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Clopidogrel can be an effective complementary prophylactic for drug-refractory migraine with patent foramen ovale

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ABSTRACT

The present study aims to determine the potential prophylactic effect of clopidogrel for migraine with patent foramen ovale (PFO) in patients who are poor responders to two or more common preventive medications. Migraineurs underwent contrast-enhanced transcranial doppler examination to confirm the presence of PFO and determine the right-to-left shunt degree. Clopidogrel 75 mg/day was added to the existing prophylactic regimen for 3 months and 6 months. The presence of PFO was found in 56.8% (151/266) of all patients with migraine and 70.2% (59/84) of migraine with aura (MHA), and among MHA a large shunt was observed in 36 patients. Twenty-six patients with drug-refractory migraine took clopidogrel 75 mg/day for 3 months. Compared with those at baseline, headache frequencies and attack durations were significantly lower ($6.17 \pm 3.93/\text{month}$ (M) vs $3.28 \pm 2.67/\text{M}$, $p=0.003$; $13.62 \pm 13.98/\text{hour}$ (H) vs $7.36 \pm 7.33/\text{H}$, $p=0.0049$, respectively); visual analog scale scores and migraine disability assessment scores were also obviously decreased (6.32 ± 1.97 vs 4.71 ± 1.20 , $p<0.001$; 22.14 ± 7.13 vs 16.00 ± 5.92 , $p=0.001$, respectively). These improvements were maintained for 6 months in 12 patients. We concluded that PFO was closely correlated with migraine, especially in MHA. Clopidogrel could act as an effective complementary prophylactic for migraine with PFO in patients with poor response to routine prophylactics.

INTRODUCTION

Many studies have shown that the incidence of patent foramen ovale (PFO) is higher in patients with migraine than in those without migraine, ranging from 15% to 90%, and is significantly higher in migraine with aura (MHA), with a prevalence of 16% to 90%.^{1,2} Conversely, the prevalence of migraine with PFO is also higher than that in normal controls, ranging from approximately 16% to 64%.² Platelet aggregation and paradoxical embolization might link cardiac right-to-left shunts (RLS) to migraine.³

Many observational trials have suggested that migraine is alleviated after PFO closure,^{4,5} but the results of three prospective, randomized controlled trials—the MIST, PRIMA, and PREMIUM studies—did not report this result.^{2,6,7} Some articles have shown that

Significance of this study**What is already known about this subject?**

► The incidence of patent foramen ovale (PFO) is higher in patients with migraine than in those without migraine; migraine is alleviated after PFO closure; clopidogrel could improve new-onset migraine after device implantation.

What are the new findings?

► PFO was closely correlated with migraine, especially in migraine with aura (MHA); a large right-to-left shunt is very common in patients with MHA; clopidogrel could play an additional prophylactic role for migraine with PFO in patients with poor response to routine prophylactics.

How might these results change the focus of research or clinical practice?

► For the patients with PFO whom traditional drug therapy has not worked, compared with invasive surgical closure, we can firstly try to use clopidogrel to maximize improvement in patients with headache symptoms.

clopidogrel inhibits platelet aggregation and modulates the release of vasoactive substances,⁸ which could improve new-onset migraine after device implantation.⁹ Therefore, some scholars believe that clopidogrel administered early in the postoperative period plays a greater role in decreasing the number of migraine events than mechanical closure.¹⁰

We therefore conducted this study to evaluate the rate of PFO in patients with migraine and to determine the effect of clopidogrel on patients with drug-refractory migraine and PFO.

