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Thrombolysis in Cervical Artery Dissection – Data from the Cervical Artery Dissection and Ischaemic Stroke Patients (CADISP) database

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Objective: To examine whether thrombolysis for stroke attributable to cervical artery dissection ($CeAD_{Stroke}$) affects outcome and major haemorrhage rates.

Methods: We used a multicentre $CeAD_{Stroke}$ database to compare $CeAD_{Stroke}$ patients treated with and without thrombolysis. Main outcome measures were favourable 3-month outcome (modified Rankin Scale 0–2) and 'major haemorrhage' [any intracranial haemorrhage (ICH) and major extracranial haemorrhage]. Adjusted odds ratios [OR (95% confidence intervals)] were calculated on the whole database and on propensity-matched groups.

Results: Among 616 $CeAD_{Stroke}$ patients, 68 (11.0%) received thrombolysis; which was used in 55 (81%) intravenously. Thrombolyzed patients had more severe strokes (median NIHSS score 16 vs. 3; $P < 0.001$) and more often occlusion of the dissected artery (66.2% vs. 39.4%; $P < 0.001$). After adjustment for stroke severity and vessel occlusion, the likelihood for favourable outcome did not differ between the treatment groups [$OR_{adjusted}$ 0.95 (95% CI 0.45–2.00)]. The propensity matching score model showed that the odds to recover favourably were virtually identical for 64 thrombolyzed and 64 non-thrombolyzed-matched $CeAD_{Stroke}$ patients [OR 1.00 (0.49–2.00)]. Haemorrhages occurred in 4 (5.9%) thrombolyzed patients, all being asymptomatic ICHs. In the non-thrombolysis group, 3 (0.6%) patients had major haemorrhages [asymptomatic ICH ($n = 2$) and major extracranial haemorrhage ($n = 1$)].

Conclusion: As thrombolysis was neither independently associated with unfavourable outcome nor with an excess of symptomatic bleedings, our findings suggest thrombolysis should not be withheld in $CeAD_{Stroke}$ patients. However, the lack of any trend towards a benefit of thrombolysis may indicate the legitimacy to search for more efficient treatment options including mechanical revascularization strategies.

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Introduction

The efficacy of thrombolysis in acute ischaemic stroke is well established [1]. However, whether this observation includes patients with strokes attributable to cervical

artery dissection ($CeAD_{Stroke}$) is less clear. CeAD is characterized by intramural haematoma. Theoretically, thrombolysis might promote and increase the intramural bleeding in CeAD and cause progressive hemodynamic worsening and infarct growth.

In turn, thrombolysis may be beneficial by inducing recanalization of the arterial thrombosis at the site of the dissection or of a distal embolus. $CeAD_{Stroke}$ patients have not been excluded from randomized placebo-controlled trials (RCT) [1,2] of thrombolysis in stroke. Treatment guidelines [3] do not advise against thrombolysis in such patients, but RCT-based data about thrombolysis versus placebo in CeAD patients are not available. Most case series reporting on $CeAD_{Stroke}$ patients treated with thrombolysis [4–8], recently meta-analysed [9], were small and lacked a comparison group. With these considerations in mind, we compared the outcome and complications of $CeAD_{Stroke}$ patients who received thrombolysis with those treated without thrombolysis (non-thrombolysis) in the multicentre Cervical Artery Dissection and Ischaemic Stroke Patients (CADISP) clinical study, the largest cohort of CeAD patients to date.

Methods

The CADISP consortium aimed at exploring genetic [10] and environmental risk factors [11] and treatment aspects of CeAD. For the CADISP clinical study, we included consecutive patients evaluated in a department of neurology with a diagnosis of CeAD or non-CeAD stroke patients, as well as referents, across 18 centres in eight countries [11]. Almost all patients were treated between 1999 and 2009; a small number of patients ($< 4\%$), ascertained through the registries of CeAD patients previously established in some of the recruiting centres, had a qualifying event before 1999. Patients were recruited both prospectively and retrospectively. Retrospective patients were selected from consecutive lists of patients treated for the qualifying event before the beginning of the study in each centre [11].

The diagnosis of CeAD was based on widely accepted diagnostic criteria [7,8]. Briefly, CeAD patients had to present with mural haematoma, aneurismal dilatation, long tapering stenosis, intimal flap, double lumen or occlusion > 2 cm above the carotid bifurcation revealing an aneurismal dilatation or a long tapering stenosis after recanalization, in a cervical artery (internal carotid or vertebral) [10,11].

