

Long-term outcome after thrombolysis in telemedical stroke care

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ABSTRACT

Background: IV thrombolysis represents the most effective acute stroke therapy. However, it is almost exclusively performed in stroke centers and is not available in most community areas. The Telemedical Pilot Project for Integrative Stroke Care (TEMPiS) was started in February 2003. Twelve community hospitals with no or very limited stroke thrombolysis experience and two stroke centers were connected via a network providing online neurologic examination and transfer of neuroradiologic scans. Following recently published preliminary results on acute phase safety of telethrombolysis, the present study reports on its long-term functional outcome.

Methods: Modified Rankin Scale (mRS), Barthel Index (BI), and mortality rate were prospectively collected 3 and 6 months after IV thrombolysis in patients of community network hospitals (telemedical group) and the stroke centers. Values of 95/100 for the BI and 0/1 for the mRS were defined as a favorable outcome.

Results: Over the first 22 months, 170 patients were treated with tPA in the telemedical hospitals and 132 in the stroke center hospitals. Mortality rates were 11.2% vs 11.5% at 3 months ($p = 0.55$) and 14.2% vs 13% at 6 months ($p = 0.45$). A good functional outcome after 6 months was found in 39.5% of the telemedical hospitals vs 30.9% of the stroke centers ($p = 0.10$) for the mRS and 47.1% vs 44.8% ($p = 0.44$) regarding the BI.

Conclusions: Mortality rates and functional outcomes for telemedicine-linked community hospitals and stroke centers were similar and comparable to the results from randomized trials.

Neurology® 2007;69:898-903

IV thrombolysis with recombinant tissue plasminogen activator (tPA) is approved in many countries for stroke treatment within 3 hours of symptom onset.^{1,2} Registries like the Canadian Alteplase for Stroke Effectiveness Study (CASES) could show its relevance in broad clinical practice.³ Nevertheless, only about 1 to 6% of all patients admitted for ischemic stroke receive a thrombolytic agent.^{4,5} Besides responsible factors like crossing the 3-hours time window and comorbidity, patients are often treated in local community hospitals where this treatment option is not routinely performed. Moreover, mortality has shown to increase significantly if only a few patients per year are treated in a single center.⁶

Recently, telemedical stroke networks have been established to support local community hospitals.^{5,7-11} It could be demonstrated that a neurologic examination^{12,13} and National Institute of Health Stroke Scale (NIHSS)^{14,15} administration is feasible by means of telemedicine. Few patients received telethrombolysis.^{8,16-20}

As treatment should be performed exclusively by physicians who are well experienced

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Editorial, see page 819

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Disclosure: The Departments of Neurology at the University of Regensburg and at the Städtisches Klinikum München GmbH, Klinikum Harlaching, have participated in studies sponsored by Boehringer Ingelheim/Germany and received financial support for their work. The company also supports the TEMPiS project by delivering Stroke-Code-Boxes for tPA use in the TEMPiS network. Since Boehringer Ingelheim is the only supplier of tPA in Germany, a potential conflict of interest is declared by the authors. Nevertheless, the study was performed and evaluated without influence from this or other companies or sponsors. Dr. Heinrich Audebert has received honoraria from Boehringer Ingelheim/Germany (supplier of tPA) and Meytec GmbH (supplier of the technical support of the network). The remaining authors have reported no further conflicts of interest.

with thrombolysis, the question arises as to whether treatment in community hospitals, telemedically supervised by a stroke expert, warrants comparable safety.

Since its start in 2003, preliminary results of the Telemedical Pilot Project for Integrative Stroke Care (TEMPiS) in Bavaria/Germany had demonstrated the feasibility of systemic thrombolysis with a rate of symptomatic hemorrhage of 7.8%. The tPA rates regarding ischemic infarcts were 4.4%.²¹ However, the major studies showed the most evident benefit after 3 months.^{1,2} Thus, the present study investigates the long-term outcome of patients after telethrombolysis compared to stroke centers and to the major tPA studies.

