

# Mechanical thrombectomy with the Penumbra recanalization device in acute ischemic stroke

*Thrombectomie mécanique avec le système de recanalisation Penumbra dans les accidents vasculaires cérébraux aigus ischémiques*

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*Abbreviations:* ACA, Anterior cerebral artery; AHA, American Heart Association; ASPECTS, Alberta Stroke Programme Early CT Score; BA, Basilar artery; CT, Computed tomography; DSA, Digital subtraction angiography; DWI, Diffusion-weighted images; ECASS, European cooperative acute stroke study; ESO, European Stroke Organisation; IAT, Intraarterial thrombolysis; ICA, Internal carotid artery; ICH, Intracerebral hemorrhage; IV, Intravenous; MCA, Middle cerebral artery; MR, Magnetic resonance; mRS, Modified Rankin scores; NIHSS, National Institutes of Health Stroke Scale; PPST, Penumbra Pivotal Stroke Trial; PROACT II, Second Prolyse in Acute Cerebral Thrombembolism Trial; PS, Penumbra system; rt-PA, Alteplase; SD, Standard deviation; SICH, Symptomatic intracranial haemorrhage; TIMI, Thrombolysis in myocardial infarction; VA, Vertebral artery.

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## Introduction

The treatment of acute ischemic stroke remains a domain of on-going clinical research. At present, intravenous alteplase (rt-PA) within 4.5 hours of onset of ischemic stroke is the only therapy that has proven effective in prospective controlled randomized multicentre trials (class I, level A) [1–8]. IAT is included into the recommendations of the ESO and the AHA for treatment of ischemic stroke within 6-hours after onset of clinical symptoms (class II, level B MCA [9–12], class III, level B BA) [13–15].

In the past years, mechanical devices have been developed and were shown to be successful in the recanalization of occluded major vessels in patients with acute ischemic stroke. The revascularization rates obtained with these devices range from 48–68% for the Merci clot retriever (Concentric Medical, Mountain View, CA, USA) [16–19] and 80–100% with the Penumbra system (Penumbra Inc., Alameda, CA, USA) [20–23]. It is yet not determined whether the improved re-opening rates that can be obtained with these new devices is reflected in a better neurological recovery and improved functional outcome, when compared to patients treated with IAT.

The PPST [23], a registry study designed to determine safety and effectiveness of the Penumbra system in opening clotted cerebral blood vessels in stroke, reported on successful revascularization of 81.6% of the treated vessels in 125 patients. All patients included have been followed clinically for 90 days postprocedure. When compared to historical data from patients included in the PROACT II [9], 90-day mortality rate was higher (PPST: 32.8%, PROACT II: 25%) and 90-day mRS  $\leq 2$  was lower (PPST: 25%, PROACT II: 40%) in patients treated with the Penumbra System, although the revascularization rate in PROACT II was lower (PPST: 81.6%, PROACT II: 66%).

The aim of this study was to compare the mortality and clinical outcome of patients with an acute stroke due to major vessel occlusion treated with the PS or IA. A retrospective matched-pair analysis was designed to address this issue.

## Methods

### Patient selection

Twenty consecutive patients with acute ischemic stroke due to major vessel occlusion (ICA, M1 segment of MCA, ACA, BA, VA) were treated at our institution between June 2008 and April 2009 with the PS. Routine baseline investigations included neurological and physical examination, assessment of NIHSS, routine blood analysis, ECG, brain imaging with either CT or MRI, and vascular imaging with either CT

Angiography or MR Angiography. The patients were stratified according to the NIHSS upon presentation in our institution and the location of the occluded target vessel. For each patient treated with the PS, we searched at random for a corresponding patient from our database of patients treated for acute ischemic stroke by IAT with rt-PA. We limited our research to patients treated between January 2002 and December 2007 in order to minimize the procedure and critical care-related bias. Matching pairs with respect to NIHSS upon presentation and location of the occluded target vessel could be defined in 20 cases. Baseline characteristics of the corresponding patients are outlined in Table 1.

### Revascularization procedure

#### Penumbra system

Revascularization procedures with the PS were performed between June 2008 and April 2009 on a biplanar angiographic system (Allura Xper FD 20/20, Philips, Best, the Netherlands) by five different, experienced interventional neuroradiologists. A bridging lysis with intravenous application of rt-PA was administered between initial imaging and the endovascular procedure in 17/20 patients with a mean dose of  $40.6 \pm 12.4$  mg rt-PA (20–60). Patients were treated under general anesthesia. In all patients the target vessel was directly catheterized with a 6F-guiding catheter or a 6F long sheath. Digital subtraction angiography was used to define the occluded vessel. The remaining dose of rt-PA was administered via a microcatheter placed proximally to the clot in 13 of 20 patients with a mean dose of  $22 \pm 8.3$  mg rt-PA (10–35). We then exchanged the microcatheter for the Penumbra catheter, placed proximally to the clot as well. The technique of mechanical thrombectomy with the PS has been described previously [23]. Eighteen patients received either IV or IA rt-PA with a mean total dose of  $54.2 \pm 17.2$  mg (20–90) (Table 1).

