ORIGINAL ARTICLE

Cluster-Randomized, Crossover Trial of Head Positioning in Acute Stroke

C.S. Anderson, H. Arima, P. Lavados, L. Billot, M.L. Hackett, V.V. Olavarría, P. Muñoz Venturelli, A. Brunser, B. Peng, L. Cui, L. Song, K. Rogers, S. Middleton, J.Y. Lim, D. Forshaw, C.E. Lightbody, M. Woodward, O. Pontes-Neto, H.A. De Silva, R.-T. Lin, T.-H. Lee, J.D. Pandian, G.E. Mead, T. Robinson, and C. Watkins, for the HeadPoST Investigators and Coordinators*

ABSTRACT

BACKGROUND

The role of supine positioning after acute stroke in improving cerebral blood flow and the countervailing risk of aspiration pneumonia have led to variation in head positioning in clinical practice. We wanted to determine whether outcomes in patients with acute ischemic stroke could be improved by positioning the patient to be lying flat (i.e., fully supine with the back horizontal and the face upwards) during treatment to increase cerebral perfusion.

METHODS

In a pragmatic, cluster-randomized, crossover trial conducted in nine countries, we assigned 11,093 patients with acute stroke (85% of the strokes were ischemic) to receive care in either a lying-flat position or a sitting-up position with the head elevated to at least 30 degrees, according to the randomization assignment of the hospital to which they were admitted; the designated position was initiated soon after hospital admission and was maintained for 24 hours. The primary outcome was degree of disability at 90 days, as assessed with the use of the modified Rankin scale (scores range from 0 to 6, with higher scores indicating greater disability and a score of 6 indicating death).

RESULTS

The median interval between the onset of stroke symptoms and the initiation of the assigned position was 14 hours (interquartile range, 5 to 35). Patients in the lying-flat group were less likely than patients in the sitting-up group to maintain the position for 24 hours (87% vs. 95%, P<0.001). In a proportional-odds model, there was no significant shift in the distribution of 90-day disability outcomes on the global modified Rankin scale between patients in the lying-flat group and patients in the sitting-up group (unadjusted odds ratio for a difference in the distribution of scores on the modified Rankin scale in the lying-flat group, 1.01; 95% confidence interval, 0.92 to 1.10; P=0.84). Mortality within 90 days was 7.3% among the patients in the lying-flat group and 7.4% among the patients in the sitting-up group (P=0.83). There were no significant between-group differences in the rates of serious adverse events, including pneumonia.

CONCLUSIONS

Disability outcomes after acute stroke did not differ significantly between patients assigned to a lying-flat position for 24 hours and patients assigned to a sitting-up position with the head elevated to at least 30 degrees for 24 hours. (Funded by the National Health and Medical Research Council of Australia; HeadPoST ClinicalTrials.gov number, NCT02162017.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Anderson at the George Institute for Global Health China at Peking University Health Science Center, Ste. 1801, Tower B, Horizon Tower, No. 6 Zhichun Rd., Beijing 100088, China, or at canderson@georgeinstitute.org.cn.

*A complete list of sites, trial investigators, and coordinators in the Head Positioning in Acute Stroke Trial (HeadPoST) is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2017;376:2437-47.
DOI: 10.1056/NEJMoa1615715

A Quick Take is available at NEJM.org

The prognosis in patients with acute ischemic stroke is determined according to the location and size of the occluded cerebral vessel,[1] the extent of collateral blood flow,[1-3] and the time to reperfusion therapy.[4] Small, nonrandomized studies have indicated that the lying-flat position (i.e., fully supine with the back horizontal and the face upwards) increases blood flow in major arteries[5,6] and improves oxygenation of the brain,[7,8] whereas a sitting-up body position with the head elevated (hereafter referred to as the "sitting-up position") may reduce intracranial pressure in patients with large hemispheric ischemic stroke.[9] Uncertainty over the role of head positioning after acute stroke and the potential risks of cardiopulmonary dysfunction and aspiration pneumonia[10] have led to ambiguous guidelines[11] and variation in clinical practice.[12] The Head Positioning in Acute Stroke Trial (HeadPoST) compared the effects of the lying-flat position with those of the sitting-up position, initiated soon after a stroke and maintained for 24 hours, in a range of health care settings and in patients with various types of acute stroke.

Methods

Trial Design and Oversight

HeadPoST was an international, multicenter, cluster-randomized, crossover, open-label trial with blinded outcome evaluation; the trial was conducted at 114 hospitals (centers) in nine countries (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Details of the design and statistical analysis plan of the trial have been published previously,[13,14] and the trial protocol is available at NEJM.org. The trial was funded by the National Health and Medical Research Council of Australia. Members of an international steering committee designed the trial and were responsible for the conduct of the trial and the reporting of the results. Staff at the George Institute for Global Health coordinated the trial, managed the database, and performed the analyses. The first author wrote the initial and subsequent drafts of the manuscript. All the authors participated in drafting the manuscript, vouch for the accuracy and completeness of the data and for the fidelity of this report to the trial protocol, and approved the decision to submit the manuscript for publication.

The protocol was approved by all regulatory authorities and ethics committees at the participating centers. A senior executive officer at each hospital acted as a "guardian" (as part of the cluster-randomized trial design) and provided consent at an institutional level for head positioning to be implemented as a low-risk intervention to clusters of patients as part of routine care; written informed consent was subsequently obtained from the patients or their approved surrogates for the collection of medical data and participation in the follow-up assessments.

A statistician who was not otherwise involved in the trial generated the randomized assignment sequence for the hospitals, stratified according to country. In accordance with the protocol, the participating centers implemented the first assigned intervention until a target number of consecutive patients was reached; then, in the crossover phase, the centers implemented the second intervention in a similar number of consecutive patients.

