

Statistical analysis plan for the Head Position in Stroke Trial (HeadPoST): an international cluster cross-over randomised trial

Laurent Billot,^{1,2} Mark Woodward,^{1,2,3,4} Hisatomi Arima,^{1,5} Maree L Hackett,^{1,6} Paula Muñoz-Venturelli,^{1,2,7} Pablo M. Lavados,^{7,8} Alejandro Brunser,⁷ Bin Peng,⁹ Liying Cui,⁹ Lily Song,^{10,11} Stephane Heritier,¹² Stephen Jan,^{1,2} Sandy Middleton,¹³ Verónica V. Olavarría,⁷ Joyce Lim,¹ Thompson Robinson,¹⁴ Octavio Pontes-Neto,¹⁵ Caroline Watkins,^{6,13} and Craig S Anderson^{1,2,11,16}

¹The George Institute for Global Health, Sydney, Australia

²School of Public Health, University of Sydney, Australia

³The George Institute for Global Health, University of Oxford, UK

⁴Department of Epidemiology, Johns Hopkins University, Baltimore, MD, USA

⁵Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

⁶College of Health and Wellbeing, University of Central Lancashire, Preston, Lancashire, UK.

⁷Unidad de Neurología Vascular, Servicio de Neurología, Departamento de Medicina Interna, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, Santiago, Chile

⁸Departamento de Ciencias Neurológicas, Facultad de Medicina, Universidad de Chile

⁹Department of Neurology, Peking Union Medical College Hospital, Beijing, China

¹⁰Department of Neurology, 85 Hospital of People's Liberation Army, Shanghai, China

¹¹The George Institute China, Peking University Health Science Center, Beijing, China

¹²Department of Epidemiology and Preventative Medicine, School of Public Health and Preventative Medicine, Monash University, Melbourne, Australia

¹³Nursing Research Institute, St Vincents Health Australia (Sydney) and Australian Catholic University, Australia

¹⁴Department of Cardiovascular Sciences and NIHR Biomedical Research Unit for Cardiovascular Sciences, University of Leicester, Leicester, UK

¹⁵Stroke Service, Neurology Division, Department of Neuroscience and Behavioural Sciences, Ribeirão Preto Medical School, University of São Paulo.

¹⁶Neurology Department, Royal Prince Alfred Hospital, Sydney, NSW, Australia

Corresponding author

Professor Craig S Anderson

The George Institute for Global Health

PO Box M201, Missenden Road, Campderdown, NSW 2050, AUSTRALIA

T: +61-2-9993-4500 F: +61-2-9993-4502

Email: canderson@georgeinstitute.org.au

Words: Abstract 259; body 957

Key words: Stroke, ischaemic stroke, clinical trial, head position, treatment, nursing care

Authors E-mails:

Paula Muñoz Venturelli:	pmventurelli@gmail.com
Hisatomi Arima:	harima@georgeinstitute.org.au
Pablo Lavados:	pablolavados@yahoo.com
Alejandro Brunser:	abrunser2002@yahoo.com
Bin Peng:	pengbin3@hotmail.com
Liyang Cui	pumchcuily@sina.com
Lily Song	lsong8185@163.com
Laurent Billot	lbillot@georgeinstitute.org.au
Maree Hackett:	mhackett@georgeinstitute.org.au
Mark Woodward	mwoodward@georgeinstitute.org.au
Stephen Jan	sjan@georgeinstitute.org.au
Stephane Heritier	stephane.heritier@monash.edu
Sandy Middleton:	Sandy.Middleton@acu.edu.au
Verónica Olavarría:	veroolavarria@yahoo.com
Joyce Lim:	jlim@georgeinstitute.org.au
Thompson Robinson:	tgr2@leicester.ac.uk
Caroline Watkins:	CLWatkins@uclan.ac.uk
Octavio Pontes-Neto:	opontesneto@fmrp.usp.br
Craig S Anderson:	canderson@georgeinstitute.org.au

Abstract

Background: There is evidence to indicate that the lying flat head position increases cerebral blood flow and oxygenation in patients with acute ischemic stroke, but how these physiological effects translate into clinical outcomes is uncertain. Uncertainty exists over the optimum position for the head of a patient with acute stroke.—The Head Position in Stroke Trial (HeadPoST) aims to determine the comparative effectiveness of lying flat (0°) compared to sitting up ($\geq 30^\circ$) head positioning, initiated within 24 hours of hospital admission for patients with acute stroke.