#### Intraarterial lysis

Revascularization procedures were performed between January 2002 and December 2006 on a biplanar angiographic system (Advantx LC/LPN+, GE Healthcare) by experienced interventional neuroradiologists. A bridging lysis was administered in 12 of 20 patients between initial imaging and the endovascular procedure with a mean dose of  $37.1 \pm 11.6$  mg rt-PA (8–50). The endovascular approach was comparable to the one described for the PS. The microcatheter with a single endhole was placed into or proximally to the thrombus with a steerable microguide wire. A superselective angiogram was performed through the microcatheter to document catheter placement. rt-PA was infused at a rate of 60 mg/h at a dose of 0.9 mg/kg bodyweight up to a maximum dose of 90 mg. The mean dose administered intraarterially

**Table 1** Patient baseline characteristics.

	Penumbra (n = 20)	IA thrombolysis (n = 20)	P-value
Age, years [mean ± S.D., (range) ]	61.9 ± 17.6 (16–9)	60.3 ± 16 (27–5)	0.78
Woman	12	10	0.54
NIHSS [mean ± S.D., (range) ]	16.6 ± 4.7 (8–7)	16.4 ± 4.7 (9–26)	0.54
ASPECTS score at presentation (n = 16)	7 ± 1.09 (5–8)	6.25 ± 2.33 (1–9)	0.29
<i>Target vessel location</i>			
Single vessel occlusion (n = 8)			
ICA	1	1	–
MCA (M1 segment)	7	7	–
Combined vessel occlusion (n = 12)			
ICA + MCA	10	10	–
ACA + MCA	1	1	–
VA + BA	1	1	–
IV thrombolysis	n = 17	n = 12	0.16 <sup>a</sup>
Mg IV rt-PA [mean ± S.D., (range) ]	40.6 ± 12.4 (20–60)	37.1 ± 11.6 (8–50)	–
Symptom-onset to IV thrombolysis	162 ± 75 (60–300)	153 ± 57 (60–275)	0.52
IA thrombolysis	n = 13	n = 20	0.008 <sup>a</sup>
Mg IA rt-PA [mean ± S.D., (range) ]	22 ± 8.3 (10–35)	39.2 ± 16.8 (13–70)	–
Total rt-PA [mean ± S.D., (range) ]	54.2 ± 17.2 (20–90)	62.6 ± 24.9 (25–120)	–
Symptom-onset to first angio series	237 ± 98 (120–550)	229 ± 66 (72–350)	0.76
First angio series to final control	137 ± 56 (40–230)	102 ± 47 (25–210)	0.006

P: Student *t* test; NIHSS: National Institutes of Health Stroke Scale; ASPECTS: Alberta Stroke Programme Early CT Score; IV: intravenous; rt-PA: alteplase; ICA: internal carotid artery; MCA: middle cerebral artery; ACA: anterior cerebral artery; BA: basilar artery; VA: vertebral artery; IA: intraarterial.

<sup>a</sup> P: 2-tailed Fischer's exact test.

was 39.2 ± 16.8 mg rt-PA (13–70), resulting in a mean total rt-PA dose of 62.6 ± 24.9 mg (25–120) in 20 patients. After administration of the complete dose of rt-PA, an angiogram via the guiding catheter/vascular sheath was performed. In those cases where the target vessels remained occluded, mechanical disruption of the thrombus was attempted with the microguide wire. The mean doses of rt-PA administered IV and IA in the IAT group of the study are outlined in Table 1.

### Post-treatment evaluation

Medical management and acute post-stroke care after the procedure was consistent with the ESO and AHA guidelines [6,7]. A CT scan was performed within 24 hours after the revascularization procedure to detect the presence of ICH. Patients were evaluated for neurologic and functional status immediately post-procedure, on the day of discharge, and 90 days (±10 days) post-treatment by the attending neurologist. Intracranial hemorrhage was defined as symptomatic in case of parenchymal hematoma, local or remote with a clinical worsening of at least four points on the NIHSS scale according to the ECASS definition [8]. A favorable clinical outcome was defined as improvement of the NIHSS by ≥ 10 points or NIHSS 0 + 1 upon discharge, and a mRs score ≤ 2 at 90 days.

