Pre-hospital factors determining regional variation in thrombolytic therapy in acute ischemic stroke

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Abstract

Background
Treatment rates with intravenous tissue plasminogen activator (tPA) vary by region, which can be partially explained by organisational models of stroke care. A recent study demonstrated that pre-hospital factors determine a higher thrombolysis rate in a centralised versus decentralised model in the North of the Netherlands.

Aim
To investigate pre-hospital factors that may explain variation in thrombolytic therapy between a centralised- and a decentralised model.

Methods
A consecutive case observational study was conducted in the North of the Netherlands comparing patients arriving within 4.5 hours in a centralised versus decentralised stroke care model. Factors investigated were transportation mode, prehospital diagnostic accuracy, and preferential referral of thrombolysis candidates. Potential confounders were adjusted using logistic regression analysis.

Results
A total of 172 and 299 arriving within 4.5 hours were enrolled in centralised and decentralised settings, respectively. The rate of transportation by emergency medical services was greater in the centralised model (adjusted OR 3.11; 95% CI, 1.59 – 6.06). Also, more misdiagnoses of stroke occurred in the central model (P=0.05). In postal code areas with and without potential preferential referral of thrombolysis candidates because of overlapping catchment areas, the odds of hospital arrival within 4.5 hours in the central vs decentral model were 2.15 (95% CI, 1.39 – 3.32) and 1.44 (95% CI, 1.04 – 2.00), respectively.

Conclusions
These results suggest that greater tPA use in centralised stroke care may relate to a lower threshold to use emergency services to transport stroke patients and partly to preferential referral of thrombolysis candidates.
Introduction

Treatment with intravenous tissue plasminogen activator (tPA) is the only proven treatment for patients with acute ischemic stroke if started within 4.5 hours (1-3). However, treatment rates with tPA in acute ischemic stroke vary considerably by region (4,5). The reasons for this variation are largely unknown. Different organisational models of acute stroke care have been suggested as explanatory variables.

We previously demonstrated a 50% greater likelihood of tPA treatment in a centralised versus decentralised model of acute stroke care (6). In this study, the centralised model consisted of 4 hospitals, in which tPA treatment was only provided in University Medical Centre Groningen (UMCG), acting as a regional stroke centre. The decentralised model consisted of 9 general hospitals each providing tPA treatment for patients in their catchment area. The centralised model yielded a larger proportion of patients presenting to the Emergency Department (ED) within the 4.5 hours time window (onset-to-door). Thus, more patients were eligible for thrombolytic therapy in the centralised model based on prehospital factors.

Aim

To investigate which prehospital organisational factors determine this benefit of the centralised model.

Methods

Study design and setting

We performed a consecutive case observational study in the North of the Netherlands. The centralised model consisted of four hospitals in which thrombolysis is provided by the UMCG, acting as stroke centre. Within its catchment area, arrangements were made with General Practitioner (GP) offices and Emergency Medical Services (EMS) to transport suspected stroke patients potentially eligible for thrombolysis to the UMCG, thereby bypassing community hospitals which may be located closer to the patient. The centralised stroke model served an approximate population of 0.58 million inhabitants with a population density of 250 inhabitants/km². The decentralised model consisted of nine community hospitals all treating patients with thrombolysis within their own catchment area. The decentralised model served a population of 1.14 million inhabitants with a population density of 190 inhabitants/km². Distances and access to healthcare services, such as the GP and EMS were comparable for both models (7).

In this study we focused on assessing prehospital organisational factors across patients arriving at the hospital within 4.5 hours, regardless of the final hospital discharge diagnosis. This means that, as opposed to a previous publication in which we focused on ischemic stroke
patients (6), those patients suffering from Transient Ischemic Attack (TIA), hemorrhage, and alternative diagnoses were also included in the current analysis (Figure 1). We also expanded the study period to August 30, 2010.

**Selection of participants**

Inclusion criteria included patient age 18 years and older who presented to the GP, EMS, or the ED from February 1 to August 30, 2010, and who were triaged as a possible stroke victim. Recurrent strokes were considered eligible for study enrollment. No limitations were made for upper age limits based on experiences in our setting and others (8,9).

