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Very Early Carotid Endarterectomy After Intravenous Thrombolysis

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WHAT THIS PAPER ADDS

The timing of carotid endarterectomy (CEA) after intravenous thrombolysis is a controversial issue. Some reports indicate that the surgery soon after thrombolytic therapy is safe. This case series suggests that CEA could be performed very early after thrombolysis, to reduce the risk of recurrence and to save the ischaemic penumbra and improve clinical outcome.

Objective/Background: The timing of carotid endarterectomy (CEA) after thrombolysis is still a matter of debate. The aim of this study was to analyse a cohort of patients undergoing urgent endarterectomy after intravenous thrombolysis for acute ischaemic stroke.

Methods: This was an observational study. Prospective databases were reviewed and matched to identify patients who underwent CEA early after intravenous thrombolysis (2009–14). The focus was carotid surgery performed within 12 hours of stroke onset in patients with a high grade ($\geq$70%) symptomatic carotid stenosis, associated with vulnerable plaques or stroke in evolution, and evidence of a significant salvageable ischaemic penumbra on perfusion computed tomography scan. Demographic and clinical information, as well as data on relevant outcomes were extracted.

Results: Thirty four consecutive stroke patients who underwent CEA within 2 weeks of thrombolysis for acute ischaemic stroke and ipsilateral high grade carotid stenosis were identified. In 11 patients the surgical procedure was performed within 12 hours of the onset of symptoms. All patients showed a clinical improvement after combined treatment. The 3 month outcome was favourable (modified Rankin Scale $\leq$ 2) in 10 patients. No haemorrhagic complications were registered. There was neither peri-operative stroke nor stroke within 3 months of surgery. One patient died from acute myocardial infarction 3 days after intervention.

Conclusion: This experience suggests that very early CEA after thrombolysis, aimed at removing the source of potential embolisation and restoring blood flow, may be safe and can lead to a favourable outcome.

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INTRODUCTION

Intravenous (IV) thrombolysis for hyperacute ischaemic stroke treatment is accepted worldwide.[1,2] The major risk of IV recombinant tissue plasminogen activator (rtPA) treatment remains intracerebral haemorrhage.[1,2] Although the half-life of rtPA is very short, the effect on the coagulation pathway seems to be prolonged.[3]

The role of carotid endarterectomy (CEA) for severe carotid stenosis is widely established.[4–7] Evidence suggests that the greatest benefit of surgery in reducing the risk of recurrent stroke is in the first 2 weeks after the index event,[6,7] and the sooner CEA is performed the higher its preventive role.[8] Timely cerebral reperfusion, and the prevention of early recurrent strokes and distal embolism from carotid plaques are key factors in treating patients who have severe ipsilateral internal carotid artery stenosis (CAS). Safety issues, mostly related to the risk of intracerebral haemorrhage and reperfusion injury, are also of great importance for successful interventions.

Although early CEA following thrombolysis seems to be safe,[9–16] the best timing of surgery after IV thrombolysis (IVT) is still a matter of debate. In particular, few data are available on urgent CEA, aimed not only at reducing the risk of recurrence, but also at achieving neurological improvement by reperfusion of the ischaemic penumbra.

The aim of this study was to analyse a cohort of patients with acute ischaemic stroke undergoing CEA within 12 hours of symptoms onset.

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METHODS

The prospective databases of thrombolysis and carotid surgery of the (Azienda Ospedaliera-Universitaria, Ferrara, Ferrara-Cona, Italy) were reviewed (2009–14) in order to identify patients with stroke and CAS who underwent IVT, and CEA after IVT. All patients were treated with IV rtPA according to national and international guidelines.[17,18] The protocol adopted for IVT is summarised in Table 1. Thereafter, patients with CAS > 50% (North American Symptomatic Carotid Endarterectomy Trial method[5]) on the symptomatic side were considered for CEA within 2 weeks. Of these, patients with high grade symptomatic carotid stenosis (≥70%) associated with vulnerable plaques (i.e., soft plaques, intraplaque haemorrhage, or ulcerated surface) and/or patients with stroke in evolution, underwent CEA within 12 h, provided that the neuro-radiological criteria for IVT were fulfilled (no evidence of haemorrhagic transformation and an Alberta Stroke Program Early CT Score [ASPECTS] score > 7). Perfusion computed tomography (CT) scan evidence of a significant salvageable ischaemic penumbra was also a requirement for very early CEA after IVT.

