A pilot trial of the MAnagement of Systolic blood pressure during Thrombectomy by Endovascular Route for acute ischaemic STROKE (the MASTERSTROKE trial)

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Authorship to be offered to 1-3 site investigators at secondary sites that recruit patients.

Background

Endovascular thrombectomy has become the new standard-of-care for acute anterior circulation strokes. [1] Immediate treatment goals include selecting patients likely to benefit from thrombectomy and providing systems of care to recanalise the occluded artery as quickly as possible [2-3]. Endovascular thrombectomy can be performed under monitored anaesthesia care (MAC), conscious sedation (CS), or general anaesthesia (GA). However, observational trials [4-5], two meta-analyses [6-7] and a post hoc analysis of a RCT [8] have demonstrated poorer outcomes in patients undergoing general anaesthesia. This could be a genuine effect attributable to general anaesthetic drugs. Equally it could be due to consequent treatment delay, could be or selection bias, with higher risk patients receiving general anaesthesia, or to blood pressure (BP) confounding outcome due to lower haemodynamic targets associated with general anaesthesia. Three small, single-centre randomised controlled trials (RCT) have compared GA with CS. The SIESTA trial randomised 150 participants and showed no differences in early neurological outcome when haemodynamic management was similar in both groups. Interestingly, functional outcome at 3 months, as measured by modified Rankin Score (mRS), was superior in the GA group (mRS 0-2 37.0% GA group v 18.2%, P=0.01) [9]. The AnStroke trial [10] randomised 90 participants with no group differences in BP decline from baseline and no difference in mRS at 3 months. The GOLIATH trial [11] randomised 128 participants and showed no statistical difference in the primary endpoint of median infarct growth (GA 8.2 [2.2-38.6] ml v CS 19.4 [2.4-79] ml, P=0.10). MAP at groin puncture was 90 mmHg (GA) v 102 mmHg (CS), P=0.01 but good functional outcome was superior in the GA group, odds ratio for better outcome 1.91 (95% CI, 1.03-3.56). This data supports the hypothesis that physiological management may be more important than the choice of MAC, CS or anaesthesia during endovascular thrombectomy for acute stroke.

The optimal management of BP in the acute phase of ischaemic stroke is unclear. The brain is vulnerable to BP variation during the acute phase, [12] caused by impaired cerebral blood flow secondary to embolus, reperfusion injury and the effects of impaired or absent cerebral autoregulation. Systemic hypotension is also likely to worsen cerebral perfusion. Conversely, systemic hypertension may be detrimental, as it is associated with the development of cerebral oedema, haemorrhagic transformation of ischaemic tissue and encephalopathy [13].

Most evidence regarding BP and stroke outcome in general is limited to large observational studies performed prior to the introduction of endovascular thrombectomy. The International Stroke Trial, published in 2002, [14] demonstrated a U-shaped relation between admission BP and favourable clinical outcomes, with an optimal systolic blood pressure (SBP) in the early/acute phase ranging from 140 to 180mmHg. Haemodynamic targets during endovascular thrombectomy are largely unreported [15-19]. Current haemodynamic management in these patients is currently based on expert opinion rather than high quality trials [3, 20]. Clinical trials that have reported haemodynamic management during endovascular thrombectomy are reported in Table 1.

Table 1. Haemodynamic data in clinical trials of endovascular thrombectomy for acute stroke

Study	Trial type	N	Group, BP, mm Hg	Group, BP, mm Hg
SIESTA [9]	RCT	150	GA, SBP 144.9 (SD 9.8)	Non-GA, SBP 147.2 (SD 8.9)
ADHB data [21]	Observational	99	GA, SBP 151.6 (25.8)	Non-GA, SBP 157.3 (29.0)
ANSTROKE [10, c]	RCT	90	GA, MAP 91 (8)	CS, 95 (11)
GOLIATH [11]	RCT	128	GA, MAP 90 (IQR 82-99)	CS, 102 (IQR88-111)
GASS [23]	Unreported RCT	350		
Henden et al [24], mRS 0-2	Observational	41	GA, MAP [a] 75 (IQR 73-83)	
Henden et al [b], mRS > 2	Observational	65	GA, MAP 77 (IQR 73-82)	

