

The Effect of In-Hospital Intervention to Reduce Door to Needle Time in Patients Receiving Tissue Plasminogen Activator

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Abstract: *Background and Objective:* Attempts have been made to confirm the diagnosis of stroke at the earliest stage and to prevent the development of neurological deficits. Tissue plasminogen activator (tPA) plays a logical role in the treatment of acute stroke by converting plasminogen to plasmin, and recent studies have shown that the drug can be injected up to four and a half hours after the onset of symptoms. The present study aimed to evaluate the effect of an in-hospital intervention to reduce door to needle (DTN) time in acute stroke patients.

Methods: This epidemiological case-control study was performed on patients with acute ischemic stroke from September to March 2016 (n= 25) (group A) who were treated with tPA according to stroke guidelines. Their basic specifications, DTN and Door to Computed Tomography scan (DTC) time were recorded. Then, from April to August 2017, an intra-hospital recipe for tPA injection was provided by investigating the obstacles and causes of intra-hospital delays. Subsequently, stroke patients receiving tPA from September to March 2017 (n= 23) (group B) were examined, and their DTN and DTC were compared with patients in the first group.

Results: The mean DTN and DTC in group A were 67.27±28.83 and 30.40±10.59 minutes, and in group B, were 45±25.98 and 22.17±8.50, minutes, respectively, which made a significant difference between the two groups (P=0.005, P=0.006, respectively). The percentage of patients with DTN less than 60 minutes increased from 52% in group A to 95.6% in group B. The percentage of patients with DTC less than 25 minutes decreased from 32% to 69.56% (P<0.001). The percentage of patients with symptomatic cerebral haemorrhage increased from 12% to 8.7% (P<0.001). The percentage of patients with independent ambulatory (mRS: 0-2) at three months after discharge increased from 48% to 56.5% (P=0.003). The mortality rate also decreased from 24% to 13.4% (P<0.001).

Conclusion: By resolving the causes of intra-hospital delays and using a proper team program, the mean DTN and DTC of patients receiving tPA were reduced. This decrease in DTN time was accompanied by reduced complications in the form of reduced symptomatic cerebral haemorrhage and mortality and improved prognosis.

Keywords: Door to Needle, Door to CT, Thrombolytic plasminogen activator.

INTRODUCTION

Functional neurological disorder (FND) has various causes, the most common being stroke. In stroke patients, the most prognostic effect is in the first 4 hours of the onset of symptoms [1]. Efforts have made to confirm the diagnosis of stroke at the earliest stage and to prevent any nerve defect from being completed without compromising the patient. Tissue plasminogen activator (tPA) converts plasminogen to plasmin. These drugs are useful in the treatment of coronary artery obstruction but are associated with a 1% risk of cerebral infarction. There is a 6% chance of symptomatic cerebral haemorrhage. With the administration of tPA at a dose of 0.9 mg/kg and less than 90 mg [2]. If intravenous tPA administered within the first 3 hours of the onset of symptoms, there is a 29-39% chance of recovery within the first 3 months. Recent studies have shown that tPA can be injected for up to 4 hours and 30 minutes after the onset of symptoms. These patients benefit from tPA less than those who receive the drug for the first 3 hours do.

They also have a higher risk of bleeding and mortality. After 4 hours, 30 minutes of symptom onset, tPA injection is ineffective and can be harmful [3, 4]. In developing countries, thrombolysis for patients with acute ischemic stroke is accessible to only 1–6% of patients, while in developed countries, this rate is up to 31%. Important barriers to thrombolytic therapy in these countries are delayed arrival of patients after symptoms start, financial problems due to the high cost of medication, lack of appropriate facilities, doctors' concerns about drug side effects, and their uncertainty about the efficacy of the drug [5]. According to the American Heart Association/American Stroke Association (AHA/ASA), patients with acute stroke should be triaged, as those with acute myocardial infarction or severe trauma, regardless of the severity of the neurological deficits. According to this, the door to Door to Computed Tomography scan (DTC) should be less than 25 minutes, and the door to needle (DTN) should be less than 60 minutes [6]. This common strategy, set by the AHA/ASA aims to DTN≤60 minutes for at least 50% of patients with acute ischemic stroke, includes 10 strategies including prior notification by Emergency Medical Service (EMS) systems, activating a medical team with a landline telephone, performing and reporting rapid brain imaging uses stroke-specific

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protocols, premixing tPA, team-based approaches, and rapid information feedback [7].

