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Original Paper

Efficacy and Safety of Endovascular Treatment in Acute Tandem Carotid Occlusions: Analysis of a Single-Center Cohort

Santiago Fernández Menéndez[a] Eduardo Murias Quintana[b]
Pedro Vega Valdés[b] Edison Morales Deza[b] Elena López-Cancio[a]
Lorena Benavente Fernández[a] Montserrat González Delgado[a]
Maria Rico-Santos[a] Sergio Calleja Puerta[a] Davinia Larrosa Campo[a]

[a]Service of Neurology, University Hospital "Central de Asturias" and ISPA, Oviedo, Spain;
[b]Service of Radiology, University Hospital "Central de Asturias" and ISPA, Oviedo, Spain

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Ischemic stroke · Tandem occlusion · Carotid stenting · Mechanical thrombectomy

Abstract
Introduction: Acute ischemic strokes with tandem occlusions, which represent 10–20% of all ischemic strokes, have a particularly poor prognosis. Since emergent treatment of tandem lesions has not been specifically addressed in randomized trials, there is an absence of standardized management. ***Objective:*** We sought to assess the efficacy and safety of acute endovascular treatment in stroke due to tandem occlusions in our center and compare the results with previous reports. ***Methods:*** From a prospective registry we analyzed data of 99 consecutive patients (males: 77.7%, mean age ± SD: 67.5 ± 9.5 years) with stroke due to tandem occlusions who underwent treatment with emergent carotid stenting and intracranial mechanical thrombectomy. Successful recanalization was defined as a TICI score of 2b-3 and a good functional outcome was defined as a modified Rankin scale score ≤2 at 90 days. Symptomatic intracranial hemorrhage (sICH) was considered when associated with worsening on the National Institutes of Health Stroke Scale (≥4 points). ***Results:*** A successful recanalization rate was achieved in 87.8 and 48.5% of the patients had a good functional outcome. sICH and mortality rates were 12.1 and 20.2%, respectively, and 21.2% of the patients received combined treatment with intravenous thrombolysis, which did not affect neither the prognosis nor the recanalization or sICH rates. The time from symptom onset to recanalization and the

Davinia Larrosa Campo
Service of Neurology, University Hospital "Central de Asturias" and ISPA
Avenida Roma s/n
ES–33011 Oviedo (Spain)
davinialc@gmail.com

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degree of recanalization were the main factors associated with prognosis and the occurrence of sICH. ***Conclusions:*** Our results suggest that endovascular treatment with emergent carotid stenting and intracranial thrombectomy in patients with acute stroke due to tandem occlusions is an effective and safe procedure.

Introduction

Acute ischemic stroke due to tandem occlusion, defined as occlusion or high-grade stenosis of the cervical internal carotid artery (ICA) with concurrent embolic occlusion of a major intracranial vessel, either the terminal ICA (tICA) or the proximal middle cerebral artery (MCA), accounts for 10–20% of all ischemic strokes. This subtype of stroke has a high incidence of thrombotic complications and a poor prognosis. Without treatment, different studies estimate that 40–69% of patients survive with severe disability or die [1]. Intravenous (i.v.) thrombolysis treatment with recombinant tissue plasminogen activator (rt-PA) achieves a recanalization rate of 9% with a 30% favorable outcome rate and a 22% mortality rate at 3 months [2–4]. Following the publication of several randomized clinical trials, current treatment guidelines recommend the administration of rt-PA followed by endovascular treatment [5]. However, in these studies, there was scarce representation of patients with tandem occlusions. Endovascular treatment of patients with tandem occlusions has been mostly reported in small and retrospective single-center studies, meaning that there is a lack of evidence for the management of this subtype of stroke.

We present the results of a series of 99 consecutive patients with acute stroke due to atherothrombotic tandem occlusions treated in our center with acute ICA stenting and intracranial thrombectomy and analyze the results in terms of efficacy and safety compared with those already published in the literature.

Material and Methods

Patient Enrollment

This is a single-center study in which we review the prospective database of patients with ischemic stroke treated in our center from January 2011 to February 2018. Patients meeting the following criteria were included: (1) acute ischemic stroke, (2) age over 18 years, (3) time from symptom onset <4.5 h up to June 2015 and <6 h thereafter (according our institutional acute stroke management protocol), (4) carotid tandem occlusion, and (5) acute endovascular treatment with angioplasty and stent placement in the cervical ICA and intracranial thrombectomy. ICA occlusions due to artery dissection were excluded.

