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# A Randomized, Controlled Trial of Acetaminophen, Ibuprofen, and Codeine for Acute Pain Relief in Children With Musculoskeletal Trauma

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## ABSTRACT

**OBJECTIVE.** Our goal was to determine which of 3 analgesics, acetaminophen, ibuprofen, or codeine, given as a single dose, provides the most efficacious analgesia for children presenting to the emergency department with pain from acute musculoskeletal injuries.

**PATIENTS AND METHODS.** Children 6 to 17 years old with pain from a musculoskeletal injury (to extremities, neck, and back) that occurred in the preceding 48 hours before presentation in the emergency department were randomly assigned to receive orally 15 mg/kg acetaminophen, 10 mg/kg ibuprofen, or 1 mg/kg codeine. Children, parents, and the research assistants were blinded to group assignment. The primary outcome was change in pain from baseline to 60 minutes after treatment with study medication as measured by using a visual analog scale.

**RESULTS.** A total of 336 patients were randomly assigned, and 300 were included in the analysis of the primary outcome (100 in the acetaminophen group, 100 in the ibuprofen group, and 100 in the codeine group). Study groups were similar in age, gender, final diagnosis, previous analgesic given, and baseline pain score. Patients in the ibuprofen group had a significantly greater improvement in pain score (mean decrease: 24 mm) than those in the codeine (mean decrease: 11 mm) and acetaminophen (mean decrease: 12 mm) groups at 60 minutes. In addition, at 60 minutes more patients in the ibuprofen group achieved adequate analgesia (as defined by a visual analog scale <30 mm) than the other 2 groups. There was no significant difference between patients in the codeine and acetaminophen groups in the change in pain score at any time period or in the number of patients achieving adequate analgesia.

**CONCLUSIONS.** For the treatment of acute traumatic musculoskeletal injuries, ibuprofen provides the best analgesia among the 3 study medications.

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### Key Words

analgesia, pain response, injury, children

### Abbreviations

ED—emergency department

VAS—visual analog scale

RCT—randomized, controlled trial

NSAID—nonsteroidal antiinflammatory drug

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**P**ATIENTS COME TO the emergency department (ED) with a variety of painful conditions, including fractures, bruises, and sprains. Within our pediatric ED, ~10% of all ED visits are for such injuries. Although providing adequate analgesia should be an important part of the ED treatment plan, numerous studies have shown that analgesia is not adequately provided to both pediatric and adult ED patients.<sup>1-6</sup>

When children are treated for pain in the ED, oral medications may be preferred. They eliminate the distress to a child of an intravenous or intramuscular injection and have a lower risk of the serious adverse events (such as apnea and aspiration) that are associated with parenteral pain medications. Although there have been studies comparing the pain relief provided by different oral analgesics in children postoperatively,<sup>7-10</sup> there are no published randomized, controlled trials (RCTs) examining the use of common oral pain medications for children with acute musculoskeletal injury in the ED. Most published studies of oral analgesia for acute musculoskeletal pain in adult ED patients do not examine the oral analgesic agents commonly prescribed for children.<sup>11-14</sup> One recent large ED-based study found no difference in pain relief between adult patients treated with paracetamol, indomethacin, diclofenac, or paracetamol combined with either nonsteroidal medication.<sup>15</sup>

The objective of this study was to determine which of 3 oral medications, acetaminophen, ibuprofen or codeine, given as a single dose, provides the most efficacious analgesia for children presenting to the ED with acute musculoskeletal traumatic injuries.

## **METHODS**

### **Study Design**

In this RCT we compared the change in pain among children with acute musculoskeletal pain treated with acetaminophen, ibuprofen, and codeine.

