Emergency Carotid Artery Stenting in Acute Ischemic Stroke

Nobuyuki Ohara, Satoshi Tateshima, James Sayre, Gary R Duckwiler, Reza Jahan, Nestor R Gonzalez, Paul M Vespa, Latisha K Ali, Sidney Starkman, Jeffrey L Saver, and David S Liebeskind

Objectives: Some acute stroke patients with intracranial arterial occlusion have concomitant extracranial carotid artery occlusion or high-grade stenosis. Emergency carotid artery stenting (CAS) is a potentially effective treatment option to enhance intracranial reperfusion for these patients, yet selection of optimal candidates for this procedure remains elusive.

Methods: We analyzed clinical data of patients who underwent emergency CAS in the setting of acute endovascular recanalization from 2005 to 2012. Reperfusion was graded with modified Thrombolysis in Cerebral Infarction (mTICI) scale. Clinical outcomes were assessed by modified Rankin Scale (mRS) at 90 days.

Results: 23 patients were included with mean age of 64.2 years, median admission NIHSS score of 20. The median initial Alberta Stroke Program Early CT Score on diffusion-weighted imaging (DWI-ASPECTS) was 7. 18 patients (78.3%) had internal carotid artery occlusion at the origin. 19 patients (82.6%) had intracranial tandem arterial occlusions. All patients successfully underwent CAS and 14 patients (60.9%) underwent additional mechanical thrombectomy. Nine patients (39.1%) were mTICI grade ≥2b. Hemorrhagic transformation with parenchymal hematoma (PH) occurred in nine patients (39.1%). At follow-up, six patients (26.1%) had a favorable outcome (mRS 0-2). The multiple logistic model yielded age (OR 1.20, 95% CI [1.02, 1.41], P = 0.03) and initial DWI-ASPECTS (OR 0.25, 95% CI [0.07, 0.92], P = 0.04) independently associated with an unfavorable outcome (mRS 3-6) and additional mechanical thrombectomy (OR 2.5, P = 0.005) was associated with PH.

Conclusions: Endovascular recanalization with emergency CAS is technically feasible. Further refinement of patient selection may reduce postprocedural hemorrhagic transformation and optimize resultant clinical outcomes.

Keywords: carotid artery stenting, acute stroke, thrombectomy

Introduction

Early and effective recanalization of occluded arteries is essential for good functional outcome of acute stroke patients with proximal arterial occlusion. Endovascular treatment, particularly mechanical thrombectomy, has played an increasing role to achieve rapid recanalization and five recently published trials have conclusively proven the benefit of mechanical thrombectomy by stent retriever over best medical therapy for selected patients. However, some patients with acute intracranial arterial occlusion have additional extracranial carotid artery occlusion or high-grade stenosis. These lesions are recognized as an independent risk factor for poor outcome in patients treated with systemic thrombolysis. Emergency carotid
artery stenting (CAS) conjunctive with or without intracranial thrombectomy is a potentially effective treatment option to enhance intracranial reperfusion for these patients. Most recent case series have reported encouraging results for this procedure. However, such stenting in the setting of acute intervention causes challenges in several technical aspects and subsequent clinical management. It also remains unclear how to optimally select patients appropriately for this procedure. We therefore evaluated the safety and effectiveness of recanalization treatment with concomitant emergency CAS.

Materials and Methods

Patient selection
All consecutive patients who underwent endovascular treatment for acute ischemic stroke at our center from May 2005 to December 2012 were prospectively entered into our institutional database according to a protocol approved by our local institutional review board. From this prospectively maintained database, we analyzed patients who presented with acute ischemic stroke with large artery occlusion within 24 h from last well known and underwent emergency CAS for extracranial cervical internal carotid artery (ICA) in the setting of endovascular treatment for intracranial reperfusion. All patients were identified with large artery occlusion on initial MR angiography. Patients who had high-grade stenosis in the cervical ICA without intracranial arterial occlusion were excluded.

