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ORIGINAL RESEARCH

Recanalization of Large Intracranial Vessels Using the Penumbra System: A Single-Center Experience

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BACKGROUND AND PURPOSE: The PS is an innovative mechanical device designed to recanalize large-vessel occlusions by thrombus aspiration. The purpose of this study was to evaluate the effectiveness and neurologic outcome of patients treated with the PS in the setting of acute ischemic stroke.

MATERIALS AND METHODS: A total of 91 patients with acute ischemic stroke due to large-vessel occlusion were treated with the PS and were included in our retrospective study. In 14 patients, only the PS was used for treatment; in 77 patients, mechanical recanalization was combined with IA and/or IV thrombolysis. Outcome was measured by using the mRS; recanalization was assessed with the TICI score.

RESULTS: Mean patient age was 62 ± 19.4 years; the average NIHSS score at hospital admission was 17. Successful recanalization was achieved in 77% of patients. Median time from arterial puncture to recanalization was 49 minutes (quartiles, 31–86 minutes). At follow-up, 36% of the patients showed an NIHSS improvement of ≥10%, and 34% of the patients with an anterior circulation occlusion had an mRS score of ≤2, whereas only 7% of the patients with a posterior occlusion had a favorable outcome at follow-up. In total, 20 patients died during hospitalization; none of these deaths were device-related.

CONCLUSIONS: In this study, the PS was an effective device for mechanical recanalization. Successful recanalization with the PS was associated with significant improvement of functional outcome in patients experiencing ischemic stroke secondary to anterior circulation occlusions.

ABBREVIATIONS: BA = basilar artery; CCA = common carotid artery; IA = intra-arterial; ICH = intracranial hemorrhage; IQR = interquartile range; mRS = modified Rankin Scale; PCA = posterior cerebral artery; PRC = Penumbra reperfusion catheter; PS = Penumbra System; SICH = symptomatic intracranial hemorrhage; TICI = thrombolysis in cerebral infarction; TIMI = thrombolysis in myocardial infarction; VA = vertebral artery

Current treatment options for acute ischemic stroke include the administration of thrombolytics, either IV or IA, and the use of thrombectomy or recanalization devices.[1-4] IV-rtPA therapy is the standard for acute stroke, improving 3-month outcome if given within the first 4.5 hours of stroke onset.[2] Nevertheless, not all patients benefit from the standard therapy mainly due to low recanalization rates.[5,6] Recanalization rates vary depending on thrombus location and extent, with very low rates shown in proximal arterial occlusions.[7] A recent study demonstrated that in patients with an acute MCA stroke and a thrombus length of >8 mm, IV-rtPA failed at recanalization, resulting in a median mRS score of 5 at discharge.[8] These studies have emphasized the need for therapeutic alternatives in selected cases, thus paving the way for the development and use of thrombectomy or recanalization devices.[9-11] In this study, we retrospectively evaluated the clinical course of 91 patients with acute stroke due to large-vessel occlusion who had undergone neurointerventional treatment with the PS (Penumbra, Alameda, California).

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Materials and Methods

Patients

Ninety-five patients were identified for our study, of which 91 (43 women, 48 men; mean age, 62 ± 19.4 years) with acute ischemic stroke due to large-vessel occlusion and treatment with the PS between October 2007 and December 2010 were finally included. Baseline investigations were physical and neurologic examinations for assessment of stroke severity with the NIHSS and the mRS, blood analysis, 12-lead electrocardiography, and finally stroke imaging.

A total of 4 patients were excluded from the current analysis due to recanalization of the occluded vessel before any mechanical intervention as documented on the first digital subtraction angiogram.

Approval of the local ethics committee and informed patient consent or consent of a legally authorized representative were obtained.

