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CASE SERIES

Parieto-Occipital Parenchymal Hemorrhage Due to Ticagrelor Loading Before Coronary Angiography: A Case Report Involving Two Patients Aged Over 65 Years

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ABSTRACT

P2Y12 inhibitors, along with aspirin, are essential therapeutic agents in dual antiplatelet therapy, the most effective approach for preventing arterial thrombosis in patients with acute coronary syndrome and a history of stent implantation. This paper reports on two cases of a rare complication resulting in acute intraparenchymal hematoma triggered by ticagrelor. It also presents a discussion on the side effects of ticagrelor-related intracranial bleeding in light of the literature. Ticagrelor, a cyclopentyl-triazolopyrimidine antiplatelet drug, is the first reversible oral P2Y12 receptor antagonist. Its side effects include bleeding, liver failure, bradycardia, dyspnea, elevated creatinine, elevated uric acid levels in the blood, and thrombotic thrombocytopenic purpura. Ticagrelor is a potent, rapid-onset, backpropagating P2Y12 receptor inhibitor used in acute coronary syndrome. Ticagrelor is generally well tolerated. One of the most common side effects is bleeding. This paper presents two cases of bleeding in the parieto-occipital region following ticagrelor loading.

Keywords: Coronary angiography, intracranial bleeding, ticagrelor

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Introduction

Ticagrelor, a cyclopentyl-triazolopyrimidine, is a directly active, reversible, and competitive P2Y12 receptor antagonist.[1] As a platelet aggregation inhibitor, ticagrelor is administered after management of acute coronary syndrome (ACS). The 2017 European Society of Cardiology Guidelines recommend ticagrelor over clopidogrel for patients with ACS.[2] For maximum effectiveness in platelet activation, ticagrelor must be administered twice a day. However, a study showed that even a single dose (>300 mg/day) of ticagrelor could inhibit platelet aggregation more effectively than clopidogrel (75 mg/day).[3] Despite the efficacy of a single high dose of ticagrelor against ACS, a loading dose of 180 mg followed by the administration of 90 mg twice daily is recommended due to the potential risk of bleeding.[4] Ticagrelor is relatively well tolerated, but side effects such as bleeding or shortness of breath may lead to its discontinuation.[5] Cases of cerebral hemorrhage due to ticagrelor overdose (1,677 mg, which is equivalent to approximately 18 tablets) have been documented.[6] This paper presents two cases of acute intraparenchymal hematoma triggered by ticagrelor. Moreover, this paper aims to discuss the side effects of ticagrelor-related intracranial bleeding in light of the literature.

Case Report

Case 1

A 75-year-old female patient (weight: 63 kg; height: 150 cm) was brought to the emergency room due to headache. Upon arrival, she had a blood pressure

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of 160/78 mmHg, a heart rate of 82 beats/min, and a respiratory rate of 18 breaths/min. The patient, who had angioplasty in six coronary vessels 15 years ago and had received a three-vessel stent 2 days prior, was given a loading dose (180 mg) of ticagrelor during the procedure. Her previous medication was clopidogrel 75 mg/day. Physical examination revealed no sign of serious trauma, a blood pressure of 140/68 mmHg, a pulse rate of 108 beats/min, and a respiratory rate of 23 breaths/min. The arterial blood gas test revealed a 7.35 pH level, 36 mmHg $PaCO_2$, 68 mmHg PaO_2, 19.1 mmol/L HCO_3, 2.8 mmol/L lactate, and 95% oxygen saturation. The patient had a history of diabetes mellitus (DM), hypertension (HT), hyperlipidemia, and coronary artery disease. No deficit was detected during neurological examination. Laboratory findings showed normal values for blood glucose, electrolytes, liver and kidney function, and coagulation parameters. Moreover, she had a hemoglobin count of 12.9 g/dL (normal: 11.5–15.5 g/dL), a leukocyte count of 10.15 µ/L (normal: 3.8–10 µ/L), a neutrophil percentage of 78% (normal: 45–78%), and a platelet count of 243,000 µ/L (normal: 100,000–400,000 µ/L). No pathology was detected based on her chest radiography results, and her electrocardiogram results showed a sinus rhythm with no pathological findings. However, her brain computed tomography (CT) scans revealed a large hematoma in the right occipital-parietal region (Fig. 1). Thus, she was admitted to the intensive care unit. At that time, the patient, who previously medicated with amlodipine 10 mg/day for her HT, had a normal blood pressure.

