

Effect of bridging with intravenous thrombolysis on cognitive function in stroke thrombectomy – An analysis of the German Stroke Registry

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Abstract

Background The targeted use of endovascular therapy (EVT), with or without intravenous thrombolysis (IVT) in acute large cerebral vessel occlusion stroke (LVOS) has been proven to be superior compared to IVT alone. Despite favorable functional outcome, many patients complain about cognitive decline after EVT. If IVT in addition to EVT has positive effects on cognitive function is unclear.

Methods We analyzed data from the German Stroke Registry (GSR, an open, multicenter and prospective observational study) and compared cognitive function 90 days after index ischemic stroke using MoCA in patients with independent ($mRS \leq 2$ pts) and excellent ($mRS = 0$ pts) functional outcome receiving combined EVT and IVT (EVT+IVT) vs. EVT alone (EVT-IVT).

Results Of the 2636 GSR patients, we included 166 patients with $mRS \leq 2$ at 90 days in our analysis. Of these, 103 patients (62%) received EVT+IVT, 63 patients (38%) were treated with EVT alone. There was no difference in reperfusion status between groups ($mTICI \geq 2b$ in both groups at 95%, $p = 0.65$). Median MoCA score in the EVT+IVT group was 20 pts (18-25 IQR) vs. 18 pts (16-21 IQR) in the EVT-IVT group ($p = 0.014$). There were more patients with cognitive impairment (defined as $MoCA < 26$ pts) in the EVT-IVT group (54 patients (86%)) compared to the EVT+IVT group (78 patients (76%)). EVT+IVT was associated with a higher MoCA score at 90 days ($mRS \leq 2$: $p = 0.033$, $B = 2.39$; $mRS = 0$: $p = 0.021$, $B = 4.38$).

Conclusions In Patients with good functional outcome after LVOS, rates of cognitive impairment are lower with combined EVT and IVT compared to EVT alone.

Background

Ischemic stroke is one of the most frequent causes of permanent physical disability worldwide (1) and, in addition, is associated with an increasing incidence of cognitive impairment and dementia (2). Even after good clinical recovery, about 30–50% of patients complain of cognitive impairment or dementia within the first year after an ischemic stroke (3–7). In the course, the prevalence of dementia even increases (8) with a broad spectrum of cognitive disturbances, ranging from mild cognitive impairment into a manifest dementia (9–12). Cognitive impairment not only reduces quality of life, but also increases mortality and health care costs (13). The exact pathogenesis so far remains unclear. Since both ischemic stroke and cognitive impairment have an increasing prevalence in older age, the exact differentiation, especially of causality, is not easy. Pendlebury et al. could show a significant deterioration of cognitive function associated with an ischemic event in patients with already beginning (age-correlated-physiological) cognitive impairment (14). Secondary analysis of the Framingham Heart Study conclude that post-stroke worsening in several dimensions of cognition cannot be explained solely by inferior cognitive performance before the stroke event or by concomitant common vascular risk factors (15). One might assume that ischemic stroke causes a significant loss of cerebral substance with insufficient compensation due to the already aged “senile” brain. The functional “reserve” is lower in old age, which is also reflected in the risk factors for a post-stroke cognitive disorder: Here, in addition to the age (> 65

years) and already known cognitive impairment, cerebral atrophy in the temporal lobe, recurrent ischemic strokes, cardioembolic infarcts and so-called “white matter lesions” are mentioned (16–19)

Early recanalizing treatment of stroke reduces ischemic lesion burden. In addition to the treatment with thrombolysis using intravenous tissue plasminogen activator (rtPA, IVT), endovascular therapy (EVT) has been shown to be the gold standard in the acute phase and significantly improves functional outcome (20–24). In addition, a recent study by López-Cancio et al. could demonstrate the benefit of EVT versus IVT alone for cognitive outcome parameters in a group of patients with good functional outcome (defined as a score on the modified Rankin Scale (mRS): ≤ 2) (25).