Imaging and Treatment

Stroke imaging was performed on a 128-section CT scanner (Somatom Definition AS+; Siemens Healthcare, Forchheim, Germany) and consisted of a noncontrast CT scan followed by CT perfusion of the brain and CT angiography of the neck and brain vessels. The site of occlusion was the proximal MCA in 39 cases, the carotid-T in 21 cases, the proximal ICA in 11 cases, the BA in 15 cases, and the CCA in 1

case. Furthermore, a combined occlusion of the distal VA and BA was detected in 3 cases, while an occlusion of the PCA was identified in 1 case. For the purposes of our study, all above-mentioned main stems as well as the proximal parts of their intracranial branches were defined as "large vessels." According to current stroke therapy guidelines,[2] patients eligible for IV-rtPA therapy (presenting within 4.5 hours of symptom onset with no significant infarction or hemorrhage detected on noncontrast CT) were started on full-dose IV-rtPA (0.9 mg/kg) in the CT suite.

After stroke imaging, patients were transferred to the angiography (Axion Artis dBa; Siemens Healthcare) suite of our department, where general anesthesia was induced. Via the femoral approach, an 8F sheath or a 6F guide catheter was advanced to the CCA or the proximal VA, depending on the site of occlusion, and diagnostic angiography was performed. A high-grade stenosis of the proximal ICA was identified in 12 cases and was treated with carotid angioplasty and stent placement by using a carotid Wallstent (Boston Scientific, Natick, Massachusetts). By using the technique described in the Penumbra Pivotal Stroke Trial,[4] we then advanced a PRC over a guidewire and positioned it directly proximal to the thrombus. Depending on the site of occlusion, different sizes of PRCs were used, ranging from an inner lumen of 1.4 (054) to 0.8 mm (032). Thrombus aspiration was then initiated with the help of an aspiration pump (−508 mm/Hg vacuum), which was connected to the PRC via an aspiration tube. To fragment thrombus and support aspiration, we then advanced an appropriately sized Penumbra separator through the thrombus and repeatedly retracted it into the catheter. This procedure was repeated as many times as the treating physician considered necessary, and additional reperfusion catheters or separators were used to aspirate further distal thrombus.

If, despite the aspiration maneuvers, the thrombus could not be removed, the physician still had the option of administering the remaining dose of rtPA IA through the reperfusion catheter and then continuing with aspiration maneuvers. Contrary to the Penumbra Pivotal Stroke Trial, where an alternative method of direct thrombus extraction was also used, we applied only the aspiration technique in our study.[4] At the end of the procedure, a flat panel detector angiographic CT was performed to rule out peri-interventional hemorrhage.[12] Further CT scans were obtained 24 hours after the intervention or in any case of neurologic deterioration, on the above-mentioned 128-section CT scanner, to exclude SICH. "Symptomatic ICH" was defined as any extravascular blood within the cranium that was the predominant cause of clinical deterioration or death. All patients who underwent angioplasty and stent placement received orally administered acetylsalicylic acid (100 mg/day) and clopidogrel (75 mg/day) for 6 weeks after the procedure. Patients with a BA thrombosis were heparinized and received anticoagulants according to the discretion of the treating neurologist. Aspirin was administered indefinitely in all other patients. All patients were routinely monitored in our intensive care unit for at least 3 days and were discharged afterward to a stroke unit or a general neurology ward thereafter. Clinical examination and duplex sonography were performed before discharge to confirm vessel patency and to obtain the clinical status of the patient. Pre- and posttreatment digital subtraction angiographies were anonymized and then sent to a PACS.

Patient and Data Evaluation

A neuroradiologist not involved in the interventions evaluated all angiographies by using the TICI score. Described by Higashida et al,[13] this score has gained acceptance among neurointerventionalists in an attempt to standardize reporting of flow restoration in neurointerventions and is currently being used in prospective trials evaluating recanalization approaches.[14,15] Neurologic scores (NIHSS, mRS) were assessed by a stroke neurologist at hospital admission and discharge as well as at discharge from the rehabilitation unit (follow-up: median, 73 days; IQR, 45–99 days). The NIHSS is a 15-item scale for measuring neurologic impairment with values ranging from 0 to 42. Higher NIHSS values indicate severe cerebral infarcts. The mRS is a scale of disability or dependence in daily activities ranging from 0 (no symptoms) to 6 (death). An mRS score of 2 means that the patient with stroke is able to look after his or her affairs without assistance.