METHODS The network was previously described.^{9-11,21} In brief, the two stroke centers of the University of Regensburg and Munich-Harlaching and 12 participating community hospitals initiated the TEMPiS network. None of the community hospitals was equipped with a stroke unit before, and the use of tPA for stroke treatment was very limited prior to the start of TEMPiS (<10 treatments per year combined for all 12 hospitals).

Local stroke wards and teams were established. All hospitals were supplied with telemedical equipment including a two-way video conferencing system providing direct communication with the patient, the possibility for remote zooming and moving of the camera, and transmission of CT/MRT images by high speed. A 24-hour availability for CT scanning, Doppler and duplex sonography, ECG, and laboratory examinations was guaranteed on-site.

The two stroke centers offered support via 24-hour standby service in a weekly rotation and were obliged to start a teleconference within 3 minutes after telephone announcement.

Continued stroke teaching took place for every regional stroke team. Specific education for the use of tPA was carried out including NIHSS training.²² The stroke experts performing the telemedical examination were certified regarding the NIHSS. Concomitantly, periodical teaching visits and seminars on stroke issues were performed.

There were several defined indications for an obligatory telemedical presentation, including possible thrombolysis. In brief, indication for the administration of tPA was the combination of the following criteria: ischemia presumed in the anterior cerebral circulation within a 3-hour time window; NIHSS score between 5 and 20 points or if below, relevant deficits as aphasia; absence of major exclusion criteria according to the National Institute of Neurological Disorders and Stroke (NINDS) protocol. For safety reasons, the upper limit of 20 points was recommended at the start of the project in the telemedical setting. The score was assessed by the stroke experts in Regensburg or Munich-Harlaching.

Patients with possible thrombolysis were first briefly screened by the local physician. Afterwards, telemedical examination and scan transmission by the stroke experts were

performed and the recommendation for or against thrombolysis was discussed with the local colleague. A report was digitally transmitted.

Earlier results showed a mean duration of approximately 15 minutes per videoconference including CT scan transmission and examination.⁹ A telemedical follow-up patient examination including the NIHSS score and CT evaluation was performed 24 to 36 hours after thrombolysis, or earlier in case of clinical deterioration. Cerebral hemorrhages were classified according to the European Cooperative Acute Stroke Study.²³ The local physicians were enabled to contact the stroke centers immediately whenever complications were observed or acute questions occurred. In general, patients were supposed to remain in the community hospitals after thrombolysis and to be transferred only in particular cases if special diagnostic or therapeutic options were not available locally.

Consecutive patients undergoing IV thrombolysis at the stroke centers at University of Regensburg and Klinikum Munich-Harlaching during the same time period served as controls. Both institutions have year-long experience in administration of systemic thrombolysis and participated in multiple clinical stroke trials.

The long-term outcome was prospectively examined in all patients receiving systemic thrombolysis within TEMPiS from February 2003 to November 2004, including survival rate and telephone interviews 3 and 6 months after thrombolysis including Barthel Index (BI)²⁴ and modified Rankin Scale (mRS).²⁵ Traditionally, good functional outcome is defined as a BI of 95 to 100 or a mRS of 0/1. All interviews were performed by a single experienced neuropsychologist. If direct contact with the patients was not achievable, the questionnaires were sent to their postal address. The general practitioners of the patients or the responsible local authorities were contacted when the correspondence was not answered. The study was approved by the local ethics committee.

