



# Randomized Controlled Trial of Intravenous Acetaminophen Versus Intravenous Hydromorphone for the Treatment of Acute Pain in the Emergency Department

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**Study objective:** As clinicians look to nonnarcotic analgesics in the emergency department (ED), it is essential to understand the effectiveness and adverse effects of nonopioid medications in comparison with existing opioid treatments. Studies of intravenous acetaminophen for acute pain in the ED demonstrate mixed results and suffer from small sample sizes and methodological limitations. This study compares intravenous hydromorphone with intravenous acetaminophen in adult ED patients presenting with acute pain.

**Methods:** This was a prospective, randomized, clinical trial comparing 1 g intravenous acetaminophen with 1 mg intravenous hydromorphone for treatment of adults with severe, acute pain in the ED. The primary outcome was between-group difference in change in numeric rating scale from baseline to 60 minutes postadministration of study medication. Secondary outcomes included the difference in proportion of patients in each group who declined additional analgesia at 60 minutes, received additional medication before 60 minutes, and developed nausea, vomiting, or pruritus.

**Results:** Of 220 subjects randomized, 103 patients in each arm had sufficient data for analysis. At 60 minutes, the mean decrease in numeric rating scale pain score was 5.3 in the hydromorphone arm and 3.3 in the acetaminophen arm, a difference of 2.0 (95% confidence interval [CI] 1.2 to 2.7) favoring hydromorphone. A greater proportion of patients in the hydromorphone arm also declined additional analgesia at 60 minutes (65% versus 44%; difference 21%; (95% CI 8% to 35%). There was no difference in the proportion of patients receiving rescue analgesia before 60 minutes. Significantly more subjects in the hydromorphone group developed nausea (19% versus 3%; difference 16%; 95% CI 4% to 28%) and vomiting (14% versus 3%; difference 11%; 95% CI 0% to 23%).

**Conclusion:** Although both 1 mg intravenous hydromorphone and 1 g intravenous acetaminophen provided clinically meaningful reductions in pain scores, treatment with hydromorphone provided both clinically and statistically greater analgesia than acetaminophen, at the cost of a higher incidence of nausea and vomiting. [Ann Emerg Med. 2019;73:133-140.]

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## INTRODUCTION

### Background

Drug overdoses and deaths have tripled during the past decade and represent a national crisis that affects millions, leading to broad-based calls for action in the media, across all levels of government, and from within the medical community itself.<sup>1-3</sup> The Centers for Disease Control and Prevention estimates that in 2015 alone, drug overdoses accounted for greater than 50,000 deaths, with more than half (63%) involving an opioid.<sup>2</sup> This has caused a shift from concerns in the 1990s about the undertreatment of pain and underuse of opioids (when assessment of pain was

first promoted as the “fifth vital sign”) to the current environment in which the administration and prescription of opioids is subject to greater scrutiny and clinicians increasingly try to treat with nonopioid analgesic alternatives.<sup>4-7</sup> This is readily apparent in the emergency department (ED) setting, where implementation of opioid reduction protocols and discussion of “opioid-free” EDs has become common.<sup>5,8-10</sup>

### Importance

Intravenous acetaminophen is a nonnarcotic analgesic approved by the Food and Drug Administration in 2010

**Editor's Capsule Summary***What is already known on this topic*

Clinicians are looking for effective, nonopioid solutions for pain management.

*What question this study addressed*

How does 1 g intravenous acetaminophen compare with 1 mg intravenous hydromorphone for treating acute pain?

*What this study adds to our knowledge*

In this randomized, double-blind trial of 220 emergency department (ED) adults, hydromorphone resulted in a significantly greater and clinically important reduction in pain scores relative to acetaminophen.

