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ORIGINAL ARTICLE

EARLY DETECTION AND REPERFUSION FOR CEREBRAL THROMBOEMBOLISM AFTER CARDIOVASCULAR SURGERY

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Abstract Background: The objective of this study was to investigate the role of immediate cerebral angiography and local thrombolysis for stroke after cardiovascular surgery.
Patients and methods: Aggressive approach including early cerebral angiography and intraarterial administration of fibrinolytic agent for stroke after cardiovascular surgery was employed. Seven patients who had stroke after surgery among 1244 patients who underwent cardiovascular surgery were enrolled this investigation.
Results: In-hospital cerebral thrombosis or thromboembolism occurred 3 to 9 days (average: 6.3±2.7 days) after surgery. Immediate cerebral angiography revealed cerebral embolism in 4 and cerebral thrombosis in 3 with occlusion or stenosis of intracranial arteries. Local, intraarterial administration of a thrombolytic agent was carried out in 5 patients with cerebral thromboembolism (n=4) or thrombosis (n=1), and complete recanalization of the occluded artery was obtained in 3 patients (60%) and partial recanalization in 2 patients (40%). Additional angioplasty for basilar artery stenosis was performed in one patient. No patients exhibited bleeding complication. All patients survived with moderate or full functional recovery.
Conclusions: Immediate cerebral angiography with/without local thrombolysis may improve functional outcome and survival in patients with postcardiotomy cerebral thromboembolism.

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Key words: cerebral embolism; cerebral infarction; cardiac surgery; stroke; local fibrinolysis.

原 著

心臓手術後の脳血栓塞栓症に対する早期脳血管造影および血管内治療の検討

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抄録 心臓手術後急性期の脳動脈血栓塞栓症に対する緊急脳血管造影と血管内治療の位置づけを検討.
対象と方法：1244例の心臓手術自験例を対象に，術後の脳血管障害例に対して，積極的脳血管造影による閉塞部位の確定と，急性期の血管内治療を行う方針で臨んだ．実際に術後脳梗塞を合併した7例を対象として，検査結果および治療成績を検討した.
結果：心臓手術後の脳血管閉塞は，術後第3～9病日，平均 6.3±2.7 病日に発生した．頭蓋内血管内の血栓溶解薬の直接投与を脳塞栓の4例と脳血栓の1例に行い，3例60％に完全な再疎通，2例40％に部分的再疎通を得た．脳底動脈の狭窄残存例1例に対して，追加的な血管形成術を行なった．手術創に再出血を起こした例はなく，全例で中等度ないしは完全な神経学的な改善が得られ，死亡例はなかった.
結論：心臓手術後の脳血栓塞栓症に対する緊急脳血管造影および血管内線溶療法は，機能予後および生命予後を改善する可能性がある.

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キーワード: 心臓手術; 脳梗塞; 脳塞栓症; 心房細動; 血管内治療.

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Introduction

Postoperative stroke is a devastating complication after cardiac surgery. The cause of stroke is multifactorial, including malperfusion to the brain due to carotid or intracranial arterial stenosis, atheroembolism due to aortic manipulation [1], and thromboembolism from the intracardiac thrombus. Embolic stroke is serious and disabling, when the patient has a large embolus [2]. In cerebral thromboembolism, large cortical infarctions with hemorrhagic transformation are common and frequently lethal [3,4]. Brainstem infarction due to acute occlusion of the basilar artery is life threatening. Although the incidence is low, treatment of postoperative cerebral throembolism is challenging because of the risks of adverse effects associated with the use of fibrinolytic agents in postoperative patients. TPA administrated intravenously 3 hours after the onset of stroke was accompanied by increased risk of hemorrhagic complications. But intraarterial approach has been shown to extend the window of therapy to 6 hours from stroke onset [5]. In this study, we evaluated the results of aggressive strategy with early diagnosis and local administration of fibrinolytic agent for stroke after cardiovascular surgery.

