The impact of intensive blood pressure management in the post-thrombolysis setting: a real-world observational study

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ABSTRACT

AIM: Systolic blood pressure (SBP) >180mmHg following stroke thrombolysis has been associated with increased bleeding and poorer outcome. Aiming for the guideline SBP of <180mmHg often leads to SBP overshoot, as treatment is only triggered if this threshold is passed. We tested whether a lower target would result in fewer high SBP protocol violations.

METHOD: This is a single-centre, sequential comparison of two blood pressure protocols. Between 2013 and 2017, the guideline-based post-thrombolysis SBP target of <180mmHg was compared with a new protocol aiming for 140–160mmHg. The primary outcome was rate of patients with SBPs >180mmHg. Secondary outcomes included rates of SBP <120mmHg, antihypertensive infusion use, symptomatic intracerebral haemorrhage (sICH) and 3-month functional independence (modified Rankin Score [mRS] 0–2). Results were adjusted for age, baseline function and stroke severity using regression analysis.

RESULTS: During the 23 months preceding and 18 months following the transition to the new protocol, 68 and 100 patients were thrombolysed respectively. Baseline characteristics were similar between groups. The odds of one or more SBPs >180mmHg trended lower in the intensive group (adjusted odds ratio [aOR] 0.61; 95% confidence interval [CI] 0.32–1.17; p=0.14). There was a higher rate of SBPs <120mmHg (aOR 3.09; 95% CI 1.49–6.40; p=0.002) in the intensive BP protocol group. sICH rate and 3-month mRS 0–2 were similar between groups.

CONCLUSIONS: The more intensive post-thrombolysis BP protocol was associated with a significant increase in sub-optimally low BP events, with a non-significant trend toward fewer high BP protocol violations and unaffected patient outcomes.

Stroke remains one of the major causes of mortality and morbidity worldwide.[1] Treatment with thrombolysis for acute ischaemic stroke (AIS) has improved outcomes but carries an increased risk of symptomatic intracerebral haemorrhage (sICH).[2] Up to 60% of patients presenting with AIS have hypertension.[3] This may be attributable to a compensatory mechanism to increase cerebral perfusion pressure, pre-existing hypertension, pain, stress and inflammatory state.[4] Systolic blood pressure (SBP) at presentation is an important prognostic factor, with both lower and higher values associated with worse outcome (U-shaped curve).[5,6]

The optimal target for blood pressure (BP) within the first 24 hours remains uncertain and is likely impacted by stroke type, cause of hypertension, type of reperfusion therapy received—if any—degree of recanalisation, type and timing of the drug, BP variability and speed of BP lowering.[2] Some guidance is available specifically for the post-thrombolysis setting. The current American Heart Association/American Stroke Association and European Stroke Organisation guidelines recommend maintaining BP below 180/105mmHg during the first 24 hours post-thrombolysis.[7,8] The ENCHANTED trial tested an intensive post-thrombolysis SBP target of 130–140mmHg compared with the guideline target. There was no improvement in independence at 90 days but there was a significant reduction in any intracranial haemorrhage.[9] In the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) patients with SBP between 141–150mmHg had a four times lower risk of sICH than patients with SBP over 170mmHg.[7] Several observational studies have found that higher post-thrombolysis SBP and BP protocol violations have been associated with an increased risk of sICH and a lower rate of favourable outcomes.[10–12] Taken together, these data suggest that post-thrombolysis SBPs >180mmHg are sub-optimal for risk of sICH and possibly functional outcomes.

A review of our thrombolysis service found that post-thrombolysis SBPs of >180mmHg were not infrequent and that use of intravenous (IV) labetalol boluses as first-line management was associated with delays in achieving SBP control. If SBP of 180mmHg is the trigger for treatment, then avoiding protocol violations of SBP >180mmHg is impossible as the protocol has to be violated in order for treatment to be initiated. We hypothesised that setting a slightly lower treatment trigger and treatment range would more consistently achieve SBP maintenance within guideline parameters without risking high rates of hypotension, and that use of protocolised continuous anti-hypertensive infusion may offer faster SBP target attainment and lower SBP variability.

The primary aim of this study was to assess whether a more intensive SBP management strategy in the first 24 hours post-thrombolysis using an "ideal range" of 140–160mmHg, and a low threshold for initiation of IV antihypertensive infusion, would reduce the frequency of SBP >180mmHg recordings.

