Acetaminophen or Nonsteroidal Anti-Inflammatory Drugs in Acute Musculoskeletal Trauma: A Multicenter, Double-Blind, Randomized, Clinical Trial

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Study objective: We determine whether pain treatment with acetaminophen was not inferior to nonsteroidal anti-inflammatory drugs or the combination of both in minor musculoskeletal trauma.

Methods: The Paracetamol or NSAIDs in Acute Musculoskeletal Trauma Study was a double-blind, randomized, clinical trial conducted in 2 general practices and 2 emergency departments in the Netherlands. A total of 547 adults, aged 18 years and older, with acute blunt minor musculoskeletal extremity trauma were randomly assigned in a 1:1:1 ratio to acetaminophen 4,000 mg/day, diclofenac 150 mg/day, or acetaminophen 4,000 mg/day+diclofenac 150 mg/day during 3 consecutive days. Patients, health care staff, and outcome assessors were blinded for treatment allocation. Follow-up for each patient was 30 days. Primary outcome measures were between-group differences in mean numeric rating scale (NRS) pain scores in rest and with movement at 90 minutes after initial drug administration compared with baseline pain scores with a predefined noninferiority margin of 0.75 NRS points. Secondary outcomes included NRS pain scores during 3 consecutive days and need for additional analgesia.

Results: One hundred eighty-two patients were treated with acetaminophen, 183 with diclofenac, and 182 with combination treatment. Intention-to-treat analysis revealed mean NRS reduction in rest −1.23 (95% confidence interval [CI] −1.50 to −0.95) and −1.72 (95% CI −2.01 to −1.44) with movement, both for acetaminophen at 90 minutes compared with baseline. Pairwise comparison in rest with diclofenac showed a difference of −0.027 (97.5% CI −0.45 to 0.39) and −0.052 (97.5% CI −0.46 to 0.36) for combination treatment. With movement, these numbers were −0.20 (97.5% CI −0.64 to 0.23) and −0.39 (97.5% CI −0.80 to 0.018), respectively. All differences were well below the predefined noninferiority margin.

Conclusion: Pain treatment with acetaminophen was not inferior to that with diclofenac or the combination of acetaminophen and diclofenac in acute minor musculoskeletal extremity trauma, both in rest and with movement. [Ann Emerg Med. 2018;71:357-368.]

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INTRODUCTION

Background and Importance

Even a short course of nonsteroidal anti-inflammatory drugs can cause serious adverse effects, especially cardiovascular, renal and gastrointestinal complications.[1] Moreover, many adverse reactions are due to drug-drug interactions with other medications.[2] Replacing nonsteroidal anti-inflammatory drugs with a less toxic but equally effective analgesic in daily clinical practice would be of benefit to health care.[1,3,4]

Acute minor musculoskeletal injuries are a leading cause of health care visits for which nonsteroidal anti-inflammatory drugs are frequently used, both as prescription drugs and over the counter.[5,6] In the United States alone, musculoskeletal injuries account for nearly 66 million physician visits annually, 77% of all injury-related visits.[7] Approximately 17 million emergency department (ED) visits involve strains, sprains, and contusions of extremities.[8] Strains and sprains are muscle and ligamentous injuries without concomitant fracture or

Editor's Capsule Summary

What is already known on this topic

The relative analgesic potency of acetaminophen versus nonsteroidal anti-inflammatory drugs is controversial.

What question this study addressed

When treating acute nonfracture musculoskeletal pain, is acetaminophen alone (4,000 mg/day) as effective 90 minutes after administration as either diclofenac alone (150 mg/day) or their combination?

What this study adds to our knowledge

In this randomized, double-blind trial of 547 adults, the analgesic effect of acetaminophen alone was not inferior to either diclofenac alone or their combination at 90 minutes and at all other measured times.

How this is relevant to clinical practice

With these standard doses, acetaminophen is no less effective than diclofenac or both drugs together for acute nonfracture musculoskeletal pain.

dislocation. A contusion is defined as a traumatic hemorrhage in skin or underlying tissues. Pain treatment is an important part of management and consists of rest, ice, compression, and elevation in combination with treatment with analgesic medication, mainly acetaminophen or nonsteroidal anti-inflammatory drugs.[5,6,9,10] Because of methodologically heterogeneous studies, it is unclear whether nonsteroidal anti-inflammatory drugs have any additional value over acetaminophen in treating pain in these common injuries.[11-14]

Goals of This Investigation

The purpose of this study was to assess whether acetaminophen is as effective as diclofenac or the combination of acetaminophen and diclofenac in treating pain in adult patients with acute minor musculoskeletal trauma of an extremity. We hypothesized that the reduction in acute pain scores with acetaminophen was noninferior to treatment with diclofenac or the combination of both medications in patients presenting to the ED, urgent care center, or general practice with acute traumatic musculoskeletal pain because this outcome would negate the rationale for using nonsteroidal anti-inflammatory drugs in these common injuries.

MATERIALS AND METHODS

Study Design

The Paracetamol or NSAIDs in Acute Musculoskeletal Trauma study was a multicenter, double-blind, randomized, noninferiority trial. The study was conducted in accordance with the principles of the Declaration of Helsinki, the Dutch Medical Research Involving Human Subjects Act, and good clinical practice guidelines. Trial approval was obtained from the institutional review board relevant to each research site and the Dutch Central Committee on Research Involving Human Subjects. The study protocol was published open access previously.[15]

Setting and Selection of Participants

The study was conducted in the EDs of 2 university hospitals, an urgent care center, and 2 general practices. In the Netherlands, urgent care centers are staffed by general physicians and are open outside office hours. All patients aged 18 years and older with nonpenetrating minor musculoskeletal trauma of an extremity occurring within 48 hours before presentation, regardless of pain severity, were potentially eligible for study participation. Exclusion criteria were explicitly described beforehand and published previously.[15] These were previous treatment with analgesia for the same injury; self-inflicted injury; presence of wound, joint dislocation, or more than one injury; presence of a fracture; daily use of acetaminophen or nonsteroidal anti-inflammatory drugs or other analgesia within 2 weeks before presentation; chronic pain; previous adverse reaction or known allergy to acetaminophen, nonsteroidal anti-inflammatory drugs, or omeprazole; a known pregnancy; previous gastrointestinal hemorrhage or perforation after nonsteroidal anti-inflammatory drug use; active or recurrent peptic ulceration or peptic bleeding (2 or more evident episodes); previous exacerbation of asthma after use of nonsteroidal anti-inflammatory drugs or acetylsalicylic acid; severe cardiac failure; liver cirrhosis; severe renal insufficiency (a known glomerular filtration rate $\leq$30 mL/min); or physical, visual, or cognitive impairment or non-Dutch speaking (unable to use numeric rating scale [NRS] pain scores or pain diary). A record was kept of all excluded patients. All injuries were treated on site and patients were not admitted for surgery subsequently. After providing written informed consent, patients were allocated to treatment. The end of the trial was defined as completed follow-up of the last included patient.

Trained research assistants and treating clinical staff approached patients for study participation. After confirmation of study eligibility, patients were randomized with an online randomization module (ALEA Software for Randomization in Clinical Trials; version 2.2; NKI/AVL,

Amsterdam, the Netherlands). The randomization list was created in advance by the statistical department and the hospital pharmacy of the Academic Medical Center. Patients were randomly allocated to a treatment arm in a 1:1:1 ratio, with a fixed block size of 9, and were stratified in subgroups younger than 60 years and 60 years and older. Packages of study medication had identical appearances and were numbered according to the randomization sequence. All patients, care providers, research assistants, and outcome assessors were blinded for assigned study medication during the complete study course.

Interventions

The study had a double-dummy design, and acetaminophen and diclofenac tablets, as well as all placebo tablets, were exclusively produced for this study (Tiofarma, Oud-Beijerland, the Netherlands) because overencapsulation was not possible. Acetaminophen and acetaminophen-placebo, as well as diclofenac and diclofenac-placebo, had identical appearances to maintain complete blinding. Each medication package contained one jar with 24 acetaminophen 500-mg or acetaminophen-placebo tablets and one jar with 9 diclofenac 50-mg or diclofenac-placebo tablets. The 3 possible treatment strategies were as follows: acetaminophen 1,000 mg 4 times daily+diclofenac-placebo 3 times daily, or acetaminophen 1,000 mg 4 times daily+diclofenac 50 mg 3 times daily, or acetaminophen-placebo 4 times daily+diclofenac 50 mg 3 times daily. All study drugs were received orally. The combination of both placebos was considered unethical. In the hospital pharmacy, the study drugs were packed in identical paper bags with the unique randomization number, and the medications were distributed to the participating sites. The first dose was administered on site directly after recruitment. At discharge, patients received a standard total dosage for 3 consecutive days after discharge, as well as explicit verbal and written instructions on further use during these 3 days. All patients received omeprazole 20 mg once daily during 3 days. Patients did not receive specific recommendations about timing of medication use and food intake.

The trial consisted of 3 study phases. Phase 1 was the acute phase at presentation until 90 minutes after study medication administration. All data were collected prospectively at corresponding points on site or, in case the patient had already been discharged, by telephone by health care staff or by research assistants. Phase 2 included 3 consecutive days after discharge. Data in regard to pain during these 3 days were collected with pain diaries and patients were contacted by telephone as well. At the end of the third study phase, which lasted from 3 to 30 days after recruitment, members of the research team contacted the patients by telephone and study participation ended.