Statistical analysis. For the statistical analysis, SPSS 12.0 (Statistical Package for Social Sciences Inc., Chicago, IL) was used. Basic characteristics were expressed in mean \pm SD or median values. To test for univariate significance, we used Fisher exact tests, chi-square tests, or Mann-Whitney *U* tests for categorical variables and Student *t* tests for continuous variables with a significance level of $p \leq 0.05$. For comparison between telemedical group and stroke centers, OR with 95% CI were calculated. We used logistic regression models to identify the most important predictors for favorable vs poor functional outcome after 3 months. The independent variables were group (telemedical or stroke center), age, NIHSS at admission, medication before stroke (platelet function inhibitors and oral anticoagulation), arterial hypertension, diabetes mellitus, chronic ischemic heart disease, atrial fibrillation, and onset to treatment time.

RESULTS Between February 2003 and November 2004, 170 patients received systemic thrombolysis in the community hospitals after telemedical consultation (telemedical group) and 132 consecutive patients were treated with tPA in the stroke centers at the University of Regensburg and at Munich-Harlaching (stroke center group). Both groups were comparable regarding baseline char-

Table 1 Baseline characteristics of concurrent patients of Telemedical Pilot Project for Integrative Stroke Care and the stroke centers

	Telemedical group, n = 170	Stroke center group, n = 132	p Value (two-tailed)
Mean age, y	69.4	69.6	0.927
Above 80 y (%)	10	13.6	0.366
Female (%)	40.6	36.4	0.633
Risk factors (%)			
Arterial hypertension	76.5	79.5	0.578
Diabetes mellitus	19.4	24.2	0.326
Chronic ischemic heart disease	18.8	13.6	0.275
Atrial fibrillation	44.1	37.1	0.240
Medication before stroke (%)			
Platelet function inhibitors	31.8	28.8	0.447
Oral anticoagulation	2.4	3.8	0.248
Localization (%)			
Right MCA territory	48.8	38.9	0.209
Left MCA territory	45.9	53.4	
Vertebrobasilar territory	5.3	7.6	
Median NIHSS on admission (range)	12 (2-25)	11 (2-34)	0.214
NIHSS 21-25 pts (%)	4.1	6.8	0.459
Mean onset to treatment time (min)	140.6	143.6	0.451
Outside 3-hours time window (%)	3.5	5.3	0.387

Further risk factors like previous stroke or smoking were not analyzed as they were not consistently documented in all hospitals.

NIHSS = NIH Stroke Scale.

acteristics like median NIHSS and onset to treatment (table 1).

After 3 and 6 months, survival could be evaluated in 169 patients (99.4%) of the telemedical group and in 132 patients (100%) of the stroke center group. Nineteen out of 169 (11.2%) of the telemedical and 15/132 (11.5%) of the stroke center patients died during the first 3 months. During the whole investigation period of 6 months, the

mortality rate was 24/169 (14.2%) in the telemedical group and 17/132 (13%) in the stroke center group. In deceased patients, any signs of cerebral hemorrhage were found in 6/24 of the telemedical and 3/17 of the stroke center patients 24 to 36 hours after thrombolytic therapy. The differences between the groups were not significant (table 2).

After 3 months, BI and mRS could be acquired in 162 patients (95%) of the telemedical group,

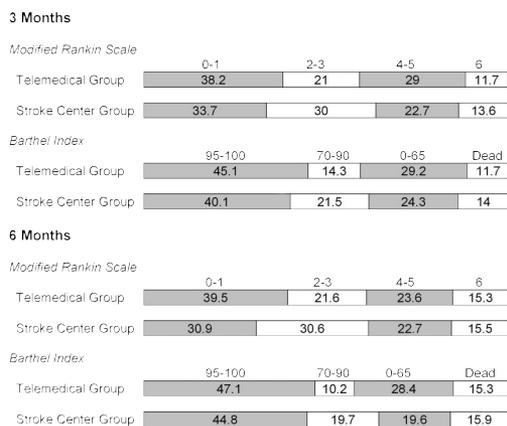
Table 2 Favorable functional outcome and mortality after 3 and 6 months

