Endovascular Treatment of Acute Embolism of the Major Cerebral Arteries
The Value of Balloon Disruption of the Embolus

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Key words: cerebral embolism, ischemic stroke, reperfusion therapy, angioplasty, fibrinolysis

Summary

This study evaluated: 1) the effect of recanalization on changing clinical outcome, 2) the relationship between dose of Urokinase (UK) and incidence of recanalization and intracranial hemorrhage, and 3) the efficacy and feasibility of balloon disruption (BD) in the treatment of acute cerebral embolism.

Sixty-one patients with acute embolism of the major cerebral arteries treated by endovascular approaches over the past nine years were retrospectively evaluated. Among them, 30 cases were treated by BD alone or in conjunction with intra-arterial fibrinolysis in the last five years. The other 31 cases, mostly treated in the first four years, were treated with intra-arterial fibrinolysis alone and were used as controls to evaluate the efficacy of BD. Control angiography was performed just after the reperfusion procedure to evaluate the degree of recanalization. Angiographic responses were graded using modified Thrombolysis in Myocardial Infarction (TIMI) criteria. Clinical outcome was evaluated using modified Rankin Scale (mRS) score at the time of discharge.

Thirty-six of the 61 patients (59.0%) achieved high-grade recanalization (TIMI grade 3). Significantly more patients attained favorable outcome (mRS score 0-1) in the high-grade recanalization group (41.7% vs. 16.0%, p < 0.05). Concerning patients treated with BD, significantly more patients attained good recanalization and significantly more patients were ambulatory (mRS score 0-3) than those treated with intra-arterial fibrinolysis alone (76.7% vs. 41.9%, p < 0.01; 70.0% vs. 41.9%, p < 0.05, respectively). A significantly lower dose of UK was used, and relatively less intracranial hemorrhage was seen in patients treated with BD than those treated with intra-arterial fibrinolysis (194,000 ± 191,000 units vs. 388,000 ± 231,000 units, p = 0.001; 16.7% vs. 38.7%, p = 0.055, respectively). Concerning morbidity and mortality of BD, there was one death caused by dissection of the M2 portion of the middle cerebral artery (MCA) that happened during BD on a distally migrated embolus.

Although no conclusions can be drawn from our study, a favorable outcome for acute embolism of the major cerebral arteries is expected by attaining good recanalization. In addition, BD is an effective technique that can achieve high-grade recanalization alone, or reducing the dose of fibrinolytic agent.

Introduction

As the most devastating type of ischemic stroke, cerebral embolism has been the major target of treatment at acute care stroke centers for the last decade. In 1996, based upon the
study conducted by the National Institute of Neurological Disorders and Stroke (NINDS), intravenous administration of recombinant tissue plasminogen activator (rt-PA) was approved by the FDA for acute cerebral stroke within three hours after onset. However, to date, only a small proportion of acute stroke patients have been treated by intravenous rt-PA. The major reasons for this are the short time-window and limited efficacy. Also, iv rt-PA cannot recanalize large emboli lodging in major intracranial arteries, judging from the relationship between NIHSS scale and clinical outcome at three months shown in the NINDS study. PROACT I and II, randomized controlled studies, have shown the efficacy of intrarterial UK injection for acute MCA occlusion with TIMI grade 0-1. The median time elapsed before the initiation of the therapy was 5.3 hours. These studies showed that even late after symptom onset, there is a hope for clinical improvement. However, the degree of recanalization shown by PROACT II is far from satisfactory; one-third of patients failed to show arterial recanalization and complete recanalization (modified TIMI grade 3) was seen only in 17.6% of cases (19/108). In addition, the incidence of intracranial haemorrhage with clinical deterioration is as high as 10.2% (11/108).

With advancement of balloon technology, there has been increased interest in mechanical recanalization of major cerebral artery occlusion. Since July 1998, we started to apply BD for cerebral embolism resistant to chemical fibrinolysis to raise the recanalization rate and reduce the incidence of haemorrhagic infarct. In this study we reviewed our treatment results and evaluated the rationale of BD in the treatment of acute embolism of major cerebral arteries.

