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Efficacy of Ticlopidine for Preventing Migraine After Transcatheter Closure of Atrial Septal Defect With Amplatzer Septal Occluder: A Case Report

Hideshi TOMITA, MD, FJCC
Kinya HATAKEYAMA, MD
Wataru SODA, MD
Toshiki KOBAYASHI, MD*

Abstract

Transcatheter closure of an atrial septal defect using the Amplatzer septal occluder is a current treatment option in Japan, but is occasionally associated with transient exacerbation or new onset migraine. Clopidogrel is effective in such a situation, but the efficacy of ticlopidine, an analog of clopidogrel, on migraine remains unclear. A 15-year-old girl presented with typical migraine attacks with aura 11 days after transcatheter closure of an atrial septal defect with an Amplatzer septal occluder. All examinations excluded thromboembolic origin of the migrain. Her symptoms disappeared completely after medication with ticlopidine.

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Key Words

■ **Congenital heart disease** ■ **Heart catheterization (Amplatzer septal occluder)**
■ **Drug therapy (ticlopidine)** ■ **Complications (migraine)**

INTRODUCTION

Transcatheter closure of an atrial septal defect (ASD) using the Amplatzer septal occluder is a current treatment option in Japan. Right-to-left shunts associated with ASD or persistent foramen ovale have been suggested as a mechanism of migraine with aura, but paradoxically, transient exacerbation or new onset migraine has occasionally been reported following transcatheter closure of an ASD or persistent foramen ovale.[1–4] Clopidogrel is effective in such a situation,[3,4] but the efficacy of ticlopidine, an analog of clopidogrel, on migraine with aura remains unknown.

We treated a 15-year-old girl with typical migraine with aura 11 days after transcatheter closure of an ASD with the Amplatzer septal occluder, and her symptoms completely disappeared after medication with ticlopidine.

CASE REPORT

A 15-year-old girl had been found on health screening when 4 months old to have a systolic murmur at the upper left sternal border. The diagnosis was ASD but closure was deferred until approval of the Amplatzer septal occluder in Japan. She remained asymptomatic during follow-up at our hospital. Two-dimensional transthoracic echocardiography documented the presence of an ostium secundum ASD complicated by significant

北海道立小児総合保健センター 循環器科: 〒047−0261 北海道小樽市銭函1丁目10−1; *埼玉医科大学 小児心臓科, 埼玉
Department of Cardiology, Hokkaido Children's Hospital and Medical Center, Hokkaido; *Department of Pediatric Cardiology, Saitama Medical School Hospital, Saitama
Address for correspondence: TOMITA H, MD, FJCC, Department of Cardiology, Hokkaido Children's Hospital and Medical Center, Zenibako 1−10−1, Otaru, Hokkaido 047−0261; E-mail: tomitah@sapmed.ac.jp
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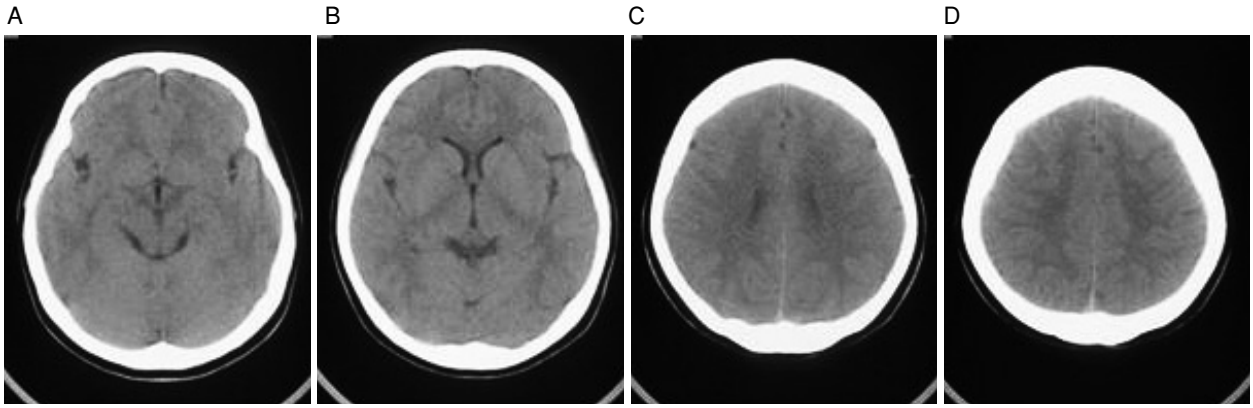

Fig. 1 Computed tomography scans (*A*−*D*) at the onset of migraine
There were no abnormal findings.

volume overload of the right heart. Cardiac catheterization revealed a Qp/Qs ratio of 2.8 : 1 with normal pulmonary artery pressure, and transesophageal echocardiography confirmed a defect of 18 mm with adequate margins. Consequently, we referred her to Saitama Medical University for transcatheter closure of the ASD with the Amplatzer septal occluder. As the balloon occlusion diameter was 21.4 mm, a 22 mm device was implanted successfully, with immediate complete closure of the defect. Detailed procedures to implant the device have been extensively described in previous reports.[5,6] Aspirin (200 mg/day) was administered from 2 days before the procedure and thereafter, and intravenous heparin was given during the catheterization to keep the activated clotting time longer than 200 sec. The clinical course after the procedure was uneventful and she returned home after 2 days.

