**Appendices A:**

**Table A.1 Comparison of perinatal characteristics of neonates in our cohort who had mild HIE and those treated with therapeutic hypothermia.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | TH | Mild HIE (no TH) | p-value |
| Number of patients | 24 | 13 |  |
| Median Gestation age (weeks) (range) | 41.1 (39.1 – 42.0) | 41.4 (38.9 – 42.4) | 0.89 |
| Median birthweight (grams) (range) | 3548 (2550 – 4620) | 3150 (2380 – 4960) | 0.12 |
| Sentinel events (%) | 5/24 (21) | 3/10 (30) | 1.00 |
| Median Apgar score at 10 minutes (range) | 6 (3 - 9) | 9 (5 - 10) | **0.000\*** |
| Respiratory support requirement (%) | 19/24 (79) | 4/13 (31) | **0.006\*** |
| Chest compression (%) | 4/23 (17) | 2/13 (15) | 1.00 |
| Median worst pH (range) | 6.91 (6.7 – 7.2) | 6.97 (6.86 - 7.28) | 0.19 |
| Median worst base deficit (range) | -16.6 (-25.9 - -1.4) | -13.7 (-21.3 - -4.7) | 0.25 |
| Seizures (%) | 17/24 (71) | 1/13 (7.7) | **0.000\*** |

The Fisher’s Exact test was used for categorical data and the Mann Whitney U test for continuous variables. \*Represents p <0.05 indicating significance. TH – therapeutic hypothermia. Sentinel events defined as either; uterine rupture, placental abruption, cord prolapse or shoulder dystocia or a combination of events. Worst pH and base deficit values recorded was either arterial/venous cord or admission venous/capillary blood gas result and when both were available the worst value was recorded.

