Original Article

Cervical carotid occlusion in acute ischemic stroke: Should we give tPA?

Theresa A. Elder[1], Leonard H. Verhey[2], Haritha Schultz[3], Eleanor S. Smith[4], Joseph G. Adel[5]

[1]Department of Neurological Surgery, University Hospitals Cleveland Medical Center, Cleveland, Ohio, [2]Department of Clinical Neurosciences, Spectrum Health, Michigan State University College of Human Medicine, Grand Rapids, Departments of [3]Internal Medicine and [4]Neurosurgery, Central Michigan University College of Medicine, [5]Department of Neuroscience, Ascension St Mary's Hospital, Saginaw, Michigan, United States.

E-mail: *Theresa A. Elder - tae26@case.edu; Leonard H. Verhey - leonard.verhey@spectrumhealth.org; Haritha Schultz - schul2h@cmich.edu; Eleanor S. Smith - smith7ec@cmich.edu; Joseph G. Adel - joseph.adel@ascension.org

*Corresponding author:
Theresa A. Elder,
Department of Neurological Surgery, University Hospitals Cleveland Medical Center, Cleveland, Ohio, Michigan, United States.

tae26@case.edu

ABSTRACT

Background: Acute ischemic stroke (AIS) due to cervical internal carotid artery (cICA) occlusion is challenging to treat, with the lower revascularization rates, higher risk for complications, and poor response to thrombolytic therapy compared to isolated intracranial occlusions. While emergent revascularization through mechanical thrombectomy (MT) improves outcomes, the impact of tissue plasminogen activator (tPA) on outcomes in this subgroup of patients remains unclear. The objective of this study is to report our preliminary experience in treating AIS with cICA occlusions secondary to severe atherosclerotic stenosis and to establish the need for further clinical studies to determine the optimal intervention strategy for these lesions.

Methods: Data were collected on patients who presented with acute cICA occlusion who underwent MT and either acute or staged carotid angioplasty and stenting. We compare patients who received tPA to those who did not, analyzing revascularization times, outcomes, and complications between the two populations, and discuss how this influenced our preferred treatment approach.

Results: Twenty-one patients met inclusion criteria, seven of who received tPA and 14 did not receive tPA before surgical intervention. Procedural and functional outcomes were similar between the two populations. TPA administration correlated with a higher rate of vessel reocclusion in staged procedures and trended toward higher rates of symptomatic ICH and 90-day mortality.

Conclusion: Emergent revascularization with acute cICA stenting carries advantages, but its safety is precluded by tPA administration. We suggest a trial which randomizes patients with cICA occlusions to receiving either tPA or dual antiplatelet therapy before surgical intervention, aiming to ultimately improved outcomes in these patients.

Keywords: Acute ischemic stroke, Carotid occlusion, Carotid stenting, Intracranial hemorrhage, Thrombectomy, Thrombolysis

INTRODUCTION

Acute stroke caused by occlusion of the extracranial internal carotid artery (ICA) is challenging to treat and carries a poor prognosis, with a mortality rate of 20–30%.[18] An estimated 15% of acute ischemic strokes (AISs) are related to an extracranial carotid occlusion, either isolated or in tandem with an intracranial large vessel occlusion (LVO).[1,2,7,10] Numerous trials have shown

superiority for mechanical thrombectomy (MT) over IV thrombolysis alone in the treatment of AIS due to LVO. There is far less data available on extracranial lesions, particularly regarding the optimal revascularization strategy and timing of treatment.[17,25] In a recent study of 627 patients with AIS due to any LVO who received preinterventional tissue plasminogen activator (tPA) with the intent to perform MT, preinterventional reperfusion to thrombolysis in cerebral infarction (TICI) 2a or greater occurred in only one out of every ten patients, and still half of these patients required MT to achieve complete reperfusion.[9] Of the patients with ICA occlusion, this number was even lower. While the study advocated for preinterventional tPA in certain scenarios, it concluded that in patients with ICA and proximal M1 occlusions, IV tPA may negatively impact outcomes by promoting clot fragmentation and worsening perfusion.

Emergent revascularization is known to improve morbidity and mortality in AIS, but does not come without risk for complications, particularly when involving occlusions of the cervical ICA (cICA).[9,15] Intracranial hemorrhage (ICH) has been reported to occur in 30–40% of cases following revascularization of the cICA, thought to be related to reperfusion injury as well as the aggressive antiplatelet therapy required when carotid artery stenting (CAS) is performed.[5] MT with emergent CAS is a well-documented approach utilized to treat AIS due to extracranial occlusion with severe atherosclerotic stenosis; however, the safety of this approach is of ongoing debate due to reports of increased rate of ICH with emergent CAS.[12,19-21,25]

Furthermore, despite the associated ICH risks, there are no specific antiplatelet therapy recommendations for the acute phase of management following CAS.[9] Anti-thrombotic agents are required to prevent intraluminal stent thrombosis; however, this therapy is contraindicated in the first 24 h following tPA administration. This leaves uncertainty regarding the safety and management of acute CAS in patients who received tPA.[11] A few recent studies have found no increase in ICH with use of antithrombotic agents even in combination with tPA; however, these studies utilized a highly heterogeneous antithrombotic drug regimen including various combinations of aspirin, heparin, intravenous glycoprotein IIb/IIIa antagonists, and clopidogrel.[4,25] The lack of standardized regimen challenges the ability to compare treatment approaches and their impact on patient outcomes, and has precluded the ability to establish a specific antiplatelet therapy protocol in this setting.

