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TITLE PAGE

i. Title: The Quest to Reduce Stroke Treatment Delays at A Melbourne Metropolitan Primary Stroke Centre over the Last Two Decades

Running head: Quest to Reduce Stroke Treatment Delays

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TEXT

INTRODUCTION

Intravenous thrombolysis (IVT) with alteplase is an effective, time sensitive treatment for eligible patients with acute ischaemic stroke (AIS).[1] Early randomised control trials and pooled meta-analysis data highlight the importance of prompt IVT administration to prevent death and dependency.[2,3] With every additional minute delay to revascularisation, there are 1.9 million neurones injured, a higher proportion of symptomatic intracranial haemorrhage and poorer functional outcomes.[4,5]

The cause of treatment delay for AIS is multifactorial.[6] Both pre-hospital and in-hospital delays, which can be measured by onset-to-door time (ODT) and door-to-needle time (DNT), respectively, have been targets of interventions.[7,8] In Australia, alteplase was first licensed for use in 2003. In an effort to improve the quality of stroke care, the Australian Stroke Clinical Registry was first piloted in 2009 with 12 participating hospitals in 2010 and has since grown to include data from 72 hospitals in 2019.[9,10] Despite the extensive literature highlighting the need for speed, the proportion of patients receiving IVT within DNT of 60 minutes has remained at 30% for the last five years in Australia.[9]

Interventions associated with faster DNT are well known and various centres have achieved dramatic DNT improvement by adopting strategies such as rapid triage/imaging protocols and early stroke team involvement.[11-13] Yet reports on the long-term sustainability of these improvements in the Australian context are scant.[14] In particular, the potential effect of

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recent advances in hyper-acute stroke therapy such as the extension of IVT treatment time window and mechanical thrombectomy based on multi-modal CT imaging findings, is lacking. Furthermore, the effect on treatment time from ever increasing number of patients presenting to the ED with 'suspected stroke' due to an ageing population and increased community awareness of stroke as an emergency condition are unknown.

A continuous quality improvement program started in 2011 at our health service. The aim of this study was to report the long-term trends in DNT since the inception of IVT at our hospital and to analyse factors that may be associated with faster DNT.

METHODS

This is a retrospective analysis of consecutive adult patients treated with IVT from 1 January 2003 to 31 December 2019 at Box Hill Hospital (BHH), Eastern Health, which is the largest health service by land area in metropolitan Melbourne (4,780 km^2) and has a primary and secondary catchment population of one million. Eastern Health has two other sites with Emergency Departments (ED) but IVT is centralised at BHH, a 621-bed tertiary teaching hospital.

The departmental database was interrogated for patients treated with IVT. Those who were transferred for mechanical thrombectomy following IVT were also included. Missing or incorrect data were infrequent but if present, two investigators (PSWP and TF) independently verified patient records with adjudication by PMCC. National Institutes of Health Stroke Scale (NIHSS) on admission was used to assess stroke severity. Scores range from 0 (normal) to 42 (death).[15] Functional status was assessed using the modified Rankin Scale (mRS), which ranges from 0 (no disability) to 6 (death).[16] 'Stroke neurologist' was defined as a neurologist who has completed a sub-specialty stroke fellowship.

Conventional DNT calculation was used. The 'door' time was defined as the time of patient arrival at ED triage. For in-hospital 'Code Stroke', the time of code activation was used as the surrogate for 'door' time. For interhospital transfer cases from Eastern Health network hospitals, BHH arrival time was used as the 'door' time. Door-to-CT time (DCT) was the time

from door to computed tomography (CT) scout film acquisition. 'Needle' time was defined as the time IVT bolus was commenced. Based on current stroke service structure, work hours have been classified into weekday or weekend 0800–1700, 1700–2200 and 2200–0800. Public holidays were included in the weekend category due to similar staffing arrangements.