**Table A.2 Individual perinatal characteristics of neonates in our cohort.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Reference | Gestational  Age (weeks) | Birth weight (grams) | TH (hours) | Apgar at 10 minutes | Respiratory support (Y/N) | Chest compressions (Y/N) | Worst pH (first hour) | Worst base deficit (first hour) | Seizure (Y/N) |
| 1 | 40.42 | 3770 | Y (72) | 4 | Y | Y | 6.82 | -18.2 | N |
| 2 | 41.71 | 3450 | Y (101.15) | 7 | Y | N | 6.81 | -18.8 | N |
| 3 | 40.57 | 3820 | Y (72) | 4 | Y | Y | 6.77 | -21.6 | Y |
| 4 | 40.14 | 2550 | Y (72) | 7 | Y | N | 6.9 | -16 | Y |
| 5 | 41.71 | 3370 | Y (72) | 5 | Y | N | 6.92 | -14 | Y |
| 6 | 41.14 | 3810 | Y (72) | 9 | Y | N | 7 | -16.4 | Y |
| 7 | 39.57 | 3200 | Y (72) | 8 | Y | N | 6.9 | -15.4 | Y |
| 8 | 41.14 | 3930 | Y (72) | 5 | Y | N | 6.87 | -17.3 | Y |
| 9 | 38.86 | 2760 | N | 9 | N | N | 7.11 | -14.4 | N |
| 10 | 41.43 | 4960 | N | 10 | N | N | 7.05 | -10.9 | N |
| 11 | 41.57 | 3930 | Y (72) | 6 | Y | N | 7 | -17.6 | Y |
| 12 | 40.28 | 3170 | Y (72) | 6 | Y | N | 6.9 | -16.6 | Y |
| 13 | 39.14 | 2620 | Y (72) | 6 | N | N | 7.2 | -12 | N |
| 14 | 40.71 | 4400 | Y (85) | 7 | Y | Y | 7.03 | -16.5 | Subclinical |
| 15 | 40.30 | 3220 | Y (72) | 7 | Y | - | 7.06 | -18.1 | Y |
| 16 | 42.00 | 4470 | Y (72) | 7 | N | N | 6.91 | -16.9 | N |
| 17 | 41.42 | 4235 | Y (72) | 7 | Y | N | 6.7 | -25.9 | N |
| 18 | 39.14 | 3340 | N | 7 | N | Y | 7.15 | -7.2 | N |
| 19 | 39.86 | 2820 | N | 10 | N | N | 6.96 | -15.9 | N |
| 20 | 41.43 | 4045 | N | 5 | Y | N | 6.91 | -20.9 | N |
| 21 | 42.43 | 2380 | N | 10 | N | N | 6.97 | -12 | N |
| 22 | 41.71 | 3360 | N | 8 | N | N | 6.9 | -18.3 | N |
| 23 | 41.71 | 3150 | N | 7 | N | N | 7.09 | -13 | y |
| 24 | 41.43 | 2540 | N | 7 | Y | N | - | - | N |
| 25 | 40.14 | 3930 | N | 9 | Y | N | 6.97 | -16.5 | N |
| 26 | 41.00 | 3520 | N | 10 | N | N | 6.86 | -21.3 | N |
| 27 | 40.00 | 3356 | Y (50) | 5 | N | N | 6.74 | -20.5 | N |
| 28 | 40.28 | 2690 | Y (96) | 6 | Y | Y | 7.12 | -1.4 | Y |
| 29 | 41.14 | 3560 | Y (72) | 9 | N | N | 6.82 | -20.4 | N |
| 30 | 40.57 | 3550 | Y (72) | 8 | Y | N | 7.05 | -13.1 | Y |
| 31 | 42.29 | 3470 | N | 9 | Y | Y | 7.28 | -4.7 | N |
| 32 | 41.57 | 3546 | Y (72) | - | N | N | 7.25 | -6.4 | Y |
| 33 | 41.14 | 3569 | Y (72) | 7 | Y | N | 6.87 | -19.3 | Y |
| 34 | 41.00 | 4620 | Y (72) | 3 | Y | N | 7.03 | -16 | Y |
| 35 | 42.00 | 3460 | Y (72) | 5 | Y | N | 7 | -9.3 | Y |
| 36 | 39.29 | 3140 | N | 9 | N | N | 6.93 | -11.2 | N |
| 37 | 41.43 | 3240 | Y (72) | 3 | Y | N | 7.14 | -8.4 | Y |

TH – therapeutic hypothermia; n/a – not available; N – no; Y – yes. Worst pH and base deficit values recorded was either arterial/venous cord or admission venous/capillary blood gas result and when both were available the worst value was recorded.

**Table A.3 The Median duration of CTG and the mode of deliveries for each CTG group.**

|  |  |  |
| --- | --- | --- |
| CTG group | Median duration of CTG trace (hours) | Mode of delivery |
| 1 | 3.2 (IQR, 2.3 – 4.1) | 3 NVD  3 Instrumental  4 EMCS |
| 2 | 5.2 (IQR, 1.1- 10.1) | 3 NVD  10 Instrumental  8 EMCS |
| 3 | 7.2 (IQR, 3.4 – 10.6) | 6 EMCS |

EMCS: emergency caesarean section, IQR: interquartile range, NVD: natural vaginal delivery.

