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Head position and cerebral blood flow in acute ischemic stroke patients: Protocol for the pilot phase, cluster randomized, Head Position in Acute Ischemic Stroke Trial (HeadPoST pilot)

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Abstract

Rationale: Few proven interventions exist for acute ischemic stroke (AIS), and most are expensive and restricted in applicability. Lying flat 'head down' positioning of AIS patients has been shown to increase by as much as 20%, mean cerebral blood flow velocities (CBFV) measured by transcranial Doppler (TCD) but whether this translates into clinical improvement is uncertain.

Aim: To determine if the lying flat position increases mean CBFV in the affected territory as compared to the sitting up position in AIS patients.

Methods and design: Head Position in Acute Ischemic Stroke Trial (HeadPoST pilot) is a cluster randomized (clusters being months), assessor-blinded end-point, phase IIb trial, where consecutive adults with anterior circulation AIS within 12 h of symptom onset are positioned to a randomized position for 48 h with TCD performed serially.

Study outcomes: Primary outcome is mean CBFV on TCD at 1 and 24 h after positioning. Secondary outcomes include: serious adverse events, neurological impairment at seven days, and death and disability at 90 days.

Sample size estimates: Assuming an increase of 8.3 (SD 11.4) cm/s in average of mean CBFV when tilted from 30° to 0°, 46 clusters are required (92 patients in total) to detect a 20% increase of mean CBFV with 90% power and 5% level of significance.

Conclusion: HeadPoST pilot is a cluster randomized multicenter clinical trial investigating the effect of head positioning on mean CBFV in anterior circulation AIS.

Keywords

Ischemic stroke, head position, transcranial Doppler, blood flow velocity, middle cerebral artery, pilot trial

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Introduction and rationale

Acute ischemic stroke (AIS) is the most common type of stroke which affects millions of people worldwide,[1] leaving most either dead or permanently disabled.[2] Few proven interventions exist for AIS—lysis or mechanical thrombectomy, antiplatelets, hemicraniectomy, and specialized acute stroke unit care[3,4]—but most are expensive and limited in applicability, being especially restricted in access for those in middle and low income countries.[5] Most interventions aim to improve brain perfusion and decrease injury within the ischemic

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penumbra region. Increasing mean arterial blood pressure or blood volume by vasodilatation could improve cerebral blood flow (CBF) through collateral arteries, leptomeningeal recruitment, and increasing residual blood flow, but none so far has demonstrated efficacy.[6] New non-pharmacological interventions to increase CBF have been recently proposed and are under study.[7,8] Several small observational studies have shown that the lying flat head position increases mean cerebral blood flow velocity (CBFV) in patients with middle cerebral artery (MCA) AIS, with associated slight increase in intracranial pressure (ICP) resulting in higher cerebral perfusion pressure (CPP).[9–12] In a recent meta-analysis, tilting the head of AIS patients down to 0° was shown to produce a significant increase in mean CBFV in the affected hemisphere, probably by increasing residual blood flow and use of collaterals.[13] However, other data are inconsistent[14] and the association between increased CBFV and any improvement in clinical outcome has yet to be demonstrated.

Current guidelines are cautious about recommendations over the ideal position of AIS patients, suggesting that only non-hypoxic patients are able to tolerate lying flat or positioned in a supine position, in the pre-emergency setting.[15] Otherwise, all other AIS patients should be positioned with their head elevated 30° in bed.[16,17] Such recommendations over elevation of the head are extrapolated from other patient groups where this positioning may reduce ICP after head injury and reduce risks of aspiration pneumonia and/or hypoxemia in ventilated patients or those with pulmonary disease.[18] However, recent data indicate that CPP increases in large hemisphere AIS patients at 0° compared to 30°,[10] such that lying flat may increase CBF and CPP even in AIS patients with raised ICP.

Transcranial Doppler (TCD) has an established role in the evaluation of cerebral hemodynamics in AIS, both as a diagnostic and therapeutic tool, and it can predict clinical severity, prognosis and arterial occlusions with similar predictive value to CT angiography.[18–20]

Objective

To determine if the lying flat head position can increase mean MCA blood flow velocities as measured by TCD. Secondary aims are to determine the safety, feasibility, and potential efficacy of lying flat on clinical outcomes in AIS.

