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Original Contribution

Ibuprofen vs acetaminophen vs their combination in the relief of musculoskeletal pain in the ED: a randomized, controlled trial

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ABSTRACT

Non-opioid analgesics are often administered to emergency department (ED) patients with musculoskeletal pain but if inadequate, opioids are given with associated potential adverse events. We tested the hypothesis that the reduction in pain scores with the combination of ibuprofen and acetaminophen would be at least 15 mm greater than with either of the agents alone. We conducted a double-blind, randomized, controlled trial of adult ED patients with acute musculoskeletal pain. Patients were randomized to oral ibuprofen 800 mg, acetaminophen 1 g, or their combination. Pain scores across the groups were compared with repeated measures analysis of variance at 20, 40, and 60 minutes. A sample of 30 patients in each group had 80% power to detect a 15 mm difference in pain scores across the groups ($\alpha = .05$). Thirty patients were randomized to each study group. Mean (SD) age was 36 (15), 54% were male, 73% were white, and 13% were Hispanic. Groups were well balanced in baseline characteristics including initial pain scores (59, 61, and 62 for ibuprofen, acetaminophen, and their combination). Pain decreased over the one hour study period for all groups ($P < .001$) with mean (SD) scores about 20 mm lower on the Visual Analogue Scale than the mean initial score. However, there was no significant difference among treatments ($P = .59$). The need for rescue analgesics was similar across groups. We conclude that the combination of ibuprofen and acetaminophen did not reduce pain scores or the need for rescue analgesics compared with either agent alone in ED patients with pain secondary to acute musculoskeletal injuries.

1. Introduction

Acute musculoskeletal pain is one of the most common reasons for visiting the emergency department (ED) [1]. Each year analgesics are prescribed nearly 100 million times in the ED, most commonly ibuprofen (19 million), acetaminophen hydrocodone (15.5 million), and acetaminophen (13 million) [1]. Due to increasing awareness and concerns for opioid abuse the American College of Emergency Physicians has come out with a clinical policy suggesting that prescription of opioids on discharge should be limited to the lowest possible dose and duration [2]. While both acetaminophen and ibuprofen are relatively effective for mild to moderate pain, the addition of an opioid analgesic is often necessary for more severe pain [3]. Since the combination of analgesics with differing modes of action has the potential to offer enhanced pain relief [4], various combinations of non-steroidal anti-inflammatory drugs and acetaminophen have been studied in order to maximize the effects of non-opioid analgesics.

The current study was designed to determine whether a combination of ibuprofen and acetaminophen was more effective than either agent alone for the management of pain associated with musculoskeletal injuries in the ED. Specifically, we tested the hypothesis that the reduction in pain scores with the combination of ibuprofen and acetaminophen would be at least 15 mm greater than with either of the non-opioid agents alone over the 1-hour study period.

2. Methods

2.1. Study design

A prospective double-blinded randomized controlled clinical study design was used to test the study hypothesis. All patients gave written informed consent and the study was approved by the institutional review board.

2.2. Setting

The study was conducted over the summer of 2010 at a tertiary care, level 1 suburban ED with an annual census of 90,000 and an affiliated residency in emergency medicine.

2.3. Patients

A convenience sample of adult patients who presented to the ED with pain (a verbal numeric pain score greater than 0 on a scale of 0 to

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10 from none to greatest) secondary to an acute musculoskeletal injury of less than 24 hours of duration when one of the study investigators was present were eligible for enrollment. Patients who had taken an opioid containing analgesic were excluded as well as those with a prior history of allergy or contraindications to ibuprofen or acetaminophen.

2.4. Randomization and masking

After collection of baseline demographic and clinical data patients were randomly assigned to one of the three treatment groups using a computerized random numbers table in a 1:1:1 ratio among the three treatments in blocks of 10. Treatment groups included ibuprofen 800 mg, acetaminophen 1 gram, or their combination administered orally as 4 similarly appearing white tablets (either 2 ibuprofen tablets with 2 placebo tablets, 2 acetaminophen tablets with 2 placebo tablets, or 2 ibuprofen tablets and 2 acetaminophen tablets). Treatment assignment was determined by opening the next of consecutively numbered opaque envelopes that contained the study medications in random order. The envelopes were prepared by pharmacy personnel unrelated to the study and kept in a research cabinet in the ED. The doses of ibuprofen and acetaminophen were chosen to be near or at their analgesic ceiling in relation to their respective dose-response curves.