Descriptive statistics and contingency tables were used for statistical evaluation. Recanalization and neurologic scores prior to and after treatment were compared with the matched-pairs Wilcoxon test. The differences of nominal variables were calculated with the χ^2 test. For continuous variables, the Mann-Whitney *U* test was applied. All scores were calculated by using the Statistical Package for the Social Sciences, Version 17 (SPSS, Chicago, Illinois). *P* values $<.05$ were considered statistically significant.

Results

Baseline Data

From October 2007 to December 2010, a total of 95 patients were identified for our study, and finally 91 were included in our analysis. All 91 patients were followed to hospital discharge; 11 patients were lost to follow-up. Median time from symptom onset to arterial puncture was 235 minutes (IQR, 206–305 minutes) with a median of 153 minutes (IQR, 124–177 minutes) from the time of admission to arterial puncture. The median time from arterial puncture to recanalization was 49 minutes (IQR, 31–86 minutes), while the overall median time from symptom onset to arterial recanalization was 294 minutes (IQR, 245–364 minutes). Of the 91 patients, 10 were treated with IV-rtPA and aspiration, 40 received combined IV-/IA-rtPA and aspiration, while 27 received only IA-rtPA before aspiration and 14 were treated solely with mechanical clot removal. Patients spent a median of 16 days (IQR, 10–23 days) in the hospital, while the time period in the rehabilitation unit and the total time of treatment were 49 (IQR, 29–66 days) and 67 (IQR, 38–96 days) days, respectively. Procedural complications included a separator tip break in 2 patients, a groin hematoma in another 2 patients, and an artery dissection in 4 patients. All 4 artery dissections were located at the cervical segment of the ICA; 3 were hemodynamically relevant and were treated with a closed-cell stent (Wallstent; Boston Scientific). Furthermore, 1 SAH was detected on direct post-interventional flat panel CT. During follow-up, there were 19 cases (20.9%) of ICH detected, with 5 of them being SICH (5.5%) and 2 being SAH. By applying the European Cooperative Acute Stroke Study classification of hemorrhagic transformation,[16] we found 5 cases of hemorrhage infarction type 1, 3 cases of hemorrhage infarction type 2, 5 cases of parenchymal hematoma type 1, and 4 cases of parenchymal hematoma type 2.

Recanalization

Before treatment, 65 patients (71%) had a TICI score of 0, and 26 (29%), a TICI score of 1. After treatment, the number of patients with TICI scores of 0 and 1 was reduced to 8 (9%) and