*How this is relevant to clinical practice*

Intravenous hydromorphone at 1 mg is superior to intravenous acetaminophen at 1 g for acute pain in ED adults.

that has been the subject of a number of clinical trials initially in the postoperative setting,<sup>11-16</sup> but more recently for the treatment of acute pain across a range of conditions, from acute extremity injury and low back pain<sup>17-19</sup> to abdominal pain and renal colic,<sup>20-26</sup> headache,<sup>27,28</sup> and scorpion stings.<sup>29</sup> However, as summarized in 2 recent reviews by Sin et al,<sup>30,31</sup> the existing literature is compromised by conflicting results, small sample sizes, methodological flaws, and a lack of reproducibility. It is therefore difficult to determine the role of intravenous acetaminophen in the treatment of acute pain in the ED.

**Goals of This Investigation**

This study seeks to better define the potential role of intravenous acetaminophen in the ED through direct comparison of intravenous acetaminophen with intravenous hydromorphone in adult ED patients presenting with acute pain.

**MATERIALS AND METHODS****Study Design and Setting**

This is a Consolidated Standards of Reporting Trials-compliant, prospective, randomized, double-blind, clinical trial comparing the effectiveness and adverse effect profiles of 1 g intravenous acetaminophen with that of 1 mg intravenous hydromorphone in the treatment of adults

with acute pain in the ED. The study was approved by the Albert Einstein College of Medicine/Montefiore Medical Center institutional review board. Subjects, many of whom are underserved minorities, were recruited from 2 adult, academic, inner-city EDs with a combined annual census of 175,000 visits.

**Selection of Participants**

Patients aged 21 to 64 years and presenting to the ED with acute pain (<7 days' duration) of sufficient severity in the judgment of the ED attending physician to warrant the use of intravenous opioids were eligible for enrollment. Exclusion criteria were previous adverse reaction to either hydromorphone or acetaminophen; use of opioids or tramadol within the previous 24 hours or use of acetaminophen or nonsteroidal anti-inflammatory medication within the preceding 8 hours; presence of a chronic pain syndrome (eg, sickle cell anemia, peripheral neuropathies); systolic blood pressure less than 100 mm Hg, pulse rate less than 60 beats/min, or oxygen saturation less than 95% on room air; alcohol or other drug intoxication; pregnant or breast feeding; use of a monoamine oxidase inhibitor, transdermal pain patches, or any medication that might interact with one of the study medications (eg, selective serotonin reuptake inhibitor, tricyclic antidepressants); and presence of a medical condition that might affect metabolism of opioid analgesics or acetaminophen (hepatitis, renal insufficiency, etc).

Patients were screened and enrolled by trained, fluently bilingual (English and Spanish) research technicians 24 hours per day, 7 days per week from June 2017 through November 2017.

**Interventions**

Patients were randomized to either 1 g intravenous acetaminophen or 1 mg intravenous hydromorphone. A research pharmacist, working in an area distant from the ED and inaccessible to ED staff, performed the randomization in blocks of 10, using an online randomization plan generator and assembled premade research medication packets that were then stored in the ED Pyxis automated medical dispensing system. Study packets for patients randomized to the acetaminophen arm contained one 100-mL bag with 1 g acetaminophen and one 0.5-mL vial containing normal saline solution. Packets for patients randomized to the hydromorphone arm contained one 100-mL bag containing normal saline solution and one 0.5-mL vial containing 1 mg hydromorphone. To preserve blinding of drug allocation, nurses injected the contents of the vial into the 100-mL bag

and administered the resultant mixture during 5 to 10 minutes. The use of a 5- to 10-minute infusion ensured a safe rate of administration of intravenous acetaminophen<sup>32</sup> and helped preserve blinding by avoiding the euphoric effect of intravenous hydromorphone push administration. Subjects, research associates, and all providers were blinded to study group assignment.

### Methods of Measurement

Patients in both groups were asked to rate their pain on a previously validated and reproducible standard verbal numeric rating scale ranging from 0 (“no pain”) through 10 (“worst pain possible”)<sup>33</sup> immediately before administration of study medication (time 0) and 60 minutes after completion of the infusion (time 60). At time 60, they were also asked the following scripted question: “Do you want more pain medication?” The treating attending physician was notified if patients indicated they wanted additional analgesia. Further pain management was at the discretion of the patient’s attending physician. In addition to the primary endpoint (change in numeric rating scale from time 0 to time 60), verbal numeric rating scale scores were also recorded at 5, 30, 90, and 120 minutes after the end of the infusion. The presence or absence of nausea or vomiting was recorded at 0, 5, 30, 60, 90, and 120 minutes. Pruritus was assessed at 60 minutes. All additional medications administered were recorded.

