low initial pain score did not require any additional pain relief. Average pain duration before presenting to hospital is 260 min. Sixty percent of renal colics are due to stones below pelvic brim.

Conclusion: The results show that sublingual piroxicam is as effective as intramuscular diclofenac. It can be easily self-administered and it overcomes the morbidity and time delay in getting intramuscular diclofenac.

Keywords: double-blind method; drug combinations; emergency treatment; adverse effects; pain measurement; renal colic; drug therapy.

INTRODUCTION

The incidence and prevalence of urinary stone disease is reported widely as increasing across the world. Stone formation is multifactorial. Persistent high temperature is positively correlated to the increased stone and colic episodes. Acute renal colic episodes seem to affect people who work outdoors mostly in these extreme conditions.(1) Acute renal colic episodes, typically described by patients as 'coming out of the blue', do cause severe distress and warrant emergency medical attention. These patients are treated with opioids and non-steroidal anti-inflammatory drugs (NSAIDs) to relieve pain in the acute setting. Most patients suffer with this sudden acute pain while waiting for medical help, as these drugs are more effective parenterally or per-rectally.

The primary objective of this study was to compare the efficacy of sublingual piroxicam with intramuscular diclofenac in relieving pain associated with acute renal colic. The secondary objective was to look for factors that can affect the severity of the pain and pain relief after treatment in acute renal colic. Also few underreported parameters in renal colic are looked into, such as pain severity and duration at presentation, site of stones in patients with renal colic and etc.

MATERIALS AND METHODS

Study Population

This study was performed in a single high volume stone center in South India. These cohorts of patients were seen in emergency department in a dedicated tertiary referral center for Urology. One hundred non-consecutive patients, who presented with acute renal colic, were enrolled for

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Table 1. Demographic and clinical characteristics of study groups.

Variables	Group A	Group B	*P* Value
Age group (years) (mean ± SD)	20-60, (33.86 ± 9.5)	19-65, (37.02 ± 9.9)	.11
Male to female ratio	39:11	42:8	.61
BMI (kg/m^2), range (mean ± SD)	14.42-33.33, (23.57 ± 3.9)	17.26-48.47, (25.18 ± 4.8)	.073
Duration of pain (min), range, (mean ± SD)	40-720, (284.1 ± 151.24)	20-725, (238.2 ± 133.94)	.111
Side of pain, right-left, (%)	22-28, (44-56)	26-24, (52-48)	.42
Site of stone, UU-MU-LU-UVJ	13-7-12-18	15-5-13-17	.55
VAS score at presentation, range, (mean ± SD)	4-10, (7.3 ± 1.59)	4-10, (7.2 ± 1.64)	.805

Abbreviations: SD, standard deviation:; BMI, body mass index; UU, upper ureter, above sacroiliac joint; MU, middle ureter, between upper and lower ends of sacroiliac joint; LU, lower ureter, below sacroiliac joint; UVJ, ureterovesical junction; VAS, Visual Analog Scale.

the study after obtaining informed verbal consent. The inclusion criteria for the study were presentation with acute renal colic with stone confirmed on imaging, willingness to participate and no analgesic intake in the last 24 h. Presence of stone was confirmed with one or a combination of kidney-ureter-bladder (KUB) X-ray, ultrasonography (US) or computed tomography (CT) scan. The hospital policy is to offer KUB X-ray as the first line investigation followed by US and then CT scan if still a diagnosis cannot be made. US is done directly in known recurrent radiolucent stone formers. In the study cohort, KUB X-ray was the predominant mode of diagnosis while some had diagnosis confirmed in US. Few patients had investigations done elsewhere like CT scan but if had presented with renal colic was also considered for study. The exclusion criteria were contraindication or hypersensitivity to NSAIDS, declined to participate, signs of infection like fever or positive urine dipstick, no stones on imaging, unable to wait for investigations such as CT scan and anatomic abnormality of the urinary tract (**Figure 1**).

