Ibuprofen Provides Analgesia Equivalent to Acetaminophen–Codeine in the Treatment of Acute Pain in Children with Extremity Injuries: A Randomized Clinical Trial

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Abstract

Objectives: This study compared the analgesic effectiveness of acetaminophen–codeine with that of ibuprofen for children with acute traumatic extremity pain, with the hypothesis that the two medications would demonstrate equivalent reduction in pain scores in an emergency department (ED) setting.

Methods: This was a randomized, double-blinded equivalence trial. Pediatric ED patients 5 to 17 years of age with acute traumatic extremity pain received acetaminophen–codeine (1 mg/kg as codeine, maximum 60 mg) or ibuprofen (10 mg/kg, maximum 400 mg). The patients provided Color Analog Scale (CAS) pain scores at baseline and at 20, 40, and 60 minutes after medication administration. The primary outcome measured was the difference in changes in pain score at 40 minutes, compared to a previously described minimal clinically significant change in pain score of 2 cm. The difference was defined as (change in ibuprofen CAS score from baseline) – (change in acetaminophen–codeine CAS score from baseline); negative values thus favor the ibuprofen group. Additional outcomes included need for rescue medication and adverse effects.

Results: The 32 acetaminophen–codeine and the 34 ibuprofen recipients in our convenience sample had indistinguishable pain scores at baseline. The intergroup differences in pain score change at 20 minutes (−0.6, 95% confidence interval [CI] = −1.5 to 0.3), 40 minutes (−0.4, 95% CI = −1.4 to 0.6), and 60 minutes (0.2, 95% CI = −0.8 to 1.2) were all less than 2 cm. Adverse effects were minimal: vomiting (one patient after acetaminophen–codeine), nausea (one patient after ibuprofen), and pruritus (one after acetaminophen–codeine). The three patients in each group who received rescue medications all had radiographically demonstrated fractures or dislocations.

Conclusions: This study found similar performance of acetaminophen–codeine and ibuprofen in analgesic effectiveness among ED patients aged 5–17 years with acute traumatic extremity pain. Both drugs provided measurable analgesia. Patients tolerated them well, with few treatment failures and minimal adverse effects.

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Children presenting to emergency departments (EDs) with painful conditions, including fractures, receive analgesics less frequently than adults.[1,2] Children with isolated, well-aligned musculoskeletal injuries may fall into the lower triage acuity levels and experience delays in their formal evaluations and pain management. Protocols for early analgesic administration have been recommended[3] and implemented in many practices. However, given the administrative barriers to narcotic administration in triage or in other outpatient-based settings, effective nonnarcotic alternatives are desirable.

The World Health Organization (WHO) pain ladder[4] recommends analgesia with oral narcotics after failure of oral nonsteroidal anti-inflammatory agents. However,

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ketorolac and ibuprofen perform similarly to codeine-containing oral analgesics in adults with acute pain.[5–7] There is little evidence to support superiority of acetaminophen–codeine to ibuprofen for children with acute pain. Following dental and otolaryngologic procedures, pediatric patients experienced similar relief from ibuprofen and acetaminophen–codeine.[8,9] In the pediatric ED setting, ibuprofen provides marginally better single-agent pain relief than either acetaminophen or codeine in the treatment of musculoskeletal pain.[10] However, a fixed combination of acetaminophen and codeine is more commonly used in the United States and no previous prospective, randomized, blinded trials have compared acetaminophen–codeine with ibuprofen for the management of acute mild to moderate traumatic musculoskeletal pain in children.

The lack of evidence for superiority of acetaminophen–codeine over ibuprofen suggested an opportunity to simplify analgesic management of children presenting to EDs with isolated, well-aligned extremity injuries. Our hypothesis was that the two agents would be comparable in analgesic effectiveness. Therefore, we sought to demonstrate analgesic equivalence between the two agents and to describe the frequency of adverse events.

METHODS

Study Design

We conducted a prospective, randomized, double-blinded comparison of acetaminophen with codeine and ibuprofen. A combined hospital and university institutional review board approved this investigation.

