CME Ibuprofen Plus Acetaminophen Versus Ibuprofen Alone for Acute Low Back Pain: An Emergency Department–based Randomized Study

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ABSTRACT

Objectives: Patients with low back pain (LBP) are often treated with nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are modestly effective for LBP, but many patients with LBP continue to suffer despite treatment with these medications. We compared pain and functional outcomes 1 week after emergency department (ED) discharge among patients randomized to a 1-week course of ibuprofen plus acetaminophen versus ibuprofen plus placebo.

Methods: This was a randomized, double-blind study conducted in two urban EDs. Patients presenting with acute, nontraumatic, nonradicular LBP of no more than 2 weeks' duration were eligible for enrollment immediately prior to discharge from an ED if they had a score > 5 on the Roland Morris Disability Questionnaire (RMDQ), a 24-item validated instrument, indicating more than minimal functional impairment. All patients were given a standardized 10-minute LBP educational session prior to discharge. The primary outcome was improvement on the RMDQ between ED discharge and 1 week later. One secondary outcome was pain intensity, as measured on a 4-point descriptive scale (severe, moderate, mild, none) at 1 week.

Results: Enrollment began in October 2018. A total of 120 patients met selection criteria and were randomized. Baseline demographic characteristics were comparable between the two groups. By 1 week after the ED visit, patients randomized to ibuprofen plus placebo reported a mean (±SD) improvement in the RMDQ of 11.9 (±9.7), while those randomized to ibuprofen plus acetaminophen reported a mean (±SD) improvement of 11.1 (±10.7). The 95% CI for the between-group difference of 0.8 was −3.0 to 4.7. At 1 week, moderate or severe pain was reported by 15 of 53 (28%) patients in the ibuprofen plus placebo group and 16 of 57 (28%) patients in the ibuprofen plus acetaminophen group (95% CI for between-group difference of 0% = −17% to 17%).

Conclusion: Among ED patients with acute, nontraumatic, nonradicular LBP, adding acetaminophen to ibuprofen does not improve outcomes within 1 week.

Low back pain (LBP) is responsible for 2.4% of visits to U.S. emergency departments (EDs) resulting in 2.7 million visits annually.[1] Pain outcomes for these patients are generally poor.[2] One week after an ED visit in an unselected LBP population, 70% of patients report persistent back pain–related functional

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impairment and 69% report continued analgesic use.[2] Three months later, 48% report functional impairment and 46% report persistent analgesic use. Among the subset of ED patients who present with acute, new-onset LBP, outcomes are generally better—most will recover, although approximately 20% of this group report moderate or severe LBP 3 months later and 30% report persistent LBP-related functional impairment despite treatment with evidence-based therapy.[3]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line medication therapy for patients with acute LBP.[4] It is not yet clear if combination therapy with more than one medication can improve LBP outcomes. For a general population of patients with acute, nonradicular LBP, combining NSAIDs with oxycodone,[3] diazepam,[5] or skeletal muscle relaxants[6,7] does not improve 1-week outcome more than treatment with NSAIDs alone. Acetaminophen is often used for acute LBP, although it is unlikely to be effective when used as monotherapy.[8] Whether or not combining an NSAID with acetaminophen can improve patient outcomes is unknown. Therefore, we conducted a randomized, placebo-controlled study among patients with acute, nonradicular LBP. We hypothesized that the combination of ibuprofen plus acetaminophen would result in better outcomes than ibuprofen plus placebo 1 week after the ED visit, as determined by improvement in the Roland Morris Disability Questionnaire (RMDQ) score.

METHODS

Overview

This was a randomized, double-blind, comparative effectiveness study conducted in two EDs of an urban health care system, in which patients were enrolled during an ED visit for musculoskeletal LBP and followed by telephone 48 hours and 7 days later. Every patient received standard-of-care therapy, consisting of ibuprofen and a LBP educational session. Additionally, patients were randomized to acetaminophen or placebo. This study was reviewed and approved by our institutional review board. It was registered at ClinicalTrials.gov (NCT03554018).