Material and Methods

Case Material

Sixty-one consecutive cases with cerebral embolism, treated by endovascular approach from September 1993 to December 2002, were reviewed retrospectively. Diagnostic criteria of cerebral embolism were based upon those of the Cerebral Embolism Task Force. Diagnosis of cerebral embolism can be made easily in most of our cases depending on sudden occurrence of neurological deficits, abrupt occlusion of the major cerebral artery on angiography and history of heart disease. There were 51 cases with acute embolism in the anterior circulation (M1 portion of the MCA and A1 portion of the anterior cerebral artery (ACA)) and ten cases with embolism in the posterior circulation (basilar artery and P1 portion of the posterior cerebral artery (PCA)).

Exclusion Criteria

Patients with 4 or 5 pre-critical modified Rankin Scale score.

Patients with obvious infarction detected by CT on admission.

Patients who arrived at the angiography suite more than six hours after onset.

Patients with occlusion of the internal carotid artery.

Patients with occlusion of the cortical cerebral artery only.

Exceptionally, seven cases with obscure time of stroke onset were included because early CT signs were confined to less than one third of the MCA distribution on admission.

Treatment Procedure

Each patient’s relative provided informed consent after the head CT scan had been interpreted by board-qualified neuroradiologists. Immediately after the placement of a sheath introducer into the femoral artery, 5000 units of Heparin were administered intravenously. Then a 5-7 French guiding catheter was placed into the relevant cervical or vertebral cerebral artery. Cerebral angiography was performed to evaluate the site of occlusion and the degree of development of collaterals. 1000 units of Heparin were added every hour during the reperfusion procedure. The tip of a microcatheter was advanced distally bypassing the embolus using a guidewire. While pulling back the microcatheter, a small amount of contrast material was injected through it to confirm the distal end of the embolus.

The procedure of intra-arterial fibrinolysis was performed as follows: Starting gentle pulsatile injection of UK with the tip of a microcatheter placed just beyond the embolus, the microcatheter was gradually pulled back towards the proximal end of the embolus. The procedure was repeated until satisfactory recanalization was attained. We used a Stealth or
**Table 1** Characteristics of study patients

<table>
<thead>
<tr>
<th></th>
<th>IA* group (N=31)</th>
<th>BD** group (N=30)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Y)</td>
<td>70 ± 8</td>
<td>70 ± 12</td>
<td>N.S.***</td>
</tr>
<tr>
<td>Gender (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>8</td>
<td>N.S.</td>
</tr>
<tr>
<td>Occlusion site (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle Cerebral Artery</td>
<td>26</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Anterior Cerebral Artery</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Posterior Cerebral Artery</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Basilar Artery</td>
<td>3</td>
<td>5</td>
<td>N.S.</td>
</tr>
<tr>
<td>Japan Coma Scale on arrival (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>12</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>10-30</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>100-300</td>
<td>8</td>
<td>8</td>
<td>N.S.</td>
</tr>
<tr>
<td>Time from onset to endovascular therapy (min)</td>
<td>176 ± 62</td>
<td>179 ± 65</td>
<td>N.S.</td>
</tr>
<tr>
<td>Period of hospitalization (days)</td>
<td>42 ± 30</td>
<td>37 ± 22</td>
<td>N.S.</td>
</tr>
<tr>
<td>Recanalization (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High grade</td>
<td>13 (41.9%)</td>
<td>23 (76.7%)</td>
<td>P = 0.006</td>
</tr>
<tr>
<td>Low grade</td>
<td>18 (58.1%)</td>
<td>7 (23.3%)</td>
<td></td>
</tr>
<tr>
<td>Consciousness alert on discharge (N)</td>
<td>9 (29.0%)</td>
<td>19 (63.3%)</td>
<td>P = 0.007</td>
</tr>
<tr>
<td>Modified Rankin Scale score 0-1 on discharge (N)</td>
<td>7 (22.6%)</td>
<td>12 (40.0%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Modified Rankin Scale score 0-3 on discharge (N)</td>
<td>13 (41.9%)</td>
<td>21 (70.0%)</td>
<td>P = 0.027</td>
</tr>
<tr>
<td>Urokinase (Units)</td>
<td>388,000 ± 231,000</td>
<td>194,000 ± 191,000</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Haemorrhagic infarct within 24 hours after the procedure (N)</td>
<td>6 (19.4%)</td>
<td>2 (6.7%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Haemorrhagic infarct during hospitalization (N)</td>
<td>12 (38.7%)</td>
<td>5 (16.7%)</td>
<td>N.S. (P = 0.055)</td>
</tr>
</tbody>
</table>