In the acute treatment of stroke IVT is often combined with EVT (“bridging-therapy”). Currently, the advantage of bridging therapy versus non-bridging is controversially discussed (26–29). Recent studies indicate a possible benefit of bridging therapy in terms of recanalization rate and functional outcome, with no significant increase in the rate of intracranial hemorrhage in the bridging group (30,31). An analysis of data from the Virtual International Stroke Trials Archive (VISTA) study suggests that stroke patients may benefit from rtPA treatment in terms of cognition (32). But it is still unclear whether bridging therapy also has positive effects on cognition compared to EVT alone.

In this study, we investigate the effects of bridging treatment (IVT+EVT) vs EVT alone (EVT-IVT) on cognitive function in patients with LVOS and good outcome.

Methods

Patient population and clinical characteristics

Available data of all patients enrolled in the German Stroke Registry – Endovascular Treatment (GSR-ET 07/2015-04/2018; ClinicalTrials.gov Identifier: NCT03356392) were included. The GSR-ET is an ongoing, open-label, prospective, multicenter registry of 25 sites in Germany, collecting consecutive patients undergoing EVT.

Group classification

Initially, patients with an mRS between 0 and 2 were selected from the entire GSR database in this study. Furthermore, only patients with a memory test after 90 days were elected for further analysis. A Bridging- (EVT+IVT) and a Non-Bridging group (EVT-IVT) were compared. Subsequently, subgroups were formed for comparison, which were analyzed separately. This includes a group with a mRS of 0 points, as well as a subgroup formation by stroke-localization (right vs. left and anterior vs. posterior cerebral circulation).

To further differentiate the cognitive impairment (CI), patient groups were formed on the basis of the 90-day MoCA scores (0-9 pts: severe CI; 10-17 pts: moderate CI; 18-25 pts: mild CI; > 25 pts. No CI). Although

this classification is currently not based on scientific evidence, the homepage offers this classification as a possible graduation of the severity of a CI (33).

Statistical analysis:

The direct group comparison was done by descriptive statistics. Categorical sizes were given with mean and standard deviation, as well as absolute frequencies. Continuous variables were given by median, quartiles, minimum and maximum. Comparative test procedures between intervention and control groups were performed by chi-square test and non-parametric method (Mann-Whitney U test), depending on variable. Missing values in variables of the data set were determined with an in-depth data analysis. For continuous and categorical independent variables with more than 10% missing values, the multiple imputation feature implemented in SPSS was used to calculate the missing values using a regression model (34). This method was used to counteract the bias of the result by complete-case analysis and to increase the validity of the study (35–37). Potential confounders were filtered out by univariate pre-testing, with a p-value <0.3 being considered predictive of the outcome "cognitive impairment". For the continuous endpoint MoCA-value after 90 days, a linear regression model was performed. Finally, the two groups with possible confounders were further processed in a multivariate logistic regression model. All calculations were based on a 5% significance level.

Statistical analysis was performed using SPSS (version 26, IBM Corporation, Armonk, New York, USA), written with Word (Microsoft Corporation, Redmond, Washington, USA). Graphics were created using Excel (ibid).

Results

Baseline-characteristics

From the 2636 patients included in the GSR the 90-day MoCA had been recorded in 215 (8.1%) patients. Of these, 166 (77.2%) patients had an independent functional outcome with a 90-day mRS \leq 2. In this group 103 (62%) patients were treated with EVT+IVT, 63 (38%) received an EVT alone. The baseline characteristics of both groups are summarized in table 1. In most cases stroke was located in the anterior cerebral circulation (n=146, 88%); the remaining 20 (12%) patients had vertebrobasilar strokes. There was a significant shorter median symptom onset to admission time in patients with EVT+IVT compared to in the EVT-IVT group (69 min, IQR 40-171 min vs 205 IQR 73-508 min in the EVT-IVT group, p<0.001). The proportion of smokers (37.1% vs. 27.3%, p=0.19) and patients with anticoagulation (28,6% vs. 0%, p<0.001) were higher in the EVT-IVT group compared to

the EVT+IVT group. Functional impairment, quantified by the National Institute of Health Stroke Scale (NIHSS) on admission was more pronounced in the EVT+IVT group (12 pts, IQR 7-16 pts, vs. 10 pts, IQR 5-15 pts, $p=0.14$) as well as the ASPECT score for the assessment of early infarct signs, which was also higher in the EVT+IVT group (9 pts, IQR 8-10 pts vs. 8 pts, IQR 7-10, $p=0.01$). At discharge, both groups showed mild symptoms with a median NIHSS of 2 points ($p=0.24$).