Endovascular treatment indication
All patients who presented with acute stroke were treated according to our institutional treatment protocols. Some patients received intravenous tissue plasminogen activator (IV tPA) at our facility or at outside hospitals and transferred to our institution for higher level of treatment. Patients were selected for endovascular therapy if stroke neurology and interventional neuroradiology services ascertained that a favorable imaging pattern (presence of salvageable areas at-risk and absence of large core) was noted on multimodal MRI or CT.

Endovascular procedure
All endovascular procedures were performed via femoral access under conscious sedation or general anesthesia. In most cases, after the diagnostic angiograms, an 8 or 9 French guide catheter was advanced to the ipsilateral common carotid artery. A balloon guide catheter was used in 13 cases (56.5%). If the ICA was completely occluded at the origin, the lesion was traversed with a microcatheter over a microwire. After confirming the lumen by injection from the microcatheter, the microwire was exchanged for a 300 cm exchange wire. To perform first angioplasty for the ICA lesion, distal protection device was used in 11 cases (47.8%). After angioplasty, intracranial angiogram was performed to confirm the intracranial occlusion. Subsequent procedures for intracranial recanalization were performed if there was a persistent intracranial arterial occlusion after proximal revascularization. Additional Intracranial thrombectomy was performed in 14 cases. In eight cases, carotid artery stenting was performed just after angioplasty, and followed by intracranial thrombectomy. In six cases, intracranial thrombectomy was performed after angioplasty for the extracranial lesion and followed by carotid artery stenting. In nine cases, additional intracranial thrombectomy was not performed because of no tandem lesion after stenting (n = 3) or acceptable reperfusion (n = 6). In cases without IV tPA prior to endovascular treatment, systematic heparinization was used during procedure. In cases with IV tPA just prior to endovascular treatment, heparinization was basically avoided during procedure. The timing and dosages of antiplatelet therapy during procedure were variable depending on cases. After procedure, antiplatelet therapy was continued unless apparent intracerebral hemorrhage (ICH) was detected. At discharge, aspirin monotherapy was used in seven cases and combined aspirin and clopidogrel in 11 cases.

Evaluation of imaging data and outcome
Preintervention MRI data was analyzed according to Alberta Stroke Program Early CT Score on diffusion weighted imaging (DWI-ASPECTS). The angiographic data was assessed by determining the rate of intracranial reperfusion classified according to Modified Thrombolysis in Cerebral Infarction (mTICI) scale after endovascular treatment. In the setting of extracranial-intracranial tandem occlusions, the most proximal intracranial occlusion was considered the target arterial lesion (TAL). When there was no intracranial occlusion, the extracranial lesion was considered the TAL. The patients underwent immediate postintervention CT scan in all cases. Follow-up MRI was typically performed 3–6 h after the procedure and at 24 h or whenever clinical worsening occurred. ICH was classified according to the European Cooperative Acute Stroke Study (ECASS) classification. We defined any hemorrhagic transformation with parenchymal hematoma (PH1 and PH2) as PH.
Clinical functional outcome was assessed with modified Rankin Scale (mRS) at 90 days. Seven patients who were lost to post-discharge follow-up were assessed by mRS at discharge. A favorable outcome was defined as mRS 0-2 and an unfavorable outcome was defined as mRS 3-6.

Statistical analysis
Statistical analysis was performed with SPSS 12.0 statistical software (Chicago, IL). Frequency and percentage values of categorical variables and mean and standard deviations of continuous variables were determined. Patient characteristics and outcomes were compared to identify predictors of two outcomes: unfavorable clinical outcome and PH. A stepwise multiple logistic regression analysis was used to select predictive valuables. A value of P < .05 was considered significant.

