

Randomized Trial

The Effect of Helicobacter Pylori Eradication on Migraine: A Randomized, Double Blind, Controlled Trial

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Background: Recent studies have shown a positive correlation between Helicobacter pylori (H. pylori) infection and migraine headache.

Objective: To study the impact of H. pylori eradication on migraine headache.

Study Design: Double blind, randomized, controlled clinical trial.

Setting: Sixty-four patients diagnosed with migraine-type headache were included in the study. The patients were randomly allocated into 2 groups: a treatment group that received migraine treatment and H. pylori eradication treatment, and a control group that received migraine treatment and a placebo in place of H. pylori eradication treatment.

Methods: There were 25 women and 7 men in the treatment group and 22 women and 10 men in the control group. The MIDAS (Migraine Disability Assessment) questionnaire was used to assess the severity of symptoms, before and after treatment.

Result: There was no significant difference between treatment group patients and control group patients with respect to age (44.6 ± 8.8 vs. 43.8 ± 13.8), clinical symptoms and signs. In the beginning of the study, patients in the treatment group had a higher MIDAS compared to patients in the control group (28.87 ± 6.18 vs. 25.43 ± 7.13 , $P < 0.05$). There was no significant difference between the treatment and control groups, with respect to the MIDAS, after treatment (20.09 ± 1.14 vs. 20.00 ± 1.150 , $P = 0.5$). General linear model, repeated measures demonstrated that the reduction in the MIDAS score was more prominent in the treatment group (Mean Square 164.25, $F: 2.02$, $P = 0.05$).

Limitations: Short-term follow up.

Conclusion: H. pylori eradication may have a beneficial role on migraine headache. This shows the significance of H. pylori treatment in the management of migraine headache among Iranian patients.

Key words: Helicobacter pylori, migraine headache.

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Helicobacter pylori, also known as H. pylori, is a bacterium that is commonly found in the stomach (1-3). It is present in approximately one-half of the world's population. The vast majority of people infected with H. pylori have no symptoms and will never develop problems. However, H. pylori

is capable of causing a number of digestive problems, including ulcers, and much less commonly, stomach cancer (1-3). Besides gastric problems, it has been associated with a number of chronic diseases such as type 2 diabetes, respiratory problems, renal failure, and chronic inflammation such as ischemic heart disease,

ischemic cerebrovascular disease, atherosclerosis, Reynaud phenomenon, and skin diseases (4-9). Previous and recent studies have suggested an association between *H. pylori* infection and migraine headache (4,10-12). Migraine is a chronic neurological disorder characterized by moderate to severe headache and nausea (13). It affects 14% of women and 6% of men, and causes severe economic burdens. Here we study the effect of *H. pylori* eradication on migraine headache.

METHODS

We performed a randomized, double-blind, placebo-controlled clinical trial. Patients were recruited from the neurology clinic of Vali-Asr Hospital, which is affiliated with Arak University of Medical Sciences. A total of 64 patients with migraine-type headache were included in the study. Migraine was diagnosed according to the criteria of the International Headache Society. Exclusion criteria included other causes of headache, except migraine, age younger than 20, titer of anti-*H. Pylori* Immunoglobulin G (IgG) < 30, prior *H. pylori* treatment, smoking, autoimmune diseases, pregnancy, hospital admission in the previous 6 months, and use of oral contraceptive pills.

The patients were randomized into control and treatment groups. The block randomization method was used to allocate the patients into the study groups. Patients in the control group received only migraine treatment ($n = 32$) and the patients in the treatment group received an *H. pylori* eradication regimen in addition to migraine treatment ($n = 32$). Randomization was blind for the patients and investigators, except for the randomizer. Patients in the 2 groups were matched for age and sex. Demographic data including age, gender, and duration of headache were recorded.

All patients received migraine treatment, including nortriptyline (10 mg daily) and sodium valproate (200 mg daily). The treatment group also received an *H. pylori* eradication regimen, including omeprazole (20 mg twice a day), metronidazole (500 mg twice a day) and clarithromycin (500 mg twice a day) for 4 weeks. During the same 4 weeks the control group received placebo capsules that were identically packaged to and indistinguishable from the *H. pylori* eradication regimen.