PATIENTS AND METHODS

This was a single-center non-randomized open-label trial. From January 2015 to March 2017, the study was conducted in the headache clinic of the neurology department at the First Affiliated Hospital, Xi'an Jiao Tong University. The inclusion criteria for patients were as follows: (1) patients with migraine diagnosed according



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to the diagnostic criteria of both episodic migraine (EM) and chronic migraine (CM) in the 2013 International Classification of Headache Disorders third edition (ICHD, beta version)¹¹ and aged 18–65 years, that CM defined as ≥ 15 headache days/month averaged over the past 3 months and aged 18–65 years; (2) patients with no positive signs of neurological disorders and negative results on head CT or MRI; (3) patients with normal ECG, routine hematuria, and coagulation tests results; (4) patients with no history of medication overuse or drug allergy. The exclusion criteria were as follows: (1) patients with other types of primary headache; (2) patients with secondary headache; (3) patients with histories of hypertension, heart disease, diabetes, or other chronic diseases; (4) patients with somatization disorders or mental disorders; (5) patients with a history of chest or head trauma; (6) pregnant or lactating women. All of the subjects underwent contrast-enhanced transcranial doppler (cTCD) imaging to determine PFO and the size of the shunt. RLS was classified according to microbubble (MB) numbers: (1) 0 MBs (negative result); (2) mild: 1–10 MBs; (3) moderate: $10 < \text{MBs} \leq 25$; (4) large: > 25 MBs.¹²

Then, we selected drug-refractory migraineurs from patients with PFO. Drug-refractory migraine was defined as ≥ 2 headache attacks/month while on at least two classes of prophylactics,⁶ including β -blockers, anticonvulsants, calcium channel blockers, tricyclics, and serotonin antagonists, for at least 3 months. All of the patients were told

of the possible preventive effects and potential side effects of clopidogrel, and they provided signed informed consent. Clopidogrel 75 mg/day was added to the existing prophylactic migraine regimen for at least 3 months. Ibuprofen was used as an acute pain reliever for unbearable headache for not more than 2 days during the experimental period. All baseline information, including headache frequency, headache duration, Migraine Disability Assessment (MIDAS) score, and headache severity, was registered in detail. Headache severity was evaluated with the visual analog scale (VAS). After 3 months and 6 months, all of the enrolled patients were re-interviewed in the headache clinic; the above indicators were measured based on the patients' headache diaries.

The trial diagram is shown in figure 1.

STATISTICAL ANALYSIS

Categorical variables are expressed as frequencies and percentages, and continuous variables are expressed as means \pm SDs. All data were tested for normality. The t-test and Wilcoxon's test were used to analyze differences between baseline data and that measured 3 or 6 months after clopidogrel treatment. One-way ANOVA or non-parametric tests were used to compare the differences among the data at baseline, 3 months and 6 months, and Bonferroni's multiple comparison test was used for post hoc tests. The p-value < 0.05 was considered an acceptable statistically significant cut-off value.

