Endovascular Management in Patients with Acute Basilar Artery Obstruction: Low-dose Intra-Arterial Urokinase and Mechanical Clot Disruption

J.S. YUN, H.S. KWAK, S.B. HWANG, G.H. CHUNG

Radiology Department, Chonbuk National University Medical School and Hospital; Jeonju, Jeonbuk, Korea

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Summary

Mechanical clot disruption for the treatment of acute basilar artery occlusion (BAO) is known to provide a benefit. We aimed to determine the safety, recanalization rate and time-to-flow restoration of mechanical clot disruption and low dose urokinase (UK) infusions for the treatment of patients with acute BAO.

Between June 2006 and June 2010, 21 patients with acute BAO underwent endovascular treatment that included angioplasty or stent placement. The time to treatment, duration of the procedure, dose of urokinase (UK), recanalization rates and symptomatic hemorrhages were analyzed. Clinical outcome measures were assessed at admission and at the time of discharge using the National Institutes of Health Stroke Scale (NIHSS) score and at three months after treatment using the modified Rankin Score (mRS).

On admission, the median NIHSS score was 13.2. Median time from symptom onset to arrival at hospital was 356 minutes, and median time from symptom onset to intraarterial thrombolysis (IAT) was 49 minutes. We used the fol-

lowing interventional treatment regimens: Intra-arterial (IA) UK and a minimal mechanical procedure (n=14), IA UK with angioplasty (n=1), IA UK with angioplasty and stent placement (n=3) and IA UK with HyperForm (n=3). The recanalization (thrombolysis in cerebral ischemia grade II or III) rate was 90.5% (19/21). There was symptomatic hemorrhage in one patient (4.8%). The median NIHSS score at discharge was 6.3. The three-month outcome was favorable (mRS: 0-2) for 14 patients (66.7%) and poor (mRS: 3-6) for seven patients (33.3%). The overall mortality at three months was 14.3% (three patients died).

Low-dose IAT with mechanical clot disruption is a safe and effective treatment for treatment for acute BAO.

Introduction

Around 15% of ischemic strokes are caused by occlusion of the arteries in the posterior circulation. The prognosis of patients with posterior circulation stroke and basilar artery occlusion (BAO) is very poor with the mortality rate being over 80%¹⁻³. If the patients are treated by intra-arterial thrombolysis (IAT), then the mortality rate decreases to 50%²⁻⁵. More than half of the surviving patients regain functional independency in daily life⁵.

Dominant etiologic factors such as local thrombosis or artery-to-artery thromboembolism originating from atherosclerotic lesions account for >50% of BAOs^{6,7}. Other major etiolo-

Abbreviation key

BA	= basilar artery
BAO	= basilar artery occlusion
IA	= intra-arterial
IAT	= intra-arterial thrombolysis
IVT	= intravenous thrombolysis
mRS	= modified Rankin Score
NIHSS	= National Institutes of Health Stroke Scale
PTA	= percutaneous angioplasty
TICI	= thrombolysis in cerebral ischemia
UK	= urokinase

gies are cardiac emboli and vertebral artery dissections. The outcome of acute BAO depends on the clinical state at presentation, the length and location of the occlusion, the degree of recanalization and the time to treatment^{2,3,8-13}. For BAO, early recanalization is known to be one of the most important factors for a good outcome⁸⁻¹⁰. Lindsberg and Mattle reported that the effect of intravenous thrombolysis (IVT) in patients with BAO was probably not very different from the effect of IAT⁵. However, in the absence of a direct comparative study, an estimated average recanalization rate of 70% for IAT may be superior to that of IVT¹⁴⁻¹⁶.

Mechanical clot disruption for the treatment of acute BAO has recently been shown to provide a benefit compared with IAT for ischemic stroke. Mechanical clot disruption was defined as the use of at least one of the following endovascular managements: (a) mechanical microcatheter and microwire clot maceration, (b) percutaneous angioplasty, (c) stent placement and (d) the use of a clot removal device. However, IAT and mechanical clot disruption in the posterior circulation (still need clinical trial based evidence). Therefore, we aimed to determine the safety, recanalization rate and time-to-flow restoration of mechanical clot disruption and low dose urokinase (UK) infusions for the treatment of patients with acute BAO.

Materials and Methods

This study received approval by the institutional research ethics board of the hospital. In addition, informed consent was obtained from the patients' families. From July 2006 to June 2010, the consecutive patients who underwent treatment with low dose intra-arterial (IA) UK combined with mechanical clot disruption for BAO were retrospectively enrolled in this study. On admission, the National Institutes of Health Stroke Scale (NIHSS) scores were assessed by a stroke neurologist. Either cerebral CT or MR was obtained for all the patients before initiation of IA treatment. The inclusion criteria of this study were the followings: 1) posterior circulation stroke symptoms within 12 hours before treatment, 2) CT or MR exclusion of hemorrhage and 3) BAO confirmed by IA digital subtraction angiography and this was treated by mechanical clot disruption with low-dose IA UK. The exclusion criteria included patients who were lost to follow-up. During the

study period, 24 patients underwent IAT combined with mechanical clot disruption. Among the 24 patients, three patients did not visit our institution after treatment and discharge from the hospital. Finally, 21 patients were eventually included in this study.

