No benefit of flat head positioning in early moderate–severe acute ischaemic stroke: a HeadPoST study subgroup analysis

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ABSTRACT
Background Although the Head Positioning in acute Stroke Trial (HeadPoST) showed no effect of the flat head position (FP; vs sitting up head position (SUP)) on functional outcome, we hypothesised that it could still offer benefits if commenced early in those with acute ischaemic stroke (AIS) of at least moderate severity.

Methods Subgroup analysis of HeadPoST in participants with National Institutes of Health Stroke Scale (NIHSS) scores ≥7, ≥10 and ≥14, randomised to FP or SUP <4.5 hours of AIS onset on functional outcomes defined by a shift in scores on the modified Rankin scale (mRS) and death/disability (mRS scores 3–6), and any cardiovascular serious adverse event. Logistic regression analyses were undertaken adjusted for study design and baseline risk factors.

Results There was no significant differential treatment effect in patient subgroups defined by increasing baseline NIHSS scores: adjusted OR and 95% CI for ordinal shift and binary (3–6) mRS scores: for NIHSS ≥ 7 (n=867) 0.92 (0.67 to 1.25) and 0.74 (0.52 to 1.04); NIHSS ≥ 10 (n=606) 0.80 (0.58 to 1.10) and 0.77 (0.49 to 1.19); NIHSS ≥ 14 (n=378) 0.82 (0.54 to 1.24) and 1.22 (0.69 to 2.14).

Conclusions Early FP had no significant effect in patients with moderate–severe AIS.

Trial registration number NCT02162017.

Small non-randomised studies1 2 indicate that patients with acute ischaemic stroke (AIS) who are positioned lying flat (FP) have increased mean cerebral blood flow velocity (CBFV) in the middle cerebral artery (MCA), as measured by transcranial Doppler (TCD). Whether this physiological association translates into improved clinical outcome has been hotly debated. The Head Positioning in Stroke Trial (HeadPoST) mechanistic pilot study3 confirmed an increased CBFV in the ipsilateral MCA (primary outcome), but without any benefit on 90-day functional outcome, which was further confirmed in the main HeadPoST4 study undertaken in over 10000 patients who were evaluated using an international pragmatic cluster cross-over design. The later study has been criticised for including a broad range of patients, many with mild deficits, who were randomised within a long time window from symptom onset, as well as for including patients with primary intracerebral haemorrhage.5 Herein, we present post-hoc analyses specifically in the subgroup of patients with AIS with moderate–severe neurological impairment, defined by National Institutes of Health Stroke Scale (NIHSS) scores ≥7, who commenced the head positioning intervention early after onset of symptoms.

METHODS
HeadPoST main was an international, multicentre, cluster-randomised, cross-over, open-label trial with blinded outcome evaluation in 11093 adults (age ≥18 years) with AIS or intracranial hemorrhage (ICH) of flat head position (0°) compared with sitting up (≥30°, SP) head positioning, applied <24 hours of admission at 114 hospitals in 9 countries during 2016–2017. The protocol is described in detail elsewhere, was approved by all ethics committees at each participating centre and involved informed consent obtained from patients or their approved surrogates.4 This study pertains to participants with AIS randomised <4.5 hours with baseline high NIHSS scores, grouped as <7, ≥7, ≥10 and ≥14. Clinical outcomes were a shift in scores on the modified Rankin scale (mRS), death or disability (mRS 3–6) and any serious cardiovascular adverse event (SAE) including stroke, cardiac or other vascular events within 90 days post randomisation. We further analysed the treatment effect by subgroups with or without large vessel occlusion (LVO) in each stratum of NIHSS score. The presence
of LVO was defined as an occlusion of MCA segments M1 or M2, terminal internal carotid artery, A1 segment of the anterior cerebral artery, P1 segment of the posterior cerebral artery or vertebral/basilar arteries on CT/MR angiography, digital subtraction, or by TCD.

Baseline characteristics and relevant hospital care were analysed with the χ² test for categorical variables, t-test for normally distributed and Wilcoxon rank sum test for skewed distribution, as appropriate. Treatment effects were analysed by ordinal logistic regression, with a hierarchical mixed model and adjustment for study design (fixed intervention effect, fixed period effect, random cluster effect and effect of the interaction between random cluster and period). Subsequent models were adjusted for baseline confounders of age, sex, region, premorbid functional grade on the mRS, history of heart disease, diabetes mellitus, or stroke, and NIHSS score, with a forward approach. Results are presented as OR and 95% CIs. A standard two-sided level p<0.05 was considered significant. All analyses were performed with SAS software V.9.4 (SAS Institute).

**RESULTS**

Online supplementary figure 1 shows the flow of patients flow according to NIHSS score subgroups. Table 1 shows the baseline demographic and clinical characteristics of 867 patients with NIHSS ≥7, which were comparable between randomised groups. Similarly, there were no significant baseline differences in patient groups of NIHSS <7 (n=950), ≥10 (n=606) or ≥14 (n=378; online supplemental appendix, tables S1–3, respectively).

