CHAPTER 3

Short door-to-needle times in acute ischemic stroke and prospective identification of its delaying factors

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A B S T R A C T

Background

The clinical benefit of intravenous thrombolysis (IVT) in acute ischemic stroke is time dependent. Several studies report a short median door-to-needle time (DNT; 20 min), mainly in large tertiary referral hospitals equipped with a level 1 emergency department, a dedicated stroke team available 24/7, and on-site neuroimaging facilities. Meanwhile, in daily practice, the majority of stroke patients are admitted to secondary care hospitals, and in practice, even the generous benchmark of the American Heart Association (a DNT of 60 min in >80% of the cases) is met for a minority of patients treated with IVT. The first objective of our study was to investigate if, in a secondary care teaching hospital rather than a tertiary referral hospital, similar short DNTs can be accomplished with an optimized IVT protocol. Our second objective was to prospectively identify factors that delay the DNT in this setting.

Methods

A multicenter, consecutive cohort study of patients treated with IVT in one of two secondary care teaching hospitals. In both hospitals, data of consecutive stroke patients as well as median DNTs and factors delaying this were prospectively assessed for each patient. Multivariable logistic regression analysis was used to evaluate associations between patient-related and logistic factors with a delayed (ie exceeding 30 min) DNT.

Results

In total, 1756 patients were admitted for ischemic stroke during the study period. Out of these, 334 (19.0%) patients were treated with IVT. The median DNT was 25 min (interquartile range: 20–35). A total of 71% (n=238) had a DNT below 30 min. In 63% of the patients treated with IVT the DNT was delayed by at least one factor. Patients without any delaying factor had a 10 min shorter median DNT compared to patients with at least one delaying factor ($p<0.001$). The following factors were independently associated with a delayed DNT: uncertainty about symptom onset, un- controlled blood pressure, fluctuating neurological deficit, other treatment before IVT, uncertainty about (anti-)

coagulation status, other patient-related factors, and incorrect triage.

Conclusions

Short median DNTs can also be accomplished in secondary care. Despite the short DNTs, several delaying factors were identified that could direct future improvement measures. This study supports the view that as a performance measure, the current DNT targets are no longer ambitious enough and it adds to the knowledge of factors delaying the DNT.

Introduction

Intravenous thrombolysis (IVT) significantly improves clinical outcome in acute ischemic stroke, but the clinical benefit of this treatment rapidly declines with the passing of time.[1] Still, the time from hospital admission to treatment, the so-called door-to-needle time (DNT), is often delayed for avoidable reasons. Several studies report a short median DNT mainly in large tertiary referral hospitals equipped with a level 1 emergency department, a dedicated stroke team available 24/7, and on-site neuroimaging facilities.[2-4] Meanwhile, in daily practice, the majority of stroke patients are admitted to smaller secondary care hospitals[5,6,] and in practice, even the generous benchmark of the American Heart Association (a DNT of 60 min in >80% of the cases)[7,8] is met for a minority of patients treated with recombinant tissue plasminogen activators (rt-PA).[9,10] Moreover, even when an optimized IVT protocol is operational, the DNT is potentially delayed by various patient-related and logistic factors. The identification of these factors could facilitate further shortening of the DNT[11], but so far, no prospective documentation of such factors has been published. The first objective of our study was therefore to investigate if, in a secondary care rather than a tertiary referral hospital, similarly short DNTs can be accomplished with an optimized IVT protocol. Our second objective was to prospectively identify factors that delay the DNT in this setting.