Outcome Measures

Primary outcomes were between-group difference in NRS pain scores between baseline and 90 minutes after initial study medication administration, as measured in rest and with extremity movement. The NRS pain score is an 11-item, validated tool to assess pain severity, in which zero is no pain and 10 is the worst pain imaginable.[16]

Other secondary outcomes were differences in pain scores at 30 and 60 minutes compared with baseline and pain during 3 consecutive days. During the first study phase, pain with movement was determined as pain with active or passive movement of the extremity involved or weight bearing in case of lower extremity injury. At home, pain with movement was defined as pain during daily activities. Proportional changes in pain of greater than or equal to 33% and number needed to treat to achieve this were calculated. Depending on normality of data, mean or median pain scores were obtained and compared between treatment groups. Furthermore, patient satisfaction with pain relief and qualitative pain experience, measured with 5-point Likert scales during the first 2 study phases, occurrence of adverse effects, and need for additional analgesia were recorded. Assessment of adverse events was standardized with predefined fields in the case report forms and the pain diaries and were specifically looked for and asked about. Differences in pain scores and occurrence of adverse events were analyzed in patient subgroups aged 60 years and older.

Primary Data Analysis

The primary outcome, between-group difference in mean NRS pain scores, was expected to be distributed normally. This was tested by inspecting the frequency distributions (histograms). Homogeneity of variances was tested with Levene's test for equality of variances.

In a previous unpublished pilot study, we found an SD of decrease in NRS pain score of 2.06 NRS points. In our noninferiority analysis, the equivalence limit was chosen at 0.75, well below a previously reported minimally clinically significant difference in NRS pain score of 1.3.[16,17] Because noninferiority was to be assessed 2 times (between acetaminophen and diclofenac and between acetaminophen and combination treatment), we used a Bonferroni adjustment of the significance level to protect against a type I error. The null hypothesis was that acetaminophen was inferior to each one of the other groups. A one-sided t test with a significance level of .0125 with the 0.75 equivalence

limit and an expected difference of zero between 2 groups would have 85% power to reject this null hypothesis, in case the sample size in each group was at least 164. With 3 groups and taking into account a loss to follow-up of 10%, the total sample size was 547 patients (Appendix E1, available online at http://www.annemergmed.com).

Baseline characteristics were reported as absolute values with proportions and, depending on normality, numeric data as mean values with 95% confidence interval (CI) or medians with quartiles. An intention-to-treat analysis was used in all outcome variables. The primary outcome, between-group mean NRS difference between 90 minutes and baseline, was presented with a 97.5% CI (Bonferroni adjustment). A one-sided noninferiority test was performed, for which $P<.025$ was considered statistically significant. Per-protocol sensitivity analysis was additionally performed to test for robustness of the primary outcome. Unpaired numeric data conforming to a normal distribution were analyzed with one-way ANOVA and Mann-Whitney *U* with 2 pairwise comparisons in case of numeric data without a normal distribution. In case of repeated measurements (pain scores during 3 consecutive days after discharge), generalized estimating equations (generalized estimating equations models) were used. Unpaired categorical data were analyzed with a χ^2 test or Fisher exact test, when appropriate. A subgroup analysis was planned and performed with patients aged 60 years and older. Hypotheses of all outcomes were tested with a noninferiority analysis. Data were analyzed with SPSS (version 23.0; SPSS, Inc., Chicago, IL) and R (version 3.3.1).

RESULTS

Characteristics of Study Subjects

Enrollment started July 13, 2013, and follow-up of the last patient was completed June 6, 2016. A total of 8,243 consecutive patients were assessed for eligibility, and after exclusion of 7,696 patients, a total of 547 patients were assigned to treatment and included in the intention-to-treat analysis (Figure 1). In the per-protocol analysis, 508 patients were included. Table 1 shows patient characteristics, trauma mechanism, and injury localization, as well as baseline pain scores. There were no significant differences

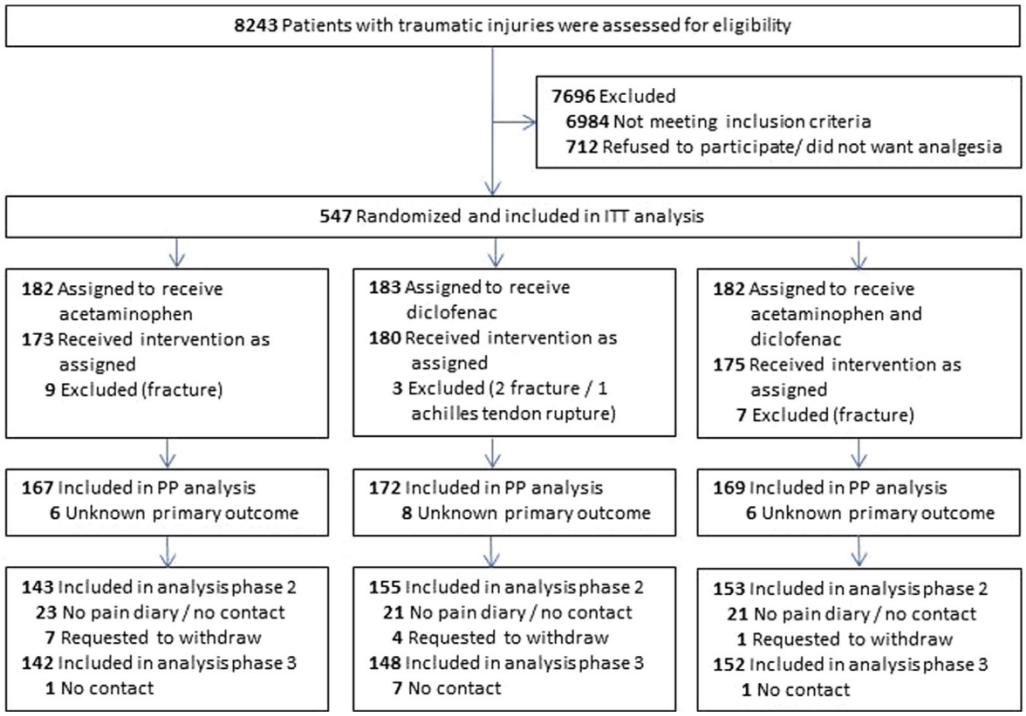

Figure 1. CONSORT patient flow chart. Pain scores at 90 minutes could not be retrieved for 20 patients (3.8%) because they never answered their telephone during follow-up, and 508 patients entered the per-protocol analysis of the primary outcome. Of these patients, 167 (32.9%) were assigned to treatment with acetaminophen, 172 (33.9%) to diclofenac, and 169 (33.3%) to the combination of acetaminophen and diclofenac. In the second phase of the study, 85% of patients were analyzed. Seven patients in the acetaminophen group, 4 in the diclofenac group, and 1 in the combination group withdrew from study participation. No pain diaries were returned and no contact by telephone could be made with 23 patients in the acetaminophen group, 21 in the diclofenac group, and 21 in the combination group. Data from the third study phase was acquired for 83.7% of all patients. *ITT*, Intention-to-treat; *PP*, per-protocol.

Table 1. Demographic and clinical characteristics.

Parameter	Acetaminophen (N=182)	Diclofenac (N=183)	Combination (N=182)
Male sex, No. (%)	109 (59.9)	95 (51.9)	99 (54.4)
Median age (IQR), y	30 (22.0–44.0)	29 (23.0–46.0)	30.5 (22.0–46.0)
≥60 y, No. (%)	14 (7.7)	14 (7.7)	14 (7.7)
Injury, No. (%)			
Contusion	105 (57.7)	116 (63.4)	101 (55.5)
Strain/sprain	68 (37.4)	64 (35.0)	74 (40.7)
Other*	9 (4.9)	3 (1.6)	7 (3.8)
Localization, No. (%)†			
Upper extremity	66 (36.3)	70 (38.3)	54 (34.7)
Lower extremity	116 (63.7)	113 (61.7)	128 (70.3)
Iced before presentation, No. (%)	49 (29.2)	46 (26.7)	47 (27.2)
Mean NRS pain score (95% CI)			
Rest	4.73 (4.37–5.10)	5.16 (4.84–5.49)	5.13 (4.74–5.51)
Movement	7.61 (7.36–7.86)	7.85 (7.62–8.07)	7.88 (7.65–8.12)

IQR, Interquartile range.
*A total of 18 patients had a fracture, initially not recognized at randomization and treatment allocation. One patient had an Achilles tendon rupture and was subsequently admitted for surgery.
†Injury localizations are specified in Table E1, available online at http://www.annemergmed.com.

between intervention groups. The median age was 30 years, and 7.1% of all patients were aged 60 years or older.

Main Results

In all 3 intervention groups, pain scores decreased after 90 minutes compared with baseline. In rest these numbers were acetaminophen –1.23 (95% CI –1.50 to –0.95), diclofenac –1.20 (95% CI –1.44 to –0.96), and –1.18 (95% CI –1.41 to –0.94) in the combination group (Tables E2 and E3, available online at http://www.annemergmed.com). With movement, these numbers were slightly higher: acetaminophen –1.72 (95% CI –2.01 to –1.44), diclofenac –1.52 (95% CI –1.77 to –1.26), and combination –1.33 (95% CI –1.55 to –1.12) (Tables E2 and E3, available online at http://www.annemergmed.com). No significant differences in NRS decreases were detected. The primary study outcome was the between-group difference of these NRS decreases in a pairwise comparison with acetaminophen. Analysis revealed a significant noninferiority difference of –0.027 NRS points (97.5% CI –0.45 to 0.39; noninferiority $P<.001$) between acetaminophen and diclofenac in rest and –0.20 NRS points (97.5% CI –0.64 to 0.23; noninferiority $P<.001$) with movement (Figure 2*A*). Between acetaminophen and combination, these differences were –0.052 (97.5% CI –0.46 to 0.36; noninferiority $P<.001$) in rest and –0.39 (97.5% CI –0.80 to 0.018; noninferiority $P<.001$) NRS points with movement (Figure 2*B*). As shown in the figures, all CI upper limits were less than the predefined noninferiority margin of 0.75, and we considered acetaminophen to be noninferior to both other treatment regimens in rest and movement. These results were supported by the per-protocol analysis (Figure 2 and Tables E4 and E5, available online at http://www.annemergmed.com).

