

A Randomized Clinical Trial of Ibuprofen Versus Acetaminophen With Codeine for Acute Pediatric Arm Fracture Pain

Amy L. Drendel, DO, MS
 Marc H. Gorelick, MD, MSCE
 Steven J. Weisman, MD
 Roger Lyon, MD
 David C. Brousseau, MD, MS
 Michael K. Kim, MD

From the Pediatric Emergency Medicine Division (Drendel, Gorelick, Brousseau, Kim), Anesthesiology and Pediatrics (Weisman), and Pediatric Division of the Section of Orthopedics (Lyon), Medical College of Wisconsin, Milwaukee, WI.
 Dr. Kim is currently affiliated with the University of Wisconsin School of Medicine and Public Health, Madison, WI.

Study objective: We compare the treatment of pain in children with arm fractures by ibuprofen 10 mg/kg versus acetaminophen with codeine 1 mg/kg/dose (codeine component).

Methods: This was a randomized, double-blind, clinical trial of children during the first 3 days after discharge from the emergency department (ED). The primary outcome was failure of the oral study medication, defined as use of the rescue medication. Pain medication use, pain scores, functional outcomes, adverse effects, and satisfaction were also assessed.

Results: Three hundred thirty-six children were randomized to treatment, 169 to ibuprofen and 167 to acetaminophen with codeine; 244 patients were analyzed. Both groups used a median of 4 doses (interquartile range 2, 6.5). The proportion of treatment failures for ibuprofen (20.3%) was lower than for acetaminophen with codeine (31.0%), though not statistically significant (difference=10.7%; 95% confidence interval -0.2 to 21.6). The proportion of children who had any function (play, sleep, eating, school) affected by pain when pain was analyzed by day after injury was significantly lower for the ibuprofen group. Significantly more children receiving acetaminophen with codeine reported adverse effects and did not want to use it for future fractures.

Conclusion: Ibuprofen was at least as effective as acetaminophen with codeine for outpatient analgesia for children with arm fractures. There was no significant difference in analgesic failure or pain scores, but children receiving ibuprofen had better functional outcomes. Children receiving ibuprofen had significantly fewer adverse effects, and both children and parents were more satisfied with ibuprofen. Ibuprofen is preferable to acetaminophen with codeine for outpatient treatment of children with uncomplicated arm fractures. [Ann Emerg Med. 2009;54:553-560.]

Provide [feedback](http://www.annemergmed.com) on this article at the journal's Web site, www.annemergmed.com.

0196-0644/\$-see front matter

Copyright © 2009 by the American College of Emergency Physicians.

doi:10.1016/j.annemergmed.2009.06.005

INTRODUCTION

Background

Children with fractures should have safe and effective outpatient analgesia initiated in the emergency department (ED). The pain experience during the first few days after an acute fracture can be substantial.¹⁻³ For these fractures, physicians have commonly recommended that children use acetaminophen with codeine or ibuprofen.¹⁻³ Neither medication's efficacy for children with fractures has been studied. Studies using a variety of pain models (perineal pain with childbirth, dental, tonsillectomy, and podiatric), have shown ibuprofen provides analgesic efficacy that is comparable or superior to that of opioids for the relief of pain.⁴⁻⁸ In an adult study of postoperative orthopedic pain, ibuprofen was found to

be more effective than acetaminophen with codeine and had a longer duration of action.⁹ A pediatric clinical trial evaluating the treatment of pain associated with musculoskeletal injuries found that ibuprofen provided better relief of pain at 1 hour and was comparable to that of codeine at 4 hours, suggesting that it should be the initial drug of choice for acute analgesia.¹⁰ In addition, it would be informative to also understand the implications of disruption of function, adverse effects including impaired bone healing, and satisfaction of parents and their children about the home treatment of pain after injury.

Importance

There is substantial practice variation in the ED-recommended treatment of pain associated with fractures.¹¹

Editor's Capsule Summary

What is already known on this topic

Ibuprofen and acetaminophen with codeine are commonly prescribed to children with fractures. Little evidence exists to support the use of one agent over the other.

What question this study addressed

This randomized controlled trial compared the efficacy and adverse effect profiles of acetaminophen with codeine and ibuprofen in the first 72 hours after emergency department discharge for children with simple arm fractures.

What this study adds to our knowledge

Ibuprofen has a better adverse effect profile and is as effective as or more effective than acetaminophen with codeine at relieving pain.

How this might change clinical practice

This study supports the use of ibuprofen as the first-line therapy for children with simple arm fractures; however, a significant proportion of patients will require additional analgesia. Providing a "backup" opioid prescription at discharge is a reasonable practice.