2.5. Measures and outcomes

Baseline demographic (eg, age, gender, race) and clinical data (eg, chief complaint, past medical history, current medications) were collected by a study investigator masked to study assignment using standardized data collection forms. Patients were then asked to mark their pain severity on a validated 100 mm horizontal visual analog scale marked “no pain” and “most severe pain” at the low and high ends, respectively [5]. Pain assessments were repeated at 20, 40 and 60 minutes after administration of the study medication using a similar scale. Patients were masked to prior pain assessments. At the end of the 60-minute study period, patients were asked whether they required any additional rescue analgesics that were prescribed at the discretion of the treating physician. Patients were also asked whether they experienced any adverse events such as epigastric pain, nausea, vomiting, or light-headedness.

2.6. Data analysis

Continuous data, such as pain scores, are summarized as means and standard deviations. Non-normality was not detected using skewness and kurtosis tests. As a result, changes in pain scores over time were compared across groups with repeated measures analysis of variance. Pain scores at each study time point were also comapred across groups with analysis of variance. Binary data (eg, need for rescue analgesics) are summarized as the percentage frequency of occurrence and compared across groups with a χ^2 test.

Assuming a standard deviation of 20 mm on the Visual Analogue Scale, a sample size of 30 patients per group would be adequate to detect a difference of 15 mm between groups (assuming acetaminophen and ibuprofen are similar and their combination will be better) with 80% power at a statistical significance level of $\alpha = .05$ [6]. A prior study has determined that the minimal clinically signifcant difference on the visual analog scale is 13 to 18 mm [7]. Data analysis was performed using SPSS 17.0 (SPSS Inc, Chicago, IL).

3. Results

Ninety-six patients were screened of which 90 met all inclusion and exclusion criteria and signed consent (Fig. 1). The 90 patients were randomized to ibuprofen (30), acetaminophen (30) or their combination (30). Overall mean (SD) age was 36 (15), 49 (54%) were male, 66 (73%) white, and 12 (13%) Hispanic. The most common location of pain was the lower extremity (37 patients, 41%), followed

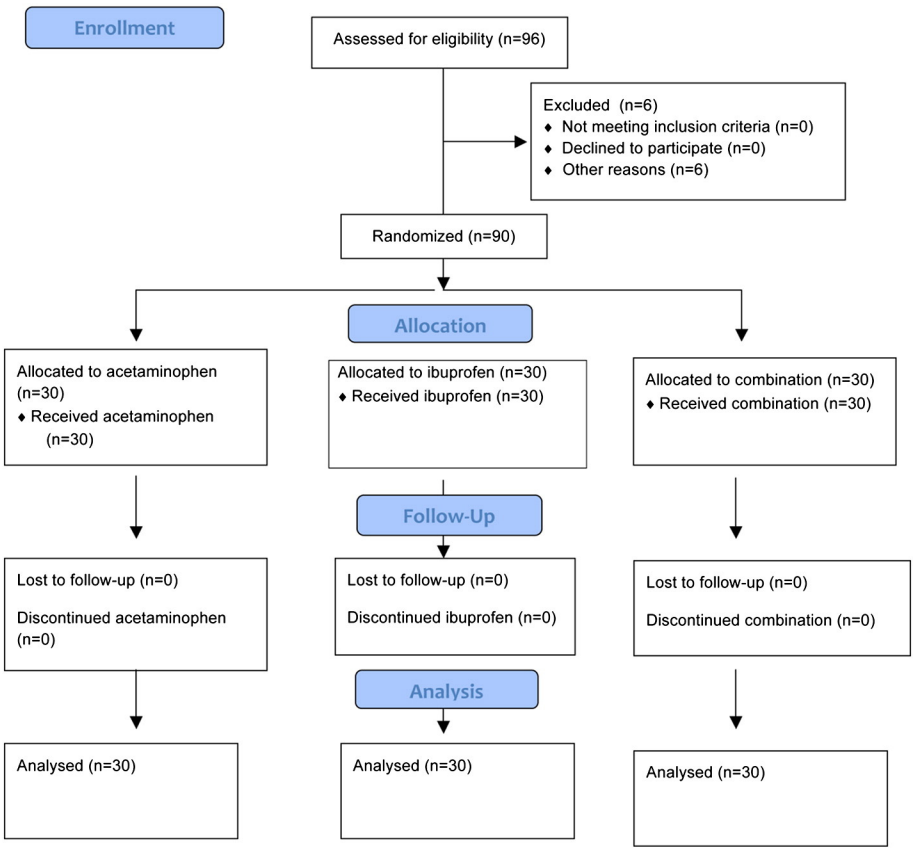

Fig. 1. Patient flow diagram.

