Intravenous Paracetamol or Morphine for the Treatment of Renal Colic: A Randomized, Placebo-Controlled Trial

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Study objective: This randomized, placebo-controlled trial evaluates the analgesic efficacy and safety of intravenous single-dose paracetamol and morphine for the treatment of renal colic.

Methods: We conducted a randomized, double-blind, placebo-controlled clinical trial comparing single intravenous doses of paracetamol (1 g), morphine (0.1 mg/kg), and placebo (normal saline solution) for patients presenting to the emergency department (ED) with suspected renal colic. Subjects with inadequate pain relief at 30 minutes received rescue fentanyl (0.75 µg/kg). We compared changes in pain intensity 30 minutes after treatment among the 3 arms, as well as the need for rescue medication and the presence of adverse effects.

Results: Six hundred forty-five consecutive patients were screened for study and 165 were entered. Eight subjects were subsequently excluded from analysis because of protocol violations and 11 were excluded because of uncertain diagnoses, leaving 146 subjects available for analysis. The mean reduction in visual analogue scale pain intensity scores at 30 minutes was 43 mm for paracetamol (95% confidence interval [CI] 35 to 51 mm), 40 mm for morphine (95% CI 29 to 52 mm), and 27 mm for placebo (95% CI 19 to 34 mm). Statistically significant mean differences in pain intensity reductions compared with those for placebo were observed for paracetamol (16; 95% CI 5 to 27; \( P < .005 \)) and morphine (14; 95% CI 0.4 to 27; \( P = .05 \)); however, no difference was found between paracetamol and morphine (2; 95% CI –13 to 16; \( P = .74 \)). Rescue analgesics at 30 minutes were required by 21 subjects (45%) receiving paracetamol, 24 subjects (49%) receiving morphine, and 34 subjects (67%) receiving placebo (\( P = .08 \)). At least 1 adverse effect was experienced by 11 (24%) receiving paracetamol, 16 (33%) receiving morphine, and 8 (16%) in the placebo group (\( P = .14 \)). There were no serious adverse events.

Conclusion: Intravenous paracetamol is an efficacious and safe treatment for ED patients with renal colic. [Ann Emerg Med. 2009;54:568-574.]

INTRODUCTION

Background

Renal colic is an intensely painful condition requiring rapid analgesic treatment. Both parenteral opioids and nonsteroidal anti-inflammatory drugs are commonly used to provide relief from renal colic, and both can have adverse effects.\(^1-4\) Paracetamol (acetaminophen) is a safe and effective analgesic administered orally or rectally. At therapeutic doses, it is associated with fewer adverse effects than either opioids or nonsteroidal anti-inflammatory drugs.\(^5\) Recently, an intravenous form of paracetamol has become available in several European countries.\(^6-10\)

Importance

The efficacy and safety of intravenous paracetamol have been established in the setting of postoperative pain; however, it has not been previously evaluated in the management of pain associated with renal colic.

Goals of This Investigation

The objective of this study was to determine the analgesic efficacy and safety of intravenous, single-dose paracetamol versus morphine versus placebo for patients presenting to the emergency department (ED) with renal colic.
Consecutive patients were enrolled 24 hours a day and 7 days a week during the study period. Study eligibility was confirmed by a senior emergency medicine resident from midnight until 8:00 AM and an attending emergency physician at all other times. In addition to the history and physical examination, the clinical evaluation of subjects included urine analysis for hematuria and emergency physician–performed ultrasonography to detect hydronephrosis; however, confirmation of the diagnosis involved computed tomography (CT), intravenous urography, radiologist-performed ultrasonography, plain radiography, and stone recovery. All patients without a history of urolithiasis underwent CT. Patients with a history of urolithiasis confirmed by CT, intravenous urography, ultrasonography, or stone recovery generally did not receive testing beyond urinanalysis and ultrasonography.

