ORIGINAL ARTICLE

Metoclopramide versus sumatriptan for treatment of migraine headache: A randomized clinical trial

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Background: There are different options to manage benign headache in the emergency department. The costs, side effects, and efficacies of the drugs used are significantly different. The aim of this study was to compare intravenous (IV) metoclopramide with subcutaneous (SC) sumatriptan in treatment of migraine headache. **Material and Methods:** In a randomized, double-blinded clinical trial study, patients presenting to the university referral emergency department with acute benign headache were allocated into two groups after obtaining their informed consent. Patients received 20 mg of IV metoclopramide or 6 mg of SC sumatriptan. Pain intensity was assessed with 10-cm visual analog scale at baseline and 60 min after treatment. **Results:** One hundred and twenty-four subjects participated. The mean age was 34.9 ± 9 years in metoclopramide group and 26.8 ± 4 years in sumatriptan group ($P < 0.0001$). The baseline pain scores were 6.47 ± 0.84 and 6.12 ± 0.73 in metoclopramide and sumatriptan groups, respectively ($P < 0.0001$). The mean of pain score decreased to 0.66 ± 0.59 cm ($P < 0.0001$) in the metoclopramide group and 1.1 ± 0.70 ($P < 0.0001$) in the sumatriptan group. Comparison of these two groups showed more pain reduction in the metoclopramide group, with a mean difference of 0.55 ± 0.13 between the groups (95% CI: 0.25-0.79 cm) ($P < 0.0001$). **Conclusion:** For treatment of migraine headache, IV metoclopramide may be superior to SC sumatriptan in the emergency department.

Key words: Headache, metoclopramide, migraine, sumatriptan

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INTRODUCTION

Acute headache is a common constellation disease in the general population.[1] It is estimated that 1-2% of emergency visits are due to headache and 90% are due to migraine, tension headache, or combined presentation. Although most of the headaches are benign, their control may cause dissatisfaction for both physician and patient.[2] Additionally, it is estimated that migraine is one of the most prevalent debilitating conditions that impair the sufferer's quality of life.[3,4] Although in outpatient setting there are different ways to abort or prevent many attacks, some patients frequently present to the emergency department (ED) while their headache is troubling and severe. In this group, there is limited evidence comparing the relative efficacy of different treatment options for relieving pain in ED.[1] For mild to moderate headaches without vomiting, various oral agents and different combinations are available. For moderate to severe headaches and those with vomiting, multiple parenteral treatments are used such as dopamine antagonist antiemetics, 5-hydroxy tryptamine 1 (5-HT1) receptor agonists, nonsteroidal anti-inflammatory drugs, and some opioids. The costs, side effects, and efficacies of these drugs have been studied earlier.[5] Recently, dopamine antagonists like metoclopramide and serotonin agonists like sumatriptan have been studied for the acute headache management.[1] Sumatriptan is a 5-HT1 agonist that causes extracranial vasoconstriction of dilated vessels in migraine headache and inhibits the release of neuropeptide in the trigeminal nerve ganglion.[6,7] Sumatriptan caused striking change in acute migraine therapy, as it provided impressive pain relief and disappearance or improvement of associated symptoms like photophobia and nausea. However, the limitations of sumatriptan and other triptans became evident in different trials. Oral administration of this drug cannot provide complete pain relief in about 50% of patients.[3] Subcutaneous (SC) sumatriptan is more effective and the success rate after 1 h is reported to be from 56 to 88%.[8] Both forms of sumatriptan are contraindicated in patients with cardiovascular disease or at risk of it; also, SC form has more side effects such as chest tightness. Thus, it is clear that alternative drugs are necessary to overcome the limitations of triptans.[3]

Dopamine hypersensitivity exists in migraine, so various dopamine antagonists are useful in the treatment of headaches. The effect of these drugs has been attributed to their antiemetic properties and also their potential for

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increasing gastric motility and inducing sedation.[7] These drugs can also enhance the absorption of other analgesics. Metoclopramide is a non-phenothiazine central dopamine antagonist and a peripheral muscarinic agonist.[6] The dopamine antagonist properties of metoclopramide can make it an effective single drug to treat acute headache.[9] In some studies, intravenous metoclopramide has been considered as an efficient single choice for relieving pain and nausea in migraine and may also considered as a monotherapy for management of pain in ED.[7] Because sumatriptan is relatively expensive and contraindicated in some patients, and also different studies have reported different effects of metoclopramide, this controlled trial was carried out to compare the efficacy of intravenous (IV) metoclopramide with SC sumatriptan in the management of migraine headache in the ED.

