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Intravenous Paracetamol, Morphine, or Ketorolac for theTreatment of Renal Colic: A Randomized Double Blind Clinical Trial

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ABSTRACT

To determine the analgesic efficacy of intravenous paracetamol versus ketorolac and morphine for the treatment of acute renal colic. This study was a double blind randomized clinical trial that prospectively conducted in emergency department (ED) during September 2012 to August 2013. Totally 150 subjects were randomly assigned in a 1:1:1 ratio to one of the following treatment groups: (1) A single dose of 1 g intravenous paracetamol (apotel) in 100 ml normal saline during 15 min; (2) A single dose of 10 mg intravenous morphine sulfate in 100 ml normal saline during 15 min; (3) A single dose of 30 mg intravenous ketorolac in 100 ml normal saline during 15 min. The severity of pain was measured based on 100 mm visual analogue scale from 0 mm to 100 mm equaling no pain to worst pain , and a verbal 4 points scales of mild, moderate, sever and very sever, respectively, just before intervention and 30 minutes after that.The pain intensity score was 36.13 ± 27.64 Visual analogue 30 min after intervention, pain score decreased significantly within 30 min compared to baseline pain intensity (P < 0.001). The most frequent adverse effect among the participants was dry mouth, which was more seen in morphine group.Similar efficacies were obtained for three medications, which were used in current study. However, the results suggested that comparing to morphine and ketorolac, paracetamol had lower complications.

Keywords:Paracetamol, Apotel, Ketorolac, Morphine, Renal Colic

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INTRODUCTION

During the last decades, the rate of renal colic has increased and it was more prevalent especially in Caucasian patients. The majority of patients with renal colic do not respond to orally or suppository treatments and need urgent and usually intravenous pain killers [1]. Narcotics, especially morphine, have been widely used for the treatment of renal colic in emergency department (ED). However, several serious restrictions including hypotension, respiratory depression, apnea and even intolerance or addictions have been reported while taking narcotics. In a meta-analysis performed by Holdgate *et al.,* it was demonstrated that NSAIDs had more success rate for pain relief and lower complications in comparison with parenteral opioids [2]. Ketorolac

has been recommended as the first line analgesic in management of renal colic. Nevertheless, it has also some complications including gastrointestinal bleeding and acute renal failure, which limited its application in some patients. IV Paracetamol is another analgesic drug which is broadly used as a pain reliever in ED (acetaminophen). It is well known as an effective and safe medication with fewer side effects compared to NSAIDs and opioids to reduce pain in patients who are referred to ED. Although, there are limited evidences regarding the role of paracetamol in the management of renal colic pain, but a number of studies demonstrated that it is superior and safer than NSAIDs and opioids [3,4]. The primary outcome of this study was to determine the analgesic efficacy of intravenous paracetamol versus ketorolac and morphine in the treatment of acute renal colic. The secondary outcomes were the need for rescue analgesia and side effects observed in treatment groups.

MATERIALS AND METHODS

This study is a double blind randomized clinical trial that prospectively conducted in ED during September 2012 to August 2013. All patients were provided with written informed consent and Ethic committee approved the study. All patients enrolled in the study were between the ages of 16 and 55 years old with acute flank pain and clinical signs and symptoms suspected renal colic. The exclusion criteria consisted of known allergy to paracetamol, morphine or ketorolac, underlying disease such as renal, hepatic, cardiac and pulmonary failure, asthma; renal and liver transplantation, hemodynamic instability, evidence of peritonitis, fever with oral temperature above 38°C [100.4°F], suspected pregnancy, known abdominal aortic aneurysm, analgesic consumption within six hours before ED presentation, drugs or opioid addiction, mental retardation, cognitive disorder and inability to speaking, and sign and symptom or laboratory data of urinary tract infection or pelvic inflammatory diseases.

The presence of hematuria was confirmed by urine analysis. Abdominopelvic computed tomography (CT) was required in order to confirm hydronephrosis, urolithiasis and nephrolithiasis in all patients. Moreover, Urology consult was requested for all patients.

All patients were randomly assigned in a 1:1:1 ratio to one of the following treatment groups: 1) A single dose of 1 g intravenous paracetamol (apotel) in 100 ml normal saline during 15 min; 2) A single dose of 10 mg intravenous morphine sulfate in 100 ml normal saline during 15 min; 3) A single dose of 30 mg intravenous ketorolac in 100 ml normal saline during 15 min. Treatment allocation assignments were put in sealed envelopes and randomly selected by a nurse who was blind to the study. The same nurse in a separate file and the patient sheet recorded serial number of each ticket (paracetamol, morphine and ketorolac) and they were matched together at the end of sampling. After drug preparation, a second nurse administrated chosen drugs. The questionnaires filled out by emergency medicine physicians the questionnaire before and 30 min after intervention. The pain visual and verbal scoring was asked from patients at beginning and 30 min after intervention and pregnancy test was performed in all female patients. If the subjects did not respond to study treatment, rescue analgesic (fentanyl [1 μg/kg, intravenously]) would have been prescribed.

