Use of a vascular reconstruction device to salvage acute ischemic occlusions refractory to traditional endovascular recanalization methods

Clinical article

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Object. Acute revascularization has been associated with improved stroke outcomes. The Prolyse in Acute Cerebral Thromboembolism (PROACT II) trial achieved recanalization rates of 66%. The Multi Mechanical Embolus Removal in Cerebral Ischemia (Multi MERCI) trial achieved recanalization in 70% of patients. However, these interventional tools are not always successful. The Enterprise vascular reconstruction device was recently introduced for treatment of cerebral aneurysms previously untreatable with endovascular techniques. The authors evaluated a multicenter experience using this stent as a salvage revascularization tool for acute stroke treatment.

Methods. Four medical centers participated in a retrospective review of endovascularly treated patients with acute stroke for cases treated with the Enterprise stent after routine interventions had been unsuccessful. Data collected included preprocedure information, intraprocedure findings, and outcomes.

Results. Twenty patients with acute stroke (mean age 61.6 ± 22 years) were treated with the Enterprise stent. Ten patients received intravenous recombinant tissue plasminogen activator before catheter intervention, without improvement. Intraarterial interventions attempted unsuccessfully before Enterprise deployment included the Merci retriever (12 patients), angioplasty (7 patients), glycoprotein IIb-IIIa inhibitor administration (12 patients), intraarterial nitroglycerin (1 patient), Wingspan stent deployment (3 patients), and Xpert stent deployment (1 patient). The mean preintervention National Institutes of Health Stroke Scale (NIHSS) score was 17 ± 6 (median 17). All patients presented with a Thrombolysis in Myocardial Infarction (TIMI) score of 0 or 1. Revascularization was achieved in all patients (75% with a TIMI score of 3, 25% with a TIMI score of 2). Improvement (≥ 4 points on the NIHSS) was documented in 75% of patients. Mean NIHSS improvement from intervention to discharge was 8 ± 7 points (median 9 points).

Conclusions. These preliminary data suggest a potential benefit to the use of the Enterprise stent when routine intervention methods fail. (DOI: 10.3171/2009.8.JNS09231)

Key Words • acute ischemic occlusion • Enterprise vascular reconstruction device • stroke • endovascular recanalization

Abbreviations used in this paper: CBV = cerebral blood volume; GP = glycoprotein; ICA = internal carotid artery; ICH = intracranial hemorrhage; IMS = Interventional Management of Stroke; MCA = middle cerebral artery; NIHSS = National Institutes of Health Stroke Scale; PEG = percutaneous endoscopic gastrostomy; TIMI = Thrombolysis in Myocardial Infarction; tPA = tissue plasminogen activator.
long-term disability in the US, with an estimated direct and indirect cost totaling $68.9 billion for 2009.19

Literature demonstrating that clinical outcome correlates with radiographic revascularization has helped provide an impetus to further investigate acute intraarterial therapies.6,10–12,14,10,21,24,28,30 particularly as evidence mounts indicating that the time to recanalization is also of critical importance.14,22,30 Use of the newest generation Merci mechanical clot retriever (Concentric Medical) with additional adjuvant intervention led to successful recanalization in 70% of patients, a result comparable to the 66% recanalization rate achieved in the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial.5 Although encouraging, there remains a substantial number of patients in whom vessel recanalization is not successful with currently approved techniques.

The results of several recent case series4,8,9,17,18,21,31 as well as extrapolation from the cardiac literature7,13,25,27 have suggested that intracranial stent deployment may be a reasonable “last resort” technique in acute stroke revascularization. Most recently, 2 patient series specifically addressed the use of self-expanding stents to obtain recanalization in patients with acute stroke, with good results.18,30 Both patient series used similar stent systems with comparable technical profiles and delivery systems, manufactured by the same company (Wingspan and Neuroform stent systems, Boston Scientific). The Wingspan system is intended for intracranial stenosis treatment and the Neuroform system for aneurysm neck reconstruction. Recently, a new self-expanding stent has become available to the endovascular community, the Enterprise Vascular Reconstruction Device (Codman Neurovascular/Cordis Corp.). This device uses a catheter-based delivery system that has been suggested to provide improved navigability and ease of deployment. Although intended solely for aneurysm-embolization assistance, there has been a developing interest in the possible utility of this device for “salvage” or “last resort” stroke intervention. Therefore, we sought to retrospectively review the experience of 4 centers at which the Enterprise stent was used to achieve acute stroke recanalization in refractory cases.