Design: An international, pragmatic, cluster randomised, crossover, open, blinded outcome assessed clinical trial. Each hospital with an established acute stroke unit (cluster) site was required to recruit up to 70-140 consecutive cases of acute stroke (one phase of head positioning before immediately crossing over to the other phase of head positioning), including both acute ischaemic stroke and intracerebral haemorrhage, in each randomised head position as a ‘business as usual’ policy.

Objective: To outline in detail the predetermined statistical analysis plan (SAP) for the study.

Methods: All accumulated data will be reviewed and formally assessed. Information regarding baseline characteristics of patients, their process of care and management will be outlined, and for each item, statistically relevant descriptive elements will be described. For the trial outcomes, the most appropriate statistical comparisons are described.

Results: A SAP was developed that is transparent, verifiable, and predetermined before completion of data collection.

Conclusions: We developed a predetermined SAP for HeadPoST to avoid analysis bias arising from prior knowledge of the findings, in order to reliably quantify the benefits and harms of lying flat versus sitting up early after the onset of acute stroke.

Trial registration: ClinicalTrials.gov identifier NCT02162017; ANZCTR identifier
ACTRN12614000483651

Uncertainty exists over the optimum position of the head of a patient with acute stroke. Surveys indicate variation in clinical practice, with few specific protocols used and lack of consensus over the most appropriate policy.¹⁻³ Some stroke guidelines provide recommendations based on a sensible extrapolation of the evidence from ventilated patients and those with head trauma, as the data pertaining to stroke patients are limited.⁴⁻⁸

A strong rationale can be made of benefits to be derived from sitting up to reduce intracranial pressure (ICP) in acute intracerebral haemorrhage (ICH)⁹ or severe acute ischaemic stroke (AIS). Yet, although a systematic review of observational studies indicates that lying flat is associated with a significant increase in ICP in patients with brain injury,¹⁰ only small changes in ICP have been noted with such head positioning in patients with large hemispheric AIS.¹¹

An argument has recently arisen for potential benefits on the ischaemic penumbra of lying flat through augmentation of cerebral blood flow (CBF), based on observational studies showing increased mean flow velocity (MFV) of the middle cerebral artery on transcranial doppler (TCD); an hypothesis being tested in the Head Position in Stroke Trial (HeadPoST) Pilot trial.^{12,13,14} [Moreover, several studies indicate that cerebral perfusion and oxygenation is reduced with elevation of the head of patients early after ischaemic stroke¹⁵ and when healthy older subjects stand up.¹⁶](#) A counter-argument against ~~such~~ [the lying flat](#) positioning, though, is that it can increase the risk of pneumonia, particularly in those fed with a nasogastric tube or mechanically ventilated.^{17,18} [However, a recent study suggests that such concerns are unjustified, as a very low frequency \(4.5-6%\) of pneumonia was found in AIS patients who lay flat following thrombolysis treatment.¹⁷⁻¹⁹](#) Furthermore, swallowing is an active process independent of gravity, and any cardiorespiratory risks from lying flat are likely reduced in non-ventilated patients through actions such as ‘side-lying’ and avoidance of feeding.^{20,21}

Whilst sitting up is common in-hospital care practice in western countries, an increasing number of stroke services have introduced the lying flat position for AIS patients on the basis of

encouraging data from small observational studies showing increased CBF on TCD.^{11,12} [Such a policy is further supported by the most recent American Heart Association / American Stroke Association Guidelines for the Early Management of Patients With Acute Ischemic Stroke where cautious recommendations were made for use of the lying flat head position in non-hypoxic patients without airway obstruction or aspiration risk.²²](#) Conversely, in low-income countries, where most of the global stroke burden exists, the lying flat position (and more prolonged immobilisation) is widely applied due to use of simple non-mechanical beds. Taken together with other geographical variations in nursing practices and hospital care policies,^{20,23} the manner in which acute stroke patients are nursed could be highly relevant to variable outcomes and adverse events from this critical illness across the world.

We initiated the HeadPoST study, as nursing care for stroke patients is a universal requirement and their correct positioning is an important clinical question. The aim is to determine the comparative effectiveness (and safety) of the lying flat versus sitting up head position in patients with acute stroke.²⁴⁻²³ Given uncertainty over the relevance of any treatment effects on a surrogate measure, such as increased CBF after AIS,^{22,25,23,26} the study has been powered to determine effects on hard clinical endpoints assessed by trained personnel blind to treatment allocation. The use of broad inclusion criteria will allow an assessment of any heterogeneity of potential benefits (and harms) between AIS and ICH, and across particular subtypes of AIS, for example lacunar versus large artery occlusion. The cluster randomised crossover design was adopted to provide efficiency gains in recruitment and for assessment of likely, modest treatment effects, whilst the pragmatic approach to the implementation of the intervention across a wide range of hospital stroke services in different countries, should enhance the external validity (generalisability) of the results. Finally, the use of remote and site monitoring procedures was to ensure adherence to the protocol, fidelity of the intervention, and high quality standards of data collection and participant registration and management.