Due to her intracranial hematoma, drugs such as heparin, low-molecular-weight heparin, and aspirin were not administered during clinical follow-up in the intensive care unit, as mutually decided upon by the relevant departments. On day 8 under intensive care, the patient experienced chest pain. The electrocardiogram taken at 02:00 AM showed inferior sinus rhythm and minimal ST elevation in V6. The electrocardiogram taken at 06:00 AM showed minimal ST regression, and the electrocardiogram taken at 4:30 PM showed T wave negativity in the inferior region. The initial troponin T value of 8 increased to 93, leading to the administration of low-molecular-weight heparin. Control brain tomography revealed a focal hyperdensity of approximately 50 mm×25 mm in the right parieto-occipital area, an indication of parenchymal hemorrhage with edematous hypodensity at the periphery. The patient could not be treated with anticoagulant drugs, such as clopidogrel. Moreover, the patient was subjected to low-molecular-weight heparin, troponin T, and electrocardiography monitoring. No pathology was seen during follow-up, and the patient was transferred to the neurosurgery department on day 15.

Case 2

A 66-year-old male patient (weight: 94 kg; height: 176 cm) presented to the clinic with occasional mild chest pain. The patient received five stents 17 years ago and was taking ticagrelor 90 mg twice a day, atorvastatin 40 mg, aspirin 100 mg, metoprolol 50 mg, and Norvasc 5 mg. Angiography revealed eccentric plaques in the proximal segment of the circumflex artery, intimal irregularities and calcific plaques in the distal part of the right coronary artery, and calcific plaques causing 30% stenosis in the lumen of the proximal segment of the left anterior descending artery. Two stents were placed based on these findings. While in the ward after angiography, the patient experienced nausea, vomiting, severe headache, and double vision. The CT results showed bleeding in the parieto-occipital region (Fig. 2). During the onset of his headache, his blood pressure, which was previously normal, rose to 180/110 mmHg and thus was given an antihypertensive medication. He was brought to the intensive care unit for close monitoring, and a low-dose nitroglycerin infusion was started. The patient had a heart rate of 65 beats/min and a respiratory rate of 16 breaths/min. An anamnesis revealed that ticagrelor loading (180 mg) was administered during stent placement. The patient had a blood pressure of 70/34 mmHg, a pulse rate of 108 beats/min, and a respiratory rate of 23 breaths/min. The arterial blood gas test showed a 7.37 pH level, 41 mmHg $PaCO_2$, 78 mmHg PaO_2, 22 mmol/L HCO_3, 1.9 mmol/L lactate, and 95% oxygen saturation. Physical examination revealed no sign of serious trauma, and no deficit was detected in the neurological examination other than diplopia. Laboratory findings showed normal values for blood glucose, electrolytes, liver and kidney function, and coagulation parameters. Normal values were also obtained for hemoglobin count (14.1 g/dL; normal: 11.5–15.5 g/dL), leukocyte count (9.15 µ/L; normal: 3.8–10 µ/L), neutrophil percentage (70%; normal: 45–78%), and platelet count (223,000 µ/L; normal: 100,000–400,000 µ/L). No pathology was detected through chest radiography, and the electrocardiography results showed a sinus rhythm with minimal ST depression. However, a large hematoma was observed in the right occipitoparietal region.

Due to the patient's intracranial hematoma, heparin, low-molecular-weight heparin, aspirin, ticagrelor, and clopidogrel were not administered during clinical follow-up in the intensive care unit. On day 4, only clopidogrel was started considering the patient's stent history. No pathology was seen during follow-up, and the patient was transferred to the cardiology service on day 8.