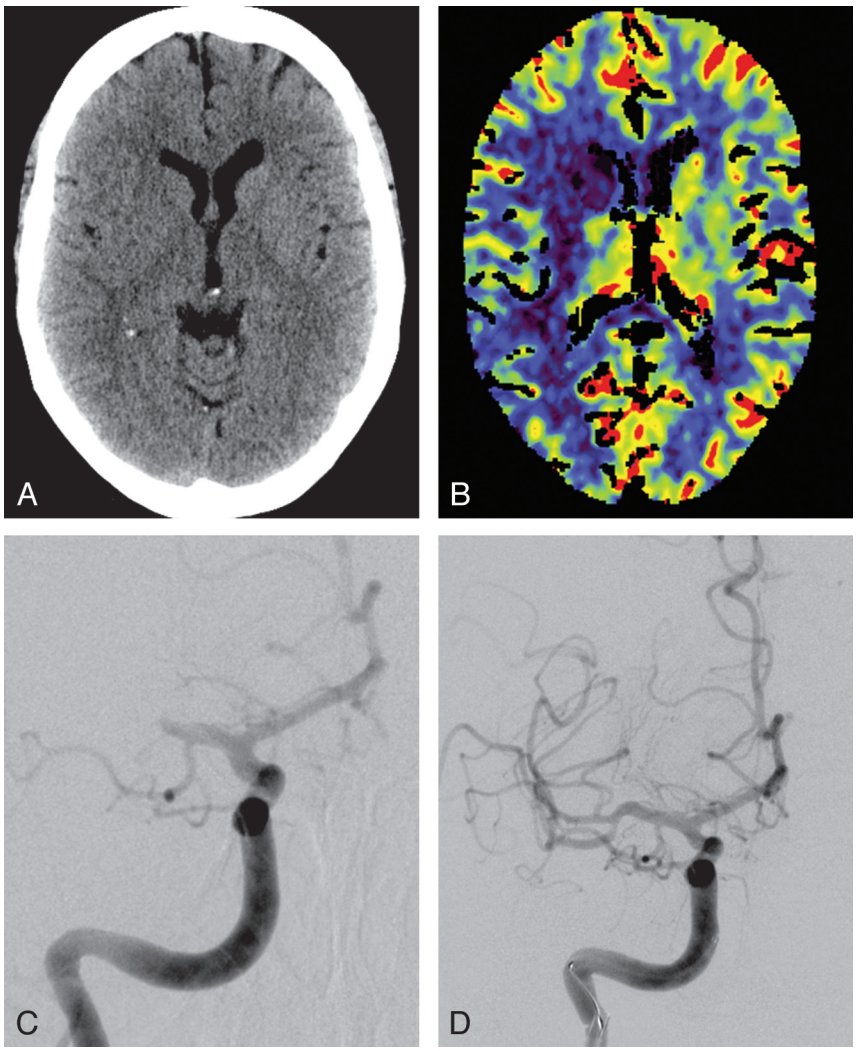

Fig 1. A 36-year-old woman with an acute left hemiparesis and an admission mRS of 5. *A* and *B*, Noncontrast CT scan shows subtle low attenuation in the right putamen and head of the caudate nucleus; CT perfusion shows a significant reduction of cerebral blood flow in the right MCA territory. *C*, After initiation of IV-rtPA, the patient was transferred to the angiography suite and a persistent occlusion (TICI 0) of the M1 segment of the right MCA is shown on the posteroanterior angiogram. *D*, Successful recanalization (TICI 3) was achieved after thrombus aspiration with the PS. Total time from symptom onset to successful recanalization was 205 minutes. The patient was discharged to the rehabilitation unit with an mRS score of 4 after 11 days, and a favorable outcome with an mRS score of 2 was diagnosed at follow-up.

1 (14%), respectively, while 21 (23%) had TICI scores of 2a, 12 (13%) had TICI scores of 2b, and finally 37 (41%) had TICI scores of 3 ($P < .001$). Thus, partial or complete reperfusion was achieved in 70 cases (77% TICI 2 or 3) (Fig 1). If one considers the site of primary occlusion, partial or complete reperfusion after treatment was achieved in 79% (31/39) of MCA occlusions; in 86% (18/21) of carotid-T occlusions; in 64% (7/11) of ICA occlusions; in 1 (100%) case of CCA occlusion; and finally in 67% (10/15), 100% (3/3), and 0% (0/1) of BA, VA + BA, or PCA occlusions ($P = .27$). Thus, a TICI 2 or 3 score was achieved in 79% of the anterior circulation occlusions and in 68% of the posterior circulation occlusions. Regarding the use of rtPA, partial or complete reperfusion was achieved in 30 (75%) cases in which IV- and IA-rtPA were combined, in 6 (60%) cases with IV-only administration of rtPA, and in 23 (85%) of the treatments with IA administration of rtPA ($P = .35$). A mean of 32 mg of rtPA was administered IA in this last group of patients. Fourteen patients did not receive lytic therapy; a TICI score of 2 or 3 was assigned to 11 (79%) of them (Table).

Treatment subgroups

	Count	Partial or Complete Reperfusion (TICI 2–3)	Favorable Outcome on Follow-Up (mRS ≤ 2)
PS only	14	11 (79%)	7/14 (50%)
IV-rtPA + PS	10	6 (60%)	0/8[a] (0%)
IA-rtPA + PS	27	23 (85%)	6/22[a] (27%)
IV + IA-rtPA + PS	40	30 (75%)	11/36[a] (31%)

[a] A total of 11 patients were lost to follow-up.

