

Original Article

A pilot randomised controlled trial of the management of systolic blood pressure during endovascular thrombectomy for acute ischaemic stroke*

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Summary

It is unknown whether systolic blood pressure augmentation during endovascular thrombectomy improves clinical outcomes. This pilot randomised controlled trial aimed to assess the feasibility of differential systolic blood pressure targeting during endovascular thrombectomy procedures for anterior circulation ischaemic stroke. Fifty-one eligible patients fulfilling the national criteria for endovascular thrombectomy were randomly assigned to receive either standard or augmented systolic blood pressure targets for the stant of anaesthesia to recenalisation of the target vessel. Systolic blood pressure targets for the standard and augmented groups were 130–150 mmHg and 160–180 mmHg, respectively. The study achieved all feasibility targets, including a recruitment rate of 3.5 participants per week and median (IQR [range]) of mean systolic blood pressure separation between groups of 139 (135–143 [115–154]) vs. 167 (150–175 [113–188]) mmHg, p < 0.001. Data completeness was 99%. Independent functional recovery at 90 days (modified Rankin Scale 0, 1 or 2) was achieved in 30 (59%) patients, which is consistent with previously published data. There were no safety concerns with trial procedures. In conclusion, a large randomised controlled efficacy trial of standard vs. augmented systolic blood pressure management during endovascular thrombectomy is feasible.

Correspondence to: C. Deng Email: carolynd@adhb.govt.nz Accepted: 4 November 2019 Keywords: blood pressure; endovascular thrombectomy; stroke *Presented in part at the Annual Scientific Meeting of the Australian and New Zealand College of Anaesthetists, Kuala Lumpur, Malaysia, May 2019. This article is accompanied by an editorial by Wiles, *Anaesthesia* 2020; **75**: 716-9. Twitter: @carolyndeng1

Introduction

Endovascular thrombectomy is the standard of care for acute ischaemic stroke caused by anterior large vessel occlusion [1]. Endovascular thrombectomy procedures are increasingly performed due to earlier presentation to hospital, rapid imaging and diagnosis, and extension of therapeutic windows to 24 h in selected patients [2–4]. Rates of successful recanalisation have been demonstrated to be greater than 80% [3, 5–8]. Despite high recanalisation rates, functional independence at three months is only achieved in approximately 50% of patients following thrombectomy [1, 3, 4].

A recent review outlined investigational therapies to protect the ischaemic penumbra by increasing cerebral oxygen delivery or decreasing cerebral oxygen demand before vessel recanalisation [9]. Many of these potential interventions are complex and have limited ability to be translated to the setting of hyperacute stroke. The balance of cerebral oxygen supply and demand is variably affected by the conduct of procedural sedation and general anaesthesia. [10, 11]. Optimal blood pressure management during thrombectomy remains an area of uncertainty [12]. The brain is vulnerable to variation in perfusion pressure due to impaired cerebral blood flow, reperfusion injury and the effects of impaired or absent cerebral autoregulation [13]. The impaired cerebral autoregulation that occurs after a stroke may be further exacerbated by general anaesthetic or sedative drugs [14].

Current haemodynamic management practices in thrombectomy patients are based on expert opinion and consensus rather than high-quality randomised evidence [12, 15]. Retrospective observational studies and a post-hoc analysis of randomised controlled trials have demonstrated an association between adverse neurological outcomes and the incidence and duration of hypotensive episodes. during endovascular thrombectomy [16, 17]. There is good evidence that general anaesthesia with blood pressure targeting is associated with long-term functional outcomes that are comparable with, and maybe even superior to, conscious sedation [5, 6, 18-21]. It is unknown whether increasing cerebral blood flow through systolic blood augmentation during pressure endovascular thrombectomy in the context of a pressure-dependent cerebral circulation improves neurological outcomes.

We performed a prospective, single-centre pilot randomised controlled trial to determine whether systolic blood pressure targeting of 130–150 mmHg or 160– 180 mmHg during endovascular thrombectomy was feasible. The aims were to: test and refine the trial protocol; establish accurate recruitment targets; and provide data to assist with sample size calculation for a definitive multicentre randomised controlled trial.

Methods

We designed this pilot study using the extension to the CONSORT guidelines for reporting pilot and feasibility trials [18]. The study protocol was approved by the Health and Disability Ethics Committee of New Zealand on a twophysician best interest consent principle, and deferred consent was obtained from each participant when they became competent. This prospective, single-centre, double-blind randomised controlled pilot trial was conducted at a tertiary metropolitan teaching hospital. Participants were included if they: had a clinical and radiological diagnosis of anterior large vessel occlusion stroke; were over 18 years of age; were previously independent, as quantified by a modified Rankin Scale (mRS) score of 0, 1 or 2; and met national eligibility criteria for thrombectomy.

