Intramuscular Drotaverine and Diclofenac in Acute Renal Colic: A Comparative Study of Analgesic Efficacy and Safety

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Conflict of Interest: None.

Financial Support: None.

Abstract

Objective. To evaluate the analgesic efficacy and safety of intramuscular drotaverine hydrochloride vs diclofenac sodium in treatment of acute renal colic.

Methods. We conducted a randomized, single-blind study comparing single intramuscular doses of drotaverine hydrochloride (80 mg) vs diclofenac sodium (75 mg) on 100 patients (50 in each arm) presenting to the emergency department (ED) with renal colic. Subjects with inadequate pain relief at 30 minutes received rescue intramuscular tramadol (100 mg). Pain intensity was recorded using a visual analog scale (VAS), which is the primary outcome measure of this study, before drug administration and 30 and 60 minutes afterwards. The drug effectiveness was defined as ≥50% decrease in pain intensity 60 minutes after intramuscular administration, without exacerbation during the following 2 hours. The need for rescue medication and the presence of adverse effects were considered as secondary outcome of the study.

Result. VAS decreased significantly (P < 0.001) with both drotaverine (52.4%) and diclofenac (49%) at 30 minutes. Reduction of VAS at 60 minutes was 61.3% with drotaverine in comparison to 60.4% with diclofenac. Forty-five patients (90%) in the drotaverine group and 44 (88%) in the diclofenac group found the therapy effective. The need for rescue medication was in five patients of the drotaverine group and six patients in the diclofenac group. There was no significant difference in safety profile in the study groups.

Conclusion. The efficacy and safety of drotaverine as analgesic in renal colic is noninferior to diclofenac and may be used as an alternative or add-on therapy to currently available options.

Key Words. Renal Colic; Drotaverine Hydrochloride; Diclofenac Sodium; Visual Analog Scale

Introduction

Acute renal colic is one of the most painful events in a person’s life. Patients usually describe this condition as “the worst of all maladies, the most sudden, the most painful, and the most irremediable pain” [1]. A precocious and efficient pain management is therefore mandatory to treat this painful condition. Renal colic is responsible for an acute pain related to the migration of calculi along the urinary tract [2]. Increased pressure/tension in the renal pelvis and ureteral wall secondary to obstruction [3], renal capsule stretching, abnormal distention, and ureteral smooth muscle spasm lead to acute pain [4]. The overpressure stimulates local release of prostaglandins, which in turn leads to vasodilatation, diuresis, and ureteral spasm. According to current recommendations, Nonsteroidal anti-inflammatory drugs (NSAIDs) should be used as standard analgesics and opioids as rescue medications [5]. Recent meta-analyses on trials using intramuscular NSAIDs reported the efficiency of both intravascular and intramuscular routes [6].

Phosphodiesterase (PDE) inhibitors are a class of drugs that inhibit the breakdown of cAMP and cGMP, enhancing smooth muscle relaxation. Therefore, PDE inhibitors may be able to decrease ureteral spasm and pain. Taher et al. identified the isoenzyme PDE IV as being dominant over other PDEs in regulation of ureteral smooth muscle [7]. Drotaverine is an effective spasmolytic, inhibiting PDE IV in the smooth muscle cells, accompanied by a mild calcium-channel blocking effect with no anticholinergic effect. Recently, Romics et al. in a randomized double-blind
controlled trial, showed that drotaverine, a selective PDE IV inhibitor, significantly reduced acute renal colic when compared with placebo [4].

The pharmacological actions of drotaverine promise important advantages over NSAIDs and this was the main incentive to explore the role of drotaverine in acute renal colic. Both NSAIDs and drotaverine hydrochloride are commonly used medication for acute renal colics and drotaverine is available in European market over 40 years and in Indian market for 15 years. But surprisingly, scientific literature lacks evidence of comparative studies assessing the efficacy and safety of the above drugs in patients of renal colic. This is the first comparative study of intramuscular drotaverine hydrochloride vs intramuscular diclofenac sodium to evaluate efficacy and safety in management of pain associated with renal colic.