Historical Background

In Tsukuba Medical Center, first attempt of intraarterial thrombolysis for cerebral embolism was performed in 1986 for an outpatient who had artificial valve and CABG. It was first successful case of intraarterial thrombolysis for acute cardiogenic thromboembolism. In 1987, we also performed intraarterial thrombolysis for cerebral thromboembolism in an outpatient who had mitral commissurotomy one month before and complete recanalization was obtained. Because neurological outcomes were satisfactory in these patients, we had been considering intraarterial thrombolysis for all stroke patients since 1986 even if the patient was early stage after cardiac operation.

Patients and methods

Patients: We analyzed seven in-hospital patients with stroke due to cerebral thromboembolism and thrombosis after cardiovascular surgery in Tsukuba Medical Center between January 1986 and October 2001. Patients with neurological damage occurring intra-operatively were excluded from this study. The incidence of inpatient cerebral thromboembolism and thrombosis was 0.6% (n=8) among 1244 adult cardiac operations performed during the same period. Morbidity in each group of surgical procedures was 0.9% (6/691) in on-pump coronary artery bypass grafting, 1.6% (1/61) in off-pump coronary artery bypass grafting, 0.4% (1/224) in valvular surgery, 0% (0/61) in combined coronary and valvular surgery, 0% (0/139) in thoracic aortic surgery, and 0% (0/68) in miscellaneous heart surgery, respectively. Our strategy for acute cerebral ischemia had been early detection by cerebral angiography and early reperfusion by intraarterial administration of urokinase. One patient who had postoperative renal failure was excluded from this study following exclusion criteria.

Methods: The causes of ischemic stroke were investigated after the onset of neurological symptoms, employing electrocardiography, chest roentgenography and echocardiography. Intracranial hemorrhage and completed cerebral infarction were excluded by computed tomography of the brain. Then, cerebral angiography

was performed immediately in all patients. The average interval between onset of symptoms and cerebral angiography was 3.3 ±1.3 hours, ranging from 2 to 6 hours (Fig 1). The etiology of stroke was determined by morphology of occluded arterial stump, degree of arterial atherosclerosis, and postoperative context of the patients.

Local, intraarterial administration of a fibrinolytic agent was considered for all patients with acute cerebral ischemia. Written informed consent, regarding risk of exacerbation of neurological symptoms due to hemorrhagic transformation of infarction and risk of wound rebleeding, was obtained before the angiography. Cardiac surgeons and stroke care team (neurosurgeon and radiologist) decided the indication for intraarteiral fibrinolytic therapy collaboratively, considering the degree of occlusion, amount of collateral blood supply, and risk of rebleeding. The hospital administrative board had approved this study as one of the subsidiary studies for intraarterila thrombolysis for acute cerebral ischemia.

Criteria for immediate cerebral angiography and local fibrinolytic therapy: All patients who exhibited stroke after uneventful cardiovascular surgery were considered to be candidates for immediate cerebral angiography. Patients who exhibited complete cerebral infarction or cerebral hemorrhage were excluded from immediate cerebral angiography. Exclusion criteria from local fibrinolysis were as follows: 1) complete cerebral infarction with formation of a low-density area on CT; 2) massive pericardial drainage after surgery; 3) thrombocytopenia; 4) persistent intracardiac thrombus; and 5) acute renal failure. One patient who underwent re-CABG, having postoperative cerebral infarction of unknown onset and acute renal failure, was excluded from this study.

Early and late neurological evaluation: All patients were evaluated by a neurologist after the onset of stroke. After intraarterial thorombolytic therapy, neurological status was clinically monitored by a neurologist and chest roentgenogram was checked regularly by cardiac surgeon to rule out intrapericardial rebleeding. Brain CT was taken on days 1, 3 and 7 (if necessary) to detect hemorrhagic transformation of cerebral infarction and brain edema. Neurological outcome was investigated in each patient. Early neurological function was evaluated by NIH stroke scale at the onset [6], while late neurological performance was assessed by the Barthel index [7]. Zero NIH stroke scale represented no neurological deficit, while maximum scale (36) represented deep coma. Full neurological recovery was defined as Barthel index of 100, indicating no disabilities remaining in daily life, while moderate recovery was defined as that of 60 to 90, indicating that some aid in daily life was necessary.

