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Full Length Research Paper

Combining 1000 mg oral acetaminophen with 75 mg intramuscular Diclofenac of analgesic efficacy for acute renal colic treatment

Hüseyin NARCI[1]*, Murat UĞUR[1], Hüküm UZUN[2] and Mustafa YANDI[3]

[1]Department of Emergency Medicine, Baskent University Faculty of Medicine, Konya, Turkey.
[2]Emergency Department, Numune Training Hospital, Trabzon, Turkey.
[3]Department of Emergency Medicine, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey.

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In this study, we compared oral acetaminophen alone versus intramuscular diclofenac alone versus both together in the treatment of acute renal colic. A prospective, randomized, and double-blind study was conducted in the Emergency Department. Patients were divided into three groups, which were given either acetaminophen + placebo (n = 25), diclofenac sodium + placebo (n = 25) or acetaminophen + diclofenac sodium (n = 25). Pain was evaluated by means of VAS of 100 mm. We monitored patients for visual analog scale (VAS), need for rescue therapy, and adverse events at different time points to at 15, 30 and 60 min. Of the 183 eligible patients, 75 entered the study. VAS pain scores and demographic data of all three groups were similar before the medical procedure (p > 0.05). No significant differences between VAS pain scores obtained soon after the application of acetaminophen or diclofenac at the 15th, 30th and 60th min were observed (p > 0.05). However, a significant difference in the VAS pain scores of the group to which the combination of acetaminophen + diclofenac was administered was observed compared to the acetaminophen group (p < 0.01). Rescue analgesics at 30 min were required by 6 (24%) subjects receiving acetaminophen, 2 (8%) subjects receiving diclofenac and 2 (8%) subjects receiving combination group. No side effects were detected. The combination of acetaminophen and diclofenac is more effective than acetaminophen alone in patients with renal colic. Orally paracetamol was not effective in the treatment of renal colic.

Key words: Acetaminophen, diclofenac, colic, kidney calculi, emergency treatment.

INTRODUCTION

Acute renal colic is one of the most agonizingly painful events of a person's life. Most active emergency departments treat at least a patient with acute renal colic per day. It is estimated that 5 to 12% of the general population will suffer once renal colic during his lifetime. Patients with acute renal colic are often seen and evaluated by emergency physicians at the beginning. Immediate initial treatment besides proper diagnosis and consultations are among the duties of the emergency physicians (Kheirollahi et al., 2010; Valerio et al., 2009).

Acetaminophen, acts by inhibiting the central pathway and prostaglandins. It is a drug with good gastrointestinal system absorption and whose analgesic effect commences early (Barkin, 2001). Clinical studies have shown it to be effective in many acute pain diseases, toothache, acute migraine attack and after surgery (Medve et al., 2001; Bağubek et al., 2010; Lipton et al., 2000; Romsing et al., 2000). NSAIDs and Acetaminophen, have long record of safety and efficacy, but have not been studied in combination for renal colic treatment in the ED.

*Corresponding author. E-mail: hsnnarci@gmail.com. Tel: 905063053233, 90332 2570606-1803.