**Methods**

**Patients**

The study has been conducted on 100 patients with clinical symptoms and signs of renal colic attending the emergency department (ED) of S. S. Hospital, a tertiary hospital in Banaras Hindu University, Varanasi, India. We enrolled all patients (18 years and above of both sexes) presenting clinical symptoms and signs of renal colic. Standardized screening tools were used to identify eligible patients. A history of unilateral colicky acute flank pain with urinalysis, abdominal X-ray, and ultrasonography findings consistent with the diagnosis of renal colic were considered as diagnostic criteria. Only patients displaying at least a visual analog scale (VAS) >50/100 were included. Patients were excluded if they had a history of peptic ulcer disease, asthma, bleeding disorder (use of oral anticoagulant); need for immediate surgical or other intervention; suspected hypersensitivity to drotaverine or NSAIDs; spasmyloitics or analgesics received within 6 hours before presenting to ED; tranquilizing or muscle-relaxant therapy used within 3 days; second- or third-degree arterioventricular block; known or suspected pregnancy; known progressive malignant disease; clinically unstable renal, hepatic or cardiac insufficiency (serum glutamate-oxalacetate transaminase >180 U/L, creatinine >250 mmol/L).

**Study Design**

The present study is a monocentric, prospective, interventional, randomized, single-blind (the patients were blinded), parallel group comparative clinical study between drotaverine hydrochloride and diclofenac sodium in patients with clinical symptoms and signs of renal colic. Study protocol and procedures complied with the principles of the Declaration of Helsinki. The study was approved by the institutional ethical committee, and procedures followed in this study were in accordance with the ethical standard established by the Ethical Guidelines for Biomedical Research on Human Subjects (Indian Council of Medical Research, 2006). Written informed consent was obtained from all the patients who participated in the study after explaining the patient’s diagnosis, the nature and purpose of a proposed treatment, the risks and benefits of a proposed treatment (drotaverine or diclofenac), and the risks and benefits of the alternative treatment. After screening (general physical examination, electrocardiography, ultrasonography, abdominal X-ray, urine, and blood samples drawn) and obtaining informed consent, patients were randomized by using computer-generated random list. Then, the patients were divided into two treatment groups. Fifty patients were allocated to the drotaverine group who received two ampoules of drotaverine hydrochloride 80 mg single intramuscular injection and another 50 patients were allocated to the diclofenac group who received diclofenac sodium 75 mg single intramuscular injection. The assessment continued for 3 hours after the intramuscular injection. During this period, the patients were monitored continuously for possible side effects and the vital signs were recorded at 30-minute intervals. VAS was recorded at 0 minute (baseline), 30 minutes and 60 minutes, and in the next 2 hours, the patients were monitored for pain exacerbation. Rescue therapy is defined as the need of intramuscular tramadol (100 mg) injection if VAS at 60 minutes is more than 50% the initial VAS.

**Efficacy and Safety Variables**

Primary outcome measure was pain intensity score at 30 and 60 minutes. VAS was used to assess the intensity of pain consisted of a 100-mm horizontal scale labeled “no pain” at 0 mm and “worst pain imaginable” at 100 mm, with values recorded to the nearest millimeters. Secondary outcome measures included the need for rescue analgesia at 60 minutes and the number of adverse events observed or reported. Those who could not tolerate pain and required rescue analgesia were excluded from the study. The drug effectiveness is defined as ≥50% decrease in pain intensity 60 minutes after intramuscular administration, without exacerbation during the following 2 hours, as well as the need for rescue medication and the presence of adverse effects.

Tolerability was assessed in terms of reported adverse experiences and vital signs measured at baseline and at the end of the study. All reported adverse drug reactions were graded according to the National Cancer Institute Common Toxicity Criteria (CTC) and compared between the groups.

**Statistical Analysis**

All statistical analyses were performed with statistical software Instat 3.036 (Statistical Services Centre, University of Reading, Reading, England). Interval data have been expressed as mean ± SD and categorical data in percentage. The main statistical tool used for primary comparison was a two-tailed student t-test (unpaired) and analysis of variance. Categorical data, expressed in 2 × 2
contingency table, were tested by Fischer’s test. The sample size calculation was based on the hypothesis of a successful treatment in 80%, defined as a decrease of VAS of 50% or more as compared with the initial value. A minimum of 46 patients per group were required to detect a 20% absolute difference of pain relief at 1 hour between the two groups with a power of 80% at the two-sided error of 0.05. The statistician was blinded to the groups during analysis.

Results

Patient Disposition and Baseline Demographics

Among 182 patients assessed for eligibility from January 2009 to October 2009, 82 could not fit into the inclusion criteria. Among 82 patients, 77 patients did not fulfill inclusion criteria and five patients declined to participate in the study. So 100 patients were randomized and allocated into two treatment groups (Figure 2). Comparison of baseline demographic and clinical characteristic of both the groups has proved the homogeneity of the study groups (Table 1). As a whole, 42% of the patients were female. The mean ages in the drotaverine and diclofenac groups were 38 years and 41 years, respectively. The baseline VAS for all the patients recruited was 79.54 ± 6.69 in the drotaverine group and 80.18 ± 9.04 in the diclofenac group. The rescue medication was needed in five patients of the drotaverine group and six patients in the diclofenac group.