**Data collection**

Identical protocols for tPA treatment (adjusted ECASS III (10)), identification and triage of suspected stroke patients, and 911 systems were used in both models. Pre-hospital data was gathered by ambulance personnel using a survey containing 16 data fields that were completed for each suspected stroke patient they transported. Hospital data was gathered upon ED arrival for all suspected stroke patients by the neurologist on call using a survey containing 28 items. Identical surveys were used by all EMS systems and hospitals participating in this study. All information was entered electronically into a central database by either the stroke neurologist, stroke nurse, or the principal investigator (M.L.). Identical stroke guidelines (11) and EMS protocols were available for GP offices and for dispatch (12) and ambulance personnel (13). In case of possible candidacy for tPA treatment high priority transport was assigned, defined as a normative value of 15 minutes between 911 call and ambulance arrival at the location of the patient. Both ambulance personnel

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*Significantly more patients arriving within 4.5 hours in the centralized system. GP indicates general practitioner, EMS, emergency medical services.

**Figure 1.** Flow chart of the study.
and the GP (either by telephonic or visit) used the Face Arm Speech Test \(^{(14)}\) as stroke identification tool. Hospital prenotification of the ED was performed in both models. National public campaigns about stroke symptoms and how to act were similar in both models.

**Outcome measures**
Factors investigated were: (1) time from stroke onset to call for help, (2) mode of referral, i.e., via EMS (911 call), via GP and subsequent self-transport, via GP and subsequent EMS transport or self-transport to hospital (3) mode of transportation and high prioritization, (4) pre-hospital diagnostic accuracy, and (5) preferential referral of tPA candidates.

Pre-hospital diagnostic accuracy was determined by comparing EMS triage stroke diagnosis to the hospital discharge diagnosis.

In postal code areas, where strokes victims might be routed through both organisational models preferential referral of potential tPA candidates to one particular model may be considered a selection bias \(^{(15)}\). Therefore, we calculated the odds ratio of presenting in hospital with a stroke within 4.5 hours for centralised versus decentralised care. These odds ratios were compared between a group of postal code areas with more than 90% of all stroke patients referred to one predominant model of care and postal code areas with a choice of models (<90% of patients in one model). We assumed that in postal code areas that refer (>90% of cases) within one model, the proportion of potential tPA candidates among all stroke patients is a model characteristic not influenced by selection bias.

**Statistical analysis**
Mann-Whitney \(U\), Fisher’s exact tests, and odds ratios were calculated for continuous and categorical variables in both organisational models. Odds ratios were adjusted for baseline characteristics age, gender, and the short version of the National Institutes of Health Stroke Scale \(^{(16)}\) using logistic regression. All factors with \(p<0.10\) in the univariate analysis were entered into the final model. SPSS 20.0 for windows software package (Chicago, Il) was used. A \(p\)-value < 0.05 was considered statistically significant.

**Informed consent and study approval**
Informed consent was obtained from all subjects participating in this study. The study was approved by the institutional review board of the UMCG.

**Results**

**Characteristics of study subjects**
A total of 471 patients arriving at the hospital within 4.5 hours were enrolled in the study, 172 in the centralised versus 299 in the decentralised model. Three patients suffered a recurrent stroke
during the study period. Figure 1 shows the distribution of the patients across both settings. Within the centralised model, 126 (73.2%) suffered ischemic stroke, 11 (6.4%) TIA, 13 (7.6%) intracranial hemorrhage, and 22 (12.8%) were diagnosed with a disease other than stroke. The leading final discharge diagnoses for the 22 patients with alternative diagnosis in the centralised model included: epilepsy or seizure (n=6), migraine (n=5), functional or medically unexplained symptoms (n=5), infection (n=3), altered level of consciousness (n=1), and other (n=2). Mean age was 67.5 years, and 90 (52.3%) were women. In the decentralised model, 237 (79.3%) suffered ischemic stroke, 9 (3.0%) TIA, 38 (12.7%) intracranial hemorrhage, and 15 (5.0%) were diagnosed with a disease other than stroke. The 15 patients with alternative diagnosis in the decentralised model included: epilepsy or seizure (n=5), functional or medically unexplained symptoms (n=3), malignancy (n=2), migraine (n=1), vertigo (n=1), delirium (n=1), and other (n=2). Mean age was 71.3 years, and 135 (45.3%) were women. Table 1 describes the baseline characteristics and Table 2 outcome measures for this subset of patients.

**Main results**

In the centralised model, 172 of 531 patients (32.4%) arrived within 4.5 hours after stroke onset compared to 299 of 1280 (23.4%) in the decentralised setting (adjusted OR 1.96; 95% CI 1.51 – 2.53).