### **Study Setting and Population**

This trial was performed between May 2002 and January 2003 at an academic, tertiary care children's hospital in Ottawa, Canada, with an annual ED census of 55 000/year (the Children's Hospital of Eastern Ontario). Children 6 to 17 years old were eligible if they presented to the ED with pain from a musculoskeletal injury (to extremities, neck, and back) occurring in the preceding 48 hours. Children were excluded if they had a contraindication to a study drug, required resuscitation, had an open fracture, had an intravenous line in place, had received 1 of the study drugs in the preceding 4 hours for acetaminophen and codeine or 6 hours for ibuprofen, or had a significant cognitive impairment. Written, informed consent was obtained. Our institutional research board approved this study.

### **Study Protocol**

A research assistant recruited participants in the ED for 8 hours daily during the study period. Once consent was obtained, baseline data and study measurements were recorded. Participants were then assigned randomly to 1 of 3 groups. Participants received either 15 mg/kg of acetaminophen (maximum dose: 650 mg), 10 mg/kg of ibuprofen (maximum dose: 600 mg) or 1 mg/kg of codeine (maximum dose: 60 mg) by mouth. These doses were chosen because they have been used in other analgesia and antipyretic trials,<sup>11,16</sup> the Compendium of Pharmaceuticals and Specialties, our national standard reference for medications lists these doses as standard, and our institution's research pharmacist confirmed these doses, including maximum doses, as standard and recommended doses. The randomization sequence was computer generated with a block size of 9. Sealed opaque envelopes were used to conceal the allocation sequence. The drugs were all purple in color, grape flavored, and given in amber syringes covered with opaque plastic bags. Because of the pharmacokinetics of the drugs, the volumes of the study drug per kilogram were similar but not identical. To maintain blinding, the triage nurse opened the randomization envelope and administered the appropriate study medication. The triage nurse was not otherwise involved in the study or in additional care of the patient. The child, parent, and research assistant were blinded to group assignment.

The use of a visual analog scale (VAS) for measuring pain was explained by the research assistant to the children. The children recorded their baseline pain score by using a VAS before randomization and the assigned study drug being administered ("time 0"). Additional pain measurements were determined every 30 minutes for 120 minutes by using the VAS, and the child was not able to view previous scores to prevent carry over bias. All children were asked at 60 minutes and every 30 minutes afterward whether they required any additional analgesia. Additional pain medication was withheld for 60 minutes after administration of the study drug. Participants discharged before 120 minutes were given materials to complete the remaining scores at the appropriate times and stamped self-addressed envelopes. Parents were contacted by telephone 2 days after their visit to determine any adverse events and encourage mailing of the data forms.

All interventions including physical examinations, additional medications, radiographs, splints, casts, and reductions that occurred during the patient ED visit were prospectively documented, as was discharge diagnosis. Adverse effects in the ED were screened by using an open-ended question, "Is there anything bothering you other than your pain?" At the 2-day follow-up, adverse effects were screened for by specific and open-ended questions. Just before ED discharge, the children, parents, and research assistants were asked which medica-

tion they thought had been given. The final diagnosis and patient disposition was determined by the attending emergency physician. Diagnoses were then broadly grouped into fractures and soft tissue injuries.

### Outcome Measurements

Baseline measurements included age, gender, pain score, and previous analgesic use. The primary outcome was change in patient's self-reported pain from baseline at 60 minutes after receipt of the study medication. Pain was measured by using a VAS (a 100-mm hatched line anchored at 1 end with a label stating "no pain" and at the other end a label stating "worst pain"). VASs have been used extensively in analgesic trials and are valid for children  $\geq 6$  years of age.<sup>17</sup> The clinically important change for a VAS is considered to range from 9 to 18 mm.<sup>18–22</sup> We chose 60 minutes after administration as the timing of the primary outcome because drugs would all have been absorbed and efficacious by that point. The child's report of pain rather than the parents' or the research assistant's was chosen because it has been shown that parents and health care workers are not accurate when assessing a child's pain.<sup>23,24</sup> Secondary outcomes included the change in VAS from baseline at 30, 90, and 120 minutes, requirement for additional analgesia, and the number of patients achieving a VAS  $< 30$  mm (defined as "adequate analgesia") at 60 and 120 minutes. This last outcome was chosen because a previous study suggested that a pain score  $< 30$  mm indicates adequate pain relief.<sup>25</sup>