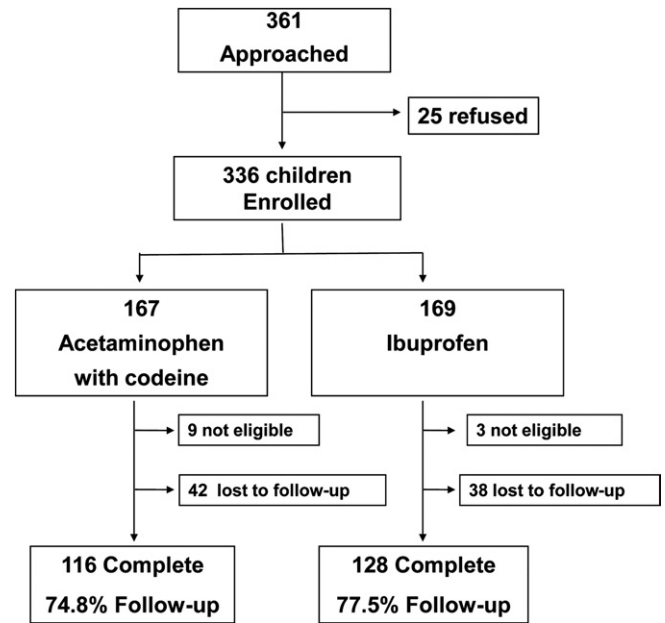


Figure 1. Study protocol flow.

Little evidence exists to inform an evidence-based approach to pain management in children with fractures.

Goal of This Investigation

The objective of this study was to determine the efficacy of the 2 most commonly prescribed medications for the outpatient treatment of children with arm fracture for the first 72 hours after the injury. This double-blind, randomized, clinical trial tested the hypothesis that ibuprofen would provide superior analgesia compared with acetaminophen with codeine for the outpatient treatment of pain for a simple arm fracture. The primary outcome was treatment failure of the assigned study medication and use of the rescue medication. Additionally, pain scores, pain-related functional limitations, adverse effects, and satisfaction were compared between the 2 study groups.

Study Design

This was a randomized, double-blind, multidose, clinical trial comparing the analgesic efficacy of ibuprofen suspension (10 mg/kg per dose) and acetaminophen with codeine suspension (1 mg/kg per dose codeine component) in the outpatient treatment of pain for a simple arm fracture. Data were prospectively collected and recorded by the child and family in a diary during the first 72 hours after discharge from

the ED. The study was reviewed and approved by the institutional review board. All patients or parents provided informed consent/assent before enrollment. This clinical trial was registered with the National Institutes of Health (ClinicalTrials.gov identifier NCT00520442).

Setting

This study was conducted in a children's hospital Level I trauma center ED with an average annual census of 60,000 patients, between August 2003 and September 2007.

Selection of Participants

Eligible patients were children aged 4 to 18 years, diagnosed with a fracture of the radius, ulna, or humerus, visualized on a standard 2-view radiograph. All fractures were confirmed by a pediatric radiologist. Radiographs showing an isolated posterior fat pad of the elbow were not included. Children were eligible if the fracture did not require reduction or manipulation in the ED and was not an open fracture.

Children were not eligible if they weighed more than 60 kg (because of the volume of dispensed pain medication), preferred tablets, were evaluated more than 12 hours after the initial injury, or were reported to have developmental delay. Children were not included if there was a history of gastrointestinal bleeding or ulceration, a bleeding disorder, a history of a low platelet count, a history of kidney disease, an uncontrolled chronic disease, or regular use of or allergy to acetaminophen, ibuprofen, or codeine. Children were also ineligible if they or their parents were unable to understand English or were inaccessible by telephone.

A convenience sample of eligible patients treated in the ED was approached for enrollment when one of the research

assistants was available between 10 AM and midnight, 7 days a week.

Figure 1 summarizes the study protocol. After eligibility criteria were confirmed, demographic data were collected. Parents and children were instructed verbally and in writing on the use of the pain scale by the research assistant. The aptitude of seriation, or ordering numbers in a series, was assessed and the pain scoring skill was practiced with the child. Families were oriented to the use of the daily diary for data collection.

All diagnosis and treatment decisions in the ED were made by board-certified pediatric emergency medicine specialists and fellows. Subjects received the usual care for fractures, including discretionary use of analgesics in the ED. All fractures were splinted by ED personnel (physicians, physician assistants, or nurse practitioners) with fiberglass or plaster wrapped with an elastic bandage. All children were discharged home with a sling and written instructions about splint care and use of rest, ice, compression, and elevation. Follow-up with an orthopedic specialist was recommended 5 to 7 days after injury. Parents were told to notify the investigators if pain treatment was inadequate.

Outcomes of interest were collected each day in the diary and returned in a provided stamped envelope. Two standard follow-up telephone calls were made during the first 72 hours after evaluation. If the completed pain diary was not received within 7 days, attempts were made by telephone to obtain study data. Participants with completed pain diaries received a \$10 Toys R Us gift certificate.

A random-number table was used to assign participants to either ibuprofen or acetaminophen with codeine by the pharmacist. Patients were block randomized in groups of 10. The treating physician, patient, parent, and all researchers were blinded to medication assignment until completion of the study. The parent and the primary investigator were unblinded only if pain relief was deemed inadequate by the parent after the rescue medication was used or if all the rescue medication provided (2 doses) was used and the child continued to need pain medication. Blinding of families was deemed successful because 3% of parents believed their child knew the assigned medication and only 36% of parents successfully guessed the assigned study medication at study completion.