*Intra-arterial fibrinolysis  **Balloon disruption  ***NS, Not significant

Gateway angioplasty balloon catheter (Boston Scientific Inc., Massachusetts, U.S.A.) with a 2.0 to 3.0 mm maximum diameter for BD. A balloon catheter was placed beside the embolus using a guidewire and was inflated applying 2-6 atm for 30-60 seconds.

Initially, BD was added when not enough revascularization was obtained by local infusion of 240,000 units of UK. When partial recanalization or dissemination of embolus was seen after BD, local UK infusion was added until satisfactory recanalization was attained. After
**Figure 1** Neurological and survival prognosis on discharge. A) Significantly more patients were discharged alert in the high-grade recanalization group than the low-grade recanalization group (p < 0.005). B) Significantly more patients attained favorable outcome (mRS score 0-1) in the high-grade recanalization group (p < 0.05), and significantly more patients were ambulatory (mRS score 0-3) in the high-grade recanalization group (p < 0.005). Significantly fewer patients died during hospitalization in the high-grade recanalization group (p < 0.05).

**Table 2** Japan Coma Scale
Japan Coma Scale for grading of impaired consciousness

<table>
<thead>
<tr>
<th>Grade</th>
<th>Consciousness Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-digit code</td>
<td>the patient is awake without any stimuli, and is:</td>
</tr>
<tr>
<td>1</td>
<td>almost fully conscious</td>
</tr>
<tr>
<td>2</td>
<td>unable to recognize time, place, or person</td>
</tr>
<tr>
<td>3</td>
<td>unable to recall name or date of birth</td>
</tr>
<tr>
<td>2-digit code</td>
<td>the patient can be aroused (then reverts to previous state after cessation of stimulation):</td>
</tr>
<tr>
<td>10</td>
<td>easily by being spoken to (or is responsive with purposeful movements, phrases, or words)**</td>
</tr>
<tr>
<td>20</td>
<td>with loud voice or shaking of shoulders (or is almost always responsive to very simple words like yes or no, or to movements)**</td>
</tr>
<tr>
<td>30</td>
<td>only by repeated mechanical stimuli</td>
</tr>
<tr>
<td>3-digit code</td>
<td>the patient cannot be aroused with any forceful mechanical stimuli, and:</td>
</tr>
<tr>
<td>100</td>
<td>responds with movements to avoid the stimulus</td>
</tr>
<tr>
<td>200</td>
<td>responds with slight movements including decerebrate and decorticate posture</td>
</tr>
<tr>
<td>300</td>
<td>does not respond at all except for change in respiratory rhythm</td>
</tr>
</tbody>
</table>

* "R" and "I" are added to the grade to indicate restlessness and incontinence of urine and feces, respectively: for example; 100-T and 30-RI. ** Criteria in parentheses are used in patients who cannot open their eyes for any reason.

experiencing dramatic recanalization in several cases by BD alone, the protocol was slightly changed as follows; BD preceded fibrinolysis when arteriosclerotic changes of the parent artery were not prominent, caliber of the obliterated artery exceeded 2 mm and few distal emboli were identified.