Clinical Outcome

The mean NIHSS score at admission was 17 ± 6.1, while the median mRS at admission was 5 (IQR, 4–5). A total of 35 patients (39%) had an NIHSS score of ≥20 at admission. At hospital discharge, mean NIHSS scores and median mRS scores had improved to 9.9 ± 6.2 ($P < .001$) and 4 (IQR, 4–5; $P = .041$) points, respectively; and finally, at follow-up, patients showed a mean NIHSS score of 6.3 (SD ± 5.6, $P < .001$) and a median mRS score of 4 (IQR, 2–6; $P = .001$). Overall 23 (29%) patients had a favorable outcome 90 days after treat-

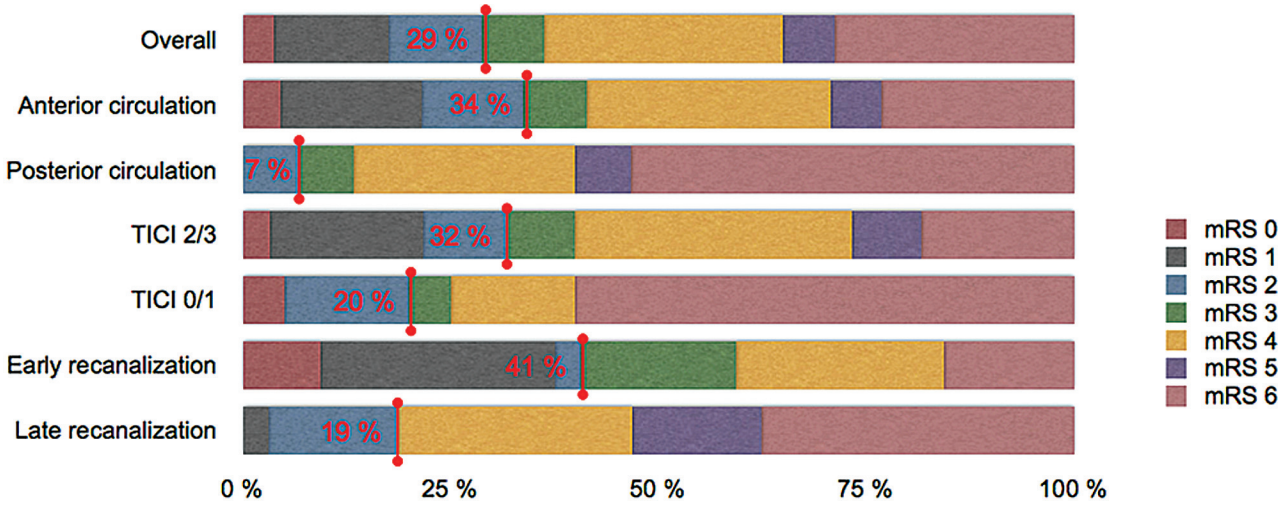

Fig 2. Chart showing the follow-up outcome (mRS) of 91 patients treated with the PS (upper bar) and the outcomes within the various categories in the population. The figures in the bars indicate the percentage of patients with a favorable outcome at follow-up.

ment or at discharge from the rehabilitation unit, defined by an mRS score of ≤2, whereas 28 (35%) patients had a "bad outcome" with an mRS score of ≥5. In 44 (48%) patients, a ≥4-point improvement on the NIHSS score was noted at hospital discharge, while 21 (23%) patients had a ≥10-point improvement on the NIHSS at the same time point. At follow-up, these numbers increased to 52 (57%) patients with a ≥4-point improvement and 33 (36%) patients with a ≥10-point improvement on the NIHSS. The all-cause mortality was 25%, with 20 patients dying during hospital treatment, and 3, after hospital discharge. Regarding the site of occlusion, a follow-up mRS score of ≤2 was observed in 10 (29%) patients with MCA occlusion, in 9 (50%) patients with carotid-T occlusion, in 3 (30%) patients with ICA occlusion, and in 1 (100%) case of PCA occlusion ($P = .10$). In contrast, a follow-up mRS score of ≥5 was obtained in 1 (100%) case of a CCA thrombus, in 8 (67%) patients with a BA occlusion, and in 2 (67%) patients with a combined BA and VA occlusion. Overall there were favorable outcomes reported on 34% of patients at follow-up after anterior circulation occlusions, while only 7% of the posterior circulation occlusions had a favorable outcome at follow-up ($P = .009$, Fig 2).

