Original Article

A survey on the effect of adding aspirin to anti-migraine drugs on the severity of headache in patients with chronic migraine headaches with lateral venous sinus stenosis in MRV

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Abstract

Introduction: One of the probable etiologies raised in patients with chronic migraine headaches is stenosis of the lateral venous sinuses of the brain, which is detectable using magnetic resonance venography (MRV). In this study, we decided to observe the effect of adding aspirin to anti-migraine medicines on the severity of headache in patients with chronic migraine headaches with lateral venous sinus stenosis in MRV. **Methods:** The study was a double-blind randomized clinical trial. Patients were included in the study in two groups including 30 people. The first group was treated with propranolol and nortriptyline, and the second group was treated with propranolol, nortriptyline, and aspirin. The severity of headache, number of headaches during one month, and duration of a headache before treatment and one, two, and three months after treatment were examined. Data were analyzed utilizing SPSS software version 19 and statistical tests like *t*-test, Chi-squared test, Paired *t*-test, and repeated measure. **Results:** The results showed that the mean severity of headache in the second group was significantly lower than the first group two months after treatment ($P = 0.003$) and three months after treatment ($P = 0.002$). Additionally, the number of headaches ($P = 0.001$) and duration of headache ($P = 0.043$) were significantly lower in the second group than the first group in the first three months after treatment. No statistically significant difference was observed between the frequency distribution of nausea/vomiting in the two groups. **Conclusion:** The addition of aspirin to anti-migraine medicines is effective in improving the severity of headache in patients with migraine with lateral venous sinus stenosis of the brain.

Keywords: Aspirin, migraine, resistant headache, sinus stenosis

Introduction

According to the International Association for the Study of Pain, pain is an offensive sensory or emotional experience that is related to actual or potential injury and has two sensory and emotional dimensions. The sensory dimension of pain indicates its severity, and the emotional dimension indicates the extent of pain that a person experiences. Pain is classified into acute and chronic categories in terms of duration.[1,2]

Chronic pain is a frequent problem that has negative effects on people's quality of life. Among chronic pains, headache

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is one of the most common chronic pains[3] such that more than 90% of people experience headaches at least one day a year, and 10%–12% of those who visit a physician have an initial complaint of a headache.[4] The International Headache Association classifies headaches into two categories: primary and secondary. Migraine is one of the most prevalent primary headaches.[5] Migraine headaches are unilateral, frequently pulsating and are usually accompanied by nausea, vomiting, fear of light, and fatigue.[6] The chronic course of migraine, in addition to physical and mental problems, decreases the quality of life and efficiency of individuals in their personal and professional lives.[7] Additionally, despite progress made in the treatment of diseases, simply 30%–40% of patients with chronic migraine headaches are satisfied with their treatment process, and many patients still experience headaches for a long time despite long-term treatment, thereby decreasing their quality of life.[8,9] Consequently, many studies were conducted to determine potential etiologies in patients with treatment-resistant chronic migraine headaches. One of the most prevalent disorders in brain imaging in patients with treatment-resistant chronic migraine headaches is stenosis of the lateral venous sinus of the brain.[10] In earlier studies, the prevalence of lateral venous sinus stenosis in patients with treatment-resistant migraine headaches was reported to be up to 92.8%.[11] Consequently, treatment of lateral venous sinus stenosis of the brain as one of the potential etiologies of treatment-resistant migraine headaches can be efficient in improving headache in these patients.

The examination of aspirin as one of the most extensively applied non-steroidal anti-inflammatory drugs (NSAIDs) employed in the treatment of chronic pain has constantly been considered and its influence in improving chronic headaches compared to placebo has been confirmed in some studies.[12,13] But there is still no obvious response to the question of whether adding aspirin to anti-migraine medicines in patients with treatment-resistant chronic migraine headaches, accompanied by lateral venous sinus stenosis in magnetic resonance venography (MRV) can be efficient in reducing headaches in these patients.

