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Research Paper

Efficacy and Safety of Parecoxib in the Treatment of Acute Renal Colic: A Randomized Clinical Trial

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Hung-Wen Chen[1], Chung-Jing Wang[2]*, Yi-Chun Su[1], Chi-Sen Hsu[3], Chien-Hsing Chang[2], Po-Chao Tsai

[1]Department of Emergency, Saint Martin De Porres Hospital, Chiayi, Taiwan, R.O.C.
[2]Division of Urology, Department of Surgery, Saint Martin De Porres Hospital, Chiayi, Taiwan, R.O.C.
[3]Department of Infection, Saint Martin De Porres Hospital, Chiayi, Taiwan, R.O.C.

*Corresponding author email. jing@stm.org.tw
Tel: +886 5 2756000 ext.: 1013;
FAX: +886-5-2788535.

Running title: **Parecoxib in the treatment of acute renal Colic.**

Abbreviations: VRS: verbal rating scale, **VAS:** visual analogue scale, **IVU:** intravenous urography.

ABSTRACT

Few clinical studies have evaluated the use of parecoxib in acute pain due to renal colic. The objective of this study is to compare the analgesic efficacy of intravenously injected parecoxib (40 mg) versus intramuscularly injected pethidine (50 mg) in reducing pain during acute renal colic attacks. This prospectively randomized controlled trial was conducted from January 2010 to December 2012. All patients visited the emergency room or outpatient clinic for acute renal colic based on their signs and symptoms, were eligible: of 212 patients, 88 were in the pethidine group, and 89 patients were in the parecoxib group. Patients with acute renal colic, were assigned to the intramuscular pethidine (50 mg) group or to the intravenous parecoxib (40 mg) group. All patients completed the validated verbal rating scale (VRS) and visual analogue scale (VAS) before the treatment (T0) and 30 (T30) and 60 min (T60) after the drug injection. The primary outcome was the analgesic efficacy of parecoxib (40 mg) intravenous injections versus pethidine (50 mg) intramuscular injections. There were significant differences between the treatment groups with regard to VRS and VAS scores at all time points. There was no comparison to a group receiving placebo therapy. It was concluded that intravenous parecoxib is both more effective than conventional intramuscular pethidine and more potent with a longer analgesic effect.

Key words: Renal colic, parecoxib, pethidine, COX-2-selective NSAID.

INTRODUCTION

Urolithiasis is a common disease and the lifetime risk of developing an acute attack is estimated at about 1 to 10% (Frank, 1989). A typical episode occurs during the night or early morning and is sudden in onset. The usual treatment for this condition includes non-steroidal anti-inflammatory drugs (NSAIDs) combined with parenteral narcotic analgesics and spasmolytic agents (Michel, 1994). In addition to severe pain, the main signs and symptoms of renal colic include nausea, vomiting, hypertension, swollen abdomen, fever, chills, and hematuria. The cyclooxygenase (COX) enzyme (Vane, 1971) exists in two distinct isoforms: COX-1, the primary site of action for nonselective NSAIDs, is present in many tissues and is necessary for physiological (homeostatic) functions such as gastric mucosal protection and normal platelet aggregation (Gudis, 2005; Brzozowski, 2005) and COX-2 is an inducible form of the COX enzyme and is expressed locally in inflamed tissues (Seibert, 1994; Otto, 1995). Although nsNSAIDs have been shown to be effective for acute and chronic pain relief, a number of adverse effects (AEs) have been associated with their use. Common side effects include rashes, headaches, dizziness, drowsiness, abdominal pain, nausea, diarrhea, constipation, and fluid retention.

Parecoxib, an injectable COX-2 selective NSAID, is currently the only available non-opioid analgesic and anti-inflammatory agent indicated for parenteral use that does not interfere with platelet aggregation (Emery, 1996; Simon, 1996). As parecoxib is intended for the short-term treatment

of acute pain, it may offer advantages versus nsNSAIDs in the treatment of acute renal colic; however, to date, few clinical studies have evaluated the use of parecoxib in acute pain due to renal colic.

The objective of this study was to compare the analgesic efficacy and safety of parecoxib (40 mg) intravenous injections versus pethidine (50 mg) intramuscular injections in their ability to reduce pain during an acute renal colic attack.