Methods

This is a single-centre, open-label, unblinded observational cohort study using a sequential comparison design to compare the rate of SBP >180mmHg protocol violations with guideline-based post-thrombolysis BP management to a more intensive strategy with an "ideal range" of SBP 140–160mmHg and a low threshold for IV antihypertensive infusion.

At Wellington Regional Hospital, the stroke service changed the protocol for management of hypertension after thrombolysis in mid-2014. The earlier protocol aimed for target SBP of <185mmHg pre- and <180mmHg post-thrombolysis for the first 24 hours after treatment. The new protocol aimed for a target SBP of <185mmHg pre-thrombolysis and 140–160mmHg post-thrombolysis for the first 24 hours. Bolus IV labetalol 10mg was to be used for SBPs above >185mmHg pre-thrombolysis. IV anti-hypertensive infusions were to be initiated if BP remained >160mmHg despite three or more IV labetalol boluses in both the pre- and post-thrombolysis period. The type of IV infusion was at the discretion of the treating physician, with IV glyceryl trinitrate (GTN), labetalol and hydralazine available. The protocol recommended GTN as the first-line drug and specified increments and decrements in the infusion rate depending on the SBP, with frequent measurement and readjustment until the SBP was within range.

We identified patients from our prospectively collected thrombolysis database with supplementary retrospective chart review to collect additional baseline characteristics, BP recordings and patient outcome data. Our patient group included all adult patients treated with IV thrombolysis for ischaemic stroke from January 2013 to January 2017. All patients had a clinical diagnosis of AIS and all received thrombolysis with IV alteplase within 4.5 hours of symptom onset. Computed tomography (CT) perfusion imaging was not in common usage during this period and a consistent thrombectomy service had not yet been implemented. There were no other service or protocol changes relevant to the post-thrombolysis management of patients at Wellington Regional Hospital during the study period.

The primary outcome was number of patients experiencing one or more SBP of >180mmHg during the first 24 hours following thrombolysis. Secondary outcomes included the proportion of patients experiencing SBPs <160mmHg, <140mmHg, <120mmHg or >200mmHg during first 24 hours, number of SBPs >180mmHg per patient, median SBP over 24 hours, >50% SBP drop between highest and lowest SBP recorded (to indicate variability), proportion receiving IV antihypertensives, sICH rate and 3-month favourable modified Rankin Score (mRS) defined as 0–2 and also as mRS 0–1. sICH was defined as a National Institutes of Health Stroke Scale (NIHSS) deterioration of >4 points or death attributable to an ICH on post-thrombolysis 24-hour CT imaging. All 24-hour CT images reporting any degree of bleeding were adjudicated by a blinded assessor (AR).

Sample size was estimated using a 60% rate of SBP >180mmHg for the standard protocol based on internal audit data and an estimated reduction of such events to 40% with the intensive protocol. With a 95% confidence level (CI) and 80% study power, this required a minimum sample size of 95 patients per group.

Statistical analysis was performed using StataIC 17.0. Dichotomous and continuous variables were compared using Chi-squared test and either *t*-test for normal and Wilcoxon Rank-Sum Test for non-normally distributed continuous variables. Logistic regression incorporated common confounders and any differences in baseline characteristics of >0.1 using a backward elimination technique to optimise model fit. Variables retained in the

final model included age, baseline NIHSS and pre-morbid mRS.

This study received Wellington Regional Hospital institutional ethics approval under the category of "service audit". The need for informed consent was waived by the Wellington Hospital Ethics Committee. This study received no external funding.

Results

During the 23 months preceding and 18 months following the transition to the new protocol, 68 and 100 patients, respectively, with AIS received IV thrombolysis. Baseline characteristics were similar between groups (shown in Table 1).

Overall, the mean (95% CI) SBP over the first 24 hours was 140.8 (137.8–143.9) in the intensive group and 147.1 (142.4–151.7) in the guideline group (mean difference [95% CI] 6.3 [0.97–11.6, p=0.02]). Fewer patients in the intensive group had one or more SBPs >180mmHg (intensive 46 [46%] vs guideline 40 [59%]), but this was not statistically significant (adjusted odds ratio [aOR] 0.61; 95% CI 0.32–1.17; p=0.14). There was a statistically significant increase in the rate of hypotension (SBP <120mmHg) recorded for the intensive management group (aOR 3.09; 95% CI 1.49–6.40; p=0.002). There was no difference in the number of patients with one or more SBP of

Table 1: Patient baseline characteristics by study group.

