Sublingual Buprenorphine in Acute Pain Management: A Double-Blind Randomized Clinical Trial

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Study objective: We compare the efficacy and safety of sublingual buprenorphine versus intravenous morphine sulfate in emergency department adults with acute bone fracture.

Methods: Enrolled patients received buprenorphine 0.4 mg sublingually or morphine 5 mg intravenously in this double-blind, double-dummy, randomized controlled trial. Patients graded their pain with a standard 11-point numeric rating scale before medication administration and 30 and 60 minutes after, and we recorded adverse reactions.

Results: We analyzed 44 and 45 patients in the buprenorphine and morphine groups, respectively. Mean pain scores were similar at 30 minutes (5.0 versus 5.0; difference 0; 95% confidence interval 0.6 to 0.8) and at 60 minutes (2.2 versus 2.2; difference 0; 95% confidence interval 0.3 to 0.3). Adverse effects observed within 30 minutes were nausea (14% versus 12%), dizziness (14% versus 22%), and hypotension (4% versus 18%).

Conclusion: For adults with acute fractures, buprenorphine 0.4 mg sublingually is as effective and safe as morphine 5 mg intravenously. [Ann Emerg Med. 2012;59:276-280.]

Please see page 277 for the Editor’s Capsule Summary of this article.

INTRODUCTION

Background

Pain is a common complaint in the emergency department (ED) and needs both psychological and pharmacologic interventions, including appropriate analgesics with appropriate dosage. Although timely, effective, and safe pain management is a standard of care in all health care organizations, “oligoanalgesia,” or undertreatment of pain, still remains a common problem in many EDs. In one study, for example, the mean waiting time to analgesia was reported to be 1 hour 46 minutes for patients with moderate and severe pain.\textsuperscript{1}

Importance

Appropriate pain management relies on selection of the appropriate analgesic and dosage.\textsuperscript{2-6} In the hectic environment of the ED, especially in crowded EDs in which only 49% of the patients in severe pain receive analgesics, 59% of patients who receive analgesics experience delays in treatment from their triage, and 20% experience delays from time of room placement,\textsuperscript{7} easy-to-use drugs are more appealing.

Morphine sulfate is the prototypic analgesic in acute pain management in the ED. It is often used intravenously with a slow rate and under close patient monitoring because of potential adverse effects such as respiratory depression, central nervous system depression, hypotension, and gastrointestinal problems. Several studies have compared morphine with other drugs such as sufentanil and fentanyl or have compared different doses of morphine.\textsuperscript{9-12} Other effective modalities and drugs, which can be more conveniently tolerated by patients and administered by nurses, may be a good alternative for morphine sulfate.

Buprenorphine is an agonist-antagonist of opioid receptors, with an analgesic potency 25 to 40 times greater than that of morphine sulfate. It has been successfully used for opioid detoxification, cancer-related pain, and postoperative pain control, with a high clinical safety profile and a more prolonged duration of action. Buprenorphine is well absorbed sublingually and is available as 0.4-, 2-, and 8-mg sublingual tablets in many countries.\textsuperscript{13}

Goals of This Investigation

The objective of this double-blind randomized clinical trial is to compare the efficacy and safety of sublingual buprenorphine...
with that of intravenous morphine sulfate in adult ED patients with acute fracture pain.

MATERIALS AND METHODS

Study Design and Setting
This prospective double-dummy, double-blind, placebo-controlled, randomized clinical trial was conducted in an academic tertiary care adult ED (annual census 50,000) and enrolled a convenience sample of patients during 12 months (February 28, 2010, to March 1, 2011). The study was approved by the ethics committee of Imam Hospital and patients provided informed consent. The trial was registered with clinicaltrials.gov (NCT 01298297).

Selection of Participants
We included patients if they were aged 16 years or older, with acute extremity fracture(s) and a pain numeric rating scale score higher than 3 of 10. We excluded patients unable to understand or communicate because of language barrier or other causes; altered consciousness because of alcohol, sedatives, or other causes; concurrent significant trauma or a life-threatening condition; known opioid allergy; history of chronic respiratory, renal, hepatic, or heart failure; administration of analgesics before ED admission; addiction to narcotics reported by either the patient or the family; pregnancy; or systolic blood pressure lower than 90 mm Hg.