Table 1
Baseline characteristics of the patients

	Acetaminophen (n = 30)	Ibuprofen (n = 30)	Combination (n = 30)
Mean (SD) age, years	34 (12)	31 (16)	37 (17)
Percent female	40.0	46.7	50.0
Race (%)			
White	73.3	63.3	83.3
Black	10.0	6.7	0
Hispanic	6.7	16.7	16.7
Asian	3.3	0	0
Other	6.7	13.3	0
Location of pain (%)			
Head/Neck	10.0	10.0	16.7
Upper extremity	30.0	43.3	50.0
Lower extremity	40.0	16.7	16.7
Back	20.0	33.3	16.7
Mechanism of injury (%)			
MVA	3.3	10.0	23.3
Fall	30.0	20.0	13.3
Lifting	6.7	6.7	10.0
No specific trauma	60.0	63.3	53.3
Mean (SD) initial pain score, mm	61 (20)	59 (24)	62 (25)

by the upper extremity (27 patients, 30%). Mechanism of injury included fall (19 patients, 21%), motor vehicle collision (11 patients, 12%), and lifting (7 patients, 8%). For most patients (53 patients, 59%), no definite injury preceded the onset of pain. There were no differences in age, gender, race, location of pain, or mechanism of injury by treatment group (Table 1). Initial pain scores ranged from 8 to 100. Mean (SD) initial pain scores were also not significantly different among treatment groups: 59 (24) mm for ibuprofen, 61 (20) mm for acetaminophen, and 62 (25) mm for the combination therapy.

Pain decreased over the 1-hour study period for all groups ($P < .001$ for overall analysis of time trend) with mean scores about 20 mm lower on the Visual Analogue Scale than the mean initial score after 60 minutes (decrease of 21 for ibuprofen, 17 for acetaminophen, and 21 for the combined group). However, there was no significant difference among treatments (Fig. 2 and Table 2, $P = .59$). At

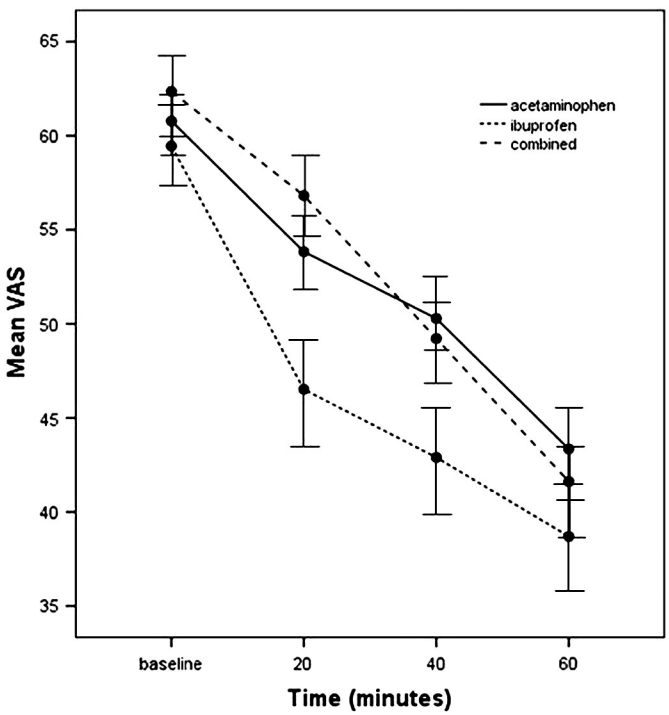

Fig. 2. Changes in pain scores over time. Error bars show standard error of the mean.