Ibuprofen suspension (100 mg/5 mL) was dosed at 10 mg/kg, rounding to the nearest milliliter of medication. Acetaminophen with codeine (120 mg/5 mg per 5 mL) was dosed according to the codeine content of 1 mg/kg, rounding to the nearest milliliter of medication. Parents were instructed to use the study medications every 4 to 6 hours as needed for pain, with a maximum of 4 allowed doses in a 24-hour period. Parents were instructed to use the rescue medication (which was the alternative medication in the study) if the pain relief was inadequate 1 hour after dosing of the study medication. The pharmacy blinded the medications to color and volume but not taste. The medication was prepared and dispensed with a

standardized verbal script by the hospital pharmacist at discharge from the ED.

Methods of Measurement

The primary outcome of interest was use of the rescue medication because of failure of study medication. Parents were instructed to give the rescue medicine if there was inadequate pain relief 1 hour after dosing of the study medication. Parents were given written and verbal recommendations to use a pain medication if the child reported a pain score of 3 or greater, which is our usual ED practice. The pain score before study medication dose and 1 hour after study medication dose and the reason for using the rescue medication were noted in the pain diary.

The modified Bieri Faces Pain Scale was the validated pain assessment tool used in this study.¹² Parents asked their child for a pain score at awakening, at bedtime, and before and 1 hour after each dose of medication. Pain score and time of day were documented in the pain diary. Daily and total median score, maximum score, and minimum score were analyzed. Change in pain intensity (initial–final pain score) with use of the analgesic was analyzed.

Each dose of medication used and the time it was given were documented by caregivers.

Caregivers and their children used a diary to record whether play, school, sleep, and eating were affected by pain each day. Caregivers noted whether the function was increased, decreased, or unchanged. Function was considered to be affected by pain if function was decreased by pain.

Tolerability of the assigned study medication was documented daily. The *Physicians' Drug Reference* lists the following adverse effects for either ibuprofen or acetaminophen with codeine: nausea, vomiting, dizziness, itching, and abdominal pain. Families noted whether these effects were present and described any other effects each day. If more than 1 dose of rescue medication was used or it was not clear which medication was associated with the adverse effect, that adverse effect was made a missing variable.

To assess the number of children with repeated fracture at the same site or fracture nonunion, hospital and clinic medical records were reviewed to document fracture type and revisits to the orthopedic clinic or the ED. Follow-up telephone calls were also made to families in fall and winter of 2008 to query about these complications.

Parent satisfaction was recorded daily with a 0 to 5 Likert scale. On day 3, the modified Total Quality Pain Management instrument was used to measure satisfaction for the parent and the child.¹³ The Total Quality Pain Management instrument is a validated quality-assurance instrument to elicit the parent and child's perception of pain management.

Primary Data Analysis

This was a superiority study, designed to detect a 50% relative reduction in the primary outcome: failure of analgesic to relieve pain within 1 hour after dosing. Before the study, failure

rates were estimated by consensus of pediatric emergency physicians to be 30%, and a 50% reduction in this rate was thought to be clinically important. Reduction to 15% would require 134 patients in each group to obtain an $\alpha=0.05$ and a $\beta=0.20$. Subgroup analysis was planned to investigate differential treatment failure when comparing younger with older children (cut points of 6 years and 12 years), sex, race/ethnicity, higher pain scores (score of 3 or greater) and fracture type.

As a secondary analysis, we hypothesized a 1-face or 20% reduction in pain intensity score between the 2 groups because this has been shown to be the minimally clinically important difference.¹⁴ With a 6-item scale, assuming SD=2, we needed 94 patients in each group to obtain an $\alpha=0.05$ and a $\beta=0.20$. Per-protocol analysis was planned to include only patients who used medication during the study.

Descriptive statistics were used to analyze the demographic data. Analysis of outcomes was carried out in the intent-to-treat model. Treatment failures, reported as a percentage, are compared with χ^2 . Doses of medication and pain severity scores are compared with the Mann-Whitney U test. Functional outcomes are reported as time to return to unaffected function and are analyzed with survival analysis. Satisfaction responses are analyzed with χ^2 and Mann-Whitney U test, when appropriate.

RESULTS

Characteristics of Study Subjects

During the study enrollment period, nearly 1,600 children were treated in the ED for arm fractures (including those requiring reduction and those with a negative radiograph result but a clinical diagnosis of fracture). Three hundred sixty-one eligible children were approached, of which 25 refused to be a part of the study, leaving 336 children enrolled (Figure 1). Patient refusal included 7 concerns about codeine, 6 no answer, 5 not interested, 2 concerns about blinding, 3 physician request, 1 concern about ibuprofen, and 1 child sensitive to medication. Twelve patients found to be ineligible were eliminated from analysis (radiology did not confirm the arm fracture for 4, and there were protocol violations for age and weight for 8 patients). We had excellent follow-up, with approximately 75% of participants completing and mailing the diary. Three diaries were completed by telephone interview. Analysis was performed for 244 children. In comparing children who participated and those who were lost to follow-up, there was no difference in the age, sex, race/ethnicity, weight, fracture type, and initial pain scores.