Results

Database review across the 4 centers identified 20 patients, with a mean age of 61.6 ± 22 years (median 66.5 years, range 27–94 years), in whom Enterprise stents were placed for acute stroke between October 2007 and August 2008. Occluded target vessels included the left M1 (8 patients), right “T” occlusion (an intracranial carotid artery bifurcation occlusion with involvement of the A1 and M1 segments; 3 patients), right M2 (3 patients), left petrous or cavernous ICA (3 patients), right posterior cerebral artery (1 patient), basilar artery (1 patient), and left M1 (1 patient). There were 2 patients for whom a stroke onset time could not be determined. For the remaining 18 patients, mean duration from stroke onset to procedural start time was 6 hours 9 minutes ± 5 hours 56 minutes (median 3 hours 55 minutes, range 1–22 hours).

Preintervention NIHSS score was 17 ± 6 (median 17, range 4–30). All patients had precatheater intervention noncontrast CT imaging performed. Of those patients, 2 had positive dense MCA signs, 2 had hypodensity already evident in the area of interest, 2 had loss of sulci in the area of interest, and 1 had an area of hyperdensity that was suggestive of early hemorrhagic transformation. In the study cohort, only 11 patients underwent (pretreatment) physiological imaging (all CT perfusion imaging studies). Seven of these 11 patients had a perfusion mismatch without evidence of already infarcted tissue (low CBV). Three had a perfusion mismatch with small areas of apparent infarction (< one-third of the “at-risk” area). One patient had extensive areas of low CBV, but underwent intervention due to strong family wishes, despite counseling that explained a low likelihood of benefit and substantially increased risk. Intravenous recombinant tPA was given to 10 patients before the catheter intervention, 4 of whom received a full National Institute of Neurological Disorders and Stroke trial tPA administration dose and 6 of whom received partial doses. Of these 6 patients, 5 received partial doses according to the IMS II trial protocol, and 1 received 50% of the National Institute of Neurological Disorders and Stroke protocol dose before the administration was halted secondary to refractory high blood pressure.
Enterprise vascular reconstruction device for acute stroke

All patients underwent Enterprise stent deployment after more accepted techniques had already been attempted and failed. Techniques used prior to Enterprise deployment included intraarterial tPA administration (3 patients), Merci mechanical clot retriever (12 patients), angioplasty (7 patients), GP IIb-IIIa inhibitor administration (12 patients), failed Wingspan stent deployment (3 patients), intraarterial nitroglycerin (1 patient), and deployment of 2 Xpert (Abbott Laboratories) stents (1 patient). Prior to Enterprise stent deployment, all patients demonstrated target vessel occlusion with TIMI scores of 0 or 1 (95% with a score of 0, 5% with a score of 1). Additional interventions performed after Enterprise deployment included angioplasty (6 patients) and GP IIb-IIIa inhibitor administration (11 patients; 6 first-time administrations, 5 maintained administrations [via infusion] in patients who had previously received bolus doses); 1 patient required a second (overlapping) Enterprise stent placement.

A final TIMI score of 2 or 3 was achieved in all patients (75% with a TIMI score of 3, 25% with a TIMI score of 2; p < 0.0001 compared with pre-Enterprise TIMI scores). Five patients developed ICH; of these 5, 2 patients experienced substantial improvement (8-point improvement in NIHSS score and was found to obtain acute recanalization may be a safe and technically feasible method for treating acute ischemic stroke.\textsuperscript{3,8,9,16–18,21,31} A stent can displace emboli or thrombi toward the margins of the vessel lumen to reestablish luminal patency, thereby restoring blood flow.