Methods

Trial design

An open, prospective, multicenter, international, cluster randomized, 'proof of concept' phase IIb controlled trial, with masked outcome assessment.

Trial population

Consecutive AIS patients presenting to emergency departments of participating centers who meet the following eligibility criteria:

1. Age $\geq$ 18 years;
2. Clinical diagnosis of anterior circulation AIS supported by brain imaging that excludes hemorrhage or other pathology to account for neurological symptoms;
3. Clinician considers it safe to be positioned either lying flat (0°) or sitting up (30°) of the head before 12 h from symptom onset;
4. Have some degree of neurological impairment defined by a National Institutes of Health Stroke Scale (NIHSS) score $\geq$ 1 upon admission to hospital;
5. Clinical uncertainty over the balance of benefits and harms of different head positioning within the first 24 h of hospital admission for AIS;
6. Able to provide informed consent.

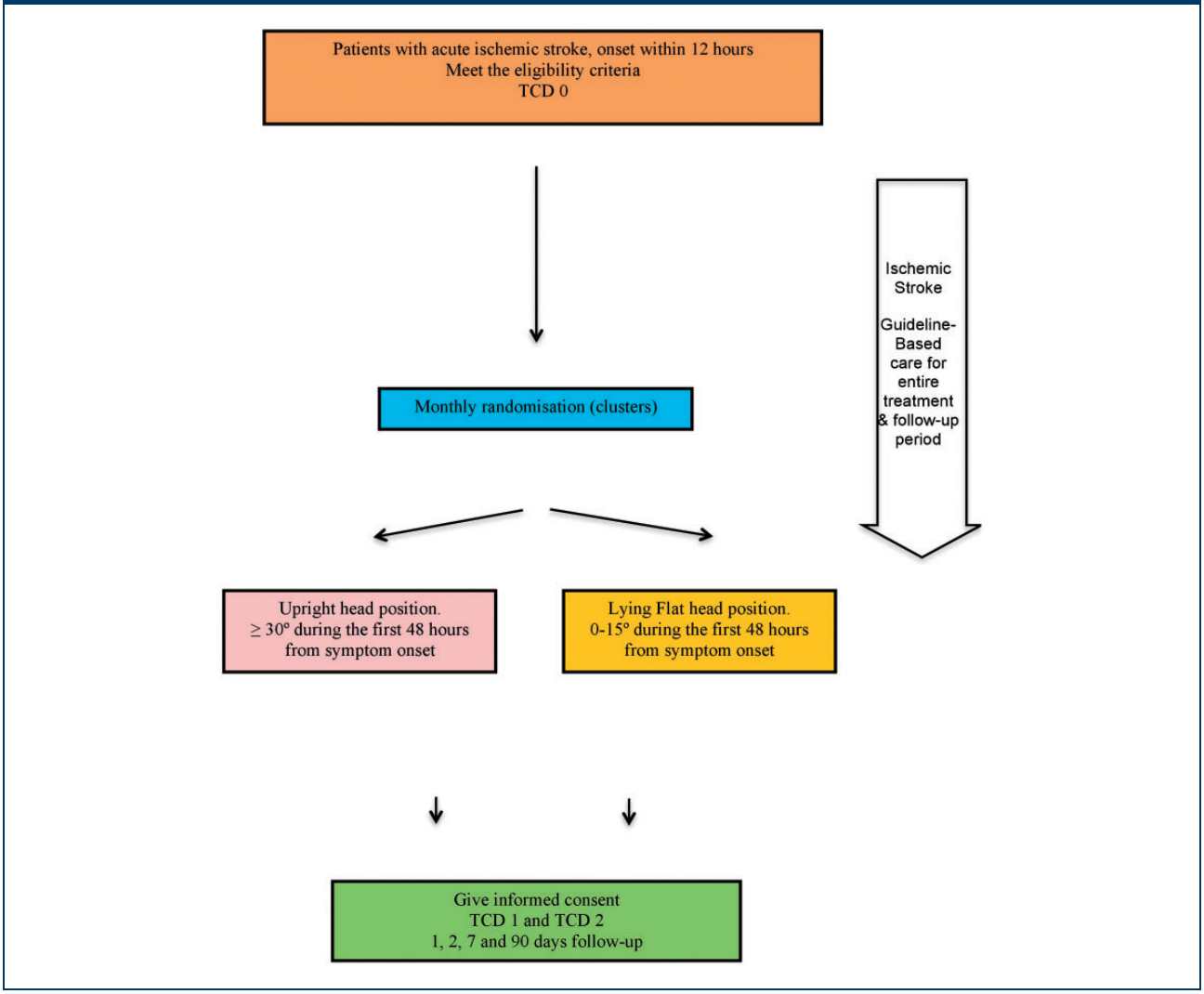
Patients are not eligible if one or more of the following exclusion criteria are present:

