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Randomized Clinical Trial of IV Acetaminophen as an Analgesic Adjunct for Older Adults with Acute Severe Pain

Dr. Andrew K. Chang, MD, MS^a, Polly E. Bijur, PhD^b, Ashar Ata, PhD^a, Caron Campbell, MD^b, Scott Pearlman, MD^b, Deborah White, MD^b, Andrew Chertoff, MD^b, Andrew Restivo, MD^b, and E. John Gallagher, MD^b

^aDepartment of Emergency Medicine, Albany Medical College, Albany, New York

^bDepartment of Emergency Medicine, Albert Einstein College of Medicine, Bronx, NY

Abstract

Objectives: Older adults are at risk for undertreatment of pain. We examined IV acetaminophen as an analgesic adjunct to IV opioids in the care of older emergency department (ED) patients with acute severe pain.

Methods: This was a randomized clinical trial conducted in two emergency departments in the Bronx, New York. Eligible adults aged 65 years and older with acute severe pain were randomized to 0.5 mg IV hydromorphone and 1 gram IV acetaminophen or 0.5 mg IV hydromorphone and 100 cc normal saline placebo. The primary outcome was the between group difference in improvement of NRS pain scores at 60 minutes. Secondary outcomes were the between group differences in the proportion of patients who chose to forgo additional pain medications at 60 minutes, the proportion who developed side effects, the proportion who required rescue analgesia, and between group differences in NRS pain scores at 5, 15, 30, and 45 minutes.

Results: 81 patients were allocated to each arm. 80 patients in the IV acetaminophen arm and 79 patients in the placebo arm had sufficient data for analysis. At 60 minutes, patients in the hydromorphone + IV acetaminophen group improved by 5.7 NRS units while those in the hydromorphone + placebo group improved by 5.2 NRS units, for a difference of 0.6 NRS units (95% CI -0.4 to 1.5). 28.7% of patients in the hydromorphone + IV acetaminophen group wanted more analgesia at 60 minutes vs. 29.1% in the hydromorphone + placebo group, for a difference of -0.4% (-14.3 to 13.5%). These differences were neither clinically nor statistically significant. Safety profiles were similar in both groups.

Conclusion: In this randomized clinical trial, the addition of IV acetaminophen to IV hydromorphone as an adjunctive analgesic for acute, severe, pain in older adults provided neither clinically nor statistically superior pain relief when compared to hydromorphone alone within the first hour of treatment.

Corresponding author: Andrew Chang, MD, MS, 150 New Scotland Ave, MC-139, Albany, NY 12205, Telephone: 518-262-0042, changal@amc.edu.

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INTRODUCTION

The population is aging rapidly, with the number of older adults expected to double in the next 20 years to about 72 million. By 2030, older adults will account for roughly 20% of the US population.¹ When these older patients visit the ED, their complaints are most commonly pain related.²

Multiple studies have shown that older adults are at higher risk for undertreatment of pain³⁻⁵ when compared to younger patients. Adequate treatment of acute pain is important not only to relieve suffering, but also to avoid poor outcomes.^{6,7} In addition, effective management of acute pain is associated with reduced persistent pain.⁸

NSAIDs are relatively contraindicated in older adults,⁹ who are more likely to experience medication-related side effects and adverse events. Use of opioid analgesics is also complicated by changes in drug pharmacokinetics and pharmacodynamics associated with aging.¹⁰

Intravenous (IV) acetaminophen represents a potentially safer analgesic in older adults and has been used extensively in patients after surgery as an adjunct to IV opioids, both to reduce the amount of opioids used and increase pain control. However, the effectiveness of IV acetaminophen as an adjuvant analgesic in the ED setting remains unknown.

We hypothesized that IV acetaminophen in combination with IV hydromorphone would provide more efficacious pain relief compared to IV hydromorphone alone at 60 minutes in adults aged 65 years and older presenting to the ED with acute severe pain.

METHODS

Design

This was a randomized clinical trial examining the analgesic efficacy of IV acetaminophen as an analgesic adjunct to IV hydromorphone for treatment of acute severe pain in older ED patients. The study was approved by the Montefiore Medical Center Institutional Review Board (IRB) and is registered in <http://www.clinicaltrials.gov> (NCT02621619). All patients provided written consent to participate in the study.

Setting

The study took place in two EDs of the Montefiore Medical Center. The Moses division is an urban teaching hospital with more than 100,000 adult visits annually, located in the west Bronx, NY. The Weiler division is a community hospital with more than 70,000 adult visits annually, located in the east Bronx, NY. Salaried, trained, full-time, bilingual (English and Spanish) research associates staffed the ED 24 hours per day, 7 days per week during the data accrual period.