	Telemedical group	Stroke center group	OR (95% CI)	p Value
3 months				
mRS 0/1 (%)	38.2	33.7	1.2 (0.7-2.0)	0.258
BI 95/100 (%)	45.1	40.1	1.3 (0.8-2.1)	0.197
Survival rate (%)	88.8	88.6	1.0 (0.7-1.4)	0.550
Any cerebral hemorrhage in deceased patients	6/24	3/17	0.6 (0.2-2.6)	0.391
6 months				
mRS 0/1 (%)	39.5	30.9	1.5 (0.9-2.4)	0.095
BI 95/100 (%)	47.1	44.8	1.1 (0.6-1.8)	0.443
Survival rate (%)	85.8	87.1	0.9 (0.5-1.8)	0.448

Differences between the telemedical and stroke center group regarding mortality rate and favorable functional outcome. The evaluation of the modified Rankin Scale (mRS) and Barthel Index (BI) based on the amount of returned questionnaires.

In this descriptive analysis, favorable functional outcome was defined as Barthel Index (BI) 95/100, modified Rankin Scale (mRS) 0/1. The evaluation of the mRS and BI score based on the amount of returned questionnaires. Stroke center patients served as controls. Percentages are given and do not always total 100 because of rounding. Missing patients were not considered.

Figure Functional outcome results of both study groups after 3 and 6 months



and in 110 patients (83%/mRS) or 107 patients (81%/BI) of the stroke center group. After 6 months, BI and mRS were performed in 157 patients (92.4%) of the telemedical group and in 110 patients (83%/mRS) or 107 patients (81%/BI) of the stroke center group. The missing data after 3 months were from patients having a median NIHSS of 12 points of the telemedical and 14 points of the stroke center group. There was no difference between the groups ($p = 0.959$)

After 3 months, a positive outcome regarding BI was seen in 73/162 (45.1%) of the telemedical and 43/107 (40.1%) of the stroke center patients (figure). A score of 0 or 1 in the mRS indicating no symptoms or a minimal handicap was found in 62/162 (38.2%) patients of the telemedical group and 37/110 (33.7%) stroke center patients. There was no significant difference between the two study groups 3 months after thrombolysis regarding a positive outcome in the BI and the mRS as demonstrated in table 2.

Six months after IV thrombolysis, 74/157 (47.1%) of the telemedical patients and 48/107 (44.8%) of the stroke center group met a BI score of 95 to 100. mRS score of 0 or 1 was seen in 62/157 (39.5%) of the telemedical and 34/110 (30.9%) of the stroke center group (figure). Differences were not significant (table 2).

In logistic regression, predictors for BI and mRS were largely identical except for onset to treatment time, which was a predictor for a good functional outcome in the BI ($p = 0.03$) but not regarding mRS. The most important predictors were NIHSS score at admission and age. Patients who were older or who had a higher NIHSS score were less likely to have a good functional outcome. Belonging to the telemedical or stroke center group had no significant influence on BI and

mRS. A detailed analysis can be found on the *Neurology* Web site at www.neurology.org.

DISCUSSION The data from the TEMPiS Project represent the largest study on thrombolysis in telemedical stroke care. More than 300 patients were included in the telemedical and stroke center groups, i.e., as many patients were treated with tPA as in each of the major randomized studies.^{1,2} The rate of thrombolysis in the participating community hospitals was raised about 10-fold by this project. Most of these patients would otherwise not have been able to reach existing stroke units in time.

Earlier results from the TEMPiS project showed feasibility of tPA management and acute phase safety of telemedical thrombolysis concerning in-hospital mortality and symptomatic hemorrhage.^{9,21} The present study demonstrates comparable outcome of the telemedical group compared to stroke centers.

