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Comparison of Tissue Plasminogen Activator Administration Management Between Telestroke Network Hospitals and Academic Stroke Centers

The Telemedical Pilot Project for Integrative Stroke Care in Bavaria/Germany

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Background and Purpose—Systemic thrombolysis is the only therapy proven to be effective for ischemic stroke. Telemedicine may help to extend its use. However, concerns remain whether management and safety of tissue plasminogen activator (tPA) administration after telemedical consultation are equivalent in less experienced hospitals compared with tPA administration in academic stroke centers.

Methods—During the second year of the ongoing Telemedical Pilot Project for Integrative Stroke Care, all systemic thrombolyses in stroke patients of the 12 regional clinics and the 2 stroke centers were recorded prospectively. Patients' demographics, stroke severity (National Institutes of Health Stroke Scale), frequency of administration, time management, protocol violations, and safety were included in the analysis.

Results—In 2004, 115 of 4727 stroke or transient ischemic attack patients (2.4%) in the community hospitals and 110 of 1889 patients in the stroke centers (5.8%) received systemic thrombolysis. Prehospital latencies were shorter in the regional hospitals despite longer distances. Door to needle times were shorter in the stroke centers. Although blood pressure was controlled more strictly in community hospitals, symptomatic intracerebral hemorrhage rate (7.8%) was higher ($P=0.14$) than in stroke centers (2.7%) but still within the range of the National Institute of Neurological Disorders and Stroke trial. In-hospital mortality rate was low in community hospitals (3.5%) and in stroke centers (4.5%).

Conclusions—Although with a lower rate of systemic thrombolysis, there was no evidence of lower treatment quality in the remote hospitals. With increasing numbers of tPA administration and growing training effects, the telestroke concept promises better coverage of systemic thrombolysis in nonurban areas. (*Stroke*. 2006;37:1822-1827.)

Key Words: stroke ■ telemedicine ■ thrombolysis

Systemic administration of recombinant tissue plasminogen activator (tPA) is still the only proven therapy specific to acute ischemic stroke. Currently in Germany, its use outside of clinical trials is reserved mainly for academic stroke centers,¹ and international guidelines recommend that “thrombolytic therapy should only be given if the diagnosis is established by a physician who has expertise in the diagnosis of stroke, and a computed tomography (CT) of the brain is assessed by physicians who have expertise in reading this imaging study.”²

Some studies investigating administration of tPA in routine clinical care found differences between academic and community hospitals. In general, tPA is used less often in community^{3,4}

compared with academic hospitals.^{5,6} In addition, there is evidence that lower expertise in tPA treatment might be associated with higher rates of in-hospital death^{1,7} or symptomatic intracerebral hemorrhages.³

One approach to increase the percentage of patients treated with tPA in routine clinical care is to develop more qualified stroke centers and to find ways to get patients to those centers faster.⁸ However, in regions with wide geographical distances between community hospitals and experienced stroke centers, telemedical networking might be a timesaving alternative to improve administration of tPA in community hospitals.^{9,10} Previously, we reported feasibility and preliminary safety data¹⁰ as well as facilitation of telethrombolysis by using a Stroke Lysis

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Box¹¹ in community hospitals. However, concerns were frequently expressed whether tPA management in telestroke networks really could achieve quality standards of stroke centers and whether the short-term complications would remain at a low level with greater patient numbers.

This study was performed to investigate the impact of telemedical networking on processes of tPA administration in community hospitals compared with academic hospitals.

Methods

Telestroke Organization

A detailed description of the Telemedical Pilot Project for Integrative Stroke Care (TEMPiS) concept was published previously.^{10–12}

In summary, TEMPiS was founded by 2 academic stroke centers (Munich-Harlaching and Regensburg) to provide specialized stroke care in a nonurban area of eastern Bavaria, where no stroke units existed. Twelve regional hospitals are participating in the project, including 2 hospitals with neurological departments and 10 hospitals in which stroke care is provided by the internal medicine departments.