The illustrated course of mean pain scores during the complete first study phase is shown in Figure 3. Comparisons at 30 and 60 minutes did not reveal significant between-group differences.

During phase 2, mean NRS pain scores decreased in all groups both in rest and with movement (Figure 4). Differences between pain scores measured at day 3 and day 1 were equal among the 3 interventions (Tables E7 and E8, available online at http://www.annemergmed.com). Using generalized estimating equations models and indexing acetaminophen at zero, NRS difference for diclofenac was –0.21 (95% CI –0.36 to –0.057) in rest and –0.67 (95% CI –0.87 to –0.46) with movement compared with acetaminophen. The comparison of combination treatment to acetaminophen yielded a relative mean difference of –0.12 (95% CI –0.29 to 0.055) in rest and –0.056 (95% CI –0.15 to 0.036) with movement. As in all comparisons, the upper CI limits were less than 0.75 and acetaminophen was considered noninferior.

During this second study phase, a total of 34 patients required additional analgesia, equally divided over the groups (Table E18, available online at http://www.annemergmed.com). There was no significant difference in patient satisfaction in regard to pain treatment during both the first and second study phase (Table 2). On a 5-point Likert scale, more than two third of patients rated their pain as decreased during both phases, irrespective of allocated treatment. During the third study phase, after finishing the course of study medications, a total of 110 patients required other analgesics (Table 2 and

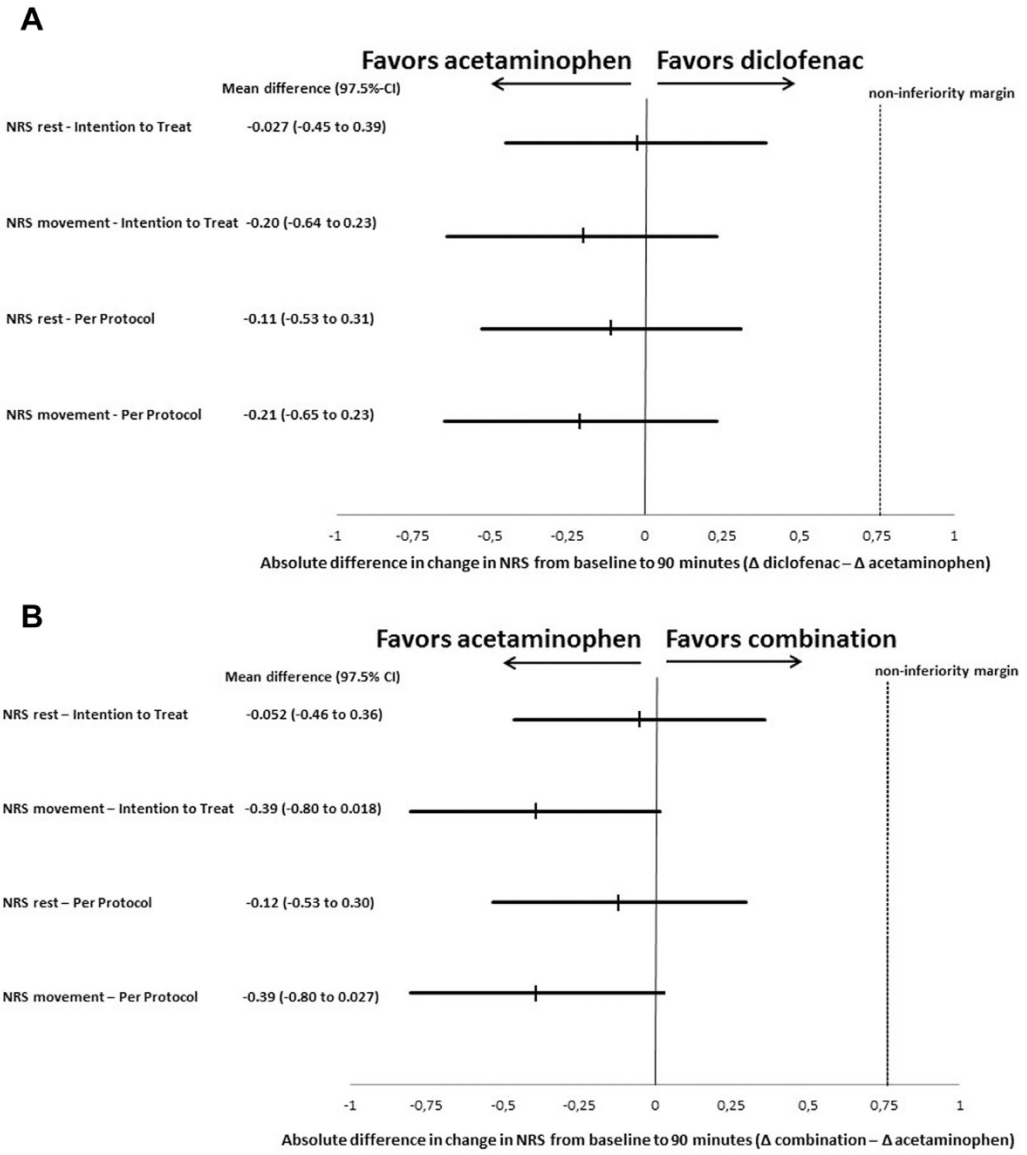

Figure 2. Comparison of acetaminophen and diclofenac in rest and with movement in study phase 1. *A*, Mean differences between NRS pain scores at 90 minutes after study drug administration compared those at baseline for the comparison of acetaminophen and diclofenac. These numbers are shown with the 97.5% CIs for measurements in rest and with movement for the intention-to-treat and the per-protocol analyses. The null hypothesis for inferiority was rejected for all 4 comparisons. *B*, Comparison of acetaminophen and combination treatment in rest and with movement in study phase 1. Mean differences between NRS pain scores at 90 minutes after study drug administration compared with those at baseline for the comparison of acetaminophen and combination treatment. These numbers are shown with the 97.5% CIs for measurements in rest and with movement for the intention-to-treat and the per-protocol analyses. The null hypothesis for inferiority was rejected for all 4 comparisons.

Table E18 [available online at http://www.annemergmed.com]). In the acetaminophen group, 33 patients used analgesics for a mean of 4.3 days (95% CI 2.0 to 6.7); in the diclofenac group, 35 patients used analgesics for 5.5 days (95% CI 3.2 to 7.8) and 42 patients in the combination group used analgesics for a mean of 3.5 days (95% CI 1.7 to 5.2). There were no differences in duration of these additional analgesic uses in the 3 treatment groups.

Subgroup analysis in patients aged 60 years and older did not reveal any differences between the 3 treatment groups (Tables E15 and E16, available online at http://www.annemergmed.com).

Occurrence of adverse events was equally divided over the 3 treatment strategies. In phase 1, no patients required medical intervention. Minor neurologic complaints, such as headache, dizziness, and tiredness, occurred more frequently in the acetaminophen

