A Randomized Trial Comparing the Efficacy of Five Oral Analgesics for Treatment of Acute Musculoskeletal Extremity Pain in the Emergency Department

Polly E. Bijur, PhD*; Benjamin W. Friedman, MD; Eddie Irizarry, MD; Andrew K. Chang, MD; E. John Gallagher, MD

*Corresponding Author. E-mail: polly.bijur@einsteinmed.org.

Study objective: We compare the efficacy and adverse effects of 5 oral analgesics in emergency department (ED) patients aged 21 to 64 years with acute musculoskeletal pain.

Methods: This was a randomized clinical trial conducted in 2 urban EDs. Patients received 400 mg ibuprofen/1,000 mg acetaminophen, 800 mg ibuprofen/1,000 mg acetaminophen, 30 mg codeine/300 mg acetaminophen, 5 mg hydrocodone/300 mg acetaminophen, or 5 mg oxycodone/325 mg acetaminophen. The primary outcome was change in pain before administration of medication (baseline) to 1 hour postbaseline. A numeric rating scale was used, varying from 0=“no pain” to 10=“worst imaginable pain.” Secondary outcomes included receipt of rescue medication and adverse effects at 1 and 2 hours postbaseline. ANOVA was used to test differences in the primary outcome between treatment groups.

Results: Six hundred participants, predominantly men and Latino, were enrolled. Change in pain from baseline to 60 minutes did not differ by treatment (P=.69). The mean change in pain in numeric rating scale units was 400 mg ibuprofen/1,000 mg acetaminophen 3.0 (95% confidence interval [CI] 2.6 to 3.5); 800 mg ibuprofen/1,000 mg acetaminophen 3.0 (95% CI 2.5 to 3.5), 30 mg codeine/300 mg acetaminophen 3.4 (95% CI 2.9 to 3.9), 5 mg hydrocodone/300 mg acetaminophen 3.1 (95% CI 2.7 to 3.5), and 5 mg oxycodone/325 mg acetaminophen 3.3 (95% CI 2.8 to 3.7). Rescue medication was received before 1 hour had elapsed by 2 patients receiving 400 mg ibuprofen/1,000 mg acetaminophen (1.7%), 3 patients receiving 800 mg ibuprofen/1,000 mg acetaminophen (2.5%), zero patients receiving 30 mg codeine/300 mg acetaminophen (0.0%), 3 patients receiving 5 mg hydrocodone/300 mg acetaminophen (2.5%), and zero patients receiving 5 mg oxycodone/325 mg acetaminophen (0.0%) (P=.21). More patients who received opioids were nauseated or vomited compared with those who did not: 6.7% versus 1.7% (5.0% difference; 95% CI 1.7% to 8.2%). The findings at 2 hours were similar.

Conclusion: No analgesic was more efficacious than others 1 or 2 hours after baseline. There was significantly more nausea and vomiting among patients treated with opioids. [Ann Emerg Med. 2021;77:345-356.]

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INTRODUCTION

A core mission of the emergency department (ED) is alleviation of pain and discomfort.[1] Oral combinations of opioid analgesics with nonopioids are frequently used for easing pain during the ED visit and after discharge. Although oral opioid analgesics are effective for controlling pain, they also have potential for misuse, dependence, and diversion that can have devastating societal consequences.[2] Despite the relatively small contribution of the ED to the opioid epidemic,[3] increasing the use of effective nonopioid medications may be part of an overall strategy to address the epidemic. It is critical to assess whether a decrease in use of oral opioid analgesics leads to less effective pain control.

Evidence about the efficacy of combining nonsteroidal anti-inflammatory drugs and acetaminophen for controlling pain is inconclusive. Most studies compare the combinations of these analgesics to that of the individual drugs and have been the subject of several reviews.[4-6] Taken as a whole, there is more consistent evidence for the superiority of combination analgesics over acetaminophen than over nonsteroidal anti-inflammatory drugs, particularly in the dental model of third molar extraction. A

Editor's Capsule Summary

What is already known on this topic

Many oral analgesic options exist for treatment of acute pain.

What question this study addressed

What are the comparative pain reduction and adverse effect outcomes of 5 common opioid or acetaminophen-ibuprofen combinations?

What this study adds to our knowledge

In 600 randomly assigned patients enrolled in 2 urban emergency departments (EDs) with acute musculoskeletal pain, there was no evidence that one approach was superior in 1- or 2-hour pain score change between the therapies, although nausea and vomiting were more frequent in those receiving an opioid.

How this is relevant to clinical practice

These observations underscore that opioids are not universally a better choice for ED acute musculoskeletal pain compared with ibuprofen and acetaminophen.

substantial number of studies also found the combination to confer superior analgesia compared with nonsteroidal anti-inflammatory drugs alone. There are few ED studies. One found the combination of 1,000 mg of acetaminophen and 800 mg of ibuprofen to be no more effective than the individual components.[7]

Three studies compared the efficacy of a nonopioid combination with opioid combination analgesics. Two found 1,000 mg of acetaminophen and 400 mg of ibuprofen to provide more analgesia than 30 mg of codeine combined with 300 mg of acetaminophen[8] or 1,000 mg acetaminophen.[9] The third study, conducted by our group, found the same dose of acetaminophen and ibuprofen to have an effect on alleviating musculoskeletal pain similar to that of the commonly used opioid combination analgesics used in the ED.[10] The current study is a replication of that study, as well as an extension of it to include an additional combination analgesic.

