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Statistical analysis plan of the head position in acute ischemic stroke trial pilot (HEADPOST pilot)

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Abstract

Background: The HEADPOST Pilot is a proof-of-concept, open, prospective, multicenter, international, cluster randomized, phase IIb controlled trial, with masked outcome assessment. The trial will test if lying flat head position initiated in patients within 12 h of onset of acute ischemic stroke involving the anterior circulation increases cerebral blood flow in the middle cerebral arteries, as measured by transcranial Doppler. The study will also assess the safety and feasibility of patients lying flat for $\geq$24 h. The trial was conducted in centers in three countries, with ability to perform early transcranial Doppler. A feature of this trial was that patients were randomized to a certain position according to the month of admission to hospital.

Objective: To outline in detail the predetermined statistical analysis plan for HEADPOST Pilot study.

Methods: All data collected by participating researchers will be reviewed and formally assessed. Information pertaining to the baseline characteristics of patients, their process of care, and the delivery of treatments will be classified, and for each item, appropriate descriptive statistical analyses are planned with comparisons made between randomized groups. For the outcomes, statistical comparisons to be made between groups are planned and described.

Results: This statistical analysis plan was developed for the analysis of the results of the HEADPOST Pilot study to be transparent, available, verifiable, and predetermined before data lock.

Conclusions: We have developed a statistical analysis plan for the HEADPOST Pilot study which is to be followed to avoid analysis bias arising from prior knowledge of the study findings.

Trial registration: The study is registered under HEADPOST-Pilot, ClinicalTrials.gov Identifier NCT01706094.

Keywords

Cerebral blood flow velocity, head position, ischemic stroke, middle cerebral artery, pilot trial, statistical analysis plan, transcranial Doppler

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Stroke is a leading cause of death and disability worldwide.[1] Acute ischemic stroke (AIS) is the most frequent pathological type, accounting for approximately 80% of cases with a case fatality of 14%–16% at 30 days, and overall likelihood of 53% in being either dead or dependant at six months.[2] Unfortunately, there are few proven acute treatments for patients with AIS, and many of them are expensive and not applicable to the majority of patients, especially those in middle- and low-income countries. Current treatment strategies include (a) care within specialized acute stroke units, (b) lysis of the thrombus with intravenous recombinant

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tissue plasminogen activator (rt-PA) within 4.5 h from the onset of symptoms; (c) mechanical thrombectomy with stent retrievers (d) decompressive hemicraniectomy in those with severe cerebral edema after middle cerebral infarction; and (e) aspirin within 48 h.[3,4] Most of these interventions aim to improve brain perfusion and decrease injury from ischemia, and some focus on preventing medical complications of stroke-related disability.

A potential acute treatment aims at improving cerebral blood flow (CBF) within the ischemic penumbral area through mechanisms that involve recruitment of collateral and leptomeningeal vessels. One approach is to increase blood pressure (BP), but such BP augmentation therapies have only been evaluated in a small number of trials and observational series involving vasopressor agents. A systematic review of 319 patients (age range 42 to 88 years, 46% male) found that although BP therapy was feasible and well tolerated, there was insufficient evidence to establish the benefits and risks on clinical outcomes.[5] A number of non-pharmacological "mechanical" interventions have also been proposed.[6] For example, the Safety and Efficacy of NeuroFlow in Acute Ischaemic (SENTIS) trial investigated the effects of a partial aortic occlusion system to increase perfusion on clinical outcomes in 515 patients within 14 h of the onset of symptoms.[7] Overall, the trial failed to demonstrate any benefits on the primary global disability outcome scale at three-months, but there were no safety concerns. Importantly, post-hoc analysis suggested that treated patients who presented with moderate neurological impairment (National Institutes of Health Stroke Scale (NIHSS) score of 8 to 14) or were over the age of 70 years within 5 h after the onset of symptoms, had improved functional recovery defined by modified Rankin scale scores.[7] A further post-hoc analysis of 192 SENTIS trial patients who underwent cerebral angiography reported that having favorable vascular profile, defined by an intact Circle of Willis and presence of collaterals with a mean arterial BP >65 mmHg at key time-points within 12 h, was independently associated with good outcome.[8] The possibility of an extended time window of benefit up to 24 h was also seen in a smaller study of 26 patients with a magnetic resonance imaging (MRI) perfusion–diffusion mismatch >20% and NIHSS score of 4 to 20.[9] Finally, in a study of 22 patients, the same group assessed the safety and feasibility of partial aortic occlusion immediately after intravenous rt-PA therapy, 77% of patients demonstrated neurological improvement at 90 days, with six of nine patients having a reduction in hypoperfused tissue volume on perfusion weighted-MRI.[10]