### Table 1: Baseline characteristics of patients who commenced head positioning within 4.5hours of acute ischaemic stroke onset with initial National Institute of Health Stroke Scale (NIHSS) score ≥7

| Baseline characteristics | Lying flat N=432 | Sitting up N=435 | P value |
|--------------------------|-----------------|-----------------|---------|
| Age (years)              | 73.1 (13.3)     | 72.3 (13.5)     | 0.35    |
| Male                     | 230 (53.2%)     | 233 (53.6%)     | 0.92    |
| Region, n (%)            |                 |                 | 0.08    |
| Australia and UK         | 294 (68.1)      | 272 (62.5)      |         |
| China and Taiwan         | 91 (21.1)       | 107 (24.6)      |         |
| India and Sri Lanka      | 13 (3.0)        | 7 (1.6)         |         |
| South America            | 34 (7.9)        | 49 (11.3)       |         |
| Hypertension, n (%)      | 288 (67.1)      | 265 (60.9)      | 0.06    |
| Previous stroke, n (%)   | 89 (20.6)       | 103 (23.7)      | 0.28    |
| Atrial fibrillation, n (%)| 95 (22.2)       | 94 (21.8)       | 0.86    |
| Heart failure, n (%)     | 36 (8.5)        | 34 (7.9)        | 0.77    |
| Diabetes mellitus, n (%) | 86 (20.0)       | 73 (16.8)       | 0.23    |
| Current smoker, n (%)    | 60 (14.2)       | 60 (14.0)       | 0.91    |
| Aspirin use, n (%)       | 141 (32.7)      | 154 (35.4)      | 0.40    |
| Anticoagulant use, n (%) | 53 (12.3)       | 47 (10.9)       | 0.50    |
| AIS category, n (%)      |                 |                 | 0.58    |
| Large vessel             | 133 (30.8)      | 134 (30.8)      |         |
| Cardioembolic            | 110 (25.5)      | 101 (23.2)      |         |
| Lacunar                  | 59 (13.7)       | 52 (12.0)       |         |
| Other                    | 130 (30.1)      | 148 (34.0)      |         |
| NIHSS at admission       | 13.0 (9.0 to 18.0) | 12.0 (9.0 to 18.0) | 0.34 |
| mRS, n (%)               |                 |                 | 0.73 |
| 0 (no symptoms)          | 251 (58.5)      | 246 (56.8)      |         |
| 1 (no significant disability) | 73 (17.0) | 73 (16.9) |
| 2 (slight disability)    | 40 (9.3)        | 47 (10.9)       |         |
| 3 (moderate disability)  | 41 (9.6)        | 42 (9.7)        |         |
| 4 (moderate/severe disability) | 22 (5.1) | 19 (4.4) |
| 5 (severe disability)    | 2 (0.5)         | 6 (1.4)         |         |

Data are n (%), mean (SD) and median (IQR).

AIS, acute ischaemic stroke; mRS, modified Rankin scale.
Table 2  90-day outcomes by baseline neurological severity

| Outcome* | Lying flat versus sitting up | OR (95% CI) | P value | aOR (95% CI) | P value |
|----------|-----------------------------|------------|--------|--------------|--------|
| NIHSS <7 | Ordinal mRS                 | 1.07 (0.83 to 1.37) | 0.62  | 1.03 (0.80 to 1.33) | 0.73  |
|          | Binary mRS 3–6              | 1.02 (0.72 to 1.45) | 0.89  | 0.93 (0.63 to 1.37) | 0.70  |
|          | Death                      | 1.31 (0.65 to 2.66) | 0.46  | Did not converge† |       |
|          | Cardiovascular SAEs*        | 1.03 (0.62 to 1.72) | 0.90  | 1.05 (0.62 to 1.78) | 0.85  |
| NIHSS ≥7 | Ordinal mRS                 | 0.94 (0.71 to 1.26) | 0.69  | 0.92 (0.67 to 1.25)‡ | 0.59  |
|          | Binary mRS 3–6              | 0.86 (0.67 to 1.15) | 0.31  | 0.74 (0.52 to 1.04) | 0.08  |
|          | Death                      | 0.91 (0.59 to 1.41) | 0.67  | 0.80 (0.51 to 1.27) | 0.34  |
|          | Cardiovascular SAEs*        | 1.31 (0.87 to 1.99) | 0.20  | 1.21 (0.79 to 1.86) | 0.37  |
| NIHSS ≥10| Ordinal mRS                 | 0.87 (0.64 to 1.19) | 0.38  | 0.80 (0.58 to 1.10) | 0.16  |
|          | Binary mRS 3–6              | 0.89 (0.61 to 1.30) | 0.55  | 0.77 (0.49 to 1.19) | 0.24  |
|          | Death                      | 0.85 (0.52 to 1.38) | 0.50  | 0.76 (0.46 to 1.24) | 0.27  |
|          | Cardiovascular SAEs*        | 1.16 (0.73 to 1.83) | 0.54  | 1.06 (0.66 to 1.70) | 0.81  |
| NIHSS ≥14| Ordinal mRS                 | 0.83 (0.56 to 1.27) | 0.36  | 0.82 (0.54 to 1.24) | 0.34  |
|          | Binary mRS 3–6              | 1.13 (0.65 to 1.98) | 0.66  | 1.05 (0.54 to 2.01) | 0.89  |
|          | Death                      | 0.70 (0.42 to 1.19) | 0.19  | 0.72 (0.40 to 1.30) | 0.28  |
|          | Cardiovascular SAEs*        | 1.29 (0.75 to 2.21) | 0.36  | 1.30 (0.73 to 2.31) | 0.38  |