Subject Selection

We conducted this study in the two EDs of an urban teaching medical center in the Bronx, New York, with over 160,000 adult visits annually. Salaried, trained, fluently bilingual (English and Spanish) research associates staffed the ED 24 hours per day, 7 days per week during the accrual period. Our goal was to include a broad representation of patients with acute musculoskeletal back pain who were likely to respond to the investigational medications. We included adults aged 21 to 69 years who presented to the ED primarily for management of LBP, defined as pain originating between the lower border of the scapulae and the upper gluteal folds. The primary clinical diagnosis, at the conclusion of the ED visit, needed to be consistent with acute nontraumatic, nonradicular, musculoskeletal LBP. We only included patients who were to be discharged home and those who had functionally impairing back pain, which we defined as a score of >5 on the RMDQ. The RMDQ is a 24-item questionnaire commonly used to measure LBP and related functional impairment on which 0 represents no impairment and 24 represents maximum impairment (Data Supplement S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13898/full). Patients could only be enrolled once.

Patients were excluded from participation for a nonmusculoskeletal etiology of low back, such as urinary tract infection or influenza-like illness; radicular pain, defined as pain radiating below the gluteal folds in a dermatomal distribution; pain duration > 2 weeks (336 hours); or a baseline LBP frequency of once per month or more frequently. Patients with substantial, direct trauma to the back within the previous month were excluded as were those who were unavailable for follow-up, those who were pregnant or breastfeeding, patients with a chronic pain syndrome defined as use of any analgesic medication on a daily or near-daily basis, and those who were allergic to or intolerant of the investigational medications.

Intervention

The pharmacist performed randomization in blocks of 4 based on a sequence generated at http://randomization.com. Patients were randomized in a 1:1 manner to one of the following two interventions:

1. The acetaminophen arm: 600 mg of ibuprofen plus 500 to 1000 mg of acetaminophen, orally, every 6 hours; or
2. The placebo arm: 600 mg of ibuprofen plus placebo, orally, every 6 hours.

In an effort to maximize effectiveness while minimizing side effects, patients were instructed to take

one of the ibuprofens and one or two of the acetaminophen/placebos every 6 hours. If one capsule of the investigational medication afforded sufficient relief, then there was no need for the patient to take the second. However, if the patient had not experienced sufficient relief within 30 minutes of taking one capsule, he or she was instructed to take the second. All study patients were given a 7-day supply of the medications/placebo.

Ibuprofen was not masked. Acetaminophen and placebo were masked by placing tablets into identical capsules, which were packed with scant amounts of lactose and sealed. This masking took place in a secure location inaccessible to ED personnel. Patients were presented with two bottles of medication. The bottle containing the ibuprofen was labeled in a typical manner. The second bottle, containing acetaminophen or placebo was labeled as investigational medication.

Prior to discharge, research personnel delivered verbally to each participant a 10-minute educational intervention, based on the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) 5-page "What is back pain?" information sheet from the National Library of Medicine's "Fun Facts: An Easy-to-Read Series of Publications for the Public" (available at https://www.niams.nih.gov/health-topics/back-pain). Each participant was informed that carefully chosen exercises and stretches may help pain and prevent future occurrences and that hot or cold packs, physical therapy, massage therapy, and acupuncture help some patients. We did not encourage participants to perform any one specific type of exercise in particular.

Measures

The primary outcome for this study was improvement on the RMDQ between ED discharge and the 7-day telephone follow-up. A 5-point improvement on this scale is generally considered a clinically significant improvement.[9] The RMDQ has good content and construct validity but has not been validated for use specifically in ED LBP patients.[9] Secondary outcomes 1 week and 48 hours after ED discharge were as follows: 1) participants' worst LBP during the previous 24 hours, using a four-item ordinal scale (severe, moderate, mild, or none); 2) the frequency of LBP during the previous 24 hours using a five-item scale (not at all, rarely, sometimes, usually, always); 3) the frequency