Key
mRS modified Rankin Score, GA general anaesthesia, SBP systolic blood pressure, SD standard deviation, ADHB Auckland District Health Board, MAP mean arterial pressure, IQR interquartile range
[a] In comparison, a BP of 140/80 would usually have a MAP of 100 mmHg
[b] In Henden et al, a relative drop MAP by 40% was associated with an odds ratio of poor neurological outcome of 2.8 (1.09-7.19), P=0.03. Mean baseline MAP was 107 mmHg in the mRS 0-2 group and 110 mmHg in the mRS > 2 group
[c] During ANSTROKE, 41% of GA had SBP fall more than 20% from baseline compared to 26% of CS patients

After stroke onset, the penumbra surrounding the established infarct zone has the potential to benefit from early recanalisation [18]. Areas of ischaemic penumbra may have impaired or absent autoregulation [25] and therefore may have a pressure dependent circulation. Many anaesthesia and sedative drugs (particularly

anaesthesia vapours such as sevoflurane and desflurane) impair cerebral autoregulation, with an additive effect in penumbral areas where autoregulation is already partially impaired [26]. Clinical outcomes may therefore be worsened by poor haemodynamic management during sedation or anaesthesia. General anaesthesia is preferred for these procedures in New Zealand [2]. Internationally however, up to 38% of patients receive GA for clot retrieval [7].

It may be the case that haemodynamic management is the most plausible explanation for the outcome differences between the observational and randomized data. To date, no studies have investigated the influence of blood pressure management during endovascular thrombectomy. We therefore propose a clinical trial of BP management to determine the balance of harm and benefit during these procedures. Both management arms are within the range of usual care in New Zealand centres [2], and are within the range of suggested BP in published guidelines [3,13-4]. A pilot trial to test feasibility of a multicenter trial is appropriate.

Objective
To determine the feasibility of conducting a multi-centre RCT of two haemodynamic management strategies during endovascular thrombectomy for acute ischaemic stroke.

Aims (feasibility)
- To assess adherence to the two haemodynamic management strategies. Adherence will be deemed adequate if overall group separation is 20mmHg and 90% of case duration is within pre-determined treatment bounds
- To assess recruitment rate. A successful recruitment rate would be recruitment of one patient per fortnight or 50% of the estimated eligible patients
- To assess acceptability and sensitivity of our outcome data collection to detect change in clinical status and data completeness. Data completeness will be deemed adequate if 95% of all trial data is complete
- To test and refine the trial CRF and protocol

Aims (scientific)
Primary outcome
- The proportion of patients with independent functional outcome as determined by a modified Rankin Score scores of 0, 1 or 2 at 3 months.

Secondary outcomes
- Proportion of patients with early neurological improvement, as defined by reduction in NIHSS score of 8 points or a score of 0 or 1 at 24 hours post-stroke onset
- All-cause mortality at 90 days
- Proportion of patients with intra-procedural complications (vessel perforation, dissection, device-related complications, haemodynamic and airway complications, reperfusion syndrome, thrombus migration or restenosis, seizures during treatment, groin haematoma)

- Proportion of patients with symptomatic intracranial haemorrhage (within 36 hours of treatment, associated with an increase of NIHSS of at least 4 points from baseline), including :

    o subarachnoid haemorrhage associated with clinical symptoms
    o symptomatic intracerebral haemorrhage (parenchymal haematoma type 2).
- Serious Adverse Event reporting, in line with ICH GCP guidelines by 90 days. This will ensure that cases of cardiovascular and respiratory complications of stroke are also assessed.

