The effect of haloperidol administration on relieving cluster headache, probable role of dopaminergic pathway; a double blind clinical trial

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Abstract: Background: The present study was carried out with the aim of assessing the effectiveness of 2.5 mg dose of haloperidol compared with its standard 5 mg dose in relieving symptoms of cluster headaches and finding out to what extent the dopaminergic pathway affects the incidence of cluster headaches.

Methods: The present study is a double-blind randomized clinical trial carried out in 3 health centers, Tehran, Iran. Patients diagnosed with cluster headache were treated by intravenous administration of 2.5 and 5 mg of haloperidol. Using a standard visual analog scale, pain severity was recorded before and 30, 60, 90, and 120 minutes after intervention. Treatment success (at least 3 points decrease in pain severity), side effects and recurrence of the headache were evaluated.

Results: Finally, 83 patients with the mean age of 23.6±13.4 years were included in the present study (66.3% male). 42 patients were treated with 2.5 mg dose of haloperidol and 41 were in the 5 mg dose haloperidol treatment group. 40 (95.2%) patients who were treated with 2.5 mg dose of haloperidol experienced a significant decrease in pain (at least 3 points decrease in pain severity) in the initial 30 minutes. During this time, all of the patients (success rate=100%) treated with 5 mg dose of the drug had a significant decrease in pain. The two doses did not have a significant difference regarding treatment success (p=0.42).

Conclusion: Results of the present study showed that both 2.5 and 5 mg doses of haloperidol have similar effectiveness in reducing cluster headaches. The high success rate observed indicates that hyperactivity of dopaminergic pathway plays an important role in onset of cluster headaches.

Keyword: Cluster Headache; Haloperidol; Dopaminergic Pathways


1. Introduction

Although for a long time it was believed that cluster headache is a primary vascular headache that results from contraction and then dilation of vessels in the head, the primary cause of this problem has not been determined. Decrease in brain serotonin levels may bring about these sudden changes in brain vessels, which consequently lead to vasoconstriction (1). Currently, it is believed to be the result of neural changes in brain and release of neuro-inflammatory peptides (1, 2). These inflammatory peptides sensitize neural fibers and caused blood vessel dilution. However, headache usually initiates before dilation of vessels. Therefore, some
researchers have suggested other mechanisms such as stimulation of pain receptors of head, neck and in the skull. These receptors might be stimulated in various diseases such as migraines, meningitis, increased intracranial pressure, and brain hemorrhage (3). Change in brain structure is another mechanism that may play a role in occurrence of cluster headaches. A part of “cortex” is thicker than normal in the brain of those affected with migraine and cluster headaches. These people may be more sensitive to other types of pain (4). In addition, dysfunction of brain “hypothalamus” can lead to cluster headaches. Knowing this, researchers hope to find a solution for this common type of headache. The role of dopamine pathway in cluster headache incidence has been highly considered in recent years (5-7). The evidence of this claim is effectiveness of anti-emetic dopamine antagonists such as metoclopramide, dihydroergotamine, sodium valproate, dexamethasone, and magnesium in severe and refractory headache (8-16). Various clinical trials have shown that administration of butyrophenones including haloperidol and droperidol has high efficiency in treating acute headaches compared to placebo (17-22). However, effectiveness of haloperidol has not been assessed in treatment of cluster headaches. In addition, the normal dose if haloperidol administration is 5 mg, which extends the probability of extrapyramidal effects of this drug such as akathisia and dystonia. One of the suggested solutions is using lower doses of this drug. Therefore, the present study was carried out with the aim of assessing the effectiveness of 2.5 mg dose of haloperidol compared with its standard 5 mg dose in relieving symptoms of cluster headaches and finding out to what extent the dopaminergic pathway affects the incidence of cluster headaches.

2. Method

2.1. Study design

The present study is a double-blind randomized clinical trial carried out in three level 3 health centers, Tehran, Iran, during 2013 and 2014. Protocol of the study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences. Patients participated voluntarily and gave informed consent. This study has been registered on the Iranian registry of clinical trials (IRCT number: IRCT2016091215640N3).