Accordingly, considering to the prevalence of lateral venous sinus stenosis of the brain as one of the etiologies introduced in patients with treatment-resistant migraine headaches and also the possible effects of aspirin in improving chronic headaches, this study was conducted in order to examine the effect of adding aspirin to anti-migraine medicines in patients with chronic migraine headaches with lateral venous sinus stenosis of the brain in MRV.

Materials and Methods

Patient population

This study was a randomized clinical trial with a before and after design that was conducted at AJA University of Medical Sciences and affiliated hospitals.

Inclusion criteria: All patients with chronic headaches (headache lasting ≤15 days a month and more than three months)[14] and diagnosed with migraine (according to the IHS diagnostic criteria) were referred to the neurology clinic of hospitals affiliated to AJA University of Medical Sciences, which had more examination indication and experienced brain MRV because of not improving the headache and there was lateral venous sinus stenosis of the brain (according to CCS diagnostic criteria) in their MRV according to reports Radiologist and Neurologist Confirmation (Interventional Fellowship)

The IHS (International Headache Society) criteria for diagnosing migraine headaches include: 1. A history of at least five attacks, including cases 2, 3, and 4. 2. Headache attacks lasting 4–72 hours. 3. Headache has two features: unilateral, pulsating, moderate-to-severe headache (hindering daily activity) and intensified headache by climbing stairs or similar activities. 4. The presence of at least one of the following cases at the time of headache: nausea/vomiting, fear of light and fear of sound.[14]

Vascular stenosis was determined using the combined conduit score (CCS). The CCS is defined as the sum of the right and left scores, that is, the highest degree of stenosis from the torcular to the distal sigmoid sinus, rated on a 0–4 scale as follows: 0, discontinuity; 1, hypoplasia or severe stenosis estimated as <25% of the cross-sectional diameter of the lumen; 2, moderate stenosis (25%–50%); 3, mild stenosis (50%–75%); and 4, no significant narrowing seen (75%–100%).[15] Stenosis was defined as a CCS score of <3. The sum of the right and left side scores provided the CCS.[16]

Exclusion criteria included patients with headache who had no criteria for chronic headache; patients with MRV evidence of other brain lesions such as tumors or vascular malformations; patients with a history of vascular disease or space-occupying brain lesions; pregnancy, lactation, contraindications to aspirin use (aspirin sensitivity, history of peptic ulcer, history of asthma) and disinclination to cooperate or continue the study [Figure 1].

Ethical considerations

This study was approved by the Ethics Committee of AJA University of Medical Sciences, Tehran, Iran and registered with the protocol number "IR.AJAUMS.REC.1399.254". Participants were provided written informed consent and were included in the study after they were provided information on treatment methods. This trial was also registered in Thai Clinical Trial Registry (TCTR20210427007) and was conducted in accordance with the Declaration of Helsinki.

Intervention

Written consent was obtained from all qualified participants before including them in the study. The patients were then divided into two groups of 30 people applying a random number table. The first group was treated with migraine maintenance (propranolol 10 mg three times daily and nortriptyline 25 mg once daily) and placebo (similar in appearance to aspirin). The second group received aspirin at a dose of 325 mg daily in addition to migraine maintenance therapy.[17]