Core Elements of TEMPiS

There are 4 core elements of TEMPiS, as follows: (1) Setup of specialized stroke wards in each hospital with 24-hour availability of diagnostic procedures including CT scan, laboratory exams, and Doppler sonography. Stroke teams were formed with doctors, specialized nurses, physiotherapists, speech therapists, and occupational therapists. Stroke treatment is based widely on standardized stroke care protocols. (2) Comprehensive and continuing stroke training for all medical staff members including training in National Institutes of Health Stroke Scale (NIHSS), implementation of a thrombolysis algorithm, and disposition of tPA protocols. (3) Implementation of a telemedicine network with daily 24-hour service using a high-speed data transmission for digital brain images and real-time clinical examination of patients via videoconference. (4) Central organization of emergency interhospital transfers, including interventional treatment of hemorrhagic complications.

To facilitate the utilization of tPA, a so-called stroke lysis box, which contains all necessary tools and medications, was developed and distributed to all community hospitals.

Indications for telemedical consultation were defined before the project start. They included presentation of all patients with a possible indication of systemic thrombolysis. The teleconsultation service in the 2 academic stroke centers is staffed with 5 full-time neurologists who must not be in charge of additional clinical duties.

Thrombolysis in the Stroke Centers

The stroke units in the 2 stroke centers were founded in 1991 (Munich-Harlaching) and 1998 (Regensburg). Both institutions have yearlong experience in administration of systemic thrombolysis and have participated in multiple clinical trials. tPA was administered according to the European approval definitions permitting tPA administration within 3 hours of onset in patients with relevant clinical deficits up to 25 points on the NIHSS.

In special cases (eg, after diffusion-perfusion mismatch examination and after an individual risk–benefit assessment), delayed tPA administration could be given later but mainly within 4 hours of onset, as suggested in the pooled analysis of tPA trials.¹³ For calculation of tPA numbers in the areas of the primary catchment, patients who were transferred from other hospitals or had an ambulance transport of >35 km were excluded.

Baseline parameters were documented in the “Lysis Protocol,” which also prescribes controls of blood pressure all 15 minutes during the tPA infusion, all 30 minutes between the second and sixth hour, and all hourly between hour 7 and hour 24.

Thrombolysis in the Community Hospitals

In the year before TEMPiS was started, a total of 10 systemic tPA treatments had been performed in all regional network hospitals. Hence, these clinics had little experience in this treatment concept.

tPA was administered using telemedicine according to the European approval definitions permitting tPA administration within 3 hours of onset using the same Lysis Protocol as in the stroke centers. For safety reasons,^{14,15} the upper limit of NIHSS was generally restricted to 20 points in the telemedical setting. Seven patients were excluded for an NIHSS score between 20 and 25.

Data Collection

From January 1, 2004, to December 31, 2004, data of all patients receiving tPA were recorded prospectively. The medical history and clinical data were documented, including time of onset, time of hospital admission, time of CT scan, and administration of the tPA bolus, as well as the clinical course of each patient. CT scans on admission and follow-up CT scans were collected as digital images. After 24 (to 36) hours, all patients treated with tPA in the community hospitals had a telemedical follow-up including transmission of follow-up imaging. In case of discharge after <7 days, vital status on day 7 was recorded using the discharge report of the rehabilitation units or via telephone.

Total numbers of patients and proportions of stroke subtypes were determined according to the data of the controlling departments.

Twenty-seven patients of the regional hospitals who received tPA using telemedicine between January and April 2004 were included already in the recently published safety analysis.¹⁰

Assessment of CT and MRI Scans

Radiological analysis was performed by a radiologist who was blinded to the clinical course of the patients.

Bleedings were categorized according to the criteria published by Fiorelli et al¹⁶ for the European Cooperative Acute Stroke Study I cohort as follows: hemorrhagic infarctions with small petechial hematoma (HI1), hemorrhagic infarctions with more confluent petechiae (HI2); parenchymal hematoma <30% of the infarcted area with some mild space-occupying effect (PH1); and parenchymal hematoma ≥30% of the infarcted area with significant space-occupying effect or clot remote from infarcted area (PH2).

In addition to the definitions of Fiorelli, the term “focal subarachnoid hemorrhage” was used by the radiologist for a small subarachnoid hemorrhage in 1 hemispheric sulcus next to the infarcted area without extension to other sulci or basal cisterns.

In the 2 stroke centers, MRI was used as follow-up imaging in 25 cases. Radiological assessment of bleeding complications was then conducted using T2*-weighted images. Fiorelli criteria of hemorrhage volume and location were used as in CT scans, and all hemorrhagic lesions were interpreted as acute except of known residual hemorrhagic defects.