Given the efficacy of tPA as the only effective drug in the acute phase of stroke and the time-dependent benefits of this drug, we decided to identify the causes of delay in the administration of tPA by examining the barriers to tPA injections, given that treatment with this drug has been started in this university centre for the past 2 years. We also attempted to reduce as much as possible the interval between patient arrival to the emergency room and drug administration, by correcting, for the causes mentioned above, and to achieve the goal of DTN less than 60 minutes to reduce complications and increase efficacy in treating patients.

METHOD

This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Code of Ethics: IR.AJUMS.REC.1396.633) as a cross-sectional epidemiological case-control study on patients who referred to the Golestan Hospital Emergency Department of Ahvaz in 2016-2017. First, in autumn and winter of 2016, the stroke code (code: 724) was activated to inform those involved in the prescription of tPA, including a neurology resident, neuroscience triage nurse, and laboratory and Computed Tomography (CT) scan technician. A neurology resident first visited patients, and after initial examination, detailed history taking, and reviewing the National Institutes of Health Stroke Scale (NIHSS), CT-scan was performed. They were then transferred to the neurology department if they had any indication of treatment according to the Stroke guidelines (n= 25). Basic characteristics including age, sex, time of onset of symptoms, associated risk factors, NIHSS, the elapsed time from the referral of patients to the hospital to performing CT-scan (Door to CT), the interval between the referral of patients to the hospital and the time taken to administer a thrombolytic agent (Door-to-Needle), and the interval between symptom onset and the time taken to administer a thrombolytic agent (Event-to-Needle) were recorded. Then, within the spring and summer of 2017, by examining the existing intra-hospital barriers and the causes of delays in prescribing tPA since the patient arrived at the hospital, these barriers were remedied as far as possible, and a guideline was provided to prescribe tPA to reduce Door-to-Needle (DTN) and DTC. After intra-hospital interventions, patients with stroke receiving tPA were evaluated for 6 months (September 2017 to February

2018) (n= 23) and their DTN and DTC were compared with those for patients in the pre-intervention group.

Interventions to remove existing barriers and reduce DTN and DTC were as follows:

- Emergency notification to Golestan Hospital via EMS before the arrival of suspected stroke patients and establish HOTLINE between pre-hospital emergencies and neurology resident;
- Transfer the patient from the triage unit to the resuscitation room through coordination with emergency medicine;
- Creating the right conditions for CT-scan and increasing the number of patient transporters;
- Sending samples of tests including PT, PTT, INR, CBC as soon as the patient enters the emergency room by the emergency nurse and examining the vital signs and insertion of two intravenous routes for the patient.
- Providing red labels related to code 724 for faster tests and CT-scan of patients.
- Informing the CT-scan technician as soon as the patient arrives at the hospital to prioritize the CT-scan and reject non-emergency patients until the patient arrives at the CT-scan section.
- Informing the lab technician to prepare the test results within 20 minutes.
- Continuous training of nurses and triage care unit and stroke unit, CT-scan and laboratory technicians, and emergency physicians, regarding the importance of time for these patients.
- Rapid control of hypertension in hypertensive patients by training and proper administration of the labetalol administration protocol and initiation of emergency blood pressure control.
- Preparation of tPA for the administration of bolus dose of tPA as soon as CT-scan is performed, after evaluation of CT-scan, and evaluation of criteria for administration of tPA for patients by neurology resident.
- The follow-up to install CT-scan in the emergency department.

The prescribed dose was 0.9 mg/kg and up to 90 mg. Ten per cent of the drug was infused in bolus form, and the remaining was infused during 1 hour.

Patients receiving tPA were admitted to the stroke unit for at least 48 hours and were monitored for vital signs. Brain CT-scan was again performed after 36 hours of administration.