Patient characteristic	Guideline N=68	Intensive N=100	P-value
Age, mean (SD)	72.8 (12.3)	71.7 (15.6)	0.65
Ethnicity, n (%)			0.43
European	50 (73.5)	83 (83)	
Māori	5 (7.4)	5 (5)	
Indian	5 (7.4)	0	
Chinese	1 (1.5)	1 (1)	
Pacific	4 (5.8)	7 (7)	
Other	1 (1.5)	0	
Unknown	2 (2.9)	0	
Female sex, n (%)	25 (37)	36 (36)	0.92
Hypertension, n (%)	40 (58.8)	49 (49)	0.21
Diabetes, n (%)	14 (20.6)	13 (13)	0.19
Atrial fibrillation, n (%)	18 (26.5)	24 (24)	0.72
Anticoagulation, n (%)	5 (7.4)	7 (7)	0.93
SBP pre-thrombolysis, median (range)	159 (109–212)	156 (102–241)	0.79
mRS prior to admission, median (range)	0 (0–4)	0 (0–5)	0.22
NIHSS at presentation, median (range)	9 (2–30)	9 (0–30)	0.96

Standard deviation = SD; systolic blood pressure = SBP; modified Rankin Score = mRS; National Institutes of Health Stroke Scale = NIHSS.

Table 2: Blood pressures and patient outcomes by study group.

	Intensive N=100	Guideline N=68	Odds ratio (95% confidence interval)	Adjusted odds ratio[§] (95% confidence interval)	P-value
SBP >200, n (%)	23 (23)	16 (24)	0.97 (0.47–2.01)	0.97 (0.46–2.01)	0.96
SBP >180[†], n (%)	**46 (46)**	**40 (59)**	**0.60 (0.32–1.11)**	**0.61 (0.32–1.17)**	**0.14**
SPB >160, n (%)	73 (73)	51 (75)	0.90 (0.45–1.82)	0.94 (0.44–2.01)	0.87
SBP <140, n (%)	98 (98)	64 (94)	3.01 (0.55–17.2)	2.7 (0.47–15.8)	0.27
SBP <120, n (%)	81 (81)	40 (59)	2.99 (1.49–5.98)	3.09 (1.49–6.40)	0.002
SBP <100, n (%)	22 (22)	10 (15)	1.64 (0.72–3.72)	1.69 (0.73–3.90)	0.22
>50% drop in SBP, n (%)	89 (89)	65 (96)	3.06 (0.55–17.2)	2.97 (0.78–11.3)	0.11
Patients given infusion, n (%)	46 (46)	21 (31)	1.91 (0.10–3.64)	2.04 (1.05–3.99)	0.04
sICH at 24 hours, n (%)	4 (4.0)	3 (4.4)	0.9 (0.20–4.17)	1.26 (0.26–6.27)	0.76
mRS 0–2 at 3-months, n (%)	55 (55)	38 (56)	1.00 (0.54–1.87)	1.27 (0.58–2.80)	0.56
mRS 0–1 at 3-months, n (%)	37 (37)	28 (41)	0.84 (0.45–1.58)	0.69 (0.32–1.52)	0.36

Systolic blood pressure = SBP; symptomatic intracerebral haemorrhage = sICH; modified Rankin Score = mRS.
†Primary study outcome.
§Model adjusted for age, premorbid mRS and National Institutes of Health Stroke Scale at presentation.
Wilcoxon Rank-Sum test p=0.93—see Figure 1 for mRS distribution.

Figure 1: Three-month modified Rankin Score Grotta chart (median [interquartile range] intensive: 2 (1–4), guideline: 2 (0–4); Wilcoxon Rank-Sum: p=0.93).