Results

In-hospital cerebral thromboembolism or thrombosis occurred 2 to 9 days (average 6.3±2.7 days) after surgery. All of these patients were free from neurological deficits in the immediate postoperative period, and stayed in the ICU for 1.3 days on average. Average age of the patients was 67±7 years, ranging from 57 to 71 years. There were 2 males and 5 females. Suspected causes of cerebral thromboembolism were atrial fibrillation in three (43%), artificial valve in one (14%), intracranial arterial stenosis in two (28%), and atheroembolism in one (14%) (Table 1). All patients except patient 3 were screened for carotid stenosis using

Table 1 Demographic data for patients with postoperative cerebral thrombosis/thromboembolism.

Patient	Surgery	Suspected cause	onset	Symptoms	onset-CAG(hrs)
1.57M	AVR+MVR	Mechanical valve	8POD	Rt. Hemiplegia, Aphasia	3
2.77F	Double CABG	Chronic Af	8POD	Rt. hemiplegia, stupor	3
3.58M	Double CABG	tAf	9POD	Rt. Hemiplegia, coma	2
4.71F	Double CABG	Intracranial stenosis	7POD	Rt. Hemiplegia	6
5.70F	Quadruple CABG	tAf	3POD	Lt. hemiplegia, coma	2
6.64F	Double OPCAB	Intracranial stenosis and atheroembolism	2POD	Lt. hemiplegia	3
7.71F	Triple CABG	Intracranial stenosis	7POD	Dysarthria, stupor, lt. hemiparesis	4

LDA: low density area on computed tomography of the brain; CAG: cerebral angiography; AVR: aortic valve replacement; MVR: mitral valve replacement; CABG: coronary artery bypass grafting; PVC: premature ventricular contraction; Af: atrial fibrillation; CI: cerebral infarction; MCA: middle cerebral artery; ICA: internal carotid artery.

Table 2 Treatment and outcome

Patient	CAG findings	Local fibrinolysis	CAG outcome	Complication	Additional procedure	NIH score	BI
1	Lt. MCA embolus	Yes (UK48×10^4)	CR	None	No	9	100
2	Lt. MCA embolus	Yes (UK96×10^4)	CR	None	No	11	100
3	Lt. ICA embolus	Yes (UK96×10^4)	PR	Hemorrhagic CI	No	10	60
4	Recanalized lt. Ica thrombus	No	CR	None	No	5	55
5	Rt.ICA thrombus	No	NR	None	No	9	45
6	Rt.ACA embolus	Yes (UK48×10^4) Emboli destruction	PR	None	No	11	60
7	Basilar artery thrombus	Yes (UK72×10^4)	CR	None	Additional PTA	10	90

NIHSS: NIH stroke scale; BI: Bathel index; UK: urokinase; CR: complete recanalization; PR: partial recanalization; NR: no recanalization.

duplex scanning before surgery, with results negative for carotid stenosis. Preoperative cerebral angiography was performed in two patients (patient 6 and 7) due to the presence of old cerebral infarction, and severe stenosis of intracranial arteries was detected in both patients. In these patients, off-pump CABG was performed in one patient and on-pump CABG using high-pressure extracorporeal circulation was performed in another. An oral anticoagulant was given to one patient who underwent double valve replacement.

The onset of stroke was sudden with flaccid hemiplegia in 6 patients, with/without deterioration of consciousness. In one patient with basilar artery stenosis, the initial symptom was subtle with mild dysarthria followed by progressive left hemiparesis. Immediate cerebral angiography revealed cerebral embolism in 4 patients and cerebral thrombosis in 3 with occlusion or stenosis of major intracranial arteries (Table 2). Local

intraarterial administration of a thrombolytic agent through a catheter monitored by repeat angiography was carried out in 5 patients, and mechanical destruction of embolus was attempted in one patient.