To prevent false-positive inclusions in the CeAD group, patients with only suspected CeAD – thus, not meeting the proposed criteria – were excluded. Patients with solely intracranial dissections were excluded, as it is still under debate whether CeAD and intracranial dissections can be regarded as one entity. We also did not include iatrogenic dissections owing to endovascular procedure.

While we used very strict criteria for the radiological features that we considered pathognomonic of dissection, the choice of the radiological tool used for the diagnosis was left to the discretion of the treating physician [11]. Diagnostic procedures differ between countries and centres, but all participating departments have a high level of expertise in clinical stroke medicine including the application of thrombolysis and a substantial track record in the management of and research on CeAD. The CADISP clinical study comprises 983 CeAD patients. Among these patients, CeAD was diagnosed by magnetic resonance angiography (MRA) in 853 (86.9%) patients (with at least one additional diagnostic tool in 82.1%), by computed tomography angiography (CTA) without MRA in 70 (7.1%) patients (with at least one additional diagnostic tool in 35.7%), by digital subtraction angiography (DSA) without MRA or CTA in 34 (3.5%) patients (52.9% of which also had a cervical ultrasound) and by cervical ultrasound only in 25 (2.5%) patients.

For the present study, all CeAD patients presenting with a stroke were selected, resulting in 646 patients. We distinguished a thrombolysis group from a non-thrombolysis group. The thrombolysis group comprised all CeAD patients who had intravenous thrombolysis (IVT), intra-arterial thrombolysis (IAT) or both (IVT-IAT) used according to the preference of the treating physicians. The application of thrombolysis followed official guidelines [3]. Neither centre excluded $CeAD_{Stroke}$ patients from thrombolysis. The non-thrombolysis group comprised all $CeAD_{Stroke}$ patients, who did not receive any kind of thrombolysis.

The following standardized variables were used from the CADISP database [10]: age, gender, stroke severity at admission as assessed by the National Institutes of Health Stroke Scale (NIHSS) score [12] applied by trained stroke neurologists at patient admission, vascular risk factors according to predefined criteria [11], site of dissection (i.e. internal carotid artery, vertebral artery and internal carotid plus vertebral artery), type of recruitment [11], presence or absence of vessel occlusion, type of first antithrombotic treatment (i.e. anticoagulation, antiplatelets and none/no information), blood glucose concentration, systolic and diastolic blood pressure, and body temperature at admission. Functional outcome was assessed by outpatient visits or telephone calls using the modified Rankin Scale (mRS) at 3 months.

All intracranial haemorrhages (ICH) were ascertained on follow-up CT or MRI obtained within 72 h after thrombolysis and additional scans in case of clinical deterioration. For the non-thrombolysis group, the usage

and timing of follow-up scan were at the discretion of the treating stroke neurologist. Applying the NINDS criteria [1], symptomatic ICH was defined as any CT/MRI-documented ICH temporally related to any deterioration in the patient's clinical condition. Fatal haemorrhage was defined as any symptomatic ICH leading to death.

Primary outcome measures were (i) favourable 3-month outcome, defined as mRS 0–2 and (ii) 'any major haemorrhage'. This includes all categories of ICH [1] and major extracranial haemorrhage. The latter was defined as a clinically apparent extracranial bleeding resulting in an intervention [13].

Statistical analyses

Comparisons of patients in the thrombolysis group and those of the non-thrombolysis group were carried out using *t*-, Mann–Whitney *U*-, chi-square and Fisher exact-tests. Data were given as mean and standard deviation (±SD) or median with interquartile range (IQR) where appropriate, respectively.

On the basis of the findings from previous research [8], the association of thrombolysis with 'favourable 3-month outcome' was adjusted for the presence of vessel patency and stroke severity by multivariate logistic regression. This association was further explored using a propensity score matching strategy. Because of important differences in key baseline characteristics between patients from the thrombolysis and non-thrombolysis groups, we used propensity score matching to balance characteristics of patients according to baseline covariates. Propensity scores for thrombolysis were estimated using a non-parsimonious multivariable logistic regression with thrombolysis as the dependent variable, and age, gender, centre, type of recruitment, stroke severity, site of dissection and vessel occlusion as covariates. We were able to match 64 patients with thrombolysis (94% of the 68 patients with thrombolysis) with 64 patients without thrombolysis who had similar propensity scores by using the nearest neighbour matching method.

Ethics

The CADISP study protocol (http://clinicaltrials.gov/ct2/show/NCT00657969) was approved by relevant local authorities in all participating centres and is conducted according to the national rules concerning ethics committee approval and informed consents.

Results

Study population

Data were suitable for analysis in 616 (95.5%) of 646 $CeAD_{Stroke}$ patients. Thirty patients were excluded for the following reasons. One patient participated in a double-blinded thrombolysis RCT and it could not be verified whether he had received thrombolysis or placebo. Twenty-nine patients were lost to follow-up. All except one belonged to the non-thrombolysis group.

