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Original Article

Efficacy and safety of combination therapy with drotaverine and ketorolac versus ketorolac monotherapy for acute renal colic: a retrospective study of 322 patients

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Abstract: Aim: To investigate the analgesic efficacy and safety of combined therapy using drotaverine and ketorolac vs ketorolac in the treatment of acute renal colic. Methods: This was a retrospective study of a consecutive cohort that included 322 emergency department (ED) patients with a diagnosis of renal colic from our hospital, from June 2014 to September 2015. Pain intensity (PI) was recorded using a visual analog scale (VAS) at different time-points after treatment. The primary outcome was defined as a decrease of 50% or more in the mean PI. The need for rescue analgesics in 120 min and occurrence of adverse effects were considered as secondary outcomes. Results: Of 322 eligible patients, 249 patients were analyzed in this study: 125 patients received ketorolac plus drotaverine and 124 patients received ketorolac only. There were significant differences in PI between the two groups at 30min and 120 min (PI: [OR 1.573, 95% CI: 1.007-3.054, $P_{30\ min}$ = 0.047], [OR 2.938, 95% CI: 1.11-7.78, $P_{120\ min}$ = 0.03] in multivariable logistic regression) (PI: [OR 1.869, 95% CI: 1.119-3.121, $P_{30\ min}$ = 0.017], [OR 2.938, 95% CI: 1.11-7.78, P_{120} min = 0.03] in univariable logistic regression). Moreover, significant differences were also found in PI in subgroup analysis of patients with mid and proximal ureteric stones (PI: [OR 3.888, 95% CI: 1.409-10.729, $P_{30\ min}$ = 0.009] in multivariable logistic regression) (PI: [OR 3.476, 95% CI: 1.363-8.865, $P_{30\ min}$ = 0.009] in univariable logistic regression). Pain relief at 120 min was obtained in 119 patients (95.2%) receiving combined therapy and in 106 patients (85.5%) receiving ketorolac (P = 0.011). Rescue analgesics were required in six patients (4.8%) receiving combined therapy and 18 patients (14.5%) receiving ketorolac (P = 0.009). Adverse events were similar between the two groups: 20 (16%) in the combined group and 16 (13%) in the ketorolac group (P = 0.843). Conclusion: Ketorolac combined with drotaverine is effective in relief of acute renal colic, especially pain due to mid and proximal ureteric lithiasis, but did not decrease PI significantly in renal colic patients with renal and distal ureteral stones. On the other hand, combined therapy with ketorolac and drotaverine was associated with a reduced use of rescue analgesics.

Keywords: Analgesia, drotaverine, renal colic, visual analog scale

Introduction

Renal colic is an acute syndrome characterized by severe flank pain arising from obstruction of the urinary tracts, with a lifetime risk of 12% in men and 6% in women [1]. The excessive pressure stimulates the local release of prostaglandins, which in turn leads to vasodilatation, diuresis, and ureteral spasm. Thus, emergency treatment of acute renal colic involves finding a rapid and effective means of analgesia after diagnosis [2]. However, the ideal analgesic regimen for acute renal colic remains controversial in ED. The guidelines of the European Association of Urology on ureteral calculi suggests the use of nonsteroidal anti-inflammatory drugs (NSAIDs) as a first-line strategy for relieving renal colic, and using opioids as rescue medica-

tion [3]. A large number of studies have recommended ketorolac (the first parenteral NSAID available in the United States) as the primary analgesic for the treatment of renal colic, given its efficiency in relieving acute pain with fewer adverse outcomes and lower costs [1, 4-6].

Regardless of their effective action as analgesics for renal colic, a number of adverse events have been associated with NSAIDs, including nausea, vomiting, rash, dizziness, hypotension, and headache [7]. Failure to relieve pain in renal colic, defined as the requirement for rescue therapy, occurs in 7% to 39% of such patients treated with NSAIDs [8].

To improve the efficiency of NSAIDs as well as to reduce the requirements for rescue analgesics, spasmolytics are frequently used for acute renal colic by medical practitioners, as they may help to relieve pain by relaxing the smooth muscle[9]. Drotaverine, a selective phosphodiesterase 4 (PDE IV) inhibitor, has previously been shown to be useful in the efficient and safe treatment of renal colic [10, 11].