All patients in this study did not undergo IVT because we did not use IV rt-PA in patients with more than three hours of symptom onset. One interventional neuroradiologist performed all the IAT procedures. Cerebral angiography and IAT were performed via a femoral approach. The initiation time of IAT was defined as when the needle puncture was done for the femoral approach. The angiographically determined occlusion sites were located in the proximal basilar artery, including the vertebro-basilar junction (n=8), the middle portion of the basilar artery (n=1) and the distal basilar artery (n=12). After demonstration of an occlusion on diagnostic angiography, an end-hole microcatheter (Excelsior SL-10; Boston Scientific, Natick, Massachusetts, USA) was advanced over a microguidewire (Transend-14; Boston Scientific) through a 6F guide catheter into the occlusion site. The microcatheter tip was placed into the thrombus, and then a 100,000 U bolus of UK diluted to 10 mL in a mixture of saline and contrast medium (7:3) was manually infused for three to five minutes. We mixed the contrast medium for early detection of recanalization during UK infusion.

Mechanical clot disruption was undertaken after 100,000 U of UK was administered. We used mechanical clot maceration with a microcatheter and a microwire (Agility 10; Cordis, Miami Lakes, FL, USA) in all the patients. Mechanical clot maceration consisted of multiple passes of the microwire through the clot. The microwire was gently rotated clockwise while being advanced. During this process, the microcatheter was often advanced multiple times over the microwire as well. After withdrawal of the microwire from the microcatheter, an additional 100,000 U of UK was manually infused for three to five minutes through the microcatheter at the site of the remaining thrombus. We used the UK for IAT based on PROACT-II study. The UK infusions were stopped immediately if the control angiograms showed complete recanalization. A reattempt at mechanical clot disruption using a microcatheter and a microwire was performed if recanalization was not achieved after UK infusion. The patients with distal migration of thrombus into the pos-

terior cerebral artery were additionally infused with 100,000 U of UK through a microcatheter at the site of the occluded artery. The patients who did not achieve complete recanalization after mechanical clot disruption using a microcatheter and a UK infusion underwent percutaneous angioplasty or/and stent placement about the severe stenosis of the vertebrobasilar artery. Percutaneous angioplasty with a coronary balloon catheter (Ma'sla Just; Asahi, Aichi, Japan) or a HyperForm compliant balloon (MicroTherapeutics, Irvine, CA, USA) was carried out in seven patients. The diameter of the coronary balloon was chosen to be 0.5 mm smaller than that of the adjacent portion of the occluded segment. The diameter of the HyperForm compliant balloon was 4×7 mm. Three patients with severe stenosis after angioplasty underwent deployment of a balloon-expandable stent (Jostent; Abbott Laboratories, Abbott Park, IL, USA). The stent was similar in size to the diameter of the normal patent vessel. The stent length was selected to be equal to or exceed the length of a target lesion. Before stent placement, clopidogrel (225-300 mg) was orally administered through an orally placed gastric tube to prevent acute stent thrombosis for those patients who were not pretreated with adequate antiplatelet medications. The patients received a maintenance dose of either aspirin (100 mg daily) or clopidogrel (75 mg daily) from the next day after the procedure.

Pre-treatment and post-treatment angiograms were evaluated by the same interventional neuroradiologist. The recanalization status was classified according to the Thrombolysis in Cerebral Ischemia (TICI) scale (grade 0: no perfusion, grade I: penetration but not perfusion, grade IIa: partial perfusion with incomplete distal filling of <50% of the expected territory, grade IIb: partial perfusion with incomplete distal filling of 50%-99% of the expected territory, grade IIc: nearly complete perfusion but with a delay of the contrast runoff, grade III: full perfusion with normal filling of the distal branches in a normal hemodynamic fashion). Recanalization was defined as TICI grades II or III.

Age, gender, the NIHSS on admission, the time from symptoms to IA therapy, duration of the procedure, the UK dose, recanalization, symptomatic intracranial hemorrhage, the NIHSS at discharge and the outcomes were recorded and analyzed. The clinical evaluation was done by stroke neurologists who were not

blinded to the treatment. A brain CT scan was routinely obtained immediately after the procedure and if the patients showed neurologic deterioration during admission. The CT scans were analyzed for hemorrhagic transformation by the same interventional neuroradiologist. The clinical outcome was assessed by the modified Rankin Scale (mRS) at three months and this was dichotomized as favorable (mRS, 0-2) or unfavorable (mRS, 3-6).