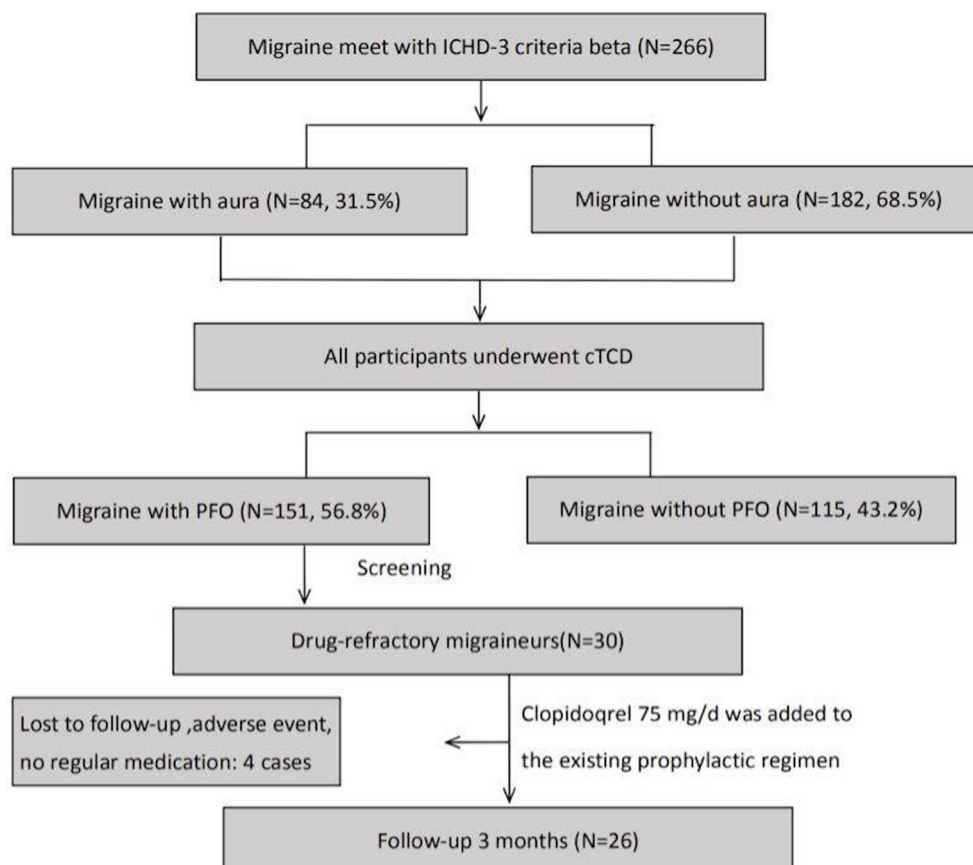


Figure 1 Trials diagram. cTCD, contrast-enhanced transcranial Doppler; ICHD-3, International Classification of Headache Disorders 3rd edition; PFO, patent foramen ovale.

Table 1 Demographic characteristics of this study population

	Migraine with aura (n=84)	Migraine without aura (n=182)	Migraine (n=266)
Sex F (%)	56/84 (66.7)	113/182 (62.1)	169/266 (63.5)
Age Mean±SD (years)	32.45±10.75	35.84±13.37	34.77±12.68
Attack frequency (/ month)	3.37±1.24	2.58±0.76	3.02±1.14
Headache duration of each onset (/h)	8.46±8.75	6.38±10.39	7.29±9.10
VAS scores	4.28±1.47	3.23±0.89	3.70±1.26
MIDAS scores	10.56±3.78	12.29±4.65	10.93±2.49
PFO+ (%)	59/84 (70.2)	92/182 (50.5)	151/266 (56.8)
Large RLS	36	29	65

MIDAS, migraine disability assessment; PFO, patent foramen ovale; RLS, right-to-left shunt; VAS, visual analog scale.

RESULTS

The demographic characteristics of each group are presented in [table 1](#). Visual aura was reported in 59 cases, sensory aura was reported in 18 cases, motor aura was reported in 5 cases, and speech/language symptoms was reported in 2 cases of MHA. The presence of PFO was observed in 56.8% (151/266) of all migraineurs and 65 patients with large shunts. Among these patients, the presence of PFO was observed in 70.2% (59/84) of those with MHA, among whom a large shunt was observed in 36 patients. The presence of PFO was found in 50.5% (92/182) of the migraine without aura (MoA) group, and a large shunt was observed in 29 patients.

Thirty drug-refractory migraineurs among the patients with PFO were screened for inclusion in the clopidogrel treatment study. Finally, 26 patients completed 3 months of treatment (3 patients were lost to follow-up, and 1 patient discontinued the intervention because of adverse events (she stopped taking clopidogrel due to increased menstruation)) ([table 2](#)). The headache frequencies and VAS scores conformed to normal distributions, and t-tests were used. Wilcoxon's tests were used to analyze headache attack durations and MIDAS scores since the data had non-normal distributions. Compared with that at baseline, the headache frequency decreased from 6.17±3.93/month (M) to 3.28±2.67/M, and the headache attack duration decreased from 13.62±13.98/hour (H) to 7.36±7.33/H, with significant differences (p=0.003; p=0.049). In addition, the VAS score and MIDAS score were also obviously lower than those at baseline (6.32±1.97 vs 4.71±1.20, p<0.001; 22.14±7.13 vs 16.00±5.92, p=0.001, respectively) ([figure 2](#)).

