



Comparison of Oral Ibuprofen at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial

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Study objective: Nonsteroidal anti-inflammatory drugs (NSAIDs) are used extensively for the management of acute pain, with ibuprofen being one of the most frequently used oral analgesics in the emergency department (ED). We compare the analgesic efficacy of oral ibuprofen at 3 different doses for adult ED patients with acute pain.

Methods: This was a randomized, double-blind trial comparing analgesic efficacy of 3 doses of oral ibuprofen (400, 600, and 800 mg) in adult ED patients with acute painful conditions. Primary outcome included difference in pain scores between the 3 groups at 60 minutes.

Results: We enrolled 225 subjects (75 per group). The difference in mean pain scores at 60 minutes between the 400- and 600-mg groups was -0.14 (95% confidence interval [CI] -0.67 to 0.39); between the 400- and 800-mg groups, 0.14 (95% CI -0.65 to 0.37); and between the 600- and 800-mg groups, 0.00 (95% CI -0.47 to 0.47). Reductions in pain scores from baseline to 60 minutes were similar for all subjects in each of the 3 groups. No adverse events occurred in any group.

Conclusion: Oral ibuprofen administered at doses of 400, 600, and 800 mg has similar analgesic efficacy for short-term pain relief in adult patients presenting to the ED with acute pain. [*Ann Emerg Med.* 2019;74:530-537.]

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INTRODUCTION

Background

Ibuprofen (eg, Advil, Motrin) is one of the most commonly used oral analgesics in the emergency department (ED) for the treatment of mild to moderate pain as a single analgesic or in combination with acetaminophen, or severe pain in combination with opioid analgesics.¹ It is a nonselective, nonsteroidal anti-inflammatory drug (NSAID) that primarily inhibits (reversibly) the activity of both cyclooxygenase-1 (constitutive) and cyclooxygenase-2 (inducible) enzymes and blocks the synthesis of prostaglandins and thromboxanes.² Ibuprofen possesses analgesic, antipyretic, and anti-inflammatory properties and is available in oral, rectal, intravenous, and topical forms. It has been widely used in the ED for treatment of a variety of acute painful conditions such as musculoskeletal pain,

dental pain, tension headache, and dysmenorrhea.¹ Ibuprofen has a half-life of 2 to 2.5 hours and is extensively metabolized in the liver and eliminated through the kidneys.² It has multiple drug-drug interactions, many of which arise from the reduction in glomerular filtration induced by blockade of cyclooxygenase or by competitive displacement of the second drug from protein-binding sites.³ Coadministration of ibuprofen with aspirin results in antagonism of the irreversible platelet inhibition induced by aspirin and loss of cardioprotective function; combination of ibuprofen with warfarin leads to worsening of gastrointestinal hemorrhage; with steroids, it leads to peptic ulcer disease; with diuretics and angiotensin-converting enzyme inhibitors, it elevates systolic blood pressure and worsens renal functions; and it increases toxicity of lithium.³⁻⁵

Editor's Capsule Summary*What is already known on this topic*

Many advocate ibuprofen doses greater than 400 mg orally, assuming a greater effect.

What question this study addressed

Do ibuprofen doses of 600 or 800 mg improve analgesia relative to 400 mg in emergency department patients with a variety of pain syndromes?

What this study adds to our knowledge

In this adequately powered, randomized, double-blind trial of 225 adults, there were similar decreases in pain scores at 60 minutes with all 3 dosages.

How this is relevant to clinical practice

Ibuprofen doses greater than 400 mg orally do not appear to provide more effective analgesia.

Importance

NSAIDs are commonly prescribed at doses above their analgesic ceiling, which is a dosing threshold beyond which any further increase in a dose will not offer an incremental analgesic advantage and potentially increases the risk of harm.^{2,6,7} The data from dental and oral surgery literature support an analgesic ceiling dose of ibuprofen of 400 mg per dose with 1,200 mg/day.⁸⁻¹⁵