Baseline characteristics were not different between the 2 groups (Table 1). The average age was 8 years and sex distribution was similar between the groups. The distribution of race/ethnicity in both groups parallels what is observed in the ED. No difference between groups was found in comparing type of arm fracture or pain scores in the ED. No differences were found between the 2 groups in the proportion of children receiving analgesic or the analgesic administered in the ED.

Table 1. Demographics

Characteristic	Acetaminophen With Codeine (n=116)	Ibuprofen (n=128)
Age, y, mean (range)	8.2 (4.2-14.9)	7.4 (4.0-17.9)
Weight, kg, mean (range)	29.4 (13.8-59.2)	27.9 (14.4-60.0)
Male, No. (%)	57 (49.1)	69 (53.9)
Race/ethnicity, No. (%)		
White	85 (73.3)	99 (77.3)
Black	11 (9.5)	18 (14.1)
Hispanic	9 (7.8)	7 (5.4)
Other	11 (9.5)	4 (3.1)
Fracture type, No. (%)		
Radius only	58 (50.0)	65 (50.8)
Ulna only	4 (3.5)	2 (1.6)
Radius and ulna	27 (23.3)	24 (18.8)
Humerus: supracondylar I	22 (19.0)	27 (21.1)
Humerus: supracondylar II	4 (3.5)	4 (3.1)
Humerus: midshaft	1 (0.9)	6 (4.7)
Pain score		
Initial median (range)	3 (0,5)	3 (0,5)
Discharge median (range)	1 (0,5)	1 (0,5)
Analgesic in ED, No. (%)		
None	36 (31.0)	45 (35.2)
Ibuprofen	30 (25.9)	36 (28.1)
Acetaminophen with codeine	30 (25.9)	27 (21.1)
Acetaminophen	6 (5.2)	6 (4.7)
Morphine	14 (12.1)	14 (10.9)

Nearly a third of children received no analgesia in the ED. A number of these patients received analgesia at home or refused analgesia in the ED. Additionally, other comfort measures were used, including ice and elevation. Only 2 children at discharge had pain scores greater than 3, making it less likely to affect home treatment outcomes.

There was no significant difference in the number of doses of medication the children in each of the study groups used during the first 3 days after discharge from the ED, which is shown graphically in Figure 2 (4 patients did not report number of doses of medication). Only 7% of children used no medication in this period. Both groups used a median of 4 doses (interquartile range [IQR] 2, 6.5). The median doses of ibuprofen and acetaminophen with codeine used were 4.5 (IQR 2, 7) and 4 (IQR 2, 6) doses, respectively.

The primary outcome was failure of the assigned study medication, leading to the use of the rescue medication. The proportion of treatment failures for children receiving ibuprofen (20.3%) was lower than that for acetaminophen with codeine (31.0%), though the difference was not statistically significant (difference=10.7%; 95% confidence interval [CI] -0.2% to 21.6%). In a per-protocol analysis excluding the 13 children (5 assigned to acetaminophen with codeine and 8 to ibuprofen) who did not use any pain medication, the difference remained nonsignificant (difference=10.7%; 95% CI -0.6% to 22.1%).

Planned subgroup analyses were performed to identify patients who might be at particular risk of not achieving

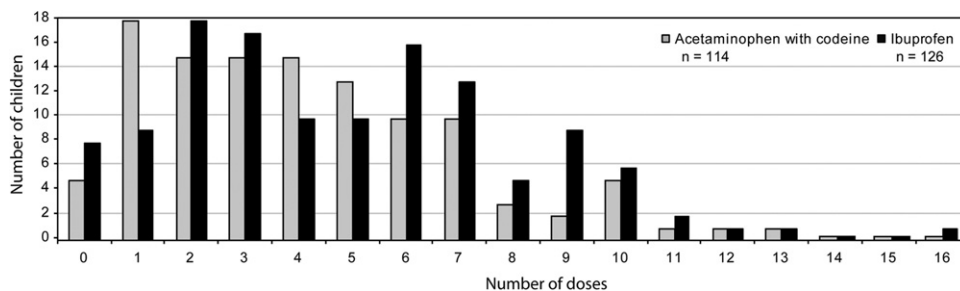


Figure 2. Total doses of analgesic used in the first 72 hours after discharge from the ED.

