Cardiopulmonary bypass using nafamostat mesilate for patients with infective endocarditis and recent intracranial hemorrhage

Takeyoshi Ota, Kenji Okada, Hiroya Kano, Yutaka Okita*

Department of Cardiovascular Surgery, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, 650-0017, Japan

Received 5 October 2006; received in revised form 24 January 2007; accepted 26 January 2007

Abstract

Infective endocarditis is a life threatening disease with high mortality and morbidity, including brain infarction concomitant with intracranial hemorrhage. Generally, patients with a recent intracranial hemorrhage are believed to be a contraindication to undergo cardiac surgery with cardiopulmonary bypass. However, some patients with infective endocarditis occasionally require an unavoidable emergent surgery because of uncontrollable heart failure or on-going thromboembolism even if complicated by intracranial hemorrhage. In this study, a cardiopulmonary bypass strategy using nafamostat mesilate as an anticoagulant for such patients is discussed based on three cases we experienced.

© 2007 Published by European Association for Cardio-Thoracic Surgery. All rights reserved.

Keywords: Nafamostat mesilate; Cardiopulmonary bypass; Intracranial hemorrhage; Infective endocarditis

1. Introduction

Infective endocarditis is a life threatening disease with high mortality and morbidity. Neurological complications make the prognosis much worse [1]. Especially, intracranial hemorrhage is the most serious complication. Patients with a recent intracranial hemorrhage are believed to be a contraindication against cardiac surgery with cardiopulmonary bypass (CPB). However, a number of acute infective endocarditis (AIE) patients with a recent intracranial hemorrhage get to require urgent surgical intervention due to progressive hemodynamic instability, large floating vegetations and uncontrollable infection, even though it might be a rare condition. Use of heparin in the traditional CPB management possibly deteriorates the intracranial hemorrhage postoperatively, which is one of the reasons making its mortality higher. Therefore, it is crucial to establish a highly secure CPB strategy in these rare patients.

Nafamostat mesilate (6-amino-2-naphthyl p-guanidinobenzoate dimethanesulfonate) is reported to reduce blood loss during CPB and postoperative course [2]. Nafamostat mesilate is a synthetic protease inhibitor that inhibits coagulation and fibrinolysis as well, which is caused by inactivating action on thrombin, plasmin, trypsin, kallikrein, coagulation factors XIIa and Xa, complements C1r and C1s [3, 4].

In this study, we report a successful CPB strategy using nafamostat mesilate as an anticoagulant for AIE patients with recent intracranial hemorrhage.

*Corresponding author. Tel.: +81-78-382-5942; fax: +81-78-382-5959. E-mail address: yokita@med.kobe-u.ac.jp (Y. Okita).

© 2007 Published by European Association for Cardio-Thoracic Surgery

2. Materials and methods

From October 1999 to March 2006, we had three AIE patients complicated with recent intracranial hemorrhage. The patient characteristics are listed in Table 1. All patients were diagnosed with AIE according to modified Duke criteria [5] and had to undergo urgent surgery in acute phase for reasons mentioned below.

Patient 1, a 75-year-old female, underwent a mitral valve repair for severe mitral regurgitation (MR) caused by healed infective endocarditis. On the 15th postoperative day (POD), systemic inflammatory response recurred and blood culture grew methicillin-resistant Staphylococcus aureus. Echocardiography revealed mild MR with small, recurrent vegetation on the mitral valve. Brain computed tomography (CT) was performed on 22nd POD because a paralysis of her left upper limb appeared, which demonstrated multiple focal cerebral bleeding in various sizes ranging from 4 to 25 mm (Fig. 1). We decided on an urgent operation on 24th POD due to the uncontrollable infection and progressive acute heart failure.