In a secondary analysis, we included these 29 patients assuming that all had (i) a favourable outcome or (ii) an unfavourable 3-month outcome (sensitivity analysis).

Thrombolysis was used in 68 (11.0%) patients. Fifty-five patients (81%) had IVT, 9 (13%) had IAT and in 4 (6%) patients, IVT was followed by IAT. A favourable outcome was reached by 32/55 (58%) patients treated with IVT and by 5/13 (38%) patients who received IAT or IVT followed by IAT. The flow diagram displays the patients' selection process and the treatment distribution, (Figure S1).

Thrombolysis group versus non-thrombolysis group

Baseline characteristics

Patients treated with thrombolysis had more severe strokes (median NIHSS score 16 vs. 3), more often occlusion of the dissected artery (66.2% vs. 39.4%) and more often dissection of the internal carotid artery (82.3% vs. 55.6%) than non-thrombolyzed patients. Mural haematoma was detected equally often in the thrombolysis group (76.7%) than in the non-thrombolysis groups (78.3%). Age, gender, vital signs at admission, type of first antithrombotic treatment and the frequency of vascular risk factors were similar in both groups (Table 1).

Outcome and complications measures

A favourable 3-month outcome was reached in fewer thrombolyzed (54.4%) than in non-thrombolyzed patients (85.4%), amounting to an unadjusted OR of 0.20 (95%CI 0.12–0.35). However, after adjustment for stroke severity and vessel occlusion, the likelihood for favourable outcome did not differ between the treatment groups [$OR_{adjusted}$ 0.95 (95% CI 0.46–2.00) Table 2]. The sensitivity analysis showed that the $OR_{adjusted}$s were similar assuming all 29 patients of the non-thrombolysis group with missing 3-month mRS had all either (i) favourable outcomes [$OR_{adjusted}$ 0.73 (95% CI 0.36–1.46)] or (ii) unfavourable 3-month outcomes [$OR_{adjusted}$ 1.07 (95% CI 0.52–2.18)], respectively.

Major haemorrhages were more frequent in thrombolyzed (5.9%) than in non-thrombolyzed (0.6%) patients [OR 11.29 (95% CI 2.47–51.59)]. However, in all four thrombolyzed patients with a major haemorrhagic complication, these were asymptomatic ICH. Symptomatic ICH and major extracranial haemorrhages did not occur. Among non-thrombolyzed patients, two patients (0.4%) had asymptomatic ICH and one patient

Table 1 Baseline characteristics of $CeAD_{Stroke}$ patients treated either with or without thrombolysis

Clinical characteristics	With thrombolysis (n = 68) (100%)	Without thrombolysis (n = 548) (100%)	P value
Demographic data			
Age: median (IQR) (years)	45 (36–50)	44 (37–51)	0.98
Male sex, number (%)	43 (63.2%)	310 (56.6%)	0.36
Stroke severity			
Median NIHSS score (IQR)	16 (10–19)	3 (1–6)	< 0.001
Range	0–23	0–33	
Dissected artery			
Internal carotid artery	56 (82.3%)	304 (55.6%)	< 0.001
Vertebral artery	11 (16.2%)	229 (41.8%)	
Internal carotid + vertebral artery	1 (1.5%)	14 (2.6%)	
Occlusion (of dissected artery)	45 (66.2%)	216 (39.4%)	< 0.001
Mural haematoma	46/60 (76.7%)	398/508 (78.3%)	0.74
Vital signs and laboratory findings, median (IQR)			
Systolic blood pressure (mm Hg)	140 (124–148)	138 (120–150)	0.89
Diastolic blood pressure (mm Hg)	80 (70–93)	80 (70–93)	0.90
Temperature (°C)	36.8 (36.4–37.2)	36.8 (36.5–37.1)	0.88
Glycaemia (g/l)	1.03 (0.90–1.29)	0.97 (0.89–1.11)	0.34
First antithrombotic treatment n (%)			
Anticoagulation	33 (48.5%)	330 (60.2%)	0.12
Antiplatelets	31 (45.6%)	180 (32.8%)	
None/no information	4 (5.9%)	38 (6.9%)	
Vascular risk factors, (%)			
Hypertension	10/67 (14.9%)	139/542 (25.6%)	0.07
Smoking (current)	22/65 (33.8%)	157/543 (28.9%)	0.47
Hypercholesterolaemia	9/67 (13.4%)	100/539 (18.6%)	0.40
Migraine	23/66 (34.8%)	197/541 (36.4%)	0.89
Diabetes mellitus	1/67 (1.5%)	13/544 (2.4%)	1.0

IQR, interquartile range.