Once patients were included in the study, computer-generated random numbers, randomized patients in to 2 groups. Pain was assessed by Visual Analog Scale (VAS), verbal scale and facial grimace scale (FGS) (**Figure 2**). Patients scored their pain in the visual and verbal scales and the author scored their pain using FGS. Patients in group A received diclofenac 75 mg intramuscularly with methylcobalamin 1500 µg sublingually as placebo and in group B patients received piroxicam 40 mg sublingually with distilled water 0.2 mL intramuscularly. The investigator and the patients were blinded for the group they belong to. The nurse administering the drugs is not blinded for safety reasons. After initial pain scoring and administration of drugs, patients were followed up at 30, 60 and 180 min for further pain scoring in all 3 scales, administration of further analgesics if needed, monitoring vital signs, recording adverse effects and data collection. Patients who needed further pain relief were given pentazocine 30 mg with promethazine 25 mg intramuscularly as rescue drugs starting from 30 min onwards as per patient's request.

The following definitions were used for the study. Severity of pain is graded as mild, (1-4) moderate (5-7) and severe (8-10) based on the VAS score. Complete pain relief is defined as no pain experienced by the subject at that point. Significant pain relief is defined as reduction in pain by 3 units in VAS score or from one group to other in verbal scale. The need for rescue drugs was defined as study failure i.e., failure of either drugs to provide effective pain relief.

Demographic and clinical characteristic of patients such as age, sex distribution, BMI, duration of pain, prior treatment if any, rescue drugs if given and its time of administration were recorded.

Statistical Analysis

The homogeneity of the descriptive variables of the two treatment groups was examined by student's *t*-test and Chi-square test. Percentage of pain improvement was analyzed with Z-test for proportions. Pain scores of two treatment groups were analyzed with Friedman

Table 2. Study outcomes in both study groups.*

Results	Group A (n = 50)	Group B (n = 50)	*P* Value	Z Value
Complete pain relief at 30 min	8/16, (6-26)	9/18, (8-28)	.79	0.84
Complete pain relief at one hour**	11/22, (11-33)	16/32, (19-45)	.26	1.27
Complete pain relief at 3 hours**	42/84, (74-94)	38/76, (64-88)	.32	1.00
Significant pain relief at 30 min***	27/54, (40-68)	29/58, (44-72)	.41	0.4
Rescue drugs	15/30, (17-43)	13/26, (14-38)	.67	0.44
Prior treatment	9/18, (7-29)	10/20, (9-31)	.80	0.26

* Data are presented as no/% (95% confidence interval).
**Excluding complete pain relief at 30 min.
***Excluding complete pain relief.

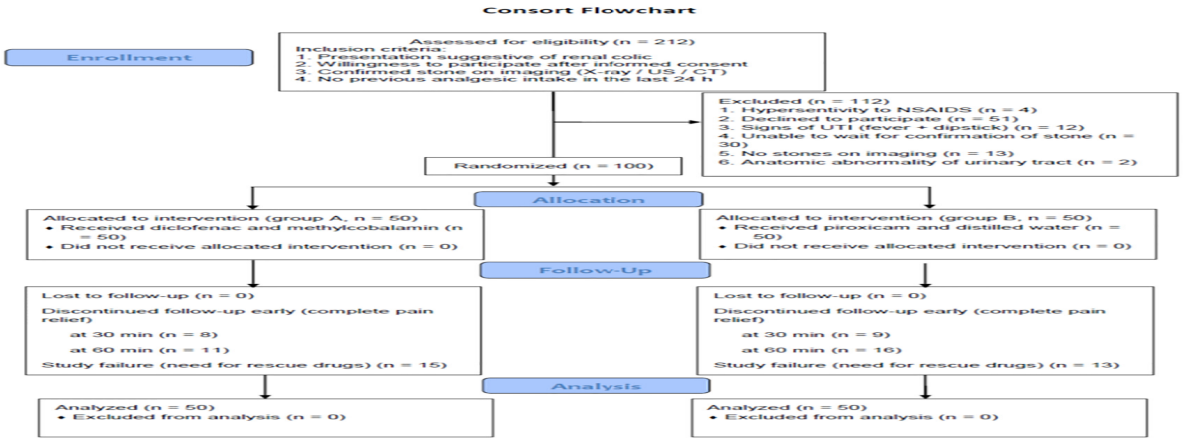

Figure 1. Study flowchart.
Abbreviations: NSAIDS, non-steroidal anti-inflammatory drugs; CT, computed tomography; US, ultrasonography; UTI, urinary tract infection.

