Door to needle time for thrombolysis: A secondary analysis of the TIPS cluster randomized controlled trial

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Research article

Keywords: Ischemic stroke, intravenous thrombolysis, implementation intervention, door-to-needle time

Posted Date: April 22nd, 2019

DOI: <https://doi.org/10.21203/rs.2.9294/v1>

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Version of Record: A version of this preprint was published at BMJ Open on December 1st, 2019. See the published version at <https://doi.org/10.1136/bmjopen-2019-032482>.

Abstract

Background The Thrombolysis ImPlementation in Stroke (TIPS) study evaluated a hospital-based intervention aimed at improving the rates of intravenous thrombolysis in Australia. The current study assessed the effects of this intervention on the door-to-needle time for intravenous thrombolysis and also determined the intervention effects on door-to-needle time within metropolitan and non-metropolitan hospital locations. **Methods** TIPS was a clustered randomized controlled trial that involved 20 hospitals in Australia, with 10 hospitals receiving a multi-component practice-change intervention. De-identified patient data collected in the trial included the arrival, assessment, and treatment times for acute ischemic stroke patients. A posthoc exploration using mixed-effects regression modelling was used to assess intervention effects on door-to-needle time, and the effects within hospital location (metropolitan versus non-metropolitan). **Results** The intervention vs. control difference in the door-to-needle times was non-significant overall or within a hospital location. To provide additional context for the findings, we also evaluated the results within each intervention hospitals. During the active-intervention period, the intervention hospitals showed a significant decrease in the door-to-needle time of 9.25 minutes (95%CI: -16.93, -1.57), but during the post-intervention period, the result was not significant. During the active intervention period, control hospitals showed a significant decrease in the door-to-needle time of 5.26 minutes (95% CI: -8.37; -2.14) and during the post-intervention period, the decrease was 12.13 minutes (95%CI: -17.44, -6.81). **Conclusion** Across these primary stroke care centres in Australia, a secular trend towards shorter door-to-needle times across both intervention and control hospitals was evident. The intervention resulted in only a modest but significant reduction within experimental groups during the active intervention period, which was not sustained during the post-intervention period.

Background

When administered to eligible patients with acute ischemic stroke, intravenous thrombolysis significantly improves patient disability¹. However, the efficacy of this treatment is highly time-dependent, with earlier treatment being associated with lower rates of unfavourable outcome²⁻³. Because of the time-dependent benefit, international guidelines have recommended the completion of all in-hospital processing and initiation of intravenous thrombolysis within 60 minutes of arrival at hospital⁴. Unfortunately, despite the potential benefits of intravenous thrombolysis among eligible patients, achieving and sustaining optimal rates of intravenous thrombolysis has been challenging⁵. In Australia, the rate of intravenous thrombolysis among all stroke patient is only 13% according to the 2017 Australian National Stroke Audit⁶. The National Stroke Audit report also indicates that only 30% of Australian eligible patients received intravenous thrombolysis within 60 minutes of their hospital arrival⁶. The time between hospital arrival and intravenous thrombolysis, the door-to-needle (DTN) time, is an important surrogate for stroke service efficiency with shorter DTN times recognised to be associated with better patient outcomes⁷. Therefore, internationally, system improvement strategies are focusing on both increasing the implementation of intravenous thrombolysis and reducing DTN times⁸.