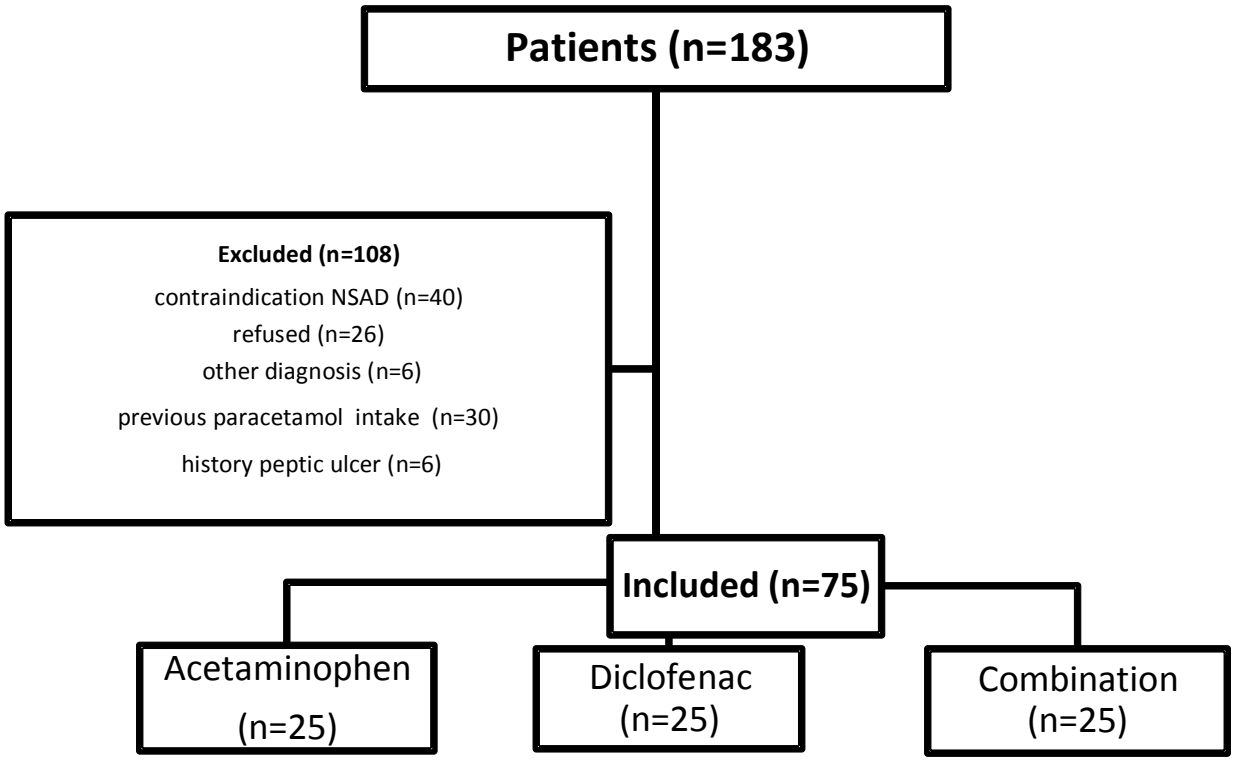

Figure 1. Flowchart of patients screened for the study.

In this study, we compared oral acetaminophen alone versus intramuscular diclofenac alone versus both together in the treatment of acute renal colic.

MATERIALS AND METHODS

This prospective, randomised, double-blind study was performed after receiving the approval of the Ethics Committee. All enrolled patients provided informed consent for participation. We enrolled all consecutive consenting patients (18 years or older) presenting clinical symptoms and signs of renal colic. Standardized screening forms were used to help identify eligible patients. In addition to the history and physical examination, the clinical evaluation of subjects included urine analysis for hematuria and radiologist-performed ultrasonography to detect hydronephrosis; however, confirmation of the diagnosis involved computed tomography (CT), intravenous urography, plain radiography, and stone recovery. Exclusion criteria included; history of peptic ulcer disease, asthma, bleeding disorder impaired renal or hepatic function, suspected hypersensivity to aspirin or NSAID or acetaminophen, pregnant and breast- feeding women. Patients could not be included if they had received analgesics within 6 hs before presentation.

Patients were randomly divided into three groups: Group A: Placebo (i. m. normal saline) given by the administration of 1 g of oral acetaminophen. Group B: Placebo tablet (starch) given by the administration of 75 mg of intramuscular diclofenac sodium. Group C: 1000 mg of oral acetaminophen given by the administration of 75 mg of i.m. diclofenac sodium.

Pain intensity was evaluated with a 100 mm VAS pain score on the 15th, 30th and 60th minute after drug administration. Drug induced side effects in all three groups were recorded over a period of 1 h. At VAS analysis, patients were asked to place a mark on a line according to pain intensity in the region. Measurements were then made in the region using a ruler (VAS: 0 = no pain, 100 = unbearable pain). Drugs were given by nurses unaware of the study. Analysis was performed by emergency medicine research assistants who did not know which group patients had been administered drugs from. There was a form prepared for the study used in collecting data of patients as a writt and checklist by the first author. The data collected by the first reviewer and then checked the data with a second blind reviewer.

All statistical analyses were performed with SPSS version 15.0 for Windows and MedCalc for Windows, version 9.3.0.0 (MedCalc Software, Mariakerke, Belgium). A minimum of 23 patients in each group would berequired to detect a 20 mm difference between groups, assuming an SD of 25 mm, 95% power, and a .05 2-sided levelof significance. At statistical analysis, Anova test was used for comparison of VAS in each group. Multiple comparisons among three group were used Tukey HSD test. Data obtained by measurement are shown as arithmetic mean ± standard deviation, and data obtained by counting are shown as number (%) $P < 0.05$ was regarded as significant.

RESULTS

Among 183 patients assessed for eligibility within 6 months, 75 could participate (Figure 1). Twenty-five were given acetaminophen + placebo (Group A), 25 diclofenac + placebo (Group B) and 25 diclofenac + acetaminophen (Group C). Fourteen of the patients in Group A were men and 11 women, average age 35.8 ± 13; 13 of the patients in Group B were men and 12 women, average age

Table 1. Baseline characteristics of patients according to the treatment group.