Twelve patients completed 6 months of follow-up. After testing for normality, the headache frequencies, VAS scores, and MIDAS scores were subjected to one-way ANOVA, and headache attack duration was analyzed by non-parametric tests. Bonferroni's multiple comparison test was used as the post hoc test. The headache frequency was lower at 3 (3.62±6.38/M) months or 6 months (2.75±1.35/M) than at baseline (6.79±3.82/M, p=0.002), with significant differences (p=0.023; p=0.003). The headache attack duration was decreased after treatment (17.00±14.05/H

Table 2 Demographic characteristics of the patients with drug-refractory migraine with patent foramen ovale

Patient	Migraine symptom	RLS	Prior medications used
1	MHA	Large	Valproate, sumatriptan
2	MoA	Moderate	Flunarizine, gabapentin
3	CM	Large	Propranolol, amitriptyline, naproxen
4	MHA	Mild	Flunarizine, gabapentin
5	MoA	Moderate	Propranolol, amitriptyline, topiramate, magnesium
6	MoA	Mild	Sumatriptan, propranolol
7	MHA	Large	Flunarizine, lamotrigine
8	MHA	Large	Flunarizine, topiramate
9	MHA	Large	Metoprolol, valproate
10	MoA	Mild	Flunarizine, amitriptyline, ibuprofen
11	MoA	Moderate	Flunarizine, propranolol
12	CM	Large	Divitamins, flunarizine, herb
13	MoA	Mild	Propranolol, topiramate
14	MoA	Mild	Topiramate, flunarizine
15	MHA	Mild	Divitamins, amitriptyline
16	MoA	Large	Flunarizine, valproate
17	MoA	Moderate	Divitamins, topiramate
18	MoA	Mild	Flunarizine, metoprolol
19	MHA	Mild	Divitamins, amitriptyline
20	MoA	Mild	Topiramate, aspirin, propranolol
21	CM	Large	Flunarizine, paracetamol
22	MoA	Large	Flunarizine, paracetamol
23	MoA	Large	Flunarizine, paracetamol, ibuprofen
24	MoA	Large	Flunarizine, paracetamol
25	MHA	Large	Flunarizine, herb
26	MHA	Large	Flunarizine, amitriptyline

CM, chronic migraine; MHA, migraine with aura; MoA, migraine without aura; RLS, right-to-left shunt.

vs 7.41±6.74/H vs 6.95±5.36/H, p=0.023), and did not show the statistical significance neither at 3 nor 6 months compared with baseline. The VAS scores (6.50±2.26 vs 4.70±0.94 vs 4.45±1.07) and MIDAS scores (27.08±5.61 vs 20.33±5.46 vs 16.67±4.46) were obviously reduced after clopidogrel treatment (p=0.049; p=0.001, respectively); the scores at 3 months (p=0.0023; p=0.009, respectively) and at 6 months (p=0.008; p<0.001, respectively) were lower than those at baseline. Interestingly, between 3 months and 6 months of treatment, there were no significant differences in the various headache indicators ([figure 3](#)).

DISCUSSION

cTCD imaging is a highly sensitive method for detecting the RLS. Its advantages are low cost and high sensitivity, which make it a common method for PFO screening in the clinic.¹³

Some existing data have shown that PFO is a risk factor for migraine although research in this area has been quite scarce. This study used cTCD technology to examine the rate of PFO in more than 300 subjects to identify the