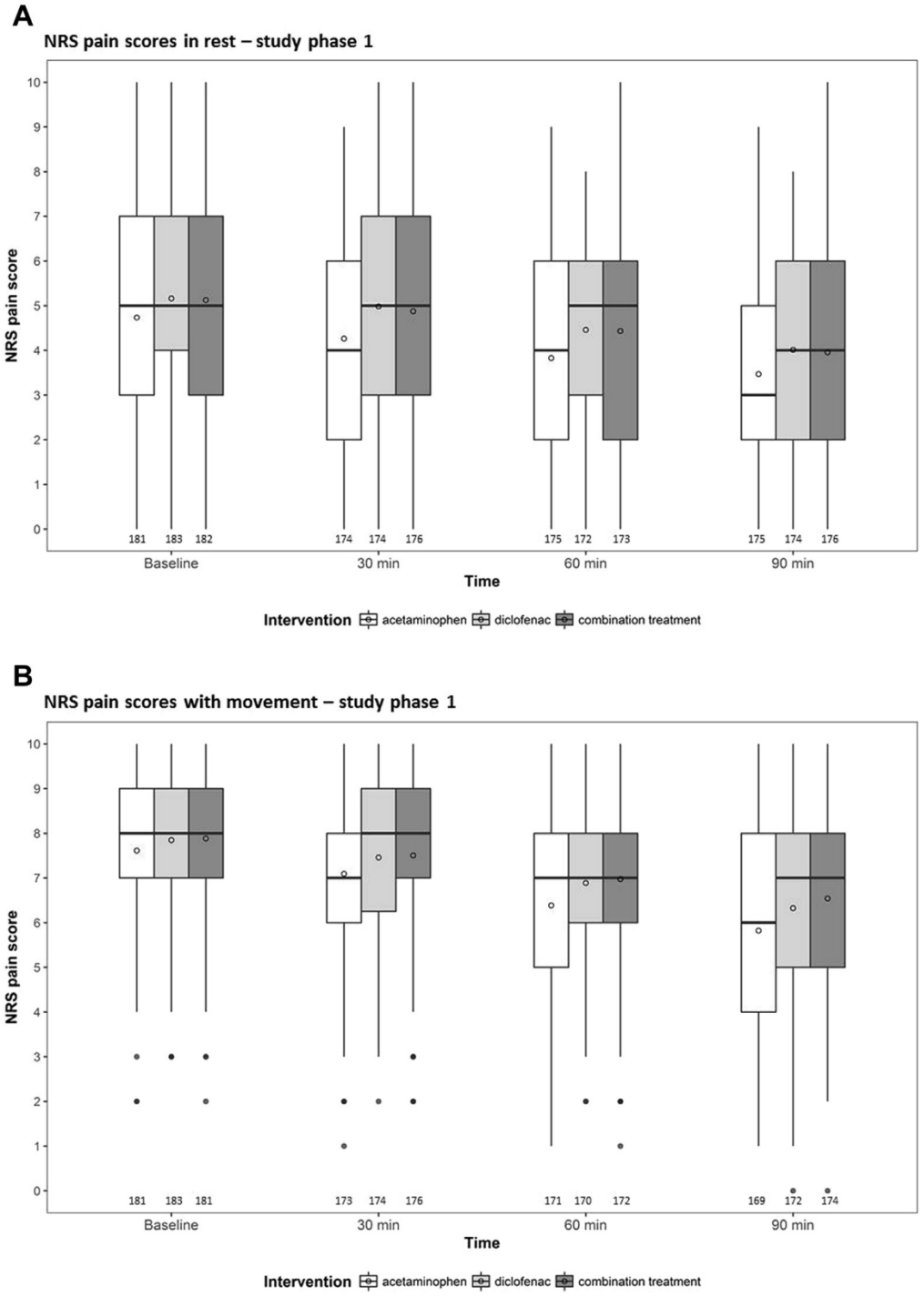

Figure 3. *A*, Box plots of NRS pain scores in rest during study phase 1. Each plot represents the interquartile range, including median NRS pain score (bold horizontal line) and mean NRS pain score (circle). The vertical lines indicate the upper and lower adjacent values. Numbers under each box plot represent the number of participants who were measured at this point. *B*, Box plots of NRS pain scores with movement during study phase 1. Each plot represents the interquartile range, including median NRS pain score (bold horizontal line) and mean NRS pain score (circle). The vertical lines indicate the upper and lower adjacent values. Outliers are shown as solid dots. Numbers under each box plot represent the number of participants who were measured at this point.

group. In phases 2 and 3, 12 potentially serious events occurred in 11 patients: chest pain when supine in 1 (combination), dyspnea in 3 (2 acetaminophen and 1 combination), dark urine in 3 (2 acetaminophen and 1 combination), and bloody stools in 5 (1 acetaminophen, 1 diclofenac, and 3 combination).

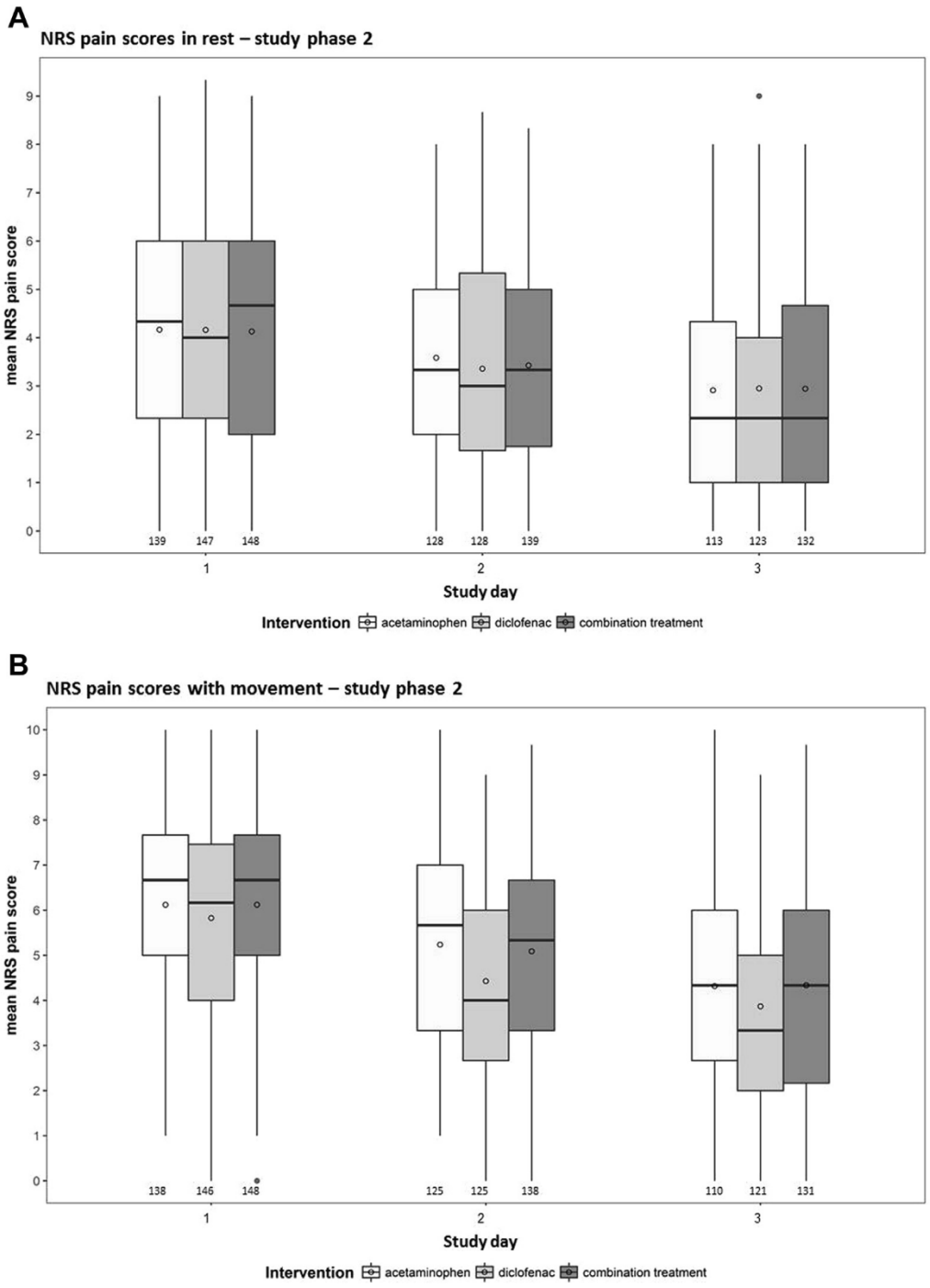

Figure 4. *A*, Box plots of NRS pain scores in rest during study phase 2. Each plot represents the interquartile range, including median NRS pain score (bold horizontal line) and mean NRS pain score (circle). The vertical lines indicate the upper and lower adjacent values. Outliers are shown as solid dots. Numbers under each box plot represent the number of participants who were measured at this point. *B*, Box plots of NRS pain scores with movement during study phase 2. Each plot represents the interquartile range, including median NRS pain score (bold horizontal line) and mean NRS pain score (circle). The vertical lines indicate the upper and lower adjacent values. Outliers are shown as solid dots. Numbers under each box plot represent the number of participants who were measured at this point.

Besides medical treatment with antibronchospastic medication in 2 dyspneic patients, no intervention was required. Adverse events, specifically, abdominal complaints and nausea, occurred equally in all groups. No patient was hospitalized because of adverse events. During the third study phase, 30 patients