As for the relation between successful or unsuccessful recanalization and clinical outcome, 32% of the patients with TICI 2 or 3 (19/60) had a follow-up mRS score of ≤2, and 27% (16/60) had a follow-up mRS score of ≥5, contrary to patients with TICI 0 or 1 who had a favorable outcome in 20% (4/20) and a bad outcome in 60% (12/20) of cases ($P = .03$). Similarly, an early recanalization (≤300 minutes after symptom onset) led to a favorable outcome in 41% (13/32) and to a bad outcome in 16% (5/32) of patients, whereas a late recanalization (>300 minutes after symptom onset) resulted 19% (6/32) and 53% (17/32) with good and bad outcomes, respectively ($P = .013$) (Fig 2). Time or outcome of recanalization and the application of rtPA were not related to the diagnosis of an ICH at follow-up ($P = .29$, $P = .38$, and $P = .58$ respectively).

Discussion

Although recent studies have demonstrated a decrease of stroke incidence in high-income countries during the past 4 decades, stroke is still the leading cause of adult disability in the United States and Europe as well as the second cause of death worldwide.[17,18] IV-rtPA is still the most beneficial proved therapy of acute ischemic stroke, but its use is limited to the 4.5 hours following symptom onset with gradually decreasing efficacy with time.[2] Other limitations of the standard therapy include the low recanalization rates of proximal large-vessel occlusions and the failure to recanalize occluded vessels depending on thrombus length.[5,8] Because there is a strong correlation between recanalization and outcome in acute ischemic stroke, with recanalization strongly associated with improved functional outcomes,[19] there is a need for therapeutic alternatives in those cases, and this is when endovascular concepts of recanalization, such as the PS, come into play. These therapeutic alternatives, including the IA administration of thrombolytic agents and other mechanical interventions such as the Merci retriever (Concentric Medical, Mountain View, California)[3] or the Solitaire device (ev3, Irvine, California),[11] show promising results but have not yet been tested in the setting of a randomized controlled trial against standard therapy.[20]

In our study, we retrospectively evaluated the angiographic series and clinical course of 91 patients with an acute ischemic stroke. The reported 77% of TICI 2 or 3 scores on postinterventional images indicates a good recanalization outcome, which is comparable with the reported recanalization in the Penumbra Pivotal Stroke Trial (82%, TIMI score).[4] This recanalization rate is higher than the one reported in the Prolyse in Acute Cerebral Thromboembolism II study[21] (66%, IA recombinant prourokinase, TIMI score) and the recanalization rates in the Multi MERCI (Mechanical Embolus REmoval in Cerebral Ischemia) trial[3] (69.5%, combined IA-rtPA and mechanical thrombectomy, TIMI score) and the EKOS study[22] (57%, IA sonography and thrombolytic therapy, TIMI score). In another study by Mattle et al,[23] 55 patients with a mainstem MCA occlusion were treated with IA-rtPA, resulting in 71% with TIMI 2 or 3 scores. The difference in some of these studies was the site of occlusion because our collective consisted of 44% of MCA and PCA occlusions and another 56% of occlusions localized in vessels with larger diameters and respective

larger thrombi (proximal or distal ICA and BA occlusions). Our rates are also significantly higher than those reported with MR angiography in patients with MCA occlusions after treatment with standard IV-rtPA therapy (38% TIMI 2 or 3).[24]

Regarding the new generation of retrievable stent devices, there are first reports that these might lead to even more effective and faster recanalizations than with the PS. Castano et al[11] reported a 90% successful recanalization (TICI 2b or 3) with a new flow-restoration device, though the authors noticed that the thrombus length was an important factor because they were forced to use thrombus retrieval before flow restoration in 4 patients with thrombus length exceeding the stent length. The median time from arterial puncture to recanalization in this study was 70 minutes, which is longer than the time reported in our study (median 49 minutes). The primary advantage of retrievable stent devices is the rapid restoration of cerebral flow by deployment of the stent, even before complete clot retrieval.