Study Setting and Population

We recruited a convenience sample of patients who presented to an urban, tertiary care children's hospital ED with a census of approximately 60,000 visits per year. An investigator, available primarily during evening hours, enrolled ED patients 5 to 17 years of age who spoke English as a primary language, complained of an isolated extremity injury with tenderness to palpation from the clavicle or femoral neck to the distal phalanges, and reported pain intensity of at least 5 of 10 points at triage. Using the hospital's pain assessment protocols, triage personnel obtained pain scores from preschool-aged patients with an adaptation of the Varni-Thompson pain scale[11] and from older children with a 10-point verbal numeric scale. We excluded patients for the following reasons: allergy or prior adverse reaction to acetaminophen, codeine, or ibuprofen; administration of any analgesic within 6 hours of presentation; significant deformity or vascular insufficiency of the extremity requiring immediate treatment as determined by the treating physician; inability to use the study pain instrument; any laceration near the suspected injury; chronic hepatic or renal disease; pregnancy; concurrent use of monoamine oxidase inhibitors; or use of central nervous system depressants such as ethanol, benzodiazepines, barbiturates, antidepressants, or recreational drugs.

Study Protocol

After obtaining informed, written consent and assent, we assigned patients to receive acetaminophen–codeine or ibuprofen using a computer-generated randomization scheme.[12] An assistant not involved in the study had assembled study packets with sealed, opaque envelopes containing an order sheet directing the nurse to administer either acetaminophen–codeine (1 mg/kg as codeine, maximum 60 mg) or ibuprofen (10 mg/kg, maximum 400 mg) in a developmentally appropriate formulation.

The medications were not identical in appearance, but were similar orange-hued liquids or white tablets, administered as supplied: 120 mg of acetaminophen with 12 mg/5 mL codeine elixir (Pharmaceutical Associates, Inc., Greenville, SC); 300 mg of acetaminophen with 30 mg of codeine tablets (UDL Laboratories, Inc., Rockford, IL); 100 mg/5 mL ibuprofen elixir (McNeil Consumer Products, Co., Fort Washington, PA); and 200 mg of ibuprofen tablets (UDL Laboratories, Inc., Rockford, IL). Although unblinded, the nurse administered the study drug using a prewritten script to avoid inadvertent disclosure or bias. The patient, parent, investigator, and treating physician were unaware of the identity of the medication. The investigator and treating physician were not present at the time of medication administration.

All patients received splints and ice packs when appropriate and then underwent radiography. The treating emergency physicians and orthopedic consultants determined all other aspects of care, including the use of additional analgesia, sedation, reduction, and immobilization. Analgesics given orally were not felt to affect fasting status and did not interfere with the timing of sedation.[13]

Measurements

The Color Analog Scale[14] (CAS) is a continuous measure, anchored at 0 and 10 cm and divided in increments of 0.25 cm. Previous investigators have validated the CAS for acute pain in untrained pediatric ED patients 5 to 16 years of age,[15,16] and described a minimum clinically significant change of 2.0 cm.[17]

An investigator followed a prepared script to instruct the patient in CAS usage and elicited patient-reported pain scores immediately prior to study medication administration and at 20, 40, and 60 minutes after administration. CAS scores were recorded to the nearest 0.25 cm. Patients could not view their previous scores. To assess the effectiveness of blinding, the investigator provided a guess of the drug assignment after recording the 60-minute pain score.

Our primary outcome measurement was the intergroup difference in changes in pain scores from baseline to 40 minutes after medication, with the difference defined as (change in ibuprofen CAS score from baseline) – (change in acetaminophen–codeine CAS score from baseline), with negative values favoring the ibuprofen group. We selected 40 minutes as our primary outcome based on the onset of analgesic effect of codeine[18] and on our intention to measure analgesic effect within a time frame meaningful to the treatment of acute pain. Our secondary outcome measures were the differences in pain score changes at 20 and 60 minutes, the use of rescue medications, and adverse reactions such as nausea, vomiting, abdominal pain, and

rash during the ED stay. A rescue medication was any additional medication specifically used as an analgesic and did not include medication given for procedural sedation and analgesia.

Data Analysis

To calculate a sample size, we determined that a difference in CAS pain score changes between the two groups of 2.0 cm or more[17] would be clinically important to detect. The null hypothesis was that the intergroup difference in mean pain score change at 40 minutes would exceed 2.0 cm. We would reject the null hypothesis and consider the two drugs equivalent if the 95% confidence interval (CI) centered on the observed difference in mean pain score changes lay between −2.0 and 2.0 cm. We calculated a sample size of 33 per group to demonstrate therapeutic equivalence[19] with alpha set at 0.05 and beta at 0.10, based on previously published clinically significant differences using CAS in untrained subjects in the pediatric ED setting (2.0 cm; standard deviation [SD] 2.5 calculated from published 95% CI data). Using SPSS (SPSS Inc., Chicago, IL), we analyzed the data with the chi-square test for categorical variables (including race/ethnicity, which was determined in a post hoc analysis by retrospective chart review), t-test for continuous variables, and Wilcoxon rank sum test for nonparametric data. We calculated differences in means and surrounding 95% CIs for all pain scores.

