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Review article

Revascularization of carotid artery occlusion using stenting versus non stenting in endovascular management of tandem occlusion stroke

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ABSTRACT

Introduction: The use of extracranial internal carotid artery (ICA) stents after mechanical thrombectomy (MT) may be a source of morbidity and mortality. Studies comparing patients who received stenting to patients who do not receive stenting have a higher number of patients with failed intracranial reperfusion in the non-stenting cohort. In this study, we analyzed the impact of extracranial ICA stenting in tandem occlusion stroke in patients with successfully intracranial reperfusion.

Methods: This monocentric, retrospective cohort observational study reviewed all consecutive MT patients from January 2013 to January 2018. All patients with occlusions in the anterior circulation due to ICA atherosclerotic plaque embolus, TOAST 1, and were successfully reperfusion of at least 50% of the initially occluded target territory were included. Patients with a concomitant extracranial, or tandem, ICA occlusion which required MT and permanent stenting (stenting cohort) were compared to patients with extracranial atheromatous ICA plaques, which did not require permanent carotid stenting but were treated only by MT (non-stenting cohort). The three endpoints of this analysis were mortality rate at 90 days, good functional outcome defined as modified rankin scale (mRS) scores 0-2 at 90 days and symptomatic ICH (sICH). Outcomes were reported as odds ratios (ORs), indicating the odds that the intervention would lead to increased mortality rate, an improvement of at least one point on the mRS in a shift analysis and decreased rate of sICH.

Results: One hundred and two patients were included of which 42 were treated by MT and ICA stenting (stenting cohort) and 60 were treated by MT without stenting (non-stenting cohort). No significant differences observed as it relates to demographic data, stroke characteristics, symptom onset to groin puncture or groin puncture to final reperfusion time intervals. Univariate logistic regression showed a higher probability of mortality at 90 days in the stenting cohort than that in the non-stenting cohort (OR 2.78, 95% CI 1.21-7.25, P=0.03). Stenting was not associated with a significant difference in functional independence at 90 days or rate of sICH compared to the non-stenting cohort.

Conclusion: Stroke patients with successful intracranial reperfusion after MT had a higher probability of mortality within 90 days when concomitant stenting of the extracranial ICA was performed compared those patients who did not receive stenting.

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1. Introduction

Stroke remains a major cause of morbidity despite the relatively recent introduction of endovascular treatment (EVT), either as mechanical thrombectomy (MT) or thromboaspiration, both of which are now consider standard level of care in the acute phase [1]. Although stroke is caused by a thromboembolism secondary to heart dysrhythmia, another frequent cause involves thromboembolism from an underlying extracranial internal carotid artery (ICA) pathology, either secondary to arterial wall dissection or to major atherosclerotic disease. These two pathologies require different therapeutic strategies in the acute phase [2]. In arterial dissection, MT of the extracranial ICA occlusions appears safer without stent placement, whereas in atherosclerosis, some retrospectives studies show there may be improved clinical outcome

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after MT and ICA stenting compared to other treatment strategies [2–4]. However, the decision to stent after EVT is more complex and requires a pragmatic approach. Oftentimes the operator must weigh the benefits and risks using different parameters of which the most important is the infarct core volume after intracranial reperfusion because the rate of symptomatic intracranial hemorrhage increases as a function of infarct core volume once double antiplatelet therapy is started [5]. We conjecture that operators will instinctually only opt for stenting when infarct core or potential infarct core volumes are small [6]. As a result, studies comparing patients who received stenting of the extracranial ICA with patients who do not receive stenting inherently contain a selection bias with a higher number of patients with failed intracranial reperfusion in the non-stenting cohort [7]. As a result, the use of ICA stents after MT may potentially be a source of morbidity and mortality. Ideally, a randomized prospective study is required to better understand the complication rate associated with extracranial ICA stenting. Alternatively, a retrospective study using homogenous stroke reperfusion characteristics in both the stenting and non-stenting cohort may more be more appropriate. In this study, we analyzed the impact of extracranial ICA stenting in tandem occlusion stroke secondary to atherosclerotic disease in patients with successfully intracranial reperfusion.