1. Any contraindication to lying flat head position (e.g. active vomiting, pneumonia, uncontrolled heart failure);
2. Considered to have a low potential for benefit from positioning due to having either a very minor or major neurological deficit;
3. High probability of death within the next 48 h;
4. Concomitant medical illness that would interfere with the outcome assessments and/or follow-up;
5. Planned early decompressive craniectomy or carotid endarterectomy;
6. Absence of sonographic temporal bone window for TCD.

Randomization

As a cluster randomized trial of the lying flat or upright head positioning, the clusters are months, whereby all patients admitted during a given month are assigned to either lying flat (intervention) or upright (control) head position (Figure 1). This allows stroke care teams to follow a monthly protocol without the need for frequent changing of position for individual patients. The random list is balanced by center and generated using the online program QuickCalcs. Because Head Position in Acute Ischemic Stroke Trial (HeadPoST pilot) is a cluster trial involving a nursing care protocol, patients are able to participate in another investigational (drug) trial if this was considered appropriate by the responsible clinician.

Figure 1. Head Position in Acute Ischemic Stroke Trial (HeadPoST pilot) flow diagram.



Interventions

Lying flat head position-based stroke care protocol. Patients are positioned to 0° as soon as possible after the diagnosis of AIS is made and after performing baseline TCD (most often in the emergency department), and this position is maintained for the next 24 h. The side-lying position is recommended for prevention of aspiration.[17,21] From 24 to 48 h, patients may have their head raised slowly to a maximum of 15° to ensure no alteration in neurological condition (i.e. avoidance of a decline in Glasgow coma scale (GCS) scores of >1 point or an increase in NIHSS score of >4 points). After 48 h, the patient may have their head elevated further to the standard 30° or more.

Upright head position-based stroke care protocol. Patients are positioned with their head up to 30° or more as soon as possible after the diagnosis of AIS, and maintain this for at least the next 48 h. If there is clear neurological deterioration, defined by a decline in GCS scores of 1 point or an increase in NIHSS of >4 points, the patient's position can be changed.

In all patients, checks of their position are made hourly during 48 h after commencement of the positioning intervention. The protocol is not to be discontinued, except if the patient/person responsible chooses to withdraw consent to participation in the study or if any of the following events should occur: (i) a serious adverse event (SAE), which in the opinion of the investigator is related to the trial protocol; and (ii) if the investigator considers is in the best interest of the subject. Follow-up data are collected for all included subjects except those who specifically withdraw consent for release of such information. We also are assessing every non-SAE, in particular intolerance to position because of back pain or other conditions.

We registered time off the position, reasons to be off and reasons to stop the assigned position.

Study outcomes

Primary outcome. The main efficacy outcome is mean CBFV, as assessed by TCD to the MCA of patients with anterior circulation AIS at 1 h (±30 min) and 24 h (±4 h) after positioning ('proof of concept' efficacy).

Secondary outcomes. They include the proportion of SAEs at seven days or at hospital discharge (if this occurs earlier) ('safety'); neurological status according to a shift in scores on the NIHSS at seven days; death or dependency, as measured by a shift in the distribution of scores on the modified Rankin Scale (mRS)[22] at 90 days; deaths by 90 days; death or dependency, as measured by mRS dichotomized 3–6 score, at 90 days; dependency, assessed by mRS score 3–5 at 90 days; pneumonia in the first seven days. Pneumonia is defined as evidence of lung infiltrates on a chest x-ray and three or more of the following symptoms: fever >38°C, rales or crackles on auscultation of the chest, sputum with gram stain showing leukocytes in large quantities, or sputum cultures showing a respiratory pathogen.[23] Feasibility of the study, especially patients being able to maintain a lying flat position for the first 24 h.