Interventions
Subjects were randomly assigned to receive either 0.4 mg sublingual buprenorphine tablets plus 5 mL of sterile water (as placebo) or 5 mg intravenous morphine sulfate plus 1 sublingual placebo. We used computer-generated randomization blocks of 4 and sealed opaque envelopes to ensure allocation concealment. Patients, physicians, nurses, and research associates all remained blinded to group assignment throughout the entire study.

Methods of Measurement
A research assistant asked subjects to grade their pain as follows: “Tell me on a scale of 0 to 10 what is the level of your pain; 0 is no pain and 10 is the worst possible pain.” This 11-point score was assessed at baseline and then 30 and 60 minutes after analgesic administration. The research assistant also recorded adverse effects, including respiratory and central nervous system depression, hypotension, nausea, vomiting, dizziness, and headache.

We monitored patients with continuous pulse oximetry and assessed vital signs at least every 15 minutes. We defined oxygen desaturation as less than 95%, hypotension as a systolic blood pressure decrease of more than 20 mm Hg, and respiratory depression as a rate below 12 breaths/min. Naloxone was immediately available.

Outcome Measures
Our primary study outcome was efficacy, as measured by pain scores 30 and 60 minutes after analgesic administration. Our secondary outcome was adverse events.

Primary Data Analysis
We compared pain scores with the Mann-Whitney test and adverse events with $\chi^2$ or Fisher exact test, with $P<.05$ regarded as significant.

We calculated our sample size according to data of Bounes et al. and assuming $\alpha=.05$ and $\beta=.20$ (2-sided), with a result of 46 patients in each group. We enrolled 110 patients to account for possible cases with missing data or withdrawals from the study.

All analyses were performed with SPSS, version 15 (SPSS, Inc., Chicago, IL) or Stata, version 10 (StataCorp, College Station, TX).

RESULTS
Characteristics of Study Subjects
Study subject flow is shown in Figure 1. Baseline characteristics were similar between groups (Table 1).

Main Results
Pain scores were similar between groups 30 and 60 minutes after medication administration (Table 2; Figure 2).

The frequency of nausea and dizziness was similar between groups (Table 3). We observed more hypotension in the morphine group; however, all such patients responded promptly to the administration of intravenous fluids. We did not observe in either group decreased level of consciousness, respiratory
depression, oxygen desaturation, seizure, or vomiting, and no naloxone was administered.

LIMITATIONS
Our study has several limitations. First, it was conducted only with patients who could participate actively in their pain scoring, and we lost intoxicated patients, patients with other distracting injuries, and patients who had an accompanying trauma or were under investigation for other reasons. Second, for practical reasons, we used fixed doses of medications in all patients, although it may be preferable to use the body weight–adjusted doses. Third, we selected 1 group of patients with pain, ie, only those with pain resulting from bone fracture. Future studies should be conducted to evaluate this medication in other settings such as in patients with abdominal pain, headache, or renal colic; in special populations such as children and elderly patients; and with higher buprenorphine doses such as 2 mg. Excluding patients with chronic respiratory or heart failure may

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**Table 1.** Baseline data in the morphine sulfate and buprenorphine groups.

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Morphine Sulfate, n=55</th>
<th>Buprenorphine, n=55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (standard deviation), y</td>
<td>35 (13)</td>
<td>35 (13)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (82)</td>
<td>44 (80)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (18)</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Mechanism of injury, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor vehicle crash</td>
<td>12 (22)</td>
<td>17 (31)</td>
</tr>
<tr>
<td>Falling</td>
<td>22 (40)</td>
<td>17 (31)</td>
</tr>
<tr>
<td>Auto-pedestrian accident</td>
<td>19 (34)</td>
<td>16 (20)</td>
</tr>
<tr>
<td>Assault</td>
<td>1 (2)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Direct injury</td>
<td>1 (2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Site of fracture, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm</td>
<td>15 (27)</td>
<td>15 (27)</td>
</tr>
<tr>
<td>Wrist</td>
<td>7 (13)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Hand</td>
<td>8 (14)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Leg</td>
<td>4 (7)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Foot</td>
<td>8 (14)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Other sites</td>
<td>13 (24)</td>
<td>15 (27)</td>
</tr>
</tbody>
</table>
mean that one should be careful when generalizing the results to older populations. Last, a noninferiority design would be more suitable for proving (or disproving) that buprenorphine is as effective as morphine sulfate in pain management.