For those patients arriving within 4.5 hours, the median patient delay from symptom onset to call for help was 28 minutes (interquartile range, 2–68) in the centralised model, vs 30 minutes (interquartile range, 9–72) in the decentralised model (P=0.16). Comparing centralised to decentralised care, referral via 911 occurred in 41.9% vs 46.8% (adjusted OR, 0.85; 95% CI, 0.56 – 1.28), referral by GP followed by self transport in 1.2% vs 10.7% (adjusted OR, 0.08; 95% CI, 0.02 – 0.35), GP plus EMS transport in 51.1% vs 36.1% (adjusted OR, 2.02; 95% CI, 1.33 – 3.06), and self-transport in 1.2% vs 4.3% (OR, 0.26; 95% CI, 0.06 – 1.16), respectively. Transportation by ambulance occurred in 93.0% in the centralised model, vs 82.9% in the decentralised model (adjusted OR, 3.11; 95% CI, 1.59 – 6.06). High priority transportation occurred in 95.0% vs 85.1%, respectively (adjusted OR, 3.67; 95% CI, 1.65 – 8.17). Of all patients triaged by EMS as stroke, 88.0% actually had a stroke in the centralised model, vs 94.3% in the decentralised model (P=0.05). In regions with and without possible preferential referral, the odds ratios for hospital arrival within 4.5 hours for centralised versus decentralised care were 2.15 (95% CI, 1.39 – 3.32) and 1.44 (95% CI, 1.04 – 2.00), respectively (P<0.01).
Discussion

This study demonstrated that pre-hospital factors in patients potentially eligible for tPA treatment differed between a centralised and decentralised acute stroke care model. The results of this study suggest a greater use and lower threshold to transport, prioritize, and refer patients potentially eligible for tPA treatment in the centralised model.

The results showed no difference between models for the time from stroke onset to call for help. Within the centralised model there was a higher rate of (1) EMS transportation of stroke patients both in the overall study population and for those referred by the GP, and (2) high priority EMS transportation. The increased use of EMS in the centralised model may have shortened prehospital delay in this group, and led to a larger proportion of patients arriving within 4.5 hours (17,18). This may explain part of the variation in tPA use between both models. Because not all patients arriving within 4.5 hours were assigned high priority transport (i.e. 95% in the centralised and 85% in the decentralised model), there is still room for improvement regarding the education of EMS providers in both models. Importantly, travel times and distances were significantly longer in the centralised model, and hence could not have contributed to the difference in the proportion of patients arriving quickly. Less severe strokes were observed in the centralised model, possibly reflecting a lower threshold of EMS services to transport potential stroke victims. Despite comparable stroke recognition tools and transport protocols for EMS systems, the threshold to transport, prioritise, and refer patients potentially eligible for tPA treatment differed between both models. Possible explanations for this difference may include the presence of a stroke champion in the centralised model, who actively promotes rapid identification and transport of potential stroke victims among GPs, EMS dispatchers, and ambulance personnel.

Table 1. Baseline characteristics patients <4.5 hours.

<table>
<thead>
<tr>
<th></th>
<th>Centralised model</th>
<th>Decentralised model</th>
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<tbody>
<tr>
<td>N</td>
<td>172</td>
<td>299</td>
</tr>
<tr>
<td>Age (y), mean (SD)</td>
<td>68 (15)</td>
<td>71 (13)*</td>
</tr>
<tr>
<td>Male, (%)</td>
<td>82 (48)</td>
<td>163 (55)</td>
</tr>
<tr>
<td>Short version of NIHSS on arrival (IQR) median</td>
<td>1 (0 – 4)</td>
<td>2 (1 – 5)*</td>
</tr>
<tr>
<td>Ischemic stroke (%)</td>
<td>126 (73)</td>
<td>237 (79)</td>
</tr>
<tr>
<td>TIA (%)</td>
<td>11 (6)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Hemorrhage (%)</td>
<td>13 (8)</td>
<td>38 (13)</td>
</tr>
<tr>
<td>Alternative diagnosis (%)</td>
<td>22 (13)</td>
<td>15 (5)*</td>
</tr>
<tr>
<td>Median distance to hospital, km (IQR)</td>
<td>26 (7 – 35)</td>
<td>10 (3 – 17)†</td>
</tr>
<tr>
<td>Median ambulance travel time to hospital (IQR)</td>
<td>19 (7 – 35)</td>
<td>11 (6 – 16)†</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; IQR, interquartile range; TIA, transient ischemic attack.
* P<0.05
† P<0.01
Analysis of patients arriving outside the 4.5 hour time window showed an identical mode of referral between models. However, in both models patients arriving outside 4.5 hours were more often triaged by the GP, and less often called 911. Notably, this appears to suggest that raising public awareness to call 911 in response to stroke symptoms might results in earlier presentation at the hospital and increased tPA use, as demonstrated in other studies (19).

Table 2. Outcome measures patients <4.5 hours.