For safety reasons, vital signs were monitored continuously by the research associates for a total of 120 minutes (blood pressure, pulse rate, and oxygen saturation) to detect any adverse effects. A predefined stepwise escalation protocol was established in the event of bradycardia (pulse rate <50 beats/min), hypotension (systolic blood pressure <90 mm Hg), or oxygen desaturation (SaO<sub>2</sub> <95%) that incorporated, in order, gentle verbal or tactile stimulation, provision of supplemental oxygen and fluids, and administration of naloxone, depending on clinical response, all under the supervision of the treating ED attending physician.

### OUTCOME MEASURES

The primary outcome was the between-group difference in change in numeric rating scale from baseline to 60 minutes after administration of study medications. Secondary effectiveness outcomes included the difference in the proportion of patients who chose to forgo additional pain medication at 60 minutes when asked “Do you want more pain medicine,” received additional analgesia before 60 minutes (defined as rescue medication), and developed nausea, vomiting, or pruritus during the study period.

### Primary Data Analysis

Descriptive statistics were calculated for all variables, using means with SDs or proportions with 95% confidence intervals (CIs). *t* Tests were used to compare the mean change in pain between groups.  $\chi^2$  Tests were used to compare the categorical outcomes. Differences between groups are presented as means or proportions with corresponding 95% CIs. An intention-to-treat analysis was performed, analyzing all enrolled patients in the groups to which they were randomized.

To detect a difference in the decrease of pain between the 2 treatment groups, we used the previously validated and reproducible minimum clinically significant difference of 1.3 numeric rating scale units or greater<sup>33-35</sup> as the smallest quantitative improvement in numeric rating scale score worth detecting. With a standard 2-tailed  $\alpha$  of .05, power of 90% to detect a difference of 1.3 numeric rating scale units or greater, and an SD of 2.8 (based on previous work), we estimated that 196 patients (98 in each group) would be required. To ensure enrollment of a minimum of 196 patients for analysis, an additional 24 subjects ( $\approx 10\%$ ) were enrolled to account for potential protocol violations and missing data. Our target enrollment was therefore 220 patients, 110 in each arm.