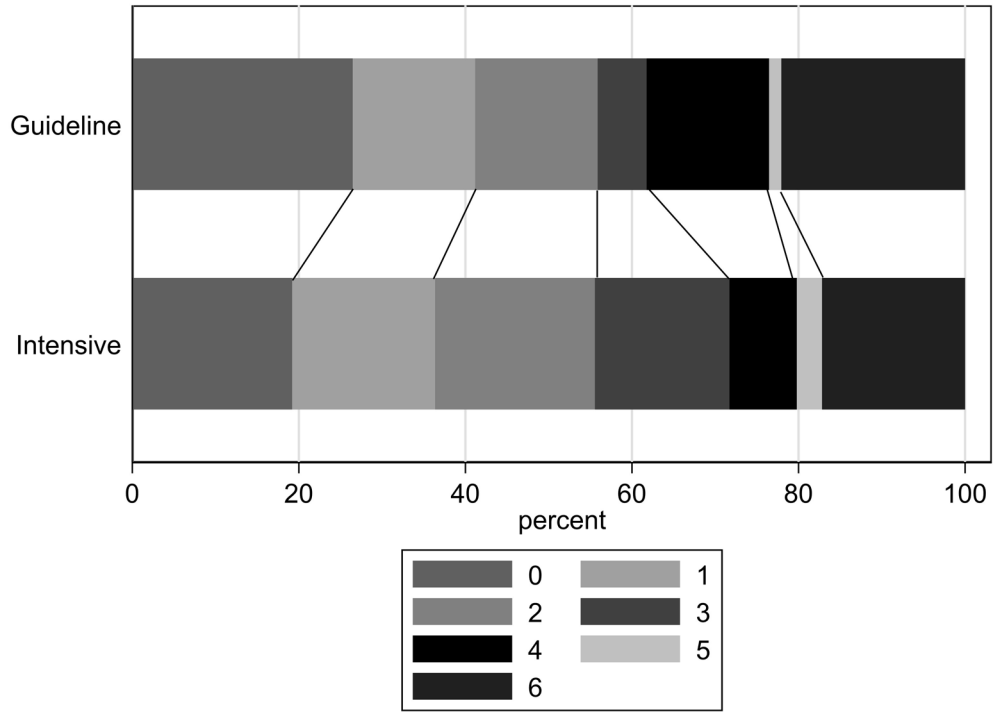

Table 3: Additional exploratory analyses.

	sICH		mRs 0–2 at 3 months	
Across entire cohort*	aOR (95% CI)	P-value	aOR (95% CI)	P-value
Number of >180mmHg events	1.25 (1.01–1.5)	0.01	0.85 (0.73–0.99)	0.04
Number of >185mmHg events	1.30 (1.01–1.59)	0.009	0.72 (0.56–0.93)	0.01
>50% drop in SBP (variability)	5.46 (0.82–36.4)	0.08	0.69 (0.18–2.7)	0.59
SBP at presentation	0.98 (0.95–1.02)	0.37	1.02 (0.99–1.04)	0.07
Added to study group model (aOR for intensive vs guideline group)**				
Number of >180mmHg events	3.4 (0.43–26.7)	0.25	0.83 (0.34–2.01)	0.68
Number of >185mmHg events	3.6 (0.43–29.8)	0.24	0.80 (0.33–1.97)	0.63
>50% drop in SBP (variability)	1.07 (0.21–5.5)	0.94	1.07 (0.45–2.56)	0.88
SBP at presentation	0.91 (0.16–5.01)	0.92	0.89 (0.37–2.15)	0.79

Symptomatic intracerebral haemorrhage = sICH; modified Rankin Score = mRS; adjusted odds ratio = aOR; confidence interval = CI; systolic blood pressure = SBP.
All models include age, pre-morbid mRS and National Institutes of Health Stroke Scale at presentation; *here, model also includes the variable listed for which the aOR is reported while study group was removed; **here, study group is included as well as the variable listed in far left column, and the aOR is reported for the intensive group compared with the guideline group.

>200, >160, <140 or <100 mmHg recorded, or with a ≥50% difference between highest and lowest recorded SBP between groups (shown in Table 2).

Favourable outcomes (mRS 0–2) at 3 months and sICH were similar between groups with and without adjustment for potential confounders (Figure 1). More patients received an IV infusion of either GTN or labetalol in the intensive BP protocol group (intensive group 46 [46%] vs guideline 21 [31%]; aOR 2.04 [1.05–3.99]; p=0.04). See Table 2 for additional detail.

We conducted additional exploratory analyses of number of SBPs >180mmHg per patient, BP variability and SBP at presentation. The mean number (standard deviation [SD]) of SBPs >180mmHg per patient was significantly lower in the intensive group (1.5 [0.22] compared with 2.8 [0.49] in the guideline group; p=0.009). A similar pattern was observed for BPs >185mmHg: there were 0.84 (1.6) events per patient in the intensive and 1.8 (3.2) in the guideline group, p=0.002. For the study group as a whole, the number of high BP events was significantly correlated with poorer functional outcome (aOR=0.85 [0.73–0.99]; p=0.038) and a higher rate of sICH (aOR 1.25 [1.06–1.48]; p=0.01) adjusting for age, pre-morbid mRS and NIHSS at presentation. SBP at presentation and BP variability were not associated with outcome or sICH (Table 3).