Reducing DTN time can be a complicated clinical process requiring coordination across departments and disciplines⁹⁻¹⁰. Successful interventions based on the redesign of modifiable hospital factors and multi-level multi-component hospital level changes have improved DTN times in some settings¹⁰. A nationwide quality improvement initiative in the United States achieved a 40% success rate in attaining the recommended 60 minutes DTN time¹¹. In contrast, in single large metropolitan comprehensive stroke centres (Helsinki and Melbourne), major reductions in DTN have been reported with multifaceted interventions¹²⁻¹³. The Thrombolysis ImPlementation in Stroke (TIPS) study, a clustered randomized controlled trial, tested a combined multi-component and multidisciplinary in-hospital approach aimed at improving intravenous thrombolysis rates at multiple sites across Australia but particularly targeting primary stroke care centres¹⁴. This intervention was based on the behaviour change wheel¹⁴. The study achieved significant improvement of intravenous thrombolysis rates in the intervention hospitals during the active intervention phase, however, this improvement was no longer significant during the post-intervention phase¹⁵. In this study, we will explore the effect of the TIPS intervention on DTN, as well as door-to-imaging (DTI), and imaging-to-needle (ITN) times. In addition, as the recommended DTN, DTI, and ITN time is < 60 minutes, < 25 minutes, and < 35 minutes respectively¹⁶, therefore, we will also explore the proportion of patients with the recommended time frame. Moreover, the quality of hospital care for stroke may vary in non-metropolitan areas as non-metropolitan hospitals are less likely to offer coordinated and dedicated services for stroke care in comparison with metropolitan hospitals¹⁷. Therefore, we will also undertake sub-group analysis to assess whether the effect is modified by metropolitan versus non-metropolitan hospital location. We hypothesised that the intervention hospitals would show a significant and sustained reduction in DTN times.

Methods

Study design, location, and duration

The study was a posthoc analysis of data from the TIPS study, a cluster-randomized controlled trial involving 20 hospitals from three Australian states: New South Wales, Queensland, and Victoria¹⁴. The study adheres to CONSORT guidelines. The hospital was the unit of randomization, with randomisation conducted using a computer-generated stratified scheme where 10 hospitals were assigned to the intervention group and 10 to the control group. The intervention hospitals received the TIPS intervention, a multi-level, multi-component, collaborative approach, whereas the control hospitals continued with standard care. Blinding was not possible because of the nature of the intervention. Study-related activities were divided into three periods:

- Pre-intervention: January 2011 to August 2013.
- Active-intervention: September 2013 to December 2014.
- Post-intervention: January 2015 to December 2015.

Hospital eligibility and recruitment

Eligible hospitals were identified from the Stroke Foundation's audit records and State-based stroke care networks. The participating hospital had a Stroke Care Unit or staffing equivalent to a stroke physician and a nurse, and were in the early stages of implementing thrombolysis. Clinical leaders were contacted by the research team, either in person or over the phone, to discuss possible participation in the study. Once agreed, a memorandum of understanding and consent agreement was co-signed by the hospital's authority and the study team. Those recruited included publicly and privately funded hospitals, as well as metropolitan and non-metropolitan hospitals. Hospitals were randomised within strata defined according to their baseline intravenous thrombolysis rates:

- Very Low: 0% to 4%
- Low: >4% to 10%
- Medium: >10%

Patient Data Eligibility

De-identified case data from patients treated with stroke thrombolysis were included in the TIPS dataset and, for the current study, only data from patients that had complete data were included and each patient was different at each time point.

Ethical Approval

Ethical approval was obtained from the Hunter New England Human Research Ethics Committee and from the University of Newcastle, Human Research Ethics Committee.

Process for Data Collection

The following details were recorded for each thrombolysed case: age, gender, date and time of stroke onset, date and time of hospital arrival, date and time of brain imaging examination, time of treatment, and patient medical history. Additionally, for each hospital the following details were considered: location (metropolitan/non-metropolitan), baseline thrombolysis rate and the implementation of TIPS intervention activity (intervention/control). These details were entered into a secure TIPS-specific database that was hosted on the Stroke Foundation's website. The database was only accessible via a secure login system and only accessible to those approved to do so. All patient data were de-identified and entered by a study-specific delegate at each participating hospital.

Interventional activity and components

The TIPS intervention was based on breakthrough collaborative methodology and the behaviour change wheel¹⁴. The intervention included activities and components which have been described previously¹⁴ and those are: situational analysis – clarifying the patient journey, change agents - educating, persuading and modelling, information-based target setting – persuasion and incentivization,

collaborative problem solving - education, modelling, and enablement, professional development – education and training, performance feedback - persuasion, modelling.

