Case Report

Diffuse Alveolar Hemorrhage in Patients Undergoing Neurointervention: A Case Report

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Abstract

Introduction: Diffuse alveolar hemorrhage (DAH) is a very rare complication but acute and life-threatening event. Clopidogrel has generally administered for neurointerventional surgery, but there were no reports of DAH related to clopidogrel in patients undergoing neurointervention.

Case Presentation: A 70-year-old male presented with DAH associated with clopidogrel after transfemoral cerebral angiography and coil embolization for cerebral aneurysm. The chest radiography showed bilateral symmetric peribronchial consolidation and bronchoscopy revealed diffuse hemorrhage on the bronchial wall at the bilateral lung. Clopidogrel was withdrawn and mechanical ventilation was applied for postoperative three days.

Conclusions: Small dose of clopidogrel (75 mg) may lead to rare, life-threatening DAH, so physicians should be aware of the possibility of DAH after neurointervention in patients who have respiratory distress, worsening alveolar infiltrates accompanied by hemoptysis.

Keywords: Clopidogrel, Pulmonary Hemorrhage, Endovascular Procedure

1. Introduction

Various antiplatelet medications are used to prevent the thromboembolic complications of endovascular interventions. However, the antiplatelet therapy is associated with an increase in the bleeding complications and the incidence in endovascular neurointervention had been reported to be up to 9.3% - 21.3% (1, 2).

Diffuse alveolar hemorrhage (DAH) is a very rare complication but an acute and life-threatening event. A few DAHs associated with thienopyridine derivatives have been previously reported in patients undergoing percutaneous coronary intervention (3-5). However, there were no reports of DAH related to thienopyridine derivatives in patients undergoing endovascular neurointervention. So, we report a case of DAH that occurred during an immediate postoperative period and associated with clopidogrel, after transfemoral cerebral angiography and coil embolization for cerebral aneurysm.

2. Case Presentation

A 70-year-old male, 151 cm and 50 kg, was diagnosed with cerebral aneurysm and admitted for transfemoral cerebral angiography (TFCA) and coil embolization. He underwent craniotomy and hematoma evacuation for hypertensive cerebellar hemorrhage 7 years ago. He diagnosed with ischemic stroke in the distribution of the right middle cerebral artery 3 years ago and residual left-side hemiparesis presented. Also, he had known with diabetes mellitus, hypertension, and hyperlipidemia, 20 years ago, 10 years ago, and 5 years ago, respectively. He had received irbesartan 150 mg per day, simvastatin 10 mg per day, and metformin 850 mg per day. There was no previous history of cardiopulmonary diseases and drug allergies. Following our standard protocol, he was received clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi pharmaceuticals, Bridgewater, NJ, USA) 75 mg per day for 3 days before the neurointervention. Preoperative laboratory findings were white blood cell count $13.8 \times 10^3/\mu L$, hemoglobin 13.2 g/dL, platelet count $217 \times 10^3/\mu L$, prothrombin time (PT) 11.4 seconds, 1.03 international normalized ratio (INR), activated partial thromboplastin time (aPTT) 29 seconds, and fasting blood glucose in the range of 10.7 - 19.2 mmol/L. Chest radiography (Figure 1A), pulmonary function test, and electrocardiogram (ECG) were within the normal range.