RESULTS

From November 2002 to February 2004, we evaluated 153 patients for eligibility and excluded 85 due to recent analgesic administration (36); subthreshold pain scores or refusal of pain medication (17); refusal of randomization (14); need for prompt intravenous therapy because of deformity, intensity of pain, or suspicion of open fracture (7); young age or immature developmental status (6); allergy to study medication (3); concurrent central nervous system depressant (1); and ineligible location (1). We eliminated two of the 68 randomized subjects due to protocol violations: benzodiazepine coadministration (1) and incorrect CAS scoring by a noninvestigator (1). The remaining 66 enrollees completed the study (Figure 1).

The groups did not differ significantly in age, sex, race/ethnicity, weight, triage pain score, immobilization, or ice application (Table 1). Radiography demonstrated fractures in 36 subjects (55%), the majority involving the forearm (Table 2). The groups were similar with regard to the frequency of fractures, dislocations, and reductions. Seven patients (11%) underwent ED or operative fracture reduction, and four (6%) required inpatient management. No procedural sedation was begun prior to the 60-minute pain score.

The mean pain scores of both groups decreased from baseline during the 60-minute observation period. Pain relief, represented by mean change in pain score from baseline score, was similar in both groups at 20, 40, and 60 minutes post–analgesic administration (Table 3). All point estimates for the intergroup differences in pain changes fell within the 2-cm minimal clinically significant difference, and all 95% CIs included zero (Figure 2).

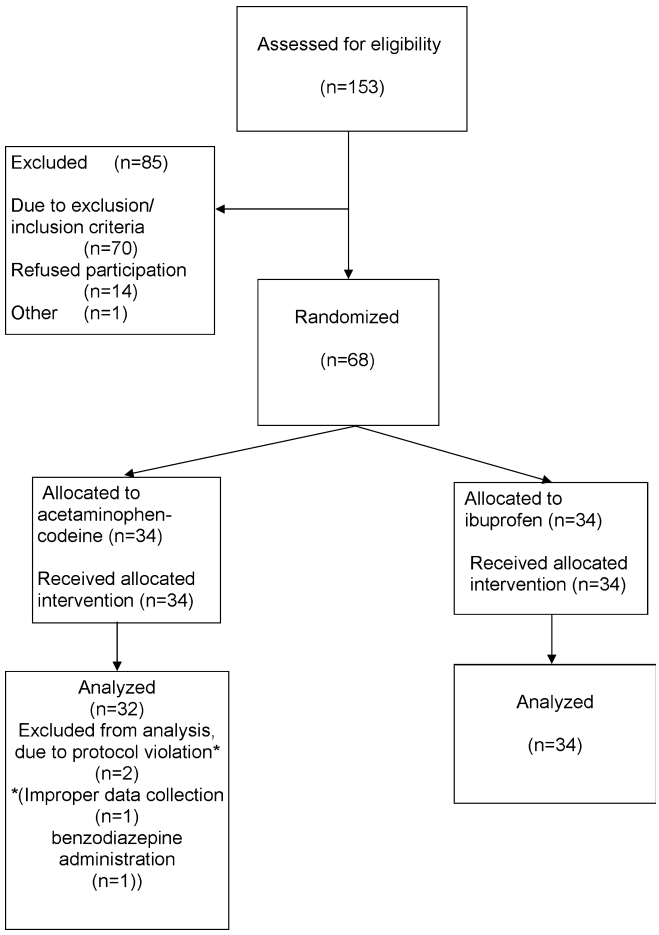

Figure 1. Diagram showing the flow of participants through each stage of the randomized trial.

Adverse reactions were infrequent and did not alter management: vomiting 4 hours after study medication and 1.5 hours after ketamine sedation (1, acetaminophen–codeine group), generalized pruritus without rash or respiratory symptoms (1, acetaminophen–codeine group), and nausea (1, ibuprofen group). Managing clinicians ordered rescue medications for three patients in each group. After the observation period, the investigator's guesses of study drug identity (provided in 62 cases) favored ibuprofen in 17 of 30 (57%) acetaminophen–codeine patients and 19 of 32 (59%) ibuprofen patients. The difference in proportions of correct guesses was not statistically significant (43% of the acetaminophen–codeine group and 59% of the ibuprofen group, p = 0.3).