Table 2. Summary of outcome results.*

Study Phase and Parameter	Acetaminophen (N=182)	Diclofenac (N=183)	Combination (N=182)
Phase 1			
≥33% NRS decrease, No. (%)†			
Rest	142 (85.5)	156 (91.8)	157 (93.5)
Movement	158 (93.5)	167 (97.1)	171 (98.3)
Additional analgesia, No. (%)	1 (0.5)	2 (1.1)	8 (4.4)
Adverse events, No. (%)‡			
Gastrointestinal	15 (8.2)	8 (4.4)	10 (5.5)
Neurologic	24 (13.2)	12 (6.6)	13 (7.1)
Other	2 (1.1)	4 (2.2)	0
Injury treatment, No. (%)§			
Immobilization	113 (62.1)	104 (56.8)	109 (59.9)
Elevation	4 (2.2)	6 (3.3)	11 (6.0)
None	65 (35.7)	73 (39.9)	62 (34.1)
Pain improvement, No. (%)			
Unbearable	0	0	0
Increased	7 (4.1)	7 (4.2)	4 (2.4)
Unchanged	33 (19.2)	43 (25.9)	43 (25.6)
Decreased	129 (75.0)	108 (65.1)	119 (70.8)
Disappeared	3 (1.7)	8 (4.8)	2 (1.2)
Patient satisfaction, No. (%)			
Not satisfied	17 (9.9)	18 (10.8)	13 (7.7)
A bit satisfied	15 (8.8)	22 (13.3)	21 (12.4)
Moderately satisfied	41 (24.0)	34 (20.5)	35 (20.7)
Satisfied	78 (45.6)	69 (41.6)	74 (43.8)
Very satisfied	20 (11.7)	23 (13.9)	26 (15.4)
Phase 2			
≥33% NRS decrease, No. (%)			
Rest	98 (89.9)	101 (86.3)	116 (89.9)
Movement	102 (92.7)	102 (86.4)	116 (89.2)
Additional analgesia, No. (%)	16 (8.8)	8 (4.4)	10 (5.5)
Adverse events, No. (%)‡			
Gastrointestinal	47 (25.8)	37 (20.2)	36 (19.8)
Neurologic	33 (18.1)	28 (15.3)	29 (15.9)
Other	13 (7.1)	2 (1.1)	2 (1.1)
Injury treatment, No. (%)§			
Ice	27 (14.8)	26 (14.2)	18 (9.9)
Immobilization	80 (44.0)	78 (42.6)	80 (44.0)
Elevation	50 (27.5)	50 (27.3)	54 (29.7)
Pain improvement, No. (%)‖			
Unbearable	0	0	0
Increased	1 (0.8)	3 (2.2)	2 (1.4)
Unchanged	15 (12.2)	14 (10.4)	18 (12.7)
Decreased	94 (76.4)	94 (70.1)	101 (71.1)
Disappeared	13 (10.6)	23 (17.2)	21 (14.8)
Patient satisfaction, No. (%)			
Not satisfied	10 (8.1)	9 (6.7)	7 (4.9)
A bit satisfied	7 (5.7)	10 (7.5)	16 (11.3)
Moderately satisfied	23 (18.7)	16 (11.9)	20 (14.1)
Satisfied	58 (47.2)	71 (53.0)	73 (51.4)
Very satisfied	25 (20.3)	28 (20.9)	26 (18.3)
Phase 3			
Adverse events, No. (%)‡			
Gastrointestinal	9 (4.9)	6 (3.3)	4 (2.2)
Neurologic	7 (3.8)	4 (2.2)	0
Other	0	1 (0.5)	2 (1.1)
Additional analgesia, No. (%)	33 (18.1)	35 (19.1)	42 (23.1)

*All analyses were performed in the intention-to-treat population. All categorical variables were analyzed with the χ^2 test.
†For more information regarding the relative pain reduction in phase 1, see Table E6, available online at http://www.annemergmed.com.
‡Symptoms included in these categories are fully described in Tables E11-E14, available online at http://www.annemergmed.com.
§Immobilization was defined as usage of a bandage, wrap, cast, or sling (in injuries of the complete upper extremity). Elevation was defined as specific advice to elevate the injured extremity or the use of a sling to elevate an injured lower arm, wrist, hand, or finger.
‖For more information regarding the relative pain reduction in phase 2, see Table E9, available online at http://www.annemergmed.com.

experienced mild adverse effects after discontinuation of study medication. All adverse events were specified and are shown in Tables E10 to E14 (available online at http://www.annemergmed.com). There were no differences in occurrence of adverse events between the 3 interventions in patients aged 60 years and older (Table E17, available online at http://www.annemergmed.com).

LIMITATIONS

Certainly our study had limitations because loss to follow-up during the second study phase was 15%. As a consequence, pain score analysis during 3 days after discharge was underpowered to draw firm conclusions about inferiority, although we do not expect that the observed trend of noninferiority would be negated and ample patients were included for a superiority analysis.[15]

Most authors of pain studies use 50% relative reduction in NRS pain scores, but in our study we chose 33% relative reduction a priori, based on recommendations of the International Association for the Study of Pain to detect a meaningful relative reduction in pain by 30%.[18]

The study was underpowered to detect differences in adverse events. Moreover, because all patients received omeprazole, we cannot draw conclusions about the rate of adverse events of all medication strategies; however, this was not the aim of the current study. Although robust evidence is lacking, coadministration of a proton-pump inhibitor might have influenced pharmacokinetics of acetaminophen. The authors of a small study in 6 healthy volunteers reported increased absorption rate when combining lansoprazole and acetaminophen, but elimination and bioavailability did not change.[19]

Last, adequacy of blinding was not assessed, for example, by interviewing patients, which might have introduced bias.

DISCUSSION

This randomized, controlled, double-blind trial in 547 adult individuals with minor acute musculoskeletal extremity trauma showed that pain management with acetaminophen alone was not inferior to diclofenac or the

combination of acetaminophen and diclofenac, both in the acute phase and during 3 consecutive days after discharge.

Although analgesics in this study were prescribed in dosages that are commonly used in daily clinical practice in Europe (acetaminophen 1,000 mg 4 times daily and diclofenac 50 mg 3 times daily), NRS pain reduction at 90 minutes after initial study medication only reached a minimally clinically significant reduction of 1.3 NRS points in the acetaminophen group in rest, according to the per-protocol analysis. Although previous studies have shown comparable results in acute pain reduction, it is not known how to address this residual pain in daily clinical practice.[11] Adding a nonsteroidal anti-inflammatory drug to acetaminophen as a second step will not lead to clinically relevant improvement in pain decrease. More potent alternatives such as opioids could be considered, but this was not the scope of the current study.

In several other nonchronic, clinical problems, direct comparison studies between acetaminophen and nonsteroidal anti-inflammatory drugs have shown various results.[20] Nonsteroidal anti-inflammatory drugs seem more effective in dental and menstrual pain, but both medications provide equivalent analgesia in orthopedic surgery and tension headache.[21,22] In regard to acute minor musculoskeletal trauma, as concluded in a Cochrane review, there is generally low-quality evidence showing no clinically important difference in analgesic efficacy between both medications.[14] Five randomized trials have compared acetaminophen with nonsteroidal anti-inflammatory drugs[11-13,23,24]; however, these studies were performed in heterogeneous study populations. Treatment with acetaminophen 4,000 mg daily during 3 days did not reveal inferiority compared with treatment with diclofenac 75 mg or indomethacin 75 mg or the acetaminophen-diclofenac combination in 300 patients with musculoskeletal injuries of an extremity.[11] The equivalence margin was 13 mm on a 0- to 100-mm visual analog scale. Selection bias could not be ruled out because patients were included only from Monday to Friday between 9 AM and 5 PM. Moreover, these results cannot be extrapolated to daily practice because diclofenac was dosed at 50% compared with usual dosages. A multicenter, randomized study in patients with ankle sprains compared acetaminophen extended release 1,300 mg 3 times daily with ibuprofen 400 mg 3 times daily. No significant differences in pain while walking were found; however, outcomes were evaluated only after 4 and 9 days.[12] Two other randomized trials did not detect a difference in visual analog scale score decrease in 100 and 90 patients treated for ankle sprains with diclofenac or acetaminophen.[23,24] However, acetaminophen dosage was relatively low (1,500 mg daily). In the first study, pain was not assessed in the acute phase, but on the second and 10th day, and after 6 weeks.[23] Selection bias might have played a role in all studies because patients who were not recruited were not accounted for. Finally, 90 patients with acute musculoskeletal pain were randomized to blinded treatment with acetaminophen 1,000 mg, ibuprofen 800 mg, or both, administered once.[13] Pain was treated equally effectively, but the study population was a convenience sample. Besides, study duration was 60 minutes. In our study, pain scores continued to decline between 60 and 90 minutes after administration of medication, so full analgesic effects might not have been detected.

Strengths in our study design were the multicenter recruitment of a heterogenous population from both primary and emergency care and using common analgesic medications and dosages. All patients who were not included were counted and documented.

In our study, diclofenac was chosen as comparison because this is the most prescribed nonsteroidal anti-inflammatory drug worldwide.[4] However, in some Western countries, including the United States and the United Kingdom, ibuprofen is preferentially used because diclofenac is available only as prescription medication. Ibuprofen is available over the counter in these countries. There is supporting evidence diclofenac is not inferior to ibuprofen in regard to analgesic efficacy and there is no pharmacologic reason it would be because both are nonselective nonsteroidal anti-inflammatory drugs inhibiting both cyclooxygenase-1 and -2 enzymes.[25,26]

Patients with postoperative pain usually receive both acetaminophen and diclofenac to optimize pain treatment.[27] The reason for combining 2 analgesic drugs with different pharmacologic modes of action is that they might work synergistically. A 2007 review concluded that this combination might have better analgesic results; however, studies from the perioperative setting, in which analgesic drugs are administered before patients experience pain, were included.[28] Moreover, medications were administered rectally and orally and used in different dosages. Therefore, these results cannot be used in a nonoperative clinical setting. Our results show that acetaminophen alone is as effective as the combination in treating pain from minor musculoskeletal trauma. Although additivity cannot be officially tested with maximal dosages, as used in our approach, these dosages are common in current daily practice.

Even though there were no differences between the interventions, there was a relatively high occurrence of adverse events observed in the acetaminophen group, which has been described previously by Dalton and Schweinle,[12] who also used high-dose acetaminophen in

their study. There might be another reason, though, because all patients received omeprazole regardless of allocated treatment. Short-term proton-pump inhibitor use could cause nausea, headache, diarrhea, abdominal pain, constipation, flatulence, rash, and dizziness.[29] All these effects were observed in our study in all groups. On the other hand, true adverse event rate in the diclofenac groups was probably underestimated because of this preventive proton-pump inhibitor use. Because our study aim was to investigate analgesic efficacy, coadministering a proton-pump inhibitor did not downgrade our study value.[15] On the contrary, administering omeprazole to all participating patients helped maintain blinding, prevented cointervention bias, and allowed us to include elderly patients and patients with gastric complaints because the recommendations of a Dutch national multidisciplinary guideline about nonsteroidal anti-inflammatory drug use and prevention of gastrointestinal injury were adhered to.[30] These recommendations include coadministering proton-pump inhibitors with nonsteroidal anti-inflammatory drugs to all elderly patients, all those with gastric complaints, all those with diabetes, and all those using anticoagulants or selective serotonin reuptake inhibitors.