We collected the following data: demographic variables; vascular risk factors; previous antithrombotic therapy; admission National Institutes of Health Stroke Scale (NIHSS) score; baseline blood glucose and blood pressure; Alberta Stroke Program Early CT Score (ASPECTS); angiographic findings; time from symptom onset to thrombolysis, to arterial puncture, and to the end of endovascular procedure; prior use of i.v. rt-PA; and technique and type of device.

Endovascular Treatment

Endovascular treatment was performed using an antegrade approach and conscious sedation as the first choice. This involves, initially, direct aspiration of the carotid obstruction and simple angioplasty (Ultrasoft 5 × 20 mm) to facilitate access to the intracranial occlusion. Subsequently, the guide catheter with a balloon is advanced through the carotid stenosis

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(concentric 8 Fr), followed by extraction of the intracranial thrombus using a stent retriever (Solitaire FR Covidien-EV3) accompanied by aspiration from the guide catheter. Last of all, a stent is implanted across the cervical carotid lesion (Wallstent; Stryker-Boston Scientific). In patients without prior antiplatelet therapy, 1 g of intravenous lysine acetylsalicylate is administered. Recanalization was assessed according to the Thrombolysis in Cerebral Infarction (TICI) scale, considering a score of 2b or 3 as complete revascularization [6].

Follow-Up Neuroimaging and Antithrombotic Treatment

To assess the infarction volume and hemorrhagic status, all of the patients underwent a follow-up CT performed 24 h after the acute therapy or earlier in case of neurological decline. After exclusion of intracranial hemorrhage, patients were started on dual antiplatelet therapy with oral acetylsalicylic acid at 100 mg and clopidogrel at 75 mg daily, with or without a loading dose at the discretion of the responsible neurologist.

Objectives

To determine the efficacy of the treatment, the clinical outcome at 3 months was analyzed according to the modified Rankin Scale (mRS) score, considering a score of 0–2 as a good functional outcome.

Safety endpoints were symptomatic intracranial hemorrhage (sICH) and all-cause mortality at 90 days. Intracranial hemorrhagic bleeds were classified as hemorrhagic infarction (HI1 and HI2) or parenchymal hematoma (PH1 and PH2) according to the definition of the ECASS II study, considering as sICH those that led to clinical deterioration, as defined by an increase ≥4 points on the NIHSS [7].

Statistical Analysis

Continuous variables were described as means (±SD) if the distribution was normal or otherwise as medians (IQR). Categorical variables were described as proportions. In the univariate analysis, Fisher's exact test, Student's t test, and the Mann-Whitney U test were used. Subsequently, a multivariate analysis was performed using Firth's logistic regression for the prognosis and logistic regression in the case of sICH and mortality rate. For this analysis, variables with a $p < 0.05$ in the univariate analysis were included. $p < 0.05$ was considered statistically significant. The data was analyzed using Rx64.3.5 software (www.r-project.org).

Results

During the recruitment period 128 patients with acute ischemic stroke due to tandem occlusions underwent endovascular treatment. Fifteen patients were excluded due to occlusion secondary to dissection and 14 patients for unknown symptom onset. The remaining 99 patients were included in the analysis.

The mean age (±SD) was 67.5±9.5 years, and 77 (77.7%) of the patients were male. The median baseline NIHSS score was 15 [8–15]. Bridging therapy with i.v. rt-PA was administered in 21 patients (21.2%). Intracranial occlusion sites were the tICA in 36 patients (36.4%) and MCA in 63 (63.6%). The mean time (±SD) from symptom onset to arterial puncture was 207.1 ± 88.1 min, without significant differences between bridging therapy and direct endovascular treatment. Other characteristics of the patients are shown in Table 1.