According to protocol, patients with symptomatic carotid stenosis ≥70%, with stable plaques (defined as plaques with a regular and smooth surface, and uniform and homogeneous echogenicity) and neurological status were scheduled to undergo CEA between 12 and 48 h, while patients with carotid stenosis ≥60% and stable plaques were treated within 14 days, according to the current guidelines. Finally, those with stenosis between 50% and 60% associated with uncomplicated plaques ($n = 7$), patients with complete occlusion ($n = 18$), and patients at high operative risk were treated with IVT only ($n = 3$). To exclude haemorrhagic transformation, all patients routinely underwent brain CT after rtPA infusion.

A panel consisting of a neurologist, a neuro-radiologist, and a vascular surgeon discussed the therapeutic approach and the timing of CEA for each patient.

All surgical procedures were performed under general anaesthesia by experienced vascular surgeons. A temporary vascular indwelling *shunt* was used routinely, and a bolus of 5000 units of unfractionated heparin was given before carotid clamping. The longitudinal arteriotomy was closed by primary closure or prosthetic patch. Resection of the vessel,

Table 1. Intravenous thrombolysis (IVT) and carotid endarterectomy (CEA) protocol for acute ischaemic stroke.

IVT	
Inclusion criteria	Age 18–80 y
	Ischaemic stroke with a measurable neurological deficit
	Onset of symptoms within 4.5 h
Exclusion criteria	Unknown time of symptom onset
	Minor or rapidly improving symptoms
	Severe stroke as assessed clinically (stupor or coma, NIHSS score > 25) or ASPECTS ≤ 7
	History or evidence of intracranial haemorrhage, clinical suspicion of subarachnoid haemorrhage
	Seizure at the onset of stroke
	Stroke or serious head trauma within the previous 3 months
	Previous stroke and diabetes mellitus
	Known intracranial arteriovenous malformation, neoplasm, or aneurysm
	Major surgery or severe trauma within the previous 3 months
	Use of heparin within the previous 48 h, with prolonged APTT, oral anticoagulant treatment (INR > 1.7)
	Platelet count <100,000/mm^3, disorders associated with an increased risk of bleeding
	Systolic pressure >185 mmHg or diastolic pressure >110 mmHg, or aggressive treatment necessary to reduce blood pressure to these limits
	Blood glucose <50 mg/dL or >400 mg/dL
	Recent (<10 days) traumatic external heart massage, obstetrical delivery, or puncture of a non-compressible blood vessel
	Manifest or recent severe or dangerous bleeding, bacterial endocarditis, pericarditis, acute pancreatitis, ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial aneurysm, arterial/venous malformation, neoplasm with increased bleeding risk, severe liver disease
Treatment	IV rTPA, 0.9 mg/kg (upper dosage 90 mg), 10% administered as a bolus, the remainder by continuous infusion over 1 h
Early CEA	
General criteria	No evidence of haemorrhagic transformation, and ASPECTS score >7 after IVT
Timing	As soon as possible within 12 h: high grade symptomatic carotid stenosis (≥70%), vulnerable plaques and/or stroke in evolution. Evidence of significant ischaemic penumbra on perfusion CT scan Between 12 and 48 h: high grade symptomatic carotid stenosis (≥70%), stable plaque, and neurological condition After 48 h and within 14 d: carotid stenosis ≥60% and stable plaque

Note. NIHSS = National Institutes of Health Stroke Scale; ASPECTS = Alberta Stroke Program Early CT Score; APTT = activated partial thromboplastin time; INR = international normalised ratio; IV = intravenous; rTPA = recombinant tissue plasminogen activator; CT = computed tomography.