The trial includes two important design features. A cluster guardian consent process was obtained from a senior executive officer at each site to apply the intervention to patients as part of routine care; and opt-in (or opt-out in all centers in Australia) written informed consent was obtained from participants, or their approved surrogate, for collection of medical data and participation in follow-up assessments. Moreover, the eligibility criteria were kept simple to facilitate implementation of the randomised head position as routine policy for nursing care, and were based on the uncertainty principle: only patients with clear indications for or contraindications to either head position, as assessed by the local physician and taking into account local guidelines and standards of practice, were excluded from participation. In addition, patients were only excluded if it was considered that the allocated head position could not be applied consistently, the neurological symptoms were reversible (i.e. diagnosis of transient ischemic attack) or not stroke related, or if they refused participation.

Herein, we describe the statistical analysis plan (SAP) for HeadPoST (see Appendix S1), which was finalised prior to completion of the data collection, and is what investigators will adhere to in analysing the results of the study. The SAP was approved and signed off by the study Steering Committee in October 2016, following completion of participant recruitment in August 2016, and before final patient follow-up in December 2016. The statistical analyses specified in the SAP occurred in January 2017.

The HeadPoST study has been designed to provide reliable evidence about the efficacy, effectiveness and safety, of a simple nursing intervention in order to provide reliable evidence to inform policy in the early management of patients with AIS and ICH.

Disclaimers

Pablo Lavados reports research grants from The George Institute and Clínica Alemana de Santiago during the conduct of the study; personal fees from Bristol Meyer Squibb for atrial fibrillation and stroke advisory board; an unrestricted research grant from Lundbeck; personal fees from AstraZeneca and Bayer as SOCRATES and ESUS NAVIGATE trials national leader and a Chilean Government research grant for the ÑANDU project outside the submitted work. Maree Hackett holds a National Heart Foundation Future Leader Fellowship. Mark Woodward holds a National Health and Medical Research Council (NHMRC) of Australia Principal Research Fellowship and Stephen Jan holds an NHMRC Senior Research Fellowship. Craig Anderson holds a Senior Principal Research Fellowship and reports Advisory Boards sitting fees from Medtronic and Astra Zeneca, and receiving travel reimbursement and honorarium from Boehringer Ingelheim and Takeda China. Verónica Olavarría received a travel grant from Boehringer Ingelheim and a research grant from Clínica Alemana. Alejandro Brunser, Paula Muñoz-Venturelli, Laurent Billot and Hisatomi Arima have no conflict of interest to declare.

References

1. Muñoz-Venturelli P, Olavarría V, González F, Brunser A, Lavados P, Arima H, Anderson CS. Head Position in the early phase of acute ischemic stroke: an international survey of current practice. *J Stroke Cerebrovasc Dis* 2015; 24: 1564-1569
2. Rowat AM. What do nurses and therapists think about the positioning of stroke patients? *J Adv Nursing* 2001; 34: 795-803.
3. Mee LY, Bee WH. A comparison study on nurses' and therapists' perception on the positioning of stroke patients in Singapore General Hospital. *Int J Nursing Prac* 2007; 13: 209-221.
4. American Association of Neuroscience Nurses. Guide to the care of the hospitalized patient with ischemic stroke. 2nd ed. Glenview: American Association of Neuroscience Nurses; 2008.
5. Summers D, Leonard A, Wentworth D, Saver JL, Simpson J, Spilker JA, et al. Comprehensive overview of nursing and interdisciplinary care of the acute ischemic stroke patient: a scientific statement from the American Heart Association. *Stroke* 2009; 40: 2911-2944.
6. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R. Guidelines for preventing health-care-associated pneumonia 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. Atlanta: Centers for Disease Control and Prevention; 2004
7. Shinohara Y, Yanagihara T, Abe K, Toshiki Y, Toshiyuki F, Takayo C, et al. Stroke in general. *J Stroke Cerebrovasc Dis* 2011; 20: S7-30.
8. Toyoda K, Steiner T, Epple C, Kern R, Nagayama M, Shinohara Y, Hennerici MG. Comparison of the European and Japanese guidelines for the acute management of intracerebral hemorrhage. *Cerebrovasc Dis* 2013; 35: 419-429.