The concept of balanced analgesia that has been suggested by earlier studies has proven to be the method of choice for achieving sufficient pain reduction by using a combination of different regimens [12]. In 2006, Safdar et al. reported that a combination of morphine and ketorolac offered pain relief superior to that offered by either drug alone, and was associated with a decreased requirement for rescue analgesics [13]. Regardless of it is an experienced treatment for the co-administration of drotaverine and ketorolac for pain relief in acute renal colic, there has been no evidence for this combined therapy. Thus, we carried out a retrospective cohort study to investigate whether the addition of drotaverine to ketorolac could improve the efficacy of pain relief in patients with acute renal colic.

Methods

Patients and inclusion criteria

We conducted a retrospective analysis of 322 adult patients (age: 18-60 years) who reported to the emergency department of Sun Yat-sen Memorial Hospital from June 2014 to September 2015, with clinical symptoms and signs of renal colic. Standardized screening tools were used to identify eligible patients. Inclusion criteria were: (1) Presenting of acute renal colic after physician evaluation by auxiliary examinations, such as ultrasonography and non-contrast computed tomography (CT); (2) Visual analogue scale (VAS) score ≥ 40 mm. Exclusion criteria: (1) Those who did not undergo ultrasonography or CT, or did not reveal a renal or ureteral stone; (2) Patients who were diagnosed not only renal but also ureter stones; (3) Patients who were pregnant or had used any spasmolytics or analgesics within the previous 6 h; (4) Those who had second or third degree atrioventricular block, malignant disease, renal failure, urogenital anomaly, or hepatic or cardiac insufficiency.

Stones in the mid-ureter, but closed to the top, were classified into the mid and proximal ureter group, and those closer to the bottom were included in the distal ureter group. Patients who only had renal stones were classified into the renal group.

Treatments

Patients who had a clinical diagnosis of suspected acute renal colic after physician evaluation by physical examination were treated with ketorolac plus drotaverine or with ketorolac only, based on physician decision. In the combined group, 125 patients received intramuscular ketorolac (60 mg) plus intravenous drotaverine hydrochloride (80 mg), while in the ketorolac group, 124 patients received intramuscular ketorolac (60 mg) only. Rescue therapy was defined as the need for morphine if the VAS score at 120 min exceeded 40 mm [14].

Data collection and endpoints

Observations and pain scores were recorded on a standard datasheet by the treating nurse at 0 (baseline), 30, 60 min, and then hourly until 2 h after commencing treatment. All patients were asked to rate the intensity of their pain on a 0- to 100-mm VAS datasheet, in which 0 indicates “no pain” and 100 indicates the “severest imaginable pain”. The primary efficacy endpoint was defined as a relative decrease of PI between baseline and each observation time, calculated as previously described [15]: [(PIBaseline-PIx)/PIBaseline)] × 100%. For example, the mPI 30 min represents the mean reduction in PI across 30 min (VAS at baseline-VAS at 30 min). The effectiveness of