**Interventions**

Subjects were randomized in a 1:1:1 ratio to receive a single intravenous dose of paracetamol (Perfalgan, Bristol Myers Squibb, Itxassou, France) (1 g in 100 mL normal saline solution), morphine (0.1 mg/kg in 100 mL normal saline solution), or placebo (100 mL normal saline solution) in a blinded fashion. The randomization schedule was prepared by an assistant blinded to the study. Treatment allocation assignments were contained in sealed envelopes. Study drugs, identical in color and appearance, were premixed by a study nurse and administered by a second nurse blinded to the study. Subjects who were judged to have inadequate pain relief at 30 minutes received rescue fentanyl 0.75 µg/kg intravenously.

**Methods of Measurements**

Subjects reported pain intensity on both a 100-mm visual analogue scale (bounded by “no pain” and “the worst pain”) and a 4-point verbal rating scale (no, mild, moderate, or severe pain) immediately before receiving the study drug and at 15 and 30 minutes after drug administration. Subjects were blinded to their previous reports. Reports of adverse events were collected spontaneously and categorized as nausea/vomiting, altered mental status, dizziness, hypotension, thorax rigidity, headache, allergy/pruritus, urinary retention, ventilation failure, and dry mouth. Any additional adverse events were noted as “other” and described on the case report form. We also collected subject demographic information, urinary stone disease history, and results of confirmatory diagnostic tests. A research assistant also performed a retrospective medical chart review, recording results of all diagnostic tests, and contacted subjects by telephone to determine the presence or absence of stone recovery.

**Outcome Measures**

Our primary outcome measure was the change in visual analogue scale pain intensity score at 15 and 30 minutes. Secondary outcome measures included the need for rescue analgesia at 30 minutes and the presence of at least 1 adverse
event. A minimum of 35 patients in each group would be required to detect a 20-mm difference between groups, assuming an SD of 25 mm, 95% power, and a .05 2-sided level of significance.

**Primary Data Analysis**

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). Normally distributed variables were expressed as mean and SD, whereas those non-normally distributed were expressed as median and interquartile range. Our primary comparison, the mean between-group change in visual analogue scale pain intensity score at 30 minutes, was tested with analysis of variance. Homogeneity of variances was tested with the Levene’s test. Secondary outcomes, including differences in the proportion of each group requiring rescue analgesia at 30 minutes and proportions experiencing at least 1 adverse event, were analyzed with \( \chi^2 \) tests. All tests of significance were 2 sided.

**RESULTS**

Six hundred forty-five consecutive patients were assessed for eligibility and 480 patients were excluded for a variety of reasons (Figure 1). Ultimately, 165 subjects were entered into the study. Eight subjects were not included in analysis because of protocol violations, including 7 with severe pain requiring rescue medication within the first 30 minutes and 1 with persistent vomiting requiring metoclopramide. An additional 11 subjects were excluded from analysis because of conflicting diagnostic information, including 8 with negative radiographic study results and 3 found to have urinary tract infections. One hundred forty-six subjects were included in the final analysis, including 46 assigned to paracetamol, 49 to morphine, and 51 to placebo.
Characteristics of Study Subjects

The subject groups appeared to be well matched for baseline characteristics and diagnostic study results (Table 1). The study sample was relatively young, with a mean age of 37 years and the majority (62%) reflecting the underlying population at risk for renal colic. Baseline pain intensity was high, with mean and median visual analogue scale scores of 71 and 74.5, respectively. Urolithiasis was diagnosed by CT in 53 subjects (36%), ultrasonography in 51 (35%), stone recovery in 24 (16%), intravenous urography in 15 (10%), and radiography in 3 (2%).

Main Results

Pain outcome measures for each group at baseline, 15 minutes, and 30 minutes are illustrated in Figures 2 and 3 and detailed in Table 2. The mean reduction in visual analogue scale pain intensity scores at 30 minutes was 43 mm for paracetamol (95% confidence interval [CI] 35 to 51 mm), 40 mm for morphine (95% CI 29 to 52 mm), and 27 mm for placebo (95% CI 19 to 34 mm). Verbal rating scale changes paralleled those of visual analogue scale changes. With 1-way analysis of variance and assuming unequal variances, statistically significant reductions in pain intensity compared with those with placebo were observed for paracetamol (\(P < 0.005\)) and morphine (\(P = 0.045\)); however, no difference was found between paracetamol and morphine (\(P = 0.74\)). Means and 95% CIs for these comparisons at 15 and 30 minutes are shown in Table 3.