### Sample Size

Previous studies have indicated that the minimal clinically significant difference in pain, as measured by a VAS, ranges from 9 to 18 mm with an SD ranging from 14 to 40 mm.<sup>18–22</sup> Given this range, we chose a 15 mm-difference (SD: 20 mm) in the change in VAS score between groups because of our minimal clinically significant difference to detect. Sample-size calculations were thus based on the following assumptions: (1) detection of a 15-mm difference between groups, (2) standard deviation of 20 mm, (3) 2-sided test, and (4) statistical power of 80% and false-positive (type I error) rate of 0.05.

Although these assumptions were appropriate, the formulae used to calculate the sample size was a posteriori found to be inadequate. First, a formula for a 2-arm trial was used and expanded to accommodate a 3-arm trial. Second, the sample size obtained by using the above assumptions required a total number of 56 participants, which was mistakenly interpreted as 56 participants per arm. Thus, we planned to enroll 168 patients in total and doubled that number to have sufficient power for the subgroup analyses.

### Data Analysis

Gender and type of injury of enrolled versus nonenrolled eligible children were compared by using  $\chi^2$  tests. Difference in age was assessed by using Student's *t* test. Comparison of continuous outcomes (such as change in VAS from baseline) between the 3 study groups was determined by using analysis of variance models, followed by Tukey posthoc tests of significance when a significant difference was observed. The number of patients achieving adequate analgesia was stratified for baseline VAS score (below or above 30 mm) and compared using study groups using a McNemar 3-way test. Other categorical outcomes (such as occurrence of adverse events or effects) were compared using  $\chi^2$  tests or Fisher's exact tests when necessary. Success in blinding was assessed by using a  $\chi^2$  test. All reported *P* values were 2-sided and deemed significant when they reached a 5% level. A priori-planned subgroups included those with baseline VAS measurements of  $> 30$  mm (because they were assumed to have more "significant pain"), patients with fractures, and patients with soft tissue injuries.

Data were first analyzed on a per protocol basis. Patients were included in per protocol analysis if they received a dose of the study drug, had baseline data, and had primary outcome data. An intention-to-treat analysis, which included all patients initially randomly selected, was performed on the primary outcome and change in pain score from baseline at 120 minutes. Data for participants on whom a complete set of information was not available were imputed by using the last value carried forward.

## RESULTS

### Patient Recruitment and Baseline Characteristics

A total of 801 children with pain secondary to acute musculoskeletal injury presented to the ED during the time research assistants were available. Seven hundred eighty children were eligible, and 336 were enrolled (Fig 1). Three hundred twenty-four families refused to consent, 48 children were not approached because the research assistant was enrolling another child, 38 children were missed, and 34 were not enrolled for other reasons. Enrolled children were discharged from the ED throughout the study period, and the number for whom outcome data were available is indicated in Fig 1. Three hundred patients had a primary outcome measurement obtained for the final analysis (Fig 1). Enrolled versus nonenrolled eligible patients were comparable in age and gender, although not randomly selected patients were slightly more likely to have soft tissue injuries than randomly selected patients (54% vs 47%). Baseline characteristics were similar in all study groups (Table 1). Twenty-three patients (22%) in the ibuprofen group, 51 (48%) in the acetaminophen group, and 23 (21%) of children in the codeine group received the maximal study drug dosages based on weight.

FIGURE 1  
Flow of participants through the study.<sup>a</sup> Included in the per protocol analysis.