Patient 2, a 76-year-old male, had a history of mitral valve replacement with a bioprosthetic valve and tricuspid annuloplasty, which resulted in leaving him bedridden with a tracheotomy because of pneumonia and chronic heart failure. Two months after the surgery, he developed AIE with mobile vegetations on the mitral bioprosthetic valve. Brain CT, which was performed for the further evaluation of convulsion, demonstrated a cerebral bleeding in the left frontal lobe (25×25 mm). In spite of his poor general condition, we decided to perform a surgery at four days after onset of brain hemorrhage because of refractory infection against intensive medical therapy.
Patient 3, a 24-year-old male, was referred to our department for perpetuated high spike fever and severe MR with a large floating vegetation (15 mm in diameter). Brain CT performed on admission demonstrated multiple small infarctions with cerebral bleeding in the parietal lobe (10 × 8 mm). There was no neurological symptom. The operative indications were: repeated embolic episodes (i.e. multiple cerebral infarction, splenic embolism) and the large mobile vegetation.

All surgeries were performed with routine procedure except CPB anticoagulation management. Brain CT was performed on the 1st POD in all patients.

Anticoagulation during CPB was managed as follows: prior to connection of the extracorporeal circuit, 100 IU/kg of heparin (our normal dosage for CPB: 200 IU/kg) was administered to obtain an activated clotting time (ACT) over 250 s. No additional heparin was administered thereafter. A heparin-coated bypass circuit (Duraflo II, MERA, Tokyo, Japan) was used comprising a membrane oxygenator (HPO-200WRHF-C, MERA). Nafamostat mesilate ranging from 0 to 2.0 mg/kg/h was administered through the venous circuit line. After 100 IU/kg of heparinization, nafamostat mesilate started with 2.0 mg/kg/h when initial ACT ranged between 250 and 275 s, 1.0 mg/kg/h between 275 and 300 s, 0.5 mg/kg/h between 300 and 350 s, 0 mg/kg/h over 350 s. ACT, for which blood samples were taken from the venous circuit line, was maintained between 250 and 400 s during CPB (our standard range: 400–600 s). The pump flow was set at 2.4–2.6 l/min/m². All patients were cooled down to 33 °C. Target mean systemic blood pressure was 50 mmHg. Nafamostat mesilate was stopped approximately 10 min before the termination of CPB. Protamine was not administered at all.

3. Results

ACT and nafamostat mesilate dosage during CPB are described in Fig. 2. Generally, ACT was well maintained during the first 100 min of CPB. However, after around 100 min, it unexpectedly exceeded the targeted range (Fig. 2a,b), which was possibly due to coagulopathy. Ten minutes after the termination of CPB, ACT levels were 112 s, 123 s, and 101 s in patient 1, 2 and 3, respectively. Systemic blood pressure remained stable at around 50 mmHg in all cases as long as urinary output was maintained (Fig. 3). Cerebral oxygen saturation monitoring demonstrated no change throughout the surgery in all patients. Brain CT performed on the 1st POD demonstrated neither deterioration nor a new occurrence of intracranial hemorrhage in all cases. Postoperative bleedings from chest tubes for immediate postoperative 8 h were 240 ml, 304 ml, 110 ml in patient 1, 2, and 3, respectively. There was no redo operation due to bleeding.

Patient 1 was extubated on the 2nd POD. No abnormal neurological symptom was noted except for the left arm paralysis, which was the same as before the surgery. Although she could get over the postoperative acute phase crisis without major complications, she died of a newly occurred brain hemorrhage on the 46th POD which was not associated with the surgery. Patient 2 required an intraaortic balloon pumping support due to low output syndrome after CPB. His postoperative neurological status remained unclear because of the sedative effect to keep his hemodynamic stable, while the CT performed on the 1st POD demonstrated no visible deterioration. He died of uncontrollable sepsis on the 7th POD. Patient 3 was extubated in the evening of surgery and his postoperative course was uneventful. No abnormal neurological symptom was noted. He was discharged on the 25th POD.
4. Discussion