Patients

Patients were eligible for inclusion in the trial if they were 18 years of age or older, presented to the emergency department or an inpatient service at a participating center, and received a clinical diagnosis of acute stroke. Patients with acute intracerebral hemorrhage (but not subarachnoid hemorrhage) were purposefully included in the trial to facilitate implementation of the intervention in consecutive patients and to explore the effects of head positioning on the risk of cerebral edema and pneumonia. Patients were excluded if the local clinician-investigator considered that the assigned head position could not be maintained consistently, if the confirmed diagnosis was a transient ischemic attack, or if the patient declined to participate in the trial. Patients were also excluded if there was a clear indication for, or contraindication to, either of the head positions.[15]

Interventions

The assigned head position was initiated in patients as soon as possible in the emergency department or other assessment area and was maintained during transfer to an inpatient unit.

Patients were asked to strictly maintain the assigned position for the next 24 hours, including when eating, drinking, and toileting unless they found it too uncomfortable to maintain or unless it was considered by the investigator, patient, or caregiver to be harmful, in which case the position could be interrupted for up to three nonconsecutive periods of under 30 minutes. Patients who were assessed as having dysphagia were given no food or drink or received nasogastric tube feeding or a modified diet while remaining in the assigned body position. For the patients in the lying-flat group, bolus rather than continuous feeding was recommended in those with a nasogastric tube, and graded elevation of the head and mobilization with toilet privileges commenced after 24 hours. For the sitting-up position, the head of the patient was elevated to at least 30 degrees by having the head of the bed raised mechanically or by the use of pillows if the bed was nonmechanical; the angle was confirmed with a protractor. Patients in this group were allowed toilet privileges outside the bed according to their level of mobility. All other management was left to the discretion of the investigators in relation to standards of care recommended in their own national guidelines.

DATA COLLECTION

Demographic and clinical data were collected at the time of presentation and included scores on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating greater severity of stroke).[16] A 24-hour bedside diary was maintained to record vital signs, lowest oxygen saturation, and interruption (with time and reason) of the assigned head position. Follow-up data were collected at 7 days (or at hospital discharge, if it occurred before 7 days), unless death occurred earlier; data included final diagnosis, repeat NIHSS scores, and assessment of disability on the modified Rankin scale (a measure of disability in which scores range from 0 to 6, with 0 indicating no symptoms at all; 1, no clinically significant disability despite symptoms; 2, slight disability; 3, moderate disability requiring some help; 4, moderately severe disability requiring assistance with daily living; 5, severe disability, bed-bound, and incontinent; and 6, death).[17,18] Trained staff, who were unaware of the randomized intervention, contacted patients by telephone for the 90-day assessment using the simplified version of the modified Rankin scale,[19,20] which requires only "yes" or "no" answers to structured questions. The European Quality of Life Group 5-Dimension Self-Report Questionnaire (EQ-5D)[21] was also used to assess quality of life with respect to mobility, self-care, usual activities, pain or discomfort, and anxiety or depression (scores range from 1 to 3, with 1 indicating no problems, 2 some or moderate problems, and 3 severe problems). The EQ-5D includes a visual-analogue scale as a single index of self-rated health status (with the scale ranging from 0 [worst imaginable health state] to 100 [best imaginable health state]).

OUTCOMES

The primary outcome was the degree of disability at 90 days, which was analyzed as an ordinal outcome across levels of disability on the modified Rankin scale.[22] Secondary outcomes included death or major disability (modified Rankin scale scores of 3 to 6) at 90 days, death within 90 days after stroke, duration of hospital stay, the individual components of the EQ-5D at 90 days, the distribution of levels across the modified Rankin scale at 7 days, and the distribution of seven levels of increasing neurologic impairment according to categorical scores on the NIHSS or death at 7 days. Serious adverse events, including pneumonia (for which additional clinical information was obtained) were recorded through trial completion. (Additional details on outcomes and serious adverse events are provided in the Supplementary Appendix.)

STATISTICAL ANALYSIS

We estimated that at least 100 patients with acute ischemic stroke would need to be assigned to a head position at each hospital (i.e., 50 patients per intervention phase [or "period"]) across 120 centers (a total of 12,000 patients) for the study to have 90% power to detect a 16% or greater relative shift in levels of disability outcome between intervention groups at 90 days in the ordinal logistic-regression analysis, at an alpha level of 0.05.[3] This calculation was based on conservative estimates of a 10% dropout rate of participating centers and a crossover rate of 5% and loss-to-follow-up rate of 10% among

patients at each center, together with an intracluster correlation of 0.03 and no interperiod correlation. This sample size was also estimated to provide 90% power to detect a 16% or greater relative shift in levels of neurologic function on the basis of categorical NIHSS scores or death at 7 days, at least a 30% lower relative rate of death by 90 days, and a 2-day shorter length of hospital stay in the lying-flat group than in the sitting-up group. However, the target number of patients for recruitment at each center was increased to 140 (i.e., 70 patients per intervention group) to account for the potential of poor implementation of head positioning among patients during the initial and crossover phases and to account for the inclusion of patients with acute intracerebral hemorrhage; a sample of 2800 patients with acute intracerebral hemorrhage was estimated to provide 90% power to detect a 25% or greater improvement (shift) in the 90-day disability outcome associated with the sitting-up position, a 25% or greater improvement in odds (shift) of survival and categorical NIHSS score at 7 days, at least a 33% lower rate of death by 90 days, and a 2-day shorter length of hospital stay, at an alpha level of 0.05 (see the Supplementary Appendix).