MATERIALS AND METHODS

Study design

The study was approved (#10B-014) by the Institutional Review Board of St. Martin De Porres Hospital in Chia-Yi city, where the work was undertaken. All procedures involving human participants were in accordance with the ethical standards of the institutional and national research committee and in compliance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was designed as a prospectively randomized controlled trial and carried out from January 2010 to December 2012.

Study population

All patients enrolled in this study visited the emergency room or outpatient clinic for acute renal colic based on their signs and symptoms. This included histories of flank pain with or without hematuria, and renal or ureteral stones identified with intravenous urography (IVU), ultrasonography, and noncontrast computerized tomography. All patients were asked to sign an informed consent form before granting their participation.

Exclusion criteria included: a history of active peptic ulceration, active dyspepsia, gastrointestinal bleeding (i.e., Crohn's disease or ulcerative colitis), and an esophageal, gastric, or duodenal ulcer within 1 month prior to the screening evaluation.

Study interventions

Patients, by the use of a random numbers table, were assigned to the intramuscular pethidine (50 mg) group or to the intravenous parecoxib (40 mg) group. All patients completed the validated verbal rating scale (VRS) and visual analogue scale (VAS) before the treatment (T0) and 30 (T30) and 60 min (T60) after the drug injection. Pain was assessed with a five-point verbal rating scale (VRS): 0: no pain; 1: mild pain; 2: moderate pain; 3: severe pain; and 4: intolerable pain. Pain intensity was also evaluated using the VAS. For the VAS, patients were presented with a standard 10 cm linear analogue scale and instructed that the left-hand side represented no pain (0 mm) while the right-hand side was maximal pain (100 mm). They were asked to draw perpendicular lines through the horizontal axis to represent the degree of pain.

Randomization

A total of 212 patients were eligible and prospectively randomized into two groups following visits to the emergency room or outpatient clinic for acute renal colic based on their signs and symptoms. In the pethidine group, 89 patients were available for consideration. Among these, six missed primary outcome and five refused to sign the consent forms and were removed from the study. In all, 78 patients enrolled in the study and received intramuscular pethidine (50 mg). In the parecoxib group, 88 patients were initially available. Among these patients, four missed primary outcome and four refused to sign the consent forms and were removed from the study. In all, 80 patients were enrolled and received intravenous parecoxib (40 mg) (Figure 1).

Study outcomes

The primary outcome measure was the analgesic efficacy of parecoxib (40 mg) intravenous injections versus pethidine (50 mg) intramuscular injections. The secondary outcome measures were the pain intensity and adverse effects.

Sample size and statistical analysis

Detection of a 30% difference in the proportions of parecoxib effectiveness in the treatment groups at a significance level of 0.05 and a power of 90% required a sample size of 75 patients per group. All analyses were conducted using SPSS® version 14.0.1. The differences in VRS and VAS between both groups were determined using the Mann-Whitney U test. The demographics were assessed with the Mann-Whitney U test and chi-square test. Adverse effects of pethidine and parecoxib were assessed with Fisher's exact test.

RESULTS

A total of 158 patients completed the study protocol, 78 in the pethidine group and 80 in the Parecoxib group. No significant statistical differences were observed in patient age, gender distribution, body mass index, and stone location (Table 1).

There were significant differences observed between the two treatment groups with regard to pain and pain intensity