test and Mann-Whitney *U* test. Agreement between two scoring systems was checked with Chi-square test. Multiple regression analysis was done to find any association between severity of pain and other observed variables. Data are presented as means with standard deviations (SD). All analyses were done using Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) version 16.0. The power of the study was calculated retrospectively. For a difference of 1, 2 and 3 unit on the VAS score the power was 61%, 92% and 99%, respectively. The alpha error was kept at 0.05. A difference of 3 units was set in initial definitions, which means the power of study is 99%.

RESULTS

The results are summarized in **Tables 1 and 2**. No significant difference was seen between the two groups in terms of age, sex, BMI, duration and severity of pain at presentation, side of pain and site of stone (**Table 1**). **Table 2** demonstrates the outcome analysis, following medication administration in both groups. The drop in pain scores recorded in the regular intervals in all 3 scales and in both groups was uniformly very significant (P = .00). However between the two groups there is no statistically significant difference in all 3 scales in terms of pain relief recorded at each interval. This confirms both groups showed similar pain relief and in a similar comparable pattern. The number of patients having pain relief either complete or partial and the rate of pain relief are similar in both groups.

Significant pain relief was noticed in both groups, 16% had complete pain relief within 30 min in group A as against 18% in group B (P = .75). Fifteen (30%) patients in group A and 13 (26%) in group B needed rescue drugs. Eighty-four percent of group A and 76% of group B had complete pain relief at the end of 3 h including patients who received rescue drugs (P = .25). Decrease in pain by each scoring method was also comparable (P = .75). No significant adverse effects noticed in both groups.

The duration of pain before presentation seems to make a difference. **Table 3** shows that both groups did not have any significant difference in degree of pain irrespective of the difference in the duration of pain in advance, however patients with longer duration of pain before presentation had better pain relief with diclofenac intramuscularly when compared to piroxicam sublingually. Between two groups it took 261 minutes on average for people with renal colic to seek medical attention. Comparison of patient reported pain score and the physicians' record of pain by FGS is shown in the **Figure 3**. Even though physicians' assessment closely follows the patient reported score, it tends to underscore albeit not statistically significant, and supporting the use of standardized and validated patient reported scales unless this can be further studied.

Multiple regression analysis was done to find any relation between severity of pain and other factors i.e. age, sex,

Table 3. Correlation between prior duration of pain and pain relief.

Correlation between prior duration of pain and pain on visit:
• Group A, r = -0.166; t value = 1.17; P = .249
• Group B, r = -0.235; t value = 1.68; P = .1
Correlation between prior duration of pain and pain after 1 h:
• Group A, r = -0.353; t value = 2.61; ***P* = .012**
• Group B, r = -0.127; t value = 0.89; P = .378

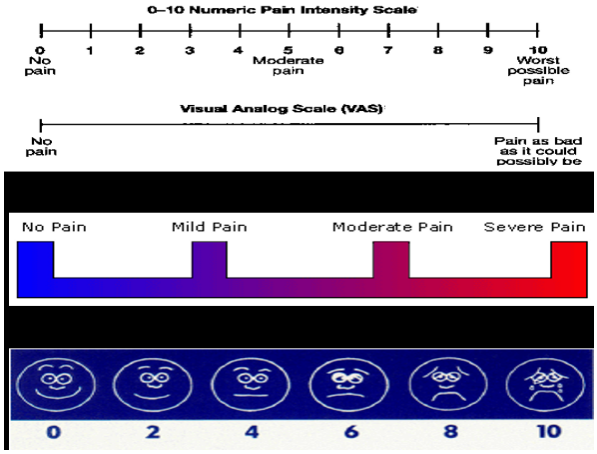

Figure 2. The 3 different pain scoring scales used in the study.
Abbreviations: VAS, Visual Analog Scale; FGS, facial grimace scale.