Methods

Data from two secondary care teaching hospitals in the Netherlands, the Slotervaart hospital (SH) and the Sint Lucas Andreas Hospital (SLAH), were collected. Both hospitals are situated on the western outskirts of Amsterdam within a 2.5-mile distance and offer round-the-clock rt-PA treatment. The stroke team in both hospitals consists of

an on-call neurologist, an on-site neurology resident available 24/7, a stroke and emergency department nurse, a radiology technician, and a laboratory analyst. In both hospitals, the neurology residents witness several rt-PA treatments and/or receive focused training before they run a shift on their own. Logistics are largely similar in both hospitals. The emergency department receives a prenotification from the ambulance announcing a patient potentially eligible for rt-PA treatment (i.e., a patient with an acute focal neurological deficit of <4.5 hour duration), allowing for preparation of the acute stroke team and clearing of the CT scan. Glucose levels and the international normalized ratio (INR) are checked with a point-of-care device, intravenous access is obtained if not already available, and blood is drawn, but rt-PA treatment is not delayed for (platelet count) results, unless there is clinical suspicion or a history of severe thrombocytopenia. At the start of the study period, all patients were asked for their weight. If asking was not possible or when the weight was unknown, it was either estimated or determined with a scale. Since 2013, both hospitals determine body weight by using a bed with a built-in scale. In both hospitals, patients have to be transported by elevator to the CT suite on the first floor. The decision to treat with rt-PA is based on a non-contrast head CT, and the rt-PA bolus is administered while the patient is still on the CT table, directly followed by a continuous infusion. Since IVT with rt-PA is the standard of care for the treatment of acute ischemic stroke, the DNT was not delayed by obtaining informed consent. Neither hospital actively lowers uncontrolled hypertension (>185/110 mm Hg). Instead, blood pressure is monitored every 10 min, and in case of a spontaneous drop within the time window for IVT, rt-PA is administered.

In both hospitals, data of consecutive stroke patients are prospectively collected and include demographic variables and the medical history. In addition, for patients treated with rt-PA, the following parameters are documented: the symptom-to-needle time (SNT), symptom-to-door time (SDT), and the DNT. The DNT is defined as the time between the moment the patient first enters the door of

the facility (and for patients already hospitalized, the moment of first consultation of a neurologist) and administration of the intravenous bolus with rt-PA. Both hospitals prospectively document previously published factors that potentially delay the DNT (Table 1).[11] Because increasingly short DNTs could potentially lead to a less accurate diagnosis and to more rt-PA-related complications, we prospectively documented the diagnosis on discharge to retrieve stroke mimics and possible hemorrhagic complications related to rt-PA treatment. For intracerebral hemorrhage, we used a pragmatic definition of blood on a CT scan explaining any clinical relevant neurological deterioration during hospital admission. The SH database also includes stroke severity on admission as measured with the National Institutes of Health Stroke Scale (NIHSS) score, the clinical location of the stroke, and the vascular risk factors. These data were reconstructed from medical records for patients in the SLAH (no missing values). Patients were included between October 2011 and October 2013. We obtained institution review board approval in both hospitals to conduct this analysis.

Statistics

Dichotomous data are described as numbers and percentages, and continuous data are presented as means with standard deviations (±SD). For non-normally distributed data, median values and interquartile ranges (IQR) are presented. Differences between the hospitals and patient groups were analyzed by the Mann-Whitney U test or t test for continuous parameters and the chi-square test for categorical parameters. A two-tailed p-value <0.05 indicated statistical significance.

A delayed DNT was defined as a DNT >30 min. This cut-off was used because it is the goal set by the Dutch Stroke Knowledge Network. First, univariable analysis was used to assess the crude association between patient characteristics or factors potentially delaying the DNT and a delayed DNT.

TABLE 1 **Potential patient related and logistic factors delaying the DNT**

Patient related factors	Logistic factors
Uncertain when symptoms started	Incorrect triage
Unknown medical history	Insufficient personnel
Uncontrolled blood pressure	Difficulties with drip or urinary catheter insertion
Fluctuating neurological deficit	Difficulties with weighing the patient
Patient has to undergo other treatment before IVT	CT scan occupied
Uncertainty on (anti-)coagulation status	Technical problems
	Laboratory results delayed
	No medication available
	Waiting for consent from patient or family
	Patient transferred from other institution

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Second, variables with a p value <0.10 in the univariable analysis were entered into a multivariable logistic regression model to identify independent predictors of a delayed DNT. Because of a significant difference in the median DNT between the hospitals, we also added the treatment location to the multivariable model. All statistical analyses were carried out using IBM SPSS Statistics version 20. Statistical significance was set at p <0.05.