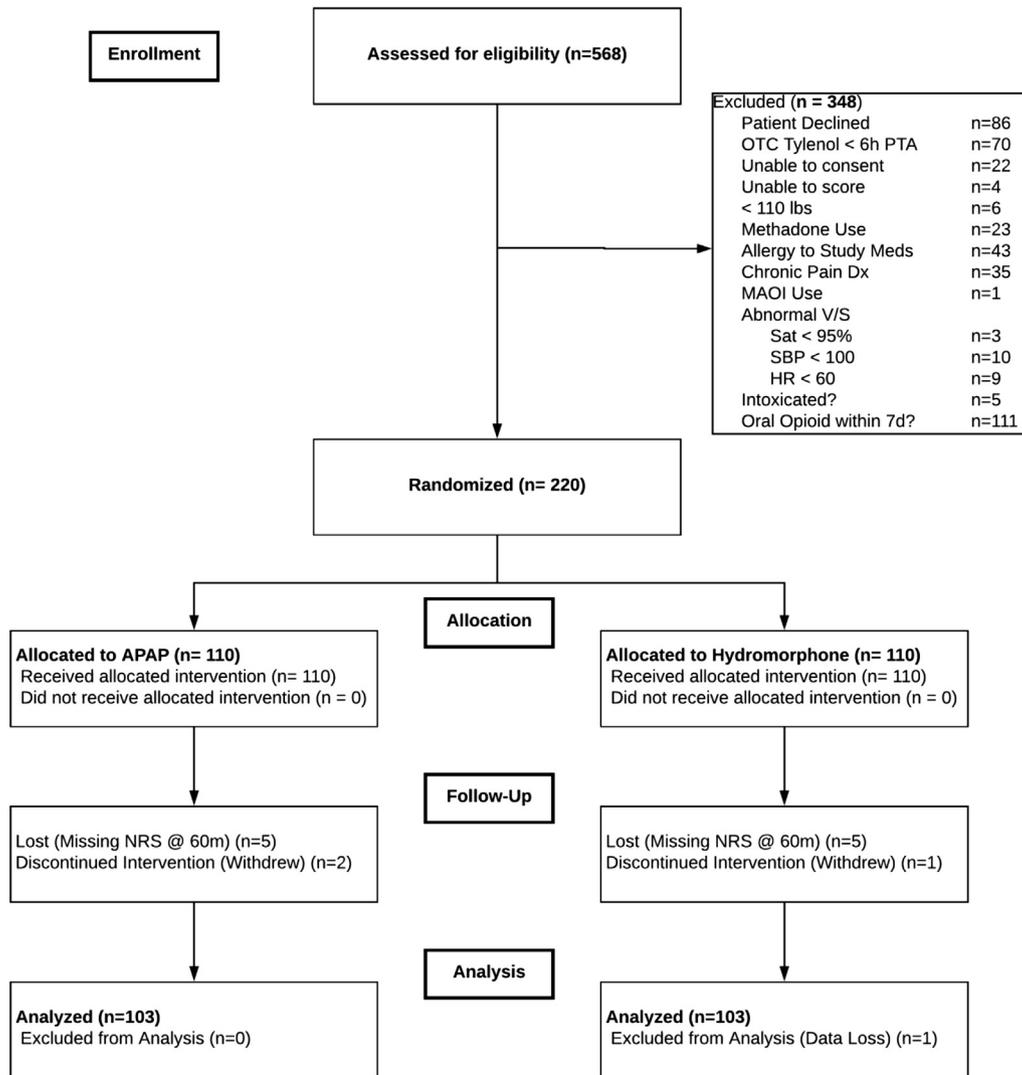
Data were entered directly into Research Electronic Data Capture (version 6.13.1; REDCap, Nashville, TN), a secure, Web-based platform maintained at the Albert Einstein College of Medicine.<sup>36</sup> Sample size computations were performed with nQuery Advisor (version 6.0; Los Angeles, CA) and R (version 3.4.3; The R Core Team, Vienna, Austria) was used for all data analyses.

## RESULTS

### Characteristics of Study Subjects

During the study period, research associates screened 568 patients for eligibility. The Consolidated Standards of Reporting Trials diagram (Figure 1) describes the flow of patients through the trial. Use of an oral opioid within the preceding 7 days was the most common reason for exclusion and accounted for approximately one third (32%) of patients excluded. A total of 220 patients met enrollment criteria, provided informed consent, were randomized, and were allocated correctly to 1 of the 2 treatment arms.

Fourteen patients, divided equally between the 2 study arms, were missing the primary endpoint (change in numeric rating scale at 60 minutes). This was most commonly because the patient was outside of the department (eg, at an imaging study) and unavailable to the research associates ( $n=9$ ), with the remainder composed of



**Figure 1.** Consolidated Standards of Reporting Trials diagram. OTC, Over-the-counter; PTA, prior to arrival; MAOI, monoamine oxidase inhibitor; APAP, acetaminophen; NRS, numeric rating scale.

3 who withdrew from participation, 1 discharged before 60 minutes, and 1 for whom data were lost because of a data entry error. The final sample included 206 patients with data available for analysis (103 in each arm), which exceeded the predefined sample size requirement of 196 (98 patients in each arm).

The 2 arms were similar in terms of sex, race or ethnicity, age, baseline pain intensity, and the presence of nausea or vomiting before administration of study medication (Table 1).

**Main Results**

At 60 minutes after study medication administration, the mean decrease in numeric rating scale pain score was 5.3 in the hydromorphone arm and 3.3 in the acetaminophen arm, representing a difference of 2.0 (95% CI 1.2 to 2.7) favoring hydromorphone (Figure 2).