We report our experience in treating cICA occlusion secondary to severe atherosclerotic stenosis in the setting of AIS. We compare revascularization times, outcomes, and complications seen in patients who have received tPA versus those who did not. From these results, we elaborate on the role of thrombolytic therapy administration in determining our selected approach and examine the impact this has on patient outcomes.

MATERIALS AND METHODS

Patient selection

We retrospectively reviewed the charts of patients presenting with AIS treated with MT between April 2017 and March 2019. We identified 107 patients who underwent anterior circulation thrombectomy of whom 23 patients harboring cICA occlusion requiring concomitant treatment. International Review Board approval was received and followed according to the institutional protocol.

Data were collected on patients' demographics, comorbidities, and other risk factors before presentation. Clinical characteristics were collected including the time, the patient was last known to be normal to the time of revascularization, revascularization time, TICI score, infarct size, ICA reocclusion in staged procedures following MT, presence of postoperative ICH, and presence of postoperative symptomatic ICH. The stroke severity was calculated according to the National Institute of Health Stroke Scale (NIHSS) on initial presentation to our institution and was recorded again at discharge.

Procedure

All MT procedures were performed by the same cerebrovascular neurosurgeon (JGA) in the endovascular suite under general anesthesia with strict blood pressure control. CT perfusion was utilized for selection of appropriate candidates for intervention based on time of onset of symptoms. All patients underwent CT angiography before the thrombectomy as a part of the workup and cervical carotid occlusion was identified before the endovascular procedure. Our cohort was divided into two time lines. Initially, the treatment approach utilized on all our patients consisted of staging all procedures and performing the second stage cervical carotid treatment based on size of infarct, hemorrhagic transformation, and response to antiplatelet therapy. Later in our series, patients who received tPA underwent staged procedures while those who did not receive tPA underwent acute stenting. TPA exclusion criteria were determined according to the American Heart Association guidelines.[23] In general, patients who were not candidates for tPA received a loading dose of Aspirin 325 mg and Clopidogrel 300 mg in preparation for possible acute carotid artery stenting. Conversely, patients who had received tPA before the thrombectomy did not receive additional antiplatelet agents before undergoing balloon angioplasty only and further cervical carotid treatment was staged. In these patients, extracranial carotid intervention timing was determined on a case-by-case basis and after obtaining a 24 h post-tPA cranial imaging.

In general, all thrombectomies were performed using a standard setup to minimize confusion and speed the process. Femoral artery access is obtained and a short 8Fr sheath is secured in place. Usually, a 90 cm 6F Neuron guide sheath (Penumbra, Alameda, CA, USA) is navigated over a 125 cm 6Fr angled tip Berenstein diagnostic catheter (Boston Scientific, Natick, MA, UA) over a 0.035' Terumo Glidewire (Terumo International Systems, Somerset, NJ, USA). Based on the arch type on CTA, an alternative to the Bernestein would be the 5F BERN 1 (Merit Medical, South Jordan UT, USA) or 5F VTK (Cook Inc., Bloomington, IN, USA) catheters. The cervical occlusion can always be crossed with this setup and the neuron sheath able to be navigated all the way into the vertical petrous carotid artery. At this point, manual suction is performed on the neuron sheath with a 60 cc syringe until regaining backflow. If angiography confirms an intracranial occlusion, we proceed with the intracranial thrombectomy [Figure 1]. An ACE Penumbra reperfusion catheter (Penumbra, Alameda, CA, USA) is navigated over a Marksman microcatheter (Medtronic Neurovascular, Irvine, CA, USA) over a Synchro 2 microwire (Stryker, Neurovascular, Fremont, CA, USA). After the lesion is crossed, the stent retriever is deployed across the occlusion, and then the stent is removed while the reperfusion catheter is connected to the aspiration pump. If there is no back flow, the reperfusion catheter is kept connected to the aspiration pump for 90 s, then removed and followed with manual suction applied to the neuron sheath; this process may need repeating. Once reperfusion is achieved, attention is turned to the cervical occlusion. A distal protection device is left in the distal cervical carotid as the neuron sheath is pulled back into the common carotid artery. For patients who had received tPA and angiography reveals severe stenosis, serial angioplasties are performed until good distal anterograde flow is regained. If patients did not receive tPA, they have been loaded with dual antiplatelet therapy, so heparin was loaded with a target ACT of around 2–2.5 baseline before the angioplasty, and then proceed as above and deploy a stent. "All patients underwent clopidogrel response testing to ensure adequate platelet response, with target P2Y12 of <200. Patients with suboptimal platelet response were switched from clopidogrel to ticagrelor as the second antiplatelet agent."