In the present retrospective review of 20 patients in whom other acute stroke interventions had already failed, we show that the use of the Enterprise stent can help achieve recanalization (100% of patients in this series). Although this is a retrospective review without prospective selection criteria, each interventionist reported the selection of the Enterprise stent secondary to its excellent navigability. This selection is supported at least, in part, by the fact that Enterprise deployment was successful in 3 patients in whom previous attempts at Wingspan stent deployment had failed. Although the small overall number of patients limits the comparison of this series to larger acute stroke trials such as IMS II\textsuperscript{15} and Multi MERCI,\textsuperscript{23} this result is not largely dissimilar to the 2 previous series involving self-expanding stents for stroke that reported 89\% and 79\% recanalization rates. Across all 3 of these studies, 47 patients have been reported as part of the patient series for self-expanding stent “rescue” for stroke. Taken together (accepting the differing devices and modes of self-expanding stent delivery), there is some implication that these technologies may be a valid “salvage” effort in acute stroke treatment. Despite their use after the failure of more conventional therapies, self-expanding stent technologies have still resulted in a recanalization rate that appears to range somewhere between 79 and 100\%, considerably higher than rates from the majority of other, nonstent-related series. Importantly, it should also be noted that some of the patients in this series also received poststent adjunctive therapy (angioplasty and/or GP IIb-IIIa administration) to maximize the achieved recanalization. Therefore, the overall clinical outcomes cannot be solely attributed to stent placement and rather should be interpreted within the context of the full course of therapy.

Additionally, in the present series, substantial clinical improvement (NIHSS improvement ≥ 4 points) was documented in 75\% of patients. Although the value of these data is limited due to the relatively short length of follow-up (until discharge) and the small number of patients, it is encouraging that clinically and statistically significant improvement could be observed even in the acute to subacute period after stent deployment. The large proportion of patients experiencing an NIHSS improve-

Discussion

Intraarterial stroke therapies have been under investigation for well over a decade. Recanalization rates achieved with current intraarterial thrombolytic agents or clot retrieval devices remain ~ 50–70\%.\textsuperscript{13,5,6,23,24} Despite advancement in thrombolytic pharmacology and clot retriever technology, achievement of higher rates of recanalization has remained elusive. Many emboli are imperious to thrombolytics because of their mature, fibrinous consistency. Emboli may also be resistant to mechanical disruption and/or removal with clot retrievers because of robust adherence to the vessel intima. Additionally, patients with underlying atherosclerotic plaque may have a thrombus lodged within existing atheromatous disease, thereby blocking efforts toward recanalization.

It has been hypothesized that stent implantation to obtain acute recanalization may be a safe and technically feasible method for treating acute ischemic stroke.\textsuperscript{3,8,9,16–18,21,31} A stent can displace emboli or thrombi toward the margins of the vessel lumen to reestablish luminal patency, thereby restoring blood flow. In the present retrospective review of 20 patients in whom other acute stroke interventions had already failed, we show that the use of the Enterprise stent can help achieve recanalization (100% of patients in this series). Although this is a retrospective review without prospective selection criteria, each interventionist reported the selection of the Enterprise stent secondary to its excellent navigability. This selection is supported at least, in part, by the fact that Enterprise deployment was successful in 3 patients in whom previous attempts at Wingspan stent deployment had failed. Although the small overall number of patients limits the comparison of this series to larger acute stroke trials such as IMS II\textsuperscript{15} and Multi MERCI,\textsuperscript{23} this result is not largely dissimilar to the 2 previous series involving self-expanding stents for stroke that reported 89\% and 79\% recanalization rates. Across all 3 of these studies, 47 patients have been reported as part of the patient series for self-expanding stent “rescue” for stroke. Taken together (accepting the differing devices and modes of self-expanding stent delivery), there is some implication that these technologies may be a valid “salvage” effort in acute stroke treatment. Despite their use after the failure of more conventional therapies, self-expanding stent technologies have still resulted in a recanalization rate that appears to range somewhere between 79 and 100\%, considerably higher than rates from the majority of other, nonstent-related series. Importantly, it should also be noted that some of the patients in this series also received poststent adjunctive therapy (angioplasty and/or GP IIb-IIIa administration) to maximize the achieved recanalization. Therefore, the overall clinical outcomes cannot be solely attributed to stent placement and rather should be interpreted within the context of the full course of therapy.