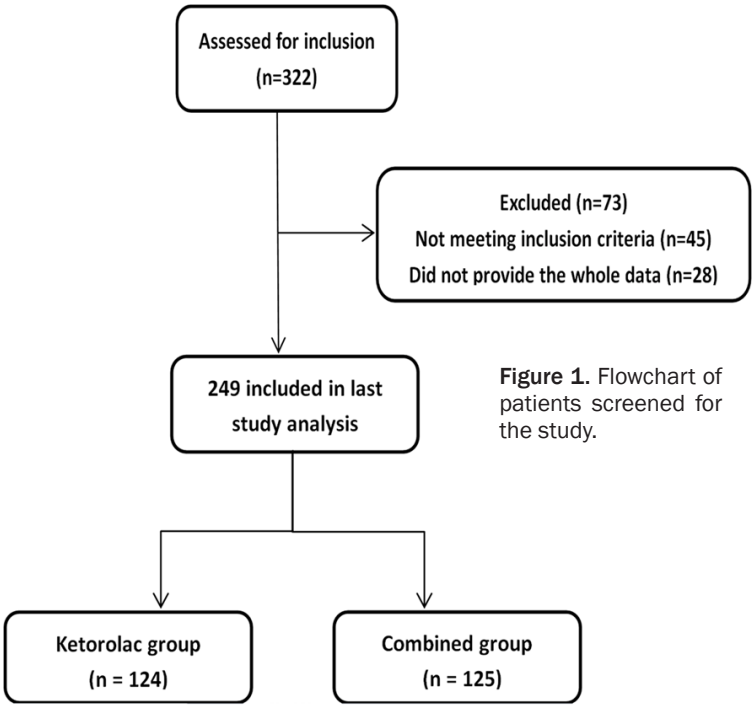

Figure 1. Flowchart of patients screened for the study.

Table 1. Baseline characteristics of the participants in the study

	Combined group (n = 125)	Ketorolac group (n = 124)	*P*-value
Age, mean ± SD	39.7 ± 10.2	41.6 ± 9.8	0.1341[a]
Gender, n (%)			0.475[b]
Male	85 (68.0)	79 (63.7)	
Female	40 (32.0)	45 (36.3)	
Baseline VAS, mean ± SD (mm)	87.2 ± 9.0	85.5 ± 9.0	0.1312[a]
Duration of pain before visit, (min)	88.9 ± 61.3	85.4 ± 54.9	0.5012[a]
History of urinary tract infection, (n)	15	10	0.292[c]
Diagnostic evaluation, n (%)			0.126[b]
CT scan	90 (72.0)	78 (62.9)	
Ultrasound	35 (28.0)	46 (37.1)	
Location of Stone, n (%)			0.707[b]
Mid and Proximal ureter	37 (29.6)	42 (33.9)	
Distal ureter	75 (60.0)	68 (54.8)	
Renal	13 (10.4)	14 (11.3)	

[a]Two sample t-test. [b]Chi-square test. [c]Fisher's exact test.

drugs was defined as a decrease of 50% or more as compared with the initial VAS, without exacerbation during the following 2 h, and without the need for rescue medication or the presence of adverse effects. The secondary end points were the need for rescue medication, and the number of adverse events presence during the 2 h of clinical observation.

Statistical analysis

Demographic variables, Diagnostic evaluation, Location of Stone, rescue analgesics and adverse events measured on a categorical scale were summarized using quality, frequencies and percentages, while continuous variables were summarized in terms of means and standard deviations (SD). The comparisons of demographic characteristics between the two cohorts were conducted using two sample t-test or Chi-square test. The comparisons of History of urinary tract infection, rescue analgesics and adverse events adverse events between study cohorts were performed using Fisher's exact test. The variation of PI in two cohorts was statistically analyzed using the univariable and multivariable and logistic regression, adjusted by age, gender, baseline VAS and duration of pain before visit. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were reported. Statistical analyses were performed with SPSS 16.0 software (SPSS Inc., Chicago, IL), and $P < 0.05$ was considered statistically significant.

Results

Characteristics of the patients

Three-hundred-and-twenty-two patients were originally included; 45 patients were then excluded because they did not meet the inclusion criteria, and 28 patients were excluded because their data sets were not complete, due to poor pain toleration during the study. Thus, eventually, 249 patients diagnosed with acute renal colic were included in the study: 125 patients received ketorolac plus drotaverine, and 124 patients receive intramuscular ketorolac only (for details, see **Figure 1**).

Table 2. Multivariable and univariable logistic regression to determine the association between the treatment method and Pain intensity in total patients

Pain parameter	Combined group (n = 125)	Ketorolac group (n = 124)	Multivariable logistic analysis			Univariable logistic analysis		
			OR	95% CI	*P*-value[a]	OR	95% CI	*P*-value
PI mean ± SD (%)								
30 min	47.1 ± 15.8	43.6 ± 13.7	1.573	1.007-3.054	0.047	1.869	1.119-3.121	0.017
60 min	63.5 ± 12.2	60.6 ± 11.6	NA	NA	0.846	1.009	0.420-2.421	0.984
120 min	82.3 ±10.4	80.0 ± 10.0	2.938	1.11-7.78	0.03	2.938	1.11-7.78	0.030

[a]Multivariate analysis, adjusted by age, gender, baseline VAS and duration of pain before visit.