Outcomes and postoperative care

All images were processed and interpreted by both the operating neurosurgeon and a nonconflicted neuroradiologist. Degree of intracranial revascularization was measured according to the TICI score, with successful reperfusion defined as TICI score of 2b or 3. All patients underwent head CT or MRI 24 h post-tPA, and infarct territory size was recorded, as well as the presence of ICH of any size or location. Symptomatic ICH was recorded as defined by any ICH found in conjunction with a decline in NIH score by four or more points. Outcomes were measured based on modified Rankin Scale (mRS) at 90 days post procedure, with good outcome defined as mRS score of 0–2. Mortality was also recorded at 90 days postoperatively in addition to length of hospital stay.

Statistical analysis

All variables were measured and compared between two groups; those patients who received tPA before intervention and those who did not receive tPA. Continuous variables were expressed as a mean and categorical variables as a percentage. Comparisons were performed using Welch *t*-test for continuous variables and Fisher exact test for frequency tables. For measuring predictors of clinical outcome, variables with $P < 0.05$ were considered statistically significant.

RESULTS

Patient characteristics

A total of 21 patients met criteria for inclusion in the study [Figure 2]. Of the 23 patients who met initial inclusion criteria, two were excluded from the study. One of these patients underwent a delayed endarterectomy and the other was planned to undergo a delayed intervention but failed to follow-up. Seven patients (33.3%) comprised the group who received tPA and 14 patients (66.7%) comprising the group who did not receive tPA before intervention. About 61.9% of patients were males ($n = 13$), with a mean age of 68.5 years overall. Patient comorbidities and risk factors for stroke were recorded including hypertension, coronary artery disease, diabetes mellitus, and atrial fibrillation, as well as patients who were active smokers. Patient demographics are further summarized in [Table 1].

Clinical and interventional characteristics

Of the seven patients who received tPA before intervention, six underwent staged CAS and one underwent stenting in the acute setting (due to inability to maintain distal flow despite angioplasty). Of the 14 patients who did not receive tPA, five underwent staged CAS and nine underwent stenting in the acute setting.

The mean NIHSS on presentation was 17 overall, with a mean of 19 among the tPA group and 16 among the non-tPA group. The mean time from the time that the patient was last known to be normal to the time of groin puncture was 392 min (due to high incidence of external transfers). Average time of reperfusion was 32.8 min overall, 25.4 min in patients who received tPA and 36.5 min in those who did not receive tPA. Overall, 95.2% of patients ($n = 20$) achieved successful reperfusion with a TICI score of 2b/3, 100% in
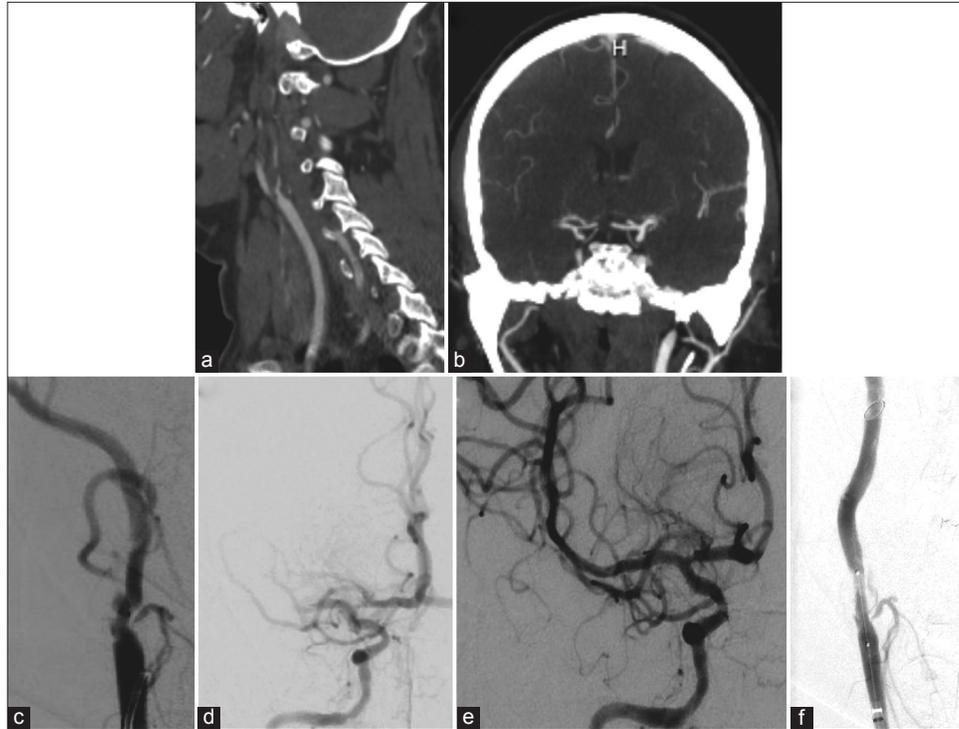
Figure 1: Intracranial thrombectomy setup. (a) Neck CTA demonstrating right ICA occlusion. (b) Head CTA demonstrating occlusion of the mid right M1 segment. (c) Angiography demonstrating complete occlusion of the ICA at its origin. (d) Cranial angiography revealing right MCA occlusion. (e) Reinstitution of normal flow through the MCA following thrombectomy. (f) Oblique cervical angiography demonstrating the setup with the distal protection device and the neuron sheath as balloon angioplasty is performed. ICA: Internal carotid artery, MCA: Middle cerebral artery.
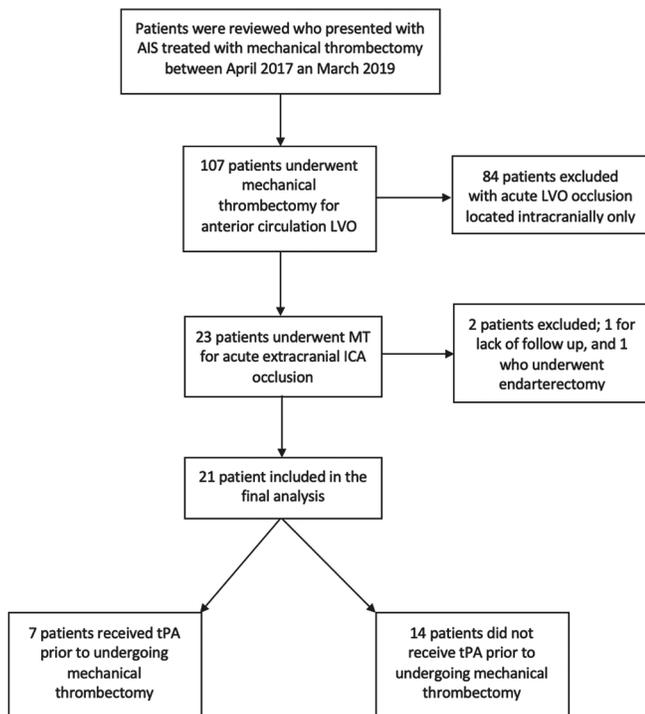