Results
A total of 23 patients met study entry criteria. Table 1 shows patient characteristics. The mean age was 64.2 ± 15.1 years. There were 15 males (65.2%) and eight females (34.8%). Five patients (21.7%) had prior ischemic stroke history. Risk factors for stroke included hypertension (52.1%), diabetes (30.4%), hyperlipidemia (26.1%), and atrial fibrillation (8.7%). Two patients (8.7%) had taken antiplatelet therapy and Two patients (8.7%) anticoagulation therapy prior to presentation. The median admission NIHSS score was 20 (range, 3–25). The mean time from last well known to arrival at our institution was 312 ± 211 min. The median DWI-ASPECTS on admission was 7 (range, 2–9). 18 patients (78.3%) had diffusion abnormality in more than 50% of the deep middle cerebral artery (MCA) territorial basal ganglia and white matter on initial MRI. All of the initial MR angiographies for the patients demonstrated major vessel (ICA or MCA) occlusion.

Ten patients (43.5%) were given IV tPA at standard protocol. Half of them had been initiated the administration at outside hospitals and transferred to our institution. The mean time from last well known to groin puncture was 463 ± 244 min. One patient presented with improved symptoms immediately after given IV tPA, but his condition deteriorated within hours, and emergent endovascular treatment was initiated. Except this patient, the mean time from initial imaging to groin puncture was 69 ± 25 min.

Diagnostic angiogram revealed ICA occlusion at the origin in 18 patients (78.3%) and extracranial ICA stenosis in five patients (21.7%), with the stenosis ranging from 67–87%. At catheter angiography, four of the patients with extracranial ICA occlusion were found to not have any intracranial occlusion despite the apparent initial presence on MRA, potentially because of interval recanalization. Thus, a total 19 patients (82.6%) had concomitant intracranial vessel occlusions at catheter angiography. The sites of intracranial occlusion were ICA terminus in 7 (36.8%), M1 in 7 (36.8%), and M2-3 in 5 (26.3%).

All patients successfully underwent CAS. However, acute stent thrombosis (AST) during procedure was occurred in four patients (17.3%). All of them had ICA occlusion at the origin due to atherosclerosis. Three of them were given IV tPA prior to procedure. All of them were not initiated antiplatelet therapy before stent placement intending to add it after confirming the successful stent placement. Two of them were given aspirin just after stent deployment. Single open-cell stent was used in all of them. The urgent treatment for AST included aspiration from guiding sheath (n = 2), aspiration from Penumbra054 catheter (Penumbra Inc, Alameda, CA) (n = 2), balloon angioplasty (n = 1), and intra-arterial abciximab injection (n = 1). In all patients, after the urgent treatment, repeat injection confirmed disappearance of thrombus and good patency of stent, though distal embolism occurred in one patient.

Among the 23 patients, 14 (60.9%) underwent additional mechanical thrombectomy for intracranial vessels. Merci retriever (Concentric Medical, Mountain View, CA) was used in eight patients, Penumbra system (Penumbra Inc) in four patients, Solitaire (Covidien, Irvine, CA) in two patients.

Table 1: Patient characteristics (n = 23)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (y)</td>
<td>64 ± 15</td>
</tr>
<tr>
<td>Male</td>
<td>15 (65.2%)</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (52.1%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (30.4%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td>Preprocedural findings/treatment</td>
<td></td>
</tr>
<tr>
<td>Initial NIHSS, median</td>
<td>20 (range, 3–25)</td>
</tr>
<tr>
<td>DWI-ASPECTS, median</td>
<td>7 (range, 2–9)</td>
</tr>
<tr>
<td>Hyperintensity in Basal Ganglia on DWI</td>
<td>18 (78.3%)</td>
</tr>
<tr>
<td>IV tPA</td>
<td>10 (43.5%)</td>
</tr>
<tr>
<td>Angiographical findings</td>
<td></td>
</tr>
<tr>
<td>ICA occlusion at the origin</td>
<td>18 (78.3%)</td>
</tr>
<tr>
<td>ICA high-grade stenosis at the origin</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td>Suspect of dissection</td>
<td>4 (17.3%)</td>
</tr>
<tr>
<td>Intracranial arterial occlusion</td>
<td>19 (82.6%)</td>
</tr>
</tbody>
</table>

y: years; NIHSS: National Institutes of Health Stroke Scale; DWI-ASPECTS: Alberta Stroke Program Early CT Score on Diffusion Weighted Imaging; IV tPA: intravenous tissue-plasminogen activator; ICA: internal carotid artery.
After the procedure, three patients (13.0%) were classified as mTICI grade 3, 6 (26.1%) as grade 2B, 11 (47.8%) as grade 2A, and 3 (13.0%) as grade 1 or 0.