**Table A.4 Hypoxia types identified on CTG, MRI injury patterns and neurodevelopmental outcomes for infants in the cohort.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Group | Reference | Type of hypoxia on CTG | TH  (Y/N) | HIE grade | MRI injury pattern | Neurodevelopmental outcome |
| 1 | **1** | Chorioamnionitis with Gradually evolving and subacute hypoxia. Maternal pulse at end. | Y | 3 | Total brain injury | Adverse |
| **2** | Chronic hypoxia | Y | 3 | Peripheral injury | Normal |
| **3** | Sinusoidal pattern – antepartum hypovolemia/ anemia | Y | 3 | Total brain injury | Normal |
| **4** | Chronic hypoxia with acute hypoxia at the end | Y | 2 | Peripheral injury | Adverse |
| **5** | Chronic hypoxia | Y | 3 | Total brain injury | Adverse |
| **6** | Chronic hypoxia | Y | 2 | Total brain injury | Adverse |
| **7** | Chronic hypoxia with acute hypoxia at the end | Y | 2 | No injury | Normal |
| **8** | Chronic hypoxia with acute hypoxia at the end | Y | 2 | No injury | Normal |
| **9** | Chronic hypoxia | N | 1 | n/a | Normal |
| **10** | Chronic hypoxia | N | 1 | n/a | Normal |
| 2 | **11** | Subacute hypoxia | Y | 3 | Peripheral injury | Normal |
| **12** | Gradually evolving hypoxia with acute hypoxia at the end | Y | 3 | Peripheral injury | Normal |
| **13** | Gradually evolving hypoxia with maternal pulse at the end | Y | 1 | Peripheral injury | Adverse |
| **14** | Gradually evolving hypoxia | Y | 0 | No injury | Normal |
| **15** | Gradually evolving hypoxia | Y | 3 | No injury | Normal |
| **16** | Subacute hypoxia | Y | 2 | No injury | Normal |
| **17** | Subacute hypoxia | Y | 1 | No injury | Normal |
| **18** | Gradually evolving hypoxia | N | 1 | n/a | Normal |
| **19** | Gradually evolving hypoxia with acute hypoxia at the end | N | 1 | n/a | Normal |
| **20** | Subacute hypoxia with acute hypoxia at the end | N | 1 | n/a | Normal |
| **21** | Gradually evolving hypoxia | N | 1 | n/a | Normal |
| **22** | Gradually evolving hypoxia | N | 1 | n/a | Normal |
| **23** | Gradually evolving hypoxia | N | 3 | Peripheral injury | Adverse |
| **24** | Subacute hypoxia with acute hypoxia at the end | N | 1 | n/a | Normal |
| **25** | Subacute hypoxia | N | 1 | n/a | Normal |
| **26** | Subacute hypoxia | N | 1 | n/a | Normal |
| **27** | Gradually evolving hypoxia with subacute hypoxia at the end | Y | 2 | n/a | n/a |
| **28** | Gradually evolving hypoxia with acute hypoxia at the end | Y | 2 | Peripheral injury | Normal |
| **29** | Gradually evolving hypoxia with subacute and acute hypoxia at the end | Y | 1 | No injury | Normal |
| **30** | Gradually evolving hypoxia with subacute and acute hypoxia at the end | Y | 3 | No injury | n/a |
| **31** | Gradually evolving hypoxia with subacute and acute hypoxia at the end | N | 1 | n/a | Normal |
| 3 | **32** | Acute hypoxia | Y | 3 | No injury | Normal |
| **33** | Acute hypoxia | Y | 2 | BGT with cortical injury | Adverse |
| **34** | Acute hypoxia | Y | 2 | BGT injury | Normal |
| **35** | Acute hypoxia | Y | 2 | No injury | Normal |
| **36** | Acute hypoxia | N | 1 | n/a | Normal |
| **37** | Chorioamnionitis with acute hypoxia at the end | Y | 3 | BGT injury | Adverse |

Group 1 - suspected chronic hypoxia or other antenatal injury; group 2 - intrapartum gradually evolving or subacute hypoxia; group 3 - intrapartum acute hypoxic injury. HIE grade/encephalopathy score: 0 - normal, 1 - mild, 2- moderate, 3- severe. BGT - to basal ganglia and thalamic injury pattern; TH – therapeutic hypothermia; n/a – not available; N – no; Y – yes.