Figure 2: Patient selection methods.

the tPA group and 92.9% in the non-tPA group; with 81% of patients overall ($n = 17$) achieving TICI score of 3. One patient achieved TICI score of 2a. Patient outcomes and complications are summarized in [Table 2].

Outcomes and complications

Average improvement in NIHSS from baseline was 7 points overall; 6 points in patients who received tPA and 7 points in patients who did not receive tPA. Final infarct size was less than one-third of the middle cerebral artery (MCA) territory in 90.5% of patients ($n = 19$), 85.7% of patients who received tPA and 92.9% of those who did not. Overall, 57.1% of patients achieved good functional outcome at 90 days postoperatively, with an equivalent rate of good functional outcome seen among both the patients who received tPA and those who did not receive tPA.

ICA reocclusion identified in staged procedures occurred in 19% of patients ($n = 4$). Three of these occurred in the tPA patient group (42.9%) and one occurred in the non-tPA group (7.1%). Postoperative ICH of any size, regardless of the presence of associate symptoms, was seen in 33.3% of total patients ($n = 7$); one from the group who received tPA

Table 1: Baseline patient characteristics.

Characteristic	All Patients (%)	Patients who received tPA (%)	Patients who did not receive tPA (%)	*P*
Total number of patients	21	7 (33.3)	14 (66.6)	
Mean age, years	68.5	65.3	69.9	0.41
Male gender	13. (61.9)	5 (71.4)	8 (57.1)	0.66
Active smoker	8 (38.1)	2 (28.6)	6 (42.9)	0.66
Prior antithrombotic agent use	6 (28.6)	2 (28.6)	4 (28.6)	0.93
Comorbidities				
Hypertension	17 (81.0)	6 (85.7)	11 (78.6)	1
Coronary artery disease	8 (38.1)	3 (42.9)	5 (35.7)	1
Diabetes	6 (28.6)	3 (42.9)	3 (21.4)	0.35
Atrial fibrillation	1 (4.8)	0 (0)	1 (7.1)	1

CAS: Carotid artery stenting, tPA: Tissue plasminogen activator

Table 2: Clinical and interventional characteristics.

Variable	All patients (*n*=21)	Patients who received tPA (*n*=7)	Patients who did not receive tPA (*n*=14)	*P*
NIH stroke score on arrival	17	19	16	0.25
Time (mins)				
From last time known normal to groin puncture	392	330.4	422.8	0.38
From groin puncture to recanalization	32.8	25.4	36.5	0.21
Extracranial intervention				
Acute CAS	10 (47.6)	1 (14.2)	9 (64.2)	0.04
Delayed CAS	11 (52.3)	6 (85.7)	5 (35.7)	0.04
Interval between MT and CAS, days	1.5	1.6	1.5	0.95
TICI 2b/3	20 (95.2)	7 (100)	13 (92.9)	1
TICI 3	17 (81.0)	7 (100)	10 (71.4)	0.25

CAS: Carotid artery stenting, ICA: Internal carotid artery, MCA: Middle cerebral artery, MT: Mechanical thrombectomy, NIH: National Institute of Health, tPA: Tissue plasminogen activator

(14.3%) and six from the group who had not received tPA (42.9%). Symptomatic ICH was seen in only 1 patient (4.8%) who was in the group who had received tPA (14.3%).