2. Methods

2.1. Patient selection

The Acute Stroke Registry and Analysis of Lausanne (ASTRAL) is a prospective registry of consecutive acute ischemic stroke patients incorporating demographic, clinical, metabolic, acute perfusion and arterial imaging about which the details have been previously published [8]. We reviewed all consecutive EVT patients from January 2013 to January 2018 from ASTRAL in order to perform this monocentric retrospective cohort observational study. We included all acute stroke patients with occlusions in the anterior circulation due to ICA atherosclerotic plaque embolus, classified as 1 according to the Trial of ORG in Acute Stroke Treatment (TOAST) classification and who were successfully treated by MT with reperfusion of at least 50 % of the initially occluded target territory, defined as Modified treatment in cerebral ischemia (mTICI) scored as 2b or 3. Atherosclerotic causes of intracranial occlusion was deduced after CT analysis of carotid bifurcation to search calcifications, stenosis or parietal irregularity and after eliminate others causes based on clinical files and neurologist conclusions. Patients with unsuccessful reperfusion of less than 50 %, scored mTICI < 2b were excluded from this study. mTICI score were provided by the operator during the procedure, a non-blinded analysis was added after the selection to confirmed the successful reperfusion above 50 %. This population was separated in two cohorts: patients with a concomitant extracranial, ICA occlusion which required MT and permanent stenting (stenting cohort) compared to patients with extracranial atheromatous ICA plaques, which did not require permanent carotid stenting treated only by MT (non-stenting cohort).

The study was approved by the institutional research ethics board. All patients were initially evaluated by a stroke neurologist and then sent for imaging according to an institutionally based stroke protocol in order to determine EVT eligibility. After initial triage, non-enhanced computed tomography (CT), CT angiography and CT perfusion imaging were performed. Patients without intracerebral hemorrhage meeting IVT criteria were treated with recombinant tissue-type plasminogen activator (rtPA) during imaging, 0.9 mg/kg, 10 % of the dose as a bolus and the remainder as an infusion for 60 min. Patients were then evaluated for EVT according to our institution's inclusion criteria: symptomatic stroke with NIH stroke score (NIHSS) > 6 for less than 24 h from symptom onset, anterior circulation arterial filling defect at the level of M1 or M2, perfusion imaging demonstrating a penumbra to core infarct mismatch (a mismatch ratio was considered present when the radio was greater than or equal to 2:1), extracranial internal carotid artery filling defect, atherosclerotic etiology according to TOAST and a modified Rankin Score (mRS) $\leq$ 2 prior to symptom onset [9]. All extracranial internal carotid artery occlusion related to dissection or cardio embolic origin, symptom onset to reperfusion time that exceeded twelve hours or an Alberta Stroke Program Early CT Score (ASPECTS) less than or equal to six were excluded. mRs evaluation were performed by neurologists based by patients clinicals files and personal history; CT scan were analyzed by an experienced diagnostic radiologist in the flow of emergencies routine CT scan; ASPECT was prospectively defined on CT scan only; perfusion imaging was treated in clinical routine on Philips IntelliSpace Portal. Penumbra was defined as a mismatch between infarct core based on non-contrast CT scan imaging and hypoperfusion based on perfusion Tmax/MTT processing imaging, at the discretion of neuro interventional radiologist.

2.2. Endovascular procedure

In all patients, EVT was performed by an experienced neurointerventionist in collaboration with an anesthesiology team under general anesthesia.