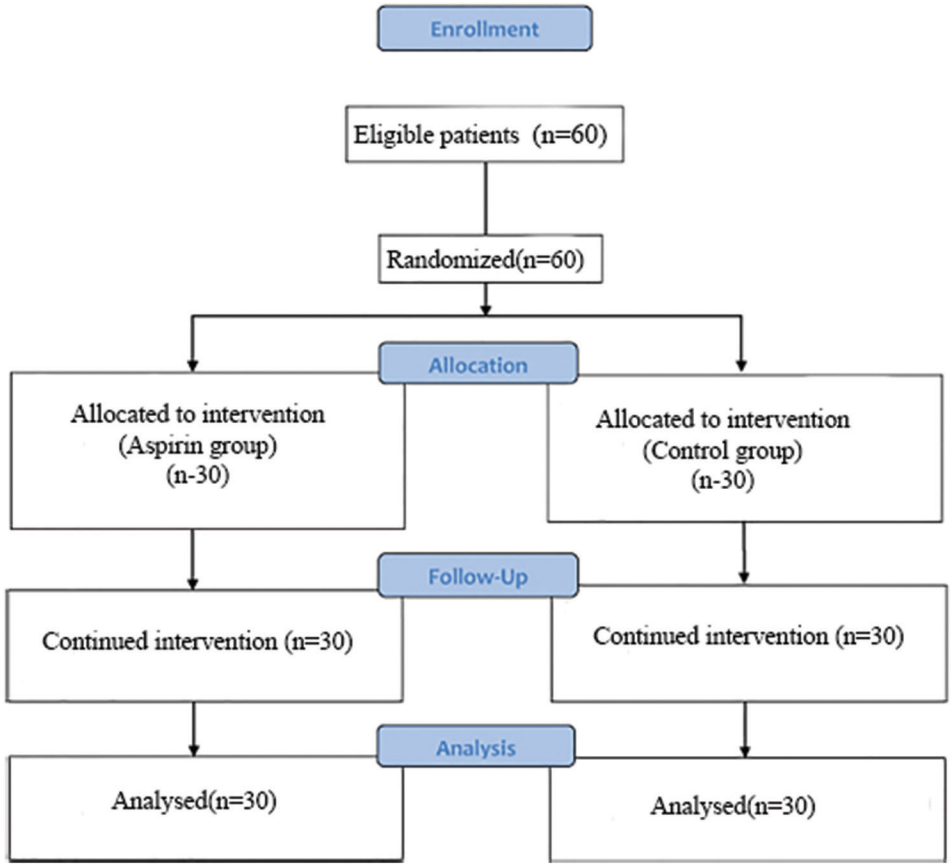

Figure 1: CONSORT Flow Diagram

Outcomes

The data were collected using tools such as a questionnaire that information included: age, gender, nausea and vomiting, pain-related factors (pain intensity, frequency of headache, and duration of headache) at the studied time. The studied times in our study were before starting the treatment, 1 month, 2 months, and 3 months after the start of treatment. Treatment-related variables included pain intensity (based on the visual analogue scale (VAS) for pain), frequency of headaches per month, duration of headache (in hours). The pain score was classified from 0 to 10 according to the (VAS) so that 0 was equivalent to no pain and 10 was equivalent to the most pain conceivable for the patient. The data were also collected through interviews with patients. The studied variables will be compared before treatment with 3 months after treatment.

Sampling and blinding

The sample size was examined according to the results of Burtscher's study in which 525 women were examined for 36 months in control and intervention groups with a dose of 100 mg of aspirin, and eventually, about 70% pain reduction in the intervention group and about 40% pain reduction and migraine development had occurred in the control group.[17] Additionally, the sample size of 22 people in each group was calculated employing the formula and placing a significance level of 5% and test power of 80%, that the final volume was estimated at 30 people in each group by considering 20% of the patients' non-cooperation.

The method of randomization was that first, the researcher completed the information related to the questionnaire, and a number between 1 and 60 was written at the top of the questionnaire, the questionnaires were then given to the statistical consultant and he/she divided the patients based on the written numbers in the questionnaire and employing a table of random numbers into two groups including 30 people.

The method of blinding was in this way that propranolol and nortriptyline (both manufactured by a similar pharmaceutical company) were given to patients in both groups. Then a placebo, which was very similar in appearance to aspirin tablets, was provided by a clinical pharmacologist and given to patients in one group, whiile patients in the other group received aspirin. Patients in both groups did not have any information about the type of prescribed medicine. The variables were studied at the desired times by the questioner who was unaware of the division of groups.