9. Palazon JH, Asensi PD, Lopez SB, Bautista FP, Candel AG. Effect of head elevation on intracranial pressure, cerebral perfusion pressure, and regional cerebral oxygen saturation in patients with cerebral hemorrhage. *Revista espanola de anestesiologia y reanimacion* 2008; 55: 289-293
10. Fan JY. Effect of backrest position on intracranial pressure and cerebral perfusion pressure in individuals with brain injury: a systematic review. *J Neurosci Nurs* 2004; 36: 278-288.
11. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of body position on intracranial pressure and cerebral perfusion in patients with large hemispheric stroke. *Stroke* 2002; 33: 497-501.
12. Wojner-Alexander AW, Garami Z, Chernyshev OY, Alexandrov AV. Heads down: flat positioning improves blood flow velocity in acute ischemic stroke. *Neurology* 2005; 64: 1354-1357.
13. Olavarria VV, Arima H, Anderson CS, Brunser AM, Muñoz-Venturelli P, Heritier S, Lavados PM. Head position and cerebral blood flow velocity in acute ischemic stroke: a systematic review and meta-analysis. *Cerebrovasc Dis* 2014; 37: 401-408.
14. Olavarría VV, Arima H, Anderson CS, Brunser A, Muñoz-Venturelli P, Billot L, Lavados PM, for the HEADPOST Pilot Investigators. Statistical analysis plan of the Head POsition in acute ischemic Stroke Trial pilot (HeadPoST pilot). *Int J Stroke* 2016 (in press)
- [15.](#) Grap MJ, Munro CL, Hummel RS, 3rd, Elswick RK, Jr., McKinney JL, Sessler CN. Effect of backrest elevation on the development of ventilator-associated pneumonia. *Am J Critical Care* 2005; 14: 325-332.
- [16.](#) [Hargroves D, Tallis R, Pomeroy V, Bhalla A. The influence of positioning upon cerebral oxygenation after acute stroke: a pilot study. *Age Ageing* 2008; 37: 581-585.](#)

- [17. Mehagnoul-Schipper DJ, Vloet LCM, MSN.; Colier WNJM, Hoefnagels WHL, Jansen RWMM. Cerebral oxygenation declines in healthy elderly subjects in response to assuming the upright position. Stroke 2000; 31: 1615-1620.](#)
- ~~15:18.~~ Metheny NA, Davis-Jackson J, Stewart BJ. Effectiveness of an aspiration risk-reduction protocol. Nurs Res 2010; 59: 18-25.
- ~~16:19.~~ Palazzo P, Brooks A, James D, Moore R, Alexandrov AV, Alexandrov AW. Risk of pneumonia associated with zero-degree head positioning in acute ischemic stroke patients treated with intravenous tissue plasminogen activator. Brain Behav 2016; 6: e00425ent 3
- ~~17:20.~~ Brethour MK, Nystrom KV, Broughton S, Kiernan TE, Perez A, Handler D, et al. Controversies in acute stroke treatment. AACN Adv Crit Care 2012; 23: 158-172.
- ~~18:21.~~ Kagaya H, Inamoto Y, Okada S, Saitoh E. Body positions and functional training to reduce aspiration in patients with dysphagia. JMAJ 2011; 54: 35-38.
- [22. Jauch EC, Saver JL, Adams Jr HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association / American Stroke Association. Stroke 2013; 44: 870-947](#)
- ~~19:23.~~ Muñoz-Venturelli P, Robinson T, Lavados PM, Olavarría VV, Arima H, Billot L, et al. Regional variation in acute stroke management. J Neurol Sci 2016 (in press, accepted 18 October 2016)
- ~~20:24.~~ Muñoz-Venturelli P, Arima H, Lavados P, Brunser A, Peng B, Cui L, et al. Head Position in Stroke Trial (HeadPoST) – sitting-up vs lying-flat positioning of patients with acute stroke: study protocol for a cluster randomised controlled trial. Trials 2015; 16: 256-267.
- ~~21:25.~~ Demchuk AM, Burgin WS, Christou I, Felberg RA, Barber PA, Hill MD, Alexandrov AV. Thrombolysis in brain ischemia (TIBI) transcranial doppler flow grades predict

clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. *Stroke* 2001; 32: 89-93.

[22.26.](#) Treger I, Streifler JY, Ring H. The relationship between mean flow velocity and functional and neurologic parameters of ischemic stroke patients undergoing rehabilitation. *Arch Phys Med Rehabil* 2005; 86: 427-430.