Table 1: Baseline Characteristics MRS ≤ 2

Variable	Bridging (n = 103)	Non-Bridging (n = 63)	p-value
Sex (n, %)			0.29
Male	55 (53.4)	39 (61.9)	
Female	48 (46.6)	24 (38.1)	
Age (mean \pm SD)	67 (± 14.28)	69 (± 11.18)	0.29
Vasc. risk-factors (n, %)			
Art. hypertension	69 (67)	45 (71.4)	0.55
Smoking	27 (27.3)	23 (37.1)	0.19
Diabetes	17 (16.5)	14 (22.2)	0.36
Dyslipidemia	39 (37.9)	23 (36.5)	0.86
Atrial fibrillation	25 (24.3)	21 (33.3)	0.21
Baseline medication (n, %)			
Aspirin	28 (28.9)	12 (20)	0.22
Clopidogrel	3 (3.1)	2 (3.3)	0.93
Anticoagulation	0 (0)	18 (28.6)	<0.001
NIHSS at admission (median points, IQR)	12 (7-16)	10 (5-15)	0.14
Symptom-onset to admission (median time, IQR)	69 (40-171)	205 (73-508)	<0.001
ASPECTS (median points, IQR)	9 (8-10)	8 (7-10)	0.01
NIHSS at discharge (median points, IQR)	2 (0-4)	2 (1-3)	0.24
MTICI $\geq 2b$ after EVT (n, %)	98 (95)	60 (95)	0.65

Table 1: Baseline-Characteristics MRS ≤ 2 ; SD: standart deviation; IQR: interquartile range

A subgroup of 54 (33.7%) patients had no stroke associated functional impairment corresponding to a 90-day mRS of 0 pts. The baseline characteristics of these patients are given in supplementary table 1. This subgroup showed differences in gender distribution with a lower proportion of male patients in the EVT+IVT group compared to the EVT-IVT group (38.5% vs. 66.7%, $p=0.06$). Again, there was a significant difference between the two groups in terms of median time between symptom onset and admission (82 min, IQR 45-236 min in the EVT+IVT group, 156 min, IQR 73-553 min in the EVT-IVT group, $p<0.001$).

Patients with bridging therapy also had a higher NIHSS on admission compared to EVT-IVT patients (NIHSS median 11 pts, IQR 7-15 in the EVT+IVT group vs. 6 pts, IQR 4-12 in the EVT-IVT group, $p=0.057$), while the NIHSS was slightly higher at discharge in the EVT-IVT group (1 pt, IQR 0-2 in the EVT-IVT and 0 pts, IQR 0-2 in the EVT+IVT group, $p=0.101$). Again, the proportion of anticoagulated patients in the EVT-IVT group was higher (33.3% vs. 0%, $p<0.001$).

MoCA-Score at day 90:

For patients with a 90-day $mRS \leq 2$, there was a significant difference in the MoCA scores between the EVT+IVT and EVT-IVT group with a median MoCA score in the EVT+IVT group of 20 points (IQR 18-25 pts) vs 18 points (IQR 16-21 pts) in the EVT-IVT group ($p=0.014$). For patients with excellent functional outcome ($mRS=0$), we also found a significantly higher MoCA score in the EVT+IVT group (21 points (IQR 18-29 pts) vs 19 points (IQR 17-21 pts), $p=0.018$).

After the adjustment for sex, age, NIHSS at admission and at discharge, symptom-onset-to-admission-time, ASPECTS, vascular-risk factors (atrial fibrillation, smoking), as well as baseline medication (aspirin and anticoagulation), a significant difference at the significance level of 5% for the 90-day MoCAs persisted for both patients with independent and excellent functional outcome ($mRS \leq 2$: $B=2.39$, $p=0.033$; $mRS=0$: $B=4.38$, $p=0.021$) (table 2). This difference was independent concerning reperfusion status after endovascular treatment since 95% reached $mTICI \geq 2b$ in both groups ($p=0.65$). The linear regression model furthermore showed a significant correlation to a poorer MoCA result after 90 days in smokers ($B=-1.91$, $p=0.038$) and older age ($B=-0.11$, $p=0.001$).