Statistical analysis

All registered data were analyzed using SPSS software version 20 for Windows (SPSS, Chicago, IL). For descriptive statistics, the mean ± SD index was used for quantitative variables with

normal distribution. The Chi-squared test and *t*-test were used for comparison of data between the two groups. Paired *t*-test was used to compare the mean of quantitative data before and after treatment. Repeated measures test was used to examine the trend of changes in study variables over time. *P* values of less than 0.05 were considered significant for all analyses.

Results

Sixty patients were included in the study. The mean age of the patients in our study was 34.11 ± 11.47 years. Of the 60 patients studied, 24 were male (40%) and 36 were female (60%).

There were no significant differences in baseline characteristics including age, gender and frequency of nausea and vomiting in specified times between the two groups [Table 1].

All patients were evaluated before treatment and then refollowed at 1, 2, and 3 months after treatment.

The results of the study on the mean severity of headache (according to VAS criteria) in the pre-treatment, one month, two months and three months after treatment, in the two groups, are shown in [Table 2]. Analysis of [Table 2] using *t*-test showed that the mean severity of headache at two months and three months after treatment in the aspirin-treated group was significantly lower than the control group. Also, according to the results of the paired *t*-test, it was found that the mean severity of headache three months after treatment compared to before treatment, in both groups, decreased significantly.

The results of the study on the mean number of headaches during a month, in the time before treatment, and one month, two months and three months after treatment, in the two groups, are shown in [Table 3].

Analysis of [Table 3] using *t*-test showed that the mean number of headaches during one month and at the three months after treatment in the aspirin-treated group was significantly lower than that in the control group.

Also, according to the results of the paired *t*-test, it was found that the mean number of headaches during one month and three months after treatment compared to before treatment, in both groups, decreased significantly.

The results of the study on the mean duration of headache in the time before treatment, and one month, two months and three months after treatment in the two groups are shown in [Table 4].

Analysis of [Table 4] using *t*-test showed that the mean duration of headache at three months after treatment in the aspirin-treated group was significantly lower than the control group.

Also, according to the results of the paired *t*-test, it was found that the mean duration of headache, three months after treatment compared to before treatment, in both groups, decreased significantly.

Table 1: Baseline characteristics and frequency of nausea and vomiting at specified times in patients randomized in the two groups

Variables	Aspirin group	control group	*P*
Number of subjects	30	30	
Age (mean±SD)	34.53±11.68	33.66±11.45	0.084*
Gender			
Male	11	13	0.598**
Female	19	17	
N & V before treatment			
No	24	22	0.542**
Yes	6	8	
N & V*** one months after treatment			
No	25	24	0.739**
Yes	5	6	
N & V two months after treatment			
No	25	26	0.718**
Yes	5	4	
N & V three months after treatment			
No	25	27	0.448**
Yes	5	3	

*t-test. **Chi-squared test. ***N & V: Nausea and vomiting

Table 2: Mean headache severity at specified times in patients randomized in the two groups

Time	Aspirin group	Control group	*P*
Before treatment	7.40±1.47	7.20±1.66	0.625*
One month after treatment	5.13±1.47	5.80±1.47	0.116*
Two months after treatment	3.03±1.18	4.63±1.90	0.003*
Three months after treatment	2.200±1.18	3.30±1.41	0.002*
Difference in mean before treatment & three months after treatment	5.200±0.33	3.900±0.38	
P	<0.0001**	<0.0001**	

*t-test. **Paired *t*-test

Table 3: Mean number of headaches during a month at specified times in patients randomized in the two groups

Time	Aspirin group	Control group	*P*
Before treatment	3.53±0.89	3.60±0.93	0.779*
One months after treatment	2.83±0.79	3.03±0.76	0.324*
Two months after treatment	1.96±0.71	2.13±0.68	0.360*
Three months after treatment	0.86±0.50	1.40±0.62	0.001*
Difference mean before treatment & three months after treatment	2.66±0.14	2.20±0.18	…….
P	<0.0001**	<0.0001**	

*t-test. **Paired *t*-test

To survey the trend of changes in the mean variables: severity of headache [Figure 2], number of headaches during a month [Figure 3] and duration of headache in hours [Figure 4] during the pre-treatment times, one month, two months and Three months after treatment, and repeated measures test was used in both groups.