Follow-up CT or MRI revealed PH in nine patients (39.1%) and 2 (8.7%) were PH2 and symptomatic. Asymptomatic subarachnoid hemorrhage occurred in one patient (4.3%).

At 90 days follow-up, six patients (26.1%) had a favorable outcome. The mortality rate was 13.0%.

In stepwise multiple logistic regression model, the variables independently associated with an unfavorable outcome were age (OR 1.20, 95% CI (1.02, 1.41), P = 0.03) and initial DWI-ASPECTS (OR 0.25, 95% CI (0.07, 0.92), P = 0.04). NIHSS, mTICI grade, and basal ganglionic hyperintensity on initial DWI were not significantly associated with clinical outcome in this model.

In the model for predicting parenchymal hematoma, mechanical thrombectomy with emergency CAS was associated with PH (OR 2.5, P = 0.005). In this model, odds ratio was estimated by using Cornfield which cannot estimate 95% Confidence Limits because of the zero cell. This means that none of the patients who did not undergo mechanical thrombectomy experienced any PH. All patients who had PH had basal ganglionic hyperintensity on initial DWI, but no significant difference was seen on multiple logistic regression analysis. There were no differences in clinical outcome and PH between patients who received IV tPA and those who did not.

Mean time from last well known to groin puncture in the patients with favorable and unfavorable outcome was 342 and 471 min, respectively. Mean time from last well known to groin puncture in the patients with and without post-procedural PH was 351 and 287 min, respectively. We could not find any significant relationship between time course and clinical outcome.

Discussion

Emergency revascularization for an occluded or severely stenotic extracranial carotid artery is recognized as a challenging procedure in acute stroke interventions.5,15,21 Pathophysiological heterogeneity in this setting according to amount of thrombus, site of tandem occluded artery, robustness of collateral circulation, and degree of cerebral ischemia often complicates our decision-making for acute intervention. Several possible reasons for opting to pursue endovascular revascularization of the extracranial carotid artery in the acute phase are recognized.11,17,22 First, early flow restoration of the extracranial carotid artery can improve intracranial perfusion either directly or through collaterals from enhanced proximal flow. Second, reopening the extracranial carotid artery makes it possible to approach the intracranial arterial occlusion causing cerebral ischemia. Third, enhanced proximal flow may help clearance of present or additional thromboemboli. Forth, stent placement may also prevent further artery to artery embolism or progression of an extracranial carotid stenosis to occlusion. These potential beneficial effects would result in rescue of ischemic lesions, prevention of early stroke progression, and reduction in long-term risk of stroke recurrence. However, it has not been well established how to select tandem lesion patients appropriately for this procedure with low possibilities of complications.

Table 2 shows recent case series of acute endovascular treatment with emergency CAS.12-14,16-18 They are all non-randomized retrospective studies. Most of the patients in these cohorts are presented with extracranial carotid and intracranial arteries tandem occlusions. These series demonstrated the technical feasibility of emergency CAS even in combination with intracranial mechanical thrombectomy, and most authors encouragingly suggested the safety and effectiveness of this procedure based on the poor natural history of this type of stroke.11,21 However, it is important to also highlight the potential risks of this procedure.

ICH after acute intervention for ischemic stroke is one of the most critical complications. The risk of ICH depends on various factors.23 All mechanical thrombectomy procedures for intracranial occlusion carry a risk of ICH, related to reperfusion injury of infarct lesions and to procedural injury to the vessel wall. The risk after emergency CAS is presumed to be higher because of more aggressive antiplatelet therapy for preventing AST, frequently use of IV tPA just prior to the stent procedure, and the potential for the carotid hyperperfusion syndrome, due to altered cerebral autoregulation from long-term lowering of perfusion by the proximal stenosis.