Patients were not included when thrombectomy was performed: for strokes associated with medical procedures, such as percutaneous cardiology or vascular interventions; following cardiac surgery or carotid endarterectomy; or within 72 h of major surgery. Patients were also not included when: haemodynamic targeting was contraindicated; they were pregnant; or there was a history of concurrent illness with an expected survival of less than 1 year.

Independent researchers produced a computergenerated sequence in blocks of four for randomisation. Allocation was concealed using sequentially numbered sealed opaque envelopes. The patient, interventional radiologist and research personnel performing outcome assessments were blinded to group allocation. The attending anaesthetist was not blinded due to the nature of the intervention. Blood pressure readings were omitted from the clinical anaesthesia record until the 90-day mRS assessment was complete.

Anaesthesia for endovascular thrombectomy at Auckland City Hospital is provided by specialist-led anaesthetic teams. The attending anaesthetist recruited and randomly allocated eligible participants. Before random allocation, the attending anaesthetists were asked to confirm their anaesthetic plan (general anaesthesia or conscious sedation). This was done to ensure that the choice of technique was not a confounding factor. Eligible patients were randomly allocated in a 1:1 ratio to either a 'standard' or 'augmented' systolic blood pressure management strategy. Target systolic blood pressure for the standard and augmented groups were 130–150 mmHg and 160– 180 mmHg from the onset of anaesthesia to recanalisation, respectively. The choice of targets was based on current understanding of the safe blood pressure range following stroke [19], previous trials [5, 6, 20] and retrospective observational data from our institution from 2011 to 2017, which showed a mean (SD) systolic blood pressure of 146 (20) mmHg [21].

Clinical management followed local standard of care with an emphasis on time-efficient delivery of the patient to endovascular thrombectomy. All patients received standard anaesthetic care and monitoring. Arterial monitoring was by radial arterial cannulation or side arm manometry from the femoral arterial sheath. Choice of anaesthetic technique and intra-operative management were at the discretion of the anaesthetist. General anaesthesia was maintained with sevoflurane, desflurane or total intravenous anaesthesia (TIVA). Methods to achieve blood pressure targets were at the discretion of the attending anaesthetist and could include alteration of the dose of sedative or anaesthetic drugs, fluid boluses and/or administration of vasoactive agents.

All thrombectomy procedures were provided by specialist interventional radiologists. Device choice and thrombectomy technique was at the discretion of the interventional radiologist. The preferred thrombectomy method employed used a Neuron 088 Max sheath (Penumbra, Oakland, CA, USA) with a direct aspiration first pass technique using the 6F SOFIA plus distal access catheter (MicroVention, Tustin, CA, USA) or the 5F SOFIA catheter. Stentrievers were reserved for cases were first pass aspiration failed to achieve recanalisation. Reperfusion was timed and graded by the modified Thrombolysis in Cerebral Ischaemia (mTICI) score [22]. Successful recanalisation was defined as mTICI categories 2c and 3 [23].

Postoperative care occurred in the PACU, stroke unit or intensive care unit as per local protocol and as deemed appropriate by the attending clinicians. Patients' tracheas were extubated and recovered in PACU until discharge criteria were met. Postoperative blood pressure management was according to local protocols. Systolic hypertension (systolic blood pressure > 180 mmHg) was actively managed with intravenous (i.v.) labetalol, nicardipine or other appropriate vasoactive drugs. Symptomatic hypotension was managed with i.v. fluids and/ or vasoactive drugs, as appropriate, to recanalisation status. All interventions were recorded in the case report form.

Baseline characteristics, past medical history and stroke characteristics were recorded on the case report form. An electronic anaesthesia record (Safer Sleep LLC, Nashville, TN, USA) was used to record: clinical details; airway management details; anaesthetic and vasoactive drug doses administered; and physiological data. Feasibility outcomes were: adherence to systolic blood pressure management strategies in both groups, which were deemed adequate if overall group separation was \geq 20 mmHg and 90% of case duration was within the target treatment range; recruitment rate, which was deemed successful if one patient was recruited every two weeks; and the acceptability and sensitivity of outcome data collection for data completeness, which was deemed adequate if at least 95% of trial data was complete.