Results

Patients

In total, 1756 patients were admitted for ischemic stroke during the study period (data not shown). Out of these, 334 (19.0%) patients [176 men (53%)] were treated with rt-PA (Table 2). The mean age was 72 years (±13.0). Cardiovascular risk factors were common: hypertension (58%); myocardial infarction or coronary disease (31%); prior transient ischemic attack or ischemic stroke (30%); dyslipidemia (37%), and current smoking (33%). The median NIHSS score on admission was 6 (IQR: 3–10). The most common clinical stroke locations were left cortical (44%) and right cortical (23%). Except for a higher rate of the left subcortical clinical stroke location in the SLAH, the case mix of patients was similar in both hospitals (Table 2).

DNTs, SNTs, Stroke Mimics, and Complications

Overall, the median DNT was 25 min (IQR: 20–35). In the SLAH, the median DNT was significantly shorter than in the SH (23 vs. 30 min; $p<0.001$). Seventy-one percent of the patients (n=238) had a DNT ≤30 min. Patients without any delaying factor had a 10 min shorter median DNT compared to patients with at least one delaying factor ($p<0.001$). The median SNT was similar between the hospitals. Symptomatic intracerebral hemorrhage (ICH) occurred in 10 patients (3.0 %). One patient (0.3%) died from a systemic hemorrhage. During follow-up, 9 patients (2.7%) turned out to have a stroke mimic (Table 3).

Factors Associated with a Delayed DNT

There were no significant differences between the group with a DNT ≤30 min and the delayed DNT group for age, sex, SNT or stroke mimic rate. Patients in the group with a DNT ≤30 min had slightly more severe strokes (median NIHSS score on admission 6 vs. 5, $p=0.054$; Table 4).

In 63% of the 334 rt-PA-treated patients, the DNT was delayed by at least one factor. In the delayed DNT group, 94% had at least

TABLE 2 Patient characteristics per hospital

Variable	Total (n=334)	SH (n=63)	SLAH (n=271)	p-value*
Age (years), mean (SD)	72 (13.0)	74 (12.0)	72 (13.2)	0.196
Men, n (%)	176 (53)	28 (44)	148 (55)	0.162
History of vascular risk factors				
(p)AF/ valvular disease, n (%)	43 (12.9)	10 (15.9)	33 (12.2)	0.410
Hypertension, n (%)	192 (58)	35 (56)	157 (58)	0.778
Myocardial infarction/ coronary disease, n (%)	102 (31)	19 (30)	83 (31)	1.00
Dyslipidemia, n (%)	124 (37)	24 (38)	100 (37)	0.885
Diabetes Mellitus, n (%)	62 (18.6)	11 (17.5)	51 (18.8)	1.00
Previous TIA/ischemic stroke, n (%)	100 (30)	25 (40)	75 (28)	0.068
Smoking, n (%)	109 (33)	15 (24)	94 (35)	0.103
Clinical stroke localisation				
Right cortical, n (%)	76 (23)	17 (27)	59 (22)	0.405
Left cortical, n (%)	146 (44)	26 (41)	120 (44)	0.676
Right subcortical, n (%)	34 (10.2)	10 (15.9)	24 (8.9)	0.107
Left subcortical, n (%)	20 (6.0)	0 (0)	20 (7.4)	0.019
Occipital, n (%)	7 (2.1)	0 (0)	7 (2.6)	0.355
Posterior circulation, n (%)	42 (12.6)	8 (12.7)	34 (12.5)	1.00
Admission NIHSS score, median (IQR)	6 (3-10)	6 (3-13)	6 (4-10)	0.556

SH = Slotervaart Hospital; SLAH = Sint Lucas Andreas Hospital; n= number of patients; SD = standard deviation; (p)AF = (paroxysmal) atrial fibrillation; TIA = transient ischemic attack; NIHSS = National Institutes of Health Stroke Scale; IQR = interquartile range.