Table 2: Influence of variables on the 90d MoCA value

Variable	Single linear regression		Multiple linear regression	
MRS ≤ 2	B (95% CI)	p-value	B (95% CI)	p-value
Bridging-therapy	2.01 (0.4-3.62)	0.015	2.39 (0.20-4.58)	0.033
Sex			0.52 (-1.08-2.12)	0.526
Age			0.11 (0.04-0.17)	0.001
Symptom-onset to admission			0.00 (-0.003-0.003)	0.842
NIHSS at admission			-0.04 (-0.17-0.09)	0.551
Smoking			1.91 (0.11-3.71)	0.038
Atrial fibrillation			-0.60 (-2.71-1.51)	0.576
Aspirin premedication			-0.5 (-2.48-1.49)	0.623
Anticoagulation			1.91 (-1.23-5.05)	0.232
ASPECT-Score			-0.25 (-0.94-0.43)	0.46
NIHSS at discharge			-0.09 (-0.29-0.12)	0.405
MRS = 0				
Bridging-therapy	3.55 (0.78-6.31)	0.013	4.38 (0.67-8.08)	0.021
Sex			0.58 (-2.1-3.26)	0.669
Age			-0.07 (-0.21-0.07)	0.319
Symptom-onset to admission			-0.003 (-0.76-1.07)	0.721
NIHSS at admission			-0.06 (-0.24-0.13)	0.56
Smoking			0.80 (-2.50-4.11)	0.63
Dyslipidemia			2.49 (-0.28-5.27)	0.078
Aspirin premedication			-2.28 (-5.41-0.86)	0.154
Anticoagulation			-0.49 (-7.32-6.34)	0.881
NIHSS at discharge			0.16 (-0.76-1.07)	0.721

Table 2: Influence of variables on the 90d MoCA value; CI: Confidence Interval

Patients with strokes in the anterior circulation receiving combined EVT and IVT tended to show a higher MoCA-score compared to the EVT-IVT group (B=2.29; p=0.061; median MoCA 20 pts (IQR 17-24 pts) vs 18 points (IQR 16-21 pts)). There were no significant differences in MoCA-scores between both groups in patients with strokes in the posterior circulation (median MoCA 21 pts, IQR 18-28 in the EVT+IVT vs 20 pts, IQR 14-27, in the EVT-IVT group; B=2.12; p=0.603) (supplementary table 2).

Cognitive Impairment

Overall, 133 of the 166 patients included in the analysis (80%) showed cognitive impairment (defined as a MoCA-score <26 points) 90 days after the index event. The rate was 76% in the EVT+IVT and 86% in the EVT-IVT group. However, this difference was not

statistically significant after correction for possible confounders ($p=0.225$; OR: 2.27). In the group with excellent functional outcome ($mRS=0$) the prevalence of cognitive impairment was significantly lower (66%) in the EVT+IVT group, compared to the EVT-IVT group (93%; $p=0.034$; OR: 23.15; table 3). In the subgroup analysis on individual examination of the stroke localization, there was no significant difference between the prevalence of cognitive impairment between the EVT+IVT and EVT-IVT group (suppl. table 3).