Even a short course of nonsteroidal anti-inflammatory drugs can cause harm, especially cardiovascular complications, and a considerable proportion of all unplanned hospital admissions are related to nonsteroidal anti-inflammatory drug use.[1,4,31,32] It is obvious that reducing the use of nonsteroidal anti-inflammatory drugs in a very common disorder, such as musculoskeletal injuries, would be of significant benefit to health care.

In conclusion, because acetaminophen is noninferior to diclofenac and the combination of acetaminophen and diclofenac, pain treatment in acute minor musculoskeletal extremity trauma in adult patients could initially consist of 1 of these 3 analgesic strategies.

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Author contributions: MLR, PL, HG, EMK, MWH, and JCG designed the trial and obtained research funding. MWH and JCG supervised the conduct of the trial. MLR and HG recruited patients and collected data in the Academic Medical Center and in Gein, ES did so at Wynia & Schinkel, and EV did so in the VU Medical Center. EMK was responsible for management, packing, and distribution of study medication. SVD performed the statistical analyses. MLR drafted the article, had full access to all study data, and had final responsibility for the decision to submit for publication. All authors contributed substantially to article revision. MLR takes responsibility for the paper as a whole.

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APPENDIX E1

Supplements to the "Materials and Methods" section

In the original study protocol, it was expected that the total number of 547 patients would be recruited in the ED and urgent care center in the Academic Medical Center, as well as in one general practice (Gein), within 1 year. This assumption was made after data analysis for all patients with minor musculoskeletal trauma and presenting to the ED in August 2012. During the study course, inclusion rate was lower than anticipated for mainly 2 reasons. First, in the period after this pilot study and before recruitment of the Paracetamol or NSAIDs in Acute Musculoskeletal Trauma study started, policy in regard to self-referrals (patients with minor musculoskeletal trauma are usually self-referred) changed. After a nationwide and regional debate, a discouragement policy about self-referring to an ED was pursued, after which the total number of patients presenting with these injuries decreased. Second, a significant proportion of patients presenting to the general practice with minor musculoskeletal trauma appeared to present after 48 hours. Because one of the inclusion criteria of the study was presentation within this time frame, these patients could not be included in the study. Because of these reasons, 2 recruiting centers were added to the study: the ED of VU Medical Center in Amsterdam and another general practice (Wynia & Schinkel).

Initially, it was predicted that 137 patients would be included in the primary care setting (general practice) to extrapolate study results to primary and emergency care. However, eventually this number was only 45 patients, versus 502 patients who were included in the ED. Of these patients, radiologic imaging was conducted for 445 patients and no imaging conducted for 57. These 57 patients could have been treated in primary care as well, bringing the total of (potential) primary care patients to 102.

Table E1. Injury localizations, specified.*

	Acetaminophen	Diclofenac	Combination
Specific localization, No. (%)			
Shoulder	10 (5.5)	12 (6.6)	14 (7.7)
Upper arm	1 (0.5)	1 (0.5)	0
Elbow	3 (1.6)	11 (6.0)	7 (3.8)
Lower arm	6 (3.3)	1 (0.5)	4 (2.2)
Wrist	9 (4.9)	13 (7.1)	7 (3.8)
Hand	19 (10.4)	17 (9.3)	15 (8.2)
Finger	18 (9.9)	15 (8.2)	7 (3.8)
Hip	3 (1.6)	3 (1.6)	5 (2.7)
Upper leg	3 (1.6)	1 (0.5)	1 (0.5)
Knee	28 (15.4)	25 (13.7)	36 (19.8)
Lower leg	6 (3.3)	8 (4.4)	6 (3.3)
Ankle	45 (24.7)	48 (26.2)	50 (27.5)
Foot	25 (13.7)	25 (13.7)	27 (14.8)
Toe	6 (3.3)	3 (1.6)	3 (1.6)

*No statistical significant differences were found between the 3 groups; however, conditions of the χ^2 test were not fulfilled because, with cross tabulation, a substantive amount of cells had an expected count less than 5.

Table E2. Intention-to-treat analysis of pain scores in the first study phase for the comparison of acetaminophen versus diclofenac.

	Acetaminophen (N=182)	Diclofenac (N=183)	Mean Difference
Mean NRS rest (95% CI)			
Baseline	4.73 (4.37 to 5.10)	5.16 (4.84 to 5.49)	−0.43 (−0.92 to 0.057)
30 min	4.26 (3.91 to 4.62)	4.98 (4.65 to 5.32)	−0.72 (−1.21 to −0.23)
60 min	3.83 (3.48 to 4.18)	4.46 (4.12 to 4.80)	−0.63 (−1.12 to −0.15)
90 min	3.47 (3.12 to 3.82)	4.01 (3.67 to 4.35)	−0.54 (−1.03 to −0.058)
Mean difference baseline and 90 min	−1.23 (−1.50 to −0.95)	−1.20 (−1.44 to −0.96)	−0.027 (−0.45 to 0.39)*
Mean NRS movement (95% CI)			
Baseline	7.61 (7.36 to 7.86)	7.85 (7.62 to 8.07)	−0.23 (−0.57 to 0.10)
30 min	7.09 (6.81 to 7.37)	7.46 (7.21 to 7.71)	−0.37 (−0.74 to 0.004)
60 min	6.39 (6.07 to 6.70)	6.89 (6.61 to 7.17)	−0.50 (−0.92 to −0.82)
90 min	5.82 (5.48 to 6.17)	6.33 (6.01 to 6.64)	−0.50 (−0.97 to −0.039)
Mean difference baseline and 90 min	−1.72 (−2.01 to −1.44)	−1.52 (−1.77 to −1.26)	−0.20 (−0.64 to 0.23)*

*For the primary outcome, a Bonferroni adjustment was used, with a 97.5% CI.

Table E3. Intention-to-treat analysis of pain scores in the first study phase for the comparison of acetaminophen versus combination.

	Acetaminophen (N=182)	Combination (N=182)	Mean Difference
Mean NRS rest (95% CI)			
Baseline	4.73 (4.37 to 5.10)	5.13 (4.74 to 5.51)	−0.39 (−0.92 to 0.14)
30 min	4.26 (3.91 to 4.62)	4.89 (4.51 to 5.26)	−0.61 (−1.13 to −0.09)
60 min	3.83 (3.48 to 4.18)	4.44 (4.07 to 4.82)	−0.61 (−1.12 to −0.092)
90 min	3.47 (3.12 to 3.82)	3.95 (3.59 to 4.32)	−0.49 (−0.99 to 0.015)
Mean difference baseline and 90 min	−1.23 (−1.50 to −0.95)	−1.18 (−1.41 to −0.94)	−0.052 (−0.46 to 0.36)*
Mean NRS movement (95% CI)			
Baseline	7.61 (7.36 to 7.86)	7.88 (7.65 to 8.12)	−0.27 (−0.61 to 0.069)
30 min	7.09 (6.81 to 7.37)	7.51 (7.24 to 7.77)	−0.41 (−0.80 to −0.030)
60 min	6.39 (6.07 to 6.70)	6.98 (6.68 to 7.28)	−0.59 (−1.03 to −0.16)
90 min	5.82 (5.48 to 6.17)	6.54 (6.23 to 6.85)	−0.72 (−1.17 to −0.26)
Mean difference baseline and 90 min	−1.72 (−2.01 to −1.44)	−1.33 (−1.55 to −1.12)	−0.39 (−0.80 to 0.018)*

*For the primary outcome, a Bonferroni adjustment was used, with a 97.5% CI.

Table E4. Per-protocol analysis of pain scores in the first study phase for the comparison of acetaminophen versus diclofenac.

	Acetaminophen (N=167)	Diclofenac (N=172)	Mean Difference
Mean NRS rest (95% CI)			
Baseline	4.73 (4.36 to 5.10)	5.21 (4.87 to 5.55)	−0.48 (−0.98 to 0.02)
90 min	3.43 (3.08 to 3.79)	4.02 (3.67 to 4.36)	−0.59 (−1.08 to−0.09)
Mean difference baseline and 90 min	−1.30 (−1.57 to −1.03)	−1.20 (−1.44 to −0.95)	−0.11 (−0.53 to 0.31)*
Mean NRS movement (95% CI)			
Baseline	7.54 (7.28 to 7.80)	7.86 (7.62 to 8.10)	−0.32 (−0.67 to 0.03)
90 min	5.77 (5.42 to 6.12)	6.34 (6.02 to 6.65)	−0.57 (−1.03 to −0.09)
Mean difference baseline and 90 min	−1.74 (−2.03 to −1.45)	−1.53 (−1.78 to −1.27)	−0.21 (−0.65 to 0.23)*

*For the primary outcome, a Bonferroni adjustment was used, with a 97.5% CI.

Table E5. Per-protocol analysis of pain scores in the first study phase for the comparison of acetaminophen versus combination.