After assessment of the occluded extracranial ICA using digital subtraction angiography (DSA), the distal tip of an 8F guiding catheter (Merci, Flowgate, Stryker Neurovascular, Fremont, USA) was placed directly in contact with the occluded site. Then, a Terumo 0.035-inch guidewire was navigated through and placed downstream from the occlusion allowing a 5F vertebral catheter to be advanced along with the 8F guiding catheter to the cervical or pre-petrosal portion of the internal carotid artery. After, the intracranial thrombus was removed either by a stent retriever system according to the neurointerventionist preference (Solitaire, Medtronic, Irvine, USA; Trevo, Stryker Neurovascular, Fremont, USA) or an aspiration device (ACE 68 aspiration system, Penumbra, Alameda, USA; Sofia 6Plus, Microvention, Tustin, USA). Following intracranial clot removal, the guiding catheter was retrieved and placed in the common carotid artery to confirm and facilitate retrograde treatment of the extracranial internal carotid artery occlusion under DSA.

In the stenting-angioplasty cohort, a self-expandable carotid stent (Wallstent, Boston Scientific, Natick, USA; CasperRx, Microvention, Tustin, USA) was deployed. If required, stents were dilated with an over-the-wire balloon catheter (Ultrasoft, Boston Scientific, Natick, USA) to achieve optimal wall apposition, vessel diameter and thus blood flow. Patients in this cohort received 250 mg acetylsalicylic acid during procedure. In the absence of ICH on CT scan at J1 in the stenting cohort, acetylsalicylic acid was maintained at 100 mg daily and clopidogrel at 75 mg daily was added after an initial 300 mg loading dose. Dual antiplatelet therapy was maintained for 90 days.

2.3. Outcomes

The three endpoints of this analysis were mortality rate at 90 days, good neurological outcome, considered functionally independent, defined as mRS scores of 0–2 at 90 days and symptomatic ICH (sICH) defined as a hemorrhage associated with an increase in NIHSS score of at least 4 points according to the European Cooperative Acute Stroke Study criteria [10,11].

2.4. Statistical analysis

Statistical analysis was performed by a statistician using a commercially available software program (MedCalc v15.8, MedCalc, Osten, Belgium) with statistical significance set at p less than 0.05. Continuous variables were expressed as median +/- range, while categorical variables were expressed as frequency and percentages. A Welsch's *t*-test was used for continuous variables as well as the Wilcoxon test when assumptions were not validated. Chisquare tests were used for categorical variables. For each outcome investigated, 3-month mortality rate, 3-month favorable clinical outcome (mRS score $\leq$ 2) and sICH; the association of the stenting cohort with all outcome parameters was assessed using univariate logistic regression. Outcomes were reported as odds ratios (ORs), indicating the odds that the intervention would lead to increased mortality rate at 90 days, an improvement of at least one point on the mRS in a shift analysis and decreased rate of sICH.

3. Results

3.1. Baseline

Between January 2013 and January 2018, 362 patients were treated by MT, of which 127 were anterior circulation strokes originating from an atherosclerotic cause. Twenty-five of these patients were excluded because they did not meet the inclusion criteria.

Among the remaining 102 patients, 42 were treated by MT and ICA stenting (stenting cohort) and 60 were treated by MT without stenting (non-stenting cohort). The following stents were used in the stenting cohort: 19 Casper (Microvention, Terumo, Tustin, USA), 18 Carotid Wallstent (Boston Scientific, Natick, USA) and 5 Protégé (ev3 Endovascular, Plymouth, USA).

Baseline characteristics and univariate comparisons of patients in the stenting and non-stenting cohort are detailed in Table 1. Stenting and non-stenting cohorts were relatively homogenous with no significant differences observed as it relates to demographic data, stroke characteristics, symptom onset to groin puncture or groin puncture to final reperfusion time intervals. A statistical trend was observed in the number of patients with two cerebrovascular risk factors which was higher in the stenting cohort compared to that in the non-stenting cohort (90 % versus 70 %, p = 0.06).

Table 2
Procedure efficacy and clinical outcome.

	Stenting (n = 42)	Non-stenting (n = 60)	p Value‡
Mortality at 90 days	9 (21 %)	4 (7 %)	0.06
Functionally independant at 90 days *	24 (56 %)	35 (58 %)	0.96
Symptomatic intracranial hemorrhage	6 (14 %)	5 (8 %)	0.53
-Hi 1/2	2 (5 %)	8 (13 %)	
-Ph 1/2	8 (9 %)	1 (2 %)	
-Subarachnoid hemorrhage	1 (2 %)	5 (8 %)	

Values are represented as n (%). *Favorable outcome = modified rankin scale score 0–2. †mRS = modified rankin scale score. ‡The P value was calculated using χ-squared.