Using an intention-to-treat approach, we performed the primary analysis of the intervention effect, as assessed by means of the modified Rankin scale, with an ordinal, logistic-regression, hierarchical, mixed model with four adjustment variables (fixed intervention effect [lying flat vs. sitting up], fixed period effect, random cluster effect, and effect of the interaction between random cluster and period).[23,24] These primary prespecified analyses were given the term "unadjusted." Consistency of intervention effect across seven prespecified subgroups (defined according to age, sex, major country and region groupings, baseline NIHSS score, time from stroke onset to commencement of intervention, major pathologic subtype, and sequence of head positioning at the hospital) was assessed by means of tests for interaction. Prespecified sensitivity analyses included two adjusted models. The first model adjusted for country (grouped as United Kingdom and Australia; China and Taiwan; India and Sri Lanka; and Chile, Brazil, and Colombia), modified Rankin scale score before stroke as a categorical variable, age as a continuous variable, and sex, and the second model adjusted for the covariates in the first model, with additional covariates of baseline NIHSS score and history of stroke, heart disease, or diabetes mellitus; multiple imputation was used if more than 10% of observations on the modified Rankin scale were missing.[25] Similar unadjusted and adjusted analyses were applied to the NIHSS score or death at 7 days after stroke. Other efficacy analyses included an unadjusted analysis of the distribution of the modified Rankin scale scores at 7 days and binary analyses of death and of death or disability (modified Rankin scale of 3 to 6) at 90 days; these binary analyses were performed with the use of hierarchical logistic-regression models. An independent data and safety monitoring board monitored the trial progress and safety; no formal interim analysis was performed. All reported P values are two-sided, and no adjustment was made for multiple comparisons. All analyses were performed with SAS software, version 9.3 (SAS Institute).

RESULTS

PATIENTS

From March 2, 2015, to November 29, 2016, a total of 11,093 of the 22,632 screened patients across 114 hospitals were assigned to a randomized head position (Fig. 1); 5295 patients were assigned to the lying-flat position and 5798 to the sitting-up position. Baseline characteristics of the patients are summarized in Table 1 (further details are provided in Tables S2 through S4 in the Supplementary Appendix). The mean age was 68 years (23% were ≥80 years of age), 40% were female, and 85% had acute ischemic stroke. The median pretreatment NIHSS score was 4 (interquartile range, 2 to 8). The time from the onset of stroke to commencement of the head position was 14.0 hours (interquartile range, 5.0 to 35.0), and the median time from presentation at the hospital to commencement of the head position was 7.0 hours (interquartile range, 2.0 to 26.0) in the lying-flat group and 7.0 hours (interquartile range, 2.0 to 27.0) in the sitting-up group.

INTERVENTION AND REESTIMATION OF SAMPLE SIZE

The median time in the assigned head position was significantly less among the patients in the lying-flat group than among the patients in the sitting-up group (23.3 hours [interquartile range, 20.0 to 24.0] vs. 24.0 hours [interquartile range, 23.0