External counterpulsation is another non-invasive mechanical intervention that some studies have shown that it increases peak diastolic and mean diastolic flow velocities on transcranial Doppler (TCD) in healthy volunteers, probably by increasing venous pressure and recruiting the collapsed vascular network which may be related to ischemia by venous steal and perfusion misdistribution.[11] One proof-of-concept study has reported a favorable trend for improvement in NIHSS score in AIS with large vessel occlusive disease receiving early (weeks 1 to 7) treatment.[7] Focal cerebral vasodilatation through the stimulation of the sphenopalatine ganglion could also augment CBF by recruiting collapsed collaterals in an ischemic hemisphere. A randomized controlled trial is testing the safety and tolerability of an implant to stimulate the sphenopalatine ganglion in patients with AIS.[12]

Whilst there may be potential benefits from all these non-invasive mechanical therapies, there is also a need for a simple and more widely applicable therapy. One simple way of increasing CBF in the collateral circulation and of augmenting blood flow into the ischemic penumbra might be through tilting the head of patients with AIS into a "lying flat" (0°) head position. Several observational studies have investigated the effects of head positioning on CBF. For example, Edlow et al.[13] reported significant reductions in CBF middle cerebral arteries (MCA) with 30° head-up tilt compared to the supine position, and this appeared to be consistent across all ages. However, there are few studies on the effect of head positioning on CBF following acute stroke, as identified in a systematic review which concluded there was insufficient evidence to make any firm recommendations for clinical practice.[14]

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 computed tomography angiography.[15] Schwarz et al.[16] assessed 18 patients with large MCA ischemic stroke who were admitted to a neurological intensive care unit (ICU) for invasive intracranial pressure (ICP) and intra-arterial BP monitoring. They reported that when patients had their heads elevated from 0° to 30°, there was no associated improvement in ICP but a significant reduction in CBF velocity (CBFV) in the MCA. Wojner-Alexandrov and colleagues[17,18] studied 20 patients with anterior circulation (hemispheric) infarction and persistent arterial occlusion within 24 h of symptom onset, reporting an average 20% increase in MCA CBFV when patients were tilted from 30° to 0°, which confirmed their findings from an earlier study. Importantly, the later study showed that an increase in CBFV was associated with neurological improvement in three patients.[17] More recently, Hunter et al.[19] confirmed improvements in MCA CBFV in the affected hemisphere of incompletely recanalized patients (based on 24 h MRI angiography appearances) by changing the body position of patients from 30° to 0°. By comparison, no significant differences were found in MCA CBFV in the unaffected or affected hemispheres of completely recanalized MCAs. However, the sample size of these studies was small ($n = 8$), and changes in CBFV were not correlated with clinical outcome or neurological improvement.

A systematic review quantified the strength of the association of head positioning on CBF. In a total of 57 patients, moving the head from 30° to 0° was associated with an increased MCA CBFV of 8.31 cm/s (95% confidence intervals [CI] 5.34 to 11.28), and moving the head from 30° to 15° increased MCA CBFV by 4.57 cm/s (95% CI 2.95 to 6.19).[20] Recently, Favilla et al.[21] showed that elevating the head of patients with anterior circulation stroke from 0° to 30° resulted in a 17% decrease in CBFV. However, not all studies have reported a benefit of "lying flat" on CBF. For example, Jack et al.[22] reported that regional cerebral perfusion improved in the semi-recumbent (30° to 45°) compared to supine position, using single photon emission tomography. Another non-randomized observational study did not show any difference in CBFV in different head elevations in patients with mild–moderate ischemic stroke compared to controls.[23]