**Radiological assessment of the result of reperfusion**

Control angiography was performed just after the reperfusion procedure to evaluate the degree of recanalization. Angiographic responses were graded using modified TIMI criteria. A high-grade recanalization, modified TIMI grade 3, was defined to be a complete or near complete recanalization with or without a few fragmented emboli in distal branches. Patients who did not meet the above mentioned criteria were included in a low-grade recanalization group.

Head CT scan was performed immediately after the reperfusion procedure, and was repeated 1-2 times within 48 hours after the procedure to detect haemorrhagic transformation of the infarct. A focal extreme hyperdense lesion seen on head CT just after the procedure but disappearing within 12 hours was regarded as leakage of contrast media. Intracranial haemorrhage seen more than 24 hours after the procedure was regarded as irrelevant to the procedure.

**Outcome Assessment**

Level of consciousness and mRS score were evaluated at the time of discharge (3 to 107 days, mean 40 days). We regarded cases with mRS scores 0 or 1 as favorable outcome, and cases with mRS scores 0,1,2 and 3 ambulatory.

**Statistical Analyses**

Continuous variables were expressed as means ± 1 SD. To determine the normal distribution of variables, we used the Shapiro-Wilk test. According to this result, Mann-Whitney U-test was used for nonparametric comparison. Differences between the groups in categorical variable were analyzed by the chi-square test or Fisher’s exact test. A P value of less than 0.05 was considered to indicate statistical significance.

![Figure 2A](image)

**Figure 2** Relationship between dose of UK and incidence of haemorrhagic infarct and recanalization. A) Degree of recanalization in IA group. There was no significant difference in dose of UK between 13 cases with high-grade recanalization and 18 cases with low-grade recanalization (p=0.135). B) Haemorrhagic infarct among 50 patients treated with UK. A significantly higher dose of UK was given to 6 patients with intracranial haemorrhage than the other 44 patients (p<0.01). The cut-off level seems to be around 400,000 Units.

**Results**

**Characteristics of the Study Population**

Thirty-one patients who underwent intra-arterial UK infusion alone were defined as the IA group, and the other thirty patients who underwent intracranial BD with or without intra-arterial UK injection were defined as the BD group. There was no significant difference in age, gender, occlusion site, Japan Coma Scale 24.25 (table 2) on arrival, time lapsed from onset of symptoms to endovascular therapy, or period of hospitalization between these two groups (table 1).
Judging from the radiological assessment criteria above, 36 out of 61 patients were defined as belonging to the high-grade recanalization group, and the other 25 to the low-grade recanalization group.

Analysis 1) Clinical improvement derived from recanalization

Comparing the high-grade recanalization group with the low-grade recanalization group, significantly more patients were discharged alert (61.1% (22/36) vs. 24.0% (6/25), p < 0.005) (figure 1A), significantly more patients attained favorable outcome (mRS score 0-1) on discharge (41.7% (15/36) vs. 16.0% (4/25), p < 0.05) (figure 1B), significantly more patients were ambulatory (mRS score 0-3) on discharge (72.2% (26/36) vs. 32.0% (8/25), p < 0.005) (figure 1B), and significantly fewer patients died during hospitalization (2.8% (1/36) vs. 24.0% (6/25), p < 0.05) (figure 1B). There was no significant difference in incidence of haemorrhagic transformation within 24 hours after stroke onset between the high-grade recanalization group and the low-grade recanalization group (11.1% (4/36) vs. 16.0% (4/25), p = 0.426). Relatively fewer patients presented haemorrhagic transfor-
Information during hospitalization in the high-grade recanalization group than the low-grade recanalization group (19.4% (7/36) vs. 28.0% (7/25), p = 0.078).