Outcomes are assessed by investigators masked to the intervention. All patients' TCD anonymized images from Clínica Alemana and Hospital Clínico de Magallanes are assessed by PMV from the George Institute for Global Health, who is unaware of the month the patient was admitted or the randomized position assigned to these centers in the different months. For patients from Royal Prince Alfred Hospital (RPAH) in Sydney, these are assessed by AB from Clínica Alemana, who is unaware of the month the patient was admitted or the randomized position assigned. Clinical outcomes are assessed in Clínica Alemana by two trained nurses, who work on shifts in orthopedic surgery and have no interaction with stroke patients. In Hospital Clínico de Magallanes assessments are performed by an experienced neurologist not involved in the management of stroke patients during this trial. In RPAH patients are assessed by a trained research assistant from the George Institute for Global Health who is not participating in patient care at the hospital.

Data collection and follow-up

Registration, baseline assessment, and initiation of the intervention are to be achieved within 30–60 min after hospital admission. Head positioning is to be recorded and adjusted if needed, on an hourly basis, by the staff nurse during the initial 48 h and blood pressure is to be recorded every 2 h within this period. Reasons and duration of any time off the assigned head position are registered. All patients are followed daily for one week (or hospital discharge if occurs earlier), and then at 90 days unless death occurs earlier (Table 1). Patients who do not follow the protocol (not positioned at all according to randomized cluster position) and/or discontinue the allocated head position are still followed up to 90 days as per the intent-to-treat principle. Demography and clinical relevant data are recorded at the time of entry into the study. Follow up data are collected at: baseline, 24 h, from day 2 to 7 (or discharge if early), and at 90 days. Brain imaging (CT and/or MRI, and TCD) is conducted according to standardized techniques at baseline and at later stages

Table 1. Schedule of evaluations

		Day			
Evaluation	Baseline	1	2	7[a]	90
Ischemic stroke diagnosis	X				
Brain imaging (CT scan or MRI)	X				
Clinical history and prior medications	X				
Head position	X	X	X		
Transcranial Doppler[b]	XX	X			
Physical exam (BP, HR, oximetry, GCS, NIHSS)	X	X		X	
Dysphagia screening test		X			
Functional assessment with mRS				X	X
Routine blood tests	X				
Standard stroke care	X	X	X	X	X
Hospitalized or not				X	
Consent	X				
Contact details for follow-up				X	

BP: blood pressure, HR: heart rate, GCS: Glasgow Coma Scale, NIHSS: National Institutes for Health Stroke Scale, mRS: modified Rankin Scale.
[a]Or the day of discharge if prior to day 7.
[b]At baseline, TCD is performed before positioning and 1 (±30 min) hour afterwards.

according to local protocols. TCD studies are performed at baseline, after 1 h (±30 min) and at 24 h (±4 h) of head positioning; data are recorded, de-identified, and read off-line by experienced neurosonologists blind to the intervention.

Data quality assurance

Before the beginning of the study, all the investigators at each center attended training sessions to review the protocol and procedures. Study monitoring is performed to assure fidelity of conduct of the study according to the protocol, Good Clinical Practice (GCP) and local requirements. At the end of the study, each center is required to store all relevant data and source documents (according to local ethics committee's requirements, or up to 5 years).

Data management

Registration and data entry are performed at participating centers via a password protected encrypted internet-based data management system. All computerized forms are electronically signed by authorized study personnel. A trained medical coder performs centralized coding of outcomes. Study data are collected and managed using Research Electronic Data Capture (REDCap) system.[24]

A committee of clinical events (CCE) and TCD review the data of every endpoint event. The CCE is integrated by experts in stroke, cardiology, pulmonary medicine, and neurosonology. Adjudication is performed masking the intervention and following a manual with detailed criteria. TCD results are assessed centrally by masked experienced neurosonologists. All relevant SAEs are reviewed and adjudicated centrally in order to ensure that they meet the same diagnostic criteria. The 90-day assessment of mRS is conducted locally by trained nursing staff masked to the intervention and other clinical information.

A data safety monitoring board (DSMB) regularly monitors SAEs (deaths, pneumonia and neurological deterioration), for which any excess would trigger discussions over stopping for harm. Reports are received by the International Coordinating Centre (ICC) and are informed to the study centers.