Results

Twenty one patients with acute BAO (6 women and 15 men) with a median age of 68.6 years (range: 47 - 87 years) met the study criteria. The clinical characteristics of the 21 patients are summarized in Table 1. The median NIHSS score was 13.2 (range: 2-33) on admission. Median time from symptom onset to arrival at hospital was 356 minutes, and median time from symptom onset to intra-arterial thrombolysis (IAT) was 49 minutes. The median IA treatment duration was 82 minutes (range: 40-140) and the UK dose was 50,000 - 400,000 U (median: 250,000U). Of these patients, six patients received an additional injection of UK due to distal migration of thrombus into the posterior cerebral artery (100,000 - 200,000 U). Four patients had severe stenosis of the basilar artery after UK infusion and mechanical clot disruption with a microcatheter and microwire. Of these patients, three received stent placement after angioplasty (Figure 1) and one underwent only angioplasty. Three patients had a mural thrombus remaining in the basilar artery after mechanical clot disruption with a microcatheter and microwire, and so mechanical clot disruption with a HyperForm compliant balloon catheter was performed. Recanalization (TICI grade II or III) was achieved in 19 patients (90.5%). Twelve patients (57.1%) were TICI grade III and seven patients (33.3%) TICI grade II. Two patients (9.5%) (TICI grade I) failed with recanalization of the posterior circulation. Of these patients, one patient had treatment due to a procedure-related subarachnoid hemorrhage and one had a diffuse, long segmental stenosis of the basilar artery. There was symptomatic hemorrhage in one patient.

Two patients (9.5%) died within one week after the procedure. One patient with hemorrhage complication died and one with incomplete recanalization due to a long segmental

Table 1 Clinical and imaging characteristics and outcomes of the 21 patients.

Age/ Gender	NHSS Score on Admission	Occlusion Site	Symptom onset (min) ^a	Time to IA therapy (min)	Duration of procedure (min)	Urokinase Dose ($\times 10^4$ U)	Angioplasty	Stent	TICI grade	Symptomatic Hemorrhage	NHSS at Discharge	mRS at 3 Months
63/M	12	VB junction	200	265	50	15	0	0	I	Yes	Death	6
81/F	17	Distal BA	360	400	80	25			IIb	No	25	6
59/M	6	Mid BA	325	375	85	20			III	No	2	2
79/F	10	Distal BA	720	770	60	20			III	No	4	2
47/M	16	VB junction	300	350	95	30 ^b			III	No	6	0
70/M	4	Distal BA	490	550	80	30			IIa	No	3	2
72/M	18	VB junction	640	680	50	20	0	0	III	No	13	3
77/F	15	VB junction	305	350	65	5			III	No	4	2
61/M	8	VB junction	330	370	90	20			IIb	No	2	2
87/F	33	Proximal BA	350	410	70	15	0		I	No	Death	6
61/M	15	VB junction	210	260	140	40 ^b	0 ^c		IIb	No	0	1
59/M	6	VB junction	700	740	125	20	0	0	III	No	27	4
80/M	17	Distal BA	180	230	90	30 ^b			IIb	No	4	1
72/M	18	Distal BA	185	235	85	30			III	No	1	0
84/M	27	Distal BA	155	210	55	30 ^b			IIb	No	9	3
70/F	10	VB junction	710	750	80	10			IIa	No	7	4
75/F	8	Distal BA	315	355	145	30			III	No	0	2
67/M	16	Distal BA	235	270	100	40 ^b	0 ^c		III	No	7	2
55/M	5	Distal BA	210	255	90	40 ^b	0 ^c		III	No	1	1
61/M	14	Distal BA	205	300	40	20			III	No	4	2
60/M	2	Distal BA	355	400	45	30			III	No	1	0

^a Time to arrival at hospital after symptom onset^b Additional urokinase injection into the posterior cerebral artery due to distal migration of thrombus^c Patients used Hyperform for angioplasty

Figure 1 A 59-year-old man with dysarthria. A) Pretreatment DWI shows limited lesion in the Rt cerebellar vermis. B) MRA shows obstruction of the basilar artery and Lt. vertebral artery. C) The initial right vertebral artery angiogram demonstrates the complete occlusion of the proximal BA. D) Recanalization was achieved after IAT with low-dose IA UK and mechanical clot disruption, but reobstruction of the vertebrobasilar junction (arrow) was generated by stenosis. E) After placement of a 2.75x12 mm stent, there was recanalization of the vertebrobasilar junction.

stenosis and an initial comatose mental status died. At discharge (19/21), the median NIHSS score was 6.3 (range: 0-27). The NIHSS score of 17 patients had improved. In two patients, the NIHSS score was increased. At the three-month follow-up, the functional outcome was favorable (mRS, 0-2) in 14 (66.7%) out of the 21 patients. The functional outcome was unfavorable (mRS, 3-6) in seven (33.3%) patients and among them three (14.3%) patients, including the two patients who died after their procedures, died within the three-month follow-up time frame.