The aim of the study was to compare the efficacy of 5 oral analgesics: 400 mg ibuprofen plus 1,000 mg acetaminophen, 800 mg ibuprofen plus 1,000 mg acetaminophen, 30 mg codeine plus 300 mg acetaminophen, 5 mg hydrocodone plus 300 mg acetaminophen, and 5 mg oxycodone plus 325 mg acetaminophen for treatment of musculoskeletal pain. The null hypothesis was that there would be no difference in efficacy of the 5 analgesics from baseline (immediately before treatment) to 1 hour postbaseline. The alternate hypothesis was that treatment with at least one of the analgesics would be more efficacious than one or more of the other analgesics and that the difference between treatments would meet a standard criterion for clinical significance commonly used in emergency medicine pain research.

MATERIALS AND METHODS

Study Design and Setting

The study was a randomized double-blind superiority trial of 5 oral analgesic combination medications. The efficacy of the analgesics was assessed 1 and 2 hours after baseline. The study took place in 2 academic EDs in the Bronx, NY, that receive greater than 180,000 visits annually. Salaried, trained, bilingual (English and Spanish), technician-level research associates staff both EDs continuously. Patients were enrolled from November 26, 2017, to November 5, 2019. The Albert Einstein College of Medicine Internal Review Board approved the study. All patients provided written consent.

Selection of Participants

Patients were eligible if they were aged 21 through 64 years; had a complaint of acute musculoskeletal pain in one or more extremities, defined as distal to and including the shoulder or hip joints; experienced pain of less than 7 days' duration; and spoke English or Spanish; the clinician planned to treat the patient in the ED with oral analgesics and was willing to use opioid analgesics or up to 800 mg ibuprofen and 1,000 mg acetaminophen; and the patient was going to receive imaging of the painful extremity. Standard practice is to give patients an oral analgesic while they await imaging and subsequent care. This criterion ensured that the majority of patients enrolled would still be in the ED when the primary outcome measure was obtained.

Patients were excluded if they did not have a cellular telephone, which could be needed for follow-up at 2 hours if they were discharged before that time; did not agree to being contacted by telephone; had received opioids, ibuprofen, or acetaminophen in the past 24 hours; had received any other prescribed or over-the-counter topical or oral analgesics in past 8 hours; had received any medicine that might interact with one of the study medications, such as antidepressant selective serotonin reuptake inhibitors or tricyclics, antipsychotics, or antimalarial medications; had

ever received methadone; had any chronic condition requiring frequent pain management such as arthritis, sickle cell disease, fibromyalgia, or any neuropathy; had a history of allergy to any of the study medications as defined by the patients; were pregnant as determined either by urine or serum human chorionic gonadotropin testing (assessed only for patients who had not reached menopause); were breastfeeding according to patient report; had a history of peptic ulcer disease; had any medical condition for which opioid analgesics, acetaminophen, or ibuprofen may be contraindicated, such as hepatitis, renal insufficiency, hypo- or hyperthyroidism, Addison's disease, or Cushing's disease; had sustained multiple injuries or laceration; or were planning to drive home after the ED visit.

Interventions

Patients were randomized to receive 400 mg of ibuprofen plus 1,000 mg of acetaminophen, 800 mg of ibuprofen plus 1,000 mg of acetaminophen, 30 mg of codeine plus 300 mg of acetaminophen, 5 mg of hydrocodone plus 300 mg of acetaminophen, or 5 mg of oxycodone plus 325 mg of acetaminophen. Patients who required rescue analgesics (based on ED attending physician discretion or patient's request) received 5 mg of oral oxycodone that could be administered at any point during the 2-hour study period. Other analgesics could also be administered in accordance with ED attending physician discretion.

We chose to test the efficacy of the 3 most commonly used opioid combination analgesics at their starting doses. Because the combination of ibuprofen and acetaminophen is not standard, we chose to study 400 mg ibuprofen and 1,000 mg acetaminophen partly to replicate a previous study conducted by our group,[10] and because this is a dose that has been found to be effective in several studies of dental pain.[9] We added 800 mg of ibuprofen combined with 1,000 mg acetaminophen. This was based on the Oxford League Table of Analgesic Efficacy, based on reviews of randomized trials of analgesics that suggest superiority of the higher dose,[11] although in a recent randomized trial a single dose of 800 mg ibuprofen was not more effective than 400 or 600 mg for treatment of musculoskeletal pain in the ED.[12]

The research pharmacist created a randomization list in blocks of 10, using an online randomization plan generator (http://www.randomization.com). The randomized allocation schedule could be accessed only by the research pharmacist, who had no role in dispensing the medication. The pharmacist masked the analgesics by inserting them into identical opaque capsules and created research packets, each with 5 tablets containing the masked investigational medication. Five capsules were needed because the amount of 1,000 mg of acetaminophen and 800 mg of ibuprofen could not fit in fewer capsules small enough for patients to comfortably swallow. All the other medications were dispensed identically to preserve blinding. The physician, nurse, and research associates were all blinded to the allocation. The randomized allocation schedule was uploaded into the electronic data collection system and study numbers were generated that corresponded to the allocation. Research packets labeled with the study numbers were removed by nurses from an automated medical dispensing system located in the ED. The nurses administered the study medication to patients under direct observation to confirm ingestion of the analgesics.

Methods of Measurement

Pain intensity was assessed on an 11-point numeric rating scale (NRS) in which 0 denotes no pain and 10 denotes worst imaginable pain.[13] The research associates used a standardized electronic data collection instrument, Research Electronic Data Capture (REDCap) (version 10; Vanderbilt University, Nashville, TN), to record the patients' rating of pain immediately before receiving the study medication (baseline), immediately before receiving rescue medication for those who received additional medication, and at 1 and 2 hours postbaseline. If patients were discharged before 2 hours, the research associates called them at the 2-hour point to obtain their pain scores.