DISCUSSION

Our data demonstrate equivalent analgesic effectiveness as demonstrated by similar decreases in CAS scores at 40 minutes postadministration between acetaminophen–codeine and ibuprofen for pediatric ED patients ages 5–17 years with acute traumatic extremity pain. The sample size provided adequate power to

Table 1
Demographic Characteristics

Characteristic	Acetaminophen–Codeine (*n* = 32)	Ibuprofen (*n* = 34)	p-value
Age (yr)	10.1 ± 3.4	10.6 ± 3.4	0.6
Sex (female)	18 (56)	12 (35)	0.14
Race/ethnicity			
African American	4 (12)	5 (15)	NS
White	13 (41)	14 (41)	
Hispanic	15 (47)	15 (44)	
Weight (kg)	43.0 ± 18.6	47.3 ± 22.8	0.4
Triage pain	7.2 ± 2.1	7.3 ± 1.9	0.6
Splint	7 (22)	13 (38)	0.2
Ice*	8 (28)	7 (24)	1.0

Data are presented either as mean ± SD or *n* (%).
*Data available for 29 in each group.

Table 2
Description of Findings

	Acetaminophen–Codeine Group (*n* = 32)	Ibuprofen Group (*n* = 34)
Fractures, No. (%)	19 (59)	17 (50)
Clavicle	1	1
Humerus	3	4
Radius and/or ulna	10	9
Metacarpal or digit	3	2
Tibia or fibula	2	1
Dislocations	2: sternoclavicular (1), patellar (1)	1: glenohumeral (1)
Reduction, No. (%)	5 (16)	2 (6)

Table 3
Color Analog Scale (CAS) Pain Scores (cm) with Intergroup Differences

	Acetaminophen–codeine Group		Ibuprofen Group		
Time After Administration	CAS (mean ± sd) (*n* = 32)	CAS change from baseline mean (95% CI)	CAS (mean ± SD) (*n* = 34)	CAS change from baseline mean (95% CI)	Difference in mean pain change* (95% CI)
Baseline	6.1 ± 2.2	—	6.9 ± 2.1	—	—
20 minutes	5.3 ± 2.3	−0.8 (−1.5, −0.1)	5.5 ± 2.7	−1.4 (−1.9, −0.8)	−0.6 (−1.5, 0.3)
40 minutes	4.4 ± 2.8	−1.7 (−2.4, −1.0)	4.8 ± 3.0	−2.1 (−2.9, −1.3)	−0.4 (−1.4, 0.6)
60 minutes	3.8 ± 2.7	−2.3 (−3.0, −1.6)	4.8 ± 3.4	−2.1 (−2.9, −1.3)	0.2 (−0.8, 1.2)

*Difference: (change in ibuprofen CAS score from baseline) – (change in acetaminophen–codeine CAS score from baseline). Negative values favor the ibuprofen group.

demonstrate that differences in changes in CAS pain scores did not exceed a clinically significant 2-cm difference. Few adverse effects occurred in either group, and their relationship to the study drugs was undetermined.

Acetaminophen–codeine and ibuprofen are commonly prescribed oral analgesics. However, few studies have compared their relative effectiveness in pediatric patients, and none have produced evidence of superiority of acetaminophen–codeine over ibuprofen. Pediatric posttonsillectomy patients randomized to acetaminophen–codeine or ibuprofen had no difference in pain or postoperative bleeding, but significantly more nausea occurred in the acetaminophen–codeine group.[8] Among children undergoing dental extraction, single doses of acetaminophen–codeine and ibuprofen provided similar pain relief 1 hour after administration.[9]

A recent study by Clark and colleagues[10] of pediatric ED patients with acute musculoskeletal pain reported that a single dose of ibuprofen provided better analgesia than either acetaminophen alone or codeine alone. Our study differs in two important respects. First, we compared ibuprofen with a drug that combines the

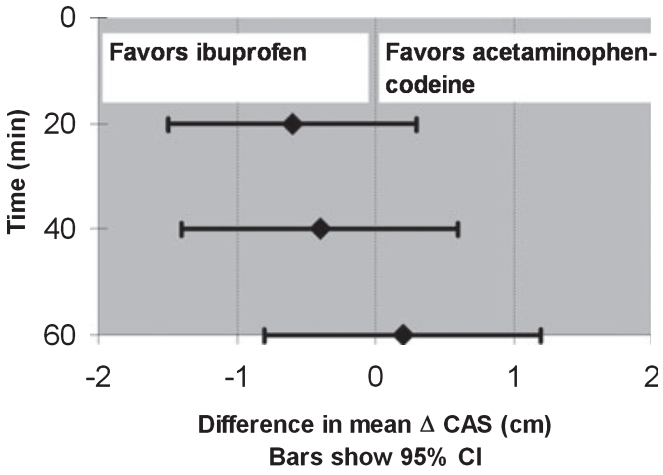

Figure 2. Difference in mean change of Color Analog Scale (CAS) pain scores over time.