Characteristic	Acetaminophen (n=25) (Group A)	Diclofenac (n=25) (Group B)	Diclofenac (n=25) (Group C)	*p* Value
Gender (M/F)	14/11	13/12	15/10	$p > 0.05$
Age (years)	35.8 ± 13	39.6 ± 18	34 ± 12	$p > 0.05$
SBP (mmHg)	130 ± 18.9	121.8 ± 26.6	124 ± 19.1	$p > 0.05$
DBP (mmHg)	81.6 ± 14.3	77.4 ± 14.3	79.2 ± 12.8	$p > 0.05$
VAS (mm)	68 ± 18.2	68.9 ± 22.8	73.3 ± 13.2	$p > 0.05$

SBP, Systolic blood pressure; DBP, diastolic blood pressure; VAS, visual analog scale.

Table 2. VAS scores observed over hour in the study groups displayed changes over time.

Drug	VAS 0	VAS 15	VAS 30	VAS 60
Acetaminophen	68 ± 18.2	56.2 ± 15.5*	42.8 ± 13.2	27.1 ± 16.9
Diclofenac	68.9 ± 22.8	46.8 ± 21.1	30.2 ± 19.53	14.1 ± 19.97
Acetaminophen + Diclofenac	73.3 ± 13.2	33.8 ± 20.87**	13.6 ± 22.4**	5.4 ± 12.2**
p Value	0.55	0.001	0.001	0.001

*, Difference between Acetaminophen and combine groups were statistically significant (Turkey HSD). **, Difference between combine and Acetaminophen groups were statistically significant (Turkey HSD).

39.6 ± 18; and 15 of the patients in Group C were men and 10 women, average age 34 ± 12. All 3 treatment groups were well matched for baseline characteristics (Table 1). When patients' systolic-diastolic blood pressure and average VAS pain scores at application were analysed there were no significantly differences among the three groups .The reduction in VAS at 60 min was 27 mm for acetaminophen, 14 mm for diclophenac and 5 mm for combination group. At the 15th minute no significant difference was observed between the diclofenac and acetaminophen groups ($p > 0.05$, 46.8 mm, 59.4 mm). VAS scores were lower for diclofenac+acetaminophen than for acetaminophen alone at 15, 30 and 60 min (Table 2). Full pain relief was established in eight (32%) patients in the acetaminophen group, eight (32%) in the diclofenac group and 20 (80%) in the acetaminophen + diclofenac group.

Rescue treatment for patients whose pain was severe and failed to improve was provided with 50 mg of intramuscular meperidine. Rescue treatment was administered to two (8%) patients in the diclofenac group, six (24%) in the acetaminophen group, and two (8%) in the acetaminophen + diclofenac group. No drug related complication or side effects were observed in any group during the course of the study.

DISCUSSION

Our results suggest that combination of acetaminophen and diclofenac is more effective than acetaminophen alone in patients with renal colic. Paracetamol was not effective in treatment renal colic. We acknowledge that our study has several limitations. A major weakness is that our study is used oral acetaminophen. Therefore, we are concerned by the number of patients from our study requiring rescue therapy after the use of oral acetaminophen. This may be related to the small sample of patients.

Renal colic is generally treated with parenteral narcotic analgesics. However, these drugs may also cause such side effects as nausea, vomiting and sedation (Caravati et al., 1989).

Non-steroid anti-inflammatory drugs (NSAIDS) possess major advantages in the treatment of renal colic. Clinical use in renal colic has given good outcomes and pathophysiology. The role of prostaglandins in ureter obstruction and smooth muscle contractility and in the regulation of renal blood flow has been established. The role of prostaglandins regarding the development of pain in renal colic has been reported ever since the 1970s. Renal pelvis pressure rises when an obstruction occurs in the ureter. Renal prostaglandin synthesis and secretion are induced. In particular, vasodilatation in the afferent arterioles and diuresis occur. Renal pelvis pressure begins to rise still further. Studies have shown that prostaglandins increase ureter smooth muscle contractile activity. NSAIDs affect renal blood flow and diuresis by inhibiting prostaglandin synthesis. At the same time, they have an effect on ureteral smooth muscle activity and on local inflammation occurring in the ureter (Valerio et al., 2009; Barkin, 2001).