### Image interpretation

Two independent raters (M.T. and J.W., with seven and 15 years of experience in neuroimaging, respectively) qualitatively evaluated pre-therapeutic MR, CT, and DSA images as well as final angiograms and follow-up CT at 24 h. Revascularization was assessed by TIMI flow classification [24]. Successful revascularization was defined as angiographic demonstration of TIMI grade 2 or 3 flow within the target vessel. The extent of the ischemic lesion was determined on pre-therapeutic CT or DWI. We used a standardized scoring system based on predefined criteria (ASPECTS) [25]. A template of two axial slices with markers for the 10 regions being scored by the ASPECTS was provided.

### Statistical methods

Standard descriptive statistics for categorical end points were the number and percent of patients with each level of the end point. For numeric end points, the standard descriptive statistics included the number of non-missing observations (*n*), the mean, the median, the S.D., the minimum value, and the maximum value. For differences in categorical variables, student *t* tests were performed. Outcomes (NIHSS improved by ≥ 10 or NIHSS 0 + 1 upon discharge, mRS score of 0 to 2 at 90 days) and mortality

rates in patients treated with the PS and IAT were compared by using two-sided Fisher's exact test with  $P$  values of  $<0.05$ , considered statistically significant. A  $P=0.05-0.10$  was regarded as a strong tendency. A statistical package (MedCalc; MediSoftware, Mariakerke, Belgium) was used to perform all calculations.

## Results

### Baseline data

Twenty-two patients were treated with the PS between June 2008 and March 2009. Twenty patients matching patients could be identified that were treated with IAT between January 2002 and December 2007. In two patients, no matches were found (NIHSS upon presentation were 7 and 10 respectively, distal ICA occlusions in both cases. The angiographic results after application of the PS remained TIMI 0 for both. Both patients died during hospitalization).

Stroke severity, location of the target vessel, patient age and mean time from symptom onset to treatment did not differ between the two groups. No significant differences were observed for the time from symptom onset to the beginning of the endovascular treatment with  $237 \pm 98$  minutes for the PS and  $229 \pm 66$  minutes for IAT ( $P=0.76$ ). The duration of the treatment differed significantly ( $P=0.006$ ) between PS with  $137 \pm 56$  minutes and  $102 \pm 47$  minutes for IAT (Table 1).

Asymptomatic ICH 24 h after the intervention were present in 7/20 patients treated with PS versus 6/20 treated with IAT. Two patients treated with PS developed a SICH and one had a fatal outcome. No SICH occurred in patients treated with IAT. These differences were statistically not significant ( $P=0.49$ ).

### Recanalization

At baseline, all 20 patients treated with the PS had a TIMI score of 0 or 1. Post-procedure, 78% achieved a TIMI score of 2 or 3 within the target vessels (31% had a TIMI score of 2, and 47% had a TIMI score of 3). The 20 matching patients treated with IAT had a baseline TIMI score of 0 or 1. Post-procedure 53% had a TIMI score of 2 or 3 within the target vessel (9% were TIMI 2, 44% were TIMI 3) (Table 2).

### Clinical outcome

Upon discharge, 2/20 patients treated with PS and 7/20 patients treated with IAT had a favorable outcome (NIHSS

improved by  $\geq 10$  or NIHSS 0+1). All cause mortality at 90 days was 3/20 patients treated with PS, and 2/20 patients treated with IAT. Upon follow-up, two patients had a mRS 0–2 in the PS group, compared to seven patients in the IAT group (Table 2).

## Discussion

In this matched-pair study, patients with ischemic stroke who underwent IAT had a better outcome than patients who were treated with the PS ( $P=0.12/0.27$ ). The outcome after IAT was more favorable even though the PS had obtained higher revascularization rates than IAT ( $P=0.06$ ).

The results of our study corroborate findings published in the recent literature [9,23]. Our revascularization rate of 78% lies in the range of the PPST [23], a multicentre registry including 125 patients treated with the PS with a reported revascularization rate of 81.6%. In the PPST, patient neurological recovery and functional outcomes showed a favorable outcome with 25% having either a NIHSS score of 0 to 1 or a  $\geq 10$ -point improvement at discharge, and 25% having a mRS score of  $\leq 2$  at 90 days. In our study, the neurological recovery and the functional outcome in patients treated with the PS was less favorable with a NIHSS score of 0 to 1 or a  $\geq 10$ -point improvement at discharge of 10%, and a mRS score of  $\leq 2$  at 90 days in 15%.

These differences might be explained by the high number of patients treated for a combined ICA/MCA occlusion in our study of 10/20 (50%), compared to 23/125 (18%) treated for ICA occlusion in the PPST. Mortality rates associated with occlusions of the terminal ICA are known to be particularly high [26].