Interventions

Figure 1 summarises 15 strategies used at our hospital over time to improve DNT with most strategies implemented since 2011/2012. Optimising workflow has been the main target of quality improvement strategies, resulting in patient registration before arrival; single-call activation of relevant hospital staff; and current 'Direct-to-CT protocol (Appendix 1). The increase in acute stroke nurse (ASN) provision from a part-time to a full-time role; and a weekly reperfusion review meeting involving a core group of personnel are important. The ASNs drive quality improvement initiatives and a weekly meeting provides a platform to review and develop quality improvement programs. Based on the above, the pre-intervention period has been defined as time frame 2003–2011 and intervention period, 2012–2019. The current acute stroke workflow and stroke team membership have been previously described.[17,18] In particular, the stroke registrar onsite time was extended from 0800–1700 to 0800–2200 in 2015, and a dedicated stroke fellow attending 'Code Stroke' on weekdays 0800–1700 was introduced in 2018 due to increasing presentations.

Statistical analysis

Differences between categorical variables were assessed with χ^2 tests and continuous variables with Kruskal-Wallis tests as appropriate. A linear regression model was fitted to the natural log of the DNT values, after excluding zero and negative ODT, which were due to in-hospital stroke and onset of stroke symptoms after ED arrival, respectively. Log transformation was chosen to reduce skewness and make the residuals acceptably close to normality (as assessed by a QQ-plot) and made the residual variance close to homogeneity. Potential explanatory variables were selected on the basis of their importance or interest. All available

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variables were considered for inclusion but only those which were significant after a first fitting were retained. The retained variables and their estimates and associated *P*-values are shown. There are a number of changes across the system over time mainly during the intervention period that can affect DNT and the effect of these interventions on DNT is difficult or impossible to measure individually. The summative effect of these measures on DNT is estimated in the regression model by a dummy variable, which we have defined and labelled as 'organisational' factor. This accounts for any system-wide factors (including those external to the hospital such as increasing volume of presentation) that have changed during the intervention period, over and above the specific factors that we can accounted for, and have been specifically addressed in our analysis. The 'organisational' factor takes the value 0 before 2012 and 1 after 2013, increasing linearly in between and remaining constant thereafter. All the analyses were performed in R studio version 3.6.1.

Ethics approval

The Office of Research and Ethics at Eastern Health approved the study as a quality assurance project (QA20/015).

RESULTS

1,250 patients were treated with IVT over the 17 years. Patient characteristics of pre-intervention and intervention periods are described in Table 1. Median DNT fluctuated between 70 to 93 minutes (interquartile ranges [IQR], 55–95 to 82–120) from 2003 to 2012, reaching 60 minutes in 2013 and nadir of 47 minutes in 2014 (Figure 2). Thereafter, the median DNT decreased from 58 minutes in 2015 to 51 minutes in 2019 with progressive tightening of IQR (46–78 to 40–62). The number of patients treated within 60 minutes of hospital arrival was 22.5% during pre-intervention period. This rose to an average of 63% during 2015–2018 and 71% in 2019. This coincides with median DCT reduction from 27 to 12 minutes (IQR, 19–42 to 8–15) between 2013 and 2019.

From the multivariate linear regression model (Table 2), seven factors were associated with DNT. Three modifiable factors were ‘Direct-to-CT’ protocol (32.6% reduction; 95% CI, 26.9–38.2%), ‘organisational’ factor (21.9% reduction; 95% CI, 16.1–27.7%) and ASN presence (6.9% reduction; 95% CI, 0.3–13.5%). Further analysis (not shown) indicated that ‘Direct-to-CT’ protocol and presence of ASN were associated, which suggests that some confounding exist between these two factors. Non-modifiable factors associated with DNT reduction were higher stroke severity (2.3% per 5-points increment of the NIHSS; 95% CI, 0.7–4.0%); longer ODT (2.9% per hour; 95% CI, 0.9–4.9%); excellent functional status pre-stroke (6.2%; 95% CI, 0.6–11.8%) and time of presentation. Presentations outside weekdays 0800–1700 had about 22–24% longer DNT (95% CIs, typically 15–30%), with the exception of weekends 0800–1700, where DNTs were 9% (95% CI, 1–16%) longer than weekdays 0800–1700. These differences in DNT based on time of presentation have reduced over time (Appendix 2). Factors such as age, sex and stroke neurologist as ‘Consultant In-Charge’ were not associated with faster DNT.