In a randomised, double-blind study Beck et al. gave 65 female patients about to undergo hysterectomy a low dose of 20 mg/kg and a high dose of 40 mg/kg of rectal acetaminophen and a 100 mg rectal diclofenac-

acetaminophen combination. Pain was evaluated with 10 cm VAS. An increase in analgesia and a reduction in the need for opioids were shown in the group receiving 40 mg/kg of acetaminophen. Subtherapeutic levels were obtained with 20 mg/kg doses. Clinically low VAS levels were obtained in both groups ($p > 0.05$ 3.2 cm, 3.4 cm) (Beck et al., 2000). Seymour (1983) compared 500 and 1000 mg acetaminophen doses postoperatively in periodontal surgery. They reported both doses to be more effective than placebos. However, they reported that the analgesic effect of the 1000 mg dose was greater in comparison to that of the 500 mg dose (Seymour, 1983). The dose of acetaminophen had to be a minimum of 1000 mg when given a single agent, because doses below 1000 mg may be insufficient (Hyllested et al., 2002).

Lipton et al. (2000) compared 1000 mg of oral acetaminophen and placebo in patients with acute migraine attack in a randomised double-blind study. Response to headache two hours after drug administration was 57.8% in the acetaminophen group and 38.7% in the placebo group. In the acetaminophen group 22.4% of patients enjoyed complete pain relief, compared to 11.3% in the placebo group. In conclusion, they reported that acetaminophen was effective and reliable in pain treatment (Romsing et al., 2000).

In a meta-analysis study of 1197 patients, Medve et al. randomly administered 650 mg of acetaminophen, 400 mg of ibuprofen or 75 mg of tramadol or an acetaminophen + tramadol combination to patients with medium and severe toothache. Pain relief was observed in the acetaminophen group in the 18th minute on average (Medve et al., 2001).

In a randomised, double-blind study, Romsing et al. compared the analgesic effects of oral diclofenac and high dose acetaminophen for pain treatment on the third day postoperatively in 48 patients undergoing tonsillectomy. They reported that diclofenac was not more effective than high dose acetaminophen (Romsing et al., 2000). The combination of paracetamol and NSAID was more effective than paracetamol or NSAID alone in 85 and 64% of relevant studies, respectively (Cliff et al., 2010). In our study, pain relief between the acetaminophen and diclofenac groups was similar. There was a statistically significant reduction in pain in the group in which the two were combined. Evident pain relief was observed at 30th minute in the acetaminophen group, and at 15th minute in the group in which both drugs were combined.

Schmidt et al. analysed postoperative pain by administering 0.65 to 1 mg/kg of rectal diclofenac or 13 to 20 mg/kg of acetaminophen to 90 patients prior to tonsillectomy. The need for anaesthetic substances and surgical approach did not change between the two groups, but due to bleeding surgery lasted longer in the diclofenac group. Pain scores and the need for meperidine were no different between the two groups. In conclusion, they reported that rectal diclofenac provided no advantage over acetaminophen in postoperative analgesia (Schmidt et al., 2001).

Cobby et al. (1999) reported that the use of acetaminophen reduced the need for morphine after hysterectomy (Cobby et al., 1999). Montgomery et al. reported that a diclofenac and acetaminophen combination reduced morphine requirement more than the use of acetaminophen alone (Montgomery et al., 1996). In our study, additional doses of rescue analgesia were administered to two (8%) patients in the diclofenac group, six (24%) patients in the acetaminophen group, and two (8%) patients in the diclofenac + acetaminophen group.

In a randomised, double-blind study of 120 patients after tooth extraction, Breivik et al. gave patients diclofenac tablets, 1000 mg of acetaminophen, a combination of both or diclofenac + acetaminophen + codeine. They reported that the diclofenac + acetaminophen combination was more effective (Breivik et al., 1999). In our study, we determined a higher analgesic effectiveness in the group in which diclofenac and acetaminophen were combined.

Grissa et al. (2011) reported that a single therapy with intravenous paracetamol more efficiently relieved pain in acute renal colic than did intramuscular piroxicam. Bektaş et al. (2011) sowed that Intravenous paracetamol is an efficacious and safe treatment for ED patients with renal colic (Bektas et al., 2009). In this study, oral paracetamol was not effective in treatment renal colic. The present study showed that diclofenac either alone or in combination with acetaminophen was effective in patients with renal colic. Oral paracetamol was not effective in treatment renal colic. It may be approriate to combine paracetamol with NSAIDs, but future studies are required. The addition of an NSAID to paracetamol seems to provide additional analgesic efficacy. However, whether this additional analgesic efficacy is a result of a true additive effect or a reflection of NSAIDs being more effective than paracetamol is not clear.

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