	Acetaminophen (N=167)	Combination (N=169)	Mean Difference
Mean NRS rest (95% CI)			
Baseline	4.73 (4.36 to 5.10)	5.09 (4.69 to 5.50)	−0.36 (−0.91 to 0.18)
90 min	3.43 (3.08 to 3.79)	3.91 (3.55 to 4.28)	−0.48 (−0.99 to 0.03)
Mean difference baseline and 90 min	−1.30 (−1.57 to −1.03)	−1.18 (−1.42 to −0.95)	−0.12 (−0.53 to 0.30)*
Mean NRS movement (95% CI)			
Baseline	7.54 (7.28 to 7.80)	7.84 (7.59 to 8.08)	−0.30 (−0.66 to 0.06)
90 min	5.77 (5.42 to 6.12)	6.50 (6.19 to 6.81)	−0.72 (−1.19 to −0.26)
Mean difference baseline and 90 min	−1.74 (−2.03 to −1.45)	−1.35 (−1.57 to −1.13)	−0.39 (−0.80 to 0.027)*

*For the primary outcome, a Bonferroni adjustment was used, with a 97.5% CI.

Table E6. Relative pain reduction in phase 1.*

	≥33% NRS Decrease	<33% NRS Decrease
Rest		
Acetaminophen	85.5	14.5
Diclofenac	91.8	8.2
ARR		6.3
NNT		15.9†
Acetaminophen	85.5	14.5
Combination	93.5	6.5
ARR		8
NNT		12.5
Movement		
Acetaminophen	93.5	6.5
Diclofenac	97.1	2.9
ARR		3.6
NNT		27.8
Acetaminophen	93.5	6.5
Combination	98.3	1.7
ARR		4.8
NNT		20.8

ARR, Absolute risk reduction; NNT, number needed to treat.
*The NNT to achieve at least a 33% relative reduction in NRS pain scores was calculated for the comparisons acetaminophen-diclofenac and for acetaminophen-combination. The ARR for not achieving a 33% relative reduction was used for this purpose.
†Statement example: 16 patients need to be treated with diclofenac to achieve a 33% NRS reduction in rest in one additional patient, compared with treatment with acetaminophen.

Table E7. Intention-to-treat analysis of pain scores in the second study phase for the comparison of acetaminophen versus diclofenac.

	Acetaminophen (N=182)	Diclofenac (N=183)	Mean Difference
Mean NRS rest (95% CI)			
Day 1	4.17 (3.79 to 4.54)	4.16 (3.79 to 4.53)	0.006 (−0.52 to 0.53)
Day 2	3.58 (3.22 to 3.95)	3.36 (2.98 to 3.74)	0.23 (−0.30 to 0.75)
Day 3	2.91 (2.52 to 3.30)	2.95 (2.56 to 3.35)	−0.04 (−0.59 to 0.51)
Mean difference day 1 and day 3	−1.27 (−1.58 to −0.96)	−1.33 (−1.66 to −0.99)	0.06 (−0.40 to 0.51)
Mean NRS movement (95% CI)			
Day 1	6.12 (5.77 to 6.47)	5.83 (5.45 to 6.21)	0.29 (−0.22 to 0.81)
Day 2	5.24 (4.84 to 5.63)	4.43 (4.03 to 4.83)	0.81 (0.25 to 1.37)
Day 3	4.32 (3.90 to 4.74)	3.87 (3.44 to 4.30)	0.45 (−0.15 to 1.05)
Mean difference day 1 and day 3	−1.99 (−2.32 to −1.67)	−1.93 (−2.29 to −1.57)	−0.06 (−0.55 to 0.43)

Table E8. Intention-to-treat analysis of pain scores in the second study phase for the comparison of acetaminophen versus combination.

	Acetaminophen (N=182)	Combination (N=182)	Mean Difference
Mean NRS rest (95% CI)			
Day 1	4.17 (3.79 to 4.54)	4.13 (3.74 to 4.51)	0.04 (−0.50 to 0.57)
Day 2	3.58 (3.22 to 3.95)	3.43 (3.07 to 3.78)	0.16 (−0.35 to 0.66)
Day 3	2.91 (2.52 to 3.30)	2.94 (2.59 to 3.30)	−0.03 (−0.55 to 0.49)
Mean difference day 1 and day 3	−1.27 (−1.58 to −0.96)	−1.20 (−1.53 to −0.88)	−0.07 (−0.52 to 0.38)
Mean NRS movement (95% CI)			
Day 1	6.12 (5.77 to 6.47)	6.12 (5.77 to 6.47)	−0.0009 (−0.49 to 0.49)
Day 2	5.24 (4.84 to 5.63)	5.09 (4.70 to 5.48)	0.15 (−0.41 to 0.70)
Day 3	4.32 (3.90 to 4.74)	4.34 (3.93 to 4.74)	−0.02 (−0.60 to 0.56)
Mean difference day 1 and day 3	−1.99 (−2.32 to −1.67)	−1.77 (−2.09 to −1.45)	−0.22 (−0.68 to 0.23)

Table E9. Relative pain reduction in the second study phase.*

	≥33% NRS Decrease	<33% NRS Decrease
Rest		
Diclofenac	86.3	13.7
Acetaminophen	89.9	10.1
ARR		3.6
NNT		27.8†
Combination	89.9	10.1
Acetaminophen	89.9	10.1
ARR		0
NNT		NA
Movement		
Diclofenac	86.4	13.6
Acetaminophen	92.7	7.3
ARR		6.3
NNT		15.9
Combination	89.2	10.8
Acetaminophen	92.7	7.3
ARR		3.5
NNT		28.6

NA, Not available.

*The NNT to achieve at least a 33% relative reduction in NRS pain scores was calculated for the comparisons acetaminophen-diclofenac and acetaminophen-combination. The ARR for not achieving a 33% relative reduction was used for this purpose.

†Statement example: approximately 28 patients need to be treated with acetaminophen to achieve a 33% NRS reduction in rest in one additional patient, compared with treatment with diclofenac.

Table E10. Adverse events specified in phase 1.*

	Acetaminophen	Diclofenac	Combination
Gastrointestinal, No. (%)			
Abdominal discomfort†	6 (3.3)	1 (0.5)	3 (1.6)
Nausea	9 (4.9)	7 (3.8)	7 (3.8)
Vomiting†	1 (0.5)	0	0
Flatulence†	1 (0.5)	0	0
Neurologic, No. (%)			
Headache†	3 (1.6)	0	2 (1.1)
Dizziness	8 (4.4)	5 (2.7)	3 (1.6)
Tiredness	13 (7.1)	7 (3.8)	10 (5.5)
Other AE, No. (%)			
Itching†	1 (0.5)	1 (0.5)	0
Sweating†	1 (0.5)	1 (0.5)	0
Dry mouth†	0	1 (0.5)	0
Feeling cold†	0	1 (0.5)	0

AE, Adverse events.

*The total sum of specified adverse events was higher than grouped adverse events because in some patients more than one adverse event occurred.

†Conditions of the χ^2 test were not fulfilled because, with cross tabulation, a substantive amount of cells had an expected count less than 5.

Table E11. Adverse events specified in the second study phase during day 1.*

	Acetaminophen	Diclofenac	Combination
Gastrointestinal, No. (%)			
Abdominal discomfort	9 (4.9)	12 (6.6)	8 (4.4)
Nausea	14 (7.7)	14 (7.7)	11 (6.0)
Vomiting†	2 (1.1)	0	1 (0.5)
Belching/flatulence†	9 (4.9)	7 (3.8)	8 (4.4)
Diarrhea†	3 (1.6)	7 (3.8)	4 (2.2)
Neurologic, No. (%)			
Headache	11 (6.0)	11 (6.0)	11 (6.0)
Dizziness	8 (4.4)	8 (4.4)	12 (6.6)
Tiredness	8 (4.4)	10 (5.5)	8 (4.4)
Restless legs†	0	1 (0.5)	0
Other AE, No. (%)			
Chest pain†	0	0	1 (0.5)
Dyspnea†	1 (0.5)	0	0
Dark urine†	2 (1.1)	0	1 (0.5)
Skin reaction/itching†	2 (1.1)	1 (0.5)	0
Sweating†	3 (1.6)	1 (0.5)	0
Pain in throat†	1 (0.5)	0	0

*The total sum of specified adverse events was higher than grouped adverse events because in some patients more than one adverse event occurred.
†Conditions of the χ^2 test were not fulfilled because, with cross tabulation, a substantive amount of cells had an expected count less than 5.

Table E12. Adverse events specified in the second study phase during day 2.*

	Acetaminophen	Diclofenac	Combination
Gastrointestinal, No. (%)			
Abdominal discomfort	11 (6.0)	12 (6.6)	9 (4.9)
Nausea	17 (9.3)	8 (4.4)	12 (6.6)
Vomiting†	5 (2.7)	0	1 (0.5)
Belching/flatulence	11 (6.0)	7 (3.8)	5 (2.7)
Diarrhea†	7 (3.8)	3 (1.6)	3 (1.6)
Blood loss rectally†	1 (0.5)	0	1 (0.5)
Neurologic, No. (%)			
Headache	12 (6.6)	7 (3.8)	12 (6.6)
Dizziness	8 (4.4)	7 (3.8)	10 (5.5)
Tiredness	8 (4.4)	8 (4.4)	9 (4.9)
Other AE, No. (%)			
Dyspnea†	1 (0.5)	0	0
Dark urine†	2 (1.1)	0	1 (0.5)
Skin reaction/itching†	1 (0.5)	1 (0.5)	0
Sweating/feverish†	2 (1.1)	0	0
Pain complete body†	0	0	1 (0.5)
Vaginal bleeding†	0	0	1 (0.5)

*The total sum of specified adverse events was higher than grouped adverse events because in some patients more than one adverse event occurred.
†Conditions of the χ^2 test were not fulfilled because, with cross tabulation, a substantive amount of cells had an expected count less than 5.