**Table A.5 MRI components for 4 regions of the brain and allocated injury patterns of infants in each of the CTG groups.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| CTG Group | Reference | Non-hypoxic Injury on CTG | MRI age | MRI scores | | | | MRI injury pattern |
| **PLIC** | **BGT** | **WM** | **CORTEX** |
| 1 | **1** | Chorioamnionitis | 12 | 2 | 3 | 3 | 3 | Total brain injury |
| **2** |  | 12 | 0 | 0 | 1 | 0 | Peripheral injury |
| **3** | Antepartum hypovolemia | 9 | 1 | 0 | 3 | 3 | Total brain injury |
| **4** |  | 15 | 0 | 0 | 3 | 1 | Peripheral injury |
| **5** |  | 6 | 1 | 2 | 3 | 3 | Total brain injury |
| **6** |  | 14 | 2 | 2 | 3 | 0 | Total brain injury |
| **7** |  | 18 | 0 | 0 | 0 | 0 | No injury |
| **8** | (Prostaglandin induced) | 27 | 0 | 0 | 0 | 0 | No injury |
| 2 | **11** |  | 8 | 0 | 0 | 3 | 3 | Peripheral injury |
| **12** |  | 10 | 0 | 0 | 1 | 0 | Peripheral injury |
| **13** |  | 8 | 0 | 0 | 1 | 0 | Peripheral injury |
| **14** |  | 10 | 0 | 0 | 0 | 0 | No injury |
| **15** |  | 8 | 0 | 0 | 0 | 0 | No injury |
| **16** |  | 14 | 0 | 0 | 0 | 0 | No injury |
| **17** |  | 9 | 0 | 0 | 0 | 0 | No injury |
| **23** | Chorioamnionitis | 7 | 0 | 0 | 3 | 2 | Peripheral injury |
| **28** |  | 10 | 0 | 0 | 2 | 1 | Peripheral injury |
| **29** |  | 14 | 0 | 0 | 0 | 0 | No injury |
| **30** |  | 7 | 0 | 0 | 0 | 0 | No injury |
| 3 | **32** |  | 6 | 0 | 0 | 0 | 0 | No injury |
| **33** |  | 9 | 2 | 3 | 0 | 2 | BGT with cortical injury |
| **34** |  | 6 | 0 | 2 | 0 | 0 | BGT injury |
| **35** |  | 60 | 0 | 0 | 0 | 0 | No injury |
| **37** | Chorioamnionitis | 6 | 1 | 2 | 0 | 0 | BGT injury |

Group 1 - suspected chronic hypoxia or other antenatal injury; group 2 - intrapartum gradually evolving or subacute hypoxia; group 3 intrapartum acute hypoxic injury; BGT - to basal ganglia and thalami; PLIC - Posterior limb of internal capsule; WM - white matter.

Key for scoring of T1 and T2 weighted neonatal MRI scans adapted from Rutherford et al., 2016.22

**PLIC:** 0 – normal, 1 – signal intensity is asymmetrical or reduced and 2 – severe injury with abnormal or reversed signal intensity bilaterally.

**BGT:** 0 – normal, 1 – mild injury (focal signal intensity abnormality), 2 – moderate injury (multifocal signal intensity abnormality) and 3 – severe injury (widespread signal intensity abnormality).

**WM:** 0 – normal, 1 – mild injury to periventricular WM only depicted by long T1 and T2 signal, 2 – subcortical WM injury depicted by long T1 and T2, or focal infarction or focal punctate lesion and, 3 – severe widespread injury depicted by long T1 and T2 ± hemorrhage ± infarction.

**Cortex:** 0 – normal, 1 – mild injury (1-2 sites of cortical highlighting/ decreased T1), 2 – moderate injury (3 sites involved), 3 – severe injury (≥3 sites involved).