Table 3: Influence of variables on Cognitive Impairment after 90 days

Variable	Univariable regression		Multivariable regression	
mRS ≤ 2	OR (95% CI)	p-value	OR (95% CI)	p-value
Bridging-therapy	1.92 (0.83-4.44)	0.126	2.27 (0.60-8.62)	0.225
Sex			1.84 (0.75-4.49)	0.181
Age			1.04 (1.00-1.07)	0.029
Symptom-onset to admission			1.00 (1.00-1.00)	0.84
NIHSS at admission			0.99 (0.93-1.07)	0.881
Smoking			0.47 (0.18-1.27)	0.136
Atrial fibrillation			0.39 (0.11-1.43)	0.154
Aspirin premedication			0.94 (0.33-2.71)	0.913
Anticoagulation			3.04 (0.41-22.69)	0.27
ASPECT-Score			1.12 (0.67-1.88)	0.635
NIHSS at discharge			1.06 (0.94-1.19)	0.354
mRS = 0				
Bridging-therapy	7.00 (0.83-59.21)	0.074	23.15 (1.26-424.73)	0.034
Sex			1.61 (0.31-8.44)	0.569
Age			1.03 (0.95-1.12)	0.498
Symptom-onset to admission			1.00 (0.99-1.01)	0.734
NIHSS at admission			1.04 (0.93-1.16)	0.517
Smoking			2.21 (0.33-14.85)	0.412
Dyslipidemia			0.33 (0.05-2.23)	0.256
Aspirin premedication			0.13 (0.01-1.32)	0.084
Anticoagulation			0.03 (0.00-0.00)	1
NIHSS at discharge			0.96 (0.51-1.79)	0.882

Table 3: Influence of variables on Cognitive Impairment after 90 days; OR: Odds Ratio, CI: Confidence Interval

Severity of Cognitive-Impairment:

Rates of moderate and severe cognitive impairment were significantly higher in the EVT-IVT (25 of 63 patients; 39.6%) versus the EVT+IVT group (25 of 103 patients, 24%;

p=0.040, OR 3.38). In patients with mRS=0, there also was a significant higher risk for moderate to severe cognitive impairment at 90 days with a prevalence of 13% in the EVT+IVT- and 33% in the EVT-IVT group (p=0.035, OR: 0.08).

Table 4: Severity of Cognitive Impairment

mRS ≤ 2	Bridging-group	Non-Bridging group	OR (95% CI)	p-value
	(n, %)	(n, %)		
No Cognitive Impairment	25 (24.3)	9 (14.3)	0.52 (0.23-1.20)	0.126
Mild Cognitive Impairment	53 (51.4)	29 (46)	0.66 (0.27-1.60)	0.355
Moderate Cognitive Impairment	25 (24.3)	24 (38.1)	0.38 (0.15-0.97)	0.042
Severe Cognitive Impairment	0 (0)	1 (1.5)	-	-
mRS = 0				
No Cognitive Impairment	13 (33.3)	1 (6.6)	0.14 (0.02-1.21)	0.074
Mild Cognitive Impairment	21 (53.8)	9 (60)	0.18 (0.02-1.59)	0.122
Moderate Cognitive Impairment	5 (12.8)	5 (33.3)	0.08 (0.01-0.83)	0.035
Severe Cognitive Impairment	0 (0)	0 (0)	-	-

Table 4: Severity of Cognitive Impairment (CI): No CI: MoCA ≥ 26 pts, Mild CI: MoCA > 17 pts, Moderate CI: MoCA > 10 pts, Severe CI: MoCA < 10 pts

Discussion

In the present study, we found lower rates of cognitive impairment in LVOS-patients treated with EVT+IVT compared to patients with EVT alone. EVT+IVT patients performed better in the 90-day MoCA compared to patients treated with EVT alone, even though the initial neurological deficits were more pronounced in the EVT+IVT group. Concerning the similar reperfusion rates in both groups and the correction for symptom onset to admission time in our analysis, IVT seems to have a positive effect not only on functional outcome-, but also on cognition after stroke. In particular, IVT seems to have the highest effect in patients with excellent functional outcome. The effect of rtPA on cognition has so far been poorly understood, and the few post-stroke studies with cognitive endpoints showed heterogeneous results (38). This is probably due to the different test methods used. At least until now, a benefit of the rtPA therapy with regard to visuoconstrictive abilities could be recognized (39).

