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Comparison of Oral Oxycodone and Naproxen in Soft Tissue Injury Pain Control: A Double Blind Randomized Clinical Trial

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Title: Comparison of Oral Oxycodone and Naproxen in Soft Tissue Injury Pain Control: A Double Blind Randomized Clinical Trial

Running title: Acute Pain Control in Emergency Department

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Key Words: Oxycodone, Naproxen, Pain Management
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ABSTRACT

Objectives: This randomized clinical trial compares the efficacy and safety of oral oxycodone (an oral opioid) with naproxen (a non-steroidal anti-inflammatory drug) in acute pain control in patients with soft tissue injury. It also evaluates the need for additional doses of analgesics in the first 24 hours of discharge from emergency department (ED).

Methods: Adult (>18 year old) patient with soft tissue injuries were enrolled in a teaching urban ED. Subjects were randomly allocated to receive a single dose of oral oxycodone (5 mg) or oral naproxen (250 mg). Pain scores and drugs adverse effects were assessed before, 30 minute, and 60 minutes after medication. Outcome: efficacy in pain control (reduction in pain scale more than 2 points) and safety (rate of side effects). The need for additional pain medication after discharge was assessed by follow up phone call 24 hours after discharge.

Results: A total of 150 patients were enrolled. Pain scores were similar in oxycodone vs. naproxen groups before (6.21±0.9 in vs. 6.0 ±1.0), 30 minutes (4.5±1.4 vs 4.4±1.2), and 60 minutes (2.5±1.3 in vs 2.6±1.3) after medication, respectively. Twelve (16.0%) patients in oral oxycodone group and 5 (6.6%) patients in naproxen group needed more analgesics in first 24 hours after ED discharge. Adverse effects were more common in oxycodone group (statistically significant difference). The most common adverse effects in oxycodone group were nausea (13.3%), vomiting (8.0%), dizziness (5.3%), drowsiness 3(4.0%) and pruritis (2.7%).
Conclusion: Oral oxycodone is as effective as naproxen in soft tissue injury pain control but has a less favorable safety profile.

Key Words: Oral Oxycodone, Naproxen, Soft Tissue Injury, Pain control

INTRODUCTION

Soft tissue injuries are common entities in the emergency departments (ED). It is estimated that up to 10% of ED visits are due to soft tissue injuries (1). Pain control is an essential component of management in such cases. In addition to patient’s comfort, adequate pain control may expedite patient’s return to normal physical activity by facilitating early controlled mobilization and exercise.

Healing following soft-tissue injury starts with an inflammatory phase. Some of the elements of this inflammatory process are necessary for healing. Some investigators have suggested that inhibiting this inflammatory phase by anti-inflammatory drugs may impair the healing process. Therefore, it might be more appropriate to administer analgesics without anti-inflammatory properties to avoid impacting the inflammatory responses. (2-5).

Oral oxycodone is an opioid with high oral bioavailability and predictable side effects. It is commonly used in patients whose pain does not respond to non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen alone (6-8).
The objective of this study was to compare the efficacy and safety of oral oxycodone with those of naproxen for treatment of pain in ED patients with soft tissue injury.

METHODS

Study Design
This study was a double-blind non-inferiority randomized clinical trial. We enrolled a convenient sample of ED patients with soft tissue injuries. The study was conducted in a tertiary academic ED with annual census of 30,000. The study was approved by institutional ethics committee and written informed consent was obtained from all patients. The trial was registered with the Iranian Registry of Clinical Trials (http://www.irct.ir, identifier: IRCT201112208104N3).

Study protocol
We included patients >18 years old with acute soft tissue injury and a pain numerical rating scale (NRS) score between 3 and 7. We excluded patients with concurrent multi-trauma or non-injury related pain, known opioid or NSAIDs allergy; narcotics addiction (reported by either the patient or the family), history of chronic respiratory, renal, hepatic, or heart failure; patients who had received analgesics before their ED presentation; pregnant patients and patients who were unable to understand or communicate because of language barrier or any other reason.
We used computer-generated randomization blocks of 4 to randomly assign patients to the two regimen groups. First group received 10 milligram oxycodone (two Oxydone, 5 mg tablet, Raha Pharmaceutical Co, Iran), orally with water. Second group received 250 milligram naproxen (Naproxen-Sobhan, 250 mg tablet, Sobhan Daroo Co, Iran), orally with water. Patients, physicians, nurses, and research assistants remained blinded to group assignment throughout the entire study. All study medications were prepared by a research assistant who was not involved in medication administration or data collection. We used sealed opaque envelopes to ensure allocation concealment.