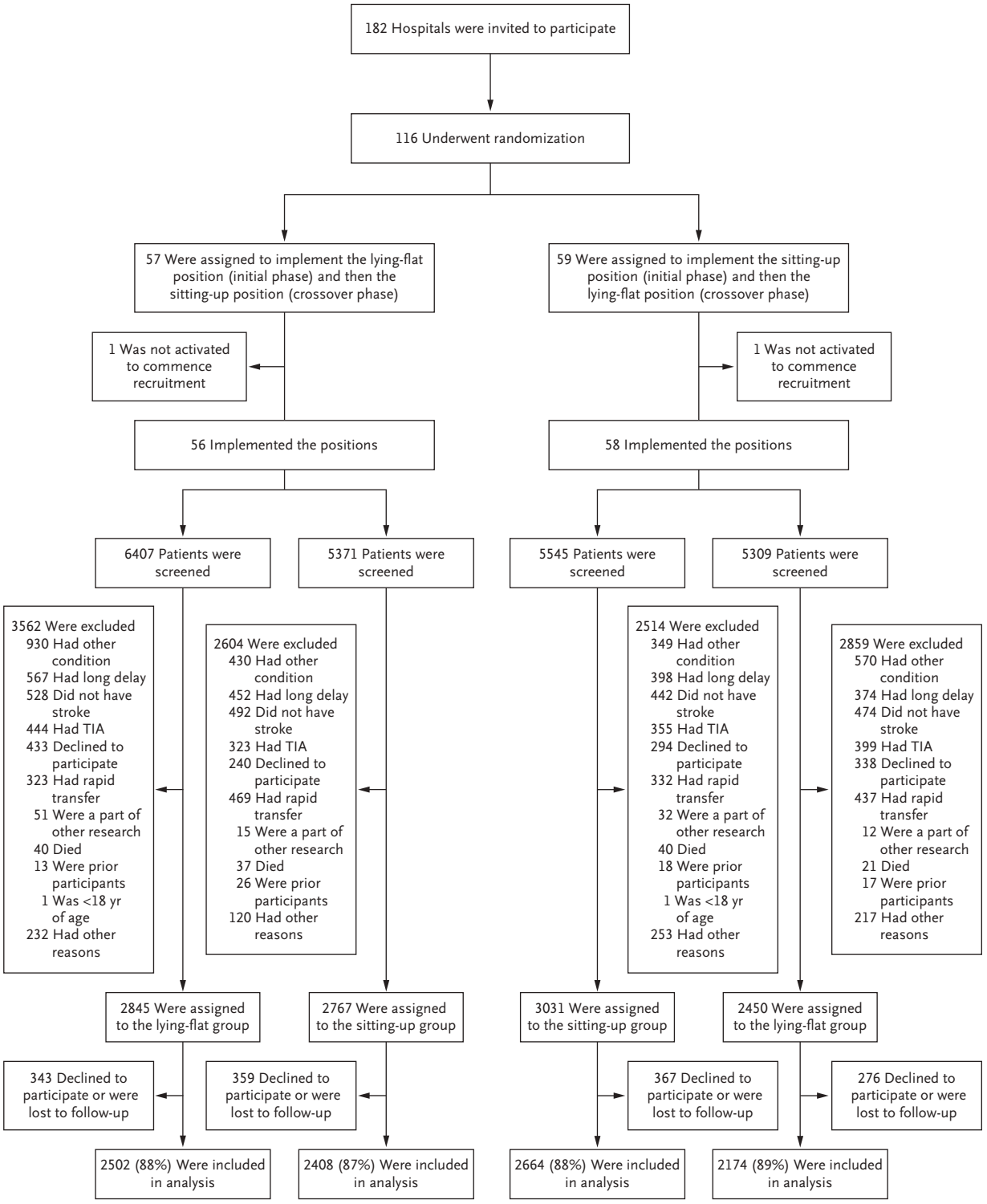

Figure 1. Randomization, Enrollment, and Follow-up.

In the lying-flat group, patients were positioned to lie fully supine with the back horizontal and the face upwards. In the sitting-up group, patients were positioned to sit up with the head elevated to at least 30 degrees. TIA denotes transient ischemic attack.

Table 1. Characteristics of the 11,093 Patients with Acute Stroke at Baseline.*

Characteristic	Lying Flat (N=5295)	Sitting Up (N=5799)
Age — yr	67.8±13.9	68.1±13.7
Female sex — no. (%)†	2140 (40.4)	2289 (39.5)
Region of recruitment — no. (%)		
Australia and United Kingdom	2214 (41.8)	2547 (43.9)
China and Taiwan	2211 (41.8)	2441 (42.1)
South America, India, and Sri Lanka	870 (16.4)	810 (14.0)
Medical history — no. (%)		
Hypertension	2711 (51.2)	2906 (50.1)
Any stroke	1238 (23.4)	1393 (24.0)
Coronary artery disease	690 (13.0)	849 (14.6)
Atrial fibrillation	555 (10.5)	621 (10.7)
Heart failure	166 (3.1)	246 (4.2)
Diabetes mellitus	1065 (20.1)	1156 (19.9)
Tobacco use	987 (18.6)	1137 (19.6)
A score of 0 (no symptoms) on the modified Rankin scale before stroke†	3218 (60.8)	3526 (60.8)
Aspirin or other antiplatelet agent use	3353 (63.3)	3656 (63.0)
Anticoagulant use	428 (8.1)	522 (9.0)
Median NIHSS score (IQR)‡	4.0 (2.0–9.0)	4.0 (2.0–8.0)
Median time from stroke onset to intervention (IQR) — hr	14.0 (5.0–35.0)	14.0 (5.0–35.0)
Median time from hospital admission to intervention (IQR) — hr	7.0 (2.0–26.0)	7.0 (2.0–27.0)
Final diagnosis at time of hospital discharge — no. (%)§		
Condition mimicking stroke	232 (4.4)	319 (5.5)
Transient ischemic attack	106 (2.0)	106 (1.8)
Acute ischemic stroke	4532 (85.6)	4953 (85.4)
Large-artery occlusion due to substantial atheroma	1390 (30.7)	1558 (31.5)
Small-vessel or perforating arteriole lacunar disease	1352 (29.8)	1511 (30.6)
Cardioembolism	592 (13.1)	643 (13.0)
Other or uncertain cause	1195 (26.4)	1235 (25.3)
Primary intracerebral hemorrhage	420 (7.9)	511 (8.8)

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the groups with the exception of region of recruitment (P=0.002), history of coronary artery disease (P=0.02), and history of heart failure (P=0.002). In the lying-flat group, patients were positioned to lie fully supine with the back horizontal and the face upwards. In the sitting-up group, patients were positioned to sit up with the head elevated to at least 30 degrees. IQR denotes interquartile range, and NIHSS National Institutes of Health Stroke Scale.

† Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating more severe disability and a score of 6 indicating death.

‡ Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurologic deficits.

§ Final diagnosis at time of hospital discharge was reported by the clinician-investigator on the basis of brain imaging and other investigations.

to 24.0], P<0.001), and the patients in the lying-flat group were more likely than the patients in the sitting-up group to prematurely cease the position within 24 hours after initiation (13.0% vs. 4.2%, P<0.001). However, there were no significant between-group differences with respect to blood oxygen saturation, blood pressure levels, or other aspects of management. Outcome assessments of scores on the modified Rankin scale could not be performed in 619 patients (11.7%) in the lying-flat group and in 726 patients (12.5%) in the sitting-up group because the patients declined to participate or were lost to follow-up (Fig. 1). The modes of assessment of modified Rankin scale scores (i.e., face-to-face assessment or assessment by telephone call to caregiver, telephone call to patient, telephone call to patient's physician, or other or uncoded) were balanced between groups. (Additional details on the interventions are provided in Tables S5 through S7 and Figs. S1 through S3 in the Supplementary Appendix.)