In our study, we found a high rate of CI after 90 days in general (80%), which is well above the expected prevalence in other studies (3,4,7). A selection-bias could occur due to the limited group size in this study: Only 10% of the patients treated in the GSR were finally given cognitive testing. This low rate is most likely to be explained by the mere necessity of a personal follow-up visit, which certainly results in a high proportion of drop-outs. In addition, the time span of 90 days between cognitive testing and index event is very tight for the assessment of a stroke-related CI. Other studies suggest an interval of at least 6 months to even speak of post-stroke dementia (12). However, an increased incidence of CI in the first period

following a stroke or even TIA has been described in other studies (6,8,40–42). Another bias in this study might occur due to the lack of cognitive testing at baseline, so no definitive statement on the incidence of CI, but only on prevalence in the course after stroke event can be made. Nonetheless, the prevalence remains considerable, bearing in mind that it refers to a patient population with good functional outcome.

A particular advantage in terms of cognition at different stroke localization could not be demonstrated. At least we could show that EVT+IVT did not yield any difference in terms of cognitive outcome in patients with stroke located in the posterior cerebral circulation. This also seems understandable when considering the brain region which is provided for by the vertebrobasilar vessels. Especially the neuropsychological and higher cognitive performance, which are queried by the testing via MoCA, are supplied with blood by the anterior cerebral circulation.

The conspicuous link between poorer MoCA testing in smokers in this study has already been observed in larger studies (43,44) and underlines the importance of nicotine abstinence as a modifiable risk factor in the post-stroke situation. Furthermore, the obvious correlation between higher age and worse performance in the MoCA test is understandable, as the prevalence of CI increases in older age (45,46).

The classification of CI into different categories (none, mild, moderate and severe CI) based on the MoCA score has yet not been validated in any study. Thus, this classification should be interpreted with an appropriate restraint. Further studies to evaluate a possible classification of CI after stroke with corresponding cut-off values in MoCA are desirable. In spite of these facts, considering the distribution of points in the individual groups, it is noticeable that significantly inferior cognitive performance (defined as a MoCA value below 17 points) occurs less frequently in the EVT+IVT than in the EVT-IVT group. This should be taken into account in the discussion about the potential benefits of a bridging therapy in the acute treatment of LVOS.

Limitation of this study is in addition to the low number of cases or high drop-out rate with the risk of selection-bias especially the retrospective, non-randomized study design. Besides, thanks to the multicenter study design of the GSR study, our results have a better overall validity.

Conclusion

Our data point to a possible benefit of bridging therapy in the controversy between bridging and non-bridging approaches. Even if the median MoCA value differs only by 2 points between the two groups after 90 days, at least this indicates a trend, which should be further verified in larger-scaled, prospective designed studies. In addition, our findings highlight the importance of routine cognitive testing in patients with favourable outcome after LVOS.

List Of Abbreviations

ASPECTS

Alberta stroke programme early CT score

CI

Cognitive Impairment

EVT

Endovascular therapy

GSR

German Stroke Registry

IQR

Interquartile range

IVT

Intravenous thrombolysis

LVOS

Large cerebral vessel occlusion stroke

MoCA

Montreal Cognitive Assessment

mRS

Modified Rankin Scale

mTICI

Modified treatment in cerebral ischemia score

NIHSS

National Institutes of Health Stroke Scale

OR

Odds Ratio

rtPA

Recombinant tissue plasminogen activator

VISTA

Virtual International Stroke Trials Archive

Declarations

1. Ethics approval and consent to participate: The study was approved by the institutional review board (ethics commission of the university medicine Göttingen; 16/2/16)
2. Consent for publication: Not applicable
3. Availability of data and materials: The data that support the findings of this study are available from the GSR-ET Collaborators but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the GSR-ET steering committee.
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6. Authors' contributions: Philipp Ettelt analyzed raw data, performed statistics, drafted and finalized the manuscript and approved the manuscript before submission.

Ilko L. Maier: designed the study and was involved in the acquisition of the data, drafted and finalized the manuscript and approved the manuscript before submission.

Marlena Schnieder: was involved in the acquisition of the data and approved the manuscript before submission.

Mathias Bähr: contributed to the manuscript and approved the manuscript before submission.

Daniel Behme: contributed to the manuscript, was involved in the acquisition of the data and approved the manuscript before submission.

Marios-Nikos Psychogios: contributed to the manuscript, was involved in the acquisition of the data and approved the manuscript before submission.

Jan Liman: contributed to the manuscript and approved the manuscript before submission.

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