Patients were recommended to continue their regular lifestyle during the study. The MIDAS (Migraine Disability Assessment) questionnaire (14-16) was used to assess the severity of symptoms, before and after treatment, in both the control and treatment groups. Diet was almost similar in composition in the 2 groups.

All patients were weighed again after 4 weeks.

This study was conducted according to the principles of the Helsinki Declaration. The local ethics review committee of Arak University of Medical Sciences approved the study protocol. All patients gave written informed consent before participating in the study.

At the beginning of the study, anti-*H. pylori* IgA and IgG were tested in patients using the enzyme-linked immunosorbent assay method. To confirm *H. pylori* eradication and treatment efficacy, the patients underwent urea breath test after treatment. Patients with eradication failure were excluded from the study.

Statistical Analysis

The statistical package SPSS 19 for Windows (SPSS Inc. Chicago, IL) was used for data analysis. Variables distributed normally are presented as mean \pm standard error of mean. Independent samples t-test was used to compare variables between treatment and placebo groups at baseline. Paired samples t-test was used to compare the baseline and 4 weeks values in each group. General linear model and repeated measures were employed to compare the mean difference of the MIDAS scores before and after treatment in the treatment and control group.

RESULTS

There were 25 women and 7 men in the treatment group and 22 men and 10 women in the control group, with a mean age of 44.6 ± 8.8 (treatment) and 43.8 ± 13.8 (control). There were no significant differences between treatment group patients and control group patients with respect to clinical symptoms and signs.

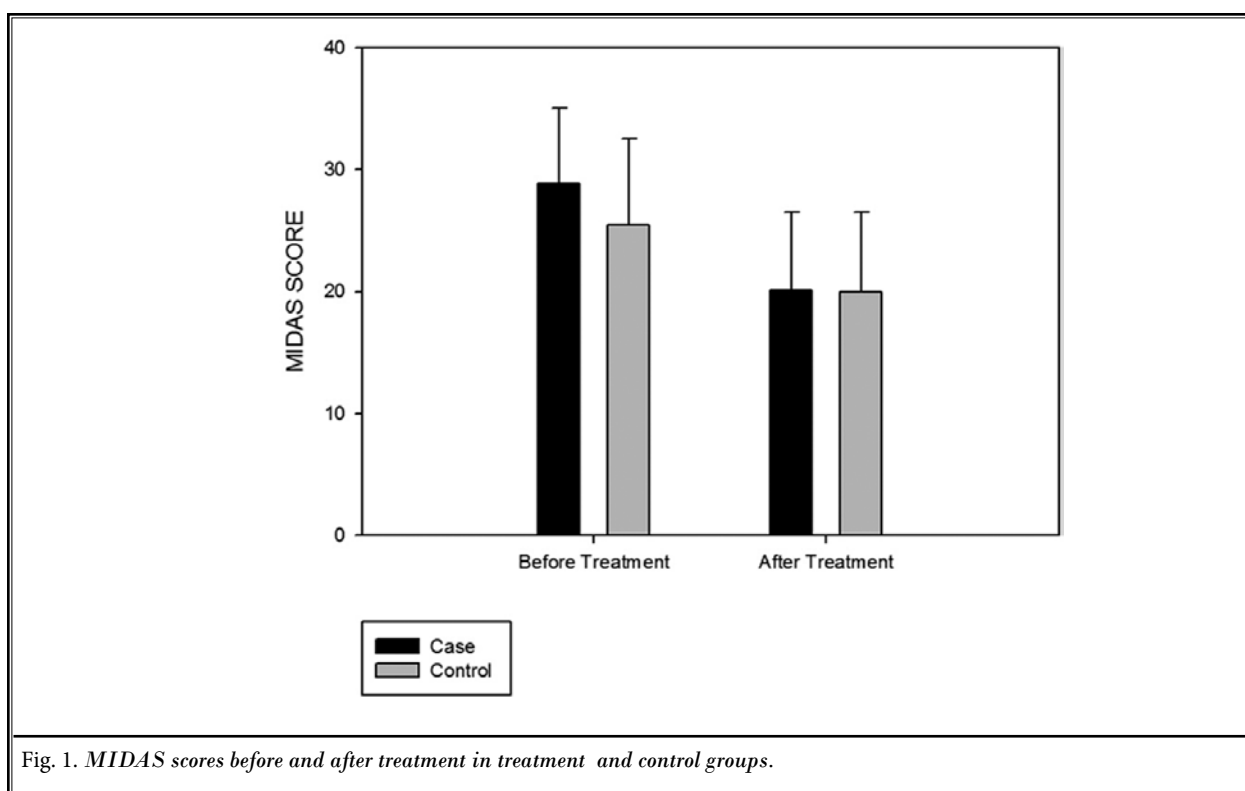
At the beginning of the study, patients in the treatment group had a higher MIDAS compared to the control group patients. We then followed all patients for one month and showed that the MIDAS decreased in both groups. There were no significant differences between the treatment and control groups with respect to the MIDAS, after treatment (Table 1). The reduction in MIDAS score was significantly higher in the treatment group compared to the control group (Fig. 1). General linear model and repeated measures demonstrated more prominent reduction of MIDAS score in the treatment group (Mean Square 164.25, $F: 2.02$, $P = 0.05$).