Table 4: Mean duration of headache at specified times in patients randomized in the two groups

Time	Aspirin group	Control group	*P*
Before treatment	6.70±1.64	6.96±1.95	0.570*
One months after treatment	5.36±1.44	5.56±1.54	0.607*
Two months after treatment	3.23±0.81	3.63±1.18	0.134*
Three months after treatment	2.03±0.80	2.50±0.93	0.043*
Difference in mean before treatment & three months after treatment	4.66±0.34	4.46±0.30	…….
P	<0.0001**	<0.0001**	

*t-test. **Paired *t*-test

The test results showed that the trend of changes in the mean severity of headache during the study times between the two groups was significant ($P = 0.010$).

However, the trend of changes in the mean number of headaches during a month ($P = 0.139$) and the mean duration of headaches ($P = 0.241$) between the two groups was not significant.

Discussion

Lateral venous stenosis of the brain has been reported as one of the potential etiologies in patients with treatment-resistant migraine headaches (up to 92.8%).[11]

Favoni conducted a study on 40 patients with chronic headaches who experienced MRV and it was specified that 19 patients (47.5%) had lateral sinus stenosis and 7 patients (17.5%) among them had bilateral stenosis and 12 patients (30%) had unilateral sinus stenosis.[18] The results of another study that was conducted in 2008 on 198 patients with chronic headache revealed that among these patients, according to MRV findings, 18 people (9%) had bilateral lateral sinus stenosis.[10] Durst conducted a study and showed that 33% of patients who referred to a clinic with a chronic headache complained of unilateral lateral sinus stenosis or hypoplasia. The frequency of bilateral lateral sinus stenosis in patients was 5% and the frequency of unilateral lateral sinus stenosis with anterior sinus hypoplasia was 1%[19] Consequently, headaches in these patients can be reduced through the treatment of lateral venous sinus stenosis of the brain as one of the potential etiologies of treatment-resistant migraine headaches.

In our study, 60% of the patients were women. It was also specified in previous studies that migraine is more prevalent in women so that, in total, the prevalence of migraine in women has been reported to be 17% and 6% per year in men.[15] Also, Favoni's study specified that among 40 patients, 32 (80%) were female.[18]

Concerning age, our study revealed that the mean age of patients in our study was 34 years. The mean age of patients was 26.7 years[18] in the Favoni study, and the mean age of patients was 31.1 years[20] in Mohammad Taheri's study. Therefore, it can be stated that migraine occurs more in the third and fourth decades of life and the results of our study were in agreement with the results of other studies.

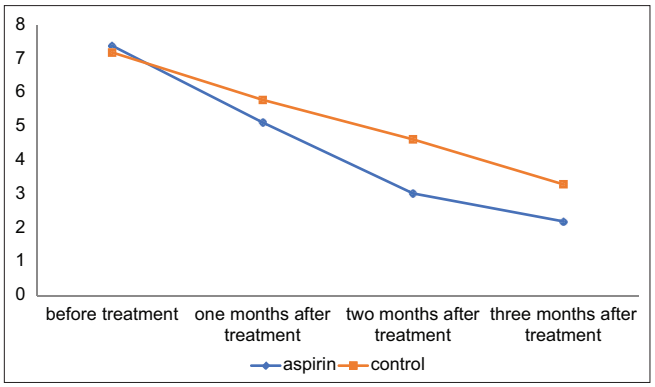

Figure 2: Trend of changes in the mean of severity of headaches at specified times in patients of the two groups