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ment ≥ 4 points exceeds that found in the recently FDA-approved Penumbra System (Penumbra, Inc.), in which 45% of patients had improvements in NIHSS score ≥ 4 points or modified Rankin Scale score of ≤ 2 observed at 30 days. These data are even more exciting given that the vessel occlusions reported herein and in the other series of self-expanding stents for “salvage” in strokes were refractory to treatment with conventional intervention techniques. However, it should be noted that none of the patients in this study underwent attempted intervention using the Penumbra System.

It should be noted that, because this study is a retrospective case series, there were no clearly defined selection parameters and patient selection is therefore subject to the variances and, at times, somewhat capricious-appearing realities of real-world clinical care. In particular, 2 cases reported in this study underwent treatment with somewhat aggressive indications: a 94-year-old patient with already evident sulcal effacement, as well as a patient with extensive low CBV on CT perfusion imaging. In each of these cases, the patient died. Certainly, the experience gained in treating these 2 patients has contributed to the future decision-making of the interventionists involved, and the exact course of care may or may not proceed along the same lines, given similar circumstances in the future. However, in medical care administered outside the rigid inclusion/exclusion criteria of a prospective clinical trial, multiple issues, clinical nuances, and unique circumstances affect each and every minute-to-minute decision, and in each of the cases noted above, the interventionist chose to proceed based on a real perceived benefit to the patient at the time. It is our goal to report all aspects of the participating centers’ experience, without data editing, so as to maximize the educational value gleaned from the retrospective review of the collective experience at these centers.

An additional interesting aspect to these data is the wide time span observed in the interval between symptom onset and treatment. Analysis of outcome and time to intervention did not demonstrate a statistically significant association. Although we cannot conclusively determine the reason for this lack of association, it may be due to the use of CT perfusion imaging as a selection criteria in the majority of cases. As an example, the 3 most delayed presentations were 22, 18, and 15 hours (left ICA, left MCA, and right M1 occlusions, respectively). All patients underwent CT perfusion scanning, which suggested salvageable tissue. These patients achieved improvements of 9, 8, and 13 points on the NIHSS, respectively (baseline NIHSS scores of 17, 24, and 13, respectively), despite their delayed presentation. Only 1 of these patients died (the 18-hour patient, as a result of complications related to PEG tube placement).

We observed the occurrence of symptomatic ICH in 2 patients (10%). This rate of ICH is comparable to that observed in other acute stroke intervention studies. The final results of the Multi MERCI trial, the IMS II trial, and the Penumbra System series demonstrated symptomatic ICH rates ranging from 9 to 10%. This symptomatic ICH rate also falls within the rates observed in the 2 previous series examining self-expanding stents for “salvage” in stroke of 0% and 22%. It should be noted that both patients who suffered symptomatic ICH had received IV recombinant tPA, had undergone CT imaging demonstrating established hypodensities (suggesting some degree of completed infarction [1 of these patients also had extensive low CBV on CT perfusion imaging]), and had received GP IIb-IIIa inhibitors. Although the number of patients in this study obviates statistical analysis to correlate such risk factors and outcome, it is reasonable to note that care should be taken in patients who have suspected established infarction and have received multiple coagulation-system-altering medications.

Overall mortality for the present series was 20%. Again, although true study-to-study analysis is not valid, these data are comparable to the findings noted in other acute stroke studies. The final results of the Multi MERCI trial, the IMS II trial, and the Penumbra System series demonstrated mortality rates ranging from 16 to 45%, and the observed mortality rate of 20% observed for this series falls well within that range. It should also be noted that 1 of the deaths in the present series occurred in a patient who had experienced a substantial recovery from the stroke but died due to a gastrointestinal bleed after PEG tube placement. Although one cannot discount the potential contribution of stent-required antiplatelet medication to this death, it does not appear to be the proximate cause of this unfortunate outcome.