Patient-level outcomes are displayed in the hybrid parallel line plot (Figure 3). Additionally, a greater proportion of patients in the hydromorphone arm declined additional analgesia at 60 minutes (65% versus 44%; difference 21%; 95% CI 8% to 35%). There was no significant difference in the proportion of patients receiving rescue analgesia before 60 minutes (Table 2).

The proportion of patients with at least 50% reduction in their numeric rating scale score from 0 to 60 minutes was 65% (67/103) in the hydromorphone arm and 35% (36/103) in the acetaminophen arm. Patients treated with hydromorphone therefore had an absolute risk reduction of 30% compared with that for acetaminophen, resulting in a number needed to treat of 4 (95% CI 3 to 6). Four patients would therefore need to be treated with hydromorphone rather than acetaminophen to achieve greater than 50% pain relief as

**Table 1.** Baseline characteristics.

Characteristic	1 mg Hydromorphone (n=110)	1 g Acetaminophen (n=110)
Women, No. (%)	63 (58)	68 (62)
<b>Race/ethnicity, No. (%)</b>		
Hispanic	71 (65)	76 (69)
Black	27 (25)	21 (19)
White	4 (3)	6 (6)
Other	8 (7)	6 (6)
Age, mean (SD), y	42 (12)	43 (13)
<b>Location of pain, No. (%)</b>		
Abdomen/pelvis	90 (82)	85 (77)
Back	8 (7)	8 (7)
Extremities	5 (5)	6 (6)
Chest	6 (6)	4 (4)
Head/neck	0	2 (2)
Other	1 (1)	5 (5)
<b>Baseline pain intensity, No. (%)</b>		
4-7	13 (11)	18 (16)
8	23 (21)	29 (27)
9	16 (15)	12 (11)
10	58 (53)	51 (46)
Nauseated or vomited before receiving medication in ED, No. (%)	62 (56)	66 (60)

measured by the numeric rating scale in one additional patient.<sup>37</sup>

Significantly more subjects developed new nausea (after reporting no nausea or vomiting at enrollment) in the

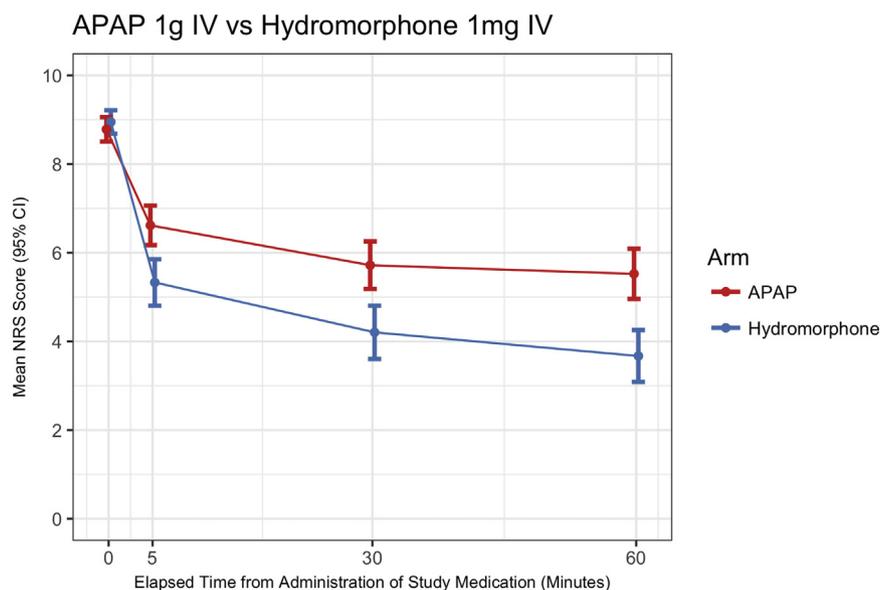
hydromorphone group (19% versus 3%; difference 16%; 95% CI 4% to 28%). There was also a trend toward more new vomiting (after reporting of no vomiting at enrollment) in the hydromorphone arm that closely approached but did not achieve statistical significance (14% versus 3%; difference 11%; 95% CI 0% to 23%) (Table 3). There was no difference between study arms in the proportion of patients who developed pruritus.