Study Design
A pragmatic, prospective, single or multicentre, double-blind randomised controlled pilot trial

Ethics
National Health and Disability Ethics (HDEC) has been applied for under the full reveiw pathway. All sites involved in the study will be required to submitted research applications to their institutional research governance pathway to gain locality approval before commencent the study.

Participants in this study are acutely incapacitated at the time of admission to hospital. Prior to the admission these patients would have been fully in command of their cognitive ability; due to the exquisite sensitivity of the brain to any insult may be at risk of irreversible injury where decision making timeframes are narrow unlike the more progressive and chronic diseases where planning and time are on the side of both the patient and the researchers. Ischaemic stroke patients are extremely incapacitated and are unable to provide consent; therefore it is essential that we undertake safe and ethical studies to provide opportunities to them to be able to participate in time-sensitive studies where there is an associated benefit in care and patient outcomes. The researchers believe that this study meets the "Best Interest" test for a non-consenting patient to satisfy the New Zealand Bill of Rights Act 1990 and HDEC given that there is minimal definitive guidance on the importance of haemodynamic management during the endovascular clot retrieval and the potential links to poor functional recovery, enrolment in this trial will restrict the range of blood pressure variation which may have additional therapeutic benefits and optimise patient outcomes.

Eligibility criteria
Inclusion
Patients diagnosed with anterior circulation stroke (internal carotid artery or proximal M1 or M2 segment of middle cerebral artery), presenting within six hours of stroke [1] onset who receive clot retrieval as per current New Zealand guidelines.
and patients presenting within 6-24 hours for highly selected ICA/MCA occlusion patients *if*
1. 'wake up' stroke; CT with no (or at most minimal) acute ischaemic
    or
2. patient ≥ 80 years (NIHSS ≥ 10 and infarct volume <21 ml on DWI or CT perfusion-CBF)
3. patient <80 years (NIHSS ≥ 10 and infarct volume < 31 ml on DWI or CT perfusion-CBF NIHSS ≥ 20 and infarct volume < 51 ml on DWI or CT perfusion-CBF)
4.

Clinical
Clinical diagnosis of ischaemic stroke causing measurable neurological deficits in a previously independent (mRS 0, 1 or 2) patient
Radiological
Evidence of arterial occlusion in
- carotid artery termination
- M1 and M2 segment middle cerebral artery

Exclusion
- 'Rescue' procedures eg acute ischaemic stroke associated with major medical procedures such as coronary artery stenting and coronary artery bypass.
- Pre-stroke mRS>=3 (indicating previous disability)
- Contra-indication to imaging with contrast agents
- Any terminal illness with expected survival less than 1 year
- Pregnant women
- Any medical condition where there is a contra-indication to either treatment arm, or haemodynamic targeting will be problematic eg severe aortic regurgitation

Setting
Angiography suites, Post-Anaesthesia Care Units (PACU) and Stroke Units at Auckland, Wellington and Christchurch Hospitals.

Randomisation

Groups will be randomly allocated by sealed envelope at each study centre. Randomisation to allocated group will be stratified by centre in blocks of four. Randomisation must occur after decision for GA, sedation or monitored anaesthesia care has been made.

Clinical management

Clinical management will follow local standard of care with an emphasis on time-efficient delivery of the patient to successful endovascular thrombectomy. Choice of monitored anaesthesia care, sedation or general anaesthesia can be a shared decision between the anaesthetist, neurologist and procedural neuroradiologist based on clinical and procedural factors. Randomisation and group allocation should only occur **after** this decision. An automated clinical anaesthesia record should note clinical summary, airway management, drugs and doses used for sedation or anaesthesia, relevant physiological data including FiO_2, $ETCO_2$ (if used), SpO_2, PR, MAP, SBP, temperature and at least one blood glucose reading during procedure.

Tight BP control has been suggested as a therapeutic target to improve outcome in acute ischaemic stroke. In this trial, participants SBP will be targetted to a maximum range of 20mm Hg, compared to the usual range of 40 mm Hg using current clinical guidelines. This is thought to improve clinical outcome by improved early clinical improvement (as measured by 24hr NIHSS) and late clinical improvement (as measured by mRS).