Secondary outcomes were the proportion of patients with independent functional outcome, defined as mRS of 0, 1 or 2 at three postoperative months; the proportion of patients with early neurological improvement as quantified with a reduction in National Institutes of Health Stroke Scale (NIHSS) score of \geq 8 points or a score of 0 or 1 at 24 h; intra-operative complications; symptomatic intracranial haemorrhage; and allcause mortality at 90 days. Intra-operative complications included: haemodynamic or device-related airway, complications; vessel perforation or dissection; reperfusion injury; thrombus migration; restenosis; seizures; and groin haematoma. Symptomatic intracranial haemorrhage included symptomatic subarachnoid haemorrhage and intracerebral haemorrhage associated with an increase in NIHSS score of \geq 4 points from baseline, occurring within 36 h of treatment. The secondary outcomes were determined by a combination of patient and clinical case note review, and telephone contact.

A target sample size of 50 was determined to be sufficient for this pilot trial based on published guidelines [24, 25]. Analyses were on an intention-to-treat basis. Systolic blood pressure separation between the two groups was assessed by comparing the median of the mean systolic blood pressure in each group using the Mann–Whitney Utest. Fisher exact tests were performed on secondary outcomes. A p value of < 0.05 was deemed statistically significant. All analyses were conducted using Stata/IC 15.1 2017 (StataCorp LLC, College Station, TX, USA).

Results

We recruited 51 patients at Auckland City Hospital between June and October 2018, of whom 28 were allocated to the standard group and 25 to the augmented group (Fig. 1). Seventy patients were screened during the study period and 19 (27%) were not included, as they did not fulfil the eligibility criteria. There were no observed differences in baseline characteristics between the two groups (Table 1). Thirteen (50%) patients were thrombolysed in the standard group compared with 7 (28%) in the augmented group. All 26 patients in the standard group, and all but one patient in the augmented group, had thrombectomy performed with general anaesthesia, reflecting usual practice at our institution. Metaraminol was the only vasoconstrictor agent used for both the standard and augmented groups. Ten (42%) patients in the augmented group received TIVA compared with three (12%) in the standard group. Successful recanalisation occurred in 80% of patients in both groups.

All feasibility outcomes were achieved (Table 2). The average recruitment rate was 3.5 participants per week, and 90% of all eligible participants were recruited. Median of mean systolic pressure readings was significantly different between the standard and augmented groups: 139 (135-143 [115-154]) vs. 167 (150-175 [113-188]) mmHg, p < 0.001 (Fig. 2). Data completeness was 99%, with 100% follow-up. Sixteen (62%) patients in the standard group and 14 (56%) patients in the augmented group were functionally independent at 90 days (p = 0.779). There were no significant differences in: early neurological improvement; all-cause mortality at 90 days; intra-operative complications; and intracerebral haemorrhage rates (Table 3). One patient in the standard group suffered vessel perforation and subsequent symptomatic intracranial

haemorrhage. Two additional patients in the standard group developed intracerebral haemorrhage noted on routine postoperative radiological imaging, but were asymptomatic.

Discussion

This pilot study demonstrates the feasibility of standard or augmented systolic blood pressure targeting during endovascular thrombectomy for anterior circulation large vessel occlusion stroke. The median difference in median systolic blood pressure of 28 mmHg between groups is clinically meaningful in this context. Trial recruitment was

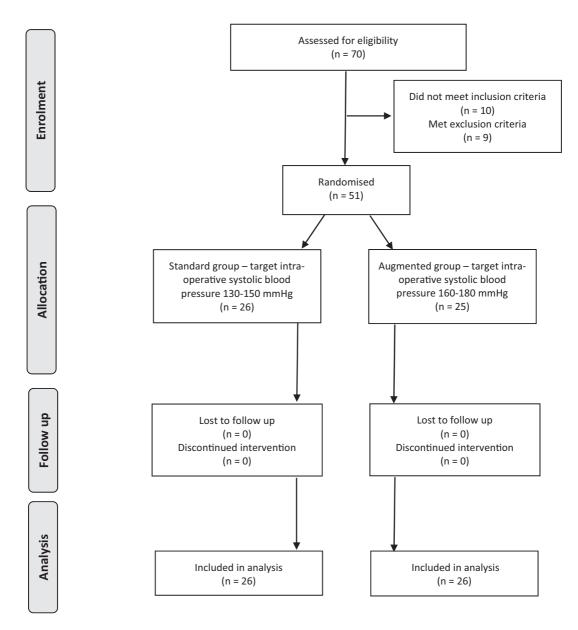


Figure 1 Participant flow diagram. [Colour figure can be viewed at wileyonlinelibrary.com]