The primary outcome was change in pain on the NRS, measured from the time before ingestion of the study medication to 1 hour later. The 1-hour interval was chosen for several reasons. First, timely pain relief is an important characteristic of an effective analgesic. Second, measuring efficacy of the initial study analgesic is complicated by subsequent receipt of rescue medication because the pain ratings reflect the effect of both initial and rescue analgesics. In our experience, few patients with musculoskeletal pain receive additional analgesics within an hour of the original dosing. Thus, using the 1-hour point allowed inferences about the effect of the study medications that were relatively unaffected by receipt of rescue medication.

To address the potential confounding associated with rescue medication, patients who received rescue medication were asked to rate their pain immediately before receipt of the additional analgesic. An adjusted change in pain was calculated by subtracting the pain rating before rescue medicine from the one at baseline. This value was substituted for the pain rating at 1 hour if an additional analgesic was given in that period because it is likely to

more accurately reflect the effect of the initial study medication.

Change in NRS scores from baseline to 2 hours postbaseline was a secondary efficacy outcome. An adjusted NRS score was calculated in the same way as the 1-hour change for patients who received rescue medications. Other secondary outcomes included receipt of rescue medication and the answer to the question, "The next time you come to the ED with acute pain, do you want to be given the same pain medication?" Satisfaction with pain relief and time to satisfaction with pain relief were measured on a 4-point Likert scale rating of very unsatisfied, unsatisfied, satisfied, or very satisfied. For analytic purposes, satisfaction was grouped into 2 categories: very unsatisfied or unsatisfied, and very satisfied or satisfied. The research associates also asked patients whether they experienced the following adverse effects at 1 and 2 hours postbaseline: nausea, vomiting, stomach pain, heartburn, gas, diarrhea, itch, rash, dizziness, and drowsiness.

Demographic characteristics were collected to describe the population from which the sample was drawn, as well as initial pain scores and the method for collecting 2-hour information: in the ED or by telephone if the patient left before 2 hours.

Primary Data Analysis

We calculated descriptive statistics for all variables, expressed as frequencies, means and SDs, medians and interquartile range, and proportions, as appropriate. The primary analysis was an ANOVA that compared the mean change in pain from baseline to 1 hour later in the 5 treatment groups. We planned to conduct *t* tests of the 10 pairs of means after a statistically significant ANOVA result (P=.05), with a Bonferroni correction to control for type I errors caused by multiple testing (ie, 0.05/10 tests=0.005). The magnitude of the effects is reported as means and 95% confidence intervals. ANOVA and χ^2 tests were used to provide overall tests of the association between treatment and each of the secondary outcomes.

The distribution of change in pain at 1 and 2 hours postbaseline in each treatment group is presented graphically.

Two exploratory analyses were conducted to assess whether one or more of the medications were more effective for treating higher levels of pain. These analyses were restricted to patients who had diagnoses of fracture and those whose initial pain rating was 10, indicating worst possible pain.

SPSS (version 24; SPSS, Armonk, NY) was used to conduct all data analyses. A significance criterion of .05 was used for tests of all secondary variables and for the exploratory analyses.

The following parameters were used to calculate the sample size: an overall 2-sided significance level of .05, 80% power, and a Δ of 1.3-NRS-unit change in pain between groups. This value was based on a validated and reliable standard definition of the minimal clinically significant difference in pain between different analgesic treatments.[14] A within-group SD of 2.6 was used to calculate the sample size, based on estimates from previous work of variability of change in pain in response to oral opioid analgesics.[15,16] We planned to use *t* tests to conduct all pairwise comparisons if the statistical significance of the overall ANOVA was less than or equal to .05. The significance criterion for the 10 pairwise tests was adjusted with the Bonferroni correction, resulting in an α of .005 (ie, 0.05/10). The sample size calculation was thus based on an α of .005 for each pairwise *t* test. Under these parameters, 110 patients were needed in each group, for a total of 550 patients. We enrolled an additional 50 patients to ensure having at least 550 patients with analyzable data (ie, a total of 600 patients, 120 in each group).

RESULTS

Characteristics of Study Subjects

The research associates screened 4,112 patients and enrolled 600. Three patients were missing all data because there were dispensing errors and were not included in the analysis. The primary reasons for ineligibility were duration of pain 7 days or longer, physician did not consider 1 or more of the study drugs to be appropriate, and pain was due to multiple injuries (Figure 1).

The treatment groups had similar demographic compositions, initial pain ratings, diagnoses, and nonpharmaceutical interventions (Table 1). A similar proportion of patients reported their 2-hour pain and other secondary outcomes in person in the ED and by telephone (Table 1). The distributions of these characteristics by treatment were not statistically significant.

Main Results

The mean decrease in pain scores from baseline to 1 hour postbaseline varied from 3.0 to 3.4 NRS units in the 5 groups (Table 2). The overall test of different change in pain by treatment was not statistically significant (P=.69). The differences were substantially less than the criterion of 1.3-NRS-unit difference as being clinically meaningful.