Nonetheless, there may be adverse consequences of "lying flat," for example, risks of oxygen desaturation, aspiration pneumonia, pulmonary oedema, raised ICP, and delayed mobilization. However, a small randomized pilot study showed that CBFV in AIS patients measured between 24 and 96 h after initial symptoms did not differ between patients mobilized early out of bed with those mobilized later.[24] With respect to concerns about oxygen saturation, a randomized trial in patients with mild–moderate stroke found no association of body position on oxygen saturation within the first 72 h of symptom onset.[25] Others concerns relate to potential aspiration and pneumonia or worsening cardiac insufficiency, especially in patients with dysphagia or cardiomyopathy. A systematic review found that 37% to 78% of stroke patients have dysphagia, depending on the diagnostic methods used, and the relative risk of pneumonia in them is 3.2 (95% CI 2.1 to 4.9), and in those with proven aspiration it increased to 11.8 (95% CI 3.4 to 39.8).[26] An observational study found that the risk of chest infections was associated with time spent at less than 30° on study day 1 in mechanically ventilated patients.[27] In addition, a quasi-experimental study reported that in mechanically ventilated ICU patients with a backrest elevated position of greater than 30°, the risk of pneumonia was 39% compared to 88% in the group with a backrest elevated position of less than 30°.[28] Whilst guidelines suggest the use of backrest elevation at greater than 30° can prevent nosocomial pneumonia, this practice is rarely followed in ICU because of concerns over hemodynamic stability and use of vasopressor therapies to maintain mean BP in these patients.[29] Furthermore, there are no data in non-ventilated or stroke patients regarding the risk of aspiration pneumonia in relation to different head positions.

Current guidelines are cautious about recommendations over the ideal position of AIS patients, suggesting that non-hypoxic patients able to tolerate lying flat should be positioned in a supine position.[30,31] Otherwise, all other AIS patients should be positioned with their head elevated 30° in bed. Such recommendations over elevation of the head are extrapolated from other patient groups where this positioning may reduce ICP after head injury and aspiration pneumonia and/or hypoxemia in ventilated patients or those with pulmonary disease. However, some data indicate that cerebral perfusion pressure (CPP) increases in large hemisphere AIS patients at 0° compared to 30°, such that lying flat may increase CBF and CPP even in AIS patients with raised ICP.[16] Moreover, practice differs between physicians, and there is a lack of consensus about the best strategy regarding head position for AIS patients in many.[32] The aim of the HEADPOST Pilot study is to determine if the lying flat head position can increase mean MCA CBFV as measured by TCD. Secondary aims are to determine the safety, feasibility, and potential clinical efficacy of lying flat on clinical outcomes in AIS.

The study protocol has been outlined elsewhere.[33] The trial will test if the lying flat head position in patients with anterior circulation AIS of less than 12 h increases CBFV in the MCA. It will also test the safety and feasibility of patients lying flat for $\geq$24 h. The trial was conducted in three countries, in centers with the ability of performing TCD in the acute setting of stroke. A unique feature was the cluster randomization of patients to particular months.

Herein we describe the statistical analysis plan (SAP) for the HEADPOST Pilot. The SAP was completed and approved prior to data lock and is to what investigators will adhere to when analyzing data regarding CBFV by TCD, safety and feasibility of lying flat head position. Inclusion of patients was completed in July 2015, and the last patient was followed up in October 2015. Data lock occurred on January 2016.

Main analysis will be by intention to treat and defined by allocated head position at each cluster using random effect mixed models. If the hypothesis of an increase of CBFV is proven, this will serve as a mechanistic explanation to the probable clinical benefits of this intervention.

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Authors' contributions

VVO and PML performed the literature search and wrote the first draft of the manuscript. All authors contributed to the study design, review, and edition of the final version of the manuscript.

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