Table 3. Multivariable and univariable logistic regression to determine the association between the treatment method and Pain intensity in patients with mid and proximal ureteric stones

Pain parameter	Combined group (n = 37)	Ketorolac group (n = 42)	Multivariable logistic analysis			Univariable logistic analysis		
			OR	95% CI	*P*-value[a]	OR	95% CI	*P*-value
PI mean ± SD (%)								
30 min	50.0 ± 11.0	42.4 ± 11.7	3.888	1.409-10.729	0.009	3.476	1.363-8.865	0.009
60 min	67.7 ± 11.1	61.2 ± 11.4	NA	NA	0.192	2.917	0.551-15.441	0.208
120 min	86.3 ± 8.2	79.8 ± 7.4	7.2	0.842-61.584	0.071	7.2	0.842-61.584	0.071

[a]Multivariate analysis, adjusted by age, gender, baseline VAS and duration of pain before visit.

Table 4. Rescue analgesics and incidence of adverse event in the study

Pain parameter	Combined group (n = 125)	Ketorolac group (n = 124)	*P*-value
Pain relief at 2 h, n (%)	119 (95.2%)	106 (85.5%)	0.011[a]
Adverse event, n (%)	12 (9.6%)	11 (8.9%)	0.843[a]
Nausea	1 (0.8%)	3 (2.4%)	
Vomiting	1 (2.4%)	2 (1.6%)	
Rash	3 (2.4%)	2 (1.6%)	
Dizziness	4 (3.2%)	2 (2.4%)	
Hypotension	2 (1.6%)	1 (0.8%)	
Headache	1 (0.8%)	1 (0.8%)	

[a]Fisher's exact test.

The characteristics of the entire patient group of 249 are shown in **Table 1**. The mean age of the total group was 41.2 years, while the female-to-male ratio was 85:164. Ureteral stones were located renally in 27 cases (10.8%), at the mid and proximal ureter in 79 (31.7%), and at the distal ureter in 143 (57.5%). Patients who were excluded had renal stones located at the mid and proximal ureter were 79 (35.6%), and at the distal ureter were 143 (64.4%) (data not show). The baseline characteristics of each group were comparable. The mean baseline VAS scores of the patients recruited were 87.2 ± 9.0 in the combined group and 85.5 ± 9.0 in ketorolac group, respectively (**Table 1**).

Efficacy

There were significant differences in PI between the two groups at 30 min and 120 min after commencing treatment (PI: [OR 1.573, 95% CI: 1.007-3.054, $P_{30\ min}$ = 0.047], [OR 2.938, 95% CI: 1.11-7.78, $P_{120\ min}$ = 0.03] in multivariable logistic regression) (PI: [OR 1.869, 95% CI: 1.119-3.121, $P_{30\ min}$ = 0.017], [OR 2.938, 95% CI: 1.11-7.78, $P_{120\ min}$ = 0.03] in univariable logistic regression) (**Table 2**). A subgroup analysis was performed between the two groups according to the location of the urinary stones. Interestingly, there was a relative decrease in the PI of patients with mid and proximal stones treated with the combination treatment at 30 min (**Table 3**; [OR 3.888, 95% CI: 1.409-10.729, $P_{30\ min}$ = 0.009] in multivariable logistic regression, [OR 3.476, 95% CI: 1.363-8.865, $P_{30\ min}$ = 0.009] in univariable logistic regression). However, we did not notice any differences in patients with renal or distal ureteric stones (**Tables 5** and **6**).