Because the final number of centers that recruited patients was lower than anticipated and because the mean number of patients with acute ischemic stroke was 13 fewer than estimated per cluster per period, the study power was reestimated with the observed degree of correlation in patient characteristics between clusters and different periods. On the basis of the mean duration in the assigned head position, we estimated that 13% of the patients with acute ischemic stroke crossed over from the lying-flat to the sitting-up position and 6% crossed over from the sitting-up to the lying flat position. Although the intracluster correlation was higher than expected (0.083), this was compensated by a high correlation of patients from different periods in the same cluster (i.e., interperiod correlation of 0.076). In accordance with these calculated intercluster and interperiod correlation values and assumptions of adherence to the randomized positions, the trial was estimated to have retained 90% power to detect a common odds ratio of 0.84 (additional details are provided in the Supplementary Appendix).

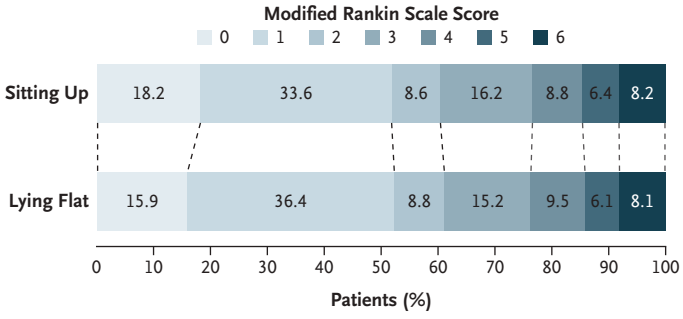

Figure 2. Intervention Effects in the Lying-Flat Group and the Sitting-Up Group at 90 Days, According to Modified Rankin Scale Score.

There was no significant shift in the distribution of 90-day disability outcomes on the global modified Rankin scale between patients in the lying-flat group and patients in the sitting-up group (odds ratio for a difference in the distribution of scores on the modified Rankin scale in the lying-flat group, 1.01; 95% confidence interval, 0.92 to 1.10; P=0.84 by a hierarchical linear mixed model with adjustment for the design by including a fixed group effect, a fixed period effect, a random cluster effect, and an effect of the interaction between random cluster and period). Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability despite symptoms, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. The odds ratios and 95% confidence intervals were adjusted for the cluster-randomized, crossover design effect.

PRIMARY AND SECONDARY OUTCOMES

There was no significant between-group difference in the primary outcome of the degree of disability at 90 days, as assessed by scores on the modified Rankin scale (unadjusted odds ratio for a difference in the distribution of scores on the modified Rankin scale in the lying-flat group, 1.01; 95% confidence interval [CI], 0.92 to 1.10; P=0.84) (Fig. 2). Sensitivity analyses with adjustment and with the use of multiple imputation for missing modified Rankin scale scores showed results similar to those of the primary analysis (Table 2); in addition, when the outcomes of patients with ischemic stroke and intracerebral hemorrhage were analyzed separately, the results were similar to the findings from the primary analysis (Tables S8 and S9 in the Supplementary Appendix).

Death or major disability (modified Rankin scale score of 3 to 6) at 90 days occurred in 38.9% of the patients in the lying-flat group and in 39.7% of the patients in the sitting-up group (odds ratio in the lying-flat group, 0.94; 95% CI, 0.85 to 1.05; P=0.25), and death within 90 days after stroke occurred in 7.3% in the lying-flat group and in 7.4% in the sitting-up group (odds

ratio in the lying-flat group, 0.98; 95% CI, 0.85 to 1.14; P=0.83) (Table 2). No significant between-group differences were evident for other outcomes, except for scores on the visual-analogue scale of the EQ-5D, which favored the lying-flat group (P=0.009). (See also Figs. S4 and S5 and Tables S10 and S11 in the Supplementary Appendix.)

In prespecified subgroup analyses, there was no significant heterogeneity in the intervention effect with respect to the primary outcome or the secondary outcomes of categorical scores on the NIHSS or death or scores on the modified Rankin scale at 7 days. Post hoc analysis indicated no heterogeneity in the intervention effect according to quintiles of baseline NIHSS scores

Table 2. Trial Outcomes and Safety.

Outcome	Lying Flat (N=4676)	Sitting Up (N=5072)	Odds Ratio with Sitting Up as Reference (95% CI)	P Value
	no./total no. (%)			
Primary outcome				
Levels of disability on the modified Rankin scale at 90 days*			1.01 (0.92–1.10)†	0.84
0 — No symptoms at all	745/4676 (15.9)	922/5072 (18.2)		
1 — No clinically significant disability despite symptoms	1704/4676 (36.4)	1703/5072 (33.6)		
2 — Slight disability	410/4676 (8.8)	438/5072 (8.6)		
3 — Moderate disability requiring some help	711/4676 (15.2)	820/5072 (16.2)		
4 — Moderately severe disability requiring assistance with daily living	444/4676 (9.5)	446/5072 (8.8)		
5 — Severe disability, bed-bound, and incontinent	283/4676 (6.1)	326/5072 (6.4)		
6 — Death	379/4676 (8.1)	417/5072 (8.2)		
Secondary outcomes				
Death or disability according to modified Rankin scale scores of 3 to 6 at 90 days	1817/4676 (38.9)	2009/5062 (39.7)	0.94 (0.85–1.05)‡	0.25
Death within 90 days after stroke	379/5185 (7.3)	417/5669 (7.4)	0.98 (0.85–1.14)‡	0.83
Levels of disability on the modified Rankin scale at 7 days*			1.02 (0.93–1.12)§	0.67
0 — No symptoms at all	835/5240 (15.9)	915/5732 (16.0)		
1 — No significant disability despite symptoms	1384/5240 (26.4)	1614/5732 (28.2)		
2 — Slight disability	1009/5240 (19.3)	1102/5732 (19.2)		
3 — Moderate disability requiring some help	707/5240 (13.5)	731/5732 (12.8)		
4 — Moderately severe disability requiring assistance with daily living	771/5240 (14.7)	798/5732 (13.9)		
5 — Severe disability, bed-bound, and incontinent	459/5240 (8.8)	496/5732 (8.7)		
6 — Death	75/5240 (1.4)	76/5727 (1.3)		
Categorical scores on the NIHSS or death at 7 days*			0.98 (0.90–1.08)¶	0.71
1 — Scores 0–4	3483/5108 (68.2)	3851/5608 (68.7)		
2 — Scores 5–9	817/5108 (16.0)	884/5608 (15.8)		
3 — Scores 10–14	410/5108 (8.0)	433/5608 (7.7)		
4 — Scores 15–19	174/5108 (3.4)	208/5608 (3.7)		
5 — Scores 20–24	103/5108 (2.0)	94/5608 (1.7)		
6 — Scores ≥25	46/5108 (0.9)	62/5608 (1.1)		
7 — Death	75/5108 (1.5)	76/5608 (1.4)		