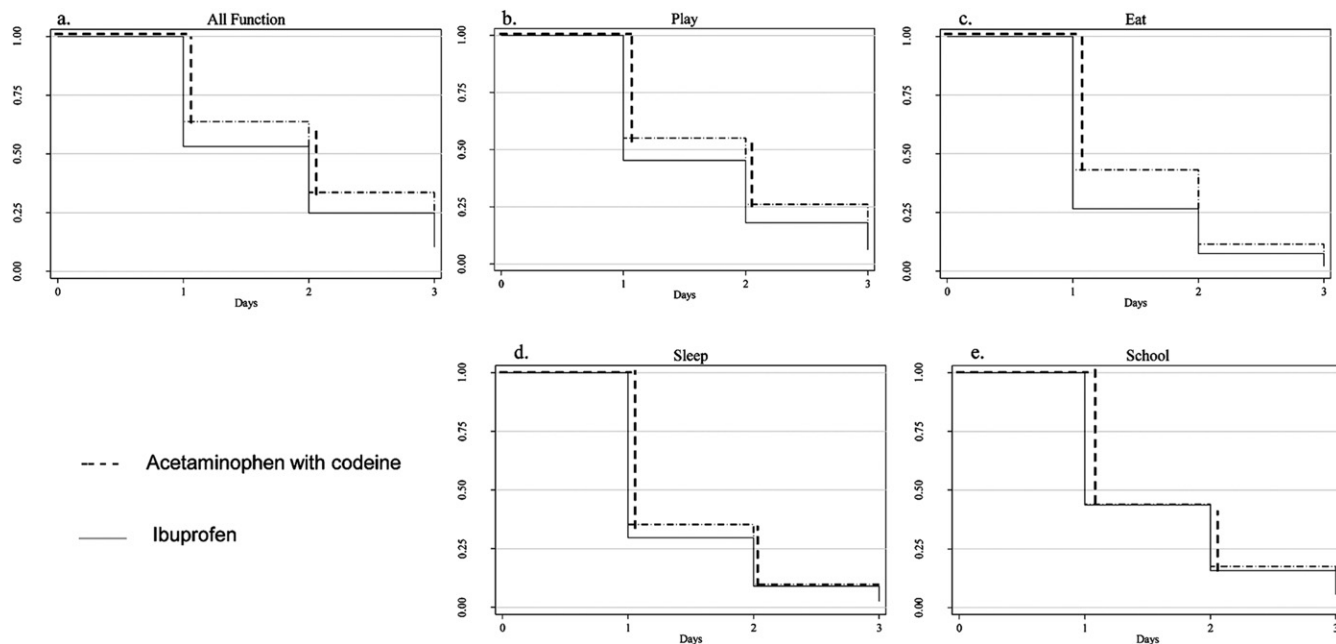


Figure 3. Proportion of children with function affected on each day.

analgesia with the assigned medication. No difference was found in the proportion of children who failed treatment when comparing younger with older children, sex, race/ethnicity, higher pain scores, or fracture type.

The total mean pain scores for day 0 (date of injury) to day 3 include the pain score at awakening, at bedtime, and before and 1 hour after each dose of medication. Children receiving ibuprofen scored 1.6 and those receiving acetaminophen with codeine scored 1.6, revealing no clinical or statistical difference in the overall pain scores between the 2 groups. In comparisons of overall daily maximum pain scores and overall minimum pain scores, no differences were found between the 2 medications. Also, comparing pain scores at each daily recorded time revealed no difference. The median reduction in pain score after use of ibuprofen was 2.0 compared with a median reduction of pain score of 1.5 after acetaminophen with codeine, which was not clinically or statistically significantly different between the 2 medications.

Each day, parents and their children reported the effect of pain on the following functional outcomes: play, school, sleep,

and eating. On the date of injury, 60% of children with fractures had at least 1 of these functions affected, and by day 3, 29.4% of children continued to have function affected by pain. The proportion of children who had any of these functions affected by pain analyzed by day after injury was significantly different in the 2 study groups (Figure 3). In evaluation of each functional outcome individually, there was a significantly lower proportion of children using ibuprofen who had play (Figure 3B) and eating (Figure 3C) affected by pain. There was little difference between groups for the effect of pain on school and sleep (Figure 3D, E). A similar pattern was seen in comparisons of the proportion of children in each group who had each function affected at any time during the 3-day follow-up.

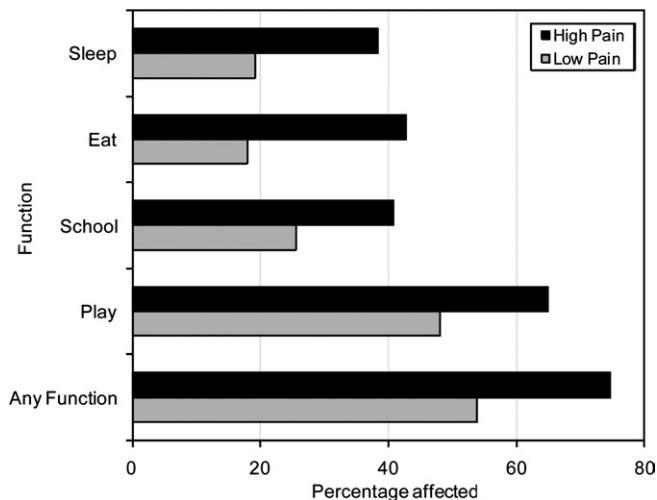
Table 2 and Figure 4 shows that children during the 3 days who report pain score of only 0, 1, or 2 (low pain) compared with those with pain score of 3 or more (high pain) have significantly more dysfunction overall and in each of the individual functions. This result suggests a correlation between improved function and lower pain scores and provides some

Table 2. More children with high pain scores had function affected.