Sample size estimates

The sample size was calculated using data from a systematic review with meta-analysis that was performed by the investigator team.[12] Four selected studies were analyzed (none were a randomized clinical trial), which included 57 patients in whom the difference in velocity of CBF was measured between the positions 0° to 30° using TCD in the MCA of the affected side of the AIS. A sample of 23 group clusters for each intervention was calculated, for a total of 46 clusters, each with an average of two patients, assuming a intracluster correlation index (ICI) of 0.037[25] to detect the difference found in the meta-analysis of 8.3 cm/s (SD 11.4), with more than 90% power and 5% level of significance. This calculation was performed using the PASS statistical software.[26]

Statistical analyses

All efficacy analyses will be performed according to the intent-to-treat principle. Given the very small cluster size and ICI, clustering will not be taken into account in the primary analysis. Analysis of safety will be performed in patients who remain in the position for over 50% of the time. Descriptive statistics of proportions will be used for the safety data. The number of patients with SAEs, the occurrence of specific SAEs and discontinuation due to SAEs, will be tabulated. Binary outcomes, such as SAEs, death or dependency, and neurological impairment, will be analyzed with $\chi 2$. The average CBFV will be compared with Student's t test if normally distributed or Wilcoxon test if the distributions are not normal. Shift analysis of the NIHSS scores at seven days and mRS scores at 90 days will be performed using ordinal logistic regression.[21] A sensitivity analysis may be undertaken for the key outcomes adjusted for confounding covariates, if there is clear imbalance between randomised groups. The following pre-specified subgroup analyses will be done: thrombolysis/thrombectomy (yes/no), NIHSS score ($<$ or ≥ 10, age ($<$ or ≥ 65 years), and the presence of collaterals in TCD (yes/no). Descriptive statistics will be used for proportions. The alpha error level is set at 0.05.

Study organization and funding

The management of HeadPoST pilot includes: a Steering Committee who has overall responsibility for the execution of study design, protocol, data collection and analysis plan, as well as publications; and an Operational Committee who is based at the ICC and in charge of the central coordination of the study. Four sites are responsible for patient recruitment and data collection in Australia and South America. The study is funded by a grant from Clínica Alemana de Santiago, Chile and by The George Institute for Global Health, University of Sydney, Australia.

Ethical approval

Ethic approval was granted from Universidad del Desarrollo, Clínica Alemana de Santiago Ethics

Committee, Santiago, Chile; the Human Ethics Review Committee RPAH Zone and RPAH Site Specific, Sydney, NSW, Australia; Hospital de Clínicas de Porto Alegre Ethics Committee, Porto Alegre, Brazil; and Hospital Clínico de Magallanes Dr Lautaro Navarro Avaria Ethics Committee, Punta Arenas, Chile.

Current status of the trial

The HeadPoST pilot trial recruited 83 patients from three centers in two countries as of May 2015. Upon review of half of the required number of clusters/patients, the DSMB has recommended continuation of the trial.

The study is registered under HeadPoST pilot, NCT01706094 in www.clinicaltrials.gov.

Discussion

Currently there is insufficient evidence to recommend a specific head position in patients with AIS. However, observational data are compelling in suggesting a beneficial effect of the lying flat head position in the initial 48 h after the onset of AIS, and without any harms. This pilot trial has been designed to determine the efficacy of lying flat on CBFV as measured by TCD (proof of concept), safety, and to explore the feasibility of this intervention in anterior circulation AIS patients, within 12 h of symptom onset and without a definite indication or contraindication to the intervention. We chose no more than 12 h from symptom onset because we hypothesized that patients within this time frame would have greater probability of changes in arterial flow velocities amenable to be influenced by head position and thus provide evidence of the mechanism by which the lying flat head position could work and be clinically significant. We did not select only patients with onset before 6 h in order to include a large sample of patients with ischemic penumbra and working collaterals that could be benefited even if not candidates to recanalization.

The study uses a cluster design to avoid contamination and facilitate conduct of the study in busy services. Experience to date indicates the intervention is feasible to implement in stroke services and without major safety concerns. The results of the HeadPoST pilot trial could have an important impact on current stroke research and ultimately, clinical practice.

This novel pilot trial is actively recruiting patients and on schedule to reach the required sample and timelines for analysis. The lying flat head position is a low cost, widely applicable, nursing intervention that may improve clinical outcomes through increases in CBF in the acute phase of AIS.

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Declaration of conflicting interests

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