Discussion

Basilar artery occlusion (BAO) is the most severe form of ischemic stroke and it has high mortality and morbidity rates. Despite all the advances in modern therapy and general medical care, the prognosis is still grim. Early recanalization has been shown to be the most important predictor of successful therapy⁸⁻¹⁰. The absence of well-balanced comparative studies of the literature-based outcomes or a large prospective randomized trial has led to a different view on the preferred therapy, that is, IVT or IAT. Lindsberg et al.¹⁷ reported a 52% recanalization rate after IV rtPA in patients with BAO. However, several series have reported rates of recanalization with IAT that were thought to be higher than that for IVT^{4,14-16}.

We performed the IAT with low-dose IA UK and mechanical clot disruption using a microcatheter and microguidewire in all the patients. Mechanical clot disruption by the use of a microcatheter/microguidewire and/or percutaneous angioplasty can provide an advantage compared with IA infusion by increasing the recanalization rate and speed and reducing the total thrombolytic dose¹⁸⁻²⁰. Noser et al.¹⁸ reported a 38% immediate recanalization rate in 32 patients with acute ischemic stroke and who were treated with mechanical clot disruption in conjunction with IA infusion of reteplase. Of the 32 patients, 22 received combined IVT-IAT. A favorable outcome was noted in 59% of the patients, with a rate of symptomatic cerebral hemorrhage of 9.4% and a mortality rate of 12.5%. Yoon et al.²⁰ reported a 100% recanalization rate in 12 patients with acute ischemic stroke and who were treated with mechanical clot disruption and low-dose IA UK after failure of IVT. A favorable outcome

was noted in 75% of the patients. Mechanical clot disruption could decrease the symptomatic intracranial hemorrhage compared with that of pharmacologic IVT-IAT. Symptomatic intracranial hemorrhage is the most feared complication of combined IVT-IAT. Previous studies of IAT with UK suggest a higher dose of IA UK leads to higher rates of symptomatic intracranial hemorrhage^{21,22}. In our study, we used a minimal amount of urokinase, and we also used the technique of mechanical clot disruption. In this study, only one patient displayed symptomatic hemorrhage (4.7%).

Most of the recent national guidelines favor endovascular thrombolysis in combination with mechanical manipulation of the thrombus. A recent meta-analysis on the therapy for BAO showed that notwithstanding better recanalization after IA therapy, the survival rates after IV and IA thrombolysis were comparable⁵. A multicenter observational study has recently shown that the bridging concept, when used as combined treatment with IA rt-PA and IV platelet glycoprotein IIb/IIIa receptor inhibitors and additional percutaneous transluminal angioplasty/stenting in cases of severe residual stenosis after IAT, might improve the neurologic outcome compared to IAT with rt-PA alone^{23,24}. Pfefferkorn T. et al.²⁵ reported a high recanalization rate after IV thrombolysis and on-demand consecutive endovascular mechanical thrombectomy using an Amplatz goose neck snare and an Angiojet in patients with acute BAO.

In our study, four patients were treated with additional mechanical thrombectomy for their residual thrombi after mechanical clot disruption with a microcatheter and microguidewire, and three patients received stenting after percutaneous angioplasty for treating the underlying atherosclerotic stenosis.

Therefore, combined mechanical thrombectomy and IAT with low-dose UK is efficient in patients with acute BAO (90.5%, 19/21). These recanalization rates are within the range of 44% to 100% reported in the previous case series and large observational studies and they are mildly superior to the rate of a recently comparable study (72-83.7%)^{23,24}.

A favorable outcome was noted in 66.7% of our patients, with a 4.7% rate of symptomatic cerebral hemorrhage and a mortality rate of 14.3%.

The limitations of our study include the lack of central adjudication of events and cerebral

angiograms and the lack of prospective follow-up of the study patients. Also, our results have to be interpreted with caution because of the retrospective nature of the study, the inhomogeneous and small patient group and the different therapies used in addition to the placement of an intracranial stent.

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Conclusions

Our study showed that low-dose IAT with mechanical clot disruption is a safe and effective treatment for treatment for acute BAO. This procedure is rapid and has a high rate of recanalization, a high survival rate and good functional outcomes.

Dr Hyo Sung Kwak
Radiology Department
Chonbuk National University Medical School and Hospital
634-18, Keum-am Dong
Jeonju, Jeonbuk 561-712 Korea, republic of
E-mail: kwak8140@jbnu.ac.kr