Adjusted pain ratings obtained immediately before rescue medication were also used in place of the 1-hour

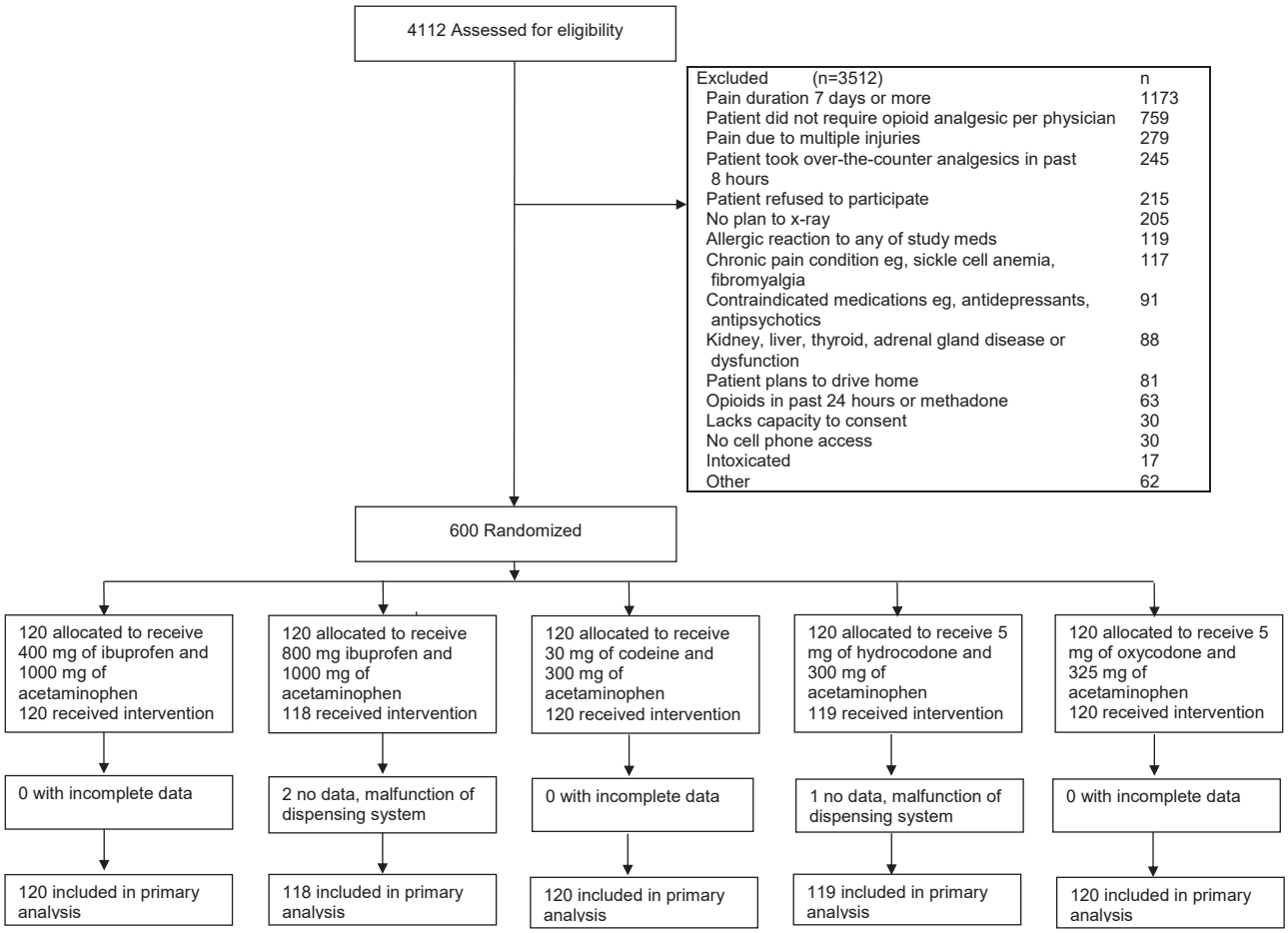

Figure 1. Patient flow diagram.

ratings. This adjustment had almost no effect on the mean reduction in pain scores (Table 2).

Few patients received rescue medication in the first hour postbaseline (8/597; 1.3%). The proportion of patients who received rescue medication did not differ by treatment (Table 2).

The findings were similar for the entire period from baseline to 2 hours postbaseline (Table 2). There were no clinically or statistically significant differences in change in pain scores between treatment groups. Approximately one quarter of patients in each group received additional analgesics, but this did not differ by group. The largest difference between percentage of patients in the 5 treatment groups who received rescue medication was less than 4%.

Two exploratory analyses were performed to assess whether the efficacy of the 5 analgesics differed for patients with presumably greater pain than others with less pain. As shown in Table 2, for patients with fractures, the difference in change in pain associated with treatment exceeded the criterion for minimal clinical significance after adjustment for rescue medication but these differences were not statistically significant. The change in pain from baseline to 2 hours was lowest in patients with fractures who were treated with 400 mg ibuprofen and 1,000 mg acetaminophen.

Figure 2*A* shows the distribution of change in pain scores from baseline to 1 hour postbaseline, adjusted for receipt of rescue medication. The figure indicates substantial and similar variability in all groups. In the entire sample, 25% of the patients had little pain relief from baseline to 1 hour postbaseline (a change of 1 NRS unit or less); patients in the highest quartile had pain scores that decreased by 5 NRS units or more. Figure 2*B* shows the adjusted decrease in pain from baseline to 2 hours in all groups. There was wide variability of response in all 5 treatment groups.

The proportion of patients satisfied with pain relief and time to pain control, and preference for the same analgesic in the future, did not differ significantly by treatment group (Table 3).

Nausea and vomiting differed significantly across the 5 groups (P=.048) (Table 4), although only 4.7% of all

Table 1. Patient characteristics.