Statistical analysis

Patient characteristics were summarised using descriptive statistics: frequency and percentages for dichotomous variables, and mean and standard deviation for continuous variables. Mixed-effects regression modelling was used to assess the effectiveness of the TIPS intervention: linear regression for DTN, DTI, and ITN times, and logistic regression for DTN time ≤ 60 minutes, DTI time ≤ 25 minutes, and ITN time ≤ 35 minutes. Each model included a hospital-level random intercept to adjust for the correlation of outcomes within the hospital. Time period (with pre-intervention as the reference), intervention group (with control as the reference), and time by intervention group interaction were included as fixed effects; and the models also adjusted for baseline hospital thrombolysis rate category (the stratification variable). Robust standard errors and an independent structure of the residual errors were used for all models.

Separate models were used to explore whether there was an observable intervention effect when the data for each location type were considered in isolation. Separate mixed-effects regression models were conducted for each location type (metropolitan and non-metropolitan). This was linear for the continuous outcome of mean DTN, DTI, ITN times, and logistic for the dichotomous outcome of the proportion of patients having DTN ≤ 60 , DTI ≤ 25 , ITN ≤ 35 minutes. The same fixed effects and hospital-level random intercept included in the primary analysis were also included in these secondary analyses. All statistical analyses were performed using Stata version 14.0 (StataCorp, College Station, TX).

Results

From January 2011 to December 2015, 1535 patients with acute ischemic stroke received thrombolysis at the 20 participating hospitals; of which 1039 (68%) had complete data regarding each time point and therefore included in this analysis. The rest were excluded as because of having missing value or not having compatibility. Of the included cases, 489 (47%) were treated in intervention hospitals and 550 (53%) were treated in control hospitals. The mean age of the patients was 72.07 (Standard Deviation, SD=13.84) years, and 499 (48%) were female. Across all hospitals, 421 (41%) patients were thrombolysed in the pre-intervention period, 364 (35%) in the active-intervention period, and 254 (24%) in the post-intervention period. Of the 20 hospitals, 12 were located in metropolitan areas and these hospitals admitted the majority of patients (n=883, 85%) (Figure 1). Of the 20 hospitals, 12 had a baseline thrombolysis rate of 0-4% (n=320, 31%), six had a baseline rate of 4-10% (n=341, 33%) and two had a baseline rate of >10%. Patient characteristics for the intervention and control hospitals over the three study periods are reported in [Table 1](#). The means and SD in DTN, DTI and ITN times for intravenous thrombolysis were 85.30 (29.88), 33.84 (19.56), and 52.00 (26.29) minutes respectively. The proportions of patients with DTN time ≤ 60 minutes, DTI time ≤ 25 minutes, and ITN time ≤ 35 minutes were 240 (23%), 410 (39%), and 322 (31%) respectively.

Change in Door-to-Needle Times

A 'difference in differences' approach was taken to explore the change in DTN times, to optimize the use of continuous data. There were no significant differences between the intervention and control hospitals in relation to the change in DTN times from the pre-intervention period to both the active and post-intervention periods ([Table 2](#)). When comparing the pre-intervention period to the active-intervention period within experimental groups, all hospitals significantly decreased their DTN times. The intervention hospitals decreased the DTN time by 9.24 minutes (95% Confidence Interval, CI: -16.92, -1.55) and the control hospitals decreased it by 5.59 minutes (95% CI: -9.00; -2.19). When comparing the pre-intervention period to the post-intervention period within experimental groups, the difference in DTN time was significant for the control hospitals, with a mean decrease of 12.13 minutes (95%CI -17.44, -6.82), but this was not significant for the intervention hospitals ([Table 2](#)). [Supplement 1](#) shows predictive margins for DTN, DTI, and ITN for both intervention and control hospitals.

When comparing hospitals based on their location, no metropolitan hospitals achieved significant reductions in DTN times from pre-intervention period to the active and post-intervention periods. However, during the active intervention period, metropolitan hospitals in the intervention group significantly decreased their DTN times by 10.19 minutes (95% CI: -18.48; -1.89); while the metropolitan hospitals in the control group showed significant reductions in DTN times during both active and post-intervention period by 4.85 and 12.22 minutes respectively (95% CI: -8.03; -1.66 and 95% CI: -18.02; -6.41). Almost similar results were found in the non-metropolitan hospitals and for the DTI and ITN times ([Table 2](#); [Supplement 2](#) & [Supplement 3](#)).