After he was monitored with ECG, noninvasive blood pressure, and pulse oxymetry, general anesthesia was in-
duced with thiopental sodium 300 mg, fentanyl 50 mcg, and rocuronium 50 mg. Intubation was performed without any difficulties and then we checked the lung sound was clear in both lung fields. General anesthesia was maintained with sevoflurane and a mixture of oxygen in air, fraction of inspired oxygen of 0.5 and the mechanical ventilator (Datex-Ohmeda S/5 anesthesia delivery unit with spirometry, Helsinki, Finland) was set volume controlled mode with tidal volume 4 - 6 mL/kg and respiratory rate 8 - 12 times/min. Positive end-expiratory pressure was set to zero. Ventilation was adjusted to achieve an end-tidal carbon dioxide tension (ETCO2) of 35 - 40 mm Hg. During procedure, definite changes of the ventilator settings and airway pressure were not occurred. Heparin sodium 1000 IU was administered intravenously for systemic anticoagulation during the operation. At the end of the operation, after recovering of spontaneous respiration and confirming four twitches in response to train-of-four stimulation, neostigmine 1.5 mg and glycopyrrolate 0.4 mg were used to reverse residual neuromuscular blockade. We confirmed the recovery of muscle power and removed the endotracheal tube. He was awake fully and had no complaints of any discomfort or respiratory disturbance and transferred to CT room. Oxygen (6 L/min) was administered via face mask with reservoir. As he was arrived to the intensive care unit (ICU), twenty minutes after extubation, the patient suddenly developed a severe cough and hemoptysis and the pulse oximeter indicated 80% - 85%. We promptly suctioned oral cavity and approximately 20 mL of fresh blood was suctioned. The vital signs measured upon arrival showed a blood pressure (BP) of 177/92 mmHg, heart rate (HR) of 100 beats per minutes (BPM) and SpO2 of 85%. After oral suction, the vital signs were BP 113/68 mmHg, HR 88 BPM, SpO2 94%. Auscultation of his lungs revealed new bilateral rhonchi and the chest radiograph revealed bilateral diffuse interstitial infiltration (Figure 1B). The blood test results were the following: pH 7.333, PaCO2 38.9, PaO2 68.6, SaO2 92.1%, HCO3- 20.8, WBC 13,700/mm3, Hb 13.8 g/dl, hematocrit 40.3%, platelet 186000/mm3. The PT was 13.1 seconds, 1.19 INR and the activated PTT was 35 seconds. He continued paroxysmal coughing that produced progressively frank hemoptysis and his respiratory status deteriorated, so the patient was intubated and fresh blood was suctioned through the endotracheal tube. His vital signs were as follows: BP 120/70 mmHg, HR 106 BPM, respiration rate 28 breaths/min, temperature 38.4, and SpO2 80%. Bronchoscopy was performed by a pulmonologist to determine the cause of hemoptysis and hypoxia. The apparent pulmonary bleeding continued bilaterally with no identifiable bleeding focus. Depending on the findings of chest radiography and bronchoscopy, we had diagnosed as DAH. Although coagulation profiles were platelet count.
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184 × 10^3/µL, PT 13.1 seconds, 1.19 INR, aPTT 35 seconds, and bleeding time 3.30 seconds, the clopidogrel and the heparin were suspected to be the cause of the DAH (hemoptysis). We discontinued the clopidogrel and administered tranexamine 500 mg and protamine 10 mg intravenously.

On the postoperative fourth day, hemoptysis had stopped and respiratory function was improved and mechanical ventilation was discontinued. The chest radiograph showed decreased infiltration of both lung fields (Figure 1E). On the postoperative five day, the patient became symptom-free and was transferred to the general ward.

3. Discussion

Diffuse alveolar hemorrhage associated with antiplatelet medication is a rare complication among the major bleeding events. Previous reports about DAH associated with antiplatelet medication were mainly reported in patients administered of glycoprotein IIb/IIIa inhibitor (6-9). Ali et al. has reviewed 1020 patients who received glycoprotein IIb/IIIa inhibitor for cardiovascular problems and reported that the incidence of DAH was 0.68% (8). Besides, DAH associated with thienopyridine derivatives was relatively rare. Furthermore, most of the previous reports were that the thienopyridine was administered for the patients undergoing acute coronary syndrome (5, 7, 9). Kilaru et al. reported the first case of DAH developing after clopidogrel 300 mg for insertion of coronary stent (5). Recently, Ikeda et al. (4) and Kim et al. (3) reported a DAH developing after the combination therapy with respectively ticlopidine 200 mg with aspirin 100 mg and clopidogrel 600 mg with aspirin 300 mg, following acute coronary syndrome. Even though they accompanied with bleeding complications, dual antiplatelet therapy with clopidogrel and aspirin is widely used to reduce the risk of thromboembolic complications of percutaneous coronary interventions and endovascular neurointerventions. The risk of thromboembolic complications has been estimated at 8% due to the thrombogenic nature of foreign guide-wire and endovascular implants (10). As a result, the dual antiplatelet therapy with aspirin (325 mg) and clopidogrel (75 mg) has been recommended for patients undergoing endovascular neurointerventions (11). In the present case, 3 days before neurointervention, the patient was administered clopidogrel 75 mg daily and during the procedure, heparin sodium 1000 IU was administered intravenously. Therefore, either clopidogrel and/or heparin may have the possibility of increasing the bleeding risk and contribute to DAH. We did not check intraoperative ACT routinely because unfractionated heparin has a half-life of about one to two hours after infusion and the usual dose of heparin for neurointervention is small. After the patient’s symptoms occurred, we conducted coagulation tests and confirmed the following results: PT 13.1 seconds (1.19 INR), aPTT 35 seconds, BT 3.30 seconds, and platelet count 184 × 10^3/µL. We have confirmed that there is no prolongation of the prothrombin time and heparin-induced thrombocytopenia.