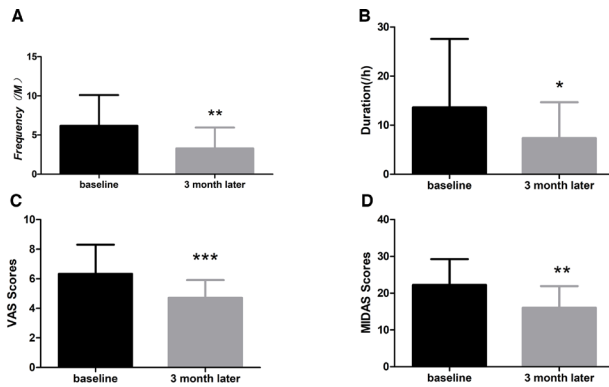


Figure 2 Comparison of frequency (A), duration (B), visual analog scale (VAS) score (C), and migraine disability assessment (MIDAS) score (D) between baseline and after clopidogrel treatment 3 months. Data are shown as means±SD. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

incidence of migraine associated with PFO and shunt size and the magnitudes of the relationships between migraine types so that readers interested in migraine associated with PFO could obtain a certain understanding.

We found PFO to be present in 56.8% of all of the patients with migraine. This result was similar to previously published findings¹⁴ in which the presence in patients with migraine was 25% higher than that in the general population.¹⁵ In our study, the prevalence rates of PFO were 70.2% in the MHA group and 50.5% in the MoA group, which were also similar to those in published studies.^{6,16} In previously published reviews, Anzola *et al*¹⁷ and Choi *et al*¹⁸ reported that PFO was related to only MHA. Tatlidede *et al*¹⁶ concluded that migraine, especially MHA, was closely related to PFO, as did Domitrz *et al*.¹⁹ In the current study, we estimated that the prevalence of PFO in migraineurs, especially those with MHA, was higher than those in the general population. The reason for this result has not yet

been clearly elucidated. It might be related to increased platelet activity and aggregation ability as well as abnormal embolism.^{3,20} Some researchers have proposed that migraine and atrial septal dysplasia might be attributable to similar autosomal inheritance.²¹ It has also been reported that the coexistence of PFO and migraine might due to a common occurrence during embryogenesis, but they are two lateral defects that are independent of each other.²²

In patients with migraine with PFO, treatment with PFO occlusion has predominated in recent decades. Observational studies involving some small samples have found that transcatheter closure of PFO improves the frequency of migraine and the severity of headache. Confirming whether PFO closure is effective in the treatment of migraine requires large-sample randomized controlled trials (RCTs). Currently, three prospective RCTs, including the MIST, PRIMA, and PREMIUM studies, have published their results. None of these three studies reached its primary end point. In addition to surgical interventions, these studies considered antiplatelet drugs, in both the occlusion group and the drug/sham group experienced therapeutic effects, with no statistically significant difference. It could be concluded that occlusion was a beneficial supplement to medical treatment, but we boldly speculate that the alleviation of migraine in the RCTs may have been due to an antiplatelet effect.

Possible mechanisms of the relationship between migraine and PFO are the presence of RLS, increased platelet aggregation activity, microembolic signals, and 5-hydroxytryptamine (5-HT) in the venous circulation. 5-HT is normally removed by the lungs; however, if it reaches the brain via circulation, it can induce local hypoxia and ischemia rather than stroke if it is present in sufficient concentrations.^{23,24} In response to the involvement of platelets in this process, we proposed prophylactic treatment of migraine with the antiplatelet drug clopidogrel bisulfate. Some scholars have suggested that clopidogrel should always be used routinely in the early postocclusion period. It is possible that the drug, rather than the occlusion device, could play a role in the relief of migraine. Wilmsuist *et al*'s study found that the combination of clopidogrel for 1 month and aspirin for 6 months was superior to aspirin alone in preventing MHA after atrial occlusion.⁹ The mechanism of clopidogrel's long-term beneficial platelet effect, unlike that of aspirin, including platelet aggregation inhibition, suggesting that platelet activation might be involved in the pathogenesis of migraine, possibly by affecting the storage of 5-HT.