The analgesic ceiling dose of ibuprofen based on these studies is lower than both the dosing regimen recommended in emergency medicine textbooks and the Food and Drug Administration–approved doses: 400 to 800 mg orally every 4 to 6 hours, with a maximum daily dose of 2,400 mg.^{15,16} Furthermore, the rates of the adverse effects of ibuprofen as a single analgesic and NSAIDs as a class are dose and duration dependent.^{17,18} A meta-analysis evaluating gastrointestinal complications of nonselective NSAIDs found that ibuprofen had the lowest odds ratio, 1.9, for development of gastrointestinal bleeding at doses of less than or equal to 1,200 mg/day. However, the odds ratios doubled to 3.9 when ibuprofen was given at doses of greater than or equal to 1,800 mg/day.^{18,19} Similarly, the relative risk of cardiovascular adverse effects nearly doubles (from 1.05 to 1.78) when ibuprofen is used in doses greater than 1,200 mg/day.¹⁸ Last, according to the Oxford League Table, the number needed to treat to achieve at least 50% pain reduction from baseline to 6 hours in patients with a variety of

painful conditions is similar between ibuprofen dosages of 400 and 600 mg.⁷

A single dose of ibuprofen of 400, 600, and even 800 mg lacks severe toxicity and does not result in serious adverse effects. Because of linear kinetic pattern, the higher dosing of ibuprofen results in a longer duration of analgesia.^{20,21} The anti-inflammatory ceiling dose of ibuprofen is much higher than its analgesic ceiling dose, with a dosing range of 2,400 to 3,200 mg/day.^{22,23}

Goals of This Investigation

We hypothesized that 400 mg of oral ibuprofen would provide analgesia comparable to that of a dose of either 600 or 800 mg for patients presenting to the ED with acute pain.

MATERIALS AND METHODS**Study Design and Setting**

We performed a randomized, double-blind, equivalency trial assessing and comparing the analgesic efficacy of 400, 600, and 800 mg of oral ibuprofen for the treatment of acute pain in the ED.

We conducted this study at a 711-bed urban community teaching hospital with an annual ED census of greater than 120,000 visits. Patient screening, enrollment, and data collection were performed by study investigators. The Maimonides Medical Center institutional review board approved the trial. We report findings of this study in accordance with the Consolidated Standards of Reporting Trials Group.²⁴

Selection of Participants

We included adult patients aged 18 years and older who presented to the ED with acute pain and warranted oral ibuprofen as determined by the treating attending physician. We excluded patients with peptic ulcer disease, gastrointestinal hemorrhage, renal or hepatic insufficiency, allergies to NSAIDs, altered mental status, and use of opioids and NSAIDs within 4 hours before arrival to the ED, and also excluded pregnant and breastfeeding patients.

Screening and enrollment of patients commenced between February 2018 and January 2019, Monday through Friday, between 8 AM and 8 PM, when an ED pharmacist was available for blinded medication preparation. Study investigators identified all potentially qualifying participants. Before enrollment, all participants provided written informed consent and Health Insurance Portability and Accountability Act authorization. For non-English speakers, we used a language-appropriate consent form and used noninvestigator, hospital-employed, trained interpreters for the acquisition of informed consent.

Interventions

The ED pharmacist on duty prepared all medications in transparent 20-mL syringes by crushing tablets of ibuprofen and incorporating them into a suspended medium (ORA-Plus; Perrigo, Allegan, MI) and sweetener (ORA-Sweet) that were mixed in a 1:1 ratio. The syringes were made according to a randomization list generated by the research manager by SPSS (version 24.0; IBM Corp, Armonk, NY). Study participants were allocated to 3 groups according to the predetermined randomization list: the first group received a single dose of oral ibuprofen at 400 mg; the second group, at 600 mg; and the third group, at 800 mg.

The research manager and statistician, who were independent of data collection, performed the programming of the randomization list, confirmation of written consent acquisition, and statistical analyses. The ED pharmacists maintained the randomization list, prepared the medication, and delivered it to the nurse caring for the study participant in a blinded manner.

The on-duty pharmacist, research manager, and statistician were the only people with knowledge of the study arm to which the participants were randomized. ED providers, study participants, and the research investigators who were responsible for data collection were blinded to the medication received. The research project team included 3 treating attending physicians (who assisted in screening and supervision of the research team), a research fellow, and 2 research associates. The research fellow and research associates were responsible for patient enrollment and data collection by

recording pain scores on a standard 0-to-10 numeric rating scale, rates of rescue medication administration, and adverse effects at baseline and 60 minutes. All study participants were triaged and had their pain scores documented by a triage nurse, which were used to determine eligibility. Before administration of the study medication, research investigators recorded pain score at baseline with a verbal numeric rating pain scale. The second pain assessment was recorded at 60 minutes (+/- 5 minutes) across all 3 groups according to our protocol and with research associates being present in the ED for the duration of the study.

Research investigators reassessed the enrolled subjects at 60 minutes with respect to their pain scores and the desire for rescue analgesia. For participants who still desired pain medication at 60 minutes, the investigators offered a rescue analgesic according to the treating attending physician preference.