There was one periprocedural mortality overall, which occurred in a patient who underwent emergent MT and angioplasty with plan for staged CAS given administration of tPA; however, the ICA reoccluded on postoperative day 1 [Figure 3]. Repeat thrombectomy with emergent CAS was performed complicated by dissection, after which the patient developed diffuse subarachnoid hemorrhage. There were no other mortalities in the 90-day postoperative period. Patient outcomes and complications are summarized in [Table 3].

DISCUSSION

In the current era of endovascular treatment, modern equipment and techniques have brought about better stroke outcomes and broadened the indications for acute intervention. However, it is uncertain how this applies to the endovascular treatment of acute cICA occlusion secondary to severe atherosclerotic stenosis. From the ongoing TITAN

collaboration trial, which aims to determine the best treatment strategy for tandem occlusions, data specific to cICA treatment suggest that emergent CAS is a feasible treatment for AIS, even in the setting of patients who received thrombolytic therapy.[16,22,25] In their analysis of the TITAN data, Zhu *et al.* reported no increase in overall ICH in patients who underwent endovascular intervention following IV thrombolytic therapy. Information was not provided on periprocedural heparin use, drug dosages, or times administered, nor data regarding reocclusion rates, context which may significantly impact outcomes. In contrast, numerous authors argue against the use of CAS in the emergent setting.[12,21] A 2018 large database study of patients who underwent CEA or CAS for cICA occlusion saw higher rates of ICH and post procedural strokes in patients who received tPA compared to patients who did not receive tPA before the intervention, and concluded that IV thrombolysis is an independent predictor of poor outcome after revascularization.[21] This study also found that the risk for these adverse events declined with time after thrombolytic administration, and that after 7 days, postoperative ICH and stroke rates were equivalent to those seen in patients who did

Table 3: Procedure outcomes.

Outcome measures	All patients (*n*=21)	Patients who received tPA (*n*=7)	Patients who did not receive tPA (*n*=14)	*P*
Final infarct size<1/3 MCA territory	19 (90.5)	6 (85.7)	13 (92.9)	1
90-day mRS=0–2	12 (57.1)	4 (57.1)	8 (57.1)	1
24 h postoperative NIH stroke score	8	6	9	0.19
Improvement in NIH stroke score from baseline at 24 h postoperative	7	6	7	0.25
Length of hospital stay (days)	7.4	7.1	7.5	0.86
Complications				
ICH	7 (33.3)	1 (14.3)	6 (42.9)	0.34
Symptomatic ICH	1 (4.8)	1 (14.3)	0 (0)	0.33
ICA reocclusion (post-MT)	4 (19.0)	3 (42.9)	1 (7.1)	0.08
Mortality (90-days)	1 (4.8)	1 (14.3)	0 (0)	0.33

ICA: Internal carotid artery, ICH: Intracranial hemorrhage, MCA: Middle cerebral artery NIHS: National Institute of Health, POD: Postoperative day, TICI: Thrombolysis in cerebral infarction, tPA: Tissue plasminogen activator, MT: Mechanical thrombectomy
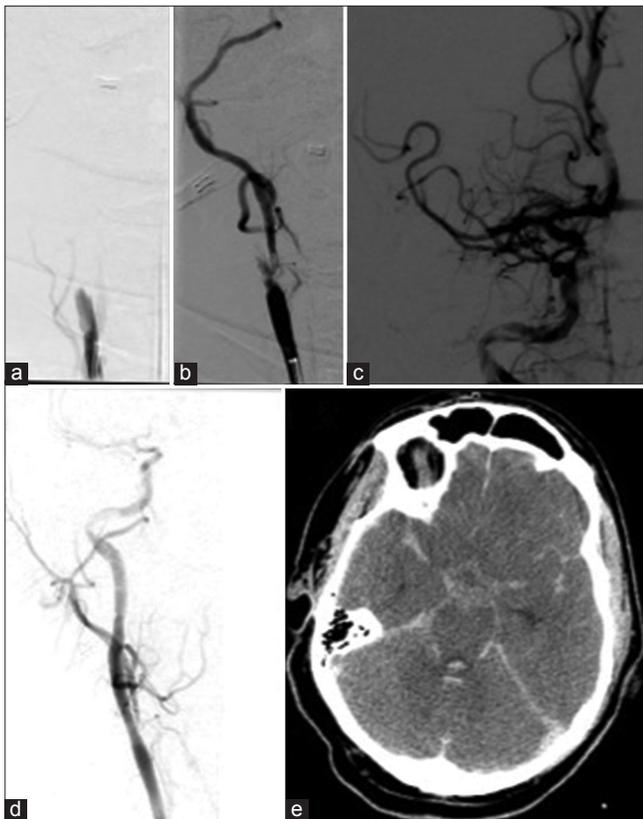

Figure 3: Staged intervention. (a) Cervical angiography demonstrating the complete occlusion of the right CCA. (b) Persistent occlusion of the cervical internal carotid artery with significant stenosis at its origin following initial aspiration thrombectomy. (c) Cranial angiography following ICA thrombectomy revealing dissection in the petrous and cavernous carotid segments, and occlusion of the mid right M1 segment. (d) Craniocervical angiography after the thrombectomy and carotid stent reconstruction demonstrating the diminished intracranial flow consistent with increased intracranial pressure. (e) CT obtained postoperatively revealing diffuse subarachnoid hemorrhage. ICA: Internal carotid artery.

not receive thrombolytics before revascularization, suggesting that delaying revascularization may be appropriate in certain patients.