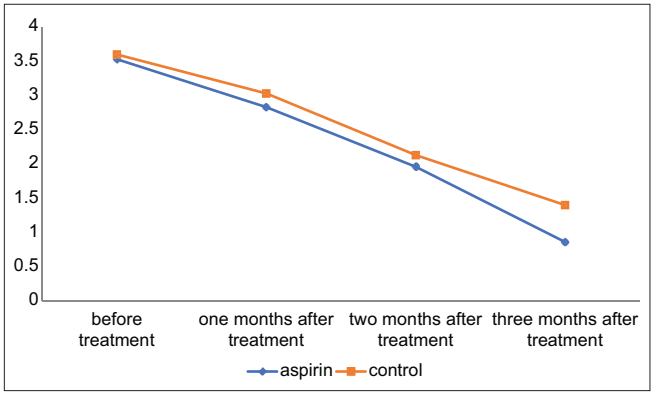

Figure 3: Trend of changes in the mean number of headaches during a month at specified times in patients of the two groups

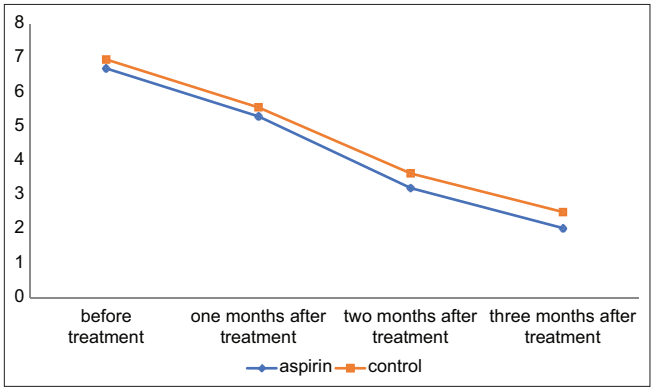

Figure 4: Trend of changes in the mean duration of headaches at specified times in patients of the two groups

Concerning the effect of aspirin on chronic headaches, although no study has been conducted on the effect of aspirin on patients with chronic headaches correlated with lateral sinus stenosis of the brain, positive results have been discovered on the effect of aspirin on chronic headaches. The study conducted by Derry that was a systematic review study of five studies and 1,812 patients

treated with aspirin showed that overall, aspirin treatment was more satisfactory for patients compared with the treatment with placebo (55% in patients treated with aspirin vs 37% in patients treated with placebo). Additionally, according to the results, no statistically significant difference was observed between the frequency distribution of side effects in aspirin and placebo groups[13]; that was in agreement with the results of our study in which there was no statistically significant difference between the frequency distribution of nausea and vomiting between the aspirin and control groups.

The study conducted by Kirthi was conducted on 13 studies and 4,222 patients treated with aspirin alone or in combination with metoclopramide, sumatriptan or placebo showed that in total, side effects were mild and transient and were more obvious in aspirin-placebo cases compared to other cases.[21]

Conclusion

The results of our study showed that the addition of aspirin to anti-migraine drugs was effective in improving headache indices (severity of headache, duration of headache and number of headaches per month) in patients with chronic migraine headaches; thus adding aspirin to the diet, edication is recommended for patients with refractory chronic migraine headaches associated with lateral venous sinus stenosis in MRV.

Abbreviations

VAS: Visual analog scale
NSAID: Non-steroidal anti-inflammatory drug
MRV: Magnetic resonance venography
IHS: International Headache Society
CCS: Combined conduit score.

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Authors' contribution

MSH did design study, wrote primary draft, submission, statistical and follow up of patients. MS supervised study and helped for diagnosis of the disease in MRV, RM advised study and helped for prescribing and dosing the drug. MZ helped for diagnosis of the disease in MRV, MY helped for writing proposal.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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