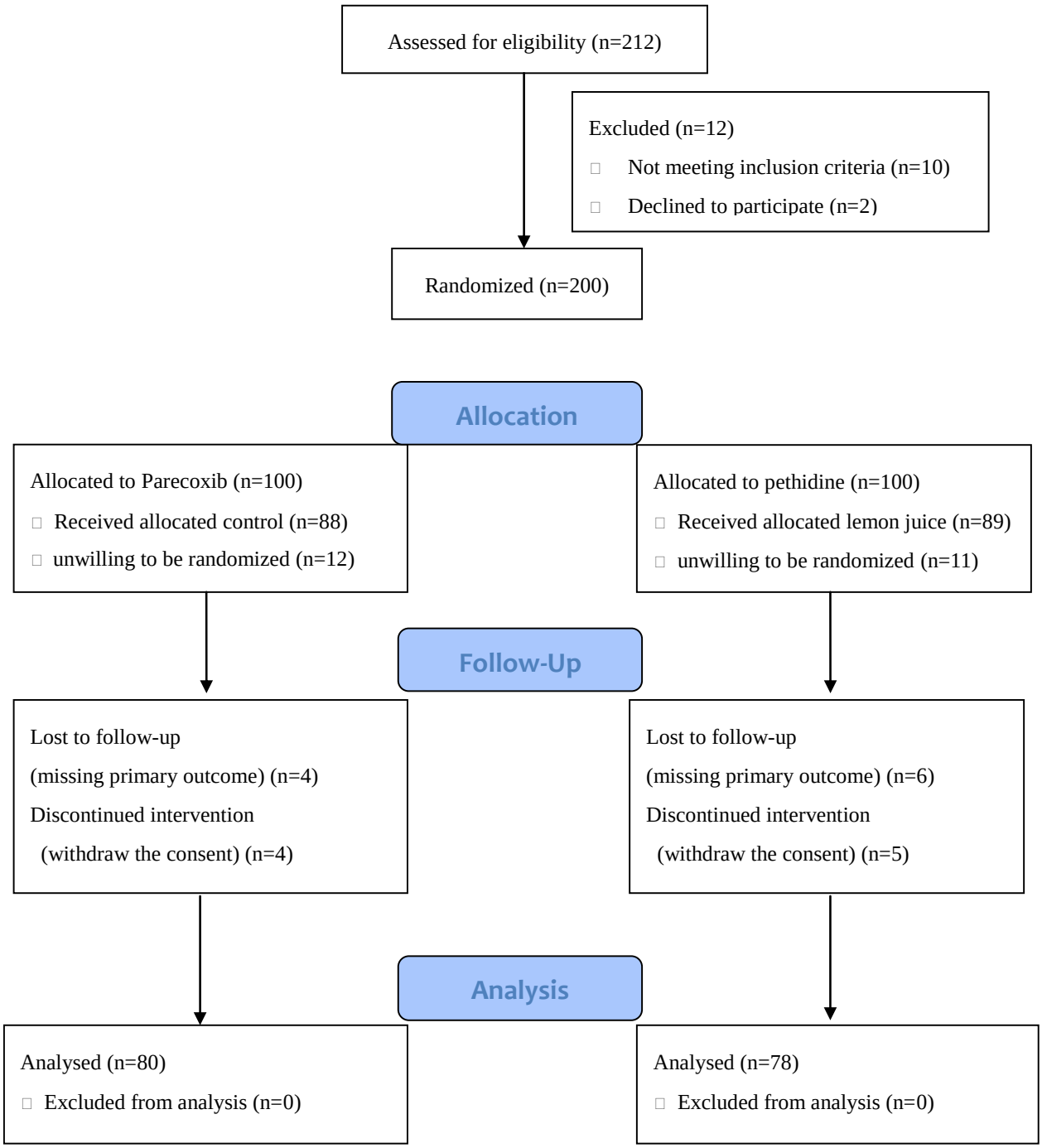

Figure 1. Summary of study disposition. Numbers of participants declining further follow-up or not responding are cumulative in direction of participant flow.

at all measurement times (Table 2). No significant difference was observed in adverse effects.

DISCUSSION

The sudden obstruction of the upper urinary tract stimulates the synthesis of prostaglandin E2 in the renal medulla (Sjodin, 1981). It also increases both the contractility of ureteral smooth muscle and the renal blood flow. Furthermore, the uretero-pelvic pressure rises, which then distends the renal capsule leading to excruciating colicky pain. Based on this pathophysiology, inhibition of prostaglandin synthesis to reverse the process is the

Table 1. Patients characteristics

Characteristic	Pethidine	Parecoxib	*P* value
	N=78	N=80	
Age(yr) [a]			0.814
Mean	50.13 ± 10.35	50.03 ± 8.93	
Range	29-79	28-76	
Gender [b]			0.504
Male	60 (76.92)	65 (81.25)	
Female	18 (23.08)	15 (18.75)	
Body mass index [a]	25.15 ± 2.19	25.14 ± 2.58	0.947
Male [a]	25.36 ± 2.19	25.38 ± 2.56	0.892
Female [a]	24.91 ± 2.53	24.65 ± 2.84	0.799
Stone location [b]			0.604
Upper	6 (7.69)	8 (10.0)	
Middle	29 (37.18)	24 (30.0)	
Lower	43 (55.13)	48 (60.0)	

Values are presented as mean±standard deviation or number (%). [a]Mann-Whitney U test. [b]Chi-square test.