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eversion endarterectomy, and re-implantation of the internal carotid artery on the common carotid artery were performed with kinked or coiled internal carotid arteries. Intra-operative Doppler was always used after CEA, to evaluate the patency of the vessel.

For each patient the following variables were extracted: demographic data; personal history with particular reference to vascular risk factors; clinical and laboratory data at admission, including the National Institutes of Health Stroke Scale (NIHSS) score; time from onset to hospital admission and to treatment; and the results of routine diagnostic examinations, which included brain CT, CT angiography (CTA) of extra- and intra-cranial vessels, CT perfusion, and carotid duplex ultrasonography (DUS). ASPECTS was assessed at the time of the initial CT scan examination.[19] Follow up information for all patients included NIHSS score after thrombolysis, at 24 h, and at 7 days; the results of the brain CT scan performed after thrombolysis, in the case of clinical deterioration; and, after CEA, clinical data (NIHSS and modified Rankin Scale [mRS]) at 30 days and 3 months; and post-surgical carotid DUS examination. mRS $\leq$2 was defined as a favourable outcome. All patients were admitted to the Stroke Unit of Azienda Ospedaliera-Universitaria, where a neurologist recorded the clinical data. The same neurologist collected the follow up information.

Statistical analysis

Continuous data were reported as mean $\pm$ SD. A paired sample *t* test was used to compare means at baseline and after therapy.

The study was approved by the local ethics committee. Patients gave their informed consent for intervention and analysis of aggregate data.

RESULTS

Between October 2009 and September 2014, 34 consecutive patients underwent CEA after IVT for acute ischaemic stroke, and 28 consecutive patients with stroke and internal carotid stenosis were treated only with IVT. The characteristics of the study patients and their outcome are summarised in Table 2. Eleven men underwent CEA within 12 h, according to the above reported criteria. Nine had stenosis >90% and a stroke in evolution; two had an unstable carotid plaque. The mean age of the patients was 67.9 $\pm$ 10.7 years (range 40.0—80.0 years). Mean NIHSS at admission was 10.0 $\pm$ 6.3 (range 6.0—23.0). At baseline, all patients had either a negative brain CT or minor hyperacute ischaemic changes: ASPECTS score was 10 in eight patients, 9 in two, and 8 in one. CTA showed high grade symptomatic CAS, and perfusion CT detected evidence of a significant ischaemic penumbra in all patients. Mean NIHSS after thrombolysis was 7.5 $\pm$ 2.0.

Neurological examination at 24 hours showed clinical improvement in all patients, six of whom experienced an improvement of at least 4 points on the NIHSS. The mean NIHSS at 24 hours was 5.0 $\pm$ 3.8, significantly lower than both the mean baseline score ($p < .001$) and the score after IVT ($p < .01$). All patients received antiplatelet medication (aspirin or clopidogrel) after 24 h.

Post-operative CT scans were negative for haemorrhagic transformation. There were neither peri-operative complications nor stroke within 3 months of CEA.

One patient died from acute myocardial infarction 3 days after CEA. This patient's post-operative NIHSS score was 2. After 3 months, the mRS was 0—1 in nine patients, and 2 in one patient. On the whole, 10 patients had a good outcome. One patient survived with moderate disability (mRS 3).

Table 2. Demographic, clinical, and outcome data of patients with stroke and carotid artery stenosis who underwent intravenous thrombolysis (IVT).