* Determined by use of the independent sample t-test for age, the Mann-Whitney U test for admission NIHSS score, and the chi-squared test for categorical variables.

one factor delaying the DNT versus 51% in the group with a DNT ≤30 min (p<0.001). The most frequently reported patient-related delaying factors were fluctuating neurological deficit (11.4%) and uncontrolled blood pressure (>185/110 mm Hg, 10.8%; Table 4). As for logistic delaying factors, the most commonly reported variables were incorrect triage (9.3%) and technical problems (9.0%; e.a., non-functioning point-of-care INR-device, problems with the elevator or computer; Table 4). In the 31 (9.3%) patients in whom incorrect triage was registered as a factor that delayed the DNT, there was no prenotification in 10 cases, 17 patients were triaged incorrectly by the emergency department nurse, and 2 patients by the neurology resident. For the two remaining patients, the reason for the incorrect triage was not registered in the prospective database.

Factors Independently Associated with a Delayed DNT

Multivariable regression analysis showed the following factors to independently predict a delayed DNT: uncertainty about symptom onset (OR 6.92, 95% CI 2.12–22.56), uncontrolled blood pressure (OR 9.06, 95% CI 3.90–21.02), fluctuating neurological deficit (OR 11.33, 95% CI 4.76–26.95), other treatment before IVT (OR 25.57, 95% CI 4.79–136.7), uncertainty about (anti-)coagulation status (OR 19.27, 95% CI 1.78–208.3), other patient-related factors (OR 5.21, 95% CI 2.08–13.04), and incorrect triage (OR 3.77, 95% CI 1.52–9.38; Table 5).

Discussion

Our results show that with an optimized IVT protocol, a short median DNT can be accomplished, also in the setting of a secondary care hospital and without the loss of accuracy. The median DNT we found is comparable with previously reported short DNTs achieved in single tertiary referral hospitals.[2-4] To the best of our knowledge, it is the first

TABLE 3 **Door-to-needle time, symptom-to-needle time, mimics and hemorrhagic complications per hospital**

Variable	Total (n=334)	SH (n=63)	SLAH (n=271)	p-value*
DNT (min), median (IQR)	25 (20-35)	30 (23-45)	23 (19-30)	<0.001
DNT <30 min, n (%)	238 (71)	33 (52)	202 (75)	0.001
SNT (min), median (IQR)	105 (79-151)	115 (85-155)	103 (75-150)	0.167
Patients with ≥1 factor delaying rt-PA treatment, n (%)	211 (63)	48 (76)	163 (60)	0.020
DNT (min) without factor delaying rt-PA treatment, median (IQR)	20 (17-23)	17 (15-22)	20 (17-23)	0.164
DNT (min) with ≥1 factor delaying rt-PA treatment, median (IQR)	30 (23-45)	38 (30-55)	28 (21-40)	<0.001
Heamorrhagic complication rate, n (%)	11 (3.3)	1 (1.6)	10 (3.7)	0.70
Symptomatic ICH <36 hours, n (%)	10 (3.0)	1 (1.6)	9 (3.3)	1.00
Symptomatic systemic haemorrhage <36 hours, n (%)	1 (0.3)	0	1 (0.4)	0.69
Stroke mimic, n (%)	9 (2.7)	2 (3.2)	7 (2.6)	0.680

SH = Slotervaart Hospital; SLAH = Sint Lucas Andreas Hospital; n= number of patients; DNT = door-to-needle time; SNT = symptom-to-needle time; IQR = interquartile range; ICH = intracerebral hemorrhage.
* Determined by use of the Mann-Whitney U test for continuous variables and the chi-squared test for categorical variables.

study that also prospectively documented factors delaying the DNT for each individual patient, allowing the identification of independent factors delaying the DNT. Ideally, the recognition of such factors leads to corrective improvement measures. For example, a logistic factor such as incorrect triage in the emergency department could prompt dedicated training programs to improve this. The patient-related factors delaying the DNT seem to be more difficult to tackle but need further appraisal. Uncertainty about symptom onset might