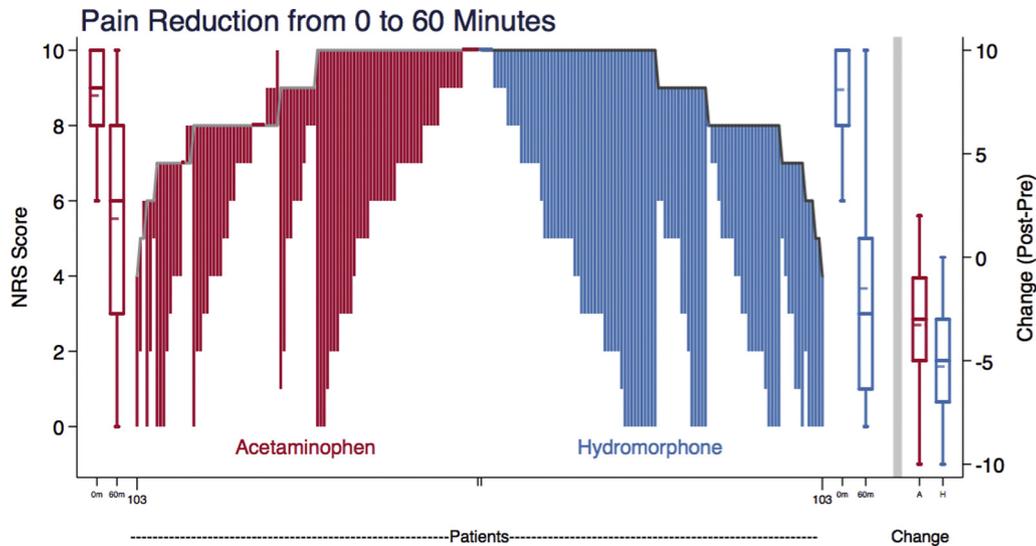
One patient in the hydromorphone group developed transient bradycardia (pulse rate 45 beats/min) after administration of study medication but was otherwise asymptomatic and required only a brief period of close monitoring.

## LIMITATIONS

Because the focus of this clinical trial was on comparative analgesic effectiveness independent of diagnosis, we included all patients presenting to the ED with severe acute pain and did not limit our enrollment to a specific diagnosis or syndrome. We may have therefore failed to identify particular diagnostic subsets of patients presenting with acute pain who may have responded more or less favorably to hydromorphone or acetaminophen.

We required subjects' pain to be of sufficient severity to warrant the use of intravenous opioids without providing any specific guidelines other than the clinical judgment of the ED attending physician. Given the substantial practice variation in physician willingness to administer opioids, it is possible that patients were more or less likely to meet enrollment criteria according to

**Figure 2.** Mean numeric rating scale pain scores by time.



**Figure 3.** Hybrid parallel line plot of individual patient responses.

their ED attending physician. However, because subjects, research associates, and all providers were blinded to study arm assignment, it is unlikely that this resulted in any differential allocation between the 2 arms. It is true, however, that this requirement by design intentionally skewed enrollment toward patients with more severe pain (median baseline numeric rating scale score was 9), and extension of our findings to patients with less severe pain may therefore be problematic.

Because we were missing primary endpoints for 14 patients, we performed a sensitivity analysis using a “best-worst and worst-best” case approach, as described by Jakobsen et al.<sup>38</sup> Our primary results and conclusions were unaffected by the missing data.

Finally, because this was a study performed in 2 urban, high-volume, inner-city EDs, extension of our findings to other populations and settings should be undertaken with caution in the absence of independent external validation.

