

Supplementary online content

| | |
|------------------------------------------------------------------------------------------------------|---|
| eTable 1. Demographics and neonatal characteristics according to treatment group..... | 2 |
| eTable 2. General movements assessment and outcomes according to treatment group | 3 |
| eTable 3. Normal/mildly abnormal MRI with adverse outcome | 4 |
| eTable 4. Moderately/severely abnormal MRI and/or absent fidgety movements with normal outcome | 4 |

eTable 1. Demographics and neonatal characteristics according to treatment group*

| | Therapeutic hypothermia (n=25) | Standard care (n=25) | Total (n=50) |
|-------------------------------------------------------|---------------------------------------|-----------------------------|---------------------|
| Inborn, n/N (%) | 13/25 (52.0) | 17/25 (68.0) | 30/50 (60.0) |
| Male gender, n/N (%) | 17/25 (68.0) | 16/25 (64.0) | 33/50 (66.0) |
| Gestational age (weeks), mean (SD) [†] | 39.1 (1.3) | 39.2 (1.4) | 39.1 (1.3) |
| Birth weight (g), mean (SD) | 2911 (483) | 2960 (553) | 2935 (515) |
| Small for gestational age, n/N (%) [‡] | 7/25 (28.0) | 7/23 (30.4) | 14/48 (29.2) |
| 5-min Apgar score, n/N (%) | | | |
| 0-3 | 5/22 (22.7) | 1/21 (4.8) | 6/43 (14.0) |
| 4-6 | 13/22 (59.1) | 12/21 (57.1) | 25/43 (58.1) |
| 7-10 | 4/22 (18.2) | 8/21 (38.1) | 12/43 (27.9) |
| Cord/blood <60min pH, mean (SD) [§] | 6.81 (0.12) | 6.93 (0.18) | 6.89 (0.17) |
| Cord/blood <60min base excess, mean (SD) [¶] | -19.6 (3.2) | -16.5 (4.6) | -17.7 (4.4) |
| HIE stage at randomisation, n/N (%) | | | |
| Moderate | 24/25 (96.0) | 24/25 (96.0) | 48/50 (96.0) |
| Severe | 1/25 (4.0) | 1/25 (4.0) | 2/50 (4.0) |
| Thompson score, median (IQR) | | | |
| At randomisation | 9 (8-10) | 9 (8.5-12) | 9 (8-11) |
| Day 7/at discharge ^{**} | 2 (1-3.25) | 2 (2-3.25) | 2 (2-3) |
| Injury pattern on MRI, n/N (%) | | | |
| Normal | 4/23 (17.4) | 2/23 (8.7) | 6/46 (13.0) |
| Only mild/moderate WM injury | 4/23 (17.4) | 5/23 (21.7) | 9/46 (19.6) |
| Only severe WM injury | 0 | 1/23 (4.3) | 1/46 (2.2) |
| Mild BGT, no/mild/moderate WM injury | 13/23 (56.5) | 6/23 (26.1) | 19/46 (41.3) |
| Mild BGT, severe WM injury | 1/23 (4.3) | 0 | 1/46 (2.2) |
| Moderate BGT, any WM injury | 1/23 (4.3) | 5/23 (21.7) | 6/46 (13.0) |
| Global | 0 | 4/23 (17.4) | 4/46 (8.7) |

*Percentages are based on the number of infants for whom data were available. HIE, hypoxic-ischaemic encephalopathy; WM, white matter; BGT, basal ganglia and thalami.

[†]Data were unavailable for two infants in the standard care group.

[‡]Small for gestational age defined as birth weight less than the 10th percentile according to the Intergrowth 21st chart.

[§]Data were unavailable for 13 infants in therapeutic hypothermia group and seven in standard care group. Cord pH was not available in outborn infants.

[¶]Data were unavailable for 14 infants in therapeutic hypothermia group and eight in standard care group. Cord base excess was not available in outborn infants.

^{**}Data were unavailable for three infants in therapeutic hypothermia group (two died) and seven in standard care group (five died).