Table 2
Mean (95% CI) pain scores over time

Group	Time of pain measurement			
	0 min	20 min	40 min	60 min
Acetaminophen	61 (53-68)	54 (46-62)	50 (42-59)	43 (33-53)
Ibuprofen	59 (50-69	47 (35-58)	43 (32-54)	39 (28-50)
Combined therapy	62 (53-72)	57 (48-66)	49 (40-59)	42 (32-51)
P value	0.93	0.39	0.69	0.81

60 minutes, 11 (36.6%) of the ibuprofen group requested rescue pain medications, compared to 10 (33.%) of the acetaminophen group and 5 (16.6%) of the combined treatment group ($P = .19$). The rate of adverse events was also similar among groups: no acetaminophen patients reported an adverse event, while 1 patient (3%) in the ibuprofen group complained of nausea and 1 patient (3%) in the combination therapy group complained of abdominal pain.

4. Discussion

Our study demonstrates that when compared to either agent alone, the oral combination of ibuprofen 800 mg and acetaminophen 1 gram does not result in greater pain relief in adult ED patients presenting with pain from acute musculoskeletal injuries. This is evidenced by the fact that the reduction in pain scores over the 60-minute study period as well as the need for rescue analgesics at the end of the study period did not differ among the three groups studied.

The results of our study differ from several prior studies suggesting that a combination of acetaminophen and ibuprofen was more effective at relieving pain than either agent alone. For example, a study of 892 patients ages 40 years and older with chronic knee pain found that after 10 days and 13 weeks of treatment the combination was superior to monotherapy suggesting that the two analgesics were additive [8]. Another study of 210 adult patients with single skin cancers of the head and neck undergoing Mohs surgery found that the combination of acetaminophen ibuprofen was more effective at relieving pain than acetaminophen alone or in combination with codeine [9]. A large number of studies in both children and adults with dental pain have also compared the combination of acetaminophen and ibuprofen with either agent alone. Mehlisch et al conducted a randomized double-blind, placebo controlled, parallel group study of 234 patients with post operative dental pain and found that concurrent ibuprofen and acetaminophen provided significantly better analgesic efficacy compared with either agent alone [10]. Other studies comparing a combination of ibuprofen and acetaminophen to either agent alone for dental pain found similar findings [11–13]. In contrast, a study by Wells et al of 71 adult patients presenting for emergency endodontic treatment found no difference in analgesic use or escape medication in patients treated with ibuprofen or an ibuprofen acetaminophen combination [14].

Ibuprofen and acetaminophen are thought to differ in their mode of action. Ibuprofen is a member of the nonsteroidal anti-inflammatory drugs that inhibit the cyclooxygenase enzymes. While the mode of action of acetaminophen is incompletely understood, it is thought to inhibit a subclass of cyclooxygenase enzyme isoforms in the central nervous system. It may also modulate the endogenous cannabinoid system and the descending serotonin pathways [15]. Thus, the combined administration of acetaminophen and ibuprofen has the potential to have an additive or synergistic effect on pain relief. Such a combination has also been shown to be more effective at relieving fever than either agent alone [16,17]. In our study we did not find any such additive or synergistic effect on pain severity in ED patients with acute musculoskeletal injuries. Why our results differ from those from most other reported studies is unclear. Some of the discrepancy may be related to differences in the type of patients, baseline pain scores, indications, study duration, and number of analgesic doses administered. It is also possible

that our study was too small to detect differences less than 15 mm in pain relief across the study groups. However, such small differences are unlikely to be of clinical significance. It is also possible that our study group of patients with acute musculoskeletal injuries was too heterogeneous to allow a more meaningful comparison across groups.

4.1. Limitations

Our study has several notable limitations. As noted above our sample may have been too small or heterogeneous to detect between group differences. While powered to detect a 15 mm difference in pain scores among the groups, our study only had 33% power to detect differences among the groups in need for rescue medication if the observed differences were the true differences. In order to attain 80% power under the same assumptions we would need 94 subjects per group. Furthermore our study was conducted at a single center that may not be representative of other settings. The study patients represent a convenience sample when an investigator was present and thus we cannot exclude a selection bias that may have affected our results. Also, our study was limited to a single dose of analgesics and a limited 60-minute observation period. It is still possible that there might be a difference among treatments when multiple doses are given over extended observation periods. We enrolled patients with pain scores greater than 0 on a verbal numeric score. Our results may have differed had we only enrolled patients with moderate or severe pain. Finally, while subjects and practitioners were masked to study assignment we did not measure the success of masking by actually asking patients whether they could guess their study assignment.

5. Conclusions

In summary our study did not find that an oral combination of acetaminophen ibuprofen was more effective at relieving the pain associated with acute musculoskeletal injuries in adult ED patients than either acetaminophen or ibuprofen alone.

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