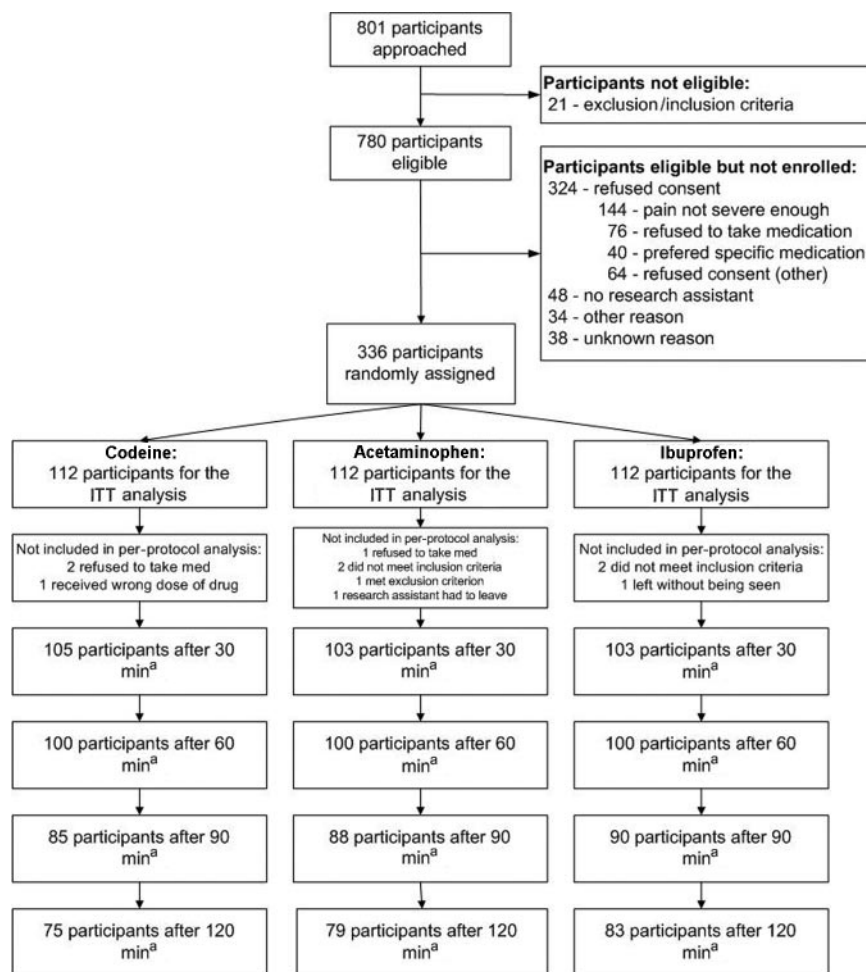


TABLE 1 Baseline Characteristics

Characteristic <sup>a</sup>	Codeine (n = 109)	Acetaminophen (n = 107)	Ibuprofen (n = 109)
Age, mean (SD), y	12.2 (3.1)	12.0 (2.9)	11.8 (2.8)
Male, n (%)	69 (63.3)	71 (66.4)	62 (56.9)
No. (mean [range]) of radiograph interventions <sup>b</sup>	70 (1 [0–3])	64 (1 [0–2])	61 (1 [0–2])
No. (mean [range]) of cast/splint interventions <sup>b</sup>	62 (1 [0–2])	60 (1 [0–2])	69 (1 [0–3])
No. (mean [range]) of fracture reductions <sup>b</sup>	11 (0 [0–1])	13 (0 [0–1])	9 (0 [0–2])
Soft tissue injury, n (%)	53 (48.6)	51 (47.7)	45 (41.3)
Fracture, n (%)	56 (51.4)	56 (52.3)	64 (58.7)
Patient's baseline pain score (VAS), mean (SD)	51 (27)	54 (25)	57 (25)
Patients with baseline pain score <30 mm, n (%)	26 (23.9)	17 (15.9)	11 (10.1)

<sup>a</sup>Includes all participants who were enrolled per protocol and for whom there were baseline data.

<sup>b</sup>Number of participants on whom an intervention was actually performed.