3.2. Efficacy and safety

Procedural efficacy and clinical outcome with univariate comparison are presented in Table 2. There was no statistical difference between the two cohorts concerning the mRS or symptomatic intracranial hemorrhage at 90 days. A statistical trend was observed in Mortality rate at 90 days which was higher in the stenting cohort compared to that in the nonstenting cohort (21 % versus 7 %, p = 0.06).

3.3. Primary outcome

The results of the univariate logistic regression comparing clinical outcome of the stenting cohort versus the non-stenting cohort are presented in Table 3. The probability of mortality at 90 days in the stenting cohort was significantly higher than that in the non-stenting cohort (OR 2.78, 95 % CI 1.21–7.25, P = 0.03). Stenting was not associated with a significant difference in functional independence at 90 days or sICH compared to the non-stenting cohort.

Table 1
Baseline characteristics.

	Stenting (n = 42)	Non-stenting (n = 60)	p Value
Demographics			
Age (years), median (range)	70 (50–92)	72.4 (46–93)	0.29
Female sex, no. (%)	11 (28 %)	23 (38 %)	0.26
Medical History			
> 2 cerebrovascular risk factors, no. (%)	38 (90 %)	42 (70 %)	0.06
Smoking, no. (%)	18 (43 %)	23 (38 %)	
Diabetes Mellitus, no. (%)	5 (12 %)	13 (22 %)	
Hypercholesterolemia, no. (%)	38 (90 %)	43 (72 %)	
Hypertension, no. (%)	31 (74 %)	43 (72 %)	
Prior Antiplatelet therapy, no. (%)	15 (36 %)	17 (28 %)	0.57
Stroke Characteristics			
Pre-stroke mRS score, median (range)*	0 (0–3)	0 (0–2)	0.30
NIHSS pre-EVT, median (range)†	15 (3–29)	16 (4–28)	0.42
ASPECTS on initial CT, median (range)‡	9 (6–10)	9 (2–10)	0.18
Bridging treatment with intravenous *t*-PA, no. (%)	35 (83 %)	46 (77 %)	0.56
Timing (minutes) Symptom onset to groin puncture, median (range)	211 (84–1006)	242 (92–1080)	0.77
Groin puncture to reperfusion, median (range)	70 (15–270)	45 (15–208)	0.96
mTICI score = 3, no. (%) §	22 (52 %)	36 (60 %)	0.57
NIHSS at 24 h, median (range)	4 (0–42)	8 (1–42)	0.47

Values are represented as median (range) or n (%). *mRS = modified rankin scale score; †NIHSS = National Institutes of Health Stroke Scale; ‡ASPECTS = Alberta Stroke Program Early CT Score; §mTICI = modified Thrombolysis in Cerebral Infarction. ¶The P value was calculated using χ-squared for discrete data and *t*-test for continuous data.

Table 3
Logistic Regression analysis when comparing stenting versus non-stenting.

	OR (95 % CI)	p Value
Mortality at 90 days	2.78 (1.21–7.25)	0.03†
Functionally independent at 90 days *	0.93 (0.52–1.63)	0.80
Symptomatic intracranial hemorrhage	1.71 (0.73–4.25)	0.34

*Favorable outcome = modified rankin scale score 0–2. †probability of mortality within 90 days in the stenting cohort.

4. Discussion

The main finding in the present series was that stroke patients with successful intracranial reperfusion after MT and concomitant stenting of the extracranial ICA were associated with a higher mortality rate at 90 days when compared those patients who received MT alone.