MATERIALS AND METHODS

This was a randomized double-blinded clinical trial conducted on adult patients with migraine, who fulfilled the International Headache Society (IHS) criteria with or without aura. Patients were recruited by emergency physician in the referral ED of a teaching hospital during 2010-2011. The sampling method was convenient. Patients were included if they were 20-60 years old and presented with acute headache similar to previous episodes, with or without phonophobia, photophobia, vomiting, or nausea. The exclusion criteria were fever or neck stiffness, altered mental state, pregnancy, recent trauma or seizure (within 24 h), focal neurological abnormality on physical examination, allergy to metoclopramide, hypertension, and cardiovascular diseases. The patients who had taken a triptan or ergot during the last 24 h were not included the study. Written informed consent was obtained from all patients and the proposal of this study was approved by the Vice Chancellor for Research of Faculty of Medicine, Isfahan University of Medical Sciences. The sample size was calculated as 62 in each group with 80% power to detect 3 cm ± 0.5 differences in visual analogue scale (VAS) score at a 5% significance level.[1]

The eligible patients were asked to grade pain on a 10-cm nonhatched VAS that had been scaled from 0 at the left end to 10 at the right end. Patients were instructed that a score of 10 signified severe pain and a score of 0 indicated no pain. The patients were assessed at baseline and 1 h after receiving treatment. Each patient was fitted with a 20-gauge IV catheter and monitored with pulse oximetry. The patients were randomly assigned to one of two treatment groups using computer-generated random numbers. The subjects of one group received 6 mg SC sumatriptan (Tehran Shimi Company, Iran) and in another group, the participants received 20 mg IV metoclopramide (Tehran Shimi Company, Iran) during 15 min to prevent extrapyramidal adverse effects. The trial medications were injected by two nurses who were considered to be a disinterested party that knew which treatment every patient received. One hour after the drug injection, the same question was asked about pain. Also, data were collected on the patients' demographic information (age, sex) and any side effects (restlessness, dystonic reactions, and sedation) experienced.

Statistical analysis

Data were entered into Statistical Package for Social Sciences (SPSS), version 19. Pain scores were reported as mean values. Independent sample *t*-test, paired *t*-test, chi-square test, and Analysis of Covariance (ANCOVA) were used for data analysis. Kolmogorov–Smirnov test was used to assess the normal distribution of the data. Analysis indicated that data were normally distributed and homogenous. The two—tailed α error was set at 0.05.

RESULTS

One hundred twenty-four patients who presented with migraine headache to the ED met the study inclusion criteria and were enrolled. The data gathering was completed for all patients and no one withdrew from the study during 60 min. The patients in both groups reported no serious drug adverse effects such as dystonia, chest pain, or chest tightness.

Data from 124 subjects were analyzed. Baseline data are shown in Table 1. Because the difference between age and baseline VAS was statistically significant with $P < 0.0001$ [Table 1], ANCOVA was used to compare the post-treatment VAS in two groups, considering age and baseline VAS score as the covariates.

At time 0 and 60 min, the means of pain score in metoclopramide group were 6.74 ± 0.84 and 0.66 ± 0.59, respectively, according to the result of paired *t*-test. The other group showed similar results: baseline pain score in sumatriptan group was 6.12 ± 0.73 that decreased to 1.1 ± 0.70 after 60 min of treatment. The differences in pain scores after treatment were statistically significant in both groups ($P < 0.001$). Figure 1 shows the treatment results in both groups. Although both regimens were effective, subjects in the metoclopramide group exhibited greater improvement in pain compared with those

Table 1: Baseline characteristics

Variable	Metoclopramide, *n*=62	Sumatriptan, *n*=62	*P* value
Age, years, mean (SD)	34.9 (9.0)	26.8 (4.0)	P <0.0001*
Male (%)	39 (62.9)	38 (61.3)	0.853
Mean pain score (0–10) at baseline (SD)	6.74 (.84)	6.12 (.73)	P < 0.0001*