A favorable angiographic result (TICI 2b-3) was achieved in 87.8% of the patients. Comparison of patients with and without successful recanalization showed no significant differences between the 2 groups. Forty-eight patients (48.5%) achieved a good functional

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Table 1. Description of the sample

Characteristic	Value
Age, years	67.55±9.5
Males	77 (77.7)
HBP	64 (64.5)
Diabetes	26 (26.3)
Dyslipidemia	58 (58.6)
Smokers	56 (56.6)
Previous CVA/TIA	17 (17.2)
Coronary heart disease	13 (13.1)
Antithrombotic therapy	42 (42.4)
ASA	26 (26.3)
Clopidogrel	2 (2.1)
ASA + clopidogrel	1 (1)
VKA	8 (8.1)
DOAC	2 (2.1)
LMWH	3 (3.1)
NIHSS	15 (13–20)
ASPECTS	8 (8–9)
Tandem occlusion	99 (100)
tICA	36 (36.4)
MCA	63 (63.6)
MCA1	47 (47.5)
MCA2	16 (16.1)
i.v. fibrinolysis, %	21 (21.2)
Time from symptom onset to arterial puncture, min	207.12±88.1
Time from symptom onset to recanalization, min	263.78±89.3
Complete arterial recanalization	87 (87.8)
Blood glucose, mg/dL	134.34±55.1
Systolic BP, mm Hg	152.42±29.8
Diastolic BP, mm Hg	82.96±21.3

The total number of patients is 99. Values are presented as means ± SD, medians (IQR), or numbers (%). HBP, high blood pressure; CVA, cerebrovascular accident (stroke); TIA, transient ischemic attack; ASA, acetylsalicylic acid; VKA, vitamin K antagonists; DOAC, direct oral anticoagulants; LMWH, low-molecular-weight heparin; BP, blood pressure.

prognosis at 3 months. Univariate analysis showed that a younger age, the absence of diabetes, a lower admission NIHSS score, a shorter time from symptom onset to arterial puncture and to arterial recanalization, successful recanalization, no sICH, and a lower baseline blood glucose were associated with a good functional prognosis (Table 2). In multivariate analysis, a younger age, no history of diabetes, a lower admission NIHSS score, a shorter time from symptom onset to arterial recanalization, successful recanalization, and a lower baseline blood glucose were independent predictors of a favorable outcome (Table 3).

sICH occurred in a total of 12 patients (12.1%), mainly in the first 24 h after the procedure (70.7%). In the univariate analysis sICH were associated with a lower ASPECTS and delayed recanalization, whereas prior i.v. rtPA was not (Table 2). In the multivariate analysis, delays from symptom onset to arterial puncture and to arterial recanalization were independently associated with sICH (Table 3).

At 3 months, 20 (20.2%) patients had died. Univariate analysis showed that older age, a history of coronary heart disease, a higher NIHSS score, lower values on the ASPECTS, no recanalization, and a longer time until recanalization were associated with a higher mortality

Table 2. Univariate analysis

	mRS 0–2		sICH		mRS 6	
	yes (*n* = 48)	no (*n* = 51)	yes (*n* = 12)	no (*n* = 87)	yes (*n* = 19)	no (*n* = 80)
Age, years	**64.8±9.2**	**70.2±9.1***	67.4±9.7	68.4±7.7	**71.3±8.5**	**66.6±9.5***
Males	39 (81.2)	38 (74.5)	9 (75.0)	68 (78.1)	14 (73.7)	63 (78.7)
HBP	29 (60.4)	35 (68.6)	8 (66.7)	56 (64.3)	15 (78.9)	49 (61.2)
Diabetes	**8 (16.6)**	**18 (35.3)***	5 (41.7)	21 (24.1)	6 (31.6)	20 (25.0)
Dyslipidemia	28 (58.3)	30 (58.8)	8 (66.7)	50 (57.5)	9 (47.4)	49 (61.2)
Smoking	27 (56.2)	29 (55.8)	8 (66.7)	48 (55.1)	12 (63.2)	44 (55.0)
Previous CVA/TIA	7 (14.6)	10 (19.6)	1 (8.3)	16 (18.4)	3 (15.8)	14 (17.5)
Coronary heart disease	4 (8.3)	9 (17.6)	1 (8.3)	12 (13.8)	**6 (31.6)**	**7 (8.7)***
Antithrombotic treatment	21 (43.7)	21 (41.2)	6 (50.0)	36 (41.3)	**12 (63.2)**	**30 (37.5)***
NIHSS	**15 (13–18)**	**18 (13–21)***	15 (13–15)	16.5 (11–21)	**21 (14–23)**	**15 (13–19)***
ASPECTS	8 (8–9)	9 (8–9)	8 (8–9)	8 (7–9)	8 (7–9)	9 (8–9)
i.v. fibrinolysis	11 (22.9)	10 (19.6)	3 (25.0)	18 (20.7)	3 (15.8)	18 (22.5)
Time from symptom onset to arterial puncture, min	**186.5±69.1**	**230.9±101.61***	**270.1±116.3**	**197.6±79.8***	218.7±99.8	204.6±85.9
Time from symptom onset to recanalization, min	**242.1±80.3**	**291.6±93.8***	**340.9±106.2**	**250.1±79.4***	**302.1±82.9**	**255.5±89.1***
Complete recanalization	48 (100)	39 (76.5)*	10 (83.3)	77 (88.5)	**14 (73.7)**	**73 (91.2)***
Blood glucose, mg/dL	**118.8±35.4**	**148.9±65.6***	**130.1±50.8**	**165.6±74.6***	151.8±66.3	130.2±51.5
Systolic BP, mm Hg	153.7±25.1	151.3±33.6	152.9±30.8	148.9±22.7	156.2±30.4	151.5±29.8
Diastolic BP, mm Hg	84.4±15.8	81.7±15.1	83.01±22.1	82.5±14.8	88.1±36.3	81.7±15.6