TABLE 4 Patient characteristics and factors delaying intravenous thrombolysis

Variable	Total (n=334)	DNT ≤30 min (n=238)	DNT >30 min (n=96)	p-value‡
Age (years), mean (SD)	72 (13.0)	72 (12.7)	73 (13.8)	0.334
Men, n (%)	176 (53)	127 (53)	49 (51)	0.718
Admission NIHSS score, median (IQR)	6 (3-10)	6 (4-11)	5 (3-8)	0.054
Symptom-to-door time, median (IQR)	73 (50-112)	75 (50-119)	70 (45-90)	0.152
Stroke mimics, n (%)	9 (2.7)	6 (2.5)	3 (3.1)	0.720
≥1 factor delaying rt-PA treatment, n (%)	211 (63)	121 (51)	90 (94)	0.001
Patient related factors				
Fluctuating neurological deficit, n (%)	38 (11.4)	13 (5.5)	25 (26)	<0.001
Uncontrolled hypertension, n (%)*	36 (10.8)	14 (5.9)	22 (23)	<0.001
Other patient related factors, n (%)†	29 (8.7)	15 (6.3)	14 (14.6)	0.019
Uncertain when symptoms started, n (%)	19 (5.7)	7 (2.9)	12 (12.5)	0.001
Unknown medical history, n (%)	19 (5.7)	10 (4.2)	9 (9.4)	0.072
Other treatment before rt-PA treatment, n (%)	9 (2.7)	2 (0.8)	7 (7.3)	0.003
Uncertainty on (anti)coagulation status, n (%)	5 (1.5)	1 (0.4)	4 (4.2)	0.025
Logistic factors				
Incorrect triage, n (%)	31 (9.3)	16 (6.7)	15 (15.6)	0.020
Technical problems, n (%)	30 (9.0)	23 (9.7)	7 (7.3)	0.673
Difficulties with drip or urinary catheter insertion, n (%)	27 (8.1)	18 (7.6)	9 (9.4)	0.658
Insufficient personnel, n (%)	18 (5.4)	15 (6.3)	3 (3.1)	0.296
CT scan occupied, n (%)	16 (4.8)	9 (3.8)	7 (7.3)	0.255
Laboratory results delayed, n (%)	12 (3.6)	7 (2.9)	5 (5.2)	0.337
No medication (rt-PA) available, n (%)	12 (3.6)	9 (3.8)	3 (3.1)	1.00
Other Logistic factors, n (%)	7 (2.1)	6 (2.5)	1 (1.0)	0.678
Waiting for consent, n (%)	4 (1.2)	2 (0.8)	2 (2.1)	0.326

be decreased by instructions and training for ambulance personnel and referring general practitioners to verify this more thoroughly before the patient is transported. Indeed, taking the history during patient transport has been helpful.[2,12] Uncertainty about (anti-) coagulation status, especially with the introduction of direct oral anticoagulants, is likely to be an increasing problem and stresses the need for a centralized registration accessible for health care workers. Another independent patient-related delaying factor was fluctuating neurological deficit. This is important in the light of the possibly relatively unknown observation that a substantial number of patients with mild or rapidly improving stroke symptoms end up with a poor final clinical outcome, particularly those with persistent large-artery occlusion.[13-17] Together with the evidence that rt-PA treatment is effective irrespective of stroke severity, this should prompt a more aggressive IVT approach.[1] Finally, an uncontrolled blood pressure was independently associated with a delayed DNT. Although many neurologists actively lower the blood pressure to enable rt-PA treatment[18], we anticipate a spontaneous drop as active lowering potentially compromises the already ischemic penumbra.[19]

Our study has some limitations. First, some data were collected retrospectively and we do not have data on how many stroke patients were not treated with rt-PA due to factors delaying rt-PA treatment

DNT = door-to-needle time; SD = standard deviation; NIHSS = National Institutes of Health Stroke Scale; IVT = intravenous thrombolysis; rt-PA = recombinant tissue plasminogen activator.

