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Cardiopulmonary bypass strategy with low-dose heparin and nafamostat mesilate in cardiac surgery: A safe option for patients with acute stroke

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Patients undergoing open cardiac surgical procedures with a history of acute stroke pose a difficult management problem. There is always the risk that cardiopulmonary bypass (CPB) and heparinization may induce intracranial hemorrhage. A multicenter study suggests that open cardiac surgical procedures can be performed safely 4 weeks after stroke¹; however, some patients with acute cardiogenic stroke occasionally require emergency surgery because of uncontrollable heart failure or ongoing thromboembolism.

Heparinized CPB with low systemic heparinization is among the therapeutic options when operating on patients with the risk of intracranial hemorrhage; however, low systemic heparinization could allow clot formation.² Nafamostat mesilate (6-amino-2-naphthyl *p*-guanidinobenzoate dimethanesulfonate, currently available in Japan and Korea) is a serine protease inhibitor that has such activities as anticoagulant effect (by inhibiting coagulation factors, XIIa, Xa, and VIIa, along with thrombin), antifibrinolytic activities (by inhibiting tissue-type and urokinase plasminogen activators), and antiplatelet actions.^{3,4} Because of a short half-life of 8 minutes, it has recently been used mainly as an anticoagulant for hemodialysis⁵ and extracorporeal membrane oxygenation⁶ in patients with bleeding tendencies. Nafamostat mesilate has been widely used in Japan as an alternative anticoagulant agent during hemodialysis, and its in vivo effect as an anticoagulant has been established.³

In this study, we report a successful CPB strategy with low-dose heparin and nafamostat mesilate as an

anticoagulant to reduce the dosage of heparin for patients with acute stroke.

MATERIALS AND METHODS

With approval of the institutional review board and patient informed consent, patients who underwent cardiac surgery with CPB with low-dose heparin and nafamostat mesilate were included. From November 2007 and January 2010, we had 17 patients with courses complicated by acute stroke. The patient characteristics are listed in Table 1. Acute stroke was detected by diffusion-weighted magnetic resonance images in 16 cases, and 1 patient had subarachnoid hemorrhage from a ruptured mycotic aneurysm. Of these patients, 14 patients had a diagnosis of active infective endocarditis according to modified Duke criteria. The remaining 3 patients had acute pulmonary embolism with atrial septal defect, left ventricular thrombus, or left atrial myxoma. Mean age was 63.9 ± 16.7 years. Seven patients (41.2%) were female. The indication for the operation was uncontrolled sepsis in 7 patients, uncontrollable heart failure in 5 patients, and ongoing thromboembolism in 5 patients. The mean interval from the onset of stroke to surgery was 2.9 ± 0.4 days. All operations were performed as routine procedures except for the CPB anticoagulation management. Brain computed tomography was performed within 3 days after the surgery in all cases.

Anticoagulation Protocol During CPB

Anticoagulation during CPB was managed as follows: before connection of the extracorporeal circuit, 0.8 mg/kg of nafamostat mesilate and 50 IU/kg of heparin (our normal dosage for CPB is 300 IU/kg) were administered to obtain a diatomaceous earth (Celite; World Minerals Inc, Santa Barbara, Calif) activated clotting time (DEACT, measured with ACTII; Medtronic Blood Management, Parker, Colo) over 250 seconds. If DEACT did not rise above 250 seconds, a 200-IU dose of heparin was administered. CPB was composed of a roller pump (Mera HAS; Senko Medical Instrument Mfg Co Ltd, Tokyo, Japan), a silicon- and heparin-coated hollow-fiber polypropylene oxygenator (Mera NHP Excelung Prime HPO-23WH-C; Senko) and a heparin-coated bypass circuit (Mera Exceline-S, 0.5-inch; Senko). After connection to the pump circuit, nafamostat mesilate and heparin were continuously infused through the venous line of the pump circuit at $0.8\text{ mg}/(\text{kg} \cdot \text{h})$ and $25\text{ IU}/(\text{kg} \cdot \text{h})$, respectively. DEACT, for which blood samples were taken from the venous circuit line every 10 minutes, was maintained between 400 and 600 seconds during CPB. If DEACT exceeded 600 seconds, the continuous infusion of heparin was reduced. An additional bolus injection of 100 IU of heparin was administered when DEACT fell below 400 seconds. Furthermore, kaolin-measured ACT (KACT, measured with Hemochron401; International Technidyne Corp, Edison, NJ) was monitored simultaneously. KACT reflects the heparin activity in

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TABLE 1. Summary of data

Case no.	Age (y)	Sex	Diagnosis	Neurologic history	Operation and time to surgery	ECC time (min)	Blood loss (g)	Outcome
1	54	M	NVE (mitral)	Right parietal hemorrhagic infarct	MVR (0 d)	138	540	Alive
2	63	M	NVE (mitral)	Multiple infarcts	MVR (4 d)	210	280	Alive
3	75	M	NVE (aortic)	Multiple infarcts	AVR (0 d)	106	580	Alive
4	62	F	NVE (mitral)	Multiple infarcts	MVR (14 d)	106	170	Alive
5	84	F	NVE (aortic), AP	SAH	AVR, CABG (28 d)	241	830	Alive
6	78	M	NVE (aortic/mitral)	Right parietal infarct	AVR, MVR (17 d)	257	330	Alive
7	38	M	NVE (aortic/mitral)	Multiple infarcts	MVR (11 d)	176	360	Alive
8	64	F	NVE (mitral)	Multiple infarcts	MVR, CABG (1 d)	155	560	Alive
9	69	M	NVE (aortic/mitral)	Right frontal infarct	AVR, MVR (1 d)	313	670	Alive
10	81	F	NVE (mitral)	Left occipital infarct	MVR (3 d)	157	200	Alive
11	70	M	NVE (mitral)	Multiple infarcts	MVR (3 d)	198	340	Alive
12	67	M	NVE (aortic)	Multiple infarcts	AVR (3 d)	103	600	Alive
13	22	M	NVE (mitral)	Multiple infarcts	MVR (1 d)	181	290	Alive
14	79	F	PVE (aortic)	Multiple infarcts	AVR (3 d)	151	450	Alive
15	79	F	Acute PTE, ASD	Right frontal infarct	ASD closure, PE (3 d)	115	1780	Alive
16	45	M	LV thrombus, AMI	Left frontal infarct	CABG, removal of thrombus (2 d)	58	210	Alive
17	57	F	LA myxoma	Right lower occipital infarct	Resection of LA myxoma (3 d)	57	100	Alive