Likewise, most recent case series of emergency CAS in tandem lesion patients, including our present study, demonstrate higher incidence of ICH as compared with previous acute endovascular treatment trials24,25 even though the endpoints of ICHs (symptomatic ICH, PH, PH2) vary among different studies. Stampfl et al.18 mentioned that the high hemorrhage rate in their study might be caused by the relatively aggressive antiplatelet therapy with a full-dose tirofiban (GP IIb/IIIa inhibitor) in most cases. Conversely, Malik et al.17 mentioned that their relatively low incidence
of PH might be due to preintervention low infarct burden. They showed that PH was associated with poor functional outcome and with increased mortality, and the only variable significantly associated with PH was the presence of a carotid terminus tandem occlusion. Our study showed additional intracranial mechanical thrombectomy with emergency CAS was associated with PH. This finding might be partly derived from confounding by indication – interventionists only pursue additional intracranial mechanical thrombectomy in patients judged not be doing well after the emergency CAS procedure. However, it is important to keep in mind that mechanical thrombectomy combined with emergency CAS might carry a larger risk of post procedural PH. Interestingly, the exceptionally low rate of symptomatic ICH which was reported by Kwak et al. might be due to their lower use of mechanical thrombectomy with emergency CAS in addition to lower NIHSS.

With regard to ICH after mechanical thrombectomy, we previously reported that PH was predicted by the distinct preintervention MRI pattern of extensive injury of the deep MCA territory vs. distal M1 MCA occlusions. Likewise in our present study, all patients who developed PH after intervention had basal ganglionic hyperintensity on initial DWI, even though it was not independently related to poor outcome once general diffusion lesion volume was taken into account. This finding might also be helpful to predict ICH after emergency CAS.

AST is a concern in emergency CAS for patients with tandem lesions. Once it occurs, following intracranial recanalization can be delayed and additional distal embolism can be happened. In our series, AST during procedure occurred in four cases (17.3%). This high frequency of AST might be caused by absence of antiplatelet therapy before stent placement as a result of concern about hemorrhagic complication after IV tPA. However, in previous case series of emergency CAS, AST during procedure was rarely described. The timings for initiation of antiplatelet therapy are different in different case series.

The reports for AST in elective CAS are much less, but the risk factors for AST are recognized as inadequate antiplatelet therapy, hypercoagulable state, vessel dissection, and stent underexpansion. It is well known that dual-antiplatelet therapy with aspirin plus clopidogrel is recommended in the management of patients undergoing elective CAS. However, in the setting of emergency CAS, particularly after systemic thrombolysis, the appropriate timing or dosage of antiplatelet medications has not been established. In the field of percutaneous coronary intervention...
(PCI) for ST-elevation myocardial infarction, for which also emergency stenting can often be undergone, a loading dose of aspirin before primary PCI and a loading dose of a P2Y12 receptor inhibitor (e.g., clopidogrel) as early as possible or at a time of primary PCI are recommended. In addition, in case of prior thrombolytic therapy with loading dose of aspirin within 24 h, a 300 mg loading dose of clopidogrel before or at the time of PCI to patients who did not receive a previous loading dose are recommended in a guideline. It is also mentioned that GP IIb/IIIa inhibitors after thrombolytic therapy is associated with high rates of bleeding and ICH, particularly in the elderly. Thus, antiplatelet therapy appears essential for averting stent thrombosis. Nevertheless, the problem is that the hemorrhagic risks in emergency CAS are often higher than those in PCI, especially if just after systemic thrombolysis. Given the increased risk of both ICH and of AST in our series, the dilemma of timing and intensity of antiplatelet therapy in emergency CAS in tandem lesion patients is challenging.

Our study showed higher age and lower initial DWI-ASPECTS predict an unfavorable outcome. These associations are, not surprisingly, similar to previous acute intervention studies. In case series for emergency CAS, Malik et al. reported that successful recanalization, baseline NIHSS score, baseline ASPECTS, and age were significantly associated with good functional outcome. Kwak et al. reported that baseline NIHSS score, TICI grade and right-sided occlusion were independently associated with unfavorable outcome.