Participants

Patients aged 65 years and older presenting to the ED with acute pain (onset within 7 days) were enrolled if their pain was of sufficient severity to warrant use of intravenous opioids in

the judgment of the ED attending physician. Exclusion criteria were as follows: history of adverse reaction to hydromorphone, morphine or acetaminophen; hypotension (systolic blood pressure < 100 mmHg); room air oxygen saturation < 95%; CO₂ measurement > 46 (measured in patients with history of COPD, history of asthma with > 20 pack-year smoking, history of < 20 pack year smoking with asthma exacerbation); heart rate < 60 beats per minute, alcohol or other drug intoxication as judged by the attending physician; use of other opioids within the past 24 hours; use of a monoamine oxidase inhibitor within 30 days; history of a chronic pain syndrome (such as sickle-cell disease, osteoarthritis, or fibromyalgia); and patients with transdermal pain patches.

Study protocol

Research associates (RAs) consented and enrolled patients referred to them by ED physicians. The RAs were fluent in English and Spanish and enrolled patients 24 hours per day, 7 days per week, from March 2016 to October 2017.

Patients were randomized after signing a written informed consent in either English or Spanish, depending on patient language preference. Both versions were approved by our IRB. Random allocation was generated with www.randomization.com, using sealed opaque envelopes opened in sequential order by the RAs immediately following enrollment.

All patients received a single dose of 0.5 mg IV hydromorphone. Patients were then randomly allocated to receive 1 gm IV acetaminophen or 100 cc of normal saline placebo. Because the vial containing IV acetaminophen is uniquely shaped and proprietary, blinding could not be accomplished using an identical vial for the placebo group. Therefore, our research pharmacist removed the acetaminophen from the vial and placed it in a previously emptied 100-cc saline bag. One hundred cc normal saline was placed in an identical 100 cc saline bag and served as placebo. Because IV acetaminophen is a clear substance, blinding was not compromised. IV acetaminophen was prepared ahead of time and replaced every 3 days if unused.

NRS pain scores, vital signs, and presence of side effects were obtained at 5, 15, 30, 45, and 60 minutes. At 60 minutes patient were also asked whether they wanted more pain medication. Subsequent care of the patients was at the discretion of the treating attending physician.

Measurements

Patients were asked to rate their pain on a previously validated and reproducible¹¹ standard verbal numerical rating scale (NRS) ranging from 0 (“no pain”) through 10 (“worst pain possible”) at 0, 5, 15, 30, 45, and 60 minutes following administration of the initial hydromorphone dose at baseline.

Systolic blood pressure, respiratory rate, oxygen saturation, nausea, vomiting, and pruritus were assessed at baseline and at 5, 15, 30, 45, and 60 minutes after initial administration of hydromorphone. Adverse events were defined as use of naloxone at any time, respiratory rate < 10 breaths per minute, room air oxygen saturation < 95%, heart rate < 50 beats per minute, and systolic blood pressure < 90 mmHg.

All additional medications administered to patients, including name of medication, dose, route of delivery, and time of administration were abstracted from the medical record during the patient's stay in the ED. This enabled the research associates to resolve any ambiguities in the medical record by speaking directly to the patient and the patient's providers in real time.

Key Outcome Measures

The primary outcome was the between group improvement in NRS pain scores from baseline to 60 minutes post administration of study medications. Additional outcomes included NRS pain scores at 5, 15, 30, and 45 minutes, a comparison of incidence of side effects and adverse events, and a comparison of the proportion of patients who choose to forgo additional pain medication at 60 minutes post-baseline when asked the question, "Do you want more pain medication?"

Data Collection and Processing

Data were collected by RAs directly on a standardized data collection instrument using REDCap, a web-based application designed to support data capture for investigational purposes. Final data was downloaded from REDCap and analyzed using IBM SPSS Statistics version 22 (Armonk, NY).

Data Analysis

All variables are shown as means with standard deviations (SD), medians with interquartile ranges (IQR), or proportions with 95% confidence intervals (95% CI) when appropriate.

Independent sample t-test was used to compare mean improvement in NRS pain scores from baseline to 60 minutes after baseline. Chi-square tests were used to compare the incidence of side effects. The differences were described as point estimates with 95% confidence intervals. To estimate precision and statistical significance, we used Wilson's method of calculating a 95% CI around differences between proportions among patients who received rescue medications and who wanted more pain medication.¹²

Sample size calculation

We estimated a sample size of 148 (74 per group) would be needed to detect a difference of at least 1.3 NRS units in the improvement in NRS pain score between the two study groups, assuming a common standard deviation of 2.8 (based on prior studies we have performed)^{13–15} for an alpha of 0.05 and 80% power. 1.3 NRS units is a previously validated and reproducible measure used to quantify the "minimum clinically significance difference" in change in NRS pain score.^{11,16,17} To account for potential protocol violations and missing data we enrolled an extra 7 patients in each group. Thus, our final target sample size was 162 subjects or 81 per group. nQuery Advisor version 6.0 (Los Angeles, CA) was used to calculate the sample size.