*Statistically significant

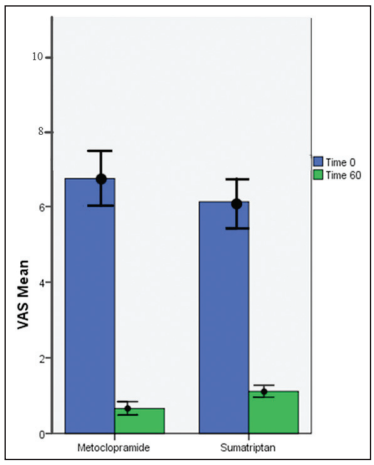

Figure 1: Mean pain score in the study groups before and after treatment VAS, visual analogue scale

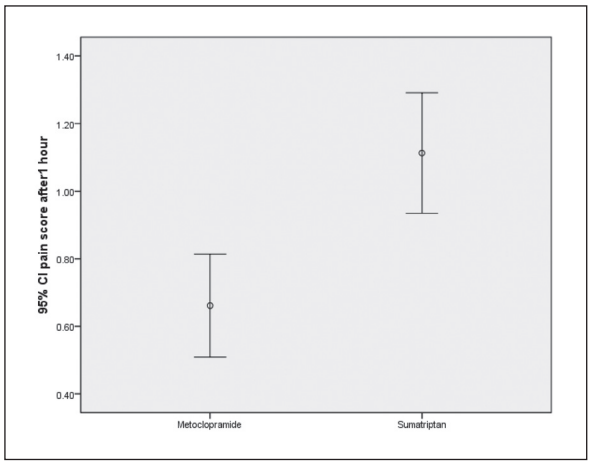

Figure 2: Error bar (confidence interval 95) of pain score 1 hour after treatment in study groups

in sumatriptan group [Figure 2]. Analysis with ANCOVA showed that the mean difference in T60 pain score between the two groups was 0.55 ± 0.13 (95% CI: 0.25–0.79 cm). This difference was statistically significant ($P < 0.001$).

DISCUSSION

This randomized controlled clinical trial showed that both metoclopramide and sumatriptan were effective treatments for migraine. Metoclopramide, however, was found to be superior in our study. It was surprising that no subjects in both groups complained of adverse effects, which may be a result of slow metoclopramide injection and the way the question about these effects was phrased. Metoclopramide has long been used for the treatment of nausea associated with migraine headaches and, also, this drug can increase the absorption of other analgesics and relieves gastric stasis. The case report studies published in 1970s suggested that patients with migraine who had taken metoclopramide to manage their nausea reported significant pain relief before receiving analgesics.[10] Subsequent studies concluded that the dopamine antagonist properties of this drug can make it effective for monotherapy in acute migraine.[9,11] The dose of metoclopramide in our study was 20 mg that was administered intravenously, and some studies have confirmed that higher dose is no better for acute migraine.[12] Other dopamine antagonists such as chlorpromazine and prochlorperazine have also demonstrated significant effects in migraine pain relief.[13,14] There are limited number of trials that compared the efficacy of metoclopramide versus sumatriptan. In some of these trials, metoclopramide had greater effect to relieve pain,[15] as seen in our study, but some trials found no significant difference between metoclopramide and sumatriptan.[16] These disparities might be the result of differences in drug doses and the settings in which each trial has been conducted. Sumatriptan is a selective serotonin agonist at the 5-HT1B/1D receptor. It is likely that this agonist activity is the primary mechanism of the therapeutic effect of this drug that causes cranial vasoconstriction and neural inhibition.[13] Although in this study sumatriptan showed lower efficacy, its effect was significant and many studies has confirmed this finding, especially for SC sumatriptan.[8]

Following up all participants in ED during 60 min was one of the strengths of our study; others include randomized controlled study design and patient blindness. Also, our study suffers from some limitations. This trial had been done in a teaching referral hospital, which results in some limitation in study generalizability. We did not assess which drug had more rapid effect and more sustained effect after hospital discharge. Moreover, there were significant differences in some baseline characteristics (age and pain score), but we solved this problem by using appropriate analyzing method. In conclusion, our study showed greater effect for IV metoclopramide in comparison to SC sumatriptan.

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