Discussion

Patients in the intensive group had a higher rate of IV antihypertensive use, lower mean SBP over the first 24 hours, non-significantly fewer SBP >180mmHg events and significantly more SBP <120mmHg events. There was no difference in sICH rate or 3-month clinical outcome.

The lack of improved clinical outcomes is in keeping with the ENCHANTED trial,[9] a phase 3 randomised control trial of intensive BP lowering in the post-thrombolysis setting, which pursued a more aggressive target (130–140mmHg) than our protocol (140–160 mmHg), although resultant SBP levels were similar: the ENCHANTED mean SBP in the intervention group was 138.8mmHg vs control 144.1mmHg at 1 hour and 144.3mmHg vs 149.8mmHg respectively at 24 hours, compared with our mean 140.8mmHg in the intensive group vs 147.1mmHg in the guideline group over the 24

hour period. Similar to our results, ENCHANTED failed to demonstrate an improvement in either 3-month mRS or sICH rate, although they did find a reduction in any ICH.

Our study was intended to be powered to detect a difference of 20% in high BP events between the groups. Our control sample fell short of the recruitment target and as a result we would have required a reduction of 23.5% to achieve statistical significance. In the event, we observed a reduction of 15%, arguably still clinically relevant but requiring a larger study to demonstrate statistical significance. The higher frequency of very low SBPs cannot be ignored. One reason for this may have been too much attention to SBP at the higher end of the scale so that nurses were less attentive when the SBP was in the "ideal range" but falling, and delayed reduction and/or stopping of the antihypertensive infusion. The protocol for changing the infusion rate may have erred on the side of too aggressive, lowering down to a too-low floor level (i.e., SBP=140mmHg). If so, these issues could be remedied by training and a slightly higher floor to the "ideal range"—e.g., SBP=150mmHg. We acknowledge, along with others, that BP management post-thrombolysis needs to be individualised, taking into account stroke type, presence of large vessel occlusion, success of recanalisation and other factors.[2] For example, it is likely that sICH risk is highest in recanalised larger strokes (implying tighter SBP control is required), while infarct growth due to hypoperfusion is of greatest concern in large vessel occlusion patients who did not recanalise where somewhat higher SBP targets are likely to be appropriate.

The choice of antihypertensives and rapidity of BP lowering may be relevant to successful outcomes. We note that the INTERACT4 trial is testing very early ambulance-based BP lowering in AIS or ICH and is using the antihypertensive agent urapidil—an α_1-adrenoceptor antagonist and a 5-HT1A receptor agonist—which may have advantages over labetalol and GTN.[13]

This study had several limitations. The relatively small sample size may have introduced type 2 error, and was under-powered for the difference in SBP detected between the groups. The observational sequential design carries the usual risks of potential confounding. The single-centre nature may limit generalisability. Finally, patients with less well-controlled BP and on IV infusions had more BPs recorded than those with primarily normal-range BPs, which may have led to potential reporting bias, especially as regards BP extremes. Strengths of the study were the prospective acquisition of data, "real-world" comprehensive coverage and completeness of follow-up.

A more aggressive approach to early BP lowering requires higher use of IV antihypertensive medication—in ENCHANTED, 63% of intensive patients vs 35% of control patients received IV medication, while in our study 46% of intensive vs 31% of guideline patients received IV medication. This has implications for nursing resource, cost of medications and equipment and the potential for IV site-related complications.

At this stage, the absence of clear benefit in our study (and ENCHANTED) and evidence of potential for harm argue against a more aggressive approach. We are trialling a new protocol with an "ideal range" of SBP 150–170mmHg, combined with training to prevent low SBP events and a more tailored approach to patients post-thrombectomy based on the presence or absence of successful recanalisation.

COMPETING INTERESTS

BH, HM and AR disclose employment at Wellington Regional Hospital during the period this study was conducted. AR also discloses employment at the University of Otago Wellington and contract work for the New Zealand Ministry of Health – Manatū Hauora, and HM discloses employment at the Medical Research Institute of New Zealand. AR is an executive committee member of the Australian and New Zealand Stroke Organisation, a board member of the New Zealand World Stroke and Asia Pacific Stroke organisations and the medical director of the New Zealand Stroke Foundation. SM has no disclosures.

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