RESULTS

Eighty-one subjects were randomized to each group for a total enrollment of 162 patients. As shown in the CONSORT flow diagram (Figure 1), 1 patient in the acetaminophen group and 2 patients in the placebo group were missing primary outcome data at 60 minutes. Therefore, our final sample was comprised of 80 patients in the acetaminophen group and 79 patients in the placebo group.

Table 1 displays baseline characteristics of the study cohort. The median age was 72 years and 38% were female. Forty-eight percent reported their pain severity as 10 (the maximum possible score) on the NRS.

Figure 2 displays baseline NRS scores, time specific NRS scores, and improvement of NRS scores. At 60 minutes (the primary outcome), the hydromorphone + IV acetaminophen group improved by 5.7 NRS units while the hydromorphone + placebo group improved by 5.2 NRS units, for a difference of 0.6 NRS units, which fell short of 1.3 NRS units^{11,16,17} making our result neither statistically nor clinically significant. Consistent with the primary endpoint, there were no clinically nor statistically significant differences between the groups at any of the time points measured during the one-hour study period (Figure 2). There were also no clinically nor statistically significant group differences between the percentage who wanted additional pain medication at 60 minutes (28.7% for IV acetaminophen group vs 29.1% for the placebo group) or who received rescue analgesia (0% for the IV acetaminophen group vs 1.3% for the IV placebo group).

Table 2 summarizes the incidence of adverse effects and side-effects by group. Nausea was relatively common in both groups while other side effects and adverse events were rare.

DISCUSSION

In our study we found that the addition of IV acetaminophen to IV hydromorphone as an adjunctive analgesic for acute, severe, pain in older adults within the first hour of treatment provided neither clinically nor statistically superior pain relief when compared to hydromorphone alone. A commonly used adage when treating older adults with pain is to “start low and go slow”. This concept developed out of concern that older adults are more likely than younger patients to experience side effects and adverse effects from various drugs, including analgesics such as opioids. However, this treatment strategy may contribute to the fact that older adults are at substantial risk for undertreatment of acute pain.^{4,5,18}

In one retrospective ED cohort study, older adults were less likely to receive pain medication than younger patients (66% vs 80%, $p=0.02$), received analgesics in a less timely fashion (74 vs 52 min, $p=0.02$), and received narcotics less frequently (89% vs 98%, $p=0.03$).¹⁹ More recently, an ED study using a national database showed that patients aged 75 years and older were 19% less likely to receive an analgesic and 15% less likely to receive an opioid than patients aged 35–54 years.⁵ Older adults who are inadequately treated for pain commonly leave the ED with significant pain. Persistent pain in older adults is associated with decreased quality of life, impaired function, and poor sleep.^{20,21} On the other hand, effective acute pain management is associated with reduced persistent pain and improved function at

6 months, as demonstrated in a study of postsurgical orthopedic patients.⁸ The overall evidence suggests that effective treatment of acute pain in older adults presenting to the ED has the potential to reduce persistent pain and improve other longer-term outcomes.^{8,22,23}

The IV form of acetaminophen was approved in the U.S. by the FDA in November 2010. Its safety profile makes it an attractive non-opioid and non-NSAID intravenous alternative for pain control. While concerns have been raised about its cost,^{24–26} critics acknowledge that there may be special populations that might benefit from its use. Older patients, given age-related changes in metabolism, such as renal function, and cognitive decline, may constitute such a group.

IV acetaminophen is infrequently used in the ED.²⁷ In the 2015 National Hospital Ambulatory Medical Care Survey it was only prescribed in 5 out of 21,000 visits. Hence, its role in the care of ED patients is relatively unknown. A recent review of 14 RCTs that examined the effect of IV acetaminophen in head-to-head comparisons with other analgesics in ED settings found limited evidence to support the use of IV acetaminophen as a primary analgesic for acute pain control.²⁸ However, the quality of evidence was poor with 10 of the 14 studies rated as having a “very low” level of evidence. Further, only four of these trials included older adults.^{29–32} Based on inferences drawn from the mean age and standard deviation provided by these four trials, very few (if any) older adults were actually enrolled.

