**Title**

A fall in systolic blood pressure 24 hours after thrombolysis for acute ischaemic stroke is associated with early neurological recovery

**Authors**

Dipender Gill1 (corresponding author), Thomas Cox2, Adarsh Aravind3, Peter Wilding4, Eleni Korompoki5, Roland Veltkamp6, Arindam Kar7

1Academic Clinical Fellow in Clinical Pharmacology and Therapeutics, Imperial College Healthcare NHS Trust and Honorary Clinical Lecturer, Imperial College London

Postal address: Postgraduate Centre, Hammersmith Hospital, Du Cane Road, London W12 0HS, United Kingdom

E-mail: dipender.gill@imperial.ac.uk

Telephone: +44 (0) 7904843810

Fax: +44 (0) 2033133464

2Core Medical Trainee, Barts Health NHS Trust

Postal address: Whipps Cross Hospital, Whipps Cross Road, London E11 1NR

E-mail: thomas.cox2@bartshealth.nhs.uk

3Honorary Academic Fellow, Imperial College Healthcare NHS Trust

Postal address: Charing Cross Hospital, Fulham Palace Road, London W6 8RF

E-mail: aaravind@nhs.net

4Clinical Research Fellow, Imperial College Healthcare NHS Trust

Postal address: Charing Cross Hospital, Fulham Palace Road, London W6 8RF

E-mail: peter.wilding@imperial.nhs.uk

5Clinical Research Fellow, Imperial College London

Postal address: Charing Cross Hospital, Fulham Palace Road, London W6 8RF

E-mail: e.korompoki@imperial.ac.uk

6Professor of Neurology, Chair of Department of Stroke Medicine, Division of Brain Sciences, Imperial College London

Postal address: Department of Stroke Medicine, Charing Cross Campus, 3 East 6, Fulham Palace Road, London W6 8RF, United Kingdom

E-mail: r.veltkamp@imperial.ac.uk

7Consultant in Stroke Medicine

Hyper-acute stroke unit Lead

Imperial College Healthcare NHS Trust

Postal address: Charing Cross Hospital, Fulham Palace Road, London W6 8RF

E-mail: Arindam.Kar@imperial.nhs.uk

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BP fall associated with early neurological recovery

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Table 1

Table 2

**Abstract (208 words)**

Background: Outcomes are worse in patients thrombolysed for acute ischaemic stroke with persistent hypertension.

Aims: To investigate whether fall in systolic blood pressure has any relationship with neurological outcome 24 hours after thrombolysis, after adjusting for potentially confounding factors.

Methods: Retrospective analysis of a single-centre database of consecutive thrombolysis cases for acute ischaemic stroke. Multivariate regression analysis was used to explore the relationship between fall in systolic blood pressure and reduction in National Institutes of Health Stroke Scale 24 hours after thrombolysis. Other potentially confounding predictor variables used in the model were systolic blood pressure on thrombolysis, blood glucose on thrombolysis, National Institutes of Health Stroke Scale on thrombolysis, administration of antihypertensive medications and the time to thrombolysis after symptom onset.

Results: A fall in systolic blood pressure 24 hour after thrombolysis is independently associated with greater improvement in National Institutes of Health Stroke Scale score 24 hours after thrombolysis (coefficient 0.051, 95% confidence interval 0.023 to 0.078, p<0.001). Thus, a reduction of 10 mmHg in systolic blood pressure after 24 hours being associated with a 0.51 point reduction in National Institutes of Health Stroke Scale.

 Conclusions: Restoration in systolic blood pressure towards normal limits after thrombolysis for acute ischaemic stroke is associated with greater early neurological improvement.

**Introduction**

Appropriate administration of intravenous thrombolysis with recombinant tissue plasminogen activator (t-PA) improves outcomes after acute ischaemic stroke (AIS) (1–3). The benefit of t-PA is attributable to lysis of occlusive thrombus and reperfusion of ischaemic but not yet infarcted brain tissue (4) .Recanalisation of occluded vessels is correlated with early clinical improvement and this benefit is sustained at 3 months (5,6). Its benefit is strongly time dependent due to reperfusion of tissue before infarction and is only clinically effective when given within 4.5 to 5 hours following symptom onset (5,7).

The relationship between blood pressure and clinical outcome in patients treated with t-PA is complex. The majority of patients will demonstrate increased blood pressure in response to AIS (8). High admission systolic blood pressure (SBP) is associated with a poorer outcome in patients who are not treated with t-PA (9,10).

Elevated blood pressure prior to or following thrombolysis is associated with an increased risk of intracranial haemorrhage (11,12). For this reason, the original NINDS trial used similar blood pressure eligibility and management algorithms to those in the early dose-finding trials which had low incidence of symptomatic intracranial haemorrhage (13). These criteria are now used in clinical practice.