Outcomes Measures

The primary outcome included a difference in mean pain scores between the 3 groups at 60 minutes. Secondary outcomes included a comparison of mean pain score differences in each group from baseline to 60 minutes, rates of adverse events, and the need for rescue analgesia at 60 minutes.

Primary Data Analysis

Research investigators recorded all data on data collection sheets (separate from clinical data), entered them into Microsoft Excel (version 2010; Microsoft, Redmond, WA), and subsequently imported the data into SPSS

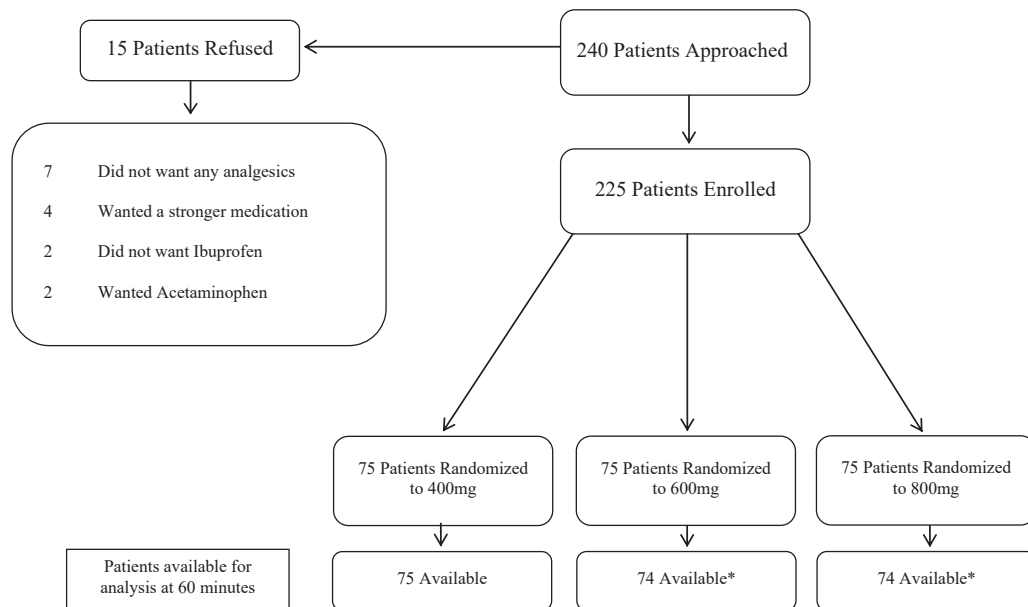


Figure 1. Patient flow through the study. *Subjects were missing data because of either discharge or transfer from the ED.

Table 1. Baseline patient characteristics.

Characteristics	Group (n)		
	400 mg (75)	600 mg (75)	800 mg (75)
Age, mean (median) [SD], y	44.9 (46) [16.2]	45.6 (48) [15.8]	42.6 (39) [15.9]
Male sex, frequency (%)	36 (48.0)	31 (41.9)	47 (63.5)
Pain, mean (median) [SD]	6.48 (6) [1.42]	6.35 (6) [1.39]	6.46 (6) [1.49]
Chief complaint			
Musculoskeletal pain	57 (76.0)*	52 (70.3)	55 (74.3)
Cutaneous pain	9 (12.0)	11 (14.9)	9 (12.2)
Dental pain	2 (2.7)	6 (8.1)	4 (5.4)
Headache	4 (5.3)	4 (5.4)	1 (1.4)
Abdominal pain	2 (2.7)	— [†]	—
Chest pain	—	1 (1.4)	2 (2.7)
Flank pain	—	—	2 (2.7)
Genitourinary pain	1 (1.3)	—	1 (1.4)
Diagnosis			
Musculoskeletal pain	46 (61.3)*	42 (56.8)	41 (55.4)
Cutaneous pain	20 (26.7)	21 (28.4)	24 (32.4)
Dental pain	1 (1.3)	6 (8.1)	4 (5.4)
Headache	4 (5.3)	4 (5.4)	2 (2.7)
Abdominal pain	2 (2.7)	—	—
Chest pain	—	1 (1.4)	1 (1.4)
Flank pain	1 (1.3)	—	1 (1.4)
Genitourinary pain	1 (1.3)	—	1 (1.4)

*Frequency (percentage within group).

[†]Dashes indicate no data.