	IVT (*n* = 28)	IVT—CEA within 12 h (*n* = 11)	IVT—CEA > 12 h < 48 h (*n* = 11)	>48 h, within 14 d (*n* = 12)
Sex (*n*)	20 M, 8 F	11 M	7 M, 4 F	8 M, 4 F
Age (y)	69.3 $\pm$ 11.0	67.9 $\pm$ 10.7	65 $\pm$ 12.7	68 $\pm$ 7.3
Onset to needle time (min)	170 $\pm$ 45	167 $\pm$ 50	175 $\pm$ 60	172 $\pm$ 58
Thrombolysis to CEA time (min)	NA	253 $\pm$ 108	30 h (10:20)	8.0 $\pm$ 1.8 d
Onset to CEA time (min)	NA	455 $\pm$ 162	34:20 h (10:40)	8.0 $\pm$ 1.9 d
NIHSS at onset	16.8 $\pm$ 6.0	10.0 $\pm$ 6.3	13.2 $\pm$ 8.6	7.0 $\pm$ 2.5
NIHSS after thrombolysis	13.6 $\pm$ 6.0	7.5 $\pm$ 1.9	12.0 $\pm$ 6.5	5.0 $\pm$ 2.3
NIHSS at 24 h	11.8 $\pm$ 8.0	5.0 $\pm$ 3.8	11.6 $\pm$ 7.6	4.8 $\pm$ 3.4
30 d mRS 0—2 (*n*)	8	10	5	8
3 mo mRS 0—1 (*n*)	5	9	3	6
3 mo mRS 0—2 (*n*)	9	10	7	8
Death (*n*)	1	1	0	0
Haemorrhagic transformation after IVT (*n*)	8	0	2	1
Petechial	6	0	1	1
Hematoma	2	0	1	0
sICH[a]	0	0	0	0
Cerebral bleeding after CEA	NA	0	0	0

Note. Data are mean $\pm$ SD unless otherwise indicated. CEA = carotid endarterectomy; M = male; F = female; NA = not applicable; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; sICH = symptomatic cerebral haemorrhage.

[a] Increase of $\geq$4 NIHSS points from baseline, or from the lowest score, or leading to death.

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Regarding the remaining patients, 11 underwent carotid surgery later than 12–48 hours after onset, and 12 had carotid surgery after 48 h–14 days (Table 2). The first group included seven men and four women, who had a mean age of 65.0 ± 12.7 years, a mean NIHSS score of 13.2 ± 8.6 at baseline and 11.6 ± 7.6 at 24 h. Two patients presented with asymptomatic haemorrhagic transformation after IVT. Overall, seven patients (63.6%) had a favourable 3 month outcome. The second group of patients (eight men, four women), treated >48 h–14 days after onset, had a mean age of 68.0 ± 7.3 years, and a mean NIHSS score of 7.0 ± 2.5 at admission and 5.0 ± 2.3 after IVT. Eight (66.6%) reported a favourable outcome after 3 months follow up. Neither NIHSS changes nor recurrences after CEA, were recorded in either group. Finally, data were recorded for 28 patients (20 men, 8 women), with a mean age of 69.3 ± 11.0 and a mean NIHSS at baseline of 16.8 ± 6.0, who underwent IVT therapy without subsequent CEA. The outcomes of these patients are reported in Table 2.

DISCUSSION

The timing of CEA after acute stroke remains a controversial issue; the greatest benefit of surgery in reducing the risk of future stroke seems to be in the first 2 weeks after the index event.[6,7] Some authors have suggested performing CEA as soon as possible in order to reduce the risk of a new ischaemic cerebrovascular event occurring.[7,20] However, along with the preventive role of carotid surgery, a therapeutic effect in the hyperacute phase could be expected by revascularisation of the ischaemic penumbra.[9] To achieve this goal, CEA should be performed within an appropriate time frame. Thus, an aggressive combined approach of IVT and very early carotid surgery has been adopted in selected patients with hyperacute ischaemic stroke with ipsilateral high grade carotid stenosis with evidence of a salvageable ischaemic penumbra.