Pre-thrombolysis elevated SBP is associated with improved leptomeningeal collateral circulation (4), which may be a physiological response to improve perfusion to the ischaemic penumbra. However, 3 month outcomes were inversely associated with pre-thrombolysis SBP in the same study (4).

In patients treated with intravenous t-PA, favourable outcome was inversely associated with the maximum, mean and variation in post-thrombolysis blood pressure over 24 hours (9). Ahmed et al showed that the association between post-thrombolysis SBP and mortality and independence at 3 months is U-shaped, with the most favourable outcome associated with SBP between 141-150mmHg (14). However the association with symptomatic intracranial haemorrhage (SICH) was linear with lower SBP associated with lower risk of SICH.

Mattle et al. showed that in patients treated with intra-arterial t-PA, early reduction in SBP is associated with early recanalization (15). Furthermore, early recanalisation was associated with improved outcome at 3 months. However there was no association with the absolute blood pressure decline and outcome. Delgado-Mederos et al. showed in patients treated with intravenous t-PA that early recanalisation was associated with a fall in systolic blood pressure (16). They did not find any association with outcome for absolute values of blood pressure, but showed that early clinical improvement was associated with reduced blood pressure variability following t-PA administration.

In this study we aimed to assess whether reduction in blood pressure 24 hours following intravenous administration of t-PA is associated with improved early neurological recovery as assessed by early improvement in National Institutes of Health Stroke Scale (NIHSS), after adjusting for potentially confounding factors.

**Methods**

*Population*

All patients transferred to Imperial College Healthcare NHS Trust (ICHNT, London, United Kingdom) hyper-acute stroke unit and consequently thrombolysed for presumed AIS between 1st October 2011 and 30th June 2015 inclusive were included. Cases of thrombectomy, later confirmed non-stroke diagnoses (after review of imaging, including magnetic resonance imaging where performed, and clinical presentation) and death within 24 hours were excluded from this study.

*Clinical parameters*

All patients undergoing thrombolysis for presumed AIS were initially assessed by a stroke physician, and underwent brain computed tomography to exclude haemorrhage or other pathology. NIHSS score was completed on admission and 24 hours following administration of t-PA. Blood pressure recordings were made on admission and following thrombolysis to monitor response. Patients with persistent elevation of blood pressure >185/105mmHg prior to thrombolysis were treated with intravenous labetalol to reduce blood pressure to below this level. Blood pressure elevations following thrombolysis were treated with both intravenous (labetalol) and oral antihypertensives (amlodipine) as clinically appropriate. Blood glucose was recorded at initial assessment.

*Statistical analysis and confounding variables*

Statistical analysis was performed using Stata 14 (StataCorp LP). Summary statistics are offered as percentages, medians and interquartile ranges (IQR). Multivariate regression analysis was used to explore the relationship between fall in SBP over the 24 hours after thrombolysis (predictor variable) with reduction NIHSS 24 hours after thrombolysis (dependent variable).

Other potentially confounding predictor variables used in the model were SBP on thrombolysis, blood glucose (mmol/L) on thrombolysis, NIHSS on thrombolysis (points), administration of antihypertensive medications (dichotomised as received antihypertensives or did not) and the time to thrombolysis after symptom onset (minutes). Age was not considered to be a confounding variable as previous studies have demonstrated that t-PA is as effective in those over 80 years compared to those under (7).

Coefficients and confidence intervals (CIs) were used as indicators of effect size; p values with a cut off of <0.05 were used as indicators of statistical significance. Univariate regression analysis was used to explore potential confounding in predictor variables that did not show an independent association with reduction in NIHSS 24 hours after thrombolysis in the multivariate model.

*Ethics*

The standard of care delivered to patients thrombolysed for AIS is under a constant cycle of clinical audit at ICHNT. Only anonymised data already acquired for service evaluation purposes was used in this work. The study proposal was reviewed locally and further ethical review was not deemed necessary.

**Results**

Between 1st October 2011 and 30th June 2015 inclusive, a total of 535 patients were consecutively treated with thrombolysis. Of these, 46 cases of thrombectomy, 50 patients later confirmed to have a non-stroke diagnosis, and 4 patients that died within 24 hours of thrombolysis were excluded, leaving a total cohort of 435 patients.

Of the 435 eligible patients, complete data on change in NIHSS after 24 hours, NIHSS on thrombolysis, SBP on thrombolysis, change in SBP 24 hours after thrombolysis, blood glucose on thrombolysis, administration of antihypertensive, and time to thrombolysis after symptom onset was available for 327 patients. The numbers of missing results for each considered parameter are given in Table 1. Missing data was attributed to lack of documentation, and was missing completely at random (17). Summary statistics for patient demographics and the parameters considered in the regression model are offered in Table 2. The median reduction in systolic blood pressure 24 hours after thrombolysis for the whole cohort was 19.5mmHg.