First of all, approximately 90% of the patients receiving tPA under telemedical supervision survived the first 3 months after stroke. The functional state as described by BI and mRS could be obtained from almost all patients. Causes of death in the telemedical group within 3 months after thrombolysis were in most cases consequences of large MCA territory infarction due to insufficient or late recanalization, but not hemorrhage as a complication of treatment. Depending on the method of definition regarding BI or mRS and timepoint, between 38.2 and 47.1% of patients showed a favorable long-term outcome after 3 to 6 months. Even if the rare missing follow-up data were assumed to reflect patients with unfavorable outcome, the overall long-term results of telemedically guided thrombolysis still remain comparable to those of certified stroke units and those of major studies.^{2,3,26} With 11.8% after 3 months, the mortality rate was less than in the CASES study (22.3%). Compared to the NINDS study (17%) the mortality rate after 6 months was also lower (table 3).

Thus, the safety and effectiveness of systemic thrombolysis performed by less experienced physicians in community hospitals in a telemedical network under guidance by stroke experts seems to be comparable to that achieved in dedicated stroke centers. It is useful to bring stroke expertise to community areas without specialized stroke facilities. We have to bear in mind though that the success of the project is due to continuous teaching for the physicians both in the community hospitals and in the stroke centers. Special-

Table 3 Comparison to the National Institute of Neurological Disorders and Stroke (NINDS) and Canadian Alteplase for Stroke Effectiveness Study (CASES) studies

	TEMPiS telemedical group	TEMPiS stroke center group	NINDS	CASES
Number of tPA-treated patients	170	132	312	1135
Median age, y	71	70	67	73
Female (%)	40.6	36.4	43	45.1
Median NIHSS at admission	12	11	14	14
mRS (0-1) after 3 months (%)	38.2	33.7	39	36.8
mRS (0-1) after 6 months (%)	39.5	30.9	41	—
BI (95-100) after 6 months (%)	47.1	43.9	50	—
Survival rate after 3 months (%)	88.2	88.7	83	77.7
Survival rate after 6 months (%)	85.9	87.1	79	—

The results of the concurrent study are compared to the major randomized tPA study of NINDS¹ and CASES.³ TEMPiS = Telemedical Pilot Project for Integrative Stroke Care.

ized multidisciplinary visits by the stroke experts, standard operation procedures, and a modern technique allowing fast and high-quality transmission of the patient examination and scans were established. Safe tPA utilization in a telemedical network can only be achieved when based on these requirements.

Nevertheless, the study is limited as it is a non-randomized trial with nonblinded interrogations. Even though the vital state could be achieved in almost every patient, the functional outcome is not known in 7.6% of the telemedical group after 6 months. TEMPiS patients seemed to be more motivated to take part in the interrogations than ordinary patients.

A further limitation was the upper NIHSS limit of 20 points at the beginning of the project. This was set as no sufficient data on telethrombolysis were existing. Regardless of the limit, eight telemedical patients with a higher score received tPA. The percentage of patients above 20 points was not much higher in the stroke centers (table 1). Nevertheless, the limit might have had an influence on the outcome data and caused a lack of comparability to the NINDS and CASES studies.

Various risk factors were documented and analyzed except for smoking and previous stroke. This might have an impact on the results even though it should influence the outcome of the stroke center group as well.

In general, the present data show that telemedical thrombolysis becomes a realistic treatment option for community areas if a transfer to a specialized stroke center is not practicable within the 3-hour time window.

ACKNOWLEDGMENT

The authors thank the Bavarian health insurance companies, the Bavarian State Ministry for Employment and Social Order, Family and Women, and the German Stroke Foundation for the support of the project and its evaluation. The stroke neurologists in the Departments of Neurology at the University of Regensburg and the Städtisches Krankenhaus München-Harlaching as well as the physicians in the participating network hospitals (Bad Tölz, Burglengenfeld, Cham, Ebersberg, Eggenfelden, Dachau, Freising, Kelheim, Mühlendorf, München-Pasing, Rosenheim, Straubing) have contributed to the success of this study, as did Horst Koch and Catherine and Paul Watkins, for their support in editing the manuscript. Finally, the authors thank their patients for their fine collaboration.

Received June 2, 2006. Accepted in final form March 21, 2007.

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