Eleven days after ASD closure, the patient presented with photophobia, flickering lights, and scotoma followed by severe pulsating headache accompanied by nausea and vomiting. The symptoms lasted several hours and occurred at least once a day ; there was no previous history of similar symptoms. After recovery from the headache, she had no neurological signs or symptoms. Computed tomography of the brain showed no abnormalities (**Fig. 1**), and transthoracic echocardiography confirmed the device to be perfectly positioned in the atrial septum, with no evidence of a shunt or thrombus on the device or anywhere else in her heart (**Fig. 2**). A consultant neurologist diagnosed the episodes as migraine with aura that met the diagnostic criteria of the International Headache Society.[7]

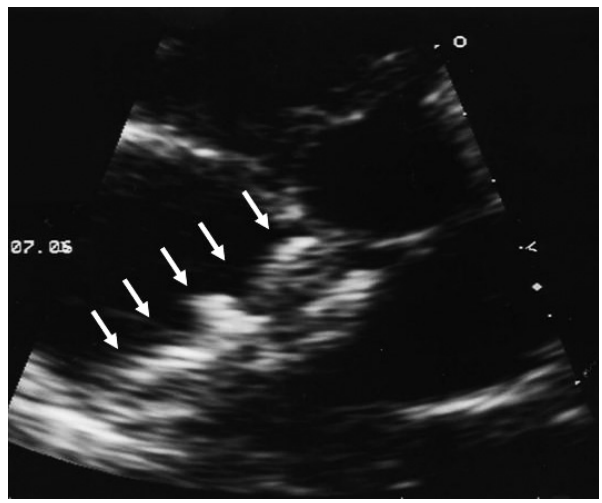

Fig. 2 Echocardiogram at the onset of migraine
The device (*arrows*) was perfectly positioned in the atrial septum with no evidence of thrombus.

In Japan, clopidogrel is only approved for the prevention of recurrent cerebrovascular ischemic events, excluding thromboembolic episodes of cardiac origin. Therefore, we added 200 mg/day of ticlopidine to the aspirin medication therapy. Informed consent for prescription of ticlopidine and necessity of blood examination at least once in 2 weeks during medication was obtained from the patient and her parents. Since ticlopidine administration was started, migraine with aura, previously a daily event, has resolved completely. Ticlopidine administration was decreased to 100 mg/day after 1 month without migraine, and was stopped 2 months after the onset of migraine. There has been no recurrence of migraine, and she had no clinical sign

or abnormality of laboratory data which suggested side effects of ticlopidine.

DISCUSSION

Transient exacerbation of existing migraine or new onset migraine have been reported in 10−40% of patients following transcatheter closure of ASD or persistent foramen ovale.[2−4] The presence of microemboli on the left side surface of the device or the liberation of vasoactive substances, such as serotonin, from platelets is regarded as the pathological mechanism of such migraine.[1,2,4] Standard medications for migraine, for example, amytriptyline, or anticoagulation with heparin or warfarin are reported to be effective for this type of migraine.[1,2] In addition, there are a few reports on the efficacy of antiplatelet medication with clopidogrel in addition to the standard regimen of aspirin,[3,4] which further suggests that platelet activation may be involved in migraine etiology under some circumstances.

Clopidogrel and ticlopidine are thienopyridine derivatives which inhibit platelet aggregation through antagonism of the adenosine diphosphate receptor, P2Y12.[8−10] Ticlopidine effectively prevents cardiovascular events in cerebrovascular, cardiovascular, and peripheral vascular disease, but has been replaced by clopidogrel in North America and Europe because of its significant and sometimes fatal adverse reactions, specifically neutropenia and bone marrow suppression.[8,9] In Japan clopidogrel is only approved for prevention of recurrent cerebrovascular ischemic events.

In our patient, ticlopidine prevented recurrence of migraine with aura as did clopidogrel in previous reports.[3,4] This is not surprising as there are several reports on the similar efficacy of ticlopidine and clopidogrel in preventing cardiovascular events.[8−10] Further randomized studies on the efficacy of thienopyridine derivatives in the prevention of migraine developing after transcatheter closure of ASD are necessary. Once its efficacy is confirmed, official approval of migraine as an indication for clopidogrel will prevent serious adverse actions from ticlopidine.

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要　　約

Amplatzer Septal Occluder 留置後の片頭痛にチクロピジンが有効であった心房中隔欠損の1例

富田　英　　畠山　欣也　　早田　航　　小林　俊樹

我が国でも Amplatzer septal occluder による心房中隔欠損の経カテーテル的閉鎖術が行われるようになったが，術後に一過性の片頭痛増悪や新たな発症が報告されている．この片頭痛にクロピドグレルが有効との報告があるが，チクロピジンの有効性に関する報告はみられない．Amplatzer septal occluder による心房中隔欠損閉鎖術の11日後に片頭痛を発症した15歳の女児を経験した．血栓，塞栓症の所見はなく，この片頭痛にはチクロピジンが著功した．

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