Table 2. (Continued.)

Outcome	Lying Flat (N=4676)	Sitting Up (N=5072)	Odds Ratio with Sitting Up as Reference (95% CI)	P Value
	no./total no. (%)			
Safety				
Patients with any serious adverse event	756/5295 (14.3)	784/5798 (13.5)	1.05 (0.91–1.20)‡	0.51
Patients with pneumonia	164/5295 (3.1)	198/5798 (3.4)	0.86 (0.68–1.08)‡	0.19

* The common odds was estimated in an ordinal logistic-regression model and indicates the increase in odds of moving from a lower level of disability or stroke severity to a higher one in the lying-flat group relative to the sitting-up group. An odds ratio of higher than 1 favors the sitting-up position.

† The odds ratio (with 95% confidence interval) and the corresponding P value for a difference in the distribution of scores on the modified Rankin scale at 90 days were obtained with the use of a hierarchical linear mixed model with adjustment for the design, including a fixed group effect, a fixed period effect, a random cluster effect, and an effect of the interaction between random cluster and period; this was the primary analysis and was given the term "unadjusted." Three adjusted analysis were performed: the first included covariates of country, modified Rankin scale score before stroke, age, and sex (odds ratio, 1.05; 95% CI, 0.96 to 1.15; P=0.30); the second included the covariates in the first adjusted analysis plus additional covariates of baseline NIHSS score and history of heart disease, stroke, or diabetes mellitus (odds ratio, 1.03; 95% CI, 0.94 to 1.13; P=0.55); and the third included the covariates in the second adjusted analysis as well as multiple imputation because more than 10% of scores on the modified Rankin scale were missing (odds ratio, 1.03; 95% CI, 0.94 to 1.13; P=0.50).

‡ The odds ratio (with 95% confidence interval) and the corresponding P value were obtained with the use of a hierarchical mixed logistic-regression model. This analysis was given the term "unadjusted."

§ The odds ratio (with 95% confidence interval) and the corresponding P value for a difference in the distribution of scores on the modified Rankin scale at 7 days were obtained with the use of a hierarchical linear mixed model with adjustment for the design, including a fixed group effect, a fixed period effect, a random cluster effect, and an effect of the interaction between random cluster and period. This analysis was given the term "unadjusted."

¶ The odds ratio (with 95% confidence interval) and the corresponding P value for a difference in the distribution of scores on the NIHSS or survival at 7 days were obtained with the use of a hierarchical linear mixed model with adjustment for the design, including a fixed group effect, a fixed period effect, a random cluster effect, and an effect of the interaction between random cluster and period. This analysis was given the term "unadjusted." Three adjusted analysis were performed: the first included covariates of country, modified Rankin scale score before stroke, age, and sex (odds ratio, 1.01; 95% CI, 0.92 to 1.10; P=0.91); the second included the covariates in the first adjusted analysis plus additional covariates of baseline NIHSS score and history of heart disease, stroke, or diabetes mellitus (odds ratio, 0.97; 95% CI, 0.88 to 1.07; P=0.52); and the third included the covariates in the second adjusted analysis as well as multiple imputation because more than 10% of scores on the modified Rankin scale were missing (odds ratio, 0.97; 95% CI, 0.88 to 1.07; P=0.51).

or time from the onset of stroke symptoms to commencement of the intervention. (See also Figs. S6 through S10 in the Supplementary Appendix.)

ADVERSE EFFECTS

No significant difference in the rate of serious adverse events was observed between the lying-flat group and the sitting-up group (14.3% and 13.5%, respectively; P=0.51) (Table 2). In particular, no significant between-group difference was observed in the rate of pneumonia. (See also Tables S12 and S13 in the Supplementary Appendix.)

DISCUSSION

In this cluster-randomized trial involving patients with acute stroke in a range of health care settings, we found no significant difference between the implementation — at a median of 14 hours after the onset of stroke — of the lying-flat head position and the sitting-up position with respect to the primary outcome of level of disability at 90 days. There were also no significant differences in mortality or in the rates of serious adverse events, including pneumonia.

Our decision to undertake a pragmatic cluster clinical trial was based on the need to avoid contamination between individual patients (i.e., an assigned intervention spilling over into the other group that was assigned to another intervention, thereby diluting the difference between the two randomized groups that are meant to be defined by each specific intervention)[26]; the crossover component facilitated the recruitment of the sample size necessary to assess small differences in clinical outcomes between interventions. The potentially confounding effect of management strategies for acute stroke appears to be low, and

completion of the statistical analysis plan before patient follow-up was concluded eliminated the potential for analytic bias. Although clinicians could not be unaware of the assigned head positions because of the practical requirements of a nursing care intervention, any selection bias introduced by differential recruitment to clusters appears to be low. The risk of bias in intervention assignment was minimized by the use of central randomization, and central blinded assessment of the primary outcome limited observer bias. The results are generalizable, because participating centers included patients with a variety of types of stroke and represented various types of clinical services,[27,28] including metropolitan and rural hospitals and various resource settings.