Analysis 2) Relationship between dose of UK and incidence of recanalization and intracranial haemorrhage

Local intra-arterial UK infusion was performed on 50 patients (31 patients of the IA group and 19 patients of the BD group). The amount of UK injected through microcatheters ranged from 120,000 to 1,020,000 units (median 270,000 Units). Concerning the relationship between dose of UK and degree of recanalization among 31 patients in IA group, there was no significant difference between 13 cases of the high-grade and 18 cases of the low-grade recanalization groups (468,000 ± 268,000 units and 330,000 ± 187,000 units, p = 0.135) (figure 2A). Haemorrhagic transformation within 24 hours after the reperfusion procedure occurred in six patients out of all 50 patients who underwent fibrinolysis (12.0% (6/50)). Dose of UK was significantly higher in haemorrhagic cases than non-haemorrhagic cases (620,000 ± 300,000 units vs. 321,000 ± 164,000 units, p < 0.01) (figure 2B).

Analysis 3) Efficacy of BD in improving clinical outcome and reducing dose of UK

Comparing the BD group with the IA group, significantly more patients attained high-grade recanalization (76.7% (23/30) vs. 41.9% (13/31), p < 0.01) (figure 3A) and significantly more patients were discharged alert (63.3% (19/30) vs. 29.0% (9/31), p < 0.01) (figure 3B). Although there was no significant difference in favorable outcome (mRS score 0-1) (40.0% (12/30) vs. 22.6% (7/31), p = 0.142), significantly more patients were ambulatory (mRS score 0-3) on discharge in the BD group than the IA group (70.0% (21/30) vs. 41.9% (13/31), p < 0.05), (figure 3C). A significantly lower dose of UK was given to the BD group than the IA group (194,000 ± 191,000 units vs. 388,000 ± 231,000 units, p = 0.001) (figure 4). Relatively less haemorrhagic transformation of infarct was seen in the BD group than the IA group during hospitalization (16.7% (5/30) vs. 38.7% (12/31), p = 0.055). Concerning the technical complications of BD, there was one death from severe subarachnoid haemorrhage caused by dissection of the MCA during the procedure.

Discussion

There has been a tremendous advance in the technique of intracranial navigation in the last two decades, and the microcatheter technique allows us to perform local intra-arterial fibrinolysis for cerebral embolism. As an embolus lodging in the major cerebral arteries is elastic hard, the tip of a microcatheter can be easily advanced between the embolus and arterial wall by the aid of a guidewire which bypasses an embolus without penetrating it. Then fibrinolysis can be performed effectively by delivering a high concentration fibrinolytic agent into the blood stagnating just distal to the embolus or directly into the embolus matrix from the microcatheter. Thus, local intra-arterial infusion of fibrinolytic agent made effective revascularization of acute obliteration of cerebral arteries, using less fibrinolytic agent, beyond the three-hour therapeutic time window.

The drawback of this therapy, however, is the increased incidence of haemorrhagic transformation. This seemed related to the high concentration of fibrinolytic agent infused locally into the ischemic area where vascular bed is also damaged. Because of this dilemma, use of a large amount of fibrinolytic agent has been withheld for patients with poor collaterals and for those with obscure time of onset. This was
the main reason for failure to achieve high-grade recanalization in more than half of our patients undergoing local intraarterial fibrinolysis (LIF) (table 1).

There is still considerable skepticism about the value of aggressive reperfusion procedure for cerebral embolism. Our study, however, demonstrated that comparing the high-grade recanalization group with the low-grade recanalization group, significantly more patients were discharged alert (figure 1A), significantly more patients attained a favorable outcome (mRS score 0-1) on discharge, significantly more patients were ambulatory (mRS score 0-3).
on discharge and significantly fewer patients died during hospitalization (figure 1B). Our study also showed that by simply increasing the dose of UK an increased rate of high-grade recanalization cannot be expected, but haemorrhagic infarction is more likely (figure 2A,B).