The efficacy and safety of extracranial ICA stenting for tandem occlusions performed in the acute phase of stroke remains controversial with some studies reporting major complications with poor clinical outcome while others report acceptable safety and good clinical outcome [12–23]. Among the major complications is sICH and is often attributed to either the required double antiplatelet therapy to maintain stent patency or the IV rtPA given in the acute phase of stroke. In this study, an increase in the rate of sICH was not observed in the stenting cohort relative to the non-stenting cohort at any point during the acute or subacute stroke treatment (14 % and 8 %, respectively). We explain these findings by the similar percentage of patients treated with iv TPA (83 % in the stenting cohort and 77 % in the non-stenting cohort) and pre-existing antiplatelet (36 % in the stenting cohort and 28 % in the non-stenting cohort). Although a loading dose of aspirin was administered after ICA stenting in patients not on anti-platelet therapy, patients in the non-stenting cohort also received aspirin at 24 h following MT. In our study, three patients in the stenting cohort had sICH after being treated with rtPA, aspirin and intravenous heparin which is a known cause for sICH [24,25]. These reports corroborate our results leading us to believe that additional periprocedural heparin in conjunction with iv TPA should be avoided regardless of procedural complications related to the stent patency [25]. Dissimilarly, Lescher and al. report sICH at 0 and 10 % respectively, in the stenting cohort and in non-stent cohort [26]. This difference could be explained by the lack of statistical power as only nine patients were included in the stent cohort versus thirty patients in the non-stent cohort [27–29].

Another stent-related complication is precocious intra-stent re-occlusion of the extracranial ICA. In 17 patients in this cohort, Casper stents, which feature two layers, were used. These double wall stents are known to be thrombogenic and as a result, these cases were complicated by an intrastent thrombus rapidly forming during the intervention without associated intra-stent re-occlusion [13,14,30,31]. In one of those cases, intravenous heparin was added by the operator and the patient died during his hospitalization from subarachnoid hemorrhage. No significant increase in mortality, intracranial hemorrhage or shift in the modified Rankin Scale score was observed in the patients who received a Casper stent compared to the other patients in this cohort who received other carotid stents (Wallstent from Boston Scientific and Protégé from Medtronic).

Additionally, all patients included in this study had follow-up CT imaging at 24-hours, but only a few were performed in conjunction with an CT-angiography and thus stent patency data at this time point was not available for analysis. Despite this missing data, we assume that any new ischemic territory in addition to the reperfused and previously occluded territory in the stenting cohort remained clinically silent because the no difference in the rate of functionally independence at 90 days was observed in the stenting cohort compared to the non-stenting cohort (56 % and 58 % respectively). A review of the published data on long-term neurological outcome in acute stroke patients treated with MT and *ACI* stenting are similar to the results of the same cohort in this study [7,12,25]. Gory and al. reported 52.2 % of patients were functionally independent at 90 days after ICA stenting and MT.

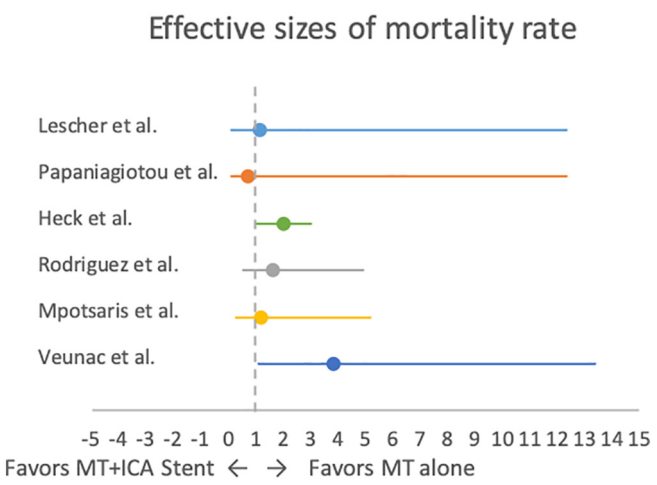

Fig. 1. Published studies on the effect on mortality rate in patients receiving internal carotid artery (ICA) stenting. Data is presented as unadjusted odds ratios comparing mechanical thrombectomy (MT) with ICA stenting to MT alone.