Characteristic	Ibuprofen 400 mg and Acetaminophen 1,000 mg	Ibuprofen 800 mg and Acetaminophen 1,000 mg	Codeine 30 mg and Acetaminophen 300 mg	Hydrocodone 5 mg and Acetaminophen 300 mg	Oxycodone 5 mg and Acetaminophen 325 mg
Total No. of patients	120	118	120	119	120
Female sex,* No. (%)	49 (41)	53 (45)	59 (49)	50 (42)	53 (44)
Age,* mean (SD)	36 (12)	38 (13)	38 (12)	39 (12)	36 (12)
Race and ethnicity,* No. (%)					
Latino	87 (72)	81 (69)	83 (69)	82 (69)	79 (66)
Black	20 (17)	32 (27)	29 (24)	28 (23)	30 (25)
Other	13 (11)	5 (4)	8 (7)	9 (8)	11 (9)
Initial pain intensity score,* No. (%)					
0–6	3 (2)	2 (2)	1 (1)	4 (3)	5 (4)
7	6 (5)	13 (11)	8 (7)	9 (8)	14 (12)
8	19 (16)	19 (16)	26 (22)	19 (16)	16 (13)
9	22 (18)	15 (13)	17 (14)	22 (19)	19 (16)
10	70 (58)	69 (59)	68 (57)	65 (55)	66 (55)
Diagnosis,* No. (%)					
Sprain or strain	68 (57)	82 (70)	68 (57)	78 (66)	75 (63)
Extremity fracture	24 (20)	14 (12)	17 (14)	11 (9)	21 (18)
Muscle pain	13 (11)	11 (9)	17 (14)	13 (11)	12 (10)
Contusion	6 (5)	6 (5)	11 (9)	10 (8)	1 (1)
Other	9 (8)	5 (4)	7 (6)	7 (6)	11 (9)
Nonpharmacologic interventions,* No. (%)					
≥1	65 (54)	67 (57)	56 (47)	55 (46)	57 (47)
2-h follow-up,* No. (%)					
In ED	83 (70)	76 (66)	73 (62)	82 (71)	82 (70)
By telephone	35 (30)	39 (34)	44 (38)	34 (29)	36 (31)

*$P>.05$.

patients experienced these adverse effects. In a post hoc analysis, nausea and vomiting were found to be more common in patients who received opioid analgesics, 6.7%, than among those who did not, 1.7% (5.0% difference; 95% confidence interval 1.7% to 8.2%). The other adverse effects were similarly distributed in the 5 groups.

LIMITATIONS

The study has several limitations. Relatively low doses of the opioid combinations were administered in this study. Higher doses might provide more relief than the nonopioid medications we evaluated. We evaluated only a single dose of each medication. Thus, we can infer that the efficacy of the medications did not differ only at the specific doses we tested. Titration to pain relief is more feasible with the opioid combination analgesics than the nonopioid analgesics we studied because of the lack of a therapeutic ceiling effect for the opioids and the smaller dose of acetaminophen. However, the doses of opioids used in this study are likely to be those most commonly prescribed for pain in the ED and at discharge, particularly in the present climate, in which the potential danger of opioid misuse and addiction is well recognized.

An important question that this study did not directly address is whether nonopioid analgesics can be prescribed at discharge in place of opioid analgesics and confer similar pain relief, thus eliminating the possibilities of diversion, misuse, and abuse. This study examined the effect of the analgesics during a 2-hour period just after ED evaluation, thus formally limiting inference to pain control in the ED.

Table 2. Efficacy of oral analgesics: decrease in pain intensity* and receipt of rescue medication.

	Ibuprofen 400 mg and Acetaminophen 1,000 mg	Ibuprofen 800 mg and Acetaminophen 1,000 mg	Codeine 30 mg and Acetaminophen 300 mg	Hydrocodone 5 mg and Acetaminophen 300 mg	Oxycodone 5 mg and Acetaminophen 325 mg	*P* Value†
Baseline to 1 h postbaseline						
Decrease in pain from baseline to 1 h, mean (95% CI) N	3.0 (2.6–3.5) 120	3.0 (2.5–3.5) 118	3.4 (2.9–3.9) 120	3.1 (2.7–3.5) 119	3.3 (2.8–3.7) 120	.69
Adjusted decrease in pain baseline to 1 h,‡ mean (95% CI) N	3.0 (2.6–3.5) 120	2.9 (2.5–3.4) 118	3.4 (2.9–3.9) 120	3.1 (2.7–3.5) 119	3.3 (2.8–3.7) 120	.61
Adjusted decrease in pain baseline to 1 h,‡ patients with initial pain rating of 10, mean (95% CI) N	3.0 (2.4–3.7) 70	3.4 (2.8–4.1) 69	3.8 (3.1–4.4) 68	3.4 (2.8–4.0) 65	3.5 (2.8–4.2) 66	.58
Adjusted decrease in pain baseline to 1 h,‡ patients with fractures, mean (95% CI) N	3.2 (2.0–4.5) 24	2.9. (1.5–4.2) 14	4.2 (2.9–5.6) 17	2.9 (1.2–4.6) 11	3.6 (2.6–4.7) 21	.57
Received rescue medication between baseline and 1 h, n/N (%)§	2/120 (1.7)	3/118 (2.5)	0/120	3/119 (2.5)	0/120	.21
Baseline to 2 h postbaseline						
Decrease in pain Baseline to 2 h, mean (95% CI) N	4.3 (3.9–4.8) 119	4.6 (4.1–5.1) 116	4.4 (3.9–4.9) 119	4.5 (4.1–5.0) 117	4.7 (4.2–5.2) 120	.85
Adjusted decrease in pain, baseline to 2 h,‖ mean (95% CI) N	3.6 (3.1–4.1) 119	4.2 (3.7–4.8) 116	3.8 (3.3–4.3) 119	3.9 (3.4–4.4) 117	4.0 (3.5–4.6) 120	.59
Adjusted decrease in pain, baseline to 2 h,‖ patients with initial pain rating of 10, mean (95% CI) N	3.7 (3.0–4.3) 70	4.8 (4.0–5.6) 68	4.2 (3.4–4.9) 67	4.5 (3.7–5.2) 65	4.6 (3.8–5.4) 66	.24
Adjusted decrease in pain, baseline to 2 h,‖ patients with fractures, mean (95% CI) N	3.0 (1.8–4.2) 24	4.9 (3.4–6.5) 13	3.7 (2.2–5.2) 17	4.1 (2.4–5.8) 10	4.5 (3.0–6.0) 21	.31

Table 2. Continued.