The mean time from onset to door in our study was 312 min and time to groin puncture was 463 min. These were obviously longer than those in recent RCTs for endovascular treatment in acute ischemic stroke. And also in other case series of emergency CAS, the time from onset to door or puncture was relatively longer. We could not find any significant relationship between time course and clinical outcome. Though these results were probably because of small sample size, the time windows for brain ischemia in the candidates for emergency CAS might be quite different from one case to another.

In summary, although we cannot absolutely conclude about the optimal management strategy, emergency CAS appears a procedure with elevated risk that should be undertaken with caution. The benefits and risks of the procedure should be balanced against other treatment options, in accordance with a specific clinical situation. Rahme et al. suggested that the decision making process should be made by the robustness of collaterals and patency of the carotid terminus. Patients in this setting have clinical symptoms caused either by a coexistent focal thrombus at the site of the intracranial occlusion or by cerebral hemodynamic insufficiency due to cervical occlusion, and sometimes both. When symptoms of patients are related to a distal intracranial occlusion, the distal lesion can be treated in isolation by advancing microcatheter, either through collateral channels or through the proximal occlusion itself. However, there may be a higher rate of reocclusion of intracranial arteries following mechanical thrombectomy when the feeding extracranial artery is occluded. When the symptoms are the result of acute cerebral hemodynamic insufficiency, isolated extracranial recanalization with stenting can be performed. Another option could be to treat patients with balloon angioplasty alone without stent placement for the extracranial lesion. This strategy would enable us to avoid giving aggressive antiplatelet therapy. In our previous report, partial proximal flow restoration after endovascular therapy for acute ICA-MCA tandem occlusions enhanced further post-procedure endogenous recanalization within 24 h. Therefore, in select cases it should be considered to perform only proximal recanalization and not to pursue additional for intracranial thrombectomy which might carry the additional risk of ICH.

Our study has limitations of a non-randomized single-center study and the small sample size. We could not find any relationship between distal thrombectomy device and clinical outcome. Recent evolution of thrombectomy device has lowered incidence of hemorrhagic complications and several case series for emergency CAS in combination with intracranial thrombectomy by using stent retriever have demonstrated relatively good results. Indeed, all the latest randomized trials which allowed inclusion of patients with extracranial carotid artery occlusion (except SWIFT PRIME) and stenosis have conclusively proven the benefit of mechanical thrombectomy with lower incidence of PH. However, the details of clinical management and outcome for the patients with tandem lesion have not been reported yet. Therefore, even in these trials, it is unclear whether thrombectomy in combination with emergency CAS is safe and effective or not. Future trials for this combination treatment should be demonstrated in larger number of selected patients.

Furthermore, longer-term clinical outcome beyond 3 months and several imaging markers with prognostic significance were not assessed in our study. Angiographic collateral grade are correlated with hemorrhagic transformation after endovascular treatment and subsequent clinical
outcome. In addition, postintervention infarct core volume, and final infarct volume are correlated with tissue fate and long-term neurologic function. Our study was not powered to detect uneven distributions of any of these markers, which may have helped identify a subgroup of patients with hemorrhagic complication and favorable outcomes.

### Disclosure Statement

Satoshi Tateshima reports consulting fees from Covidien, Stryker, Blockade Medical. David S Liebeskind reports consulting fees from Stryker, Covidien, Zoll (modest). Gary R Duckwiler reports consulting agreements with Asahi Medical and Sequent Medical. Gary R Duckwiler reports consulting fee from Covidien. Reza Jahan reports consulting fees from Covidien and Stryker. Jeffrey L Saver is a scientific consultant regarding trial design and conduct to Covidien, CoAxia, Stryker, BrainsGate, Genervon, and Grifols. Jeffrey L Saver has served as an unpaid site investigator in multicenter trials run by Lundbeck and Covidien. The University of California has patent rights in retrieval devices for stroke. All remaining authors have declared no conflicts of interest.

### References