<table>
<thead>
<tr>
<th></th>
<th>Centralised system</th>
<th>Decentralised system</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>172</td>
<td>299</td>
</tr>
<tr>
<td>Time between stroke onset and call for help (IQR)</td>
<td>28 (2 – 68)</td>
<td>30 (9 – 72)</td>
</tr>
<tr>
<td>Time between stroke onset and EMS activation (IQR)</td>
<td>37 (5 – 72)</td>
<td>30 (8 – 66)</td>
</tr>
<tr>
<td>Mode of referral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency services, 911 call (%)</td>
<td>72 (42)</td>
<td>140 (47)</td>
</tr>
<tr>
<td>GP referrals (%)</td>
<td>2 (1)</td>
<td>32 (11)</td>
</tr>
<tr>
<td>GP referrals plus emergency services (%)</td>
<td>88 (51)</td>
<td>108 (36)†</td>
</tr>
<tr>
<td>Self transport (%)</td>
<td>2 (1)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>8 (5)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Mode of transportation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transported by EMS (%)</td>
<td>160 (93)</td>
<td>248 (83)†</td>
</tr>
<tr>
<td>High priority transport (%)</td>
<td>152 (95)</td>
<td>211 (85)*</td>
</tr>
<tr>
<td>Pre-hospital diagnostic accuracy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMS stroke diagnosis (n)</td>
<td>117</td>
<td>194</td>
</tr>
<tr>
<td>Hospital discharge stroke diagnosis (%)</td>
<td>103 (88)</td>
<td>183 (94)*</td>
</tr>
<tr>
<td>Proportion treated with tPA (%)</td>
<td>63 (35)</td>
<td>109 (37)</td>
</tr>
<tr>
<td>Exclusion GP referrals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>84</td>
<td>160</td>
</tr>
<tr>
<td>Median delay between stroke onset and call for help, minutes (IQR)</td>
<td>13 (1 – 57)</td>
<td>19 (5 – 47)</td>
</tr>
<tr>
<td>Transported by EMS (%)</td>
<td>74 (88)</td>
<td>141 (88)</td>
</tr>
<tr>
<td>High priority transport (%)</td>
<td>71 (96)</td>
<td>124 (88)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; GP, general practitioner; EMS, emergency medical services.

*P<0.05  
†P<0.01

More misdiagnoses by EMS were observed in the centralised model. This may suggest a more liberal referral policy of EMS. However, this policy may also lead to higher proportions of patients...
eligible for tPA treatment. Further cost-effectiveness studies are needed to evaluate this liberal policy of EMS services. The proportion of cerebral emergencies that ultimately did not appear to be an ischemic stroke, particularly TIA, did not differ across organisational models. This category of patients, however, does imply that emergency services have to be well trained and alert to perform adequate triage.

The analyses on preferential referral showed that, in regions where more than 90% of patients were referred to one predominant model of care, patients were one and a half times as likely to present in hospital within 4.5 hours in the centralised setting. This may be the result of a combination of experience and exposure to tPA, continuing medical education and new trainees entering into the workforce (20). In regions where both models co-existed and competed for stroke patients, a preference for the central model was revealed. This may be due to the EMS recognizing the UMCG and its stroke team as actively promoting thrombolysis and always available, resulting in preferential hospitalization of thrombolysis candidates (21). The causes for this selection preference deserve further study, as this preference may ultimately affect further implementation efforts.

There are several study limitations. First, the subgroup analysis concerning preferential referral was only defined a posteriori and cannot definitively refute or confirm preferential referral. Nonetheless, it is a novel explorative analysis that gives a good indication of the impact a selection preference may have had on the results of the comparative cohort study and addresses concerns that were raised in the literature (15). Also, it may allow a more accurate estimation of the gains to be made by re-organising acute stroke care. Second, because only suspected stroke victims were investigated, and not all patients, transported by ambulance to the participating hospitals during the study period, we were unable to estimate the total number of true and false negative triages. Finally, it cannot be excluded that pre-hospital factors not identified in this study may partly explain some of the differences between the models. Specifically, non-organisational prehospital factors such as demographic and other patient characteristics including race, educational level, facial droop, comorbidity, living status, and risk factors for stroke such as diabetes or a history of heart failure (22) lay outside the scope of this study and were therefore not included in the analysis. Demographic studies of the adherence areas however did not reveal any relevant differences across respective catchment areas (23).

**Conclusions**

In summary, lower threshold for use of EMS and high priority transport of potential stroke patients, and partly a preferential referral of potential tPA candidates to a centralised organisational model were identified as prehospital factors contributing to variation in tPA use. These factors warrant further concerted action to improve acute stroke care.
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References