	Ibuprofen 400 mg and Acetaminophen 1,000 mg	Ibuprofen 800 mg and Acetaminophen 1,000 mg	Codeine 30 mg and Acetaminophen 300 mg	Hydrocodone 5 mg and Acetaminophen 300 mg	Oxycodone 5 mg and Acetaminophen 325 mg	*P* Value[†]
Received rescue medication between baseline and 2 h, n/N (%)[§]	29/120 (24.2)	28/116 (24.1)	26/119 (21.8)	27/118 (22.9)	28/120 (23.3)	.99

CI, Confidence interval.
*Pain intensity measured by NRS score.
[†]Significance of ANOVA test of overall association between treatment and outcome.
[‡]NRS score at rescue, used to calculate adjusted decrease in pain for patients who received rescue medication between baseline and 1 hour postbaseline.
[§]n Is the number of patients who received rescue medication; N is the total number of patients in treatment group.
[‖]NRS score at rescue, used to calculate adjusted decrease in pain for patients who received rescue medication between baseline and 2 hours postbaseline.

The combination of ibuprofen and acetaminophen at the doses used in this study is not commercially available in the United States. A combination product is available in Australia and New Zealand, but it is at lower dosages of both drugs than what was used in this study. Although both drugs are available without a prescription in the United States, in our experience, many patients prefer "prescription strength" medication because they believe these medications are more effective than over-the-counter analgesics. Furthermore, some insurance plans will cover the same over-the-counter medications if there is a prescription for the larger amount.

Patients who left the ED before the 2-hour point were called by the research associates and asked about their pain, satisfaction, and adverse effects. It is possible that this different mode of obtaining the information affected the responses; however, the percentage of patients who were contacted by telephone in each group was similar, making it unlikely this would affect the outcomes.

A large number of statistical tests were performed. The probability of observing one significant test result was high. Only one test result was statistically significant, indicating that patients who received the opioid combination drugs had more nausea and vomiting than those who did not. Although it is possible this was due to chance, nausea and vomiting are well-known adverse effects of opioid analgesics, and thus the significant test result is likely to reflect a true consequence of the opioid medications.

The results of this study are not directly generalizable to all patients who present to the ED with musculoskeletal pain. Some of the exclusion criteria were chosen for patient safety: receiving medications that might interact with the study drugs, and conditions such as kidney and liver dysfunction. It is likely that these patients would be excluded as part of routine clinical practice. Doctors and nurse practitioners who were responsible for the patients' care had to be willing to give oral opioids to patients; thus, it is possible that patients in the study were in more pain than the general population of patients presenting with musculoskeletal pain. The sample was predominantly Latino; thus, the findings can most clearly be generalized to this group of patients.

DISCUSSION

Because of the increase in prescription opioid–related overdoses and deaths since the 1990s,[2] some question the widespread use of oral opioids. Recent data from the National Hospital Ambulatory Care Survey indicate a substantial decrease in ED visits from 2010 (21.5%) to 2017 (14.6%) at which an oral opioid was prescribed.[17] Although this may be encouraging from a societal perspective, what the national data cannot indicate is whether pain control in the ED has been less than optimal during this period because of change in class of analgesic prescribed.

The results of this study indicate that, on average, there was no difference in the efficacy of the opioid and nonopioid combination analgesics, or in satisfaction with the analgesics for ED patients with musculoskeletal pain. We did not detect the specified difference in change in pain, 1.3 NRS units, that would indicate the superiority of any treatment over another. None of the test results of efficacy or satisfaction were statistically significant. This suggests that on average, starting pain treatment with the nonopioid combination for patients with musculoskeletal pain may not lessen pain relief compared with treatment with the opioid-containing analgesics.

These findings are consistent with those of a prior study conducted by our group.[10] In that study, we compared a single dose of the opioid combinations