Multivariate regression analysis revealed that reduction in NIHSS after 24 hours was independently associated with NIHSS on thrombolysis, SBP on thrombolysis, and reduction in SBP 24 hours after thrombolysis. Moreover, blood glucose on thrombolysis, but not use of antihypertensive medications or time to thrombolysis after symptom onset, was inversely associated with neurological improvement at 24 hours (Table 3). A fall in SBP 24 hour after thrombolysis is independently associated with greater improvement in NIHSS score 24 hours after thrombolysis (coefficient 0.051, 95% confidence interval 0.023 to 0.078, p<0.001). This translates as a reduction of 10 mmHg in SBP after 24 hours being associated with a 0.51 point reduction in NIHSS score.

The absence of an independent association between time to thrombolysis after symptom onset and neurological improvement at 24 hours is likely explained by a confounding association between NIHSS score on thrombolysis and time to thrombolysis after symptom onset, with more severe strokes having a shorter time to thrombolysis (univariate linear regression of NIHSS at thrombolysis, predictor variable, and time to thrombolysis after symptom onset, dependent variable, 377 results, coefficient -1.62, 95% confidence interval -2.61 to -0.629, p=0.001).

**Discussion**

We have demonstrated that a fall in SBP 24 hours after thrombolysis is independently associated with greater early improvement in NIHSS and that this fall is around half an NIHSS point for every 10mmHg reduction in SBP. We have also shown, in line with previous work, that initial SBP (9,10), and blood glucose on thrombolysis (18,19), are inversely related to early neurological improvement. This may be attributed to a lower rate of complete recanalization and thus worse clinical outcomes in hyperglycaemic patients (18).

Ahmed et al. have shown an inverse relationship between SBP following thrombolysis and improved outcome (14). Our results suggest that this effect may also be reflected in early neurological improvement.

The observed reduction in SBP may attributable to successful recanalisation (15,16). A fall in blood pressure following thrombolysis may represent a physiological response to reduced requirement for leptomeningeal collateral circulation (4). Thus, restoration in SBP towards normal limits after thrombolysis may in part be a surrogate marker for successful reperfusion to ischaemic brain tissue (8,20,21). This is further supported by Delgado-Mederos et al., who showed that SBP variability is associated with worse outcome in stroke patients without recanalization, with no such association in recanalized patients (16).

Brott et al. demonstrated in the NINDS t-PA trial that patients treated with t-PA who were hypertensive and received antihypertensive therapy following t-PA were less likely to have a favourable outcome than those who were hypertensive and did not receive antihypertensive therapy (13). We did not demonstrate an effect of the use of antihypertensive medications on early neurological recovery. It may be that early reduction in SBP is a marker of recovery but should not be pursued as a target in itself.

We have not investigated whether the reduction in SBP and early improvements in neurological function are sustained at 3 months. Furthermore, as this is a single-centre retrospective study it is only possible to demonstrate association between our variables. This work is further limited by missing data, resulting in 25% of the cohort not being included in the multivariate regression model (Table 1). Data was missing completely at random, and the distribution of results (as represented by percentage, median and interquartile range) is similar for the patients for which results are available, as compared to those used in the multivariate model. This would suggest that missing data is unlikely to have created bias in this analysis. We have also not been able to include other possible confounders (prior use of antihypertensive medications, history of hypertension, comorbidities, etc.) within the model.

Further work might aim to replicate these findings in an independent cohort of patients thrombolysed for AIS, with concurrent measurement of cerebral perfusion to investigate how this relates to the physiological changes and early neurological recovery and outcome.

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**Table legends**

Table 1: The number and proportion of missing data; 327 observations were considered in the multivariate regression analysis

Table 2: Summary statistics for patient demographics and the considered parameters; median and interquartile ranges for non-parametric variables, proportions for binary outcomes

Table 3: Results of multivariate regression analysis; 327 observation, adjusted R2 0.177

**Conflicts of interest**

Roland Veltkamp has received speakers honoraria, consulting honoraria and research support from Bayer, BMS, Biogen, Boehringer Ingelheim, Daiichi Sankyo, Medtro-nic, Morphosys, Pfizer as well as research support from the Deutsche Forschungsgemeinschaft (VE 196/3-1) and the Else-Kroener Fresenius Stiftung. The remaining authors declare no conflicts of interest.

**Author contributions**

Dipender Gill performed the literature search, created the tables, designed the study, collected the data, analysed the data, interpreted the data and wrote the manuscript.

Thomas Cox performed the literature search, interpreted the data and wrote the manuscript.

Adarsh Aravind performed the literature search, interpreted the data and wrote the manuscript.

Peter Wilding performed the literature search, interpreted the data and wrote the manuscript.

Eleni Korompoki performed the literature search, interpreted the data and wrote the manuscript.

Roland Veltkamp designed the study, analysed the data, interpreted the data and revised the manuscript.

Arindam Kar designed the study, collected the data, analysed the data, interpreted the data and revised the manuscript.