Discussion

Ticagrelor use has increased recently. However, incidences of drug interaction and side effects in elderly patients have

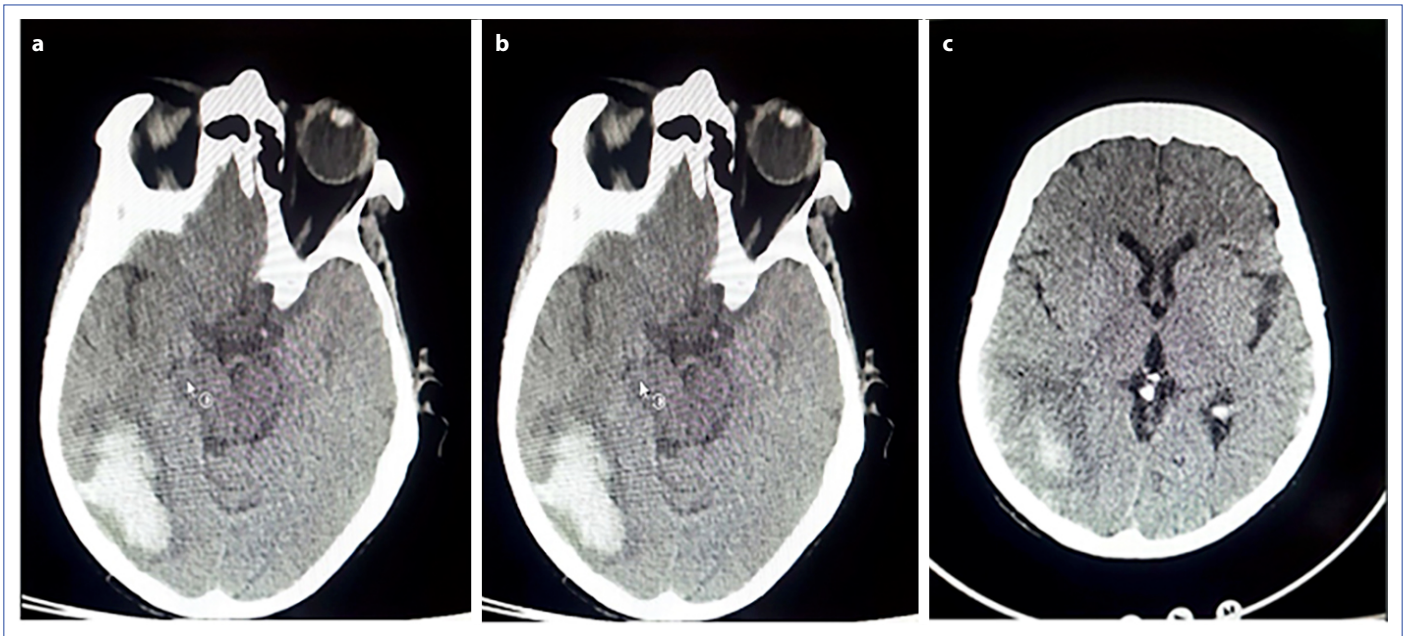

Figure 1. Large-sized hematoma in the right occipital-parietal region of the first patient.