The proportion of patients with Door-to-Needle times ≤ 60 minutes

There were no significant differences between the intervention and control hospitals with regards to any change in the proportions of patients with DTN time ≤ 60 minutes from pre-intervention to either the active or post-intervention periods. However, across periods, there were significant changes from the pre-intervention phase to the post-intervention phase for both the intervention (OR: 1.90; 95%CI: 1.09, 3.32) and control hospitals (OR: 1.87; 95%CI: 1.12, 3.13); [Table 3](#). No within- or between-group differences in the proportion of patients with DTN time ≤ 60 minutes was observed by the hospital's location ([Table 3](#)). Results with DTI time ≤ 25 minutes, and ITN time ≤ 35 minutes are shown in [Supplement 4](#) & [Supplement 5](#).

Discussion

Here we reported the relative effect of the TIPS intervention in reducing the duration of within-hospital processes for intravenous thrombolysis. The intervention did not have a significant effect on any of the treatment times studied and there were no differences in treatment time associated with the non-metropolitan or metropolitan location. However, further within-group analyses did provide further information on the way in which practices at study sites were changing during the study period. During the active intervention period, intervention hospitals did show a significant decrease of DTN time but

control hospitals also showed a significant decrease in DTN time at both active and post-intervention periods. Moreover, metro hospitals from the intervention arm showed a significant decrease in DTN time during the active intervention period but metro and non-metro hospitals from the control arm also showed a significant decrease in DTN time at both active and post-intervention periods. The primary outcome of the TIPS intervention, the difference in proportion of intravenous thrombolysis between groups, showed a small significant intervention vs. control difference during active intervention phase (OR=1.6; 95% CI; 1.1; 2.3) but a non-significant outcome during the post-interventional phase (Rate difference=1.1%; 95% CI; -1.5 to 3.7)¹⁵. Therefore, the non-significant intervention vs. control result of DTN time mirrored the primary outcome result reported previously, i.e. intravenous thrombolysis rates.

Numerous studies have provided evidence for a variety of strategies to improve DTN time for intravenous thrombolysis. Previous single centre studies report DTN reductions of 8 to 47 minutes from pre to post implementation of improvement strategies¹⁸. However, most of the single centre studies were limited to small numbers of patients (<500; except Helsinki Model (ref)) and varied across hospital types, layout and regional policies⁷. On the other hand, multi-centre studies evaluated their intervention effect over a long period of time e.g. US-Target: stroke from 2003 to 2009 and SITS-WATCH 2003-2011¹⁹. The changes described in TIPS occurred only over a five-year period (2011-2015). TIPS was a multicentre study over a time period when intravenous thrombolysis was the focus of various national efforts to improve implementation rates. It is, therefore, possible that the intervention effects may have been partly associated with changes in national and state-level policies and events during the study period. From 2010, the Australian health system implemented several health policies to improve the management of stroke such as clinical guidelines for stroke management 2010, which provided a series of evidence-based recommendations relating to the management of stroke in Australia²⁰. The continuum of care covered by the guidelines includes pre-hospital and acute phases of care. In addition, the establishment of the Australian Stroke Coalition, a joint venture of the Stroke Foundation and the Stroke Society of Australasia, focussed attention on improvement in processes of care and developed six areas of priority for action: acute stroke care including thrombolysis and stroke unit care, rehabilitation, community involvement, workforce, training and professional development, pooled data collection and quality development²¹. In 2015, the Stroke Foundation developed an innovative online resource that has information and support for clinicians and administrators working in stroke. It included the latest evidence, linked health professionals with their peers, provided monitoring data on current practice, shared success stories of sites that have improved care and offered tools and resources to maximise the quality of stroke care delivered⁶. The secular trends seen in improvements in process of care may well have emerged, in part, due to these national systems-level factors.