(version 24.0) and SAS (version 9.4; SAS Institute, Inc., Cary, NC) for statistical analyses. Data were described in terms of mean (SD) or 95% confidence limits for continuous variables, and frequency (percentage) for categorical variables. Data analyses of the pain scores were based on the principle of intention to treat.

For data analysis, we used frequency distributions and multilevel models to assess a differences in pain scores between groups. We proposed that the 400-mg dose of oral ibuprofen would provide similar pain relief by

Table 2. Pain scores for all groups over time.

Time	Group, mg	Mean (SD)	95% CI
Baseline	400	6.48 (1.42)	4–9
	600	6.35 (1.39)	4–8
	800	6.46 (1.49)	4–9
60 min	400	4.36 (1.71)	1–4
	600	4.50 (1.53)	1–3
	800	4.50 (1.39)	1–4

demonstrating change (difference) in pain score comparable to that of 600 and 800 mg between baseline and 60 minutes. In accordance with Bijur²⁵ and Holdgate et al,²⁶ we assumed a minimal clinically significant difference of 1.3 points between the 3 groups at the 60-minute pain assessment and an SD of 3.0. A power analysis determined that a sample of 69 subjects per group provided at least 80% power to detect a minimal clinically significant difference of at least 1.3 points at 60 minutes, with $\alpha=.05$. We enrolled 75 patients per group to account for missing data caused by patient dropout or loss to follow-up (discharged or left the ED before 60 minutes).

RESULTS

We enrolled 225 subjects (75 in each group) in our study, with 223 patients available at 60 minutes for data analysis. The patient flow diagram is illustrated in Figure 1. Baseline characteristics with respect to age, sex, and initial pain score were similar between all 3 groups (Table 1). In addition, all 3 groups were relatively similar with respect to chief complaints and final diagnoses, primarily musculoskeletal (sprain, strain, and fractures) and cutaneous pain (rashes, lacerations, and abscess) (Table 1). Furthermore, 3 patients in the 400-mg group, 2 in 600-mg group, and 4 in the 800-mg group received nonopioid analgesia (tablet, topical preparation, or both) before enrollment in the study (Appendix E1, available online at <http://www.annemergmed.com>). At 60 minutes after medication administration, study participants who were randomized to 400 mg of oral ibuprofen improved from a mean pain numeric rating scale score at baseline of 6.48 to a mean score of 4.36 (difference 2.12; 95% confidence interval [CI] 1 to 4), the 600-mg group improved from 6.35 to 4.50 (difference 1.85; 95% CI 1 to 3), and the 800-mg group improved from 6.46 to 4.50 (difference 1.95; 95% CI 1 to 4) (Table 2). Reductions in pain scores from baseline to 60 minutes were similar for each group. We observed no clinically meaningful differences in the mean numeric rating scale pain scores between the 3 dose groups at 60 minutes. The difference in mean pain scores at 60 minutes between

Table 3. Difference in mean pain scores between all groups at baseline and 60 minutes.

Time	Comparison, mg	Difference (95% CI)
Baseline	400 to 600	0.13 (–0.33 to 0.59)
	400 to 800	0.02 (–0.45 to 0.50)
	600 to 800	–0.11 (–0.58 to 0.36)
60 min	400 to 600	–0.14 (–0.67 to 0.39)
	400 to 800	–0.14 (–0.65 to 0.37)
	600 to 800	0.00 (–0.47 to 0.47)

the 400- and 600-mg groups was -0.14 (95% CI -0.67 to 0.39); between the 400- and 800-mg groups, -0.14 (95% CI -0.65 to 0.37); and between the 600- and 800-mg groups, 0.00 (95% CI -0.47 to 0.47) (Table 3).

Similarly, we found no clinically meaningful difference in the mean numeric rating scale score between the 3 groups when study participants were split into 2 sets of pain scores (numeric rating scale ≤ 5 and ≥ 6) (Appendix E2, available online at <http://www.annemergmed.com>). The full graphic

depiction of a change in numeric rating scale pain score from baseline to 60 minutes between the 3 groups according to the initial pain score is presented in Appendix E3, available online at <http://www.annemergmed.com>.

Furthermore, at 60 minutes after ibuprofen administration, the pain ratings across the 3 study groups were similar (Figure 2).