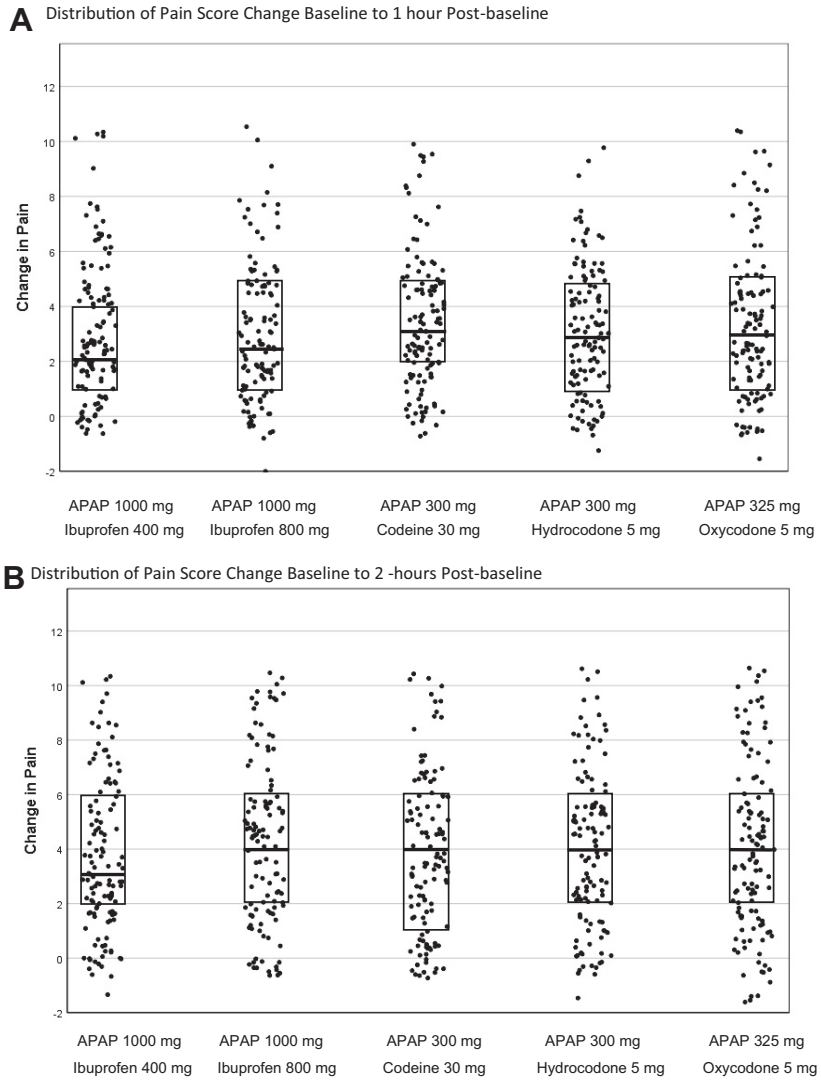

Figure 2. *A*, Change in pain baseline to 1 hour post-baseline by treatment group. *B*, Change in pain baseline to 2 hours post-baseline by treatment group. Dots indicate individuals' change in pain adujsted for rescue medication. Higher numbers indicate greater decline in pain. The bottom of the box indicates the 25th percentile, the top of the box indicates the 75th percentile, the line inside the box is the median. Data points are offset for visual clarity. *APAP*, Acetaminophen.

(acetaminophen and codeine, hydrocodone, or oxycodone) against one another and with the nonopioid combination of 400 mg of ibuprofen and 1,000 mg of acetaminophen. The efficacy of the nonopioid combination and satisfaction with pain relief were not different from that of the 3 commonly used opioid combination analgesics. Furthermore, the efficacy of the 3 opioid combinations was indistinguishable between combinations. The current study, which is a replication of that earlier study, has confirmed those results.

The cause of pain may influence the efficacy of the analgesics. In studies conducted by our group that found no difference between opioid and nonopioid analgesics, all patients presented with musculoskeletal pain. In contrast, results of 2 other studies suggest that the combination of ibuprofen and acetaminophen is superior to codeine and acetaminophen for postoperative pain control.[8,9] The comparisons with codeine were made in patients with postsurgical pain after micrographic surgery of head and neck lesions[8] and extraction of the third molar.[9] Recognition of these differences by cause suggests that the lack of association between treatment and musculoskeletal pain relief cannot be assumed to generalize to other types of pain treated in the ED.

In a continued search for a safe and effective analgesic, we added a treatment group with a higher dose of ibuprofen (800 mg of ibuprofen and 1,000 mg of acetaminophen). In the 2007 Oxford League Table of Analgesic Efficacy, studies of 600 or 800 mg of ibuprofen combined had the lowest

Table 3. Satisfaction with medication.

Outcome	Ibuprofen 400 mg and Acetaminophen 1,000 mg, n/N (%)	Ibuprofen 800 mg and Acetaminophen 1,000 mg, n/N (%)	Codeine 30 mg and Acetaminophen 300 mg, n/N (%)	Hydrocodone 5 mg and Acetaminophen 300 mg, n/N (%)	Oxycodone 5 mg and Acetaminophen 325 mg, n/N (%)	*P* Value*
Baseline to 1 h postbaseline						
Satisfied with pain relief	82/120 (68.3)	87/118 (73.7)	84/120 (70.0)	86/119 (72.3)	89/120 (74.2)	.83
Satisfied with time to pain relief	88/120 (73.3)	95/118 (80.5)	85/120 (70.8)	90/119 (75.6)	98/120 (81.7)	.22
Prefer same analgesic in future	77/119 (64.7)	83/118 (70.3)	77/120 (64.2)	81/118 (68.6)	79/120 (65.8)	.83
Baseline to 2 h postbaseline						
Satisfied with pain relief	88/118 (74.6)	93/115 (80.9)	93/119 (78.2)	91/117 (77.8)	99/120 (82.5)	.62
Satisfied with time to pain relief	90/118 (76.3)	96/115 (83.5)	90/119 (75.6)	92/117 (78.6)	103/120 (85.8)	.20
Prefer same analgesic in future	78/119 (65.5)	83/116 (71.6)	75/118 (63.6)	89/117 (76.1)	81/118 (68.6)	.25

*Significance of χ^2 test of overall association between treatment and outcome.

number needed to treat of the commonly used oral analgesics, 1.7 (95% confidence interval 1.4 to 2.3), compared with 2.5 (95% confidence interval 2.4 to 2.7) for 400 mg ibuprofen.[11] This needs to be interpreted with caution because the number of patients in the studies of the higher doses of ibuprofen was small. Nonetheless, these estimates from a series of randomized trials suggested that combining 800 mg of ibuprofen with acetaminophen might be a promising strategy to increase analgesic efficacy of nonopioid analgesics. We did not find the higher dose of ibuprofen to improve analgesia compared with 400 mg ibuprofen combined with 1,000 mg acetaminophen. Similarly, a recently published study found no difference between 800, 600, and 400 mg of ibuprofen for ED patients

Table 4. Adverse effects by treatment during 2-hour study period.