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	Standard systolic blood pressure n = 26	Augmented systolic blood pressure n = 25
Age; years	67 (14)	66(17)
Sex; female	9 (35%)	6(24%)
Ethnicity		
Māori	5 (19%)	4(16%)
Pacific	2 (8%)	5 (20%)
Asian	2(8%)	0(0%)
European	17 (65%)	16(64)
Baseline NIHSS	13 (10–17 [4–26])	15 (11–21 [4–29])
Site of vessel occlusion ^a		
ICA	5	2
M1	15	20
M2	8	10
Diabetes	6 (23%)	6 (24%)
Peripheral vascular disease	1 (4%)	1 (4%)
Atrial fibrillation	10 (38%)	13 (52%)
Hypertension	16 (62%)	17 (68%)
Dyslipidaemia	13 (50%)	14(56%)
Ischaemic heart disease	8(31%)	12 (48%)
Previous stroke/transient ischaemic attack	3(12%)	5 (20%)
Smoking status		
Never	14 (54%)	11 (44%)
Ex-smoker	7 (27%)	9 (36%)
Current smoker	5 (19%)	5 (20%)
Thrombolysed	13 (50%)	7 (28%)
mTICI 2c or 3	21 (81%)	20 (80%)
General anaesthesia	26(100%)	24(96%)
Anaesthetic technique		
Volatile	23 (88%)	14 (58%)
TIVA	3(12%)	10 (42%)
Time to recanalisation; min	28 (19–51 [8–120])	43 (23–56 [6–112])

 Table 1
 Baseline characteristics of participants undergoing endovascular thrombectomy for anterior circulation ischaemic stroke. Values are mean (SD), number (proportion) or median (IQR [range]).

NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; M1, M1 segment of middle cerebral artery; M2, M2 segment of middle cerebral artery; mTICI, modified Treatment in Cerebral Ischaemia; TIVA, total intravenous anaesthesia. ^aAn individual may have more than one site of vessel occlusion.

Table	2	Feasibility outcomes.
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Feasibility outcome	Target	Result
Recruitment rate	0.5 participants/week	3.5 participants/week
Difference in median of mean systolic blood pressure between groups	20 mmHg	28 mmHg
Data completeness	> 95%	> 99%

performed by treating clinicians and the recruitment rate was high in the emergency setting of an acute stroke. Data completeness was satisfactory and results were analysed using a predefined statistical analysis plan. There were no significant differences in the secondary outcomes between the groups, but this study was not powered to detect differences for these outcomes. Functional independence occurred in 60%, which is consistent with published data [7, 8].

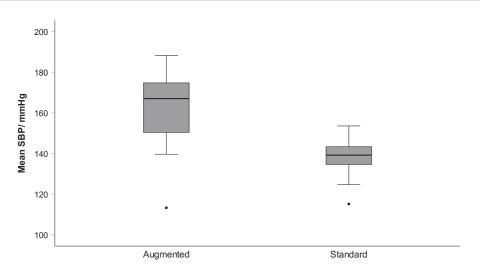


Figure 2 Median of mean systolic blood pressure in the standard and augmented systolic blood pressure groups during endovascular thrombectomy. Box depicts median and IQR; whiskers, $1.5 \times IQR$; dots, outliers. SBP, systolic blood pressure. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 3 Secondary outcomes for participants in the standard and augmented systolic blood pressure groups during endovascular thrombectomy. Values are number (proportion).

Secondary outcome	Standard systolic blood pressure n = 26	Augmented systolic blood pressure n = 25	p value
Good functional recovery at 90 days (mRS 0, 1 or 2)	16 (62%)	14(56%)	0.779
Early neurological improvement ^a	17 (65%)	14 (56%)	0.572
All-cause mortality at 90 days	5 (19%)	4(16%)	1.000
Intra-operative complications	1 (4%)	0 (0%)	0.510
Symptomatic intracranial haemorrhage	1 (4%)	0(0%)	1.000

mRS, modified Rankin Score.

^aDefined as reduction in 24 h National Institutes of Health Stroke Scale (NIHSS) score of \geq 8 from baseline, or a score of 0 or 1 at 24 h.

There were no intra-operative complications or intracerebral haemorrhages in the augmented group, suggesting there are no safety concerns (Appendix S1).