With respect to the use of rescue analgesia at 60 minutes, 4 patients in the 400- and 800-mg groups and 1

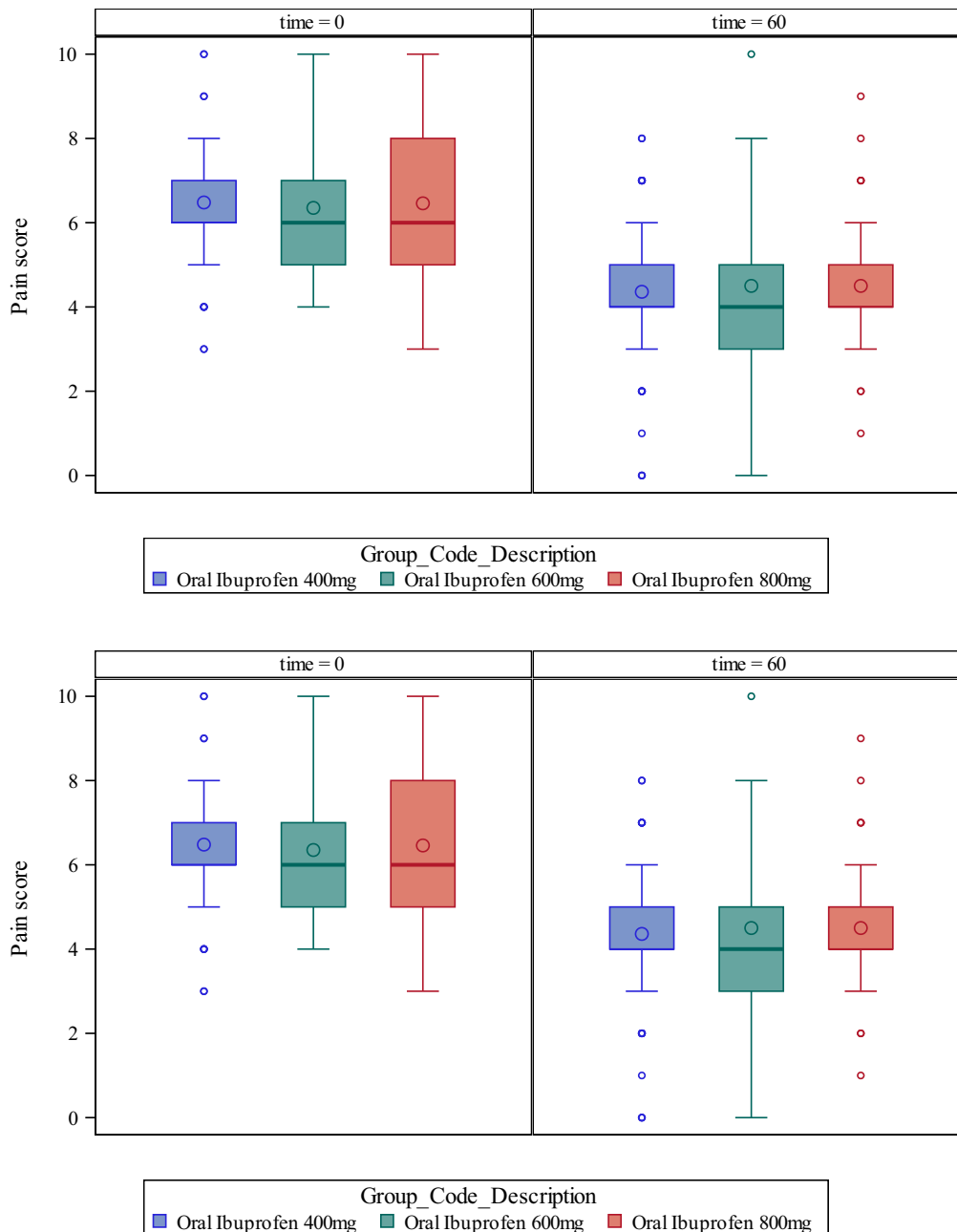


Figure 2. Patient pain scores. Circles inside of box plots represent means. Dots represent outliers. Whiskers are values that are 1.5 interquartile range above the 75th percentile and 1.5 interquartile range below the 25th percentile.

patient in the 600-mg group received either a single agent (tablet or topical preparation) or combination of both (Table 4). There were no clinically concerning adverse effects related to the study medications.