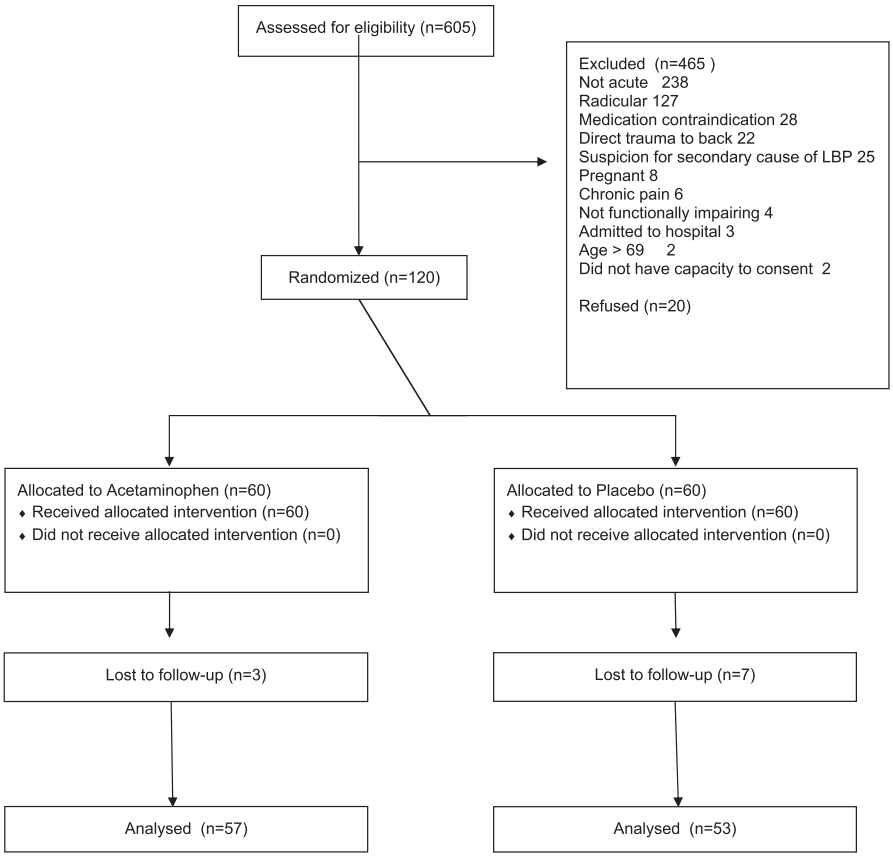

Figure 1 CONSORT flow diagram.

of any analgesic or LBP medication use during the previous 24 hours; 4) satisfaction with treatment, as measured by response to the question, "The next time you have back pain, do you want to take the same medications you've been taking this past week?"; 5) the day post–ED discharge the participant was able to return to usual activities; and 6) the frequency of visits to any health care provider. Adverse events were ascertained by asking patients to report any symptoms attributable to the medications. Outcome assessors were blinded to treatment arm.

Data Analysis

The primary analysis was intention to treat. All eligible participants with available data were analyzed based on group assignment, regardless of frequency of medication use. The primary outcome was a comparison of the change in RMDQ between baseline and 1 week. These results are reported as means with standard deviations (SDs) and difference between means with 95% confidence intervals (CIs). Dichotomous secondary outcomes are reported as proportions with 95% CI and difference between proportions with 95% CI. We considered differences to be statistically significant if the 95% CI did not cross zero.

Sample Size Calculation

We based assumptions on previous work. The mean improvement in RMDQ among those who receives NSAIDs alone was 10.2. The SD was 8.9. A widely accepted minimum clinically important improvement of 5 points on the RMDQ[10] required those randomized to acetaminophen to demonstrate a mean improvement of 15.2 on the RMDQ. Using a standard alpha of 0.05 and a beta of 0.20, we determined the need for 50 subjects in each arm. To account for protocol violations and lost-to-follow-up, we intended to enroll a total of 120 patients.

RESULTS

Enrollment commenced in October 2018 and concluded 8 months later. Altogether, 605 patients were screened for eligibility and 120 were randomized (Figure 1). The median baseline RMDQ score among all participants was 18.5, indicating substantial LBP-related functional impairment. We report other baseline characteristics in Table 1.

By 1 week after the ED visit, patients randomized to ibuprofen plus placebo reported a mean (±SD) improvement in the RMDQ of 11.9 (±9.7), while those randomized to ibuprofen plus acetaminophen reported a mean (±SD) improvement of 11.1 (±10.7). The 95% CI for the between-group difference of 0.8 was −3.0 to 4.7. At the 1-week follow-up, slightly more than 25% of both study groups reported moderate or severe pain (Table 2). The median RMDQ score in the acetaminophen group was 2 (interquartile range [IQR] = 0 to 13) and in the placebo group was 2 as well (IQR = 0 to 17). We report other 1-week outcomes in Table 2. Most patients did not follow up with another health care provider during the week after ED discharge.