eTable 2. General movements assessment and outcomes according to treatment group*

| | Therapeutic hypothermia (n=25) | Standard care (n=25) | Total (n=50) | P value |
|---------------------------------------------|---------------------------------------|-----------------------------|---------------------|--------------------|
| Fidgety movements | | | | |
| Absent (-) | 3/21 (14.3) | 6/18 (33.3) | 9/39 (23.1) | 0.255 [†] |
| Sporadic (+/-) | 4/21 (19.0) | 6/18 (33.3) | 10/39 (25.6) | |
| Intermittent (+) | 12/21 (57.1) | 6/18 (33.3) | 18/39 (46.2) | |
| Continual (++) | 1/21 (4.8) | 0 | 1/39 (2.6) | |
| Exaggerated | 1/21 (4.8) | 0 | 1/39 (2.6) | |
| Adverse outcome[‡] | 5/24 (20.8) | 12/23 (52.2) | 17/47 (36.2) | 0.025 |
| Death | 2/24 (8.3) | 6/23 (26.1) | 8/47 (17.0) | 0.105 |
| Bayley-III cognitive composite score | | | | 0.019 |
| <70 | 0 | 3/16 (18.8) | 3/38 (7.9) | |
| 70-84 | 2/22 (9.1) | 3/16 (18.8) | 5/38 (13.2) | |
| ≥85 | 20/22 (90.9) | 10/16 (62.5) | 30/38 (78.9) | |
| Bayley-III motor composite score | | | | 0.074 |
| <70 | 0 | 3/16 (18.8) | 3/38 (7.9) | |
| 70-84 | 2/22 (9.1) | 1/16 (6.3) | 3/38 (7.9) | |
| ≥85 | 20/22 (90.9) | 12/16 (75.0) | 32/38 (84.2) | |
| Cerebral palsy | 1/22 (4.5) | 3/16 (18.8) | 4/38 (10.5) | 0.159 |
| GMFCS | | | | |
| Level 1 | 1/22 (4.5) | 1/16 (6.3) | 2/38 (5.3) | |
| Level 5 | 0 | 2/16 (12.5) | 2/38 (5.3) | |

*Percentages are based on the number of infants for whom data were available. Bayley-III, Bayley Scales of Infant and Toddler Development, third edition; GMFCS, gross motor function classification system.

[†]P value based on Fisher exact test on absent versus present fidgety movements.

[‡]Adverse outcome defined as death, cerebral palsy with GMFCS level 3-5 or Bayley-III cognitive and/or motor composite score <85.

eTable 3. Normal/mildly abnormal MRI* with adverse outcome**

| No | Rando- misation | BGT | PLIC | WM | Fidgety movements | Bayley-III cognitive CS | Bayley-III motor CS | CP |
|----|--------------------|--------|-----------|----------|----------------------|-------------------------------|------------------------|----|
| 1 | Non-cooled | Mild | Normal | Normal | Absent | 80 | 79 | No |
| 2 | Cooled | Normal | Normal | Moderate | Intermittent | 100 | 76 | No |
| 3 | Cooled | Mild | Equivocal | Moderate | Intermittent | 80 | 70 | No |
| 4 | Cooled | Mild | Equivocal | Normal | Intermittent | 80 | 89 | No |
| 5 | Non-cooled | Mild | Normal | Moderate | Sporadic | 80 | 118 | No |

BGT, basal ganglia and thalami; PLIC, posterior limb of the internal capsule; WM, white matter; Bayley-III, Bayley Scales of Infant and Toddler Development, third edition; CS, composite score; CP, cerebral palsy.

*Normal/mildly abnormal MRI defined as normal/mild BGT score and/or normal/mild/moderate WM score.

**Adverse outcome defined as death, cerebral palsy with gross motor function classification system (GMFCS) level 3-5 or Bayley-III cognitive and/or motor composite score <85.

eTable 4. Moderately/severely abnormal MRI* and/or absent fidgety movements with normal outcome**

| No | Rando- misation | BGT | PLIC | WM | Fidgety movements | Bayley-III cognitive CS | Bayley- III motor CS | CP |
|----|--------------------|----------|-----------|--------|----------------------|-------------------------------|----------------------------|----|
| 6 | Cooled | Normal | Normal | Mild | Absent | 90 | 112 | No |
| 7 | Cooled | Mild | Normal | Mild | Absent | 95 | 91 | No |
| 8 | Cooled | Mild | Normal | Severe | Intermittent | 95 | 100 | No |
| 9 | Non-cooled | Normal | Normal | Severe | Intermittent | 100 | 115 | No |
| 10 | Cooled | Moderate | Equivocal | Normal | Absent | 100 | 118 | No |

BGT, basal ganglia and thalami; PLIC, posterior limb of the internal capsule; WM, white matter; Bayley-III, Bayley Scales of Infant and Toddler Development, third edition; CS, composite score; CP, cerebral palsy.

*Moderately/severely abnormal MRI defined as moderate/severe BGT score and/or absent PLIC and/or severe WM score.

**Normal outcome defined as survival without cerebral palsy with gross motor function classification system (GMFCS) level 3-5 or Bayley-III cognitive and/or motor composite score <85.