Functional Outcome	Low Pain, %	High Pain, %	Difference, % (95% CI)
Any function (n=234)	53.8	74.7	20.8 (5.9-35.8)
Play (n=232)	48.1	65.0	16.9 (1.7-32.1)
School (n=218)	25.5	40.7	15.2 (1.1-29.3)
Eat (n=230)	18.0	42.8	24.8 (11.9-37.6)
Sleep (n=227)	19.1	38.3	19.1 (5.8-32.4)

Low pain: if maximum pain score during the study period was 0, 1, or 2.

High pain: if maximum pain score during the study period was 3, 4, or 5.

**Figure 4.** More children with high pain scores had function affected.

validation of the parent report of whether pain affected function.

Adverse effects are tabulated in Table 3. The percentage of children reporting an adverse effect during the first 3 days of treatment was significantly higher in the acetaminophen with codeine group; 50.9% of children receiving acetaminophen with codeine reported any adverse effect compared with 29.5% of those receiving ibuprofen. A statistically significant higher report of nausea and vomiting was also observed for children receiving acetaminophen with codeine. Overall, between the 2 treatment regimens, children receiving ibuprofen reported fewer adverse effects.

All of the patients participating in the clinical trial were followed for at least 1 and up to 4 years after enrollment to assess for refracture. Of the participants in the study, 92% followed up in the hospital's orthopedic clinic for the acute definitive treatment of their fracture. Telephone follow-up of at least 1 year was attained for 47.5% of the children. At telephone follow-up, information about other fractures was collected. Medical record review was also performed for all patients enrolled during the 4-year study period to identify children with new visits to the orthopedic clinic to identify refractures. Four

Table 3. Adverse events.

Adverse Effect	Acetaminophen With Codeine, Ibuprofen, %		Difference, % (95% CI)
	%	%	
Any effect (n=234)	50.9	29.5	21.4 (9.1 to 33.7)
Nausea (n=231)	18.0	5.0	13 (4.8 to 21.1)
Vomiting (n=230)	11.0	2.4	8 (2.0-15.0)
Drowsy (n=231)	30.6	20.8	9.8 (-1.4 to 21)
Dizzy (n=231)	5.4	2.5	2.9 (-2.1 to 8.0)
Constipation (n=233)	1.7	2.5	-0.7 (-4.3 to 3.0)
Other (n=232)	10.8	6.6	4.1 (-3.1 to 11.4)

(1.6%) children had another fracture at the same site within 1 year of the original fracture. Of those, 3 received acetaminophen with codeine and 1 received ibuprofen. No fracture nonunions were reported in this cohort.

Satisfaction was measured daily with a Likert scale. On day 1, 85.8% of parents of children receiving ibuprofen were very satisfied or satisfied compared with only 67.3% of parents of children receiving acetaminophen with codeine (difference 18.5%; 95% CI 7.3% to 29.6%). As a measure of satisfaction, at the end of the study, we asked the children whether they would want this same medication again if they experienced a broken arm. Of the children who said they would not use that medication again, 27.5% were in the acetaminophen with codeine group compared with only 10.0% in the ibuprofen group (difference=17.8%; 95% CI 7.3% to 28.3%). When asked why, the reason disproportionately associated with dissatisfaction in the children receiving acetaminophen with codeine was taste, with 63.8% of children receiving acetaminophen with codeine preferring a better taste compared with only 30.4% of children receiving ibuprofen.

LIMITATIONS

The strengths of the study lie in its randomized, controlled design; its simple, practical, safe method of delivery of analgesia; and its attempt to reflect the real world, as far as reasonably possible.

A convenience sample of patients was used for enrollment and depended on research assistant availability in the ED. Although we know the total number of fracture patients treated during the study period, no record was kept of potential patients who met eligibility criteria and were not enrolled when the research assistants were not present. Review of a sample of 10% of all fractures evaluated in the ED during the period of enrollment shows no difference in demographic information, fracture type, or initial pain scores compared with that of the enrolled patients.

The doses of the medication used in this study reflect prescribing practices in our department and standard recommended doses of these agents. These doses may not reflect those used in other health care settings. It is possible that higher doses produce greater analgesic effect, but other studies will be required to address this issue.

This study did not include placebo because we did not consider it ethical to deny patients some form of analgesia. We cannot be sure whether the reduction in pain score during the 3 days was a result of natural healing or partial placebo effect, rather than a true analgesic effect of the medication.

Parents administered the medication to their children at their own discretion, with both written and verbal standardized advice on use of the medication. There is significant variability in the parents' threshold to give a medication to their child, which might affect a number of outcomes. The randomized nature of the clinical trial should minimize this variability between treatment groups.

Only patients with arm fractures not requiring reduction were included in this study. It is unclear whether these findings can be applied to children with displaced fractures requiring reduction.