We ascertained outcomes at 48 hours as well. At this time point, nearly half of the participants reported moderate or severe pain (Table 3), without substantial

Table 1
Baseline Characteristics

Variable	Ibuprofen + Acetaminophen (*n* = 60)	Ibuprofen + Placebo (*n* = 60)
Age (years)	41 (±12)	41 (±13)
Sex		
Men	31 (52)	32 (53)
Women	29 (48)	28 (47)
Work status		
Unemployed	5 (8)	3 (5)
<30 hours/week	7 (12)	10 (17)
≥30 hours/week	48 (80)	47 (78)
RMDQ at time of ED visit	18 (14–23)	19 (16–23)
Duration of LBP prior to presentation to ED (hours)	48 (24–96)	48 (12–96)
Previous episodes of LBP		
Never before	9 (15)	11 (18)
Few times before	30 (50)	39 (65)
At least once/ year	21 (35)	10 (17)
Start Back Tool		
Low risk	44 (73)	44 (73)
Medium risk	6 (10)	6 (10)
High risk	10 (17)	10 (17)

Values are reported as mean (±SD), *n* (%), or median (IQR). The RMDQ is a 24-item instrument measuring LBP-related functional impairment. On this instrument, 0 represents no LBP-related functional impairment and 24 represents maximum functional impairment. The Start Back Tool is a nine-item low back prediction instrument that includes questions about upper spine and leg pain, low back–related functional impairment, depression, and catastrophizing at some time during the preceding 2 weeks (https://www.keele.ac.uk/sbst/startbacktool). In the outpatient setting, it is associated with long-term functional outcomes and reduces LBP-related health care costs by directing care toward those patients who most need it.[18]
IQR = interquartile range; LBP = low back pain; RMDQ = Roland Morris Disability Questionnaire.

Table 2
One-week Outcomes

Outcome Variable	Ibuprofen + Acetaminophen (n = 60)	Ibuprofen + Placebo (n = 60)	Difference Between Acetaminophen and Placebo, % (95% CI)
Worst LBP during previous 24 hours			
Mild/none	41 (72%)	38 (72%)	0 (−17% to 17%)
Moderate/severe	16 (28%)	15 (28%)	
Missing	3	7	
Frequency of LBP during previous 24 hours			
Never/rarely	34 (60%)	32 (60%)	1%* (−18% to 19%)†
Sometimes	11 (19%)	14 (26%)	
Frequently/always	12 (21%)	7 (13%)	
Missing	3	7	
Use of medication for LBP previous 24 hours			
No meds	21 (37%)	20 (38%)	2%* (−17% to 20%)
Took meds	36 (63%)	32 (62%)	
Missing	3	8	
Patient desires same medications during subsequent episode of LBP‡			
Yes	45 (80%)	40 (75%)	5% (−11% to 20%)§
No	7 (13%)	6 (11%)	
Not sure	4 (7%)	7 (13%)	
Missing	4	7	
Number of days until able to return to usual activities, median (IQR)	2 (1 to 5)	3 (2 to 7)	0.6 (−0.5 to 1.7)‖
No subsequent visit to any health care provider	50 (88%)	49 (94%)	7%* (−4% to 17%)
Subsequent ED visit	1	1	
Primary care	4	1	
Physical therapy	1	1	
Pain management	2	0	

IQR = interquartile range; LBP = low back pain.
*Rounded.
†Never/rarely versus sometimes/frequently/always.
‡Participants were asked: "The next time you have back pain, do you want to take the same medications you've been taking this past week?"
§Yes versus no/not sure.
‖95% CI calculated for mean difference.

differences between the groups. The median RMDQ score in the acetaminophen group was 10 (IQR = 0 to 20) and in the placebo group was 12 (IQR = 0 to 18).

The study medications were generally well tolerated. At the 48-hour follow-up, three of 59 (5%) acetaminophen patients and four of 58 (7%) placebo patients reported experiencing new symptoms that they attributed to the study medications. At the 7-day follow-up, five of 56 (9%) acetaminophen patients and two of 53 (4%) placebo patients reported new symptoms, which they attributed to the medication. In the acetaminophen group, these were: abdominal pain or diarrhea (×3), drowsiness (×2), and dizziness (×2). In the placebo group, these were blurry vision, diarrhea, dizziness, nausea, and drowsiness.

DISCUSSION

In this randomized, double-blind, placebo-controlled study, adding acetaminophen to ibuprofen did not improve 48-hour or 7-day outcomes among patients with acute, nonradicular LBP presenting to the ED. One week after ED discharge, many patients with LBP improved substantially, although about one-quarter of the sample continued to report moderate or severe pain or low back–related functional impairment.