Adverse Effect	Ibuprofen 400 mg and Acetaminophen 1,000 mg	Ibuprofen 800 mg and Acetaminophen 1,000 mg	Codeine 30 mg and Acetaminophen 300 mg	Hydrocodone 5 mg and Acetaminophen 300 mg	Oxycodone 5 mg and Acetaminophen 325 mg	*P* Value*
No. of patients	120	118	120	119	120	
Drowsy/dizzy/lightheaded, No. (%)	25 (20.8)	37 (31.4)	27 (22.5)	32 (26.9)	36 (30.0)	.27
Nausea/vomiting, No. (%)	2 (1.7)	2 (1.7)	6 (5.0)	10 (8.4)	8 (6.7)	.05
Abdominal pain/heartburn, No. (%)	2 (1.7)	2 (1.7)	4 (3.3)	5 (4.2)	4 (3.3)	.66
Gas/diarrhea, No. (%)	2 (1.7)	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)	.96
Rash/itch, No. (%)	0	2 (1.7)	2 (1.7)	3 (1.7)	0	.26

*Significance of χ^2 test of overall association between treatment and adverse effect.

with acute musculoskeletal pain.[12] The lack of additional benefit is likely to reflect the analgesic ceiling of ibuprofen.

The absence of statistically significant differences in efficacy of the 5 analgesics was also found when analyses were restricted to patients who may have had higher pain intensity, evidenced by pain ratings of 10 (worst imaginable pain) or by diagnosis of fracture. However, the study was not powered to address these subgroups of the sample. The difference in efficacy between the lower dose of ibuprofen and acetaminophen and several other analgesic combinations 2 hours postbaseline met the criterion for clinical significance. These exploratory analyses suggest that 400 mg ibuprofen and 1,000 mg of acetaminophen might provide inferior pain control for patients with higher levels of pain and warrant further study with adequate power.

The wide variability of pain relief provided by each of the analgesic combinations studied is highlighted in Figure 2. Focus on mean or median responses obscures the fact that many patients fail to achieve adequate analgesia even though the mean or median decline is substantial. One quarter of all patients in the current study reported less than a 2-NRS-point decrease in pain from baseline to 1 hour postbaseline. Similarly, one quarter of the patients received rescue medication. Variable response to both opioid and nonopioid analgesics highlights the need to identify individual characteristics that can help inform clinical decisions about analgesics to assess adjunctive analgesics and continue the quest for new analgesics that provide effective analgesia for more patients in pain.

The incidence of adverse effects was low and similar across groups, with the exception of nausea and vomiting. Nausea and vomiting were substantially more frequent in patients who received opioids than those who did not. These well-known adverse effects further contribute to a clinical decision to treat with nonopioid analgesics.

In summary, the study indicates that in ED patients with musculoskeletal pain, there was no difference in the efficacy of the opioid and nonopioid combination analgesics or in satisfaction with the analgesics. There were also no differences in the incidence of adverse effects, with the exception of nausea and vomiting, which had a higher incidence in patients treated with opioid analgesics than in those who received nonopioid analgesics.

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Author affiliations: From the Department of Emergency Medicine, Albert Einstein College of Medicine, Bronx, NY (Bijur, Friedman, Irizarry, Gallagher); and the Department of Emergency Medicine, Albany Medical Center, Albany, NY (Chang).

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IMAGES IN EMERGENCY MEDICINE

(continued from p. 316)

DIAGNOSIS:

Vaso-occlusive crisis and osteomyelitis in sickle cell disease. Images were suggestive of vaso-occlusive crisis in sickle cell disease complicated by osteomyelitis. Intravenous antibiotic therapy (clindamycin and cefotaxime) was started, with complete recovery in 14 days.

Sickle cell disease results from the presence of abnormal globin chains within hemoglobin. Individuals with the disease are susceptible to a variety of complications, including vaso-occlusive crisis and infections such as osteomyelitis. Musculoskeletal manifestations of sickle cell disease are a cause of significant morbidity for children, so early recognition and treatment is essential to minimize complications. Differentiating vaso-occlusive crisis from osteomyelitis is a diagnostic challenge, with limited evidence guiding management.[1]

Ultrasonography is a useful and fast tool in diagnosing osteomyelitis in patients with sickle cell disease (sensitivity 76%), allowing characterization of soft tissue changes, fluid collections greater than 4 mm, and periosteal reaction.[2,3]

MRI is the criterion standard for evaluation in sickle cell disease, demonstrating loculated fluid collections with or without sequestration and cortical defects with fluid collections in adjacent soft tissue. Contrast enhancement may allow a significant diagnostic gain[4,5] to provide an accurate distinction between vaso-occlusive crisis and osteomyelitis.

Author affiliations: From the Department of Pediatrics, University of Ferrara, Arcispedale Sant'Anna University Hospital, Ferrara, Italy (Staccioni, Guadagno); and the Department of Radiodiagnostics (Minguzzi) and Department of Pediatrics (Marchetti), Santa Maria delle Croci Hospital, Ravenna, Italy.

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