There are no prospective randomised controlled trials assessing blood pressure management during endovascular thrombectomy. Retrospective studies and post-hoc analyses have demonstrated conflicting results. A recently published meta-analysis found nine nonrandomised studies assessing the effects of blood pressure endovascular thrombectomy on functional durina outcomes [26]. Five studies found an association between intra-operative hypotension and adverse postoperative outcomes. Four studies did not find an association; three of which had strict intra-operative systolic blood pressure targeting (140–180 mmHg). This suggests that hypotension during thrombectomy may be harmful, and that early observational studies showing worse functional outcomes

after general anaesthesia may be confounded by poor haemodynamic management, leading to higher rates of hypotension and greater blood pressure variability in the general anaesthesia group. This is the first randomised controlled trial to assess the effects of blood pressure augmentation during endovascular thrombectomy on functional recovery. Systolic blood pressure augmentation may increase blood flow to the pressure-dependent penumbral circulation. Furthermore, undiagnosed hypertension affects 15% of the population [27], and less than 50% of patients with treated hypertension achieve recommended blood pressure targets [28]. Systolic blood pressure augmentation during thrombectomy may be beneficial for this group of patients.

There is interest in individualising blood pressure targets during endovascular thrombectomy. Petersen et al. conducted a study of 65 patients using near infrared spectroscopy to define individual mean arterial pressures that result in optimal cerebral autoregulation after thrombectomy [29]. This study reported an association between time spent with mean arterial pressure above the upper limit of autoregulation and worse functional recovery at discharge and at 90 days, and more haemorrhagic transformation and symptomatic intracranial haemorrhage. Although individualised blood pressure targets may be attractive, it is difficult to ascertain baseline blood pressure in the context of a hyperacute stroke. Time available to ascertain medical history is limited and the majority of patients show a profound and transient increase in blood pressure after stroke masking true baseline blood pressure. The ability to monitor near infrared spectroscopy during thrombectomy is also limited by the need for complete radiological imaging of the cerebral circulation. Absolute blood pressure targeting is the simplest and most pragmatic trial design in the hyperacute setting.

A limitation of our study was that, due to the nature of the intervention, the attending anaesthetist was not blinded. Most patients undergoing endovascular thrombectomy in this study received general anaesthesia, as this is the preferred anaesthetic technique at our institution. This may limit the generalisability of this study to other institutions where conscious sedation or local anaesthesia is more frequently used. More patients in the augmented group received TIVA. It is unclear whether this was due to random allocation differences between groups or bias in the choice of technique related to allocation of the systolic blood pressure targets. The protocol for the multicentre trial has been changed so that attending anaesthetists will be asked to indicate their choice of anaesthetic technique before randomisation. Rates of thrombolysis will be monitored, but this is expected to be equivalent in the future large trial. Bias was otherwise minimised as the patient, treating neurologists, interventional radiologists and outcome assessors were blinded.

Changes to the protocol of the definitive trial will be made as a result of our pilot study experience. Firstly, the primary outcome of the multicentre trial will be the mean 90day mRS instead of the proportion of patients with independent functional recovery at 90 days, as reported in this pilot study. This will be a more patient-centred outcome, as it detects clinically significant improvements in functional recovery that would otherwise be missed with a dichotomous outcome. Secondly, the larger trial will be limited to endovascular thrombectomy with general anaesthesia. There is evidence that: outcomes after general anaesthesia may be superior to conscious sedation [30]; haemodynamic targeting is challenging during conscious sedation; and the effects of systolic blood pressure augmentation may be enhanced due to additional impairment of cerebral autoregulation.

The target sample size for the conversion trial is 550 participants. We believe a treatment effect that is clinically important is a 10% increase in functional independence (mRS 0, 1 or 2) at three postoperative months. This is a similar effect size as has been demonstrated in observational data [31–33] and is equivalent to a group one proportion, $P_1 = 0.58$ (current national data) improving to $P_2 = 0.68$. Statistical modelling was performed with a balanced distribution of improvement in mRS categories. An expected favourable shift in mRS based on local data demonstrates that 550 participants will provide 90% power to detect the proportion of patients who will improve an equivalent of 0.5 points on the modified Rankin Scale at three postoperative months. This takes into account an expected 10% loss to follow-up rate.

In conclusion, a large, definitive randomised controlled trial of standard vs. augmented systolic blood pressure management during endovascular thrombectomy is scientifically warranted and feasible, and clinically important differences in systolic blood pressure can be achieved. The MASTERSTROKE study, a large, multicentre trial, has now been funded and will begin recruiting in 2019.

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Appendix S1. Serious adverse events reported in this pilot study.

Number	Category	Adverse event	Code	Severity
1	Nervous system disorder	Intracranial haemorrhage	10022763	2-Moderate
2	Nervous system disorder	Intracranial haemorrhage	10022763	1 – Asymptomatic
3	Nervous system disorder	Intracranial haemorrhage	10022763	1-Asymptomatic