The negative results of this trial suggest that any modification of cerebral blood flow that may have occurred as a result of head positioning initiated within 24 hours was insufficient to reduce the neurologic deficit associated with acute stroke. Although we did not reach the planned sample size, an analysis of the degree to which clusters were related to each other indicated that the trial retained power to assess the prespecified intervention effect. Because the primary analysis provided an odds ratio for the intervention effect that was close to 1.0 and had a narrow confidence interval, it is unlikely that a true difference in the disability outcome was missed. Although there was no heterogeneity of the intervention effect with respect to the primary outcome in prespecified subgroups, these analyses had low statistical power. Most of the patients in our trial had the assigned head position implemented after the time window for reperfusion with thrombolytic or endovascular treatment had passed, and the patients had mostly mild neurologic deficits from a range of causes of stroke. It is possible that earlier initiation of head position after the onset of symptoms when the ischemic penumbra is potentially modifiable may have produced different results.

The rate of pneumonia was lower in our trial than in some other series[29] but was similar to the rates in stroke registries[27] and in a retrospective study of lying-flat positioning in patients with acute ischemic stroke.[30] The low rates in this trial might relate to careful assessment and care of patients, including the use of dysphagia screening protocols and feeding regimens, as well as the exclusion of high-risk patients such as those who underwent intubation.

In conclusion, the lying-flat head position, as compared to the sitting-up position, initiated early after presentation and maintained for 24 hours, did not alter disability outcomes in patients with acute stroke.

Presented in part at the American Heart Association–American Stroke Association International Stroke Conference, Houston, February 22–24, 2017.

Supported by a research grant (1066966) from the National Health and Medical Research Council of Australia.

Dr. Anderson reports receiving advisory board fees from Medtronic and AstraZeneca and lecture fees and travel support from Takeda China and Boehringer Ingelheim; Dr. Arima, receiving lecture fees from Takeda, Daiichi Sankyo, Astellas, and Aska Pharmaceuticals; Dr. Lavados, receiving support to attend meetings from Boehringer Ingelheim, grant support, fees for serving as country leader for the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS) trial, and travel support from Bayer, grant support and fees for serving as country leader for the Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial from AstraZeneca, and grant support from Comisión Nacional de Investigación Científica y Tecnológica (CONICYT); Dr. Hackett, receiving travel support from Boehringer Ingelheim; Dr. Olavarría, receiving grant support from the George Institute for Global Health; Dr. Muñoz Venturelli, receiving grant support from Clínica Alemana de Santiago and support from the George Institute for Global Health, paid to the author's institution; Dr. Brunser, receiving grant support from Clínica Alemana; Dr. Woodward, receiving consulting fees from Amgen; Dr. Pontes-Neto, receiving lecture fees from Boehringer Ingelheim and Medtronic; and Dr. Robinson, receiving lecture fees and advisory panel fees from Bayer, lecture fees from Boehringer Ingelheim, and advisory panel fees from Daiichi Sankyo. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who participated in this trial and their relatives; the clinical and research teams of the various emergency departments, intensive care units, stroke units, and neurology departments; and the staff at the George Institute for Global Health in Australia and China who worked on the study.

APPENDIX

The authors' full names and academic degrees are as follows: Craig S. Anderson, M.D., Ph.D., Hisatomi Arima, M.D., Ph.D., Pablo Lavados, M.D., M.P.H., 0000-0002-4975-9793Laurent Billot, M.Res., Maree L. Hackett, Ph.D., Verónica V. Olavarría, M.D., Paula Muñoz Venturelli, M.D., Ph.D., Alejandro Brunser, M.D., Bin Peng, M.D., Liying Cui, M.D., Lily Song, M.D., Ph.D., Kris Rogers, M.Biostat., Ph.D., Sandy Middleton, Ph.D., Joyce Y. Lim, M.Nurs., Denise Forshaw, PG.Cert., C. Elizabeth Lightbody, Ph.D., Mark Woodward, Ph.D., Octavio Pontes-Neto, M.D., H. Asita De Silva, D.Phil., Ruey-Tay Lin, M.D., Tsong-Hai Lee, M.D., Ph.D., Jeyaraj D. Pandian, D.M., Gillian E. Mead, M.D., Thompson Robinson, M.D., and Caroline Watkins, Ph.D.