Table 2 Multivariable regression analysis

Variables predicting favourable outcome[a]	P value	Odds ratio	95% CI
NIHSS score (each point)	< 0.001	0.82	0.78–0.86
Occlusion of dissected artery	0.16	0.66	0.37–1.18
Thrombolysis	0.89	0.95	0.45–2.00

Odds for [a]modified Rankin Scale 0–2 at 3 months in $CeAD_{Stroke}$ patients treated with compared to those treated without thrombolysis adjusted for stroke severity and the presence of vessel occlusion.

(0.2%) had a major extracranial haemorrhage (i.e. a psoas haematoma requiring transfusion). The groups did not differ with regard to the secondary 3-month outcomes death, recurrent stroke or recurrent dissection. Details of the unadjusted outcomes are shown on Table S1.

The propensity score was computed for 64 of the 68 thrombolyzed patients with available NIHSS scores at admission. Thrombolyzed and non-thrombolyzed patients were well matched for age, gender, stroke severity, site of dissection (i.e. carotid versus vertebral), systolic and diastolic blood pressure, body temperature and glucose level at admission, vessel patency and vascular risk factors (Table S2). Favourable outcome was observed as often among thrombolyzed as among non-thrombolyzed $CeAD_{Stroke}$ patients [OR 1.0 (0.49–2.0)] (Table 3).

Discussion

Principal findings

The comparison of thrombolyzed and non-thrombolyzed $CeAD_{Stroke}$ patients showed the following main findings: (i) The odds to recover favourably were virtually identical for both treatment groups after adjustments for outcome predictive baseline variables and (ii) major haemorrhage occurred more often in the thrombolysis group. However, none was a symptomatic ICH.

Findings in the context of the current literature

More than half of the thrombolyzed $CeAD_{Stroke}$ patients did have a favourable outcome – that is, mRS 0–2 after 3 months – which is similar to results obtained in smaller series (3/6 [6], 4/11 [5], 3/7 [7] and 17/33 [4]) and a meta-analysis across retrospective case series and case reports (55.6%) published recently [9]. Furthermore,

Table 3 Propensity analysis: 3-month outcome in $CeAD_{Stroke}$ patients treated with and without thrombolysis

Outcome variables after 3 months *n* (%)	CeAD with thrombolysis, *n* = 64 (%)	CeAD without thrombolysis, *n* = 64 (%)	*P* value	Odds ratio	95% CI
Favourable outcome (mRS[a] 0–2)	35 (54.7)	35 (54.7)	1	1	0.49–2.0
Functional outcome[a]					
mRS 0	7 (10.9)	2 (3.1)	0.63		
mRS 1	12 (18.7)	18 (28.1)			
mRS 2	16 (25.0)	15 (23.4)			
mRS 3	18 (28.1)	16 (25)			
mRS 4	9 (14.1)	11 (17.2)			
mRS 5	1 (1.6)	1 (1.6)			
mRS 3–5 without details	1 (1.6)	1 (1.6)			
Any major haemorrhage	4 (6.2)	0 (0)	0.11		
Intracranial haemorrhage (all)	4 (6.2)	0			
Asymptomatic	4 (6.2)	0			
Symptomatic[b]	0	0			
Fatal[c]	0	0			
Major extracranial haemorrhage[d]	0	0			
Death (all causes)	0 (0)	0 (0)	–	–	–
Recurrent ischaemic stroke	3 (4.7)	1 (1.6)	0.61	3.0	0.31–30.1
Recurrent dissection	3 (4.7)	2 (3.2)	1	1.5	0.24–9.3

[a]Modified Rankin Scale; [b]Any CT/MRI-documented intracranial haemorrhage (ICH) that was temporally related to any deterioration in the patient's clinical condition [1]. [c]Any symptomatic ICH leading to death. [d]Any clinically apparent extracranial bleeding resulting in an intervention [13].

this rate is similar to those reported in RCTs [1,2] or the SITS-ISTR registry [14] of IV thrombolysis for the stroke of miscellaneous causes.