In 5 patients who underwent local thrombolysis, recanalization of the occluded artery was obtained by intracarotid administration of urokinase in a total dose of 48 or $96x10^4$ units (Figure 1). Complete recanalization of the occluded artery was achieved in 3 patients (60%) and partial recanalization in 2 patients (40%) [8]. Although a tiny hemorrhagic cerebral infarction, which had been detected by the CT, occurred in one patient (case 3) who underwent local thrombolysis, NIH stroke scale showed significant improvement in the local fibrinolysis group. In case 7, additional balloon angioplasty for residual stenosis of the basilar artery was performed one week after fibrinolytic therapy.

Although one patient underwent resternotomy due to sternal dehiscence, no patients exhibited rebleeding into the pericardial space or wound bleeding. Blood transfusion was necessary in one patient who underwent intraarterial thrombolysis and two patients who underwent cerebral angiography alone. Functional outcome of the patients are shown in Table 2. While full recovery was obtained in three patients with complete recanalization (60% in whom local thrombolysis was performed), moderate disability remained in four patients (40% of thrombolytic group, 100% of angiography group).

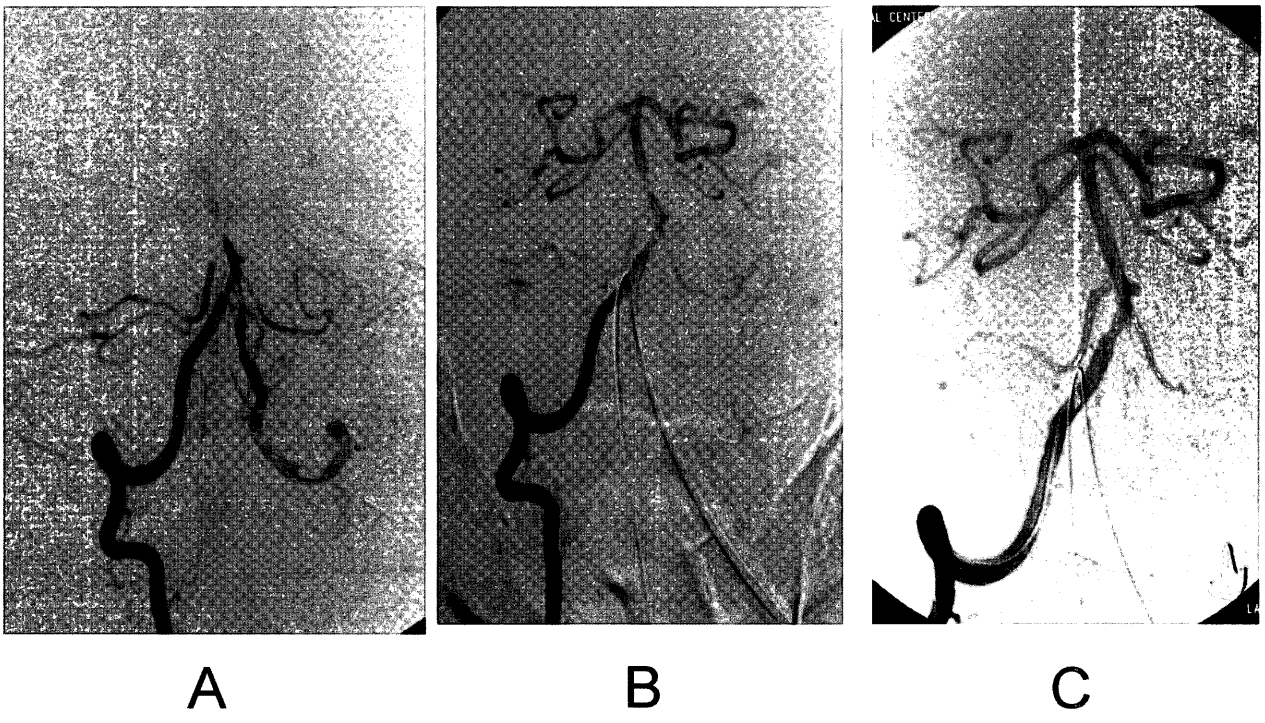

Figure 1 Cerebral angiogram before (A) and after (B) local administration of urokinase in case 7. Additional angioplasty was performed on 14 POD (C).