Patient neurological recovery and functional outcomes in the IAT group of our matched-pair study was 7/20 (35%) having a mRS  $\leq 2$  at 90 days. This 90-day mRS score was comparable to the treated group in the PROACT II study with 48/121 (40%) [9].

The cause of the disparity observed between the revascularization rate and the functional outcome in our matched-pair analysis, as well as in the direct comparison between patients treated in PPST and the treated group in the PROACT II study, needs further consideration.

The timing of the treatment might explain the differences in outcome between the PS group and patients treated with IAT. The time between onset of symptoms and beginning of the revascularization procedure (IVT, IAT and PS) did not differ between groups. But the duration of the recanalization procedure was significantly longer in the PS group

**Table 2** Angiographic, imaging, neurological, and functional outcomes.

	Penumbra ( $n=20$ )	IA thrombolysis ( $n=20$ )	$P$ value
TIMI grade 2/3 (target vessels, $n=32$ )	25/32 (78%)	17/32 (53%)	0.06
Discharge NIHSS 0–1 or NIHSS improved $\geq 10$	2	7	0.12
mRs $\leq 2$ at 90 days	3	7	0.27
Death at 90 days	3	2	1

$P$ : 2-tailed Fischer's exact test; TIMI: thrombolysis in myocardial infarction; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin scores.

( $P=0.006$ ), resulting in a longer time from onset of symptoms to revascularization/final control ( $P=0.12$ ).

The longer duration of the PS procedure can not be explained by the fact that 13 of 20 patients had an IAT with rt-PA before the Penumbra procedure requiring an extra time of  $22 \pm 8$  minutes (mean  $\pm$  S.D.). Actually, the mean duration of the procedure in the PS group was longer in those patients who did not have an IAT with rt-PA before thrombus aspiration. This observation might indicate that the direct administration of rt-PA within the thrombus facilitates subsequent aspiration with the PS.

Another factor potentially influencing the outcome is the hemorrhage rate. In our matched-pair analysis, the occurrence of asymptomatic hemorrhage was evenly distributed between groups. Symptomatic hemorrhages occurred more often in the PS group. These symptomatic hemorrhages were probably reperfusion hemorrhages – in both cases, TIMI 3 results had been obtained.

The initial size of the ischemic area influences the outcome [27,28]. The ASPECTS scores in the IAT group were higher, indicating larger affected areas when compared to patients treated with the PS. This observation might be biased. The ASPECTS score was derived from CT and DWI data with a much higher number of pre-interventional CT's in the IAT arm of the study.

Our results are in contrast to another retrospective monocentric analysis of the PS for the treatment of large-vessel occlusion in acute stroke [29]. Kulcsár et al., reported results in 27 consecutive patients with a recanalization rate to TIC1 2 or 3 in 25 patients (93%) with a good functional outcome ( $mRS \leq 2$ ) in 13 (48%). The differences to the results of our study might be attributable to various factors:

- mean NIHSS in our study was 2–3 points higher (NIHSS:  $16.6 \pm 4.7$  [8–27], versus NIHSS  $14 \pm 7$ ). The range of NIHSS is not given in the study by Kulcsár et al. Yet, the higher standard deviation in their study indicates that some patients included must have had a NIHSS score even below 7. In the Penumbra pivotal trial, inclusion of patients was restricted to a baseline NIHSS score of  $\geq 8$  [23]. These differences might in part explain the better outcome reported by Kulcsár et al;
- in our study, 11/20 (55%) patients presented with a carotid-T occlusion, whereas only 5/27 (19%) in the study population of Kulcsár et al. presented this condition known to be related with a generally worse outcome when compared to MCA occlusion;
- in the study of Kulcsár et al., 4/27 (15%) patients received additional angioplasty with stent placement. This fact limits the number of cases where revascularization is attributable solely to the PS to 21/27 (78%) – which is exactly the revascularization rate we have obtained in our series with exclusive use of the PS.

The main limitation of our study is the small sample size, limiting the statistical power. The study therefore, is of observational nature and reflects our experience with the PS in comparison to IAT. We declare a potential selection bias. Our current protocol in the treatment of acute ischemic stroke due to major vessel occlusion (ICA, M1, BA) includes initial IV lysis with rt-PA, followed by IA administration of the remaining one third of rt-PA and subsequent

aspiration of the thrombus. This approach might have led to a selection of patients who were refractory to IAT, presenting with a larger thrombus load or a larger number of organized thrombi.

## Conclusion

The PS is effective in re-opening occluded major arteries. Our data seems to indicate that not all patients benefit clinically from improved revascularization of occluded major arteries. Patient selection and ideal timing for treatment with this powerful tool need to be determined in a comparative study of a larger scale.

## Conflict of interest statement

The author Christian A. Taschner has a proctoring contract with Penumbra Inc. The remaining authors declare to have no conflict of interest.

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