Values are presented as means ± SD, medians (IQR), or numbers (%). HBP, high blood pressure; TIA, transient ischemic attack; BP, blood pressure. * $p < 0.05$.

Table 3. Multivariate analysis

	OR	95% CI	*p*
mRS 0–2			
Age	0.94	0.85–0.99	0.048
Diabetes	0.18	0.04–0.78	0.022
NIHSS	0.80	0.69–0.93	0.004
Time from symptom onset to arterial puncture	1.00	0.97–1.02	0.772
Time from symptom onset to recanalization	0.99	0.97–0.99	0.030
Complete recanalization	43.27	1.01–1,839.92	0.049
Blood glucose	0.98	0.97–1.00	0.010
Symptomatic intracranial hemorrhage			
Age	0.98	0.96–1.01	0.244
Time from symptom onset to arterial puncture	1.04	1.01–1.07	0.035
Time from symptom onset to recanalization	1.03	1.01–1.05	0.002
Mortality			
Age	1.21	1.02–1.55	0.07
Coronary heart disease	12.68	1.64–113.79	0.017
Antithrombotic therapy	2.92	0.48–22.70	0.260
NIHSS	1.25	1.03–1.58	0.038
Time from symptom onset to arterial puncture	1.01	1.00–1.02	0.025
Complete recanalization	0.01	0.00–0.14	0.003

rate (Table 2). In multivariate analysis, coronary heart disease, a higher NIHSS score, a longer time from symptom onset to arterial recanalization, and no recanalization were independently associated with mortality (Table 3).

Discussion/Conclusion

Although ischemic strokes due to cervical ICA occlusion have a poor prognosis, with high percentages of patients in a situation of dependency and a high mortality rate, this type of stroke has been poorly represented in randomized clinical trials (32.3% in MR CLEAN, 18.6% in REVASCAT, 17% in ESCAPE, and excluded in the SWIFT PRIME and EXTEND-IA studies). As a consequence, consensus on the therapeutic approach to maximize recanalization success while minimizing treatment-related complications continues to be the subject of debate. The results of our study suggest that endovascular treatment of acute stroke due to tandem occlusions, by means of an antegrade approach with angioplasty, intracranial mechanical thrombectomy, and implantation of a cervical stent, is an effective and safe technique.

With a good clinical outcome of 48.5% at 3 months, our results are similar to those of previous reports [16–20], mostly nonrandomized, small, and retrospective single-center studies, in which a favorable prognosis is described in 36–64% of the patients. These results are also in line with those reported in acute ischemic stroke with isolated intracranial occlusions [8]. Similar data were reported in 2 recent meta-analyses, with rates of 53% for good clinical outcome at 3 months (95% CI 43–62) in the study of Sadeh-Gonik et al. [9] and 44% (95% CI 33–55) in the study of Sivan-Hoffmann et al. [10]. Lastly, a subanalysis of the ESCAPE study in patients with tandem occlusions showed a favorable outcome at 3 months in 60% of the cases [11].

In our series, successful arterial recanalization was an independent predictor of a good clinical outcome and of a reduction in mortality rates. Compared to rt-PA treatment alone, with recanalization rates <10% in patients with tandem occlusion [2], the percentage of patients with complete recanalization is far superior after endovascular treatment. In our study, the complete arterial recanalization rate was 87.8%, similar to previous reports in which rates of 83–94% were found [8, 12–14, 20] and consistent with a recent meta-analysis that reported a rate of 78% (95% CI 73–82) [15]. Overall, it is considered that successful recanalization increases the likelihood of a good functional prognosis by 4.4 times and decreases the mortality rate by up to 4-fold [21].