We think it is crucial to stress the multiple limitations of this investigation. The data were collated retrospectively and, therefore, are subject to all inherent biases associated with such an investigation. Additionally, the overall number of patients is relatively small, although it remains the largest series to date of self-expanding stent “rescue” for acute stroke. Additionally, the patients are heterogeneous in presentation, as well as in the details of their intervention (aside from receiving Enterprise stent placement), and therefore definite conclusions are not determinable. It should also be stressed that the use of the Enterprise stent in these cases was off-label. The decision to use this device in an off-label manner reflects each physician’s personal decision-making regarding the best course of care for his or her patient in the acute setting. In each case, the specific physicians were required, in a timely manner, to notify their local institutional review board and the FDA of a protocol deviation with a humanitarian exemption for use of the device. Lastly, it should be reported that 2 of the patients evaluated in this series were previously reported as part of a 2-patient case series describing the ability of the Enterprise stent to access areas inaccessible to other techniques.

Conclusions

This study lends increasing evidence to the concept of using self-expanding stent technology to aid in the treatment of acute stroke. Additionally, it provides the first evidence that the Enterprise Vascular Reconstruction Device behaves in a comparable manner to self-expanding stents previously evaluated. Based on these findings and the increasing literature concerning this topic, future prospective studies may be indicated.
Disclosure
Dr. Boulos has received a research grant from the American Heart Association, other research support from the Herman & Sunny Stall Chair, and serves as a member of the speakers’ bureau for Terumo. Dr. Hanel serves on the speaker’s bureau for Codman as a scientific advisor to Neurovax. Dr. Hopkins has an ownership interest in AccessClosure, Boston Scientific, and Micrus; serves as a consultant to Abbott, Bard, Boston Scientific, Codis, and Micrus; serves on the advisory board for AccessClosure and Micrus; has received research support from Toshiba; has a consulting relationship with W. L. Gore; and has received honoraria from Bard, Boston Scientific, and Corvis. Dr. Levy receives research grant support, other research support (devices), and honoraria from Boston Scientific; research support from Micrus Endovascular and ev3, Inc.; has ownership interests in Intratec Medical, Ltd., and Mynx Access Closure; serves as a consultant on the board of Scientific Advisors to Codman Neurovascular; serves as a consultant receiving fees on a per-project, per-hour basis only for Micrus Endovascular, ev3, and TheraSyn Sensors, Inc.; and receives fees for carotid stent training from Abbott Vascular and ev3. Dr. Linfante serves on the speaker’s bureau for EK Therapeutics, and serves as a consultant to and receives honoraria from Micrus Endovascular. Dr. Mocco has received a research grant from the Brain Aneurysm Foundation. He has previously received a one-time honorarium from Codis. Dr. Siddiqui has received a research grant from the University at Buffalo, serves as a consultant to Codman Neurovascular/Cordis Corporation, Concentric Medical, ev3, and Micrus Endovascular; serves on speakers’ bureaus for Cordis and Genentech; has received honoraria from Genentech, Neocure, an American Association of Corporate, Concentric Medical, ev3, and Micrus Endovascular; serves on speakers’ bureaus for Cordis and Genentech; has received honoraria from Genentech, Neocure, an American Association of Corporate, Concentric Medical, ev3, and Micrus Endovascular; serves on speakers’ bureaus for Cordis and Genentech; has received honoraria from Genentech, Neocure, an American Association of Corporate, Concentric Medical, ev3, and Micrus Endovascular; serves on speakers’ bureaus for Cordis and Genentech; has received honoraria from Genentech, Neocure, an American Association of Corporate, Concentric Medical, ev3, and Micrus Endovascular; serves on speakers’ bureaus for Cordis and Genentech; 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