Study procedures

The patients will be allocated to one of two SBP strategies during randomization.
'Standard' – maintain SBP at 140+-10mmHg from MAC, sedation or anaesthesia onset until recanalization
'Augmented' - maintain SBP at 170+-10mmHg from MAC, sedation or anaesthesia onset until recanalization
The methods to achieve SBP targets will be left to the discretion of the procedural anaesthetist but may include vasoactive drugs, alteration in sedative or anesthetic drug doses or fluid management. These interventions will be recorded in the CRF. If intravenous anaesthesia is used, total propofol dosage should also be recorded.

Post-procedure management

Post-procedure care will be in the PACU, Stroke Unit or Intensive Care Unit. SBP will not be managed actively after complete recanalization with associated improvement in neurology (if SBP < 180 mmHg). Systolic hypertension (SBP > 180 mmHg) will be actively managed with intravenous labetalol or nicardipine boluses or other appropriate vasoactive drugs. Symptomatic hypotension, with or without recanalization but with neurological symptoms and signs will be managed with intravenous fluids and/or vasopressors as clinically appropriate by the attending anaesthetist in PACU and neurologist on the ward. These interventions will be recorded in the CRF.

Patients will be recovered in a PACU until sedative and anaesthetic drugs have worn off.
Placement to Stroke Unit, HDU or ICU will be at discretion of supervising clinicians. Physiological data will be recorded electronically for 24 hours post-procedure.

Blinding

The patient, procedural neuroradiologist and research personnel performing outcome assessments will be blinded to group allocation. The procedural anaesthetist will be unblinded. The clinical anaesthesia record will omit the BP record in the patients notes until after the 3-month assessment. Local procedures will be instituted to ensure immediate unblinding, and access to the BP record, should this be necessary.

Statistical Methods

Sample size is 30 if the trial remains a single-centre pilot and 50 if Wellington and Christchurch Hospitals participate. This is consistent with previous pilot trial experience [27] and published guidelines [28] and is estimated to be the number recruited over a four-month period if 50% of eligible patients are recruited. Primary analyses will be by intention to treat (ITT). Feasibility outcomes will be described with simple descriptive statistics. Inferential statistics for the primary and secondary outcomes will be with chi-squared testing. Any continuous data will be transformed as appropriate, before Students t-testing. P-values will be

reported when appropriate. The primary and secondary outcomes will report the event rate and 95% confidence interval (CI).

Sample size for a large trial will be based on the proportion of patients experiencing good late neurological outcomes (mRS 0-2 at 3 months). Table 2 presents expected sample sizes based on initial proportions of good outcome of 54% (current ADHB value), 62%, and 71% (EXTEND-IA values, a trial with selection criteria favouring better overall outcome than current clinical inclusion criteria), and absolute treatment effects of 10%, 8% and 5%. For context, the absolute treatment effect in recategorization to good outcome was 20% in the pooled trial meta-analysis [1]. Sample sizes were based on two sample equality, sample equivalence, sampling ratio of 1:1, 1 −β= 0.8, α = 0.05. Sample sizes are approximately 33% larger when 1 – beta is 0.9.

Table 2. Estimation of expected large trial size sample size based on expected group proportions and clinically relevant group differences in proportions, 1 −β= 0.8, α = 0.05.

Group 1 proportion	Group 2 proportion	Effect size	Sample size
0.54	0.64	0.1	752
	0.62	0.08	1186
	0.59	0.05	3074
0.62	0.72	0.1	686
	0.70	0.08	1092
	0.67	0.05	2862
0.71	0.81	0.1	564
	0.79	0.08	912
	0.76	0.05	2434

Trial management
Anaesthesia Research (Trial coordination, site induction, funding, recruitment logs, randomization, data-logging, monitoring group allocation adherence, data quality audit)
Neurology Research (Outcome assessment, adverse event and serious adverse event reporting)

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