Moreover, the dose of thienopyridine for neurointervention was smaller than the dose for PCI. However, there is a high level of inter-individual variability in the antiplatelet response to clopidogrel (12) and in the patients with hyper-response to clopidogrel there might be at increased risk of hemorrhagic complications (13). Goh et al. showed the correlation between hyper-response to clopidogrel and the increased risk of hemorrhagic complications in patients undergoing neurointerventional procedures (2). We were assumed that the DAH might be due to the potential hyper-response to clopidogrel rather than systemic heparin.

Clinically, DAH may be considered by the symptoms of dyspnea, hemoptysis, and cough and the presence of new infiltrations on chest radiography. Diffuse alveolar hemorrhage may be misdiagnosed as pneumonia or pulmonary edema because hypoxemia and chest radiographic infiltration are common findings in these conditions. So, hemoptysis is an important clue to a diagnosis of DAH. Diffuse alveolar hemorrhage can be diagnosed by using chest computed tomography (CT), chest magnetic resonance imaging (MRI), and bronchoscopy. Among them, early bronchoscopy is especially recommended if the diagnosis is uncertain and vital signs were unstable (14). Because transporting the patient for CT or MRI scan might be dangerous when the patient was hemodynamically unstable. In the present case, we confirmed the diagnosis using bronchoscopy. After emergency situation, the additional chest CT or chest MRI scan were not performed because of the patient’s refusal for financial reason.

It was important to consider the differential diagnosis of DAH due to the antiplatelet therapy in the present case. The patient did not have any characteristics indicating Wegener granulomatosis, Goodpasture syndrome, or systemic lupus erythematosus, which are causes of DAH, and symptoms of DAH improved after the clopidogrel was discontinued, so specific serologic tests and tissue biopsy were not examined. In addition, the bronchoscopic findings of no inflammation, edema, and hyaline membranes on the bronchial wall and this suggested that the clopidogrel was the sole cause of DAH.

Misdiagnosis of DAH can result in fatal results and early suspicion is important. Treatment for DAH is supportive (5, 15). The first, all medications, which have antiplatelet or antithrombotic effect, should be discontinued
and reversed as soon as possible. The second, the patients with DAH are managed to maintain lung reserves and oxygenation with aggressive pulmonary care. The pulmonary cares are supplemental oxygen, bronchodilators, intubation, protective strategies for the less involved lung, and mechanical ventilation. If DAH combined with autoimmune condition, the application of corticosteroid and immune suppressive agents should be considered. The prognosis remains poor in patients with thienopyridine associated DAH. Among the previously reported three cases, two patients had died although optimal treatment was performed (10, 12, 13).

In conclusion, a general clopidogrel has been administered to the patients undergoing neurointervention without fear or worry; however, the results the current study showed that such dose of clopidogrel (75 mg) may lead to rare, life-threatening DAH. Therefore, physicians should be aware of the possibility of DAH in patients receiving clopidogrel undergoing neurointervention, who have respiratory distress, worsening alveolar infiltrates accompanied by hemoptysis.

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Footnotes

Authors’ Contribution: Yun Suk Cheo participated in the management of the patient developed and Ae Ryoung Lee abstracted data, wrote the manuscript, and reviewed the references.

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