According to the National Institute of Neurological Disorders and Stroke (NINDS) definition,¹⁷ hemorrhage was considered symptomatic “if it was not seen on a previous CT scan and there had subsequently been either a suspicion of hemorrhage and any decline of neurologic status.” Intracerebral hemorrhages were assessed as treatment related when they were observed within the first 36 hours.

Statistical Analysis

The χ^2 test and Fisher exact test were used to compare proportions. Mann–Whitney *U* test was used to test nonparametrical variables. Patients who were transferred from other hospitals to 1 of the 2 stroke centers (n=7) or who were treated after 4 hours using the mismatch concept of MRI images (n=1) were excluded from the calculations of prehospital and in-hospital time intervals. For analysis of in-hospital processes, 2 patients (both in academic centers) were excluded because exact times of drug administration and of initial CT scan were not accessible. Data were analyzed using the Statistical Package for Social Sciences (SPSS v12).

TABLE 1. Proportions of Stroke Subtypes and tPA Administrations

| 2004 | Community Hospitals | Stroke Centers | P Value |
|---|---------------------|----------------|---------|
| All stroke/TIA patients | 4727 | 1883 | |
| Classification, n (%) | | | |
| Cerebral infarcts | 2603 (55.1) | 1286 (68) | |
| Intracerebral hemorrhages | 341 (7.2) | 171 (9.1) | |
| Subarachnoid hemorrhages | 78 (1.6) | 27 (1.4) | |
| TIA | 1482 (31.4) | 374 (19.9) | |
| Undetermined | 223 (4.7) | 25 (1.3) | |
| Percentage of patients treated with tPA (%) | | | |
| Percentage of all strokes | 115 (2.4) | 110 (5.8) | <0.01 |
| Percentage of ischemic infarcts | 115 (4.4) | 110 (8.6) | <0.01 |
| No. of systemic thrombolyses in patients living in the catchment area of <35 km | 115 (100) | 93 (84.5) | |
| No. of tPA patients admitted within 90 minutes of onset, n (%) | 94 (82) | 71 (71*) | 0.06 |
| Administration of tPA bolus >3 hours of onset, n (%) | 6 (5.2) | 16 (14.5) | 0.02 |
| No. of patients receiving tPA within 120 minutes, n (%) | 36 (31.3) | 33 (30.0) | 0.49 |
| No. of patients receiving tPA within 90 minutes, n (%) | 6 (5.2) | 11 (9.6) | 0.13 |

*After exclusion of 10 patients (see Methods).

Results

In 2004, 115 of all 4727 ischemic and hemorrhagic stroke and transient ischemic attack (TIA) patients (2.4%) received tPA in the 12 regional hospitals, and 110 of 1889 (5.8%) cases were treated with systemic thrombolysis in the 2 stroke centers. Stroke severity was similar in both settings with median NIHSS of 12 in the regional clinics and of 11 in the academic hospitals.

The numbers of tPA treatments ranged from 6 to 15 per clinic in the community hospitals and 21 to 89 in the academic centers. The percentages of patients receiving tPA varied from 1.5% (of all stroke or TIA patients) to 4.8% in the regional clinics and from 3.5% to 6.9% in the stroke centers. The percentage of patients receiving tPA was twice as much in the stroke centers.

Distributions of admitted patients (Table 1) and characteristics (Table 2) of patients treated with tPA in community hospitals are compared with those treated in academic centers.

The number of patients receiving tPA after >3 hours of onset or stroke severity of >20 points on the NIHSS was higher in the academic centers.

Excluding these patients and patients who were transferred from other hospitals (n=5) or had a helicopter transport for

TABLE 2. Characteristics of Patients Receiving tPA in Community and Academic Hospitals