The pain relief assessment also favored the combined group (95.2%) compared to ketoro-

Table 5. Multivariable and univariable logistic regression to determine the association between the treatment method and Pain intensity in patients with renal stones

Pain parameter	Combined group (n = 13)	ketorolac group (n = 14)	Multivariable logistic analysis			Univariable logistic analysis		
			OR	95% CI	*P*-value[a]	OR	95% CI	*P*-value
PI mean ± SD (%)								
30 min	38.9 ± 10.3	39.5 ± 8.0	NA	NA	0.957	1.083	0.061-19.313	0.957
60 min	57.7 ± 12.6	58.8 ± 8.6	NA	NA	0.998	NA	NA	0.998
120 min	78.7 ± 11.2	79.2 ± 12.8	NA	NA	0.29	NA	NA	0.999

[a]Multivariate analysis, adjusted by age, gender, baseline VAS and duration of pain before visit.

Table 6. Multivariable and univariable logistic regression to determine the association between the treatment method and Pain intensity in patients with distal ureteric stones

Pain parameter	Combined group (n = 75)	Ketorolac group (n = 68)	Multivariable logistic analysis			Univariable logistic analysis		
			OR	95% CI	*P*-value[a]	OR	95% CI	*P*-value
PI mean ± SD (%)								
30 min	47.2 ± 10.3	45.1 ± 10.0	NA	NA	0.42	1.537	0.78-3.03	0.214
60 min	62.5 ± 7.5	60.6 ± 7.1	NA	NA	0.872	1.111	0.307-4.018	0.872
120 min	81.0 ± 10.9	80.3 ± 10.7	NA	NA	0.101	2.708	0.794-9.239	0.112

[a]Multivariate analysis, adjusted by age, gender, baseline VAS and duration of pain before visit.

lac group at the endpoint (85.7%); this difference was also significant ($P = 0.011$). Rescue analgesics were required by six patients (4.8%) at 120 min in the combined group, compared to 18 patients (14.5%) in the ketorolac group ($P = 0.009$; **Table 4**).

Safety

The adverse events in the two groups are shown in **Table 4**. There were 18 (14.5%) patients in the combined group and six (4.8%) patients in the ketorolac group who experienced adverse events. The frequency and adverse events were not different between the two treatment groups during the clinical observation period ($P = 0.843$). The percentage of patients who had at least one adverse event was 6.4% (8 patients/12 events) in the combined group and 5.6% (7 patients/11 events) in the ketorolac group. No adverse events were considered sufficiently serious to require stopping the treatment.

Discussion

Renal colic is the consequence of acute dilation of the urinary tract proximal to an obstructing insult, along with a smooth muscle spasm at the site of obstruction that is caused by calculus [1, 11], and pain relief for such patients is an urgent task for clinical doctors in the emergency department. The classic therapy is pethidine plus hyoscine N-butylbromide (HBB), but a higher ratio of side effects was observed with this therapy. According to a systematic review of 20 trials, NSAIDs are more effective and safer for analgesia in renal colic patients than opioids [16]. Thus, NSAIDs have been regarded as the first line analgesic treatment in this condition.

Spasmolytics are frequently used for acute abdominal disease by medical practitioners, as they theoretically help to relieve pain by relaxing the smooth muscles [9]. The most widely used spasmolytics for smooth muscle spasms include anticholinergics, alpha-receptor blockers, calcium channel blockers, and non-atropine, non-papaverine phosphodiesterase inhibitors. Anticholinergics have been treated as second-line drugs for relieving spasms, due to the adverse effects caused by their anticholinergic action. Alpha-receptor blockers and calcium channel blockers usually lead to hypotension [17-19]. Non-atropine, non non-papaverine spasmolytics, such as phloroglucinol, do not have the anticholinergic effects, and have been proven to be effective for reducing pain caused

by gastrointestinal tract colic [20, 21]. Drotaverine, a selective PDE IV inhibitor, has also been reported to be as effective and safe as NSAIDs in renal colic patients, without the severe side effects. Dash et al. have shown that 90% of patients in a drotaverine-treatment group and 88% in a diclofenac-treatment group found the therapy effective [10]. Romics and colleagues found that drotaverine was effective in 79% of patients without serious complications [11]. Moreover, the drug price is too low to increase any much cost. However, few previous reports have paid attention to combination therapy comprising spasmolytics and NSAIDs in renal colic patients.