Interestingly, sub-group analysis based on metropolitan and non-metropolitan hospitals followed a similar pattern of overall DTN times, as did DTI and ITN times. Also, around a quarter (23%) of patients had DTN times ≤ 60 minutes and around one third had DTI ≤ 25 minutes (39%) and ITN ≤ 35 minutes (31%) which are lower than other study results²². Even so, further research is needed to reduce in-hospital assessment processing times.

Conclusions

The neutral overall result highlights that the components of the intervention were not sufficiently robust to modify the processes of care. The reasons behind this non-significant result may be the changes in acute stroke care that were already occurring at the time, structural barriers to change in complex health systems, workforce capability and capacity to drive change, and/or a lack of focus on change enablement among clinical and managerial leadership. Future TIPS analyses will investigate quantitative and qualitative data to identify whether intervention components impacted change in process of care with the aim of informing potential future implementation strategies.

Abbreviations

DTI: Door-to-Imaging

DTN: Door-to-Needle

ITN: Imaging-to-Needle

NHMRC: National Health and Medical Research Council

NSW: New South Wales

TIPS: Thrombolysis ImPlementation in Stroke

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Hunter New England Human Research Ethics Committee and from the University of Newcastle, Human Research Ethics Committee. Written informed consent was not taken from the patients as the study collected anonymous patient data from the hospital record and the intervention was implemented at the hospital level.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no competing interests.

Funding

This study was funded by the National Health and Medical Research Council (NHMRC) partnership grant (569328), part-funded by an NHMRC Practitioner Fellowship (1043913) and NHMRC Translating Research Into Practice fellowship, and included partnership grant contribution funding from Boehringer Ingelheim, in-kind support from Agency for Clinical Innovation Stroke Care Network/Stroke Services New South Wales (NSW), Stroke Foundation and NSW Cardiovascular Research Network-National Heart Foundation, with a cash contribution from the Victorian Stroke Clinical Network and infrastructure funding from the Hunter Medical Research Institute and The University of Newcastle. The funders had no input into the design, data collection, analysis, interpretation of study findings, or preparation of manuscript.

Authors' Contributions

MGH, CLP and CRL designed and prepared the study concept. MGH and AH analysed the data with advice from CLP, JRA and CDE. MGH drafted the manuscript with advice from CLP, JRA, AR, EK, CAD, AH, AHM, IH and CRL on method of data analysis, presentation of results. CLP, JRA, AR, EK, CAD, AH, AHM, IH and CRL were involved in critical revision of the manuscript. All authors read and approved the final manuscript.

Acknowledgement

We are thankful to all staffs and patients from the participating hospitals for their kind participation and support during the study period.

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Tables

Table 1: Patient characteristics between intervention and control hospitals over the three study periods (Pre, active and post)

Characteristics	Pre-intervention, n = 421		Active intervention, n = 364		Post-intervention, n = 254	
	Intervention n = 202	Control n = 219	Intervention n = 177	Control n = 187	Intervention n = 110	Control n = 144
Age in years						
Mean (SD)	72.46 (13.02)	70.87 (13.57)	73.42 (13.94)	73.30 (13.48)	74.57 (13.52)	70.78 (15.66)
Gender						
Female, n (%)	96 (48)	104 (47)	94 (53)	93 (50)	45 (41)	67 (47)
Pre-stroke modified Rankin Score (mRS), n (%)						
0	118 (64)	132 (66)	103 (62)	109 (63)	69 (66)	78 (65)
1	22 (12)	27 (13)	12 (7)	18 (10)	7 (7)	11 (9)
2	22 (12)	19 (9)	28 (17)	30 (17)	16 (15)	14 (12)
3	19 (10)	18 (9)	18 (11)	13 (7)	11 (11)	11 (9)
4	3 (2)	18 (9)	3 (2)	13 (7)	1 (1)	5 (4)
5	0 (0)	3 (2)	1 (1)	4 (2)	0 (0)	1 (1)
5		2 (1)		0 (0)		
On admission National Institute of Health Stroke Scale (NIHSS)						
Mean (SD)	10.51 (6.47)	11.32 (6.84)	10.4 (7.14)	11.19 (6.35)	11.72 (6.77)	10.52 (6.93)

Table 2: Effect of intervention on DTN time for thrombolysis.