individual agents and weight-based doses they chose (acetaminophen 10 mg/kg and codeine 1 mg/kg). This combination is widely available and commonly used in clinical practice. Second, despite its statistical significance, the analgesic superiority of ibuprofen over either acetaminophen or codeine reported by Clark et al. was less than their chosen 15-mm minimal clinical significant change. We designed our study to assess equivalence rather than superiority and feel that this design was appropriate, given the combined effects of acetaminophen and codeine and the limited advantage of ibuprofen over either agent alone. Despite differences, both studies challenge the reputed superiority of a mild narcotic over ibuprofen for acute musculoskeletal pain in children.

Although we demonstrated analgesic equivalence, we observed disappointingly modest pain reduction associated with either agent. This finding may result either from anxiety or suboptimal analgesic potency. Similar first hour results were observed by Koller et al.,[20] when they compared the effectiveness of oxycodone and ibuprofen in a comparable patient population. Nonetheless, the limited use of rescue medications suggests that both drugs, when combined with nonpharmacologic measures, provided adequate analgesia.

Our study extends prior work on acetaminophen–codeine and ibuprofen to demonstrate comparable single dose efficacies of these analgesics in the treatment of pediatric ED patients with moderate pain resulting from acute musculoskeletal trauma. Other clinicians may be able to generalize our findings to ambulatory settings in which children require rapid relief of acute traumatic extremity pain. Since administration of codeine-containing analgesics may be difficult to implement prior to provider evaluation, a policy encouraging early administration of ibuprofen to selected children with acute isolated extremity injuries may well hasten analgesic administration.

LIMITATIONS

We recognize several limitations in the measurement and comparison of analgesic effects. Although a placebo effect may contribute to observed clinical outcomes, we did not believe it necessary or ethical to create a placebo arm when comparing two drugs with previously demonstrated efficacy [4–10]

Codeine's analgesic efficacy depends partly on metabolism to morphine by the cytochrome P450 enzyme CYP2D6. Polymorphism in this gene is responsible for significant variability in metabolism and has been reported to vary by race and ethnicity.[21] In a retrospective chart review, the ethnic backgrounds of our treatment groups appear similar; however, unmeasured pharmacogenetic variability may have accounted for a subtherapeutic effect in some patients.

Some clinicians may question the cutoff point for ibuprofen we chose for patients heavier than 40 kg. We selected this 400-mg maximum dose for ibuprofen based on our intention to minimize adverse effects and previously published analgesia trials.[5,22]

One of our entry criteria was a minimum triage pain score of 5. While attempting to choose patients with the greatest potential for demonstrable improvement, we may have selected a population with painful conditions inadequately treated by the oral route. Factors unrelated to study drugs may have contributed to pain scores, including patient anxiety, parental comforting measures, the use of ice, splinting, the passage of time, and the manipulation involved in radiographic and physical examinations.

The nonconsecutive enrollment may have permitted enrollment of patients whose injuries were differently amenable to oral analgesia than those of a general population. We believe that our randomization process adequately countered any potential nonpharmacologic influences and selection bias. Because we designed the study as an effectiveness trial, we permit the variability introduced by clinicians in routine practice.

Due to financial constraints we were unable to prepare identical study medications, thus preventing complete blinding of patients and parents. We addressed this limitation by the use of scripted directions to minimize unblinding during interaction between nurse and patient and by requiring that investigators and other physicians be absent during drug administration. To assess our blinding, we asked investigators to guess the study drug assignments and found the difference in correct guesses no greater than predicted by chance.

Our definition of equivalence and our sample size calculations assumed that a 2 cm intergroup difference in CAS score changes was a clinically significant threshold. This minimal clinically significant change, as originally derived, pertains to pain score changes within groups,[17] rather than between groups. Although our use of this minimal clinically significant change deviated from its initial definition, the original investigators have used their data on minimal clinically significant change to perform similar comparisons in pain reduction in later work.[23]

CONCLUSIONS

We found similar performance of acetaminophen–codeine and ibuprofen in analgesic effectiveness among ED patients aged 5–17 years with acute traumatic extremity pain. Both drugs provided measurable

analgesia. Patients tolerated them well, with few treatment failures and minimal adverse effects. A facility-specific clinical practice guideline promoting the early administration of ibuprofen may provide preferred triage analgesia for pediatric ED patients with acute traumatic musculoskeletal pain.

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