

Fatal Pulmonary Haemorrhage with the Combined Use of Abciximab and Fibrinolytic Agent

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ABSTRACT

The increased bleeding risk associated with the use of abciximab has been well reported. The risk appears to be amplified when abciximab is administered concurrently with a fibrinolytic agent. We report and review the literature on the occurrence of a case of fatal pulmonary haemorrhage, a rare bleeding complication, in a patient who received both these drugs.

Keywords: abciximab, fibrinolytic, angioplasty, pulmonary haemorrhage

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INTRODUCTION

Abciximab, a monoclonal antibody to platelet glycoprotein IIb/IIIa receptor, has been shown to improve the safety of patients undergoing percutaneous coronary intervention. However, its use is also associated with significant risk of bleeding complications. The combined use of standard doses of fibrinolytic agents, specifically streptokinase, and abciximab has been reported to be associated with unacceptable high bleeding rates⁽¹⁾. We report a case of fatal pulmonary haemorrhage in a patient who received both abciximab and full dose of streptokinase.

CASE REPORT

A 53-year-old Chinese lady with cardiovascular risk factors of hypertension, hyperlipidemia and family history of premature coronary artery disease was admitted to the Emergency Room for sudden onset of chest pain. She had a history of antecedent angina pectoris for the last one year. There were associated symptoms of profuse diaphoresis and near syncope. Her presenting 12-lead electrocardiogram showed evidence of acute inferoposterior and right ventricular myocardial infarction. There was mild pulmonary congestion on her chest radiograph (Fig. 1). Aspirin dose of 300 mg was given. The patient was next mechanically ventilated because of unresponsiveness and hypotension. Intravenous streptokinase at a dose

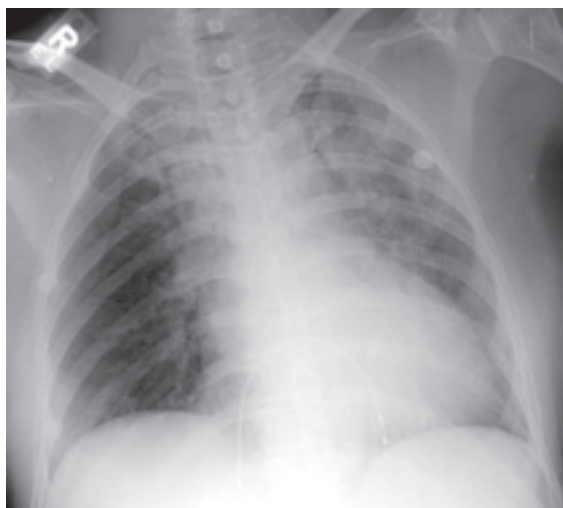


Fig. 1 Initial chest radiograph showing pulmonary congestion.

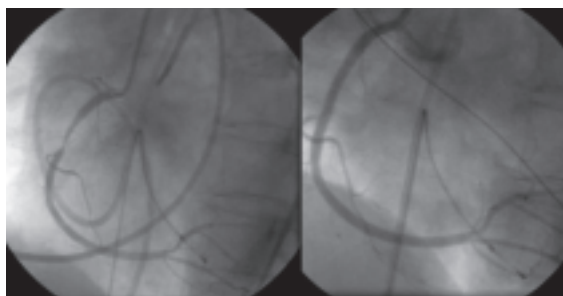


Fig. 2 Right coronary artery stenosis before and after coronary stent implantation.

of 1.5 megaunits was administered over 60 minutes. A temporary pacing wire was inserted via the right common femoral vein because of haemodynamically significant high grade atrioventricular block. A Swan-Ganz catheter was also inserted for central haemodynamic monitoring with an opening wedge pressure of 15mmHg. A total of three litres of fluid were infused because of persistent hypotension. Bedside echocardiography showed a hypokinetic inferior wall segment with overall left ventricular ejection fraction visually estimated to be 40%. Given her unstable haemodynamic status despite fibrinolytic therapy, a decision was made to proceed with emergent rescue angioplasty nine hours later. Coronary angiography revealed a high grade 95% discrete stenosis in the mid segment of the

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Fig. 3 Chest radiograph showing diffuse alveolar infiltrates.

right coronary artery with normal antegrade flow (Fig. 2). Low heparin dose of 2,000 units was administered prior to the percutaneous coronary angioplasty procedure based on an estimated body weight of 60 kg. The vessel was successfully revascularised with the implantation of a 3.5 x 16 mm NIR coronary stent. Post-procedurally, there was residual slow antegrade flow and a standard bolus (0.25 mg/kg) and infusion (10 ug/min) dose of abciximab was commenced as a “bail-out” or “rescue” therapy. The maximum activated clotting time recorded after that was 249 seconds. The patient was stable after the interventional procedure. However five hours later, she became hypotensive. There was an aspirate of fresh blood from her endotracheal tube and persistent hypoxemia was encountered despite mechanical oxygenation. Her chest radiograph showed marked pulmonary congestion (Fig. 3) and her haemoglobin showed a significant drop from 9.7 g% to 5.6 g%. The platelet count was $136 \times 10^9/L$. There was no evidence of bleeding in the groin or gastrointestinal tract. The abciximab was immediately reversed with platelet infusion but this did not arrest the pulmonary bleed. Despite continued active resuscitation, her condition deteriorated and she finally succumbed from severe hypoxemia.