While our data only reflect the preferred treatment approach of a single surgeon, this carries the unique advantage of removing any confounding variables related to variation in surgical techniques and strategies employed between different surgeons. Overall outcomes in our patient population as a whole were comparable to those reported in recent literature in terms of mRS score and improvement in NIHSS from baseline. However, our cohort of patients demonstrated superior revascularization times, and with a higher proportion of patients achieving successful revascularization.[15,25] Papanagiotou *et al.* reported outcomes for tandem occlusion patients treated using various approaches, with average revascularization times of 76 min for the group who received thrombolytics preoperatively and 87 min for the group treated without thrombolytic therapy.[15] Mpotsaris *et al.* reported a similar trend, reporting revascularization times of 110–130 min with and without tPA, respectively.[14] Similarly, our average revascularization time was 25.4 min among patients who received tPA, compared to 36.5 min among those who did not receive tPA. Papanagiotou *et al.* reported the highest recanalization rate in the thrombolytic therapy group at 83% and Mpotsaris *et al.* reported a rate of 87.[14,15] Zhu *et al.* reported similar results from the TITAN collaboration data, achieving successful revascularization in 79% of patients who underwent cervical carotid treatment in addition to intracranial MT. Our patients overall demonstrated a 95% rate of successful recanalization, 81% of who achieved TICI score of 3; The tPA group and the non-tPA group demonstrated a 100% and 92.9% rate of successful recanalization, respectively. Of note, however, is that among the patients who underwent a staged procedure, the rate of reocclusion following initial thrombectomy was

much higher among the group who received tPA compared to the group who did not receive tPA (43% and 7%, respectively), approaching statistical significance ($P = 0.08$) but limited by the small sample size.

The incidence of ICH in our overall study population was consistent with what has been reported in recent studies, including results of the TITAN registry.[4,8,15,25] ICH of any size, regardless of symptoms associated, was seen in seven patients overall (33.3%); symptomatic ICH occurred in 1 patient (4.8%). There remains a discrepancy regarding the impact of both tPA administration and of CAS timing on ICH incidence. A 2019 study of 76 patients with cICA occlusions compared outcomes between patients who underwent acute CAS versus those who did not, reporting acute CAS to be independently associated with post procedure ICH as well as poor clinical outcomes, and no difference between the two groups in regards to reperfusion success rate.[12] However, IV thrombolytics were administered in approximately half of the patients within each group and outcomes were not compared between those who received tPA and those who did not. On the other hand, the TITAN collaboration data reported no impact of tPA administration on ICH rates in patients with tandem occlusions who underwent emergent stenting and reported a significantly higher reperfusion success rate among patients who underwent CAS compared to those who underwent MT only. This data did not include drug doses and administration time and the treatment strategy was left to the interventionalists discretion. Another study reported a series of 107 patients with ICAO and without tandem LVO who underwent emergent CAS and demonstrated a 6.5% rate of ICH. This study concluded that acute stenting is both safe and feasible; however, patients who received tPA were excluded from the study, and all included patients received 325 mg Aspirin and 600 mg Clopidogrel preoperatively, supporting our preferred approach.[8]

In our study, overall outcomes were similar between the two patient populations in regard to the primary outcome of functional status (mRS 0–2). Regarding complications, the most notable difference seen between the two groups was a higher rate of ICA reocclusion among the patients who received tPA compared to those who did not. The incidence of ICH following reperfusion was higher among the group that had not received tPA; however, the only symptomatic ICH was seen in the tPA group. The only mortality occurred in a patient who had received tPA, whose ICA reoccluded before performing staged CAS, and later went on to develop diffuse ICH.

Our patient population is very small to perform statistical analysis or derive solid conclusions. However, based on our institution's experience and the outcomes seen among patients treated with various approaches, it does not appear that tPA administration improves outcomes in this specific patient population. We think that it is critical to consider the potential benefit of withholding tPA when determining the optimal treatment for any patient presenting with AIS involving the cICA. The greatest benefit of withholding tPA in this clinical scenario is in the ability to administer loading doses of dual antiplatelet therapy before MT and administer heparin intraoperatively, setting the stage to optimally perform CAS at the time of MT. Staged stenting may be a reasonable option for patients who received tPA; however, the risk for stroke theoretically increases in the interval between initial MT and staged CAS, and this option inadvertently increases the length of hospital stay.