Intravenous acetaminophen is widely used as an adjunct to IV opioid analgesics for treatment of pain in surgical patients. Evaluation of this treatment regimen most often relies on measuring the amount of IV opioids the patient receives in the post-operative period, usually 24 or 48 hours following the operation. The assumption is that the less IV opioid the patient receives, either administered via patient-controlled pumps or by ED staff, the greater the pain relief. A recent review of 25 randomized trials that compared IV acetaminophen plus IV opioid in morphine equivalent units (MEU) to IV opioid alone or in combination with placebo, found that in the 24 hours after surgery the median reduction in MEU in patients who received IV acetaminophen was 18 mg (95% CI: 15 mg to 22 mg) compared to a standardized 50 mg administration of IV opioid in MEUs.³³ The authors a priori defined a large, clinically significant reduction of opioid use as at least 20 mg of IV opioid in MEU.

Unlike the post-operative studies, we did not find the addition of 1000 mg IV acetaminophen to 0.5 mg IV hydromorphone to increase pain relief in older patients treated in two EDs. The proportion of patients who wanted additional analgesia 60 minutes after the initial dose and the incidence of side effects were nearly identical in the two groups. We were unable to find any studies that assessed the use of IV acetaminophen as an adjunct to IV opioids in the ED that would be more comparable to our study than the many post-operative studies. Thus, our study does not support the use of IV acetaminophen as an adjuvant analgesic to hydromorphone.

LIMITATIONS

There are several limitations to our study. Although we removed acetaminophen from its proprietary and uniquely shaped vial in order to maintain blinding, there is some suggestion

in the literature that IV acetaminophen may cause pain during infusion.³⁴ Thus, it is possible that unmasking occurred and we were unable to detect that because we did not specifically ask patients whether they felt pain during infusion of study medication. To our knowledge, however, no patients in either arm commented on, or volunteered, any information about discomfort during infusion of any of the study medications.

Another limitation of our study was the relatively short duration (60 minutes). We chose this because we were interested in the short-term analgesic effect of IV acetaminophen in treating acute severe pain, and because we were also concerned about the potential confounding effects of additional rescue analgesia that might have occurred with longer followup times. About 29% of patients in each group requested additional analgesia at 60 minutes, suggesting that our concerns about confounding might at least have some face and content validity.

Since our study was conducted in older adults, our results do not necessarily extend to younger patients, nor to populations with a different ethnic makeup compared to ours, which was approximately 64% Latino and 20% African-American.

CONCLUSIONS

The addition of IV acetaminophen to IV hydromorphone as an adjunctive analgesic for acute, severe, pain in older adults within the first hour of treatment provided neither clinically nor statistically superior pain relief when compared to hydromorphone alone.

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Figure 1:
CONSORT Diagram

Figure 2:

Graphical representation of change in NRS pain scores over time by group

Table 1:

Baseline Characteristics

Characteristic	IV acetaminophen n=80	Placebo n=79
Sex; N(%)		
Female	30 (37.5)	31 (39.2)
Male	50 (62.5)	48 (60.8)
Race/ethnicity; N(%)		
Hispanic	51 (63.7)	51 (64.6)
African-American	20 (25.0)	12 (15.2)
White	7 (8.8)	13 (16.5)
Other	2 (2.5)	3 (3.8)
Age (years) Median (IQR) ^a	72 (69, 79)	72 (68, 77)
Baseline Pain intensity; N(%)		
5–7	13 (16.3)	10 (12.7)
8	14 (17.5)	24 (30.4)
9	14 (17.5)	8 (10.1)
10	39 (48.8)	37 (46.8)
Nauseated before receiving study medication in ED; N(%)	34 (42.5)	38 (48.1)
Vomited before receiving study medication in ED; N(%)	17 (21.3)	18 (22.8)

^aIQR: interquartile range

Table 2:

Side effects and adverse events by group

Outcome	IV acetaminophen n=80	Placebo n=79	Difference (95% CI)
Nausea ^a ; N(%)	8/46 (17.4)	8/41 (19.5)	-2.1 (-18.8, 14.1)
Vomiting ^a ; N(%)	2/46 (4.3)	1/41 (2.4)	1.9 (-8.7, 12.3)
Pruritus; N(%)	4/80 (5.0)	1/79 (1.3)	3.9 (-2.6, 11.0)
Heart rate < 50/min; N(%)	1 (1.3)	0 (0)	1.3 (-3.5, 6.7)
Oxygen saturation < 95%; N(%)	1 (1.3)	2 (2.5)	-1.3 (-7.6, 4.5)
Systolic blood pressure < 90 mm Hg; N(%)	0/80 (0)	1/79 (1.3)	-1.3 (-6.8, 3.4)
Respiratory rate < 10/minute; N(%)	0 (0)	0 (0)	0 (-4.6, 4.6)

^a Among patients who were neither nauseated nor vomiting before receiving study medication