2.2. Patients

In this study, patients diagnosed with cluster headache based on International Headache Society criteria were included (23). Inclusion criteria consisted of cluster headache, presence of headache when administering the drug, absence of systemic diseases, and a pain score higher than 4 cm based on visual analog scale (VAS). Exclusion criteria consisted of not wanting to participate in the study, having migraine or tension headache, the patient visiting with the first headache attack, allergy to haloperidol, pregnancy, renal failure, lactating, and using other analgesics. Panel 1 shows cluster headache diagnosis criteria in this study.

2.3. Intervention

In the present study, patients were divided into 2 random groups treated with either 2.5 mg or 5 mg dose of haloperidol. Drug was administered via intravenous infusion of its solution in 100 ml normal saline during 10 minutes. Randomization was done based on randomized permuted blocks (block size of 4). To ensure blinding, drug preparation, its administration, and patient evaluation were done by different people. Drugs were prepared in anonymous packs by a pharmacologist and given to the researchers. An emergency medicine resident prescribed drugs and another emergency medicine specialist evaluated the pain score of patients. If headache intensity had not decreased during the first half an hour after drug administration, the in-charge physician was allowed to use a rescue dose for the patient. Rescue dose included morphine with 5 mg dose.

2.4. Data gathering

In addition to demographic variables (age, sex, occupation, education, and drug allergies), pain severity of the patients was measured and recorded based on standard 10-cm visual analog scale (VAS) (24). Pain severity was assessed before and 30, 60, 90, and 120 minutes after administration of its solution.

Panel 1: Diagnosis criteria of cluster headache based on International Headache Society standards

A) At least 5 attacks fulfilling criteria B-D
B) Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)
C) Either or both of the following:
1- at least one of the following symptoms or signs, ipsilateral to the headache:
   a) conjunctival injection and/or lacrimation
   b) nasal congestion and/or rhinorrhea
   c) eyelid oedema
   d) forehead and facial sweating
   e) forehead and facial flushing
   f) sensation of fullness in the ear
   g) miosis and/or ptosis
2- a sense of restlessness or agitation
D) Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active
E) Not better accounted for by another ICHD-3 diagnosis.
administration of haloperidol. If the pain was completely relieved after this time, the patient would be discharged based on the in-charge physician’s opinion. To evaluate the side effects of the drug and recurrence of headache, patients were followed for 48 hours. It should be noted that a 3-point decrease in pain severity based on VAS was considered as success in treatment.

2.5. Endpoint
The primary endpoint studied was treatment success or failure. When the patients did not report any decrease in headache, a 5 mg dose of morphine was prescribed and the patient was counted as a case of treatment failure. If the pain did not decrease at least 3 points on the VAS scale during the 2 hours it was also counted as treatment failure. Secondary endpoint was recurrence of the problem, side effects of the drug, and return of the headache in less than 48 hours after discharge.

2.6. Statistical analyses
Sample size calculation was done based on the minimum clinically significant difference, which is 3 cm improvement based on VAS. According to previous studies, treatment success rate in the group treated with 5 mg dose of haloperidol and placebo group was 80% and 15%, respectively. Considering α = 0.05 and β = 0.01, as well as 20% loss to follow-up, the required sample size was estimated to be 39 patients.

Data were analyzed using STATA 11.0 software. Pain severity of patients was reported as mean ± standard deviation (SD) on admission, and 30, 60, 90, and 120 minutes after initiation of treatment. After confirming the normal distribution of the data, t-test was used to compare quantitative demographic characteristics, and chi-squared or Fisher’s exact test were applied for qualitative ones. To evaluate intragroup changes of pain severity based on time, repeated measures ANOVA was used; and to assess the difference between the 2 groups, two-way repeated measures ANOVA and Bonferroni post hoc test was applied. Finally the rate of treatment success (3 points decrease in pain severity) was compared between the groups using non-parametric (Wilcoxon-type) test for trend. P <0.05 was considered as significance level.

3. Result
Over the course of the study, 192 patients were presented with headache. 105 of them were excluded due to the exclusion criteria. 4 patients were excluded during randomization. Finally, 83 patients with the mean age of 23.6±13.4 years were included in the present study (66.3% male) (Figure 1). 42 patients were treated with 2.5 mg dose of haloperidol and 41 were in the 5 mg dose haloperidol treatment group. Demographic data and baseline characteristics of the studied patients did not show a difference between the 2 groups (Table 1).