The authors' affiliations are as follows: the George Institute for Global Health (C.S.A., H.A., L.B., M.L.H., P.M.V., K.R., J.Y.L., M.W.) and Faculty of Medicine (C.S.A., L.B., M.L.H., L.S., K.R., J.Y.L., M.W.), University of New South Wales, the Neurology Department, Royal Prince Alfred Hospital, Sydney Health Partners (C.S.A.), the Nursing Research Institute, St. Vincent's Health (S.M.), and Australian Catholic University (S.M., C.W.) — all in Sydney; the George Institute China at Peking University Health Science Center (C.S.A., L.S.) and the Department of Neurology, Peking Union Medical College Hospital (B.P., L.C.) Beijing, and the Department of Neurology, 85 Hospital of People's Liberation Army, Shanghai (L.S.) — all in China; the Department of Preventive Medicine and Public Health, Faculty of Medicine, Fukuoka University, Fukuoka, Japan (H.A.); the Department of Neurology and Psychiatry, Clínica Alemana de Santiago (P.L., V.V.O., P.M.V., A.B.), Facultad de Medicina, Clínica Alemana Universidad del Desarrollo (P.L.), and Departamento de Ciencias Neurológicas, Facultad de Medicina, Universidad de Chile (P.L.) — all in Santiago, Chile; the College of Health and Wellbeing, University of Central Lancashire, Preston (M.L.H., D.F., C.E.L., C.W.), the George Institute for Global Health, University of Oxford (M.W.), the Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh (G.E.M.), and the Department of Cardiovascular Sciences and NIHR Biomedical Research Unit, University of Leicester, Leicester (T.R.) — all in the United Kingdom; the Department of Epidemiology, Johns Hopkins University, Baltimore (M.W.); the Stroke Service–Neurology Division, Department of Neuroscience and Behavior, Ribeirão Preto School of Medicine, University of São Paulo, São Paulo (O.P.-N.); the Clinical Trials Unit, Department of Pharmacology, Faculty of Medicine, University of Kelaniya, Kelaniya, Sri Lanka (H.A.D.S.); the Department of Neurology, Christian Medical College, Ludhiana, India (J.D.P.); and the Department of Neurology, Kaohsiung Medical University and Hospital, Kaohsiung (R.-T.L.), and the Stroke Center and Department of Neurology, Linkou Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taoyuan (T.-H.L.) — both in Taiwan.

REFERENCES

1. Menon BK, Goyal M. Clots, collaterals, and the intracranial arterial tree. Stroke 2016;47:1972-3.
2. Shuaib A, Butcher K, Mohammad AA, Saqqur M, Liebeskind DS. Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target. Lancet Neurol 2011; 10:909-21.
3. Bang OY, Saver JL, Kim SJ, et al. Collateral flow predicts response to endovascular therapy for acute ischemic stroke. Stroke 2011;42:693-9.
4. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet 2014;384:1929-35.
5. Wojner-Alexander AW, Garami Z, Chernyshev OY, Alexandrov AV. Heads down: flat positioning improves blood flow velocity in acute ischemic stroke. Neurology 2005;64:1354-7.
6. Olavarría VV, Arima H, Anderson CS, et al. Head position and cerebral blood flow velocity in acute ischemic stroke: a systematic review and meta-analysis. Cerebrovasc Dis 2014;37:401-8.
7. Hargroves D, Tallis R, Pomeroy V, Bhalla A. The influence of positioning upon cerebral oxygenation after acute stroke: a pilot study. Age Ageing 2008;37:581-5.
8. Mehagnoul-Schipper DJ, Vloet LCM, Colier WN, Hoefnagels WH, Jansen RW. Cerebral oxygenation declines in healthy elderly subjects in response to assuming the upright position. Stroke 2000;31:1615-20.
9. 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.
10. Tyson SF, Nightingale P. The effects of position on oxygen saturation in acute stroke: a systematic review. Clin Rehabil 2004;18:863-71.
11. Jauch EC, Saver JL, Adams HP Jr, 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.
12. Muñoz Venturelli P, Olavarría V, González F, et al. Head position in the early phase of acute ischemic stroke: an international survey of current practice. J Stroke Cerebrovasc Dis 2015;24:1564-9.
13. Muñoz-Venturelli P, Arima H, Lavados P, 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.
14. Billot L, Woodward M, Arima H, et al. Statistical analysis plan for the Head Position in Stroke Trial (HeadPoST): an international cluster cross-over randomised trial. Int J Stroke 2017 March 24 (Epub ahead of print).
15. Sackett DL. Why randomized controlled trials fail but needn't: 1. Failure to gain "coal-face" commitment and to use the uncertainty principle. CMAJ 2000;162: 1311-4.
16. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-70.
17. Quinn TJ, Dawson J, Walters MR, Lees KR. Reliability of the modified Rankin Scale: a systematic review. Stroke 2009; 40:3393-5.
18. Quinn TJ, Dawson J, Walters MR, Lees KR. Functional outcome measures in contemporary stroke trials. Int J Stroke 2009; 4:200-5.
19. Bruno A, Akinwuntan AE, Lin C, et al. Simplified modified Rankin Scale Questionnaire: reproducibility over the telephone and validation with quality of life. Stroke 2011;42:2276-9.
20. Dennis M, Mead G, Doubal F, Graham C. Determining the modified Rankin score after stroke by postal and telephone questionnaires. Stroke 2012;43:851-3.
21. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-43.
22. Bath PMW, Lees KR, Schellinger PD, et al. Statistical analysis of the primary outcome in acute stroke trials. Stroke 2012;43:1171-8.
23. Morgan KE, Forbes AB, Keogh RH, Jairath V, Kahan BC. Choosing appropriate analysis methods for cluster randomised cross-over trials with a binary outcome. Stat Med 2017;36:318-33.
24. Turner RM, White IR, Croudace T. Analysis of cluster randomized cross-over trial data: a comparison of methods. Stat Med 2007;26:274-89.
25. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16:219-42.
26. Sutton CJ, Watkins CL, Dey P. Illustrating problems faced by stroke researchers: a review of cluster-randomized controlled trials. Int J Stroke 2013;8:566-74.
27. Cumbler E, Wald H, Bhatt DL, et al. Quality of care and outcomes for in-hospital ischemic stroke: findings from the National Get With The Guidelines-Stroke. Stroke 2014;45:231-8.
28. Wang Y, Cui L, Ji X, et al. The China National Stroke Registry for patients with acute cerebrovascular events: design, rationale, and baseline patient characteristics. Int J Stroke 2011;6:355-61.
29. Katzan IL. It is time to attack pneumonia head-on. Stroke 2015;46:1153-4.
30. 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(2):e00425.