Adjustment for stroke severity and vessel occlusion entailed a virtually identical functional outcome for the thrombolysis group and the non-thrombolysis group. The lack of any trend towards a potential benefit of thrombolysis was somewhat surprising, as thrombolysis is known as safe and efficacious independent of the underlying stroke mechanism [1]. In line with the current findings, seven carotid artery dissection patients treated with IV thrombolysis, tended towards an outcome worse than that of seven carotid dissection patients not treated with IVT [15]. In addition, among stroke patients treated with IVT, CeAD patients did not recover as well as IVT treated with a stroke cause other than CeAD [8,16]. These findings indicate that $CeAD_{Stroke}$ patients might not benefit from thrombolysis as much as other stroke patients do, possibly due to the high rate of extracranial arterial occlusions (i.e. 67.6%) as a negative prognostic factor [17]. Most thrombolyzed patients in our series were treated with IVT. Thus, the search for potentially more effective treatment options seems legitimate. As such, endovascular procedures have been reported feasible and potentially beneficial in some case reports or small series [7,18–21].

The overall rate of 'major haemorrhage' was increased in the thrombolysis group compared to the non-thrombolysis group. However, all 'major haemorrhages' among thrombolyzed patients were asymptomatic ICHs. In addition, their rate was lower than reported in the NINDS [1] and the ECASS-3 [2] studies adhering to the same definitions. As symptomatic ICHs as well as major extracranial haemorrhages were absent in the thrombolysis group, suggesting certain safety of thrombolysis in such patients with regard to symptomatic bleeding complications.

Strengths and limitations

This is the largest study addressing the impact of thrombolysis in $CeAD_{Stroke}$ patients.

Moreover, we used a comparison group, which was absent in most of the previous studies [4–7]. More importantly and as a novelty of this study, we assessed the effect of thrombolysis in $CeAD_{Stroke}$ patients by a direct comparison of $CeAD_{Stroke}$ patients treated with thrombolysis versus those treated without thrombolysis.

In addition, data on the patency of the dissected artery as an outcome predictor is provided, which was missing in some previous CeAD studies [5,8]. Moreover, the systematic ascertainment of exhaustive clinical, radiological and laboratory data enabled corrections for several potentially confounding variables using two different approaches. Thus, our findings might be considered the best evidence currently available in the absence of a randomized controlled trial.

Corrections with multivariate regression analysis and with a propensity score model lead to virtually identical results. In particular, the consistency of the point estimates by both approaches (i.e. 0.95 and 1.0, respectively) underlines the assumption that thrombolysis might not influence outcome in $CeAD_{Stroke}$ patients, substantially.

Nevertheless, we are aware of several limitations. First, our study was an exploratory observational analysis and not a randomized controlled trial. In addition, details about the reasons why patients in the control group did not receive thrombolysis were lacking, including details about the exact time interval between stroke onset and admission; (although admission too late after symptom onset and minor stroke severity was assumingly the most frequent causes for not receiving thrombolysis). Second, because baseline characteristics between thrombolyzed and non-thrombolyzed patients were different, the possibility of residual confounding after adjustment is not excluded. Because of the size of the smallest group [i.e. those with unfavourable outcome after thrombolysis ($n = 31$)], the number of variables which could be used for adjustments had been limited. If we – nevertheless – had added 'site of dissection' as additional covariate (next to 'stroke severity' and 'vessel occlusion'), still the likelihood for favourable outcome would have been comparable between the treatment groups [$OR_{adjusted\ also\ for\ site\ of\ disscetion}$ 0.95 (95% CI 0.45–2.00)]. Furthermore, if we had limited the analysis only to the prospectively recruited patients, the odds for favourable outcome were similar, too [$OR_{adjusted;\ prospectively\ recruited\ patients}$ 0.95 (95% CI 0.32–2.77)]. Third, the sample size of the thrombolysis group was not sufficient to evaluate the efficacy of thrombolysis in $CeAD_{Stroke}$ patients. Fourth, the absence of any death at 3 months indicates that we studied a selected $CeAD_{Stroke}$ population. Severely affected patients were less likely to participate because informed consent was an ethical requirement for participation in this study. Data on how often each treatment group was affected by this selection bias were unavailable. Thus, our observations on functional outcome should be interpreted cautiously. Fifth, data about recanalization rates were not available. For the future, details about frequency and timing of recanalization would be important for a meaningful comparison of IVT with endovascular approaches, which was beyond the focus of the current study.

In the absence of data based on a higher level of evidence, our findings suggest thrombolysis should not be withheld in $CeAD_{Stroke}$ patients as thrombolysis was neither independently associated with unfavourable outcome nor with an excess of symptomatic bleedings. However, the lack of any trend towards a benefit of thrombolysis indicates the legitimacy to search for more efficient treatment options including mechanical revascularization strategies.

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Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow diagram of the patients' selection and treatment allocation.

Table S1. Unadjusted 3-month-outcome of CeAD-Stroke-patients treated either with or without thrombolysis.

Table S2. Propensity score model: clinical characteristics of CeAD-Stroke-patients treated with and without thrombolysis.

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