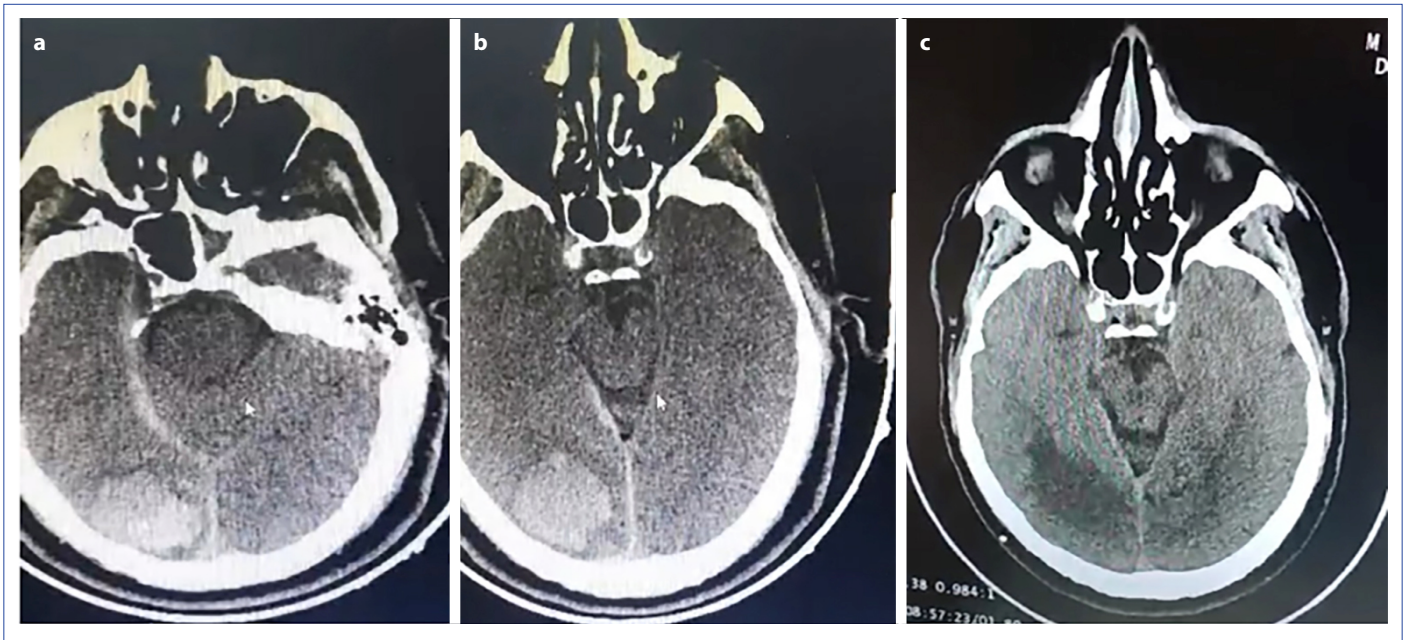

Figure 2. Large-sized hematoma in the right occipital-parietal region of the second patient.

also increased.[7] Although ticagrelor reduces the risk of major vascular events after acute myocardial infarction (AMI), it increases the risk of bleeding. Bleeding events in AMI patients are associated with poor prognosis and increased mortality.[8] Since 2011 in Sweden, the standard antithrombotic treatment following AMI is the combination of aspirin and ticagrelor in accordance with the international recommendations based on the PLATO (Platelet Inhibition and Patient Outcomes) study. Patients with a previous ischemic stroke and patients with Acute Coronary Syndrome who have had a previous ischemic stroke can be treated with ticagrelor for up to 12 months. If the patient is to undergo elective surgery and an antiplatelet effect is not desired, ticagrelor should be discontinued 5 days before surgery.[9] Overall, there was no difference in total major or fatal bleeding events, but non-coronary artery bypass graft major bleeding was more common in patients treated with ticagrelor. While intracranial hemorrhage

(ICH) is a rare condition, fatal ICH events were higher in patients treated with ticagrelor than in those treated with clopidogrel. Due to the low incidence of ICH events, the above findings and the ICH data from a recent randomized trial are inconclusive.[10] Fatal bleeding caused by ticagrelor is likely multifactorial because the first patient was 75 years old and had DM and HT, whereas the second patient had a sudden increase in blood pressure after angiography. In the THALES study (Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and Aspirin for the Prevention of Stroke and Death), when added to aspirin, ticagrelor reduced the incidence of stroke and death but increased the risk of serious bleeding compared with placebo.[11] Further studies are needed to determine which patients are suited for ticagrelor monotherapy to tailor treatment to individual characteristics and thus ensure efficacy and safety. We believe that ticagrelor dose should be adjusted according to body weight and that the topical medications used previously should be taken into consideration.

It may also help improve the short- and long-term tolerability of ticagrelor in the future. Learning how ticagrelor works when used in conjunction with new secondary prevention drugs will provide opportunities to improve the secondary prevention of cardiovascular diseases.

Treatment-induced brain parenchymal hemorrhage may be rare but nonetheless a possible adverse effect of ticagrelor. When administering a loading dose of ticagrelor, medical practitioners should carefully consider patients' history, age, and indications, and they must be cautious about the above side effect. Given its short plasma half-life, ticagrelor should be taken twice a day. However, it should be noted that ticagrelor is associated with more bleeding complications than clopidogrel. The two cases presented herein show the need to closely monitor bleeding in patients receiving a loading dose or higher doses of ticagrelor.

Disclosures

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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