Numerous new trials are seeking answers to similar questions regarding intracranial LVO, but to the best of our knowledge, none of these will provide answers regarding the utility of thrombolysis in acute cICA occlusion, nor will they help establish guidelines regarding the safety of acute CAS following systemic thrombolytic therapy and the appropriate intraoperative and postoperative antiplatelet therapy in the setting of thrombolytic therapy. The SWIFT DIRECT trial (Bridging Thrombolysis vs. Direct MT in AIS) and Multicenter Randomized Clinical trial of Endovascular Treatment for AIS in the Netherlands excluded extracranial carotid occlusions, despite identifying that these lesions have an even lower response to thrombolytic therapy than more distally located thrombi.[13] Furthermore, this trial does not address the question of whether stroke patients arriving at facilities without endovascular treatment capabilities should be pretreated with IV-tPA versus directly referred to centers with endovascular capabilities. The Rescue Stenting for Failed Endovascular Thrombectomy in AIS trial attempts to better define the role and safety of acute CAS; however, this trial leaves all thrombolytic therapy and anti-platelet therapy regimens up to the discretion of the operator, leaving significant room for uncontrolled confounding variables. In the TITAN trial, while a form of dual antiplatelet therapy is administered in all experimental groups, tPA administration is nonstandard, and reocclusion rates are not reported. In addition, there have been multiple recent reports proposing the option of acute stenting on tPA with follow-up ASA/Plavix loading; however, the supporting data are greatly underpowered, with the largest series reporting on 12 patients.[3,6,24] Further investigation may establish the safety and feasibility of this option and should be explored.

We reviewed our institutional data during the same time frame as the study group. The average time from hospital arrival to CT completion was 24 min, average time from arrival to tPA administration was 63 min, and average time from arrival to CTA completion was 46 min. Based on these numbers, the decision to withhold tPA on patients with cervical carotid occlusion would not delay tPA administration to patients who are otherwise candidates.

Based on our experience and review of the literature, it would be reasonable to conduct a randomized prospective clinical trial, randomizing patients with acute cICA occlusion to receive either tPA or dual antiplatelet therapy before surgical revascularization, and compare outcomes between the two treatments.

This study has numerous limitations inherent to any retrospective study, specifically regarding the lack of randomization, and the confounding factors that impacted the treatment received. Given the current treatment guidelines, all patients who arrived within the safe tPA window and without contraindications received tPA. As such, the patients who did not receive tPA had a longer time from symptom onset to groin puncture on average (but this did not negatively impact outcomes). There was a 3-point difference in baseline NIHS score between the two populations; however, the change from baseline was equivocal between the two groups, as was the remainder of baseline demographics and comorbid disorders. Another significant limitation is the small sample size, limiting the conclusions that can be drawn from the small population, and only provide support for the need for a larger independent study.

CONCLUSION

Despite the small sample size, when comparing outcomes solely based on whether or not tPA was administered, our two cohorts of patients demonstrate relatively similar outcomes. Performing CAS acutely carries its advantages but is precluded by the administration of tPA. We suggest considering randomizing patients to tPA versus dual antiplatelet therapy with cICA occlusion in efforts to improve outcome in this subset of patients who suffer an AIS.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Anadani M, Spiotta A, Alawieh A, Turjman F, Piotin M, Steglich-Arnholm H, *et al.* Effect of extracranial lesion severity on outcome of endovascular thrombectomy in patients with anterior circulation tandem occlusion: Analysis of the TITAN registry. J Neurointerv Surg 2019;11:970-4.

2. Assis Z, Menon BK, Goyal M, Demchuk AM, Shankar J, Rempel JL, *et al.* Acute ischemic stroke with tandem lesions: Technical endovascular management and clinical outcomes from the ESCAPE trial. J Neurointerv Surg 2018;10:429-33.

3. Brandel MG, Elsawaf Y, Rennert RC, Steinberg JA, Santiago-Dieppa DR, Wali AR, *et al.* Antiplatelet therapy within 24 hours of tPA: Lessons learned from patients requiring combined thrombectomy and stenting for acute ischemic stroke. J Cerebrovasc Endovasc Neurosurg 2020;22:1-7.

4. Gory B, Haussen DC, Piotin M, Steglich-Arnholm H, Holtmannspötter M, Labreuche J, *et al.* Impact of intravenous thrombolysis and emergent carotid stenting on reperfusion and clinical outcomes in patients with acute stroke with tandem lesion treated with thrombectomy: A collaborative pooled analysis. Eur J Neurol 2018;25:1115-20.

5. Gunka I, Krajickova D, Lesko M, Jiska S, Raupach J, Lojik M, *et al.* Emergent carotid thromboendarterectomy for acute symptomatic occlusion of the extracranial internal carotid artery. Vasc Endovascular Surg 2017;51:176-82.

6. Han YF, Dai QL, Chen XL, Xiong YY, Yin Q, Xu GL, *et al.* Emergent loading dose of antiplatelets for stenting after IV rt-PA in acute ischemic stroke: A feasibility study. Int J Neurosci 2018;128:311-7.