ECC, Extracorporeal circulation; M, male; NVE, native valve endocarditis; MVR, mitral valve replacement; AVR, aortic valve replacement; F, female; AP, angina pectoris; SAH, subarachnoid hemorrhage; CABG, coronary artery bypass grafting; PVE, prosthetic valve endocarditis; PTE, pulmonary thromboembolism; ASD, atrial septal defect; PE, pulmonary embolectomy; LV, left ventricular; AMI, acute myocardial infarction; LA, left atrial.

the blood under the combined use of nafamostat mesilate because kaolin absorbs nafamostat mesilate, thus minimizing its effect on KACT.⁷ The value of KACT was kept between 200 and 300 seconds. If the KACT reading fell below 200 seconds, a 200-IU dose of heparin was added.

The pump flow was set at 2.4 to 2.6 L/(min · m²). All patients were cooled to mild hypothermia (33°C–34°C). Target mean systemic blood pressure was 60 mm Hg. Cerebral oxygenation was monitored with a near-infrared oxygen monitor (INVOS 4100; Somanetics Corporation, Troy, Mich). The pump flow was adjusted to keep the cerebral oxygenation saturation value the same as at the anesthetic induction. After weaning from CPB and decannulation, residual heparin was reversed with protamine sulfate. Dosage of protamine sulfate was 1 mg for every 100 IU of initial heparin.

RESULTS

Mean dosages of nafamostat mesilate and heparin were 164 ± 64 mg and 704 ± 314 IU, respectively. The changes in DEACT and KACT during CPB are shown in Figure 1. Total blood loss and homologous red blood cell and blood requirements were 487 ± 387 g, 437 ± 359 mL, and 673 ± 456 mL, respectively. In-hospital mortality was 0%. Postoperative brain computed tomography demonstrated neither deterioration nor a new occurrence of intracranial hemorrhage in all patients.

FIGURE 1. Diatomaceous earth- and kaolin-derived clotting time (ACT) values during cardiopulmonary bypass (CPB). Gray zone represents target range for diatomaceous earth-derived activated clotting time.

DISCUSSION

Nafamostat mesilate has been used as an anticoagulant in substitution for heparin in the situations of CPB, left ventricular assist devices, and hemodialysis. The main advantages of nafamostat mesilate are its short half-life and its functioning to inactivate coagulation, fibrinolysis, and platelet aggregation. Murase and colleagues⁸ demonstrated that nafamostat mesilate inhibits fibrinolysis, preserves platelet function during CPB, and reduces blood loss. Ota and associates⁹ demonstrated successful CPB management with mesilate for 3 patients with recent intracranial hemorrhage. Both groups emphasized that inhibition of fibrinolysis activation was the most important supplementary effect of nafamostat mesilate, because as excessive fibrinolysis can cause intracranial bleeding during and after CPB.^{8,9} On the other hand, heparin enhances fibrinolytic activity during CPB, leading to dissolution of clots and recurrence of bleeding. In this study we demonstrated successful CPB management with a continuous infusion of nafamostat mesilate in open heart surgical procedures for patients after acute stroke.

Some authors have maintained that low-dose heparin can achieve adequate anticoagulation during CPB, but Ovrurn and coworkers² reported that clot formation in the cardiectomy reservoir occurred during CPB with low-dose heparin. In our opinion, low-dose heparinization during CPB should not be routinely used because of the risk of clot formation; however, it provides an advantage for patients with the risk of bleeding. We believe that the combination of low-dose heparin and nafamostat

mesilate can produce safer anticoagulation than can low-dose heparin.

Limitations to the current study include small sample size, the lack of a control group, the lack of data on fibrinolysis, and the study's retrospective nature. Further prospective analysis is needed to confirm the advantage of our CPB strategy with low-dose heparin and nafamostat mesilate for patients with bleeding risks.

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Transcatheter aortic valve implantation combined with conventional heart surgery: Hybrid approach for complex cardiac pathologic features

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A new hybrid approach, the combination of transcatheter aortic valve implantation (TAVI) and conventional cardiac

surgery, might be a possible solution for patients considered not suitable for complex conventional surgery. We have summarized our preliminary experience.¹⁻³

BRIEF CLINICAL REPORT

From April 2008 to October 2011, 11 patients underwent simultaneous conventional cardiac surgery and TAVI with or without additional percutaneous coronary intervention (PCI) (Table 1). Ten patients had severe aortic valve stenosis, and one (patient 11) had pure insufficiency. The combined procedure was the first heart operation in 6 patients, the second in 3 patients, the third in 1 patient, and the fourth in 1 patient.

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