Concerning the atherosclerotic occlusion of the major cerebral arteries, a microcatheter can be easily passed through the clot matrix. Recanalization can be attained by disrupting the thrombus by frequent passage of a microcatheter and delivering a small amount of fibrinolytic agent. As there is a high tendency to re-occlude, BD on the atheromatous plaque is necessary to ensure patency of the vessel. Angioplasty for atherosclerotic vessels needs higher balloon inflation pressure than that for vasospasm. Though the previous experience with BD for intracranial circulation is limited, the major complication rate was as high as 38% in early 90’s and 9-10% in mid-90’s. Because of these problems, the target of LIF has been restricted to cerebral embolism at many institutes. In the last several years, however, a high profile angioplasty balloon catheter that allows precise calibration of the inflation diameter became available. In addition to such technical advance, by selecting short concentric or moderately eccentric lesions as the main targets of treatment, there has been a remarkable improvement in treatment results of BD for intracranial atherosclerotic lesions and a prominent reduction in the complication rate.

Encouraged by these results, some Japanese interventionists started to perform angioplasty in the late 90’s on cerebral embolism after a failed attempt at chemical fibrinolysis. Our study clearly showed the positive effects of BD: significantly more patients attained high-grade recanalization (figure 3A), and significantly more patients were discharged alert in the BD group than the IA group (figure 3B). There was no significant difference in favorable outcome (mRS score 0-1). This is because of the severity of stroke caused by the occlusion of the major cerebral arterial trunk. However, significantly more patients were ambulatory (mRS score 0-3) on discharge in the BD group than the IA group (figure 3C). Also, it may be said that BD contributed to reducing the dose of UK used for recanalization, but it did not contribute to reduce the incidence of haemorrhagic infarction (figure 4).

Concerning the technical complications of BD, there was one death from severe subarachnoid haemorrhage caused by dissection of the M2 portion of the MCA. This complication happened when performing balloon angioplasty on an embolus that was partially fibrinolysed and dislodged distally. Our experience showed that balloon angioplasty of cerebral embolism can be performed safely if restricted to the pathology of more proximal cerebral arteries.

Alternative treatments for emboli resistant to fibrinolytic therapy and BD are eagerly awaited. What will be the future treatment for cerebral embolism? Some authors claim that combined intravenous and intra-arterial therapy is better than LIF. Also, there are many papers on the dramatic effects of glycoprotein IIb-IIIa receptor inhibitor abciximab on resistant emboli. However, the relatively high incidence of symptomatic or catastrophic haemorrhage cannot be avoided by such powerful chemical measures.

Occasionally a resistant cerebral embolus can be quickly recovered by a transcatheter approach using a commercially available snare for foreign bodies. Encouraged by such success, several investigators are working on a cerebral embolus retriever to raise the success rate and enhance the safety factor.

Conclusions

Although no final conclusions can be made from our retrospective study, a favorable outcome for acute embolism of the major cerebral arteries is expected by attaining good recanalization. In addition, BD is an effective technique that can achieve high-grade recanalization by itself or reducing the dose of fibrinolytic agent. Intracranial BD is deemed a safe and effective procedure for acute cerebral embolism to improve clinical outcome.

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References


EDITORIAL COMMENT

The authors report a series of 61 patients with occlusion of intracranial artery treated by endovascular method. Thirty of them were treated by balloon disruption alone or in conjunction with intra-arterial fibrinolysis. Thirty-one patients treated by intra-arterial fibrinolysis alone were used as the control group.

In this paper, the authors conclude that:
- A favourable outcome can be obtained in case of good recanalization
- balloon disruption is an effective technique

This paper is interesting because it shows:
- doses of urokinase can be reduced if this treatment is associated with a balloon disruption of the arterial lesion
- the reduction of risk of intracerebral haemorrhage

However if this study does not bring definitive arguments, to prove the efficacy of balloon disruption, it shows the feasibility of their techniques.

The evidence that we need would certainly require prospective randomized study and acute determination whether the occlusion is exclusively located on one internal carotid branch and if associated with additional common carotid artery lesions. The size of the embolus is certainly important. MR imaging would certainly be contributive in the follow up of such interesting study.

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