The numbers of annual stroke admissions increased 4-fold to 748 and annual ‘Code Strokes’ increased 10-fold to 1,298 (Figure 2). Despite increasing presentations and IVT, sustained improvement in DNT is observed (Appendix 3). During the intervention period, older and less independent patients have been thrombolysed, and presentations via emergency medical services have increased (Table 1). Proportions of patients presenting during weekdays 0800–1700 have remained stable at approximately 40%. Since its introduction in 2013, ‘Direct-to-CT’ protocol has been increasingly used at all hours (Appendix 4). A higher proportion of patients have achieved functional independence at 3 months during the intervention period than during the pre-intervention period (P<0.001; Table 3). Non-significant differences in mortality (14.1 versus 15.6%, P=0.475) and symptomatic intracranial haemorrhage (3.9 versus 5.3%, P=0.251) were seen between pre-intervention and intervention periods.

DISCUSSION

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We have shown sustained, incremental DNT reductions since 2011 despite increasing patient presentations over time. A number of factors associated with faster DNT were identified, with the 'Direct-to-CT' protocol being the most important followed by 'organisational' factor, time of presentation and ASN presence. Strategies targeting work flow and sustained clinician behaviour change, further supported by increased staffing of the stroke team likely resulted in improved parallel, rather than serial processing in acute stroke assessment, akin to the 'pit-stop' model of Formula 1 racing. The aim of 'Direct-to-CT' protocol at our centre was to minimise the significant time spend in multiple transfers/handover of patients prior to imaging. This study confirms the direct impact of 'Direct-to-CT' protocol in reducing DNT (32.6%, $P<0.001$), which is consistent with experiences at other centres.[12,13]

'Organisational' factor had the second biggest impact on DNT reduction (21.9%, $P<0.001$). This factor is important as it likely captures the effect of difficult to measure or unmeasurable variables, such as summative systemic improvement, clinician behaviour change and staffing.[19,20]

Clinician behaviour change related to DNT reduction and IVT implementation has been recognised as one of the most difficult factors to improve in the Australian context.[21,22] The term clinician is used in its broadest sense – any staff who has clinical contact with the patients - paramedics, nursing and medical imaging technologists are included. The sheer number of staff members in these roles makes any sustained behaviour change in the individual clinician extremely difficult. We found that by creating a culture of 'no-fault' and continuous quality improvement within the ED and stroke team, members are much more likely to work together with the collective goal of reducing delays in providing hyper-acute treatment. This effort is supported by the weekly reperfusion meeting between core members of the stroke team – ASN, stroke registrar, fellow and lead stroke neurologist, as well as quarterly meeting with the wider stakeholders. Our data suggests we have successfully implemented our 'Direct-to-CT' protocol 24/7 despite the presence of only one member of usual stroke team outside weekday 0800–1700 (Appendix 4). Tightening of DNT interquartile ranges are suggestive of less variation in the overall workflow.

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Improved staffing for 'Code Stroke' in our context since 2015 has resulted in sustained DNT reduction despite increasing presentations for AIS assessment. Typically, 0800–1700 has been the best staffed period despite approximately 60% of IVT occurring outside this timeframe. This finding confirms a striking mismatch between historical staffing and service requirements. Based on this discrepancy, onsite stroke registrar coverage was extended from 1700 to 2200. The working hours of ASN and stroke neurologists have, however, remained relatively static.

Our study is the first to quantify the magnitude of ASN's impact on DNT. Presence of ASN resulted in DNT reduction of 6.9% (P=0.005). Despite ASN being a likely confounding variable, we have controlled for this in our analysis. Prior to this study, ASN was seen to be associated with shorter DNT but the magnitude of impact on DNT was unclear.[23] There is potential to improve after-hours DNT by increasing the ASN workforce to include an ASN in the after-hours stroke team, particularly at high volume centres. This might be a more cost-effective investment than expansion of non-specialist junior medical workforce for hyperacute stroke care. Although it is plausible that an ED 'stroke champion' model would be beneficial for DNT, this has not been formally studied and there are significant practical barriers to developing and maintaining a sufficiently large, skilled workforce to allow a 'stroke champion' to be rostered for all after-hours ED shifts in a high volume ED.