LIMITATIONS

This was a single-center study in which study participants were enrolled as a convenience sample according to the availability of members of both the research and pharmacy teams, which may have led to selection bias caused by underrepresentation of patients who may have presented to the ED late at night. A small sample size of 225 subjects and the short duration (60 minutes) of the study were inadequate to assess the variance in safety of the 3 different study medication doses. The study duration was inadequate to compare the different doses with respect to their adverse effect profiles such as gastrointestinal distress because there was no subject follow-up after 60 minutes post-study drug administration and after discharge. Our study did not assess whether higher doses may have resulted in pain relief beyond 60 minutes. Although longer observational time in the ED (up to 4 to 6 hours) might have resulted in differences in analgesia between the 3 groups, we based our decision to use a 60-minute time frame on our departmental practices of reassessing and frequently discharging patients within 1 hour after they receive oral ibuprofen for their painful conditions.

DISCUSSION

Ibuprofen is widely administered for pain management in a variety of inpatient and outpatient settings worldwide. Because of its analgesic and anti-inflammatory properties and availability in parenteral, enteral, and topical forms, it is frequently used as a first-line analgesic (either alone or in combination with acetaminophen) for alleviating a variety of acute traumatic and nontraumatic and chronic painful conditions in the ED.^{27,28} In the ED setting, ibuprofen is

often prescribed in doses above its analgesic ceiling threshold.^{1,7} When acute pain is managed, however, the analgesic ceiling dose of ibuprofen at 400 mg is sufficient to reduce pain and inflammation.^{2,18} However, the only difference between the analgesic ceiling dose of ibuprofen and the higher doses may be the duration of analgesia because NSAIDs follow the linear kinetic pattern.⁷

We compared the analgesic efficacy of 3 commonly used dosing regimens of oral ibuprofen in the ED for patients presenting with a variety of acute painful conditions. We were able to demonstrate that for short-term pain relief (up to 60 minutes), administration of ibuprofen at 400, 600, and 800 mg resulted in a similar change in pain score. Furthermore, we showed that a mean change in pain score in each group (2 points) at 60 minutes was significantly larger than the cutoff used for statistical analysis of 1.3 points. From a clinical perspective, this change translates into an average of 30% change in intensity of pain from baseline.

Despite our inability to assess and compare the safety of 3 doses of oral ibuprofen, and to compare the duration of analgesia between the 3 groups beyond the duration of the study, we believe that our results support the analgesic efficacy of 400 mg of ibuprofen per dose for managing acute pain in the ED.

To our knowledge, this is the first study conducted in the ED that supports the concept of an analgesic ceiling dose for 400 mg of ibuprofen. Because oral ibuprofen is the most common analgesic used in the ED and at discharge, we hope that the results of our study will make ED clinicians consider a lower dose of ibuprofen for managing pain. Although presumably a single dose of 400, 600, or even 800 mg would not cause serious adverse effects, it is the prescribing practices at discharge that can be problematic. All too often a discharge prescription for ibuprofen from the ED includes a supra-analgesic dosing regimen with longer-than-recommended duration of treatment that might lead to development of potentially serious adverse effects. Thus, by changing a prescribing practice in the ED at least for lower doses of ibuprofen, there is a potential to reduce harm associated with NSAID use.

Last, the results of the study that compared the effects of a placebo analgesic injection versus placebo oral analgesia in ED patients with acute musculoskeletal pain demonstrated similar change in pain score up to 2 hours, thus challenging the belief that parenteral NSAIDs confer a selective placebo effect stemming from patients' beliefs that injections result in better pain relief than tablets.²⁹

We firmly believe that with proper patient and provider education supported by the evidence, the myth of better pain relief with "prescription-only" dosages will be debunked.

Table 4. Number of patients receiving rescue medication at 60 minutes.

Group, mg	Frequency (%)	Type of Medication*
400	4 (5.3)	1, Lidoderm Patch 1, Methocarbamol 1, Lidoderm patch+methocarbamol 1, Acetaminophen+Lidoderm patch+gabapentin
600	1 (1.4)	1, Lidoderm patch+methocarbamol
800	4 (5.4)	2, Lidoderm patch 2, Lidoderm patch+methocarbamol

*Numbers indicate the number of patients receiving medication.

In summary, ibuprofen has similar analgesic efficacy profiles at single oral dosing regimens of 400, 600, and 800 mg for short-term treatment of moderate to severe acute pain in the ED.

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Author contributions: SM was responsible for study concept and design. All authors were responsible for acquisition, analysis, and interpretation of data. AL and PF were responsible for statistical analysis. SM and JD drafted the article. SM and JM were responsible for critical revision of the article for important intellectual content. SM, AL, and JM were responsible for study supervision. SM takes responsibility for the paper as a whole.

All authors attest to meeting the four [ICMJE.org](http://www.icmje.org) authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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