| 2004 | Community Hospitals | Stroke Centers | P Value |
|--|---------------------|----------------|---------|
| Age (years) | | | 0.82 |
| Mean (SD) | 69.7 (10.7) | 69.8 (11.4) | |
| Range | 36–93 | 35–94 | |
| Female (%) | 50 (44) | 41 (37) | 0.19 |
| Hypertension | 87 (75.7) | 86 (78.2) | 0.75 |
| Diabetes | 22 (19.1) | 25 (22.7) | 0.51 |
| Hyperlipidemia | 23 (23.0) | 49 (44.5) | <0.01 |
| Atrial fibrillation | 24 (20.9) | 45 (40.9) | <0.01 |
| Platelet inhibitors before admission | 38 (33) | 32 (29) | 0.57 |
| Oral anticoagulation before admission | 3 (2.6) | 8 (7.3) | 0.13 |
| Blood glucose level at admission | | | |
| Mean (SD) | 125.3 (39.1) | 132.0 (37.0) | |
| Median (range) | 116.0 (60–304) | 123 (62–284) | 0.05 |
| International normalized ratio | | | |
| Mean (SD) | 1.034 (0.13) | 1.041 (0.12) | |
| Median (range) | 1.0 (0.8–1.5) | 1.0 (0.8–1.7) | 0.53 |
| Systolic blood pressure at admission (mean) | 160.0 (27.5) | 160.7 (28.8) | 0.61 |
| Diastolic blood pressure at admission (mean) | 86.6 (14.3) | 81.9 (15.4) | 0.048 |
| Systolic blood pressure before tPA (mean) | 156.7 (20.0) | 155.7 (21.4) | 0.99 |
| Diastolic blood pressure before tPA (mean) | 82.3 (12.6) | 80.8 (15.8) | 0.81 |
| NIHSS at inclusion | | | |
| Mean (SD) | 12.4 (4.9) | 11.9 (5.3) | |
| Median (IQR) | 12 (9–16) | 11 (8–16) | 0.18 |
| Range | 4–24 | 2–25 | |
| Patients with NIHSS score >20 | 3 (2.6) | 8 (7.0) | 0.16 |

IQR indicates interquartile range.

>35 km (n=11), the remaining tPA rate was still significantly higher (5.0% versus 2.4%) in the stroke centers.

Significant differences were found for hyperlipidemia, atrial fibrillation, and diastolic blood pressure at admission.

There were no statistically significant differences in mortality and symptomatic hemorrhage rate, although symptomatic hemorrhages were more frequent in the community hospitals (Table 3).

In patients treated with an NIHSS score >20, no symptomatic hemorrhage occurred. One patient died in-hospital because of a sepsis after pneumonia. In patients who received tPA beyond the 3-hour time window, there was only 1 symptomatic hemorrhage.

TABLE 3. Complications After tPA Treatment

| | Community Hospitals n=115 | Stroke Centers n=110 | P Value |
|--|------------------------------|-------------------------|------------|
| Categorization of intracranial bleeding n (%)* | | | |
| HI1 | 18 (15.6) | 10 (9.1) | 0.16 |
| HI2 | 6 (5.2) | 6 (5.5) | 1.0 |
| PH1 | 7 (6.1) | 2 (1.8) | 0.17 |
| PH2 | 5 (4.3) | 3 (2.7) | 0.72 |
| Focal subarachnoid hemorrhage** | 3 (2.6) | 0 | |
| Symptomatic hemorrhages (%; 95% CI) | 9 (7.8; 3.6–14.3) | 3 (2.7; 0.6–7.8) | 0.14 |
| Mortality within 7 days, n (%; 95% CI) | 4 (3.5; 1.0–8.7) | 1 (0.9; 0.0–5.0) | 0.37 |
| In-hospital mortality, n (%; 95% CI) | 4 (3.5; 1.0–8.7) | 5 (4.5; 1.5–10.3) | 0.74 |

*For categorization, see Methods; **all in combination with PH1 hemorrhages.

As shown in Table 4, time to admission and time from admission to first imaging was shorter in the community hospitals, whereas latency from CT to tPA bolus and total door to needle time was shorter in the stroke centers. Overall time from symptom onset to treatment was similar in both groups. Blood pressure was controlled more strictly in the remote hospitals.

Discussion

The data of the present analysis indicate that quality of tPA management was comparable in community and academic hospitals. As for the time intervals of prehospital and in-hospital management, it is noteworthy that time of onset to admission was shorter in the community hospitals despite often longer transport distances in rural areas. The slightly longer in-hospital time in community hospitals (especially the time from first imaging to treatment), might be attributed to the time needed for teleconsultation. Although the admission to CT time was shorter in the regional clinics, the CT to treatment interval took ≈17 minutes longer, which corresponds to the average duration of teleconsultations.¹⁰