Data were analyzed using descriptive statistics, paired independent t-test and paired comparison test. Results were analyzed by SPSS software, and the significance level was considered less than 0.05.

RESULTS

There was no significant difference between pre- and post-intervention groups in terms of mean age,

NIHSS score and Event-to-Door time. There was no statistically significant difference in their distribution based on gender, history of hypertension, diabetes, ischemic heart disease (IHD) and smoking ($P>0.05$) (Table 1).

The mean time of Door to CT, Door-to-Needle, and Event-to-Needle were significantly lower in the post-intervention group ($P <0.05$). The percentage of patients with Door-to-Needle less than 25 and 60 minutes and patients with independent ambulatory or mRS = 0-2 was significantly higher in the post-intervention group ($P <0.05$). Patients with symptomatic Intracerebral Hemorrhage (ICH) within 36 h and mortality rate were significantly lower in the post-intervention group ($P <0.05$) (Table 2).

Table 1: Comparison of Demographic and Clinical Information of Patients in of Pre- and Post-Intervention Groups

| Variables | | Pre-intervention (N=25) | Post-intervention (N=23) | P-value | Total (N=48) |
|------------------------|--------|--------------------------|--------------------------|---------|--------------|
| Age (years) | | 66.12±13.43 (37 – 76) | 68.52±8.71 (49 – 83) | 0.4 | 67.89±12.14 |
| Gender | Male | 16 (64) | 10 (43.5) | 0.1 | 26 (54.2) |
| | Female | 9 (36) | 13 (56.5) | | 22 (45.8) |
| NIHSS | | 12.92±3.14 | 12.86±3.02 | 0.9 | 12.04±3.11 |
| Event to Door | | 74.6±41.5 | 70.65±43.20 | 0.2 | 71.89±41.90 |
| Diabetes | | 5 (20) | 10 (43.5) | 0.08 | 15 (31.2) |
| Hypertension | | 23 (92) | 17 (73.9) | 0.1 | 40 (83.3) |
| Ischemic Heart Disease | | 6 (24) | 8 (34.8) | 0.08 | 14 (29.2) |
| Smoking | | 11 (44) | 10 (43.5) | 0.8 | 14 (29.2) |

Data are expressed as mean±SD or number (%).

The statistical test used was the t-test or Chi-square test.

*P-value<0.05 was considered as the statistical significance level.

Table 2: Comparison of the Results of the Pre- and Post-Intervention Groups

| Variables | Pre-intervention (N=25) | Post-intervention (N=23) | P-value |
|---|-------------------------|--------------------------|----------------------|
| Door-to-CT | 30.40±40.59 | 22.17±8.50 | 0.005 [*] |
| Door-to-Needle | 67.28±27.83 | 45±25.98 | 0.006 [*] |
| DTN time ≤ 60 min | 13 (52) | 22 (95.6) | <0.0001 [*] |
| DTC time ≤ 25 min | 8 (32) | 16 (69.56) | <0.0001 [*] |
| Event to Needle | 146.08±33.46 | 115.21±40.60 | 0.007 [*] |
| Symptomatic ICH within 36h | 6 (24) | 3 (13.04) | <0.0001 [*] |
| Independent Ambulatory Status (mRS: 0-2) [#] | 12 (48) | 13 (56.5) | 0.003 [*] |
| Mortality | 6 (24) | 3 (13.4) | <0.0001 [*] |

Data are expressed as mean±SD or number (%).

The statistical test used was the t-test or Chi-square test.

*P-value<0.05 was considered as the statistical significance level.

[#]The modified Rankin Scale (mRS).

DISCUSSION

The study population consisted of patients with acute ischemic stroke who had been treated with tPA. After the removal of barriers to delayed tPA administration, patients were evaluated in the pre- and post-intervention groups and DTN and DTC time were compared in the two groups.