The rate of sICH in our study was 12.1%, with longer times from symptom onset to arterial puncture and to arterial recanalization being independent risk factors for its occurrence. A higher admission NIHSS score, a longer time to recanalization, and the absence of arterial reperfusion were found to be independent risk factors for death, with a mortality rate in our series of 20.2%. These results are in agreement with those previously reported, which describe sICH rates of 5–15% and mortality rates of 13.2–22% [8, 12, 16–18, 22], and they also similar to those published in 2 recent meta-analysis that reported an sICH rate of 7% and a mortality rate of 13–14% [9, 10]. Likewise, a recent study found no differences in terms of hemorrhagic complications between patients presenting with an isolated intracranial occlusion compared to tandem occlusions, even after administration of antiplatelet therapy [23]. However, other authors have described an increased rate of sICH among patients with tandem occlusions treated with emergent stenting [11, 15, 24]. In this clinical setting an individualized approach to treatment is mandatory.

Currently, acute stroke treatment guidelines recommend administration of i.v. thrombolysis in every eligible patient, regardless of the endovascular approach [5]. Emergent stenting of tandem occlusions implies a particularly significant risk of bleeding as early antiplatelet therapy is indicated for the prevention of rethrombosis [14]. In our study, the clinical outcome at 3 months, the rate of arterial recanalization, and the appearance of hemorrhagic complications were not affected by prior treatment with rt-PA, whereas a longer time from symptom onset to arterial puncture and the degree of arterial recanalization were associated with a worse prognosis and an increased risk of sICH and death. i.v. thrombolysis may delay the start of endovascular treatment, as reflected in the results of the ESCAPE study [25], among others. This is why many authors question the indication of prior administration of rt-PA, with a very low probability of success and increased risk of bleeding, when endovascular treatment is readily available, as is the case in our center.

Unlike elective carotid artery stenting in secondary stroke prevention for patients with significant carotid stenosis, which is widely accepted as an alternative to endarterectomy, the endovascular approach in the acute treatment of ICA occlusion remains unclear. Angioplasty and stent implantation in the acute phase improves the collateral flow in the penumbra tissue, facilitates access to the intracranial occlusion, and directly treats the extracranial lesion, reducing the risk of reembolisation and restenosis. In fact, despite the potential risks, a comparative study between simple angioplasty and stent implantation in patients with tandem occlusions treated in the acute phase showed no differences in terms of clinical outcomes, mortality, or recanalization rates [15].

Our study has several limitations. This was a nonrandomized study of a single center compared with those published in the medical literature. In addition, the heterogeneity in the inclusion criteria, etiology, and endovascular techniques used in previous published data and ours makes comparisons and result extrapolation difficult. However, the main advantage is the homogeneity in the endovascular technique across the sample, always performed by the same experienced interventional neuroradiologists, which minimizes differences related to distinct approaches and to the learning curve.

Our study suggests that endovascular treatment with ICA stenting and intracranial thrombectomy in patients with acute stroke due to tandem occlusion is an effective and safe procedure. The results of our series show that prior administration of rt-PA does not affect the functional outcome, while delayed treatment initiation and absence of recanalization are the main risk factors for a poor prognosis and hemorrhagic complications. Randomized studies are needed to confirm our results and to established evidence-based guidelines for the management of emergent ischemic stroke with tandem occlusion.

Statement of Ethics

All of the patients or their legal representatives provided written informed consent. The ethics committee of our hospital accepted the treatment protocol, the study, and the publication of this work.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

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Author Contributions

Santiago Fernández Menéndez: data collection, analysis, and interpretation; critical revision; and approval of the final version of this work. Eduardo Murias Quintana and Sergio Calleja Puerta: responsibility for the integrity of this study, analysis and interpretation of data, critical revision, and approval of the final version of this work. Pedro Vega Valdés, Edison Morales Deza, Elena López-Cancio, Lorena Benavente Fernández, Montserrat González Delgado, and María Rico-Santos: analysis and interpretation of data, critical revision, and approval of the final version of this work. Davinia Larrosa Campo: responsibility for the integrity of this study, study design, data collection, analysis and interpretation of data, statistical analysis, literature research, text writing, critical revision, and approval of the final version of this work.

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