As monotherapy, acetaminophen appears to be ineffective for patients with acute LBP.[8] With regard to combination therapy, we have shown that when combined with an NSAID, acetaminophen has no additive benefit. In another study of acute LBP, a 3-day course of 400 mg of ibuprofen TID was compared with 200

Table 3
The 48-hour Outcomes

Outcome Variable	Ibuprofen + Acetaminophen (n = 59)	Ibuprofen + Placebo (n = 58)	Difference Between Acetaminophen and Placebo, % (95%CI)
Improvement in RMDQ from baseline	7.8 (9.5)	7.8 (9.6)	0.1* (−3.4 to 3.5)
Worst LBP previous 24 hours			
Mild/none	32 (54%)	33 (57%)	3% (−15% to 21%)
Moderate/severe	27 (46%)	25 (43%)	
Frequency of LBP during previous 24 hours			
Never/rarely	19 (32%)	20 (34%)	2% (−15% to 19%)†
Sometimes	20 (34%)	15 (26%)	
Frequently/always	20 (34%)	23 (40%)	
Use of medication for LBP within 24 hours			
No meds	9 (15%)	13 (22%)	7% (−7% to 21%)
Took meds	50 (85%)	45 (78%)	

The RMDQ is a 24-item instrument measuring LBP related functional impairment. On this instrument, 0 represents no LBP-related functional impairment and 24 represents maximum functional impairment.
LBP = low back pain; RMDQ = Roland Morris Disability Questionnaire.
*Rounded.
†Never/rarely versus sometime/frequently/always.

mg of ibuprofen plus 325 mg of acetaminophen TID.[11] By the end of the study period, 25 of 40 (63%) patients in the ibuprofen arm required rescue medication or reported pain worse than mild versus 19 of 40 (48%) patients in the combination arm (95% CI for between-group difference of 15% = −7% to 37%). In ED-based trials of the combination of NSAID plus acetaminophen versus NSAID alone for musculoskeletal pain, the combination has generally not proven superior. Among 327 patients with acute traumatic musculoskeletal pain, the combination of 50 mg of diclofenac plus 1,000 mg of acetaminophen was no more efficacious than diclofenac alone at rest and with movement. In both groups, pain scores decreased only modestly 90 minutes after medication ingestion and improved in more than 85% of patients after 3 days.[12] In another ED-based study, the combination of 800 mg of ibuprofen plus 1,000 mg of acetaminophen was no more efficacious than ibuprofen alone among 60 patients with acute musculoskeletal pain. In both groups, the pain decreased by about one-third 1 hour later.[13] In a study of 25 mg of indomethacin, 25 mg of diclofenac, or 25 mg of diclofenac plus 1 gram of paracetamol among 229 patients with isolated limb injury, there were no important between-group differences within 2 hours or during the subsequent days.[14]

In general, the utility of medications for patients with acute LBP has been underwhelming. NSAIDs are efficacious, though only modestly, and are frequently accompanied by adverse medication effects.[15] Adding oxycodone,[3] diazepam,[5] or skeletal muscle relaxants[6,7] to NSAIDs does not result in improved outcomes. Generally, with the passage of time, most patients who present to an ED with acute, nonradicular LBP improve. For the 25% or so who do not improve, it is unclear what medication, if any, to offer. It is also unclear if rapid access to physical therapy or complementary therapies will offer benefit to patients who are taking prescription NSAIDs.[16]

As has been seen in previous work, a majority of patients with acute, nonradicular LBP demonstrate substantial improvement after 1 week, but nearly one-quarter continue to report moderate or severe pain and functional impairment.[17] Unfortunately, it has proven difficult to predict during the baseline ED visit which patients are most likely to experience poor back pain–related outcomes.[17] Clinicians should prepare all patients for the possibility that their pain and functional impairment may linger for at least 1 week and in many cases longer.[17]

LIMITATIONS

There were severe limitations of our study design. First, this study was conducted in two urban EDs serving a socioeconomically depressed population. Because back pain outcomes may be associated with socioeconomic variables such as access to treatment, our results can most appropriately be generalized to EDs

that serve similar patient populations. Second, while we provided all patients with LBP education, which indicated that stretching and physical therapy may be of use, we did not provide patients with a standard regimen of physical therapy. It is not clear whether the combination of medication plus physical therapy may have resulted in improved outcomes.

CONCLUSION

In conclusion, among ED patients with acute, nontraumatic, nonradicular low back pain, adding acetaminophen to ibuprofen does not improve outcomes within 1 week.

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Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13898/full

Data Supplement S1. The Roland Morris Disability Questionnaire.