There are few reports considering CEA after IVT. A systematic review included 77 patients who underwent CEA following thrombolysis,[12] and the pooled analysis of data showed an overall 30 day post-operative haemorrhagic risk of 3% (2/77), while the 30 day post-operative morbidity was 4%, mostly represented by bleeding from the wound, without post-operative recurrences or mortality. More recently, a nationwide Swedish study of 79 patients receiving IV thrombolysis followed by CEA ($n = 71$) or carotid stenting ($n = 6$) found a 30 day risk of recurrent stroke of 2.5%, without intracranial haemorrhagic complications or deaths, while the most frequent complication was surgical bleeding (3.8%).[16] A retrospective registry based, case controlled study analysed 202 patients who had IVT prior to surgery, with a median time from onset of stroke to CEA of 12 days, and found that the 30 day combined stroke and death rate was 3.5%, similar to that observed for patients who underwent CEA alone.[14]

The safety of CEA after thrombolysis was substantially confirmed by Mandavia et al.,[15] whose meta-analysis included 114 patients with stroke who underwent CEA ≤14 days after thrombolysis: the authors found a stroke or death rate similar to that of the operation without thrombolysis.[15] Only six patients underwent surgery within 12 hours of symptom onset (Table 3). Five were treated within 5 hours (mean 170 ± 94 minutes): three experienced an improvement of at least 4 points on the NIHSS; one presented with a basal ganglia haematoma. The final outcome was favourable for three patients. Finally, one patient reported by McPherson et al. was treated after 6 hours, and the outcome was good, with an improvement of 19 points on the NIHSS and no peri-operative complications or recurrent vascular events.[9]

Table 3. Studies evaluating patients treated with intravenous thrombolysis and subsequent carotid endarterectomy.

Study (first author, year)	Patients (*n*)	Patients treated within 12 h
McPherson (2001)[9]	5	1 (6 h)
Bartoli (2009)[10]	12	NR (range 1–16 h)
Crozier (2011)[11]	10	0 (range 2–23 d)
Shalhoub (2011)[22]	5	0 (range 4–9 d)
Leseche (2012)[23]	7	NR (range 1–14 d)
Yong (2013)[12]	7	0 (range 2–12 d)
Koraen-Smith (2014)[16]	71	NR (range 0–108 d)
Rathenborg (2013)[13]	22	0 (range 7–13 d)
Benes (2014)[24]	5	5 (range 85–290 min)

Data on very early CEA after IVT are therefore scarce. To the best of the authors' knowledge, the present case series reports the shortest time interval between IVT and subsequent CEA (median 5 hours). The present protocol was implemented on the basis of literature data,[4–7,9,10] to assess the safety of early carotid intervention after thrombolysis performed at a different time to IVT and to verify whether a very early intervention can be a viable option not only to prevent early recurrence, but also to treat the target event.

In the group with very early CEA, no peri-operative complications or ischaemic stroke recurrence were observed at the 3 month follow up. The only death registered in the present case series seems to be related to polidistrectual vascular impairment rather than as a consequence of IVT or carotid surgery. The major concern is the risk of intracerebral bleeding compounded by the effect of rtPA on the coagulation pathway and reperfusion injury.[1,2,21] No haemorrhagic transformation was seen in this case series. Indeed, a significant clinical improvement was seen in 55% of included patients. The present experience suggests that very early CEA after IVT in carefully selected patients is a safe approach leading to a good outcome, and could have a true therapeutic role, not just a preventative one.

The small sample size and the retrospective nature of the study does not allow for any definite conclusions to be drawn. Moreover, the patients underwent surgery at different times according to predefined criteria; therefore, no comparison between the different groups of patients treated at different times can be made. The data are preliminary and require further confirmation by larger studies.

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However, the data suggest that early CEA is safe, and encourage an "aggressive" approach in patients with hyperacute ischaemic stroke and ipsilateral high grade stenosis of the carotid artery, when preceded by careful preoperative evaluation.

CONCLUSIONS

The present case series suggests that very early carotid endarterectomy after thrombolysis may be safe. A fast surgical approach to acute carotid high grade stenosis after thrombolysis might be a reasonable revascularisation therapy. Careful pre-surgical evaluation, including penumbra imaging, is essential.

CONFLICT OF INTEREST

None.

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None.

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