	Intervention			Control			Intervention vs. Control
	Number of Events	Mean ± SD	Difference in means from pre- intervention period (95% CI)	Number of Events	Mean ± SD	Difference in means from pre- intervention period (95% CI)	Difference in means from pre- intervention period (95% CI)
Pre- Intervention Period	202	87.70 ± 30.31	Reference	219	92.30 ± 29.13	Reference	Reference
Active Intervention period	177	77.24 ± 27.77	-9.24 (-16.92; -1.55)*	187	86.41 ± 29.25	-5.59 (-9.00; -2.19)*	-3.99 (-12.27; 4.28)
Post Intervention Period	110	84.83 ± 32.63	-3.80 (-19.36; 11.76)	144	80.08 ± 28.81	-12.13 (-17.44; -6.82)*	8.33 (-8.10; 24.76)
Metropolitan Hospitals only							
Pre- Intervention Period	157	88.28 ± 31.04	Reference	205	91.73 ± 28.91	Reference	Reference
Active Intervention period	135	76.77 ± 25.90	-10.19 (-18.48; -1.89)*	174	86.54 ± 29.72	-4.85 (-8.03; -1.66)*	-5.34 (-14.15; 3.48)
Post Intervention Period	79	86.42 ± 31.64	-3.03 (-23.89; 17.83)	133	79.39 ± 28.72	-12.22 (-18.02; -6.41)*	9.19 (-12.37; 30.74)
Non- Metropolitan							

Hospitals only							
Pre- Intervention Period	45	85.69 ± 27.83	Reference	14	100.6 ± 32.27	Reference	Reference
Active Intervention period	42	78.74 ± 33.39	-6.28 (-24.49; 11.92)	13	84.69 ± 22.91	-15.98 (-19.34; -12.62)*	4.93 (-14.27; 24.14)
Post Intervention Period	31	80.77 ± 35.25	-5.44 (-22.52; 11.63)	11	88.45 ± 29.97	-12.24 (-22.58; -1.89)*	6.86 (-13.11; 26.83)

*p-value<0.05 considered as significant

**Reference pre-intervention

***Linear mixed model controlling for group based on baseline thrombolysis rate

Table 3: Effect of intervention on the proportion of patients had DTN time $\leq$ 60 minutes.

	Intervention			Control			Intervention vs. Control
	Total Number	Number of Patients with DTN $\leq$ 60 minutes	Odds Ratio (95% CI)	Total Number	Number of Patients with DTN $\leq$ 60 minutes	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Pre- Intervention Period	202	39	Reference	219	38	Reference	Reference
Active Intervention period	177	47	1.42 (0.86- 2.35)	187	43	1.43 (0.87- 2.36)	0.99 (0.49- 2.02)
Post Intervention Period	110	33	1.90 (1.09- 3.32)*	144	40	1.87 (1.12- 3.13)*	1.01 (0.47- 2.17)
Metropolitan Hospitals only							
Pre- Intervention Period	157	30	Reference	205	36	Reference	Reference
Active Intervention period	135	34	1.31 (0.73- 2.34)	174	42	1.50 (0.90- 2.50)	0.87 (0.40- 1.89)
Post Intervention Period	79	21	1.60 (0.83- 3.11)	133	38	1.91 (1.12- 3.26)*	0.84 (0.36- 1.96)
Non- Metropolitan							

Hospitals only							
Pre-Intervention Period	45	9	Reference	14	2	Reference	Reference
Active Intervention period	42	13	1.78 (0.66-4.81)	13	1	0.51 (0.04-6.48)	3.51 (0.23-54.47)
Post Intervention Period	31	12	2.80 (0.96-8.15)	11	2	1.35 (0.15-11.78)	2.08 (0.19-23.31)

*p-value<0.05 considered as significant

**Reference pre-intervention

***Linear mixed model controlling for group based on baseline thrombolysis rate

Figures

Figure 1

Distribution of patients between intervention and control hospitals across various hospital location.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplement1.tif](#)
- [supplement2.pdf](#)
- [supplement3.doc](#)