DISCUSSION

Once discharged home from the ED, children with fractures continue to have pain and functional limitations. To our knowledge, this is one of the few clinical trials involving children to evaluate outcomes associated with the treatment of pain in the outpatient setting. In this study, ibuprofen and acetaminophen with codeine have comparable rates of successful analgesia. To our knowledge, no other clinical trial has assessed a child's pain *after* discharge from the ED. A recently published study compared oxycodone, ibuprofen, and the combination of both medications 120 minutes after dosing in the ED and found no significant difference among the groups.¹⁵ Another study compared acetaminophen, codeine, and ibuprofen for the acute treatment of musculoskeletal pain 60 minutes after dosing and found that ibuprofen provided the desired analgesic effect, with the greatest improvement in pain score and also achievement of adequate analgesia.¹⁰ A recent postsurgical study followed adult patients after discharge and found, when ibuprofen and codeine were compared, no difference was found in pain scores.¹⁶ Therefore, either medication appears to be a reasonable option for the treatment of arm fracture pain after discharge from the ED. However, in this study, in each treatment group, as many as 30% of children failed treatment if prescribed a single analgesic; provision of a rescue medication is therefore important. Of the children who used the rescue medication, 92% had at least a 1-face reduction in pain after using the alternative medication.

Although analgesic failure rates were not significantly different, important differences were observed for the children in the 2 analgesic regimens with regard to function and adverse effects that might influence the choice of agent. This study shows that children have important functional limitations after "minor" injuries, which have not been previously reported in the literature. Ibuprofen consistently outperformed acetaminophen with codeine when the effect of pain on play was assessed. It is unclear whether the analgesic effect has a causal relationship with the reported functional outcomes. However, in this study, functional outcomes for children with

pain scores of 3 or more were significantly different, suggesting that normal function does correlate with lower pain scores.

The report of adverse effects in this study was high but comparable with that of reports in other multidose pain trials performed in the outpatient setting.¹⁶ Daily collection of this information may increase reporting, and it may be difficult for families to discern effects associated with the medications and those related to the injury. It is clear, however, that acetaminophen with codeine is poorly tolerated by children and has low child and parent satisfaction reports. Given the known problems with compliance with prescribed medication after discharge from the ED, these findings should influence the choices that physicians make in prescribing medication.¹⁷⁻¹⁹

One potential explanation for the better results with ibuprofen is interindividual genetic differences in drug metabolism that are known to affect analgesic effectiveness for codeine.²⁰⁻²³ It is unclear whether the differences would remain if we stratified for those individuals in the analysis who are poor metabolizers of codeine. Furthermore, there are differences in metabolism that are evident as a child develops that might also affect analgesic effect, though no age differences were found in comparing the primary outcomes that were assessed in this study.²⁴⁻²⁶

Some clinicians are uneasy prescribing ibuprofen for fractures because of the theoretical concern that inhibition of the inflammatory process may affect fracture healing. Currently, there is evidence from animal studies that shows that nonsteroidal anti-inflammatory drugs can adversely affect fracture healing, but there is no conclusive evidence in human studies.^{27,28} No studies have evaluated the effect of ibuprofen on fracture healing in children. This study did not find an association between refracture or nonunion and use of ibuprofen. To prospectively ascertain the affect of ibuprofen on second fractures if the proportion of children affected in our study is representative, a post hoc power analysis shows that more than 900 children in each study arm would be needed to show a significant increase in fractures in children receiving ibuprofen. A larger study is needed to evaluate the concerns for healing with respect to nonsteroidal anti-inflammatory drug use.

In conclusion, ibuprofen was at least as effective as acetaminophen with codeine in providing outpatient analgesia for children with arm fractures not requiring reduction. There was no significant difference in analgesic failure and pain scores, but children receiving ibuprofen had better functional outcomes; specifically, play. Children receiving ibuprofen had significantly fewer adverse effects, and both children and parents were more satisfied with ibuprofen. Ibuprofen is preferable to acetaminophen with codeine for outpatient treatment of children with uncomplicated arm fractures.

Supervising editor: Knox H. Todd, MD, MPH

Author contributions: ALD, MHG, SJW, RL, DCB, and MKK conceived the study and designed the trial. ALD and MKK obtained research funding and supervised the conduct of the

trial and data collection. ALD managed the data, including quality control. MHG provided statistical advice on study design and assisted ALD in analyzing the data; ALD drafted the article, and all authors contributed substantially to its revision. ALD takes responsibility for the paper as a whole.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement. From July 2003 to July 2005, the Children's Hospital Foundation, Milwaukee, WI, provided \$4,500 towards gift cards that were given to patients who completed the study.

Publication dates: Received for publication March 2, 2009. Revision received April 30, 2009. Accepted for publication May 15, 2009. Available online August 18, 2009.

Presented at the Pediatric Academic Society meeting, May 2008, Honolulu, HI; the Emergency Medicine Research Forum, May 2008, Milwaukee, WI; and the Society of Academic Emergency Medicine meeting, June 2008, Washington, DC.

Reprints not available from the authors.

Address for correspondence: Amy L. Drendel, DO, MS, Pediatric Emergency Medicine, Children's Hospital of Wisconsin, PO Box 1997, Suite C550, Milwaukee, WI 53201-1997; 414-266-6672, fax 414-266-2635; E-mail adrendel@mcw.edu.