Boubaker et al. have reported that the addition of phloroglucinol did not improve the efficiency of piroxicam in relieving pain in renal colic patients after 60 min [22]. Another study by Fu et al. also found that the addition of phloroglucinol to parecoxib had no marked impact on pain relief by 120 min, but that it resulted in faster improvement of pain relief and fewer requirements for rescue analgesics than the use of parecoxib alone [14]. However, in this study, we found that the PI reported by patients were significantly different between the 2 groups at 30 min and 120 min ($P_{30\ min}$ = 0.047, $P_{120\ min}$ = 0.03 in multivariable logistic regression and $P_{30\ min}$ = 0.017, $P_{120\ min}$ = 0.03 in univariable logistic regression).

Whether location of stones influences relief of pain is largely unknown and need further investigation. Eisner et al. reported that, in patients presenting to the emergency department for renal colic, ureteral stones were at the UPJ in 10.6%, between the UPJ and the iliac vessels in 23.4%, and at the crossing of the ureter crosses anterior to the iliac vessels in 1.1% of patients, which accounted for 34.1% stones at the mid and proximal ureter. Colic ureteral stones were located between the iliac vessels and the ureterovesical junction in 4.3% and at the ureterovesical junction in 60.6% of patients, representing 64.9% stones found in the ureter [23]. In our study, excluding patients with renal stones, stones were located at the mid and proximal ureter in 79 (35.6%) patients, and at the distal ureter in 143 (64.4%) patients, which was in agreement with earlier studies. Interestingly, subgroup analysis found that, in the combined group, significantly lower PI were reported by patients with mid and proximal ureteric lithiasis, suggesting a previously unrecognized relationship between the location of stones and the efficacy of treatment of renal colic. Unfortunately, we did not notice any differences in VAS scores and PI between the two groups in renal colic patients with renal and distal ureteral stones. Drotaverine was shown to inhibit human cAMP-specific phosphodiesterase type 4 enzyme and block Ca^{2+} channels to release non-vascular smooth muscle [24]. Thus we hypothesize that one of the reason may be the distribution and type of Ca^{2+} channels in proximal, mid and distal ureter [25]. Another reasonable explanation is that the three parts of ureter are regulated by different autonomic nerve from the tenth thoracic nerve to the second lumbar nerve, which may result in different reaction caused by drotaverine (Alan et al. 2006). Yet these hypotheses with focused investigations remain to be done.

Furthermore, the pain relief assessment favored the combined group (95.2%) rather than the ketorolac group (85.7%) at the endpoint (P = 0.011). In terms of the need for rescue medication, the combined group (4.8%) was superior to the ketorolac group (14.5%; P = 0.009). Cevik et al. [26] found that rescue analgesics were required by 39% of patients receiving tenoxicam, 24% receiving lornoxicam, and 19% receiving dexketoprofen at 30 min, while Holdgate and Pollock reported that 18.9% of patients treated with NSAIDs required rescue analgesics [16]. In contrast to the above studies, our results suggested that the addition of drotaverine to ketorolac is effective for pain relief of renal colic, especially in patients with middle and proximal ureteral lithiasis.

Our results showed that addition of drotaverine to ketorolac did not result in increased adverse effects (P = 0.843). The most common adverse drug reaction in the combined group was dizziness (four patients) and hypotension (three patients), and no serious adverse events were noted during the period of observation.

There were several limitations to this study that should be addressed. Firstly, this is a retrospective study with nonrandomized design, which makes it difficult to achieve groups with comparable demographic and clinical baseline characteristics. Thus, we took every possible step to reduce potential bias and achieve comparable baseline characteristics between the

groups. Secondly, because the patients' data were collected from a single center emergency department, the observed results may not be generalizable to the larger population. Finally, the sample size of this study was not large enough to detect small effects of the variables evaluated. Therefore, a randomized, double-blinded and multi-center clinical trial could provide more reliable information.

Conclusions

We have here demonstrated that ketorolac combined with drotaverine is effective in the relief of acute renal colic, especially pain due to mid and proximal ureteric lithiasis, but this combination does not improve the PI significantly in renal colic patients with renal and distal ureteral stones. On the other hand, combined therapy with ketorolac and drotaverine was associated with reduced use of rescue analgesia.

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Disclosure of conflict of interest

None.

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