7. Heck DV, Brown MD. Carotid stenting and intracranial thrombectomy for treatment of acute stroke due to tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage. J Neurointerv Surg 2015;7:170-5.

8. Jadhav A, Panczykowski D, Jumaa M, Aghaebrahim A, Ranginani M, Nguyen F, *et al.* Angioplasty and stenting for symptomatic extracranial non-tandem internal carotid artery occlusion. J Neurointerv Surg 2018;10:1155-60.

9. Kaesmacher J, Giarrusso M, Zibold F, Mosimann PJ, Dobrocky T, Piechowiak E, *et al.* Rates and quality of preinterventional reperfusion in patients with direct access to endovascular treatment. Stroke 2018;49:1924-32.

10. Kim YS, Garami Z, Mikulik R, Molina CA, Alexandrov AV, Collaborators C. Early recanalization rates and clinical outcomes in patients with tandem internal carotid artery/middle cerebral artery occlusion and isolated middle cerebral artery occlusion. Stroke 2005;36:869-71.

11. Matsumoto A, Kawai N, Yabuno S, Hirashita K, Yunoki M, Yoshino K. Treatment strategy for progressive cervical internal carotid artery stenosis under restriction of the use of antiplatelet drugs. World Neurosurg 2019;130:e438-43.

12. Min JH, Lee SJ, Hong JM, Choi JW, Kang DH, Kim YW, *et al.* Clinical impact of intracerebral hemorrhage after hyperacute extracranial stenting in patients with ischemic stroke. Neurointervention 2019;14:107-15.

13. Mokin M, Ansari SA, McTaggart RA, Bulsara KR, Goyal M, Chen M, *et al.* Indications for thrombectomy in acute ischemic stroke from emergent large vessel occlusion (ELVO): Report of the SNIS standards and guidelines committee. J Neurointerv Surg 2019;11:215-20.

14. Mpotsaris A, Kabbasch C, Borggrefe J, Gontu V, Soderman M. Stenting of the cervical internal carotid artery in acute stroke management: The Karolinska experience. Interv Neuroradiol 2017;23:159-65.

15. Papanagiotou P, Haussen DC, Turjman F, Labreuche J, Piotin M, Kastrup A, *et al.* Carotid stenting with antithrombotic agents and intracranial thrombectomy leads to the highest recanalization rate in patients with acute stroke with tandem lesions. JACC Cardiovasc Interv 2018;11:1290-9.

16. Pfaff JA, Maurer C, Broussalis E, Janssen H, Blanc R, Dargazanli C, *et al.* Acute thromboses and occlusions of dual layer carotid stents in endovascular treatment of tandem occlusions. J Neurointerv Surg 2019;12:33-7.

17. Rubiera M, Alvarez-Sabín J, Ribo M, Montaner J, Santamarina E, Arenillas JF, *et al.* Predictors of early arterial reocclusion after tissue plasminogen activator-induced recanalization in acute ischemic stroke. Stroke 2005;36:1452-6.

18. Schubert J, Witte OW, Settmacher U, Mayer TE, Günther A, Zanow J, *et al.* Acute stroke treatment by surgical recanalization of extracranial internal carotid artery occlusion: A single center experience. Vasc Endovasc Surg 2019;53:21-7.

19. Sultan-Qurraie A, Witt T, de Havenon A, Ribo M, Zaidat OO. SEIMLESS: Simultaneous extracranial, intracranial management of (tandem) lessions in stroke. J Neurointerv Surg 2019;11:879-83.

20. van de Graaf RA, Chalos V, Del Zoppo GJ, van der Lugt A, Dippel DW, Roozenbeek B. Periprocedural antithrombotic treatment during acute mechanical thrombectomy for ischemic stroke: A systematic review. Front Neurol 2018;9:238.

21. Vellimana AK, Washington CW, Yarbrough CK, Pilgram TK, Hoh BL, Derdeyn CP, *et al.* Thrombolysis is an independent risk factor for poor outcome after carotid revascularization. Neurosurgery 2018;83:922-30.

22. Wallocha M, Chapot R, Nordmeyer H, Fiehler J, Weber R, Stracke CP. Treatment methods and early neurologic improvement after endovascular treatment of tandem occlusions in acute ischemic stroke. Front Neurol 2019;10:127.

23. Warner JJ, Harrington RA, Sacco RL, Elkind MS. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke. Stroke 2019;50:3331-2.

24. Xian Y, Federspiel JJ, Grau-Sepulveda M, Hernandez AF, Schwamm LH, Bhatt DL, *et al.* Risks and benefits associated with prestroke antiplatelet therapy among patients with acute ischemic stroke treated with intravenous tissue plasminogen activator. JAMA Neurol 2016;73:50-9.

25. Zhu F, Bracard S, Anxionnat R, Derelle AL, Tonnelet R, Liao L, *et al.* Impact of emergent cervical carotid stenting in tandem occlusion strokes treated by thrombectomy: A review of the TITAN collaboration. Front Neurol 2019;10:206.