* ie admission blood pressure exceeding 185/110 mm Hg

† Difficulties in making the CT-scan due physical restlessness or agitation; language barriers; consultation of a surgeon because of a recent operation; and diagnostic uncertainty.

‡ Determined by use of the independent sample t-test for age, the Mann-Whitney U test for admission NIHSS score and symptom-to-door time, and the chi-squared test for categorical variables.

TABLE 5 Factors independently associated with a DNT >30 min (n=334)

Variable	Univariable Analysis OR (95% CI)‡	p-value§	Multivariable Analysis OR (95% CI)‡	p-value§
Age, year	1.01 (0.99-1.03)	0.333		
Sex, men	1.10 (0.68-1.76)	0.701		
Admission NIHSS score	0.95 (0.91-1,00)	0.045	0.99 (0.93-1.05)	0.680
Symptom-to-door time, min	1.00 (1.00-1.00)	0.195		
Treatment center, SH	2.82 (1.60-4.98)	<0.001	1.96 (0.97-3.94)	0.060
Patient related factors				
Fluctuating neurological deficit	6.10 (2.96-12.54)	<0.001	11.33 (4.76-26.95)	<0.001
Uncontrolled hypertension*	4.76 (2.32-9.77)	<0.001	9.06 (3.90-21.02)	<0.001
Other Patient related factors†	2.54 (1.17-5.50)	0.018	5.21 (2.08-13.04)	<0.001
Uncertain when symptoms started	4.71 (1.80-12.37)	0.002	6.92 (2.12-22.56)	0.001
Unknown medical history	2.36 (0.93-6.00)	0.072	1.21 (0.30-4.89)	0.787
Other treatment before IVT	9.28 (1.90-45.52)	0.006	25.57 (4.79-136.65)	<0.001
Uncertainty on (anti) coagulation status	10.30 (1.14-93.42)	0.038	19.27 (1.78-208.27)	0.015
Logistic factors				
Incorrect triage	2.57 (1.22-5.43)	0.014	3.77 (1.52-9.38)	0.004
Technical problems	0.74 (0.31-1.78)	0.494		
Difficulties with drip or urinary catheter insertion	1.26 (0.55-2.92)	0.583		
Insufficient personnel	0.48 (0.14-1.70)	0.254		
CT scan occupied	2.00 (0.72-5.54)	0.181		
Laboratory results delayed	1.81 (0.56-5.86)	0.320		
No medication (rt-PA) available	0.82 (0.22-3.10)	0.771		
Other Logistic factors	0.41 (0.05-3.43)	0.408		
Waiting for consent	2.51 (0.35-18.10)	0.361		

and thus not registered. The primary parameters, however, were all prospectively collected, and although missing data on delaying factors in patients not treated with rt-PA could have led to an underestimation of the delaying factors, we have no reason to think that this would change the outcome. Second, we only documented the frequency of a delaying factor and not the net number of minutes lost with every factor delaying rt-PA treatment. Third, the use of the pragmatic symptomatic ICH definition could have led to an underestimation of the complication rate, since it is likely that patients with rapidly progressive stroke symptoms or severe neurological deficit have not always received a follow-up CT scan. Finally, this is an observational study not allowing for conclusions on the causality of the associations. However, we feel it is a good reflection of clinical practice and supports the previously stated view that current DNT targets[7,8] are no longer ambitious enough. In an era with rapidly developing, often elaborate (endovascular) acute stroke therapies, significant clinical gain can still be achieved relatively easily by simply implementing what we already know what is best: to shorten the DNT.

NIHSS = National Institutes of Health Stroke Scale; SH = Slotervaart Hospital; rt-PA = recombinant tissue plasminogen activator; IVT = Intravenous thrombolysis.

* ie admission blood pressure exceeding 185/110 mm Hg

† Difficulties in making the CT-scan due physical restlessness or agitation; language barriers; consultation of a surgeon because of a recent operation; and diagnostic uncertainty.

‡ OR for door-to-needle time (≤30 min/>30 min) and its 95% Wald CI.

§ p-value of Wald chi-squared test

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