**Table A.6 Neurodevelopmental outcomes for infants in each CTG group.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Group | Reference | BSID III | | | | | | | | | | | | Outcome | | | Comments | | |
| Y/N | Age (years) | Cognitive | | | Language | | | Motor | | |  | | | |  | | |
| 1 | **1** | Y | 3.21 | 55 | | | 47 | | | 46 | | | Adverse | | | | Cerebral palsy GMFCS 5 | | |
| **2** | Y | 2.5 | 100 | | | 94 | | | 100 | | | Normal | | | |  | | |
| **3** | N | 3.75 | Clinical review | | | | | | | | | Normal | | | |  | | |
| **4** | Y | 3.25 | 95 | | | 100 | | | 82 | | | Adverse | | | |  | | |
| **5** | Y | 1.5 | 55 | | | 55 | | | 55 | | | Adverse | | | | Cerebral palsy GMFCS 5 | | |
| **6** | Y | 2 | 55 | | | 55 | | | 55 | | | Adverse | | | | Cerebral palsy GMFCS 4 | | |
| **7** | N | 0.58 | Clinical review | | | | | | | | Normal | | | | |  | | |
| **8** | Y | 2.8 | 120 | | | 115 | | | 100 | | | Normal | | | |  | | |
| **9** | N | 2 | Clinical review | | | | | | | | Normal | | | | |  | | |
| **10** | N | 2 | Clinical review | | | | | | | | Normal | | | | |  | | |
| 2 | **11** | N | 3.92 | ASQ-3 assessment | | | | | | | | Normal | | | | |  | | |
| **12** | Y | 2.99 | 110 | | | 109 | | | 103 | | | Normal | | | |  | | |
| **13** | Y | 2.76 | 55 | | | 47 | | | 100 | | | Adverse | | | |  | | |
| **14** | Y | 1.55 | 85 | | | 74 | | | 85 | | | Normal | | | |  | | |
| **15** | N | 1.25 | Clinical review | | | | | | | | Normal | | | | |  | | |
| **16** | N | 0.75 | Clinical review | | | | | | | | Normal | | | | |  | | |
| **17** | Y | 2.42 | 100 | | 94 | | 112 | | | | Normal | | | | |  | | |
| **18** | Y | 3.25 | 145 | | | 121 | | | 115 | | | Normal | | | |  | | |
| **19** | Y | 3.2 | 95 | | | 86 | | | 100 | | | Normal | | | |  | | |
| **20** | Y | 3.2 | 145 | | | 118 | | | 112 | | | Normal | | | |  | | |
| **21** | Y | 3.29 | 135 | | | 124 | | | 115 | | | Normal | | | |  | | |
| **22** | N |  | | Clinical review | | | | | | | | | Normal | | |  | | |
| **23** | Y | 3.04 | 75 | | | 65 | | | 46 | | | Adverse | | | |  | | |
| **24** | N |  | | Clinical review | | | | | | | | | Normal | | |  | | |
| **25** | N | 3.75 | Clinical review | | | | | | | | Normal | | | | | Improving ASD | | |
| **26** | N |  | | Clinical review | | | | | | | | | Normal | | |  | | |
| **28** | Y | 2.27 | | 105 | 109 | | | 107 | | | Normal | | | |  | | |
| **29** | Y | 2 | | 100 | 100 | | | 103 | | | Normal | | | |  | | |
| **31** | N |  | | Clinical review | | | | | | | | | Normal | | |  | | |
| 3 | **32** | Y | 0.42 | 100 | | | 100 | | | 100 | | | Normal | | | |  | | |
| **33** | Y | 3.47 | 55 | | | 55 | | | 55 | | | Adverse | | | |  | | |
| **34** | Y | 2.53 | 100 | | | 89 | | | 91 | | | Normal | | | |  | | |
| **35** | N | 3.42 | Clinical review | | | | | | | | Normal | | | | |  | | |
| **36** | N |  | | Clinical review | | | | | | Normal | | | |  | | |
| **37** | Y | 2.88 | | 55 | 55 | | 55 | | | Adverse | | | | Cerebral palsy GMFCS 5 | | |

Group 1 - suspected chronic hypoxia or other antenatal injury; group 2