### Change in Pain and Adequacy of Analgesia

Overall, patients showed improvement in pain from baseline over the course of the study. At 30 minutes, however, there was no significant difference in change in pain score among the 3 groups. From 60 minutes and onward, patients in the ibuprofen group had significantly greater improvement in pain score than those in the codeine and acetaminophen groups. There was no significant difference in the change in pain score be-

tween codeine and acetaminophen groups at any time period (Table 2). In addition, at 60 minutes more patients in the ibuprofen achieved adequate analgesia (as defined by a VAS <30 mm) than the other 2 groups. There was no statistical difference between the codeine and acetaminophen groups (Table 2). Over the course of the trial, there was no significant difference in the number of patients requiring additional analgesic (22.2% of codeine, 15.6% of acetaminophen, and 14.3% of ibu-



**TABLE 2** Change in Pain Score (VAS) From Baseline and Number of Patients Who Achieved Adequate Analgesia

Outcome	Codeine			Acetaminophen			Ibuprofen			P
	N <sup>a</sup>	Mean or n (%)	95% CL	N	Mean or n (%)	95% CL	N	Mean or n (%)	95% CL	
Change in VAS from baseline										
30 min	105	-10	-14, -6	103	-7	-12, -3	103	-12	-16, -9	.230
60 min	100	-11	-16, -5	100	-12	-16, -8	100	-24	-29, -20	<.001
90 min	85	-13	-20, -6	88	-17	-23, -12	90	-29	-34, -23	.001
120 min	75	-17	-25, -9	79	-20	-25, -14	83	-31	-37, -26	.004
VAS <30 mm <sup>b</sup>										
60 min	100	40 (40)	31, 50	100	36 (36)	27, 46	100	52 (52)	42, 62	<.001
120 min	75	39 (52)	41, 63	79	27 (47)	36, 58	83	51 (61)	42, 62	.170

Posthoc test significance (Tukey): VAS at 60 minutes: acetaminophen versus codeine ( $P = .98$ ), acetaminophen versus ibuprofen ( $P = .001$ ), codeine versus ibuprofen ( $P < .001$ ); VAS at 90 minutes: acetaminophen versus codeine ( $P = .55$ ), acetaminophen versus ibuprofen ( $P = .016$ ), codeine versus ibuprofen ( $P = .001$ ); VAS at 120 minutes: acetaminophen versus codeine ( $P = .85$ ), acetaminophen versus ibuprofen ( $P = .026$ ), codeine versus ibuprofen ( $P = .006$ ); VAS <30 mm at 60 minutes: acetaminophen versus codeine ( $P = .85$ ), acetaminophen versus ibuprofen ( $P = .026$ ), codeine versus ibuprofen ( $P = .006$ ). CL indicates confidence limit. Adequate analgesia was defined as a VAS <30 mm.

<sup>a</sup> The number of patients at each time decreased because patients were discharged home from the ED and did not return pain scores for later time periods.

<sup>b</sup> Because we have no data on patients who did not complete the VAS at home after discharge, these data represent cross-sectional data on those patients on whom VAS scores were available.

profen patients;  $P = .32$ ). All of these medications were given after measurement of the primary outcome, thus the analysis was not adjusted for these additional treatments. The intention-to-treat analysis for change in pain score from baseline at 60 and 120 minutes and number of patients achieving adequate analgesic gave similar results to the per protocol analysis (data not shown).

#### Adverse Effects and Adverse Events

No significant adverse effects were reported while study participants were in the ED. One child in the codeine group was accidentally administered 5 mg/kg of codeine as a single dose. This child was withdrawn from the study, treated with oral charcoal, monitored in the ED, and had no adverse outcome. At 48-hour telephone follow-up, there was no significant difference in the number of patients reporting minor adverse effects (such as nausea, sleepiness, and constipation), with 16 (16.2%) of 99 patients in the codeine group, 8 (7.7%) of 104 patients in the acetaminophen group, and 11 (10.9%) of 101 patients in the ibuprofen group reporting  $\geq 1$  adverse effect ( $P = .16$ ).

#### Subgroup Comparisons

Details of subgroup comparisons are reported in Table 3. Among patients with fractures, ibuprofen resulted in significantly better improvement in pain than the other medications at both 60 and 120 minutes. There was no statistical difference between codeine and acetaminophen. Among patients with a soft tissue injury, there was no significant difference in change in pain score among any of the 3 medications at 60 or 120 minutes. When only patients with pain >30 mm were considered in the analysis, ibuprofen was significantly better than the other medications at 60 minutes. The other drugs were equivalent. At 120 minutes, both ibuprofen and codeine had similar effects and were significantly better than acetaminophen.