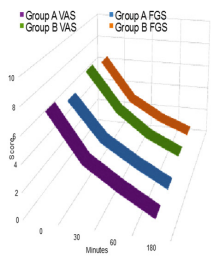

Figure 3. Comparison of patient reported and physician recorded pain scores.
Abbreviation: VAS, Visual Analog Scale.

BMI, previous illness, presence of red blood cell (RBC) in urine, type of pain relief received (diclofenac or piroxicam) and site of calculus. After adjusting for other variables only age was found to be positively correlated with severity of pain (r = 0.32). It was statistically significant (P = .001). However it could explain only 9% of the variance (adjusted R2 = 0.09). The final regression model provided by the stepwise regression is the linear equation:

Pain score = 5.41 + 0.05 × age

There was no multicollinearity in r (tolerance = 1.0). This meant that older patients presented with more severe pain and also showed better pain relief. Another analysis was done to find any relation between decrease in pain score at different intervals and other factors i.e. age, sex, BMI, previous illness, urine RBC, type of pain relief received (diclofenac or piroxicam) and site of calculus. After adjusting for other variables only BMI was found to be negatively correlated with decrease in pain score after 30 min (r = .24). It was statistically significant (P = .015). However it could explain only 5% of the variance (adjusted R2 = 0.05). The final regression model provided by the stepwise regression is the linear equation:

Decrease in pain score = 6.4 – 0.124 × BMI

There was no multicollinearity in r (tolerance = 1.0). This means that patients with larger BMI had lesser pain relief at 30 min but at 60 min and later they matched that of patients with lesser BMI. The drugs given in the study are standard doses and not weight adjusted. Whether it is due to fewer doses per unit body volume or delay in absorption or distribution remains to be elucidated. For instance in diclofenac arm if part of the drug is injected subcutaneously due to thicker fat layer might contribute to any delay in pain relief.

DISCUSSION

Different group of drugs have been studied and reported for the use of pain relief in acute renal colic. Opioids have remained the mainstay of treatment of acute renal colics until the turn of the century, but with significant side effects such as nausea, vomiting, constipation and drowsiness. In addition larger doses can cause respiratory depression and hypotension. However in vitro studies comparing it with NSAIDS regarding ureteric tone and pressure changes showed conflicting results for opioids which generally produced increased or no ureteric activity and favoring NSAIDS which produced abrupt inhibition.[2] NSAIDS is still the first line drug recommended and used widely. Analgesia can be provided by oral, parenteral or rectal NSAIDS; these can be given to treat an acute exacerbation of pain or more regularly to provide background analgesia.[3]

NSAIDS enjoys grade A recommendation by the European Association of Urology (EAU) panel while National Institute for Health and Care Excellence (NICE) in UK specifically recommends diclofenac 75 mg intramuscular as first line medication.[4,5] Even though few studies proved that 50 mg of diclofenac given three times a day has no morphine sparing effect, it is still the first drug of choice.[6] Many NSAIDs are available; the main differences between them are the incidence and type of adverse events, predominantly gastric irritation and ulceration. Selective inhibition of cyclooxygenase-2 (COX)-2 improves gastrointestinal tolerance but still has a detrimental effect on renal and cardiac function in those with pre-existing disease. Typically, COX-2 is up regulated locally in response to an inflammatory stimulus, and therefore drugs able to selectively inhibit COX-2 should limit their effects to the affected area. Although selective COX-2 inhibitor reduces ureteric contractility as effectively as non-selective COX-2 inhibitor in vitro, its efficacy in treating renal colic remains to be elucidated,[7] and since they are orally administered they have a delayed onset of action.