The severity of pain was measured based on 100 mm visual analogue scale from 0 mm to 100 mm equaling no pain to worst pain, and a verbal 4 points scales of mild, moderate, sever and very sever, respectively, just before and 30 minute after intervention. Demographic data of participants and complications of study drugs including vomiting, dry mouth, pruritus, chest wall rigidity, dizziness, headache, altered mental status, hypotension (systolic blood pressure below 90 mm Hg), urinary retention, respiratory failure and any other complication were collected. In addition, the results of laboratory tests and radiology imaging were recorded. All subjects were discharged from ED after 6 h and followed up with telephone 24 h and 48 h later for control of pain recurring as a secondary goal of study. All abdominopelvic CT scans were reported by radiologist, urologist and EM specialist.

The reduction of at least 50% in visual or two points reduction in verbal scale at 20 minute from intervention were considered aspositive response to therapy.

The data was analyzed using SPSS version 19. The normal distribution of quantitative variables was tested with kolmogorov smirnov test. The pain

intensity at time zero between three treatment groups was analyzed with analysis of variance (ANOVA). The primary outcomes including within and between groups changes were tested with paired t-test and ANOVA, respectively. The secondary outcomes were analyzed with chi square and ANOVA to determine the difference of side effects and need to rescue analgesic after 30 min, respectively. The significant level set as less than 0.05.

RESULTS

Totally, 150 subjects met inclusion criteria and equally divided into three groups (50 per each group). Of these 150 participants, 111 (74%) were male and 39 (26%) were female. The mean age of participants was 33.51 ± 10.12.

The most frequent sign and symptom complained by patients was flank pain (N=141, P=94%), and followed by referral inguinal pain (N= 81, P=54%). Table 1 demonstrates the history, signs and symptoms of participants.As revealed in Table 2, it seems that there is no remarkable difference between groups for baseline characteristics.

The pain intensity score within 30 min after intervention was 36.13 ± 27.64. Visual analogue pain score decreased significantly within 30 min compared to baseline pain intensity (P < 0.001). The details of treatment outcome are listed in table 3 and figures below.

The most frequent adverse effect among the participants was dry mouth, which was more seen in morphine group. There was not any complication in paracetamol group.

Table 1: The findings of history, sign and symptom

Finding	Yes	No
History of recent pain	67(44.7%)	83(55.3%)
flank pain	141(94%)	9*(6%)
Dysuria	20(13.3%)	130(86.7%)
Frequency	23(15.3%)	127(84.7%)
Nausea & vomiting	74(49.3%)	76(50.7%)
Referral inguinal pain	81(54%)	69(46%)
Referral abdominal pain	33(22%)	117(78%)
CVA tenderness	19(12.7%)	131(87.3%)

**The original location of pain was in hypogaster*

Table 2: Baseline characteristics

Characteristics	Ketorolac	Morphine	Paracetamol	Significance
Male	39(78%)	39(78%)	33 (66%)	NS*
Nausea & Vomiting	23(46%)	25(50%)	26(52%)	NS
Gross hematuria	28(56%)	32(64%)	26 (54%)	NS
Nephrolithiasis	10(20%)	12(24%)	7 (14%)	NS
Urethrolithiasis	12(24%)	12(24%)	13(26%)	NS
Uvj stone	3(6%)	7(14%)	3(6%)	NS
Bladder stone	4(8%)	5(10%)	2(4%)	NS
Hydronephrosis	15 (30%)	23 (46%)	15 (30%)	NS
Mean visual analogue scale score	76.3±15.1	79.9± 15.3	76.1±13.9	NS
Nephrolithiasis and Urethrolithiasis	7(14%)	3(6%)	6(12%)	NS
Nephrolithiasis and Bladder stone	3(6%)	2(4%)	5(10%)	NS
Urethrolithiasis and Bladder stone	6(12%)	4(8%)	7(14%)	NS
Nephrolithiasis and Uvj stone	3(6%)	2(4%)	4(8%)	NS
Bladder stone and Uvj stone	2(4%)	3(6%)	4(8%)	NS

**NS: not significant*

Table 3: Mean reduction in pain intensity of treatment groups

Group	Ketorolac	Morphine	Paracetamol
Baseline visual analogue scale scoreMean ± SD at 0 min	76.3 ± 15.1	79.9± 15.3	76.1 ± 13.9
Visualanalogue scale score at 30 minMean ± SD	38.9 ± 28.8	35.9±28.0	33.6 ± 26.2
Reduction in visual analogue scale score at 30 minMean ± SD(95% CI)	37.4 ± 27.7 (29.5 – 45.2)	44 ± 24.5 (37 – 50.9)	42.5 ± 24.4 (35.5 – 49.5)

DISCUSSION

This study showed similar efficacy for three medications, which were tested. However, the results suggested that comparing to morphine and ketorolac, paracetamol had lower complications.