Adjusted OR (aOR) obtained for further adjusted age, sex, region groups, premorbid grade (0–1 vs 2–5) according to modified Rankin scale (mRS) assessed at baseline, comorbidity of heart disease, stroke or diabetes mellitus and National Institutes of Health Stroke Scale (NIHSS) at baseline as continuous variable.

*Cardiovascular serious adverse events (SAEs) include cerebrovascular events, cardiac events or other vascular events.
†Hierarchical model cannot be converge due to very few cases of death in this subgroup.
‡Hierarchical model only adjusted study design, age, sex, region groups, premorbid grade (0–1 vs 2–5) according to mRS assessed at baseline and comorbidity of heart disease, stroke or diabetes mellitus.

90 days post randomisation, there was no significant difference in functional recovery by ordinal mRS (adjusted OR (aOR) 0.92, 95% CI 0.67 to 1.25), binary mRS scores 3–6 (aOR 0.74, 95% CI 0.52 to 1.04) or any cardiovascular SAE (aOR 1.21, 95% CI 0.79 to 1.86, table 2) in NIHSS ≥7 group. Likewise, there were no significant differences in the treatment effects on these outcomes in patients with NIHSS scores <7, ≥10 and ≥14 (table 2; online supplementary figure 2). The probability of a good outcome was significantly greater in the patients with LVO and an NIHSS <7 (p=0.005 for interaction).

**DISCUSSION**

In these post-hoc analyses of participants in the HeadPoST study with more severe neurological deficit, there was no differential effect of randomised head positioning commenced early after onset of symptoms on functional outcomes or cardiovascular SAE. These patients had a high likelihood of a large ischaemic penumbra, based on an early time window after symptom onset and high probability of underlying LVO by virtue of an initial NIHSS score ≥7. Although we cannot exclude the possibility of missing a more modest effect from low statistical power in subgroups or of poor fidelity of the intervention, these results provide further confirmation that any change in MCA CBFV from the FP does not appear to translate into improved clinical outcomes as compared with SP in patients with severe AIS.

We have previously shown that in the FP group, 14% more patients had an increase of CBFV of ≥8 cm/s over 24 hours in the ipsilateral MCA when compared with SP after AIS. While this increase in CBFV could influence NIHSS score improvement after AIS, this may not necessarily influence overall recovery at 90 days, as such change in CBFV represents only an increase of 13%–17% of the flow velocity of a normal artery. It is unknown if such a modest increase in flow velocity is able to maintain viable penumbra over a longer period of time, even up to 24 hours. TCD evaluations of acute MCA occlusions in AIS are usually scored on the Thrombolysis in Brain Ischaemia (TIBI) scale (from 0 being occluded to 5 representing normal flow velocity), and have shown that a change in ultrasonographic flow patterns from a TIBI signal of 0–3 to 4–5 is associated with good functional outcome. These changes in TIBI scores represent a minimum threefold increase in flow.
velocity of an affected artery (change from TIBI 3–5). Thus, it is unlikely that an increase of 13% in flow velocity in 14% of patients, who were assigned to FP, could have had a significant effect on overall recovery. Moreover, no study has shown that changes in CBFV equate to improvements in the ischaemic penumbra. Even within patients with AIS with the highest NIHSS scores (≥10 and ≥14), we could not detect a treatment effect. Nevertheless, we did find a significant interaction between LVO and low NIHSS, favouring FP, which could indicate that these patients have good collaterals from mild clinical manifestations. The findings could also be due to chance in only 42 patients randomised to FP.

One explanation for our neutral results in patients with high NIHSS scores is that FP has no effect if there is no collateral blood flow, even in the very early stages of AIS. It is possible that FP could still have some effect in highly selected patients, such as those with LVO and very competent collaterals, or those with incomplete reperfusion from lysis or mechanical thrombectomy therapies, but this will be challenging to prove in a randomised trial.

An important caveat is that while our study included a very large number of randomised patients who had severe strokes, only a small proportion had imaging confirmation of the location and extent of vessel occlusion. Moreover, these are post-hoc analyses of subgroups and thus prone to bias and random effects.

In summary, the use of FP of patients early after the onset of moderate–severe AIS was not associated with functional recovery, but could be effective in patients with low NIHSS and LVO.

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