COMPARISON OF SUBLINGUAL BUPRENORPHINE AND INTERVENOUS MORPHINE IN PAIN RELIEF AND SIDE EFFECTS IN PATIENTS WITH PRIMARY HEADACHE ADMITTED IN GOLESTAN HOSPITAL EMERGENCY DEPARTMENT

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ABSTRACT
Conflict of Interests: No

INTRODUCTION

Primary headache disorders (PHD) are the most common neurological complaints worldwide (global 1-year prevalence is 46 % and global lifetime prevalence is 64 %)¹¹, which make serious disability that interfering with activities of daily living. The most common types of PHD are tension-type headaches (TTH) and migraines (MIG) (10-18% and 31-90%, respectively).²³ A large variety of treatment options are available for PHD, many with FDA approval and many that are used off-label. The main drugs are used for treatment of PHD are including Triptans, dihydroergotamine, anti-emetic dopamine-antagonists, non-steroidal anti-inflammatory drugs, opioids, and valproic acid⁴ that provide pain-relief at 2 hours post-treatment in about 60% of patients and pain freedom at 2 hours post-treatment in about 30% of patients⁵,⁶, which shows that the current pharmacological treatments for PHD are often suboptimal.⁴

Buprenorphine is a μ-agonist and κ-antagonist, which is derived from thebaine.⁷,⁸ Recently, an interest on prescribing sublingual buprenorphine tablets for chronic pain treatment⁹ and
post-operative pain\cite{10} have been increased, particularly for those concerned about the abuse potential of current opioid therapies (such as morphine, oxycodone, fentanyl, and hydromorphone).\cite{9} As to best of our knowledge, there isn't prospective study about prescribing sublingual buprenorphine for treatment of pain relief in patients with PHD, therefore, this study was designed to evaluate and compare clinical efficacy of sublingual buprenorphine and intravenous morphine in patients with PHD.

**METHODS AND MATERIALS**

**Study design and target group**
This prospective double-blind clinical trial was conducted in Emergency Department of Ahvaz Golestan Hospital, south-west of Iran from November 2015 to May 2016. The trial was registered in the Iranian Registry of Clinical Trials under the number IRCT2015030821379N1. Patients who received sublingual buprenorphine therapy (intervention group) were compared to patients who used intravenous morphine therapy (control group). Inclusion criteria was patients aged 18 to 55 years old, patients with PHD according to International Headache Society criteria, negative pregnancy tests and appropriate contraception during the study period. Exclusion criteria was observation of side effects such as gastrointestinal or any other unwanted side effects caused by drugs, history of seizures, patients with cardiovascular disorders, hepatic, renal, and metabolic disorders, patients with fever (T> 38 °C), patients with unstable hemodynamics (BP <90 mmHg), pregnant patients, patients with a history of drug addiction, patients with allergic history to opioids, patients receiving analgesic therapy 6 hours before admission, patients with age <18 years and > 55 years, dissatisfaction to participate in the research project, lack of use the medication in groups for three consecutive days or a week intermittently (no history of proper treatment by a neurologist, etc.). We also excluded patients with uncompleted data. All patients enrolled in this study with an attack of headache with evidence of having PHD, after receiving appropriate treatment and improving the symptoms, were referred to a neurologist for further and proper treatment.

**Participants**
The study flowchart is shown in figure 1. One hundred forty five patients with a diagnosis of PHD, who had been diagnosed by emergency physicians and based on clinical and para-clinical findings according to International Headache Society criteria and inclusion and exclusion criteria were included.
The participants were randomly allocated in two groups using a block randomization procedure with matched subjects in each block based on sex and age. One hundred forty patients completed the study; 70 from intervention group and 70 from control group. The study received ethics approval from the Ethics Committee of Ahvaz University of Medical Sciences (IR.AJUMS.REC.1394.73), and all participants gave written informed consent.

After obtaining informed consent, eligible patients were enrolled. Patients in the intervention group received sublingual buprenorphine 2mg tablet and patients in the control group received intravenous morphine with dose of 0.1mg/kg and sublingual placebo tablet with same color and shape. Then pain score (using numeric rating scale (NRS)), hemodynamic parameters and side effects including nausea, vomiting, itching, drowsiness, and dizziness in the both groups were recorded for each 20 minutes. If the patients did not feel 3 unit reduction in pain severity (based on NRS) up to 40 minutes after prescribing the drugs, fentanyl with dose of 1 μgr/kg was prescribed.

**Data analysis**

Data were analyzed and reported only for patients who completed the trial. Statistical analysis of data was performed using SPSS version 22 software. To compare qualitative variables between groups Chi-square test was performed. The normal distribution of all studied parameters was checked with Kolmogorov-Smirnov test. Student t-test and paired t-test were used for variables which were distributed in a normal way, besides Mann-Whitney and Wilcoxon test were performed for variables that have not normal distribution. The two tailed p-value < 0.05 were considered significant.

**RESULTS**

Demographic features in terms of age (P=0.736), sex (P=0.865) and the type of PHD (P=0.794) in both groups were similar (Table 1). Five patients were dropped out and finally, 140 patients completed the study. Before intervention, studied variables did not show a significant differences between the groups (P>0.05).