The characteristics of the enrolled patients were similar to those in the MIST⁶ and PRIMA⁷ studies. All the patients had drug-refractory migraine and RLS. Due to the difficulty in enrolling patients with refractory migraine, it was challenging to enroll enough patients for matching, so our study was a self-controlled trial. In the overall migraine population, data including headache attack frequency, headache duration, and VAS and MIDAS scores should theoretically follow normal distributions. The non-normal distributions in this study may be due to the small sample size and poor overall representativeness. The headache durations and MIDAS scores of the sample were not normally distributed, so we used Wilcoxon's tests. Our study showed that headache symptoms were mitigated by the use of clopidogrel.

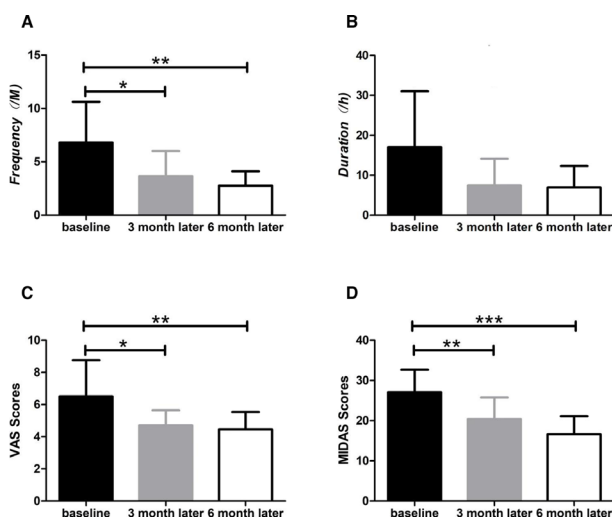


Figure 3 Comparison of frequency (A), duration (B), visual analog scale (VAS) score (C), and migraine disability assessment (MIDAS) score (D) between baseline and 3, 6 months later. Data are shown as means±SD. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

At the end of the 3-month follow-up period, headache attack frequencies and durations and the VAS and MIDAS scores were significantly decreased compared with those at baseline. Some studies obtained similar positive conclusions.^{25–27} Only 12 patients completed all 6 months of treatment. Compared with the results at 3 months, the results at 6 months were not statistically significant. According to the results at the two time points, the improvement effect of clopidogrel seemed to reach its maximum effect at 3 months of treatment, and prolonging the medication course did not further improve headache symptoms. We think that this may be related to the small sample size. In addition, we speculate that with prolonged disease courses, patients experience anxiety and depression, and their threshold for pain may decrease, resulting in increased subjective feelings after the same intensity of pain stimulation.

Throughout therapeutic drug development history, clinical treatment guided by clear pathogenesis has been emphasized. Regarding the treatment of migraine, PFO has been a popular research topic. According to the results of the three published RCTs, surgical treatment for RLS in patients with refractory migraine seems to be of little significance. In addition, surgical closure is an invasive operation with risks of incision infection, arrhythmia, and cardiac tamponade, and the cost is relatively high. Our study found that clopidogrel hydrogen sulfate had some preventive effects in patients with a prolonged treatment course, but it did not further improve the symptoms of headache. Therefore, in patients for whom traditional drug therapy has not worked, clopidogrel hydrogen sulfate can be administered to maximize improvement in patients with headache symptoms.

There are obvious limitations in this study that must be further improved. First, due to the lack of a randomized control group, there may be certain selection bias, memory bias, and confounding, but the analysis of the benefits of the medication and its durations in multiple subjects rather than a single patient indicated a notable difference from the placebo effect. However, the sample size in this study was small, so generalization and the validity of the conclusions are limited.

CONCLUSIONS

PFO is closely correlated with migraine, especially MHA. A large RLS is very common in patients with MHA. Clopidogrel could play an additional prophylactic role in migraine with PFO. However, this result must be further verified in large-scale, case-controlled, double-blind, placebo-parallel clinical trials.

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Competing interests None declared.

Patient consent for publication Not required.

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