We found that excellent pre-stroke functional status, higher stroke severity, and longer ODT have small independent associations with faster DNT. The first two are expected whilst the latter is difficult to interpret given the increased IVT window for eligible patients in recent years (Figure 1). Before the extended IVT window era, the inverse relationship of ODT and DNT, however, is generally considered a reflection of a lack of treatment urgency when patients present earlier.

The reasons for the relative stagnation of DNT despite tightening of interquartile ranges in the last few years remain unclear. Preliminary analysis of cases treated at BHH between 2018 and 2019 shows that 30% were treated at DNT longer than 60 minutes, and approximately 90% of these cases had documented delays due to eligibility, medical and hospital related

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reasons.[24,25] Half of these delays were due to non-modifiable patient factors surrounding eligibility ascertainment and management of acute medical conditions. In similar vein, currently 25% of patients are thrombolysed within 40 minutes with median DCT and median multi-modal CT completion time of 10 and 15 minutes, respectively.[26] Hence, in 75% of patients, more than 15 minutes are spent after CT completion on decision making, IVT preparation and addressing above-mentioned delay factors. Indeed, whether the high number of 'Code Stroke' in recent years play a role in the stagnation of DNT require further investigation. This effect is difficult to quantify, as volume will potentially enhance workflow efficiency up to a certain point, then become a barrier to further improvement by overwhelming the system (Appendix 3). The first step would be to assess the resources required for a 'Code Stroke' attendance, and work is currently underway to examine this.

Significant improvement in functional outcomes was seen during the intervention period, which is consistent with findings from large registry studies.[5,27] It is likely that our result is confounded to a degree by the impact of mechanical thrombectomy, which has been standard of care since 2015 for patients with large vessel occlusion and performed in 17.2% of patients. There was no increase in adverse outcomes as measured by proportion of cases with symptomatic intracerebral haemorrhage and death despite treatment of older and less independent patient groups during the intervention period compared to pre-intervention period (mRS 3-4, 8 versus 3%). Mortality outcome was comparable to Safe Implementation of Treatments in Stroke International data.[28]

Our study shows that system change at a local level can improve delivery of IVT within the DNT of 60 minutes. In Australia this target is met in only approximately 30% of total IVT cases. This calls for renewed system change at local, state and national levels as has been achieved overseas.[7,29] Strategies aimed at improving 'Code Stroke' work flow and optimising stroke team membership need to be brainstormed and tailored to each health service. Establishment of local hospital working groups with closer networking between local stakeholders including emergency medical services, medical imaging and ED is of paramount importance. The Australian Stroke Clinical Registry has been publishing regular reports since

2010 but only 72 out of 120 Australian hospitals with stroke units participate in the data collection. National policy change to involve and support all Australian stroke centres in a centralised national initiative similar to the American Target:Stroke model[7] may improve national DNT and patient outcome.

There are the usual limitations of a single centre retrospective study however most metropolitan primary stroke centres in Australia would have similar service structure to ours. Secondly, the birds-eye view over last two decades means there is limited ability to assess delay factors in individual cases that may offer better understanding of DNT variability. The strength of our study is that when compared to multi-centre, registry-based studies, our cohort allows for more granular examination of factors associated with DNT. Our analysis has examined strategies which were sequentially and incrementally implemented over 17 years. However, the fact that interventions were introduced over time does not make the regression assumptions invalid, since the model has explanatory variables which do not depend explicitly on time (apart from the 'organisational' factor). Thus, for example, although the probability of an ASN being present may depend on the date, ASN presence is either true or false, and the results of the regression model are conditional on what values the explanatory variables actually take on a given occasion. Examination of the autocorrelation function of the residuals showed no evidence of serial correlation. We can therefore conclude that the factors we have identified as associated with faster or slower DNT are on their own significant and not confounded by interventions implemented over time.

In conclusion, targeted quality improvement initiatives resulted in gradual, sustained improvement in DNT at our hospital over 17 years. 'Direct-to-CT protocol' has the greatest effect on achieving faster DNT, followed by 'organisational' factors and the presence of ASN. The barriers to further, significant improvement in median DNT in the context of increasing 'Code Stroke' presentations in recent years require further investigation.

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