During the same period, we had 28 cases of AIE surgery (native valve: 23, prosthetic valve: 5). Surgical indications were serious heart failure (n=16; 57%), large vegetation (n=7; 25%) and uncontrollable sepsis (n=5; 18%), respectively. Seven patients (25%) had a history of stroke as a complication in acute phase surgery. Three patients (11%) had a recent intracranial hemorrhage. General consensus for surgical indications for infective endocarditis is hemodynamic instability, persistence of sepsis, existence of mobile large vegetations (recommended size >10 mm), perivalvular infection, prosthetic or fungal infective endocarditis, etc. [6]. Perioperative cerebral bleeding, including newly onset and deterioration of preoperative hemorrhage, is associated with high hospital mortality [7]. The majority of the authors agree that cardiac surgery should be deferred for at least four weeks after intracranial hemorrhage [7, 8]. Nevertheless, it is a possible situation that some patients with AIE with recent intracranial hemorrhage have to be operated on in acute phase, otherwise they would die. We applied nafamostat mesilate to an anticoagulant during CPB for AIE patients with recent intracranial hemorrhage.

Nafamostat mesilate has been used as an anticoagulant in substitution for heparin for extracorporeal membrane oxygenation, left ventricular assist device and hemodialysis [9, 10]. Main advantages of nafamostat mesilate are its very short half-life and functions to inactivate coagulation, fibrinolysis and platelet aggregation. In this study, we confirmed no additional bleeding just before the surgeries, which meant that primary and secondary hemostasis had happened in the bleeding lesion at the surgeries. In these circumstances, using traditional CPB must be crucial because clots in the bleeding area would be deconstructed by fibrinolysis activation during CPB [11]. Some literature demonstrated that fibrinolysis was significantly inhibited during CPB when using nafamostat mesilate [12], which could be an important function in the present study for...
preventing progression of perioperative intracranial hemorrhage. On the other hand, heparin enhances fibrinolytic activity during CPB, leading to dissolution of the clots and to recurrence of bleeding [13]. In this study, we accomplished the successful CPB management with continuous use of nafamostat mesilate.

As for process of metabolism, nafamostat mesilate is rapidly metabolized in liver and blood. The half-life is 1.1 min in $\alpha$ phase and 23.1 min in $\beta$ phase. Indeed, ACT was normalized immediately after CPB termination without protamine in all cases. However, we recognized that ACT had a tendency to rise excessively around 100 min after we used nafamostat ranging between 0–2.0 mg/kg/h to maintain the targeted ACT during CPB. Given mild hypothermia causing delay of metabolism of nafamostat mesilate, we estimated that blood concentration of nafamostat mesilate was kept at least 0.1–1.0 $\times 10^{-6}$ M which was enough to inhibit coagulation, fibrinolysis and platelet aggregation. Inhibition of fibrinolysis activation is the most important supplemental effect of nafamostat mesilate, as excessive fibrinolysis can cause intracranial bleeding during or after CPB [2].

With regard to perfusion pressure, we set a targeted systemic pressure of 50 mmHg during CPB. We reduced blood pressure quite slowly down to 50 mmHg as long as urinary output was obtained, which might be part of the reason for no additional or no worsening neurological events.

Despite the contributions of this study, several limitations have to be addressed. First, since the study had a small number of patients, further study is necessary in order to demonstrate the safety of our CPB strategy. Second, we possess no laboratory data about coagulation and fibrinolysis, while those data might not be able to reflect the effect of nafamostat mesilate properly due to severe inflammatory activity of AIE. We plan to measure not only data of the coagulation and fibrinolysis system but the blood concentration of nafamostat mesilate during CPB in future cases.

In conclusion, we reported the novel CPB strategy with nafamostat mesilate as an anticoagulant. The strategy might be potentially safe and useful to prevent deterioration of recent intracranial hemorrhage complicated with AIE in intraoperative and acute postoperative terms.

References