Finally, stenting of the extracranial tandem occlusion at the ICA after MT was associate with a higher probability of mortality at 90 days in the stenting cohort (21 %) relative to the non-stenting cohort (7 %), OR = 2.78 (1.21–7.25), p = 0.03.

There is high variability in 90-day mortality rates in literature for patients who were successfully and unsuccessfully recanalized. Fig. 1 graphically shows the effect of ICA stenting regardless of reperfusion status from existing studies in the literature using unadjusted odds ratio comparing MT with ICA stenting to MT alone. Those datas were obtained from meta analysis; Rotem SivanHoffmann et al. [23]. Lescher and al. report a mortality rate at 11 % in the ICA stenting cohort whereas Rodriguez et al., Brehme et al. and Papaniagiotou et al. reported 30 %, 19 % and 11.4 %, respectively. In tandem occlusion reviewed by Gory et al., mortality rate regardless of treatment were reported to be 13.2 % at 90 days [26,32]. More interestingly, Heck and al. report a 39 % mortality in the ICA stenting cohort, most likely due to periprocedural abciximab use which led to an increase in sICH and 90-day mortality [33]. Lamanna et al in analyzing 20 patients treated by MT in acute stroke with ICA stenting, showed that sICH and three month mortality rates were 10 % and 15 %, respectively. Those results are comparable to those in the stenting group in the presented study and to the results of Lockau et al and Spiotta et al who reported respectively 18.9 % and 18.8 % of mortality at three months. Additionally, Grigoryan et al. report a 90-day mortality of 18.9 % in their reported tandem occlusion population [34].

Further studies using existing stroke databases in addition to a prospective study would reinforce our findings. Currently, the TITAN database (Thrombectomies In TANdem Lesions) is a large multicentric database including patients presenting with anterior circulation stroke associated with a tandem occlusion from January 2012 to September 2016 which has already been used for several publications [35–38]. Mortality rates in those patients who were successfully recanalization, considered mTICI > 2b, with and without concomitant emergent stenting remain unpublished [35]. Additionally, one randomized study comparing ICA stenting to no-stenting in patients with tandem carotid lesions undergoing

thrombectomy, which found no significant difference in mortality rate between the ICA stenting group compared to the group treated without stenting, did not include a subgroup analysis of mortality on patients who were successfully recanalized [39].

Finally, when faced with this clinical situation, operators must decide whether stenting should or should not be performed. Those who decide to stent following MT will perform this procedure presumably when reperfusion scores are equal to or greater than mTICI = 2b and ischemic lesions are limited to a small infarct core. This is corroborated by the fact that ICA stenting appears to operators as a more beneficial strategy for patients and thus is commonly performed following successful reperfusion [40,41]. Maus et al. showed that 91 % of patients treated with ICA stenting in a retrograde approach, were successfully reperfused. In unsuccessful reperfusion, operators would presumably opt out of ICA stenting as there would not be any advantage to maintain blood flow to a downstream vascular territory when a concomitant intracranial occlusion is present.

4.1. Limitations

Because our study was monocentric, we were unable to control for variations in operator performance, a potential source of bias in multicentric studies. Additionally, patients who were ineligible for ICA stenting and reassigned to the non-stenting cohort due to poor reperfusion results (mTICI 0-2a) were excluded, yielding two homogenous cohorts for analysis. Nevertheless, our study has the limitations of a retrospective design. More importantly, patients were assigned to each cohort based on the operator's choice.

5. Conclusion

Our data indicates that patients treated by MT had a higher probability of mortality within 90 days when concomitant ICA stent was performed when compared to those who did not receive stenting after correcting for possible confounding factors as reperfusion success. A prospective randomized study in atherosclerotic tandem occlusions, comparing the long-term outcome of a stenting cohort to a non-stenting cohort following successful reperfusion would better support our findings regarding stenting of the extracranial ICA in acute ischemic stroke.

Furthermore, we caution the readership of results in retrospectives studies concerning ICA stenting.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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