#### Blinding

Patients and parents seemed to be adequately blinded to the identity of the study medication, choosing the correct response no greater than chance would allow. The research assistants, however, correctly identified the study drug as acetaminophen in 52% of cases and ibu-

**TABLE 3** Mean Change in VAS From Baseline Among Patients With Fractures, Soft Tissue Injuries, and Baseline VAS >30 mm

Subgroup <sup>a</sup>	Codeine		Acetaminophen		Ibuprofen		P
	n	Mean (95% CLs)	n	Mean (95% CLs)	n	Mean (95% CLs)	
Patients with fractures							
60 min	50	-7 (-8, -6)	51	-14 (-19, -9)	58	-29 (-35, -22)	<.001
120 min	42	-13 (-24, -3)	42	-20 (-28, -13)	48	-41 (-49, -33)	<.001
Patients with soft tissue injuries							
60 min	50	-14 (-22, -7)	49	-9 (-16, -2)	42	-19 (-24, -13)	.150
120 min	33	-22 (-34, -10)	37	-19 (-28, -9)	35	-18 (-26, -11)	.860
Patients with VAS >30 mm at baseline							
60 min	74	-18 (-24, -12)	84	-13 (-18, -8)	89	-27 (-32, -22)	.001
120 min	54	-27 (-35, -19)	66	-23 (-29, -17)	77	-34 (-40, -28)	.060

CL indicates confidence limit.

<sup>a</sup> The number of patients at each time decreased as patients were discharged home from the ED and did not return pain scores for later time periods.

profen in 42% of cases, which is greater than would be expected by chance.

## DISCUSSION

ED visits for painful conditions such as fractures, bruises, and sprains are extremely common. Despite this, analgesia is often not adequately provided to patients and in particular, to pediatric patients.<sup>1-6</sup> Our study, the first to our knowledge to compare 3 commonly used oral medications in the treatment of pain from musculoskeletal injuries in children, has shown that ibuprofen provides better acute pain relief for these children than acetaminophen or codeine. Children receiving ibuprofen were also more likely to obtain adequate analgesia. We found no difference in the number of adverse effects among the 3 medications. Interestingly, in the subgroup analysis ibuprofen resulted in a greater improvement in pain scores among patients with fracture compared with codeine or acetaminophen, but no statistical difference between the 3 medications was seen among patients with soft tissue injuries. Given that the baseline pain score among patients with soft tissue injuries was the same as that among patients with fractures, this cannot be related to a lower "room for improvement" among patients with soft tissue injuries. The etiology of this difference is not clear but may reflect a difference in physiology of pain between the 2 groups. Perhaps the antiinflammatory effects of ibuprofen are responsible for the better pain relief.

It is also important to note that although ibuprofen was more efficacious in providing adequate analgesia, only 52% of children in this group could be defined as receiving "adequate analgesia" at 60 minutes. In addition, although codeine and acetaminophen did result in some improvement in pain, the actual level of improvement (a change of 10–11 mm on the VAS) is only just within the range previous studies have suggested to represent a significant improvement in pain.<sup>18-22</sup> Thus, although ibuprofen provided better pain relief than codeine and acetaminophen in our study, it seems that ibuprofen alone is not adequate for relieving pain in all children with musculoskeletal injuries.