Results showed that the mean of pain score at different times in the control group were lower than the intervention group, that in 20th minute in sublingual buprenorphine group was 8.8 and in control group was 7.62 (P<0.001). Moreover, this differences remains significant in 40th minutes. (P<0.001) While pain score did not differ significantly in both groups after 60 minutes (3.94 vs 3.98, P=0.812). Moreover, side effects including nausea, vomiting, itching,
drowsiness, respiratory depression, and dizziness did not different between two groups in totally (P>0.05).

![Study Flowchart](consort_format)

**Table 1:** Studied variables during different periods of time in both buprenorphine and control groups

<table>
<thead>
<tr>
<th>Group Variables</th>
<th>Buprenorphine</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>39.2 ± 6.87</td>
<td>39.58 ± 6.65</td>
<td>0.736</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>38 (54.3 %)</td>
<td>37 (52.9 %)</td>
<td>0.865</td>
</tr>
<tr>
<td>Type of PHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster</td>
<td>2 (2.9 %)</td>
<td>3 (4.3 %)</td>
<td>0.794</td>
</tr>
<tr>
<td>Migraine</td>
<td>46 (65.7 %)</td>
<td>48 (68.6 %)</td>
<td></td>
</tr>
<tr>
<td>Tension</td>
<td>22 (31.4 %)</td>
<td>19 (27.1 %)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before intervention</td>
<td>9.84 ± 0.36</td>
<td>9.92 ± 0.25</td>
<td>0.113</td>
</tr>
<tr>
<td>20 th min</td>
<td>8.8 ± 1.59</td>
<td>7.62 ± 1.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40 th min</td>
<td>7.9 ± 2.11</td>
<td>6.31 ± 2.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60 th min</td>
<td>3.94 ± 1.14</td>
<td>3.98 ± 0.98</td>
<td>0.812</td>
</tr>
<tr>
<td>Response to treatment</td>
<td>16 (22.9 %)</td>
<td>37 (52.9 %)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>---------------------------------------</td>
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<td>--------</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>7 (10 %)</td>
<td>8 (11.4 %)</td>
<td>0.785</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4 (5.7 %)</td>
<td>11 (15.7 %)</td>
<td>0.056</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3 (4.3 %)</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (22.9 %)</td>
<td>14 (20 %)</td>
<td>0.68</td>
</tr>
<tr>
<td>Itching</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

DISCUSSION

According to our results, prescribing intravenous morphine decreased pain score significantly without having serious side effects. However, the sublingual buprenorphine decreased pain score, but it was lower than intravenous morphine. Therefore, we can understand that intravenous morphine is more effective in reduction the pain in PHD patients. There is not a study in this field, therefore we used the articles which used sublingual buprenorphine in other patients such as patients with chronic pain or patients under the surgery.

In the study performed by Soltani et al. showed that sublingual buprenorphine administration before anesthesia induction in closed reduction surgery can lead to better postoperative pain control in comparison to intravenous morphine. Finally they recommended that sublingual is a suitable drug in closed reduction surgery. Payandemehr et al. showed that sublingual buprenorphine (2 mg) is as effective as morphine sulfate (0.1 mg/kg) in acute renal colic pain management. In another study performed by Rosen et al. concluded that sublingual buprenorphine is indeed being used to treat chronic pain; however, the circumstances when this occurs are not entirely clear. Alizadeh et al. confirmed the efficacy of sublingual buprenorphine as a non-invasive, but effective method for management of post-operative pain in opioid dependent patients. These differences in the results of different studies and our study may due to different sample size, different race with different demographic features with different chief complaint) and lack of controlling for risk factors common in both conditions may cause different results. Moreover, we did not focus on specific PHD, and we include all the patients with PHD (migraine, cluster and tension headache). Moreover, different dosage and different compound of sublingual buprenorphine may cause significant differences between our result and the other studies.

As we found, some side effects such as hypotension was more in control group and on the other hand, intravenous morphine is more invasive as compared to sublingual buprenorphine, therefore another prospective study with larger sample size is needed in order to evaluate the therapeutic effects of sublingual buprenorphine. Moreover, buprenorphine is similar in
structure to morphine, but approximately 33 times more potent. Buprenorphine has higher affinity and its effect takes much longer (half-life of 166 minutes). The onset action of buprenorphine is slow, its peak effect may not occur until 3 hours, but its effect duration is prolonged (<10 hours). Therefore, in short periods of time morphine has better effect, indeed we need to evaluate and compare these two drug for longer periods of time.

CONCLUSIONS
The results of this study showed the beneficial effects of intravenous morphine in headache attacks of PHD patients in short periods of time, on the other hand, sublingual buprenorphine decreased the pain for longer periods of time, which could be prescribed as a treatment in addition to standard therapy and significantly lead to better control of headache attacks in the long term. Therefore, sublingual buprenorphine can be used as a supplemental drug along with standard treatment in PHD patients with severe headache attacks admitted to emergency department.

Conflicts of interest
The authors have indicated that they have no conflicts of interests regarding the content of this article.

ACKNOWLEDGMENTS
This study was financially supported by Technology and Research Development Department of Jundishapur Medical Sciences University, Ahvaz, Southwest Iran. We gratefully acknowledge the dedicated efforts of the investigators, the coordinators, the volunteer patients who participated in this study, and the Clinical Research Development Units (CRDU) of Ahvaz Golestan hospital.

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