Discussion

Incidence of adverse neurologic events has been estimated to be 1-6% in patients undergoing elective coronary bypass grafting. Acute occlusion of major cerebral arteries due to thromboembolism induces large cerebral infarction accompanied by consequential swelling of the brain. Intractable brain edema in massive cerebral infarction may be fatal [2-4,9]. Although spontaneous recanalization of an occluded artery may occur within 24 hours to 1 week in 14% of patients with cerebral embolism, no significant neurologic improvement was demonstrated following spontaneous recanalization [5,10]. Immediate restoration of cerebral blood flow within a short period after cerebral infarction may improve morbidity and mortality [2,11]. Efficacy of fibrinolytic agents in acute ischemic stroke has been demonstrated in recent large randomized studies [11]. However, intravenous administration of tissue plasminogen activator 3 hours after the onset of stroke was accompanied increased risk of hemorrhagic transformation of the infarction. On the other hand, intraarterial administration of fibrinolytic agent has been shown to extend the window of therapy to 6 hours from stroke onset. In the PROACT study, partial recanalization was significantly greater in a local administration of a pro-UK group than a placebo group, while the incidence of intracranial hemorrhagic deterioration was the same [5]. Several large case series of treatment by local thrombolysis with urokinase or tissue plasminogen activator reported complete or partial recanalization in 74% of the patients, higher than that of intravenous administration, with a lower incidence of symptomatic intracranial hemorrhage than that reported for intravenous thrombolysis [12]. These results suggest potential benefits and acceptable safety of intraarterial thrombolysis. To determine the indication for thrombolytic therapy, detection of reversible ischemic area is important. Even in irreversible ischemia, brain CT may not show any signs for several hours after occlusion of the artery. Recently, diffusion MRI enables differentiation between reversible area called "penumbra" and irreversible area under the criteria of cerebral blood flow. However, diffusion MRI had not been available in our hospital. Therefore, when the patient exhibited neurological deficit with negative CT, verification of arterial occlusion site by cerebral angiography was justified.

Use of fibrinolytic agents may induce as much hemorrhagic infarction as surgical site bleeding. Hemorrhagic cerebral infarction is accompanied by acute expansion of the lesion and surrounding edema, resulting in functional deterioration and death [4]. Risk factors for hemorrhagic transformation are severity of initial neurological deficit and baseline CT scan findings in an odds ratio of 3.5 [13,14].

Interval between onset and reperfusion is also an important predictor for hemorrhagic infarction. Because the interval between the onset and angiography was short in our patients, neurological improvement was marked when early recanalization of the cerebral artery was obtained. Although one patient showed a small hemorrhagic infarction on CT, brain swelling was minimal and moderate functional recovery was obtained. Another concern regarding the use of fibrinolytic agent is the risk of rebleeding from surgical wound. Moazami and colleagues reported the effectiveness of intraarterial thrombolysis in thirteen cardiac surgery patients with recanalization and neurologic improvement rate of 46% and 38%, respectively [15]. In their series, no patient

exhibited surgical wound rebleeding. In local thrombolysis, the dose of fibrinolytic agent could be reduced to the minimum amount required to recanalize the target arteries, because the effect of fibrinolytic agent was directly verified by angiography and minimal required dose could be determined. Direct intervention to the occluded cerebral artery is also possible when immediate cerebral angiography can be performed, as in case 6. In case 7, delayed additional angioplasty was also efficacious.

In conclusion, early direct cerebral angiography is beneficial in postoperative ischemic stroke. Local thrombolytic therapy and mechanical manipulation of the embolus may reduce mortality and improve functional prognosis without serious complications in properly selected patients.

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