DISCUSSION

Glycoprotein IIb/IIIa receptor inhibitors, a new potent class of antiplatelet agents, are now being widely used in a variety of clinical situations, namely,

as an adjunctive therapy during percutaneous coronary interventions and for patients with acute coronary syndromes.

This was the first case of reported pulmonary haemorrhage in our own registry of Asian patients who had received abciximab while undergoing percutaneous coronary revascularisation⁽²⁾. Pulmonary haemorrhage as a bleeding complication of abciximab is an uncommon occurrence. It usually manifests as an acute onset of dyspnoea after the administration of the antiplatelet agent, the development of moderate to severe haemoptysis, a marked decrease in haemoglobin and an increase in pulmonary infiltrates on the chest radiograph. Although there was no autopsy performed, the clinical presentation was typical of pulmonary haemorrhage in this patient here. The differential diagnosis of intractable acute pulmonary oedema is less likely here because of the only mildly impaired left ventricular function.

Despite its infrequent occurrence, pulmonary haemorrhage has been consistently reported in many of the published large clinical trials of abciximab. In the four major trials of EPIC⁽³⁾, EPILOG⁽⁴⁾, CAPTURE⁽⁵⁾ and EPISTENT⁽⁶⁾, pulmonary haemorrhage occurred in 10 of 5,382 (0.19%) enrolled patients. The risk factors for the development of this complication are uncertain due to its rare occurrence. Aguirre et al⁽⁷⁾ in the EPIC trial analysis identified several clinical factors which increased the bleeding risk of abciximab. These included greater age, the female sex, lower weight, abciximab therapy, and duration and complexity of the procedure. Khanlou et al⁽⁸⁾ noted in his series of patients with pulmonary haemorrhage that the presence of underlying lung conditions, such as chronic obstructive airway disease, pulmonary hypertension and a high pulmonary capillary wedge pressure might be associated with an increased risk of this potentially fatal complication. Similar observation of the association between elevated pulmonary capillary pressure and pulmonary haemorrhage was also reported by Ali et al in his series of three cases⁽⁹⁾. The presence of pulmonary congestion prior to abciximab administration has also been suggested as a predisposing factor for alveolar haemorrhage. Sitges et al⁽¹⁰⁾ described in his case report, an ex-smoker who had clinical and radiographic evidence of pulmonary congestion who subsequently developed pulmonary haemorrhage. Our patient had no history of tobacco abuse but did indeed have mildly congested lung field on her presenting chest radiograph. Her pulmonary wedge pressure was at the upper normal limits of 13mmHg.

The concomitant administration of a fibrinolytic agent and abciximab may have been contributory to

this complication. Our patient had received the full dose of streptokinase and abciximab nine hours apart during her hospitalisation. This combination was noted to result in excess bleeding and excess mortality in the TIMI 14 study resulting in its premature termination⁽¹⁾. Four (67%) out of six patients in that study arm developed major haemorrhage in the study: three had instrumentation-related bleeding and one had intracerebral haemorrhage. Sundlof et al⁽¹¹⁾ also reported a 23% incidence of major bleeding complication when abciximab was used in conjunction with rescue percutaneous coronary angioplasty within a mean of four hours of failed thrombolytic therapy (front-loaded 100 mg alteplase). This observation was attributed to the prolonged fibrinolytic activity from plasmin which has a long half-life. The combination of streptokinase with other glycoprotein IIb/IIIa receptor inhibitors, such as the eptifibatide⁽¹²⁾, has also been associated with an increased risk of bleeding.

The dosage of heparin given concurrently may also be contributory. In the earlier trials (EPIC, CAPTURE and EPILOG subgroup) where the standard dose of heparin of 100 U/kg was given, pulmonary haemorrhage was reported in 9 (0.31%) of 2898 patients. In the later trials where the dose of weight-adjusted heparin was reduced to 70 U/kg, the frequency of pulmonary haemorrhage was reduced to 1 (0.04%) of 2,484 patients. This is consistent with the overall reduction in the risk of bleeding complications with the use of low dose weight-adjusted heparin. Indeed, the dose of heparin has been further reduced in my centre to 50 U/kg with consequent lowered intraprocedural activated clotting time to decrease bleeding risk⁽¹³⁾. While only 2,000 units of heparin were given in this patient, it is possible that the total combination of fibrinolytic, heparin and abciximab had resulted in the bleeding complication.

The occurrence of pulmonary haemorrhage is not confined to abciximab among the GP IIb/IIIa inhibitors. Tirofiban, a synthetic nonpeptide GP IIb/IIIa inhibitor, has been reported to cause diffuse alveolar haemorrhage, when used with heparin in a patient⁽⁹⁾. Fortunately, the patient responded to aggressive pulmonary toilet and blood transfusion.

Pulmonary haemorrhage is a serious and potentially life-threatening condition. Treatment is mainly supportive with discontinuation of all antiplatelet and anticoagulant agents. Platelet transfusion may be used

to reverse the effect of abciximab quickly but has no significant effect on tirofiban-induced platelet inhibition. Mechanical ventilation and blood transfusion may be employed if clinically indicated.

CONCLUSION

This case illustrated a rare bleeding complication of abciximab, which occurred in the setting of a patient who had just received full dose of streptokinase therapy. The recognition of pulmonary haemorrhage requires a high index of suspicion and the diagnosis is usually made after the exclusion of other causes of acute respiratory distress diseases. Clinician must bear in mind the increased bleeding risk of fibrinolytic and abciximab when considering the combined use of these therapies.

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