Efficacy Analysis

Table 2 reveals that change in VAS from baseline to 30 minutes and 60 minutes has decreased in a time-dependent manner in both the groups significantly (*P < 0.001; Figure 1). In Table 3, we have presented the mean difference in VAS over different time period. There is a mean decrease of VAS by 41.7 mm (52.4%) in the drotaverine group in comparison to 39.3 mm (49%) in the diclofenac group from baseline to 30 minutes postdrug. The mean change in VAS in the drotaverine group after 30 minutes was compared with that of the diclofenac group by unpaired *t*-test and it was found nonsignificant (*P = 0.22). The mean changes from baseline to 60 minutes postdrug were 48.78 mm (61.3%) and 48.46 mm (60.4%) in the drotaverine group and

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Drotaverine Group</th>
<th>Diclofenac Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients recruited</td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>38.3 ± 10.2</td>
<td>40.8 ± 11.7</td>
<td>0.44</td>
</tr>
<tr>
<td>Number of female patients (%)</td>
<td>19 (38%)</td>
<td>23 (46%)</td>
<td>0.54</td>
</tr>
<tr>
<td>VAS (in mm)</td>
<td>79.54 ± 6.69</td>
<td>80.18 ± 9.04</td>
<td>0.69</td>
</tr>
<tr>
<td>History of renal colic</td>
<td>8</td>
<td>11</td>
<td>0.61</td>
</tr>
<tr>
<td>History of ureteric colic</td>
<td>11</td>
<td>16</td>
<td>0.37</td>
</tr>
<tr>
<td>History of urinary tract infection</td>
<td>10</td>
<td>9</td>
<td>0.90</td>
</tr>
<tr>
<td>History of urogenital anomaly</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Number of patients needed rescue medication</td>
<td>5</td>
<td>6</td>
<td>0.99</td>
</tr>
<tr>
<td>Adverse drug reactions</td>
<td>8</td>
<td>11</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Table 1 Baseline demographic data and clinical characteristics of the patients (N = 100) participated in the study

Table 2 Change in VAS in the study groups from baseline to 30 minutes and 60 minutes in the patients available for analysis

<table>
<thead>
<tr>
<th>VAS (in mm)</th>
<th>Drotaverine Group</th>
<th>Diclofenac Group</th>
<th>95% Confidence Interval</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>At baseline (0 minute)</td>
<td>79.54 ± 6.69</td>
<td>80.18 ± 9.04</td>
<td>−3.7983 to 2.5183</td>
<td>0.69</td>
</tr>
<tr>
<td>30 minutes</td>
<td>37.84 ± 13.2</td>
<td>40.88 ± 10.97</td>
<td>−7.8588 to 0.7788</td>
<td>0.21</td>
</tr>
<tr>
<td>60 minutes</td>
<td>30.76 ± 8.95</td>
<td>31.72 ± 8.10</td>
<td>−4.3485 to 2.4285</td>
<td>0.57</td>
</tr>
</tbody>
</table>

* Statistically significant.
† ANOVA.
‡ Unpaired *t*-test.
Data in mean ± SD.
diclofenac group, respectively, and this change was also statistically nonsignificant \( P = 0.82 \). The mean change from 30 minutes to 60 minutes postdrug in the drotaverine group (7.08 mm) was found not to be significant \( P = 0.11 \) over the diclofenac group (9.16 mm). By considering a ≥50% decrease in VAS as drug effectiveness, we found that in 45 patients in the drotaverine group and 44 patients in the diclofenac group, treatment was effective \( P = 0.99 \); relative risk = 1.023; 95% CI = 0.8910 to 1.174).

Secondary outcome measures included the need for rescue analgesia at 60 minutes and the number of adverse events observed or reported. Five patients in the drotaverine group and six patients in the diclofenac group needed rescue medication. No patient in either group showed aggravation of pain in next 2 hours of follow-up.

**Safety Analysis**

The number of adverse events reported in the drotaverine group and diclofenac group were 8 and 11, respectively. Analysis of this result by Fischer’s exact test was statistically not significant \( P = 0.61 \); relative risk = 0.73; 95% CI = 0.3196 to 1.655). In the drotaverine group, feeling of dizziness was reported in four patients, headache in three patients, and hypotension in one patient, whereas in the diclofenac group, six patients reported of nausea/vomiting, three patients complained of dizziness, and two patients complained of abdominal burning/pain. According to the CTC grading of adverse drug reactions (CTC version 2.0), all the reported side effects were graded as mild.