**DISCUSSION**

As shown in Figure 2, both medications provided rapid, clinically significant reductions in pain within the first 5 minutes, followed by continuous, more gradual decreases to the primary endpoint at 60 minutes. Although both arms achieved a clinically significant reduction in pain, patients in the hydromorphone arm reported both a clinically and statistically significant greater mean reduction in numeric rating scale scores. There was, however, a greater incidence of nausea and vomiting in patients who received hydromorphone, although, as described above, there was no difference in the proportion who declined additional pain medication at 60 minutes. It therefore appears unlikely that patients declined additional analgesia to avoid the unpleasant adverse effects of nausea and vomiting.

Interpretation of these results in the context of previous studies is limited somewhat by the fact that no other published trials used hydromorphone as a comparator, opting instead to contrast acetaminophen with morphine,<sup>18,20-22,24,25,27,39</sup> tramadol,<sup>26</sup> nonsteroidal

**Table 2.** Efficacy outcomes by group.

Outcome	1 mg Hydromorphone	1 g Acetaminophen	Difference (95% CI)
<b>Primary outcome</b>			
Mean change in numeric rating scale, baseline to 60 min (SD)	5.3 (2.8)	3.3 (2.8)	2.0 (1.2 to 2.7)
<b>Secondary outcomes, No. (%)*</b>			
Declined additional analgesia at 60 min	67 (65)	45 (44)	21 (8 to 35)
Received rescue analgesia before 60 min	2 (2)	3 (3)	-1 (-5 to 3)

\*Rescue analgesia before 60 minutes was at the discretion of the treating clinician. All subjects were asked whether they required additional analgesia at 60 minutes.

**Table 3.** Adverse medication effects by group.

Outcome, No. (%)	1 mg Hydromorphone	1 g Acetaminophen	Difference (95% CI)
Nausea*	8/43 (19)	1/40 (3)	16 (4 to 28)
Vomiting†	6/43 (14)	1/40 (3)	11 (0 to 23)
Pruritus	3/103 (3)	2/103 (2)	1 (–3 to 5)

\*Refers only to patients who did not have nausea or vomiting before study medication and then developed nausea within 120 minutes of receiving study medication.

†Refers only to patients who did not have nausea or vomiting before study medication and then developed vomiting within 120 minutes of receiving study medication.

anti-inflammatory medications,<sup>23,28</sup> or topical therapies (ie, ice, lidocaine).<sup>29</sup>

Nonetheless, trials that directly compared intravenous acetaminophen with intravenous morphine as the opioid comparator reported mixed results, with the majority failing to demonstrate a difference between treatment arms,<sup>18,22,24,39</sup> 2 favoring acetaminophen,<sup>20,27</sup> and 1 concluding that intravenous morphine provided superior relief.<sup>21</sup> However, critical acceptance of these results is hampered by incomplete or missing descriptions of blinding procedures,<sup>20-22,24,27</sup> allocation concealment,<sup>18,21,27</sup> and power or sample size calculations.<sup>21,27</sup> One study by Pathan et al<sup>39</sup> of patients presenting to the hospital with a preimaging clinical diagnosis of renal colic failed to demonstrate a difference between acetaminophen and morphine, although acetaminophen appeared to be more effective in a subset analysis of patients with documented ureteral calculi confirmed on ED imaging.

The current study overcomes the aforementioned limitations and provides evidence for the analgesic superiority of intravenous hydromorphone over intravenous acetaminophen in adults presenting to the ED with undifferentiated acute pain, albeit with associated increases in nausea and vomiting in the hydromorphone group.

In conclusion, although both 1 mg intravenous hydromorphone and 1 g intravenous acetaminophen provided clinically meaningful reductions in pain scores, treatment with hydromorphone provided both clinically and statistically significantly greater relief than acetaminophen, at the cost of a higher incidence of nausea and vomiting.

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*Author contributions:* DPB, PEB, and EJG conceived and designed the study, provided statistical advice on study design, analyzed the

data, and drafted the article. DPB supervised data collection and managed its retrieval and storage, had full access to all the data in the study, and takes responsibility for the integrity of the data and accuracy of the analysis. All authors contributed substantially to article revision. DPB takes responsibility for the paper as a whole.

All authors attest to meeting the four [ICMJE.org](http://www.icmje.org) authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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