In the pre-intervention group, the mean DTN was 67.28 minutes, and the mean DTC was 30.40 minutes. In the intervention group, the mean DTN was 45 minutes, and the mean DTC was 22.17 minutes. Fifty-two per cent of patients in the pre-intervention group had DTN \leq 60 minutes, while it was 95.6% in the post-intervention group ($P<0.001$). The results showed that 32% of patients in the pre-intervention group and 69.56% in the post-intervention group had DTC \leq 25 minutes, and there was a significant difference between the two groups ($P<0.001$). Mean DTC and DTN in patients with acute ischemic stroke receiving tPA were significantly different in the pre- and post-intervention groups ($P= 0.006$ and $P= 0.005$, respectively). According to the AHA/ASA Guidelines for acute stroke patients receiving tPA, the DTN should be less than 60 minutes in at least 50% of patients, and the DTC should be less than 25 minutes [6]. In our study, the percentage of patients with DTN less than 60 minutes increased from 52% in the pre-intervention group to 95.6% in post-intervention group and DTC less than 25 minutes increased from 32% to 56.69%. In a study conducted by Busby *et al.* [8], after in-hospital interventions and developing a protocol called CODE FAST for treating patients with acute stroke, the mean DTN decreased from 62 to 25 minutes, and the mean DTC decreased from 16 to 8 minutes. In our study, with the removal of existing barriers, the mean DTN was reduced from 67.28 to 45 minutes, and the mean DTC was reduced from 30.40 to 22.17 minutes. In the study conducted by Fonarow *et al.* [9], after applying the proposed AHA ten-fold strategy, the percentage of patients with DTN $<$ 60 decreased from 26% to 41.3%, with a decrease in symptomatic ICH and an increase in cases independent ambulatory (MRS = 0-2). Sadeghi *et al.* designed a study for evaluating the effect of simple in-hospital interventions on reducing DTC time and reaching door-to-needle DTN time of less than 60 minutes. Their results showed that the interventions significantly reduced DTC and DTN time [10]. In the present study, the percentage of patients with DTN less than 60 minutes increased almost twice, and the percentage of patients with symptomatic ICH decreased from 12% in the pre-intervention group to

8.7% in the post-intervention group. The percentage of patients with MRS ranging from 0 to 2 increased from 48% to 56.5%, which showed a significant difference in the reduction of symptomatic ICH and improvement of MRS in the intervention group. The mortality rate also decreased from 24% to 13.4% in the intervention group. Overall, improvement in DTN time in the intervention group was associated with reduced complications and improved prognosis.

The present study was performed only on patients receiving tPA in one hospital, and therefore we had limited data. Consequently, it is recommended to conduct studies with a larger sample size as well as over a more extended period by gathering information from other diagnostic and treatment centres nationwide. It is also recommended to train the public about the golden age of drug administration and the benefits of this treatment through urban and rural health centres, as well as broadcast and mass media.

CONCLUSION

The data and results of this study showed that due to the efficacy of tPA as the only effective drug in the acute phase of stroke and the time-dependent benefits of the administration of this drug, delaying tPA prescribing can be identified by establishing a proper team-building approach and coordinating the staff involved including triage physician, nurse, neurology resident, CT-scan supervisor, and in-hospital laboratory. By modifying these barriers, we can minimize the time gap between patient arrival to the emergency room and medication administration, so that the DTN of less than 60 minutes can be achieved to reduce the complications and increase the efficacy of this drug in the treatment of patients.

ABBREVIATION

| | |
|-------|--|
| tPA | = Tissue plasminogen activator |
| CT | = Computed Tomography |
| DTN | = Door to needle |
| DTC | = Door to CT |
| FND | = Functional neurological disorder |
| NIHSS | = The National Institutes of Health Stroke Scale |
| mRS | = The modified Rankin Scale |
| EMS | = Emergency Medical Service |

DECLARATION**Ethics Approval**

The study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethics code: IR.AJUMS.REC.1396.633).

Consent for Publication

This manuscript has not been published and is not under consideration for publication elsewhere in whole or in part. No conflicts of interest exist in the submission of this manuscript, and the manuscript has been approved for publication by all listed authors.

Availability of Data and Material

The data used to support the findings of this study are available from the corresponding author upon request.

Competing Interests

None of the authors has any financial and personal relationships with other people or organizations that could potentially and inappropriately influence this work and its conclusions. Authors declared no competing interest in publishing this paper.

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