Although no study has performed a direct comparison of these medications among children with musculoskeletal injuries, other studies have shown ibuprofen to be better than acetaminophen for other painful conditions.<sup>16,26</sup> For example, ibuprofen has been shown to be superior to acetaminophen for pain control in tonsillitis<sup>26</sup> and for pain related to migraines.<sup>16</sup> Two studies have compared pain relief with ibuprofen to an acetaminophen-codeine combined preparation<sup>7,8</sup> post tonsillectomy. Results are conflicting, with 1 study suggesting similar pain relief<sup>8</sup> and another suggesting that the combined acetaminophen-codeine preparation may be slightly better.<sup>7</sup> Neither of these studies used ibuprofen at 10 mg/kg per dose. In a study of patients with acute

low back pain, another nonsteroidal antiinflammatory drug (NSAID), oral ketorolac, was found to give no better pain relief than an acetaminophen-codeine preparation.<sup>11</sup> In contrast to our results, many of these studies suggested the narcotic analgesics were associated with greater adverse effects than NSAIDs.<sup>8,10,11</sup> Most of these studies, however, treated patients with multiple medication doses. A large ( $n = 300$ ) ED study of adult patients with pain from acute musculoskeletal injury found no difference in pain relief among patients treated with paracetamol, indomethacin, diclofenac, or a combination of paracetamol and NSAIDs. The dose of indomethacin and diclofenac, although dosages commonly used, were not the maximum doses allowed. In addition, unlike our study, only a small number of patients had fractures.<sup>15</sup> One small, nonrandomized 3-arm trial (76 patients) compared the effect of "standard care" (ice and elevation), "standard care" plus 10 mg/kg ibuprofen, and "standard care" plus distraction on pain relief in children with fractures. Interestingly, this trial found that ibuprofen added no pain relief benefit to standard care, although distraction was beneficial.<sup>27</sup>

There have been concerns expressed regarding the effect of NSAIDs on bone metabolism and fracture healing. Animal studies have suggested that multiple doses of indomethacin, aspirin, and ibuprofen<sup>27-30</sup> can all affect the healing of variety of fractures in rats. Retrospective studies in humans have given inconsistent results. No prospective RCTs have examined the effect of ibuprofen on fracture healing. One RCT examining the use of piroxicam found no significant delay in healing of Colle's fractures<sup>31</sup> whereas another RCT found that a 6-week course of indomethacin significantly increased the risk of nonunion of acetabular fractures.<sup>32</sup> There is no evidence that a single dose of ibuprofen is associated with delayed fracture healing in humans. In addition, because NSAIDs inhibit platelet aggregation and prolong bleeding time, their use could increase the risk of bleeding. However, a recent systematic review found no increase in bleeding when NSAIDs were used for pain control post tonsillectomy.<sup>33</sup> However, over-the-counter NSAIDs such as ibuprofen and naproxen have been associated with an increased risk of serious gastrointestinal toxicity (including gastrointestinal bleeds),<sup>34</sup> although this risk seems to be related to length of usage.<sup>35</sup>

Limitations of this study include the large number of eligible patients who were not recruited for the study. The study patients were, however, similar to the non-enrolled patients with regards to their baseline characteristics, including age and gender, although they more likely to have fractures as their final diagnosis. Interestingly, the most common reason for refusal of consent was that the parents felt the child's pain was not severe enough to justify pain medication. This suggests that education of parents regarding the benefits and efficacy of analgesics for children may be necessary. Although 36

randomly selected patients did not have primary outcome data, we had sufficient sample size to demonstrate a difference between study medications. Furthermore, although no difference was noted in adverse effects among the study groups, this study was not powered to detect rare, serious adverse events. In addition, the number of adverse effects reported may increase when a checklist is used for screening.<sup>36</sup> In the ED, we used an open-ended question, although our 2-day follow-up included a checklist and open-ended question. More children in the acetaminophen group received the maximum study drug dose than in the ibuprofen and codeine group. Although we chose our maximum drug doses on the basis of previous studies and standard doses, it is possible that the use of higher maximum doses of codeine or acetaminophen might have resulted in better pain relief with these medications.