There are two studies where piroxicam has been investigated as an alternative to intramuscular diclofenac and it was known to be effective and comparable in both intramuscular and sublingual route in both the studies.[8,9] This study has also confirmed the efficacy of piroxicam in sublingual form. Sublingual route will bypass liver metabolism and helps attaining early therapeutic blood levels. Even though present study is not a longitudinal or a population-based study, the small cohort of 100 patients in this study gives some interesting observations about the pattern of acute renal colics and its management. This study has also thrown few insights into stone colic presentation in Southern India. Even though there are widespread reports and estimates that stone disease in females are increasing, if not matching men, in the study cohort, the incidence of acute renal colic, is 4 times more common in men than women.

The role of obesity in urolithiasis is inconclusive. Epidemiologic studies have shown that the incident of stone risk, increases with increasing BMI, and no further increase in risk is noticed when the BMI > 30 kg/m^2.[10] Kadlec and colleagues concluded in their study of 590 patients that obesity has little effect on stone composition until a very high (> 40 kg/m^2) BMI is reached.[11] Obesity seems be a risk factor for urolithiasis but the mean BMI in the study group is within the normal range. It either means BMI is not a significant factor in Indian stone formers or at least it is not predictive factor for acute renal colic in Indian men. However increasing BMI seems to affect initial pain relief in this study population.

Acute renal colic seems to affect both sides almost equally with no preference to any particular side. While there is no side predilection in the study cohort, there is definitely a site predilection. We showed that 35% of acute renal colics are due stones lodged in ureterovesical junction, while another 25% of acute renal colics are due to lower ureteral stones. While it is known that acute renal colic causes severe pain, there is paucity of studies documenting this in a measurable scale. In this study the

average VAS core is just above 7 out of a scale of 0 to 10, where ten being the maximum pain patient is aware of and zero being no pain. We did not actually find any difference in severity of pain between men and women or the laterality of stone. But patients who had acute renal colics and stones in the past seem to present earlier. Almost all patients who have recorded a pain score of 4 and 5 on the numeric scale have had stones and renal colics in the past and had presented earlier this time. An even more interesting finding is that, because of their early presentation and intervention, none of these patients needed rescue drugs. Their pain scores became zero in 30 min in most of them and none had any pain at one hour.

In the era of PROMS (patient reported outcome measures), the physicians recording of patients pain (pertaining to pain recording) still closely parallels patients own recording, albeit marginally underscored. This can have practical implications. Some patients find it annoying when questioned about the scale of pain, as was observed in this study as well, and any compassionate healthcare personnel can clearly understand the physical suffering of a patient. A good relevance for this study lies in the fact that many patients present late as seen in **Table 1**, sometimes as late as 12 h. The delay is not due low severity of pain in most of these patients. Patients take an average of 4-5 h overall to seek medical help and in the study scenario it is due to factors like, distance from hospital, arranging travel, cover for work, family and etc. Considering the last two observations i.e. early intervention relieves pain quicker with no need for rescue drugs and multiple factors causing delay for medical attention, a case for using sublingual piroxicam as a patient initiated management for acute renal colic, at least in known stone formers can be made. The morbidity of intramuscular diclofenac is not very well documented and is in fact under reported. The peak serum concentration is seen in 2-4 h with both diclofenac and piroxicam, but the latter has a half-life of about 45-50 h against 1-2 h of the former. So whether piroxicam can provide pain free episodes over a longer duration, in addition to relieving acute pain remains to be evaluated.

We do acknowledge certain limitations of the study. The size of the stones was not recorded and quite a lot of patients were excluded before randomization itself as per the criteria. The power of the study was calculated retrospectively but given a good sample size it remains at 99%. We also did not do any subgroup analysis, however that was not the original objectives of the study.

CONCLUSION

Acute renal colics still seem to be affecting men more commonly and early treatment seems to improve pain faster. Sublingual piroxicam is as effective as intramuscular diclofenac. It has the advantage of ease of self-administration and overcomes the morbidity and time delay in getting access to intramuscular diclofenac. It could be considered for self-start pain relief treatment in known stone former patients with no contraindications. This study strengthens evidence supporting the use of sublingual piroxicam in acute renal colics.

CONFLICT OF INTEREST

None declared.

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