Our results are also important for patients who are not eligible for lytic therapy because we report a 79% recanalization rate in 14 patients without application of rtPA. Patients after major surgery, with an elevated international normalized ratio or presenting after the 4.5-hour time window for lytic therapy, still have a chance for successful recanalization and improved outcomes with use of the PS. Another interesting result is the lower recanalization rate of 60% in patients in whom full-dose rtPA had already been administered before accessing the site of occlusion with a catheter. Additional administration of IA-rtPA after full-dose IV-rtPA could be considered in those cases because Shaltoni et al[25] demonstrated that IA-rtPA after full-dose IV-rtPA appears safe and that a higher rate of recanalization and favorable outcome can be achieved.

Regarding clinical outcomes, again, results similar to those in the Penumbra Pivotal Stroke Trial were observed with 23% of patients with an NIHSS score of ≥10 at hospital discharge and a follow-up mRS of ≤2 in 29% of our patients. All-cause mortality and overall ICH and SICH rates were also comparable with those in historical controls.[3,4,21,22] Thirty-two percent of patients had a favorable outcome after successful recanalization, whereas 20% showed a favorable outcome without recanalization. While the absolute differences between these 2 groups were not great, the relative differences were both large and statistically significant. The percentage of favorable outcome in our study is lower than that reported in a pooled analysis of IV-rtPA trials (49% mRS of ≤2),[26] but one has to take into consideration the impact of the baseline NIHSS score on independent outcome. Whereas patients in this pooled analysis demonstrated a mean NIHSS score of 11, patients in our study had a baseline NIHSS score of 17. As discussed in those clinical trials, 44% of the patients presenting with a baseline NIHSS score of 11 are going to experience an independent outcome without any specific therapy (placebo group). With a mean NIHSS score of 18, this percentage drops to 10%–15%.[20,27,28]

Another important factor significantly affecting favorable outcome in our study is the time from symptom onset to partial or successful recanalization. Whereas Mattle et al[23] reported a mean of 244 minutes from symptom onset to treatment, it took us a median of 294 minutes to recanalize the occluded vessels. This aspect, combined with the greater variety of occlusions in our study as described above, may explain the difference in favorable outcomes and mortality between our patients and those treated by Mattle et al (29% mRS ≤2, 25% mortality versus 53% mRS ≤2, 7% mortality).

The main limitation of our study is its retrospective character and the absence of a control group for comparison of clinical outcomes. Our results can only be compared with historical controls, and it is very difficult to comment on the favorable outcome rates because there is no control group in this study.[20] However, the replication of trial results in real world practice and in a relatively large number of patients is also essential for device implementation in acute stroke treatment.[29] Another limitation is the heterogeneity of size and site of occlusion in our collective. Finally, because interventions were performed by an experienced neuroradiologist and care was provided within an intensive care unit, our findings may not be generalizable to other settings.

Conclusions

The results of our retrospective single-center study confirm the effectiveness of the PS for mechanical recanalization. Successful and early recanalization with the PS was associated with significant improvement of functional outcome in patients experiencing ischemic stroke secondary to anterior circulation occlusions.

Disclosures: Marios-Nikos Psychogios—*RELATED: Support for Travel to Meetings for the Study or Other Purposes*: RSNA, Penumbra, *Comments*: In 2010, I received travel grants for basic flight and hotel accommodation expenses from Penumbra Inc (Alameda, California) for participation in the 96th Scientific Assembly and Annual Meeting of the RSNA, Chicago, Illinois, November 28–December 3, 2010. Andreas Kreusch—*RELATED: Support for Travel to Meetings for the Study or Other Purposes*: Penumbra, *Comments*: Travel grant for visit to the production site.

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