In addition, the obtained results showed that there were no significant differences between three groups for rescue analgesia.

Bektas *et al*., conducted a double-blind, placebo-controlled, clinical trial and compared intravenous paracetamol and morphine with placebo for the management of acute renal colic pain. The author reported that the efficacy of both intravenous paracetamol and morphine was similar, provided that superior pain relief is given rather placebo [3].

In another study by Craig *et al*., [5], 55 patients with isolated limb trauma enrolled and received intravenous paracetamol (1 g) or morphine (10 mg) during 15 min. The pain score was recorded at 0, 5, 15, 30 and 60 min after administration. They showed that the analgesic efficacy of intravenous morphine was similar to intravenous paracetamol at any time interval. They also illustrated that the need for rescue analgesia between both groups was not statistically significant. However, treatment complication was significantly higher in morphine group compared to paracetamol group. These findings were comparable with our results.

Azizkhani *et al*., compared the efficacy of 10 mg of intravenous morphine and 1 g of intravenous acetaminophen for the treatment of renal colic. Intravenous morphine was significantly superior to paracetamol. But, they also reported that the frequency of side effects including dizziness and arterial hypotension, in morphine group were significantly higher than acetaminophen group [1].

Serinken *et al*., conducted a double blind, randomized clinical trial to assess the safety and efficacy of intravenous morphine (0.1 mg/kg) Vs paracetamol (1 g) for renal colic. Both treatment groups had similar efficacy, but adverse effects in morphine groups were higher than paracetamol [6].

Ghuman *et al*., conducted a double blind trial to compare the analgesic effect of combination of 5 mg morphine and 15 mg ketorolac with 5 mg morphine and 15 mg ketorolac alone. Their results demonstrated that combination of morphine and ketorolac was significantly better than morphine or ketorolac alone. There was no significant difference between morphine and ketorolac alone. Their study demonstrated that number of patients who required rescue analgesia in combination group was significantly lower than both ketorolac and morphine alone groups. On the other hand, patients who received morphine had significantly higher adverse reactions compared to combination and ketorolac groups [7]. The results of our study also showed that morphine and ketorolac had similar efficacy for renal colic. Also, the adverse reactions among ketorolac group were higher than morphine. These differences were not statistically significant.

In a systematic review by Holdgate *et al.,* the analgesic efficacy of NSAIDS Vs opioids for acute renal colic was assessed. They demonstrated that NSAIDS have a better analgesic effect and lower side effects than opioids. It is notable that the most opioid which was employed in their review was pethedin [8].

As mentioned above, several investigations mutually compared the efficacy of morphine, NSAIDS and paracetamol for treatment of renal colic. The majority of these studies have consensus on similar efficacy of morphine, ketorolak and paracetamol for renal colic pain relief. On the other hand, some investigators have reported higher adverse effects for morphine compared with paracetamol and ketorolak.

Additionally, some evidences have suggested that frequently use of ketorolac is associated with increased risk of gastrointestinal bleeding [9]. Grissa et al. compared the effectiveness of 1 g intravenous paracetamol Vs 20 mg intramuscular piroxicam. They has concluded that after 90 min, the pain relieved in 80% of patients in paracetamol group. However, the success rate in piroxicam subjects was only 48%. [10]. All of these findings indicate the superiority of paracetamole over morphine and ketorolak for renal colic pain management.

Limitation

This study was limited by several factors. In this study, we evaluated the pain severity after 30 minutes and followed the patients for 6 h. We did not measure the time of pain relief in the population studied. Also, we did not evaluate the pain severity after 30 min and have no idea that which medication has longer effect.

CONCLUSION

Our findings showed that the analgesic efficacy of intravenous morphine, ketorolac and paracetamol was similar. In addition, this study showed that patients who received intravenous paracetamol showed lower complications compared with ones who received morphine and ketorolac. Additionally, paracetamol subjects required less rescue analgesic in comparison with ketorolac subjects. Hence, it can be concluded that intravenous paracetamol (1 g) is an effective and safe medication for treatment of patients with acute renal colic. However, based on the several investigations employed combination of analgesic drugs, patients with severe renal colic pain may respond to combination treatments. Since this is the first study compared three analgesic groups of medications, and further studies are recommended for confirming these results.

Conflict of interest

There is no conflict of interest.

Acknowledgment

Trail was registered in www.irct.ir and IRCT ID: 201207211033N1)

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