**Discussion**

Relief of pain becomes an urgent and daunting task for the physicians in ED patients with renal colic. NSAIDs like diclofenac sodium are commonly used drugs for analgesia in renal colics in the Indian setup. Opioids are generally used as rescue medications because they cause analgesia mediated through the central nervous system and associated with higher adverse events especially on the nervous and gastrointestinal systems [6]. Spasmolytic effect of anticholinergic drugs is inconsistent and transient. Their high-dose requirement results in significant side effect limiting their uses [8,9]. NSAIDs have been found to be effective in analgesia for renal colics but they have their possible limitations [10]. Failure to relieve pain in renal colic, defined as requirement for rescue therapy, occurs in 7% to 39% with NSAIDs [9]. NSAIDs are avoided for specific categories of patients such as pregnant women [11,12]. The use of NSAIDs is also restricted by several underlying conditions such as allergy or gastrointestinal bleeding [13].

Drotaverine is an effective spasmolytic, inhibiting PDE type IV in the smooth muscle cells, accompanied by a mild calcium-channel blocking effect with no anticholinergic effect [4]. In daily practice, it is generally used as a spasmylic that can be administered orally, intramuscularly, or intravenously. It is more commonly used in gynecological disorders because of good efficacy and safety profile. To our knowledge, this is the first clinical study assessing efficacy and safety of intramuscular drotaverine hydrochloride and intramuscular diclofenac sodium.
in the setting of acute renal colic. There are very limited studies on efficacy of drotaverine as a spasmolytic in renal colic.

The initial VAS was elevated in both groups but the difference was not significant. Pain (measured as per VAS) decreased significantly in the drotaverine group and it was equivalent to the diclofenac group at 30 and 60 minutes. The percentage reduction in VAS with drotaverine at 30 and 60 minutes was marginally more than that of the diclofenac but the change was not statistically significant. From the above data, we can infer that both drotaverine and diclofenac had effective analgesia and drotaverine is noninferior to diclofenac. The number of patients requiring rescue medication (intramuscular tramadol injection) in the drotaverine group and diclofenac group were 5 and 6, respectively. In our study, drotaverine was found to be effective in 90% (45/50) patients. In a previous study done by Romics et al., drotaverine showed effectiveness in 79% patients with renal colic [4] and our study result (82%) corroborates with this study. In the diclofenac group, the therapy was effective in 88% (44/50). In the Cochrane database Diclofenac has been mentioned to be effective in 61–93% [6].

Table 3  Comparative analysis of changes in VAS in the study groups

<table>
<thead>
<tr>
<th>Time Difference</th>
<th>Mean Difference in VAS (in mm)</th>
<th>95% Confidence Interval (CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (time 0) to 30 minutes</td>
<td>Drotaverine Group 41.70 ± 10.41</td>
<td>−1.4827 to 6.2827</td>
<td>0.22</td>
</tr>
<tr>
<td>Baseline (time 0) to 60 minutes</td>
<td>Diclofenac Group 39.30 ± 9.11</td>
<td>−2.3959 to 3.0359</td>
<td>0.61</td>
</tr>
<tr>
<td>30 minutes to 60 minutes</td>
<td>Drotaverine Group 48.78 ± 6.65</td>
<td>−4.6316 to 0.47158</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Diclofenac Group 48.46 ± 7.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.16 ± 5.93</td>
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</table>

* Unpaired t-test.
Data in mean ± SD.
The most common adverse drug reaction in the drotaverine group was dizziness and hypotension, which may be attributed to the calcium channel antagonistic action of drotaverine on smooth muscles including blood vessels. In the diclofenac group, reported adverse events were nausea, vomiting, dizziness, and abdominal pain. The adverse events were mild and transient. The number of adverse events was more in the diclofenac group in comparison to the drotaverine group.

The main limitation of the study was its monocentric, single-blinded design, relatively small sample size, and use of one pain scale. A double-blinded design and the use of other pain scales could have made the study better.

In conclusion, drotaverine has been found effective in reductions in pain intensity after a single dose and was comparable and noninferior to diclofenac. The safety profile of the drotaverine is also matchable to diclofenac. Intramuscular drotaverine may represent an alternative or add-on analgesic to currently available options for renal colic. Its place in analgesic armamentarium can be confirmed by a double-blind, randomized, large population clinical trials.

References
1 Healy M. Journeying with the “stone”: Montaigne’s healing travel journal. Lit Med 2005;24:231–49.