**DISCUSSION**

Our study showed that sublingual buprenorphine can decrease acute fracture pain in ED patients as effectively as intravenous morphine, and with a similar safety profile. Considering that the range in differences (confidence intervals) between the pain scores of the 2 groups at each point does not include values that are clinically important, effective equivalence between the 2 regimens can be concluded. We observed no serious or persistent adverse effects with either drug.

Our findings about buprenorphine are compatible with those in the study conducted by Risbo et al., in which the effect of sublingual buprenorphine in postoperative pain management was evaluated in 50 patients who had elective knee joint surgery. This study showed that buprenorphine was as effective as morphine in pain relief and had a superior safety profile. In another study, 80 patients undergoing abdominal surgery exhibited consistently lower pain scores with buprenorphine sublingually than did those receiving morphine intramuscularly.

Abid et al. compared the efficacy and safety of sublingual buprenorphine with subcutaneous morphine in 50 patients with cesarean section and showed that the pain relief was similar in 2 groups, whereas more morphine patients experienced pruritus. In this study, nurses considered buprenorphine to be more efficient, easier to use, and safer than subcutaneous morphine.

Buprenorphine use has also resulted in greater patient satisfaction than placebo in patients with hip/knee osteoarthritis and chronic low back pain. In a large surveillance study, buprenorphine was administered to 13,179 patients by different physicians in different doses to control moderate and severe cancer-related and noncancer-related pain. About 80% of patients reported their pain relief as good or very good, and less than 5% of patients discontinued their drug because of unsatisfactory results. But buprenorphine is not routinely used in EDs and has not been evaluated for acute pain management in ED patients.

In summary, we found that sublingual buprenorphine is as effective as intravenous morphine for pain relief in adult patients presenting with fractures. Because sublingual dosing

### Table 2. Pain numeric rating scale scores before medication administration and 30 and 60 minutes after.

<table>
<thead>
<tr>
<th>Time</th>
<th>Regimen</th>
<th>Median (95% CI)</th>
<th>Mean</th>
<th>SD</th>
<th>SEM</th>
<th>P Value</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score 0</td>
<td>Bup</td>
<td>8 (7 to 9)</td>
<td>8.0</td>
<td>1.7</td>
<td>0.2</td>
<td>.2</td>
<td>0.3 (−0.3 to 1.0)</td>
</tr>
<tr>
<td></td>
<td>MS</td>
<td>8 (7 to 8)</td>
<td>7.7</td>
<td>1.7</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 30</td>
<td>Bup</td>
<td>5 (4 to 6)</td>
<td>5.0</td>
<td>1.8</td>
<td>0.3</td>
<td>1.0</td>
<td>0.0 (−0.6 to 0.8)</td>
</tr>
<tr>
<td></td>
<td>MS</td>
<td>5 (4 to 6)</td>
<td>5.0</td>
<td>1.7</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 60</td>
<td>Bup</td>
<td>2 (2 to 3)</td>
<td>2.2</td>
<td>0.7</td>
<td>0.1</td>
<td>.9</td>
<td>0.0 (−0.3 to 0.3)</td>
</tr>
<tr>
<td></td>
<td>MS</td>
<td>2 (2 to 3)</td>
<td>2.2</td>
<td>0.7</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, Confidence interval; SD, standard deviation; SEM, standard error of mean; Bup, buprenorphine group; MS, morphine sulfate group.

*Mann-Whitney test.

### Table 3. Frequency of occurrence of adverse events in sublingual buprenorphine and intravenous morphine sulfate groups.

<table>
<thead>
<tr>
<th>Adverse Events, No. (%)</th>
<th>Buprenorphine</th>
<th>Morphine</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 min (n=49)</td>
<td>60 min (n=44)</td>
<td>30 min (n=50)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (14)</td>
<td>0</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (14)</td>
<td>0</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (4)</td>
<td>0</td>
<td>9 (18)</td>
</tr>
</tbody>
</table>

*χ² Test.
†Fisher-exact test.
allows for easier and quicker administration, buprenorphine appears to be a promising alternative to intravenous morphine for acute pain management.

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**Author contributions:** MJ, MF, and SZ conceived the study, designed the trial, and obtained research funding. MJ and MF supervised the conduct of the trial and data collection. MF undertook recruitment of participating patients and managed the data, including quality control. MM-L and SZ provided statistical advice on study design and analyzed the data. MJ and MF drafted the article, and all authors contributed substantially to its revision. MJ takes responsibility for the paper as a whole.

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