Men had a higher MIDAS score both before (33.4 ± 5.02 vs. 27.5 ± 5.9 ; $P < 0.05$) and after treatment (26.5 ± 3.5 vs. 19.5 ± 6.3 ; $P < 0.01$). We repeated the analysis stratifying the patients according to their educational status. Educated patients had a lower MIDAS score, both before (25.6 ± 6.63 vs. 26.8 ± 3.9 ; $P = 0.69$) and

Table 1. Primary characteristics of patients.

	Treatment Group (n = 32)	Control Group(n = 32)	P Value
Female	25	22	NS
Male	7	10	NS
Educated	5	4	NS
Uneducated	27	28	NS
Age (years)	44.6 ± 8.8	43.8 ± 13.8	NS
MIDAS1	28.87 ± 6.18	25.43 ± 7.13	< 0.05
MIDAS2	20.09 ± 6.4	20.00 ± 6.5	NS

NS = nonsignificant.



after (17.3 ± 7.6 vs. 22.2± 4.3; $P = 0.17$) treatment than uneducated patients.

DISCUSSION

Our findings clearly demonstrated that *H. pylori* eradication significantly improved the clinical symptoms of migraine, measured with the MIDAS score. This was significant after multiple adjustments for age and sex, using a general linear model. The findings of the current study confirm those of the previous studies (17,18).

Consistent with our findings, it has been shown that patients with *H. pylori* have a higher risk of migraine headache compared to those without infection (19). A preliminary study showed that about 40% of patients who have primary headache were seropositive for *H. pylori* infection (20). Moreover, eradication of *H. pylori* resulted in a significant improvement of clinical symptoms of migraine (20,21). Several mechanisms have been proposed linking *H. pylori* infection with migraine headache, including acute phase in-

inflammation and oxidative stress (13,22-23). It has been shown that nitric oxide imbalance due to *H. pylori* infection results in migraine headache (24). Gasbarrini et al (25) showed that CagA-positive *H. pylori* strains are strongly associated with migraine with aura. This was explained by a higher inflammatory response of the gastric mucosa to more virulent strains, which release substances that may act as triggers of vasospasm in peculiar cerebral arterial districts, probably implicated in the "aura" phenomenon (25). This may explain the improvement of migraine headache following *H. pylori* eradication.

The principal limitation of the present study is its short-term follow-up and duration; however, we took advantage of a relatively large sample size and close

similarity between groups in most of the potentially confounding variables. Another limitation of our study is that we did not assess the patient's global response. It is recommended this be assessed in future similar studies.

CONCLUSION

We showed the potential value of *H. pylori* eradication on improvement of migraine headache. This may show the significance of *H. pylori* treatment in the management of migraine headache among Iranian patients.

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