Overall, 67 subjects (46%) required rescue drug at 30 minutes and 35 (24%) experienced at least 1 adverse effect. Rescue analgesics at 30 minutes were required by 21 subjects (46%) receiving paracetamol, 24 subjects (49%) receiving morphine, and 34 subjects (68%) receiving placebo (\(P = 0.079\)). At least 1 adverse effect was experienced by 11 (24%) receiving paracetamol, 16 (33%) receiving morphine, and 8 (16%) in the placebo group (\(P = 0.139\)). There were no serious adverse events (Table 4).

LIMITATIONS

This study had several limitations that should be mentioned. We chose to remove patients from analysis if they required rescue analgesics within the first 30 minutes of the study and if their ultimate diagnosis was unclear. In retrospect, we should have planned an intention-to-treat analysis; however, the number of patients excluded from analysis was relatively small and spread among all 3 study arms.

In addition, we studied patients for only the initial 30 minutes of their ED care. It is possible that, had we extended...
the time of our study, we would have obtained different results. Although we cannot make statements about pain experiences after the 30-minute study period, rapid pain control is important in the setting of renal colic, and we believe this early interval is of sufficient importance to both patient and clinician to justify our study design.

Some adverse effects such as nausea and vomiting may be related to renal colic rather than the study drug. Although we collected adverse effect data, we did not assess the likelihood that the adverse effect could be attributed to the study drug at data collection. In addition, we did not weigh our subjects and relied on self-report of weight to calculate morphine doses. It is possible that the doses used were based on poor weight estimates; however, we suspect such errors were small, and randomization should have minimized any effect on study outcomes.

Finally, some will criticize our decision to include a placebo arm in a study of renal colic because of ethics considerations. This is a contentious area in which standards are evolving. Given the short period of our study (30 minutes) and the use of rescue medication for intractable pain, the investigators and our institutional review board thought this was a reasonable decision.

DISCUSSION

Our findings suggest that intravenous paracetamol is an efficacious and safe treatment for ED patients with renal colic. Although our sample size was not sufficient to perform an equivalency trial, reductions in pain intensity after a single dose of intravenous paracetamol tended to be comparable to, if not greater than, those reported after intravenous morphine, particularly at 15 minutes. The suggestion of a very early paracetamol analgesic effect is intriguing and deserves future study.

To our knowledge, this is the first clinical trial of intravenous paracetamol, either in the ED or in the setting of acute renal colic. There is also little published research on intravenous paracetamol in different clinical pain models.

A well-designed, double-blind, double-dummy, placebo-controlled study by Moller et al found both intravenous paracetamol and its prodrug, propacetamol, to provide superior pain relief over placebo in a third-molar extraction model, with median times to onset of perceptible pain relief of 8 minutes and 6 minutes, respectively. In this study, local pain at the infusion site occurred among half of those receiving intravenous propacetamol and none of the intravenous paracetamol recipients.

Murat et al compared the analgesic efficacy of intravenous paracetamol and propacetamol in children aged 1 to 12 years and undergoing inguinal hernia repair. For ethical reasons, they did not use a double-dummy protocol because this would have required intravenous infusions in both arms. No differences were observed between the 2 arms on a variety of pain intensity, pain relief, and global satisfaction measures, whereas again, injection site pain was noted more commonly among those receiving intravenous propacetamol (33% versus 15%).

In a postoperative orthopedic pain model of adults undergoing total hip or knee replacement, Sinatra et al reported that subjects receiving intravenous paracetamol or propacetamol required 33% and 29% less morphine during a 24-hour period compared with those receiving placebo. Using a 10-mm reduction in visual analogue scale pain intensity as an indicator of meaningful pain relief, they estimated that time to onset of analgesia with use of either intravenous paracetamol or propacetamol was less than 15 minutes, with a mean time to peak analgesic effect of 30 minutes.