Table E13. Adverse events specified in the second study phase during day 3.*

	Acetaminophen	Diclofenac	Combination
Gastrointestinal, No. (%)			
Abdominal discomfort	5 (2.7)	9 (4.9)	6 (3.3)
Nausea	11 (6.0)	6 (3.3)	11 (6.0)
Vomiting†	2 (1.1)	0	0
Belching/flatulence	11 (6.0)	7 (3.8)	6 (3.3)
Diarrhea	3 (1.6)	4 (2.2)	5 (2.7)
Blood loss rectally†	1 (0.5)	0	1 (0.5)
Neurologic, No. (%)			
Headache	8 (4.4)	6 (3.3)	7 (3.8)
Dizziness	6 (3.3)	4 (2.2)	7 (3.8)
Tiredness	6 (3.3)	7 (3.8)	9 (4.9)
Other AE, No. (%)			
Dyspnea†	1 (0.5)	0	0
Dark urine†	1 (0.5)	0	1 (0.5)
Skin reaction/itching†	1 (0.5)	1 (0.5)	0
Sweating/feverish†	4 (2.2)	0	0
Pain complete body†	0	0	1 (0.5)
Vaginal bleeding†	0	0	1 (0.5)

*The total sum of specified adverse events was higher than grouped adverse events because in some patients more than one adverse event occurred.
†Conditions of the χ^2 test were not fulfilled because, with cross tabulation, a substantive amount of cells had an expected count less than 5.

Table E14. Adverse events specified in the third study phase.*

	Acetaminophen	Diclofenac	Combination
Gastrointestinal, No. (%)			
Abdominal discomfort	4 (2.2)	3 (1.6)	1 (0.5)
Nausea	4 (2.2)	2 (1.1)	1 (0.5)
Vomiting	2 (1.1)	0	0
Belching/flatulence	0	0	1 (0.5)
Diarrhea	2 (1.1)	2 (1.1)	0
Blood loss rectally	0	1 (0.5)	1 (0.5)
Neurologic, No. (%)			
Headache	3 (1.6)	1 (0.5)	0
Dizziness	2 (1.1)	1 (0.5)	0
Tiredness	4 (2.2)	3 (1.6)	0
Other AE, No. (%)			
Dyspnea	0	0	1 (0.5)
Skin reaction/itching	0	1 (0.5)	1 (0.5)

*The total sum of specified adverse events was higher than grouped adverse events because in some patients more than one adverse event occurred. In all comparisons, conditions of the χ^2 test were not fulfilled because, with cross tabulation, a substantive amount of cells had an expected count less than 5.

Table E15. Subgroup analysis of NRS pain scores in patients aged 60 years and older for the comparison of acetaminophen versus diclofenac.*

	Acetaminophen (N=14)	Diclofenac (N=14)	Mean Difference
Phase 1			
Mean NRS rest (95% CI)			
Baseline	3.93 (2.10 to 5.76)	5.29 (3.66 to 6.91)	−1.36 (−3.69 to 0.97)
90 min	2.46 (1.24 to 3.69)	3.79 (2.20 to 5.37)	−1.32 (−3.23 to 0.59)
Mean difference baseline and 90 min	−1.00 (−2.80 to 0.80)	−1.50 (−2.43 to −0.57)	0.50 (−1.37 to 2.37)
Mean NRS movement (95% CI)			
Baseline	7.43 (6.26 to 8.60)	7.71 (7.02 to 8.41)	−0.29 (−1.58 to 1.01)
90 min	5.38 (3.67 to 7.10)	5.79 (4.54 to 7.03)	−0.40 (−2.39 to 1.59)
Mean difference baseline and 90 min	−1.85 (−3.34 to −0.35)	−1.93 (−3.12 to −0.74)	0.08 (−1.72 to 1.89)
Phase 2			
Mean NRS rest (95% CI)			
Day 1	3.19 (1.66 to 4.73)	3.33 (1.92 to 4.75)	−0.14 (−2.11 to 1.83)
Day 3	2.53 (0.88 to 4.19)	2.53 (1.38 to 3.67)	0.008 (−1.82 to 1.83)
Mean difference day 1 and day 3	−1.00 (−2.39 to 0.39)	−0.63 (−2.17 to 0.92)	−0.38 (−2.36 to 1.61)
Mean NRS movement (95% CI)			
Day 1	5.61 (3.73 to 7.49)	4.31 (2.75 to 5.87)	1.30 (−0.99 to 3.60)
Day 3	4.81 (2.58 to 7.05)	2.85 (1.58 to 4.12)	1.97 (−0.24 to 4.18)
Mean difference day 1 and day 3	−1.85 (−3.76 to 0.056)	−1.25 (−2.88 to 0.39)	−0.60 (−2.94 to 1.74)

*All analyses were performed in the intention-to-treat population. All continuous variables were compared with independent *t* tests and reported as mean differences with 95% CIs.

Table E16. Subgroup analysis of NRS pain scores in patients aged 60 years and older for the comparison of acetaminophen versus combination.*

	Acetaminophen (N=14)	Combination (N=14)	Mean Difference
Phase 1			
Mean NRS rest (95% CI)			
Baseline	3.93 (2.10 to 5.76)	5.57 (3.87 to 7.28)	−1.64 (−4.03 to 0.74)
90 min	2.46 (1.24 to 3.69)	4.29 (2.57 to 6.00)	−1.82 (−3.86 to 0.21)
Mean difference baseline and 90 min	−1.00 (−2.80 to 0.80)	−1.29 (−1.86 to −0.71)	0.29 (−1.57 to 2.14)
Mean NRS movement (95% CI)			
Baseline	7.43 (6.26 to 8.60)	8.57 (7.59 to 9.55)	−1.14 (−2.60 to 0.31)
90 min	5.38 (3.67 to 7.10)	7.50 (6.55 to 8.45)	−2.11 (−4.01 to −0.22)
Mean difference baseline and 90 min	−1.85 (−3.34 to −0.35)	−1.07 (−1.93 to −0.21)	−0.77 (−2.38 to 0.83)
Phase 2			
Mean NRS rest (95% CI)			
Day 1	3.19 (1.66 to 4.73)	4.45 (2.85 to 6.06)	−1.26 (−3.34 to 0.82)
Day 3	2.53 (0.88 to 4.19)	2.06 (0.96 to 3.16)	0.47 (−1.35 to 2.29)
Mean difference day 1 and day 3	−1.00 (−2.39 to 0.39)	−2.39 (−3.79 to −0.10)	1.39 (−0.45 to 3.24)
Mean NRS movement (95% CI)			
Day 1	5.61 (3.73 to 7.49)	6.58 (5.31 to 7.84)	−0.96 (−3.12 to 1.19)
Day 3	4.81 (2.58 to 7.05)	2.33 (1.27 to 3.39)	2.48 (0.29 to 4.68)
Mean difference day 1 and day 3	−1.85 (−3.76 to 0.056)	−4.13 (−5.71 to −2.55)	2.28 (0.013 to 4.55)

*All analyses were performed in the intention-to-treat population. All continuous variables were compared with independent *t* tests and reported as mean differences with 95% CIs.

Table E17. Subgroup analysis of adverse events in patients aged 60 years and older.*

	Acetaminophen (N=14)	Diclofenac (N=14)	Combination (N=14)
Phase 1			
Adverse events, No. (%)			
Gastrointestinal	1 (9.1)	0	0
Neurologic	2 (18.2)	1 (7.1)	0
Other	0	1 (7.1)	0
Phase 2			
Adverse events, No. (%)			
Gastrointestinal	1 (9.1)	4 (28.6)	1 (9.1)
Neurologic	2 (18.2)	1 (7.1)	2 (18.2)
Other	1 (9.1)	1 (7.1)	0
Phase 3			
Adverse events			
Gastrointestinal	0	0	0
Neurologic	0	0	0
Other	0	0	0

*All analyses were performed in the intention-to-treat population. All categorical variables were analyzed with the χ^2 test.

Table E18. Additional analgesia required in all study phases, specified.

	Acetaminophen	Diclofenac	Combination
Phase 1			
Acetaminophen	1	—*	—
NSAID	—	1	3
Opioid	—	1	1
Acetaminophen+NSAID	—	—	—
Acetaminophen+opioid	—	—	1
NSAID+opioid	—	—	1
Local infiltration	—	—	1
Unknown†	—	—	1
Total use in phase 1	1	2	8
Phase 2			
Acetaminophen	4	3	1
NSAID	7	1	3
Opioid	—	2	2
Acetaminophen+NSAID	2	1	1
Acetaminophen+opioid	3	1	2
Unknown‡	—	—	1
Total use in phase 2	16	8	10
Phase 3			
Acetaminophen	17	14	20
NSAID	9	12	11
Opioid	4	2	1
Acetaminophen+NSAID	3	4	6
Acetaminophen+opioid	—	2	2
Acetaminophen+NSAID+ opioid	—	1	1
Unknown‡	—	—	1
Total use in phase 3	33	35	42

NSAID, Nonsteroidal anti-inflammatory drug.
*Dashes indicate that there were no patients in this category.
†One patient discontinued study medication after the first phase and received unspecified over-the-counter analgesics.
‡One patient discontinued study medication and continued with unspecified analgesics prescribed by another physician.