This study may be further limited by the difficulty in blinding. Although the Consolidated Standards of Reporting Trials (CONSORT) statement<sup>37</sup> recommends reporting "how the success of blinding was evaluated," recently there has been debate regarding the correct way to assess the adequacy of blinding in RCTs.<sup>38-41</sup> In our study, we asked patients, parents, and research assistants to guess which study medication was received. We found that the research assistant was correctly identified the study drug as acetaminophen in 52% of cases and ibuprofen in 42% of cases, which suggested that blinding may not have been adequate. However, we feel this does not invalidate the results in that neither the participants nor the parents seemed able to determine which study drug the child received, and the primary outcome was the child's self-reported change in pain.

In conclusion, our study demonstrates that among children with pain from acute musculoskeletal injuries presenting to a pediatric ED, a single dose of ibuprofen provides greater pain relief than codeine or acetaminophen.

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## PFIZER WILL REDUCE SALES FORCE

"Pfizer, the world's largest drug company, said . . . that it would lay off almost 2400 sales representatives and managers, which is a fifth of its United States sales force. . . . The move may indicate the beginning of a wider retrenchment by Pfizer and the rest of the drug industry. Drug makers have sharply increased the size of their sales forces over the last decade as the research productivity of the companies has plunged and the pipeline of important new drugs has dwindled. The bloated sales forces, analysts say, have alienated doctors and contributed to high drug prices. Because Pfizer led the sales force expansion, other companies will probably follow its decision to cut back."

Berenson A. *New York Times*. November 29, 2006

Noted by JFL, MD

**Sicherer SH, Simons FER; Section on Allergy and Immunology. Self-injectable Epinephrine for First-Aid Management of Anaphylaxis. PEDIATRICS 2007;119:638–646.**

An error occurred in the American Academy of Pediatrics clinical report “Self-injectable Epinephrine for First-Aid Management of Anaphylaxis” published in the March 2007 issue of *Pediatrics* (doi:10.1542/peds.2006-3689). On page 640, under the heading Epinephrine Autoinjectors: 0.15 or 0.30 mg?, line 10, the authors wrote: “(0.012 mg/kg) rather than an underdose (0.06 mg/kg).” It should read: “(0.012 mg/kg) rather than an underdose (0.006 mg/kg).”

doi:10.1542/peds.2007-1193

**Clark E, Plint AC, Correll R, Gaboury I, Passi B. A Randomized, Controlled Trial of Acetaminophen, Ibuprofen, and Codeine for Acute Pain Relief in Children With Musculoskeletal Trauma. PEDIATRICS 2007;119:460–467.**

An error occurred in the article by Clark et al, titled “A Randomized, Controlled Trial of Acetaminophen, Ibuprofen, and Codeine for Acute Pain Relief in Children With Musculoskeletal Trauma,” published in the March 2007 issue of *Pediatrics* (doi:10.1542/peds.2006-1347). On page 462, Data Analysis section, lines 8–11, the authors wrote: “Categorical outcomes (such as adequate analgesia achieved) were compared using  $\chi^2$  tests or Fisher’s exact tests when necessary.” It should read: “The number of patients achieving adequate analgesia was stratified for baseline VAS score (below or above 30 mm) and compared using study groups using a McNemar 3-way test. Other categorical outcomes (such as occurrence of adverse events or effects) were compared using  $\chi^2$  tests or Fisher’s exact tests when necessary.”

doi:10.1542/peds.2007-1194

**Nord KM, Kandel J, Lefkowitz JH, et al. Multiple Cutaneous Infantile Hemangiomas Associated With Hepatic Angiosarcoma: Case Report and Review of the Literature. PEDIATRICS 2006;118:e907–e913.**

An error occurred in the article by Nord et al, titled “Multiple Cutaneous Infantile Hemangiomas Associated With Hepatic Angiosarcoma: Case Report and Review of the Literature,” published in the September 2006 issue of *Pediatrics Electronic Pages* (doi:10.1542/peds.2006-0183). In Table 1 on page e911, the authors wrote “Died” as the outcome of case 7. It should read “Alive.”

doi:10.1542/peds.2007-1196

## A Randomized, Controlled Trial of Acetaminophen, Ibuprofen, and Codeine for Acute Pain Relief in Children With Musculoskeletal Trauma

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