Table 2. Randomization study results.

Varible	Pethidine	Parecoxib	*P* value
Pain(VAS)(T0) [a]	81.46 ± 5.59	81.65 ± 4.90	0.937
Pain(VAS)(T30) [a]	43.88 ± 7.87	37.75 ± 4.08	< 0.001
Pain(VAS)(T60) [a]	25.83 ± 4.82	18.61 ± 2.84	< 0.001
Pain(VRS)(T0) [a]	3.76 ± 0.51	3.70 ± 0.46	0.231
Pain(VRS)(T30) [a]	1.88 ± 0.51	1.19 ± 0.55	< 0.001
Pain(VRS)(T60) [a]	0.96 ± 0.41	0.66 ± 0.48	< 0.001
Adverse effects [b]			0.078
Nausea	12 (40.0)	5 (29.41)	
Vomiting	8 (26.67)	4 (23.53)	
Dizziness	3 (10.0)	7 (41.18)	
Drowiness	7 (23.33)	1 (5.88)	

Values are presented as mean±standard deviation or number (%). ***p < 0.001, [a]Mann-Whitney U test, [b]Fisher's exact test.

therapeutic goal in decreasing renal colic pain. Traditionally, NSAIDS, which act on the cyclooxygenase pathway of arachidonic acid metabolism to block prostaglandin biosynthesis, are often combined with spasmolytics and even narcotic analgesics and play a crucial role in the treatment of acute renal colic (Michel, 1994). However, the effects of oral spasmolytics and NSAIDs greatly diminish in renal colic associated with severe gastrointestinal symptoms, and their use in patients allergic to NSAIDs is prohibited. When given orally, opiates show a large first-pass effect, thus, their oral use is precluded in the management of acute pain. Due to the colicky nature of the pain and despite the development of new potent NSAIDs, treatment of renal colic necessitates a narcotic analgesic. Because of the addictive properties of opiate drugs, their storage and use bring legal and practical concerns.

The COX-2 selective NSAID parecoxib has also been used in the treatment of acute pain. However, unlike ketoprofen, parecoxib, another widely used drug to treat renal colic pain, does not cause inhibition of platelet function (Noveck, 2001; Munsterhjelm, 2006), thus, avoiding the risk of bleeding. In contrast to certain parenteral NSAID formulations that require setting up a slow intravenous infusion, parecoxib can be injected rapidly and directly into a vein, which is a useful property in the busy emergency room setting and outpatient clinic.

Phillips et al. (2009) previously evaluated the use of celecoxib, the only other currently approved COX-2 selective NSAID available for the management of acute renal colic. In their prospective, randomized, controlled clinical trial of 53 patients, they found no significant differences between celecoxib and the placebo for either pain scores or narcotic requirements. Moreover, Glina (2011) reported the first use of parecoxib in their study, and based on the findings of the primary analysis, parecoxib was not inferior to ketoprofen in the treatment of acute pain due to renal colic. Additionally, there were no significant treatment differences between parecoxib and ketoprofen for any of the secondary efficacy endpoints.

Parecoxib was well tolerated in our study and demonstrated a superior safety profile compared to pethidine. However, there were no obvious safety concerns related to the administration of either parecoxib or pethidine in this study.

We conclude that intravenous parecoxib is more effective than conventional intramuscular pethidine; it is also more potent and has a longer analgesic effect. Because of its wide safety margin, lack of physical dependence, and convenience of administration, intravenous parecoxib provides an excellent alternative to acute and maintenance treatments in renal colic patients.

Conclusions

Intravenous parecoxib is more effective than intramuscular pethidine in the treatment of pain due to acute renal colic; it is also well tolerated and has a comparable safety profile.

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