Van Aken et al used a double-blind, double-dummy protocol to compare the analgesic efficacy of 2 g intravenous propacetamol to 10 mg of intramuscular morphine and to placebo in subjects undergoing third-molar extraction. Using a number of analgesia measures, both propacetamol and morphine provided superior efficacy compared with placebo but were not different from each other. Finally, intravenous paracetamol and placebo were compared as analgesic adjuncts to a continuous tramadol infusion in patients undergoing cardiac surgery. Subjects receiving paracetamol reported less pain at rest 12, 18, and 24 hours after the operation and required less rescue morphine during 3 days than subjects receiving placebo (48 mg versus 97 mg), although the latter difference was not statistically significant \( (P=.27) \).
Intravenous paracetamol is an efficacious and safe treatment for ED patients with renal colic. Intravenous paracetamol represents an alternative or supplemental analgesic to currently available parenteral agents. Its place in the ED analgesic armamentarium deserves further study.

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Author contributions: FB and CE conceived the study, designed the trial, and obtained research funding. FB, CE, OK, and EG supervised the conduct of the trial and data collection. FB and CE provided statistical advice on study design and analyzed the data. FB, CE, and YC drafted the article, and all authors contributed substantially to its revision. MC evaluated the Uriner computed tomography. FB takes responsibility for the paper as a whole.

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Table 2. Pain outcome measures.

<table>
<thead>
<tr>
<th>Pain outcome measures</th>
<th>Paracetamol</th>
<th>Morphine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual analogue scale score, median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>73 (55 to 87)</td>
<td>78 (64 to 98)</td>
<td>73 (53 to 87)</td>
</tr>
<tr>
<td>15 min</td>
<td>21.5 (9 to 38)</td>
<td>40 (20 to 68)</td>
<td>57 (29 to 57)</td>
</tr>
<tr>
<td>30 min</td>
<td>19 (5 to 42)</td>
<td>23 (4 to 59)</td>
<td>33 (15 to 66)</td>
</tr>
<tr>
<td><strong>Visual analogue scale change from baseline, median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>44.5 (23 to 66)</td>
<td>30 (7 to 51)</td>
<td>11 (–3 to 29)</td>
</tr>
<tr>
<td>30 min</td>
<td>41.5 (24 to 63)</td>
<td>43 (7 to 73)</td>
<td>24 (5 to 45)</td>
</tr>
<tr>
<td><strong>Verbal rating scale score, median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4 (3 to 4)</td>
<td>4 (3 to 4)</td>
<td>4 (3 to 4)</td>
</tr>
<tr>
<td>15 min</td>
<td>2 (2 to 3)</td>
<td>3 (2 to 3)</td>
<td>3 (2 to 4)</td>
</tr>
<tr>
<td>30 min</td>
<td>2 (1 to 3)</td>
<td>2 (1 to 3)</td>
<td>3 (2 to 3)</td>
</tr>
</tbody>
</table>

Table 3. Differences in reductions of visual analogue scale scores between groups at 15 and 30 minutes.

<table>
<thead>
<tr>
<th>Mean Differences</th>
<th>Paracetamol vs Morphine</th>
<th>Paracetamol vs Placebo</th>
<th>Morphine vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction at 15 min, mean (95% CI)</td>
<td>13 (0.1 to 25)</td>
<td>26 (15 to 38)</td>
<td>14 (3 to 25)</td>
</tr>
<tr>
<td>Reduction at 30 min, mean (95% CI)</td>
<td>2 (–13 to 16)</td>
<td>16 (5 to 27)</td>
<td>14 (0.4 to 27)</td>
</tr>
</tbody>
</table>

Table 4. Adverse effects.

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Paracetamol, No. (%)</th>
<th>Morphine, No. (%)</th>
<th>Placebo, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 effect</td>
<td>11 (24)</td>
<td>16 (33)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>7 (15)</td>
<td>9 (18)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (7)</td>
<td>4 (8)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Nonspecific symptoms</td>
<td>4 (9)</td>
<td>10 (20)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Intravenous paracetamol is an efficacious and safe treatment for ED patients with renal colic. Intravenous paracetamol represents an alternative or supplemental analgesic to currently available parenteral agents. Its place in the ED analgesic armamentarium deserves further study.

References


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