REFERENCES

- Oakley EA, Ooi KS, Barnett PL. A randomized controlled trial of 2 methods of immobilizing torus fractures of the distal forearm. *Pediatr Emerg Care*. 2008;24:65-70.
- Drendel AL, Lyon R, Bergholte J, et al. Outpatient pediatric pain management practices for fractures. *Pediatr Emerg Care*. 2006;22:94-99.
- Plint AC, Perry JJ, Correll R, et al. A randomized, controlled trial of removable splinting versus casting for wrist buckle fractures in children. *Pediatrics*. 2006;117:691-697.
- Peter E, Janssen p, Grange C, et al. Ibuprofen versus acetaminophen with codeine for the relief of perineal pain after childbirth: a randomized controlled trial. *CMAJ*. 2001;165:1203-1209.
- Wittenberg M, Kinney K, Black J. Comparison of ibuprofen and acetaminophen-codeine in postoperative foot pain. *J Am Podiatry Assoc*. 1984;74:233-237.
- Forbes J, Kehm C, Grodin C, et al. Evaluation of ketoralac, ibuprofen, acetaminophen, and acetaminophen-codeine combination in postoperative oral surgery pain. *Pharmacotherapy*. 1990;10:94S-105S.
- Raeder J, Steine S, Vatsgar T. Oral ibuprofen versus paracetamol plus codeine for analgesia after ambulatory surgery. *Anesth Analg*. 2001;92:1470-1472.
- St. Charles C, Matt B, Hamilton M, et al. A comparison of ibuprofen versus acetaminophen with codeine in the young tonsillectomy patient. *Otolaryngol Head Neck Surg*. 1997;117:76-82.
- Heidrich G, Slavic-Svircev V, Kaiko R. Efficacy and quality of ibuprofen and acetaminophen plus codeine analgesia. *Pain*. 1985;22:385-397.
- Clark E, Plint AC, Correll R, et al. A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics*. 2007;119:460-467.
- Yen K, Kim M, Stremiski ES, et al. Effect of ethnicity and race on the use of pain medications in children with long bone fractures in the emergency department. *Ann Emerg Med*. 2003;42:41-47.
- Hicks CL, von Baeyer CL, Spafford PA, et al. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain*. 2001;93:173-183.
- Foster RL, Varni JW. Measuring the quality of children's postoperative pain management: initial validation of the child/parent Total Quality Pain Management (TQPM) instruments. *J Pain Symptom Manage*. 2002;23:201-210.
- Bulloch B, Tenenbein M. Assessment of clinically significant changes in acute pain in children. *Acad Emerg Med*. 2002;9:199-202.
- Koller DM, Myers AB, Lorenz D, et al. Effectiveness of oxycodone, ibuprofen, or the combination in the initial management of orthopedic injury-related pain in children. *Pediatr Emerg Care*. 2007;23:627-633.
- Mitchell A, van Zanten SV, Inglis K, et al. A randomized controlled trial comparing acetaminophen plus ibuprofen versus acetaminophen plus codeine plus caffeine after outpatient general surgery. *J Am Coll Surg*. 2008;206:472-479. Epub 2007 Nov 26.
- Winnick S, Lucas DO, Hartman AL, et al. How do you improve compliance? *Pediatrics*. 2005;115:e718-724.
- Matsui DM. Drug compliance in pediatrics. Clinical and research issues. *Pediatr Clin North Am*. 1997;44:1-14.
- Matsui D, Joubert GI, Dykxhoorn S, et al. Compliance with prescription filling in the pediatric emergency department. *Arch Pediatr Adolesc Med*. 2000;154:195-198.
- Drendel AL. Pharmacogenomics of analgesic agents. *Clin Pediatr Emerg Med*. 2007;8:262-267.
- Chen ZR, Somogyi AA, Reynolds G, et al. Disposition and metabolism of codeine after single and chronic doses in one poor and seven extensive metabolisers. *Br J Clin Pharmacol*. 1991;31:381-390.
- Persson K, Sjoström S, Sigurdardóttir I, et al. Patient-controlled analgesia (PCA) with codeine for postoperative pain relief in ten extensive metabolisers and one poor metaboliser of dextromethorphan. *Br J Clin Pharmacol*. 1995;39:182-186.
- Poulsen L, Riishede L, Brosen K, et al. Codeine in post-operative pain. Study of the influence of sparteine phenotype and serum concentrations of morphine and morphine-6-glucuronide. *Eur J Clin Pharmacol*. 1998;54:451-454.
- Treluyer JM, Jacqz-Aigrain E, Alvarez F, et al. Expression of CYP2D6 in developing human liver. *Eur J Biochem*. 1991;202:583-588.
- Blake MJ, Gaedigk A, Pearce RE, et al. Ontogeny of dextromethorphan O- and N-demethylation in the first year of life. *Clin Pharmacol Ther*. 2007;81:510-516.
- Williams DG, Patel A, Howard RF. Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth*. 2002;89:839-845.
- Wheeler P, Batt ME. Do non-steroidal anti-inflammatory drugs adversely affect stress fracture healing? a short review. *Br J Sports Med*. 2005;39:65-69.
- Clarke S, Lecky F. Do non-steroidal anti-inflammatory drugs cause a delay in fracture-healing? *Emerg Med J*. 2005;22:652-653.