Similar results were found for patient characteristics as well as for time from onset to tPA administration. The percentage of patients with symptomatic hemorrhage was higher in the community hospitals, but this difference was not statistically significant. The overall symptomatic hemorrhage rate in community hospitals was within the range of the NINDS trial¹⁷ (7.8% versus 6.4%) and a meta-analysis of previous publications¹⁸ (5.2%). However, the symptomatic hemorrhage rate in the academic stroke centers was within the lowest rates reported so far.^{19,20} This may reflect statistical variations in small sample numbers. Considering the very strict definition of symptomatic hemorrhage in the current analysis, these data do not pose major safety

TABLE 4. Processes of tPA Management

| | Community Hospitals | Stroke Centers | P Value |
|---|---------------------|----------------|------------|
| Time interval, minutes | | | |
| Onset to admission | | | |
| Mean (SD) | 64 (26) | 74 (31) | <0.01 |
| Median (IQR) | 60 (50–80) | 70 (56–92) | |
| Range | 0–134 | 0–172 | |
| Admission to CT time | | | |
| Mean (SD) | 17 (9) | 27 (16) | <0.01 |
| Median (IQR) | 15 (10–23) | 24 (15–36) | |
| Range | 1–42 | 1–101 | |
| CT to treatment time | | | |
| Mean (SD) | 51 (22) | 34 (22) | <0.01 |
| Median (IQR) | 48 (35–61) | 29 (20–51) | |
| Range | 10–112 | 3–109 | |
| Admission to treatment time | | | |
| Mean (SD) | 68 (23) | 61 (23) | 0.03 |
| Median (IQR) | 65 (50–82) | 57 (47–75) | |
| Range | 25–130 | 15–135 | |
| Onset to treatment | | | |
| Mean (SD) | 134 (30) | 135 (38) | 0.81 |
| Median (IQR) | 135 (115–154) | 135 (110–165) | |
| Range | 65–210 | 15–220 | |
| Highest systolic blood pressure during 24 hours after tPA (mean) | 147.7 (17.3) | 174.0 (23.7) | <0.01 |
| Highest diastolic blood pressure during 24 hours after tPA (mean) | 76.1 (9.6) | 91.3 (14.6) | <0.01 |
| Length of in-hospital stay (days) | | | |
| Mean (SD) | 10.3 (4.4) | 10.5 (6.3) | |
| Median (IQR) | 10 (8–13) | 9 (6–13) | 0.53 |

IQR indicates interquartile range.

concerns. In other studies, different definitions were used. In some of these definitions, hemorrhages were taken as symptomatic only if parenchymal hemorrhages (PH1 and PH2) were observed.¹⁹ In other reports, clinical deterioration was defined as worsening of neurological symptoms resulting in an increase of the NIHSS score^{6,21} or in a “critical decline of neurological status.”²² Using these definitions, the symptomatic hemorrhage rate in our samples would have been 6.1% in the community hospitals and 1.8% in the academic hospitals.

Although patient selection in the regional hospital was restricted to an upper limit of the NIHSS score of 20, the low mortality rate of 3.5% in the regional hospitals argues for the safe management of patients with tPA administration, especially considering the previously reported in-hospital mortality rate of 13.4% in German hospitals, with <6 thrombolytic treatments per year¹ and 9.4% in experienced hospitals.⁷ In fact, in-hospital mortality in both groups was lower than the previously reported

rates of in-hospital death after systemic thrombolysis.^{1,3,6,21,23–27} Also, mortality within 7 days remained lower than in randomized tPA stroke trials within a 3-hour¹⁷ and 6-hour time window^{28–29} or observational series.^{10,30}

The rate of tPA treatments in community hospitals remained significantly lower than in stroke centers, even after exclusion of all patients who had admission transports of >35 km and patients with onset to treatment time of >3 hours. Whereas in the year before the project start, only 10 stroke patients had received tPA in the regional hospitals,¹⁰ the numbers of patients treated with systemic tPA was >10-fold higher during the 2-year project period. Higher proportions of thrombolytic therapy are only achievable with continuous educational activities, as described in several publications.^{19,21,30} Both the participating academic and community hospitals are currently attempting to improve public awareness for stroke symptoms and prehospital stroke care.

Conclusion

Telemedical support offers a novel and pragmatic way to extend the benefits of systemic thrombolysis to rural areas. tPA administration can be conducted in regional hospitals with similar treatment quality. The symptomatic hemorrhage rate within the range of previous published trials requires further observation. Increasing the proportion of patients receiving this therapy remains an important objective for telemedical networks.

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