At the beginning of the study, the severity of pain felt by the patients in 2.5 mg haloperidol and 5 mg haloperidol groups was 9.2±1.3 and 9.4±1.1, respectively (p=0.56). The patients’ pain significantly decreased 30, 60, 90, and 120 minutes after drug administration and reached 3.9±1.3, 2.9±2.3, 1.4±0.3, and 0.7±0.3, respectively in 2.5
These scores were 4.1 ± 1.1, 2.2 ± 1.9, 0.9 ± 0.3, and 0.6 ± 0.3, respectively in 5 mg haloperidol group (df: 4, 112; F = 284.0; p < 0.0001) (Table 2 and Figure 2). However, comparison of the 2 groups in the mentioned times revealed that the 2 doses of haloperidol had similar efficacy in reducing pain (df: 4, 216; F = 2.0; p = 0.12).

40 (95.2%) patients who were treated with 2.5 mg dose of haloperidol experienced a significant decrease in pain (at least 3 points decrease in pain severity) in the initial 30 minutes. During this time, all of the patients treated with 5 mg dose of the drug had a significant decrease in pain. 100% success in reducing pain was seen 90 minutes after treatment initiation in 2.5 mg haloperidol treatment group.

Non-parametric trend showed that there is no significant difference between the 2 doses regarding treatment success (p = 0.42) (Table 2).

It should be noted that 48-hour follow-up of the patients did not reveal any case of recurring headache or adverse effects of the drug. Only 2 (2.4%) reported drowsiness (1 in the 5 mg group and 1 in the 2.5 mg group) (p = 0.99).

4. Discussion

The present study aimed to compare the effectiveness of haloperidol with 2 doses of 2.5 and 5 mg in relieving cluster headaches for the first time. Findings showed that both doses of haloperidol had similar effectiveness in relieving headache. The notable point was the high success rate of haloperidol (100% with 5 mg dose and 95.2% with 2.5 mg dose) in the initial 30 minutes after drug administration. Although subcutaneous sumatriptan and oxygen therapy are the first line of cluster headache treatment (25),
a few existing studies show that treatment with antipsy-
chotic drugs such as chlorpromazine and olanzapine may prevent the incidence of these types of headache (26-28). These studies suggest that inhibition of D2 do-
pamine receptors could be beneficial in treating cluster headache. Yet, the scarcity of these studies has resulted in the antipsychotic drugs being considered only as the second or third line of treatment. Haloperidol is an an-
tagons of dopaminergic receptors. Haloperidol also in-
hibits α-adrenergic and muscarinic receptors to some extent (5-7). This may be the reason that administration of this drug has led to relief of cluster headache in the current study.

However, a study in 2013 showed that cluster headache is accompanied by impaired dopaminergic stimulation. The study revealed that a decrease in sensitivity of dop-
paminergic neurons is seen in the hypothalamus of pa-
tients with cluster headache (29). By measuring serum growth hormone, prolactin and cortisol levels, the study concluded that decreased sensitivity to dopamine might lead to cluster headaches. In contrary, there is a study that have shown the platelet level of dopamine is very high in patients with cluster headache (30).

Until now, no study has been done to evaluate the effect of haloperidol administration in cluster headaches. Yet, some studies have evaluated the effectiveness of this drug in migraine headaches. Effectiveness of this drug in relieving migraine headaches is not surprising since dop-
paminergic pathway of hypothalamus plays an impor-
tant role in this type of headache. In a case series, Fisher showed that haloperidol with a 5 mg dose leads to complete relief from migraine headache within 25 to 65 minutes of its administration (22). Honkaniemi et al. showed that the same dose of haloperidol results in a 79% treatment success rate (21). Monzillo et al. estimated the successful treatment rate of 5 mg haloperidol to be 82% (20). The present study showed that the ef-
effectiveness of 2.5 mg dose of haloperidol is similar to its 5 mg dose for the first time. Therefore, using its 2.5 mg
dose could reduce the side effects of this drug. Among the limitations of this study is its short follow-up period. Although the patients were followed for 48 hours (2 half-lives of haloperidol), some side effects of the drug might show up after this time. In addition, convenience sampling was used for selecting participants, which might lead to selection bias.

5. Conclusion:

Results of the present study showed that both 2.5 and 5 mg doses of haloperidol as dopamine receptor antag-
nist have similar effectiveness in reducing cluster head-
aches. The high success rate observed indicates that hyperactivity of dopaminergic pathway plays an im-
portant role in onset of cluster headaches.

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9. Author contribution

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