We assessed pain scores (by NRS) and drugs adverse effects (including nausea, vomiting, dizziness, headache, itching, flushing, hypotension, respiratory or CNS depression) before, 30 and 60 minutes after medication administration. A telephone follow up was made after 24 hours to ask about the additional analgesics use and adverse effects.

Our primary outcome measure was analgesics efficacy defined as a reduction in the mean pain score by more than 2 points at 30 and 60 minutes after medication administration. Our secondary outcome measure was drugs adverse effects.

Data Analysis

Descriptive statistics are presented as mean and standard deviation. Student t-test was used to compare the means of quantitative variables in two independent samples. The rate of adverse effects in each group were compared with Chi-square test. We considered p<0.05 as significant. Our study was a non-inferiority trial on continious variable (pain score). We used the formula
n=2×[(Z1−α+Z1−β)/σ0]×2×S×2 for calculating the sample size. By considering α=0.05, β=0.20, 
p=0.80, σ0=3 and S=6 the sample size was calculated as 49 in each group. All data analyses were 
performed with SPSS, version 16 (SPSS, Inc., Chicago, IL).

RESULTS

Basic characteristics of study patients

Baseline characteristics were similar in both groups (table 1). Study subjects flow is illustrated as 
CONSORT diagram (figure 1).

Main results

Both drugs were effective in pain control and pain scores were similar before, 30 and 60 minutes 
after medication administration in both oral oxycodone and naproxen groups (Figure 2). Twelve 
(16.0%) patients in oral oxycodone group and 5 (6.6%) patients in naproxen group needed more 
analgesics in the first 24 hours after ED discharge. This difference was not statistically 
significant (P=0.07).

From 150 studied patients, 12 (16%) experienced nausea, 6 (8%) experienced vomiting and 
epigastric pain. Dizziness occurred in 4 (5.3%) of patients and drowsiness and pruritis were seen 
in 3 (4%) and 2 (2.7%) of patients, respectively. Adverse effects were more common in oral 
oxycodone group (P=0.0001). In oral oxycodone group, nausea occurred in 10 (13.3%) patients, 
vomiting occurred in 6 (8.0%) patients, dizziness occurred in 4 (5.3%) patients, drowsiness 
occurred in 3 (4.0%) patients and pruritis occurred in 2 (2.7%) patients. In naproxen group only 4
(5.3%) patients experienced nausea and no other side effect was reported. Adverse reactions are summarized in table 2.

**DISCUSSION**

Adequate soft tissue pain control is achieved by different pharmacologic and non-pharmacologic interventions such as using RICE (rest, ice, compression and elevation) (10) while avoiding HARM (heat, alcohol, re-injury and massage) (11). There is a diverse range of analgesics to control soft tissue injury pain. NSAIDs, which are commonly used to control the soft tissue pain inhibit the inflammatory enzymes and decrease platelet aggregation. Some investigators have suggested that this effect might lead to increased bleeding and swelling at the injury site as well as delaying the healing process (12). In addition, NSAIDs have substantial side effects, especially in patients with underlying health problems. Gastrointestinal side effects (the most common side effect, seen in 10-30% of patients), nephrotoxicity, bronchospasm, thrombotic cardiovascular events including stroke and myocardial infarction are potential adverse effects of NSAIDs (13-14). These potential side effects should alert the physicians to prescribe these medications while taking into consideration the patient’s comorbid condition, specific type of injury and severity of pain and for the shortest duration possible (15).

Some studies promote the use of safer medications such as paracetamol. Paracetamol has been proven to be as effective as NSAIDs (and perhaps more effective) while having no demonstrable effect on the healing process (16-18). Oral opioids are potent analgesics for moderate to severe
acute pain control and an important alternative for NSAIDs in patients with soft tissue injury (19-20). The efficacy of hydrocodone/ibuprofen on ibuprofen alone and hydrocodone/acetaminophen on acetaminophen alone has been shown in different studies (21-23). The efficacy of single oral dose of oxycodone in comparison with intramuscular morphine or NSAIDs and its efficacy and safety in comparison with intravenous morphine sulfate have also been shown in other studies (24-26).

Our study showed that both oral oxycodone and naproxen are effective in soft tissue injury pain control. Although, oral oxycodone had a less favorable safety profile, as adverse effects were more common in oral oxycodone group. Our results are similar to study results of Lovell et al who also showed that oral oxycodone has more adverse effects than NSAIDs (valdecoxib) in treating ED patients with acute musculoskeletal pain (27). Another study on 601 patients also showed that 84% of patients who used oral oxycodone to control their acute pain experienced its side effects. The use of oxycodone was associated with decrease patients’ quality of life and level of activity as drowsiness occurred in 56% of patients, dizziness occurred in 43% of patients, nausea occurred in 30% of patients and itching occurred in about 27% of patients (28).

Our study has some limitations. We just prescribed a single fixed dose of drugs for patients with soft tissue injury. Other studies with different doses and enrolling patients with different causes of pain might further assess the safety and efficacy of oral oxycodone and naproxen. The exact effect of NSAIDs on healing processes is not clearly defined yet and more complementary studies may be helpful. We included young people in our study and our results might not be generalized to geriatric population. We have also studied the patients with different causes of
soft tissue injury; more specific studies on subgroups with similar mechanism of injury may be beneficial.

CONCLUSION

Oral oxycodone is as effective as naproxen in soft tissue injury pain control but has a less favorable safety profile.

Conflict of interest disclosure

All authors declare that they have no conflict of interest.

Compliance with Ethical Requirements

This study was approved by institutional ethics committee and written informed consent was obtained from all patients. Trial was registered at irct.ir (identifier: IRCT201112208104N3).

Funding statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
REFERENCES


Randomized patients (n=150)

Allocated to Oral Oxycodone Group (n=75) and Received 10 milligram oxycodone

Lost to follow-up (n=0) Refuse to continue participation (n=0)

75 Analyzed: Excluded from analysis (n=0)

Allocated to Naproxen Group (n=75) and Received 75 milligram naproxen

Lost to follow-up (n=0) Refuse to continue participation (n=0)

75 Analyzed: Excluded from analysis (n=0)

Excluded Patients (n=29):
- Not meeting inclusion criteria (n=21)
- Narcotic addiction (n=20)
- Self-medicated with analgesics before ED arrival (n=3)
- Pregnant (n=1)
- Known GI disorder (n=6)
- Known allergy to naproxen (n=1)
- Refuse to Participate (n=8)

Subjects Assessed for Eligibility (n=179)

Figure 1. CONSORT diagram showing participants flow in study
Figure 2. Pain scores before, 30 and 60 minutes after medication.
Table 1. Baseline data of patients in 2 regimen groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Oxycodone (n=75)</th>
<th>Naproxen (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (±SD), years</td>
<td>34.1 (±10.7)</td>
<td>36.8 (±11.2)</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (56.0)</td>
<td>43 (57.3)</td>
</tr>
<tr>
<td>Female</td>
<td>33 (44.0)</td>
<td>32 (42.7)</td>
</tr>
<tr>
<td>Type of injury, No., (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ligamentous and capsular sprain</td>
<td>32 (42.7)</td>
<td>39 (52.0)</td>
</tr>
<tr>
<td>Muscle strain</td>
<td>15 (20.0)</td>
<td>20 (26.7)</td>
</tr>
<tr>
<td>Contusion and bruising</td>
<td>14 (18.7)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Low back and lumbosacral injury</td>
<td>10 (13.3)</td>
<td>7 (9.3)</td>
</tr>
<tr>
<td>Intervertebral disk problems</td>
<td>4 (5.3)</td>
<td>5 (6.7)</td>
</tr>
<tr>
<td>Pain score at presentation, Mean (±SD)</td>
<td>6.21 (±0.9)</td>
<td>6.0 (±1.0)</td>
</tr>
</tbody>
</table>
Table 2. Rate of adverse drug reactions in two studied groups

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Oxycodone (n=75)</th>
<th>Naproxen (n=75)</th>
<th>Total (n=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>10 (13.3%)</td>
<td>2 (2.7%)</td>
<td>12 (16%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (8.0%)</td>
<td>0 (0.0%)</td>
<td>6 (8.0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (5.3%)</td>
<td>0 (0.0%)</td>
<td>4 (5.3%)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3 (4.0%)</td>
<td>0 (0.0%)</td>
<td>3 (4.0%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (2.7%)</td>
<td>0 (0.0%)</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>2 (2.7%)</td>
<td>4 (5.3%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Total</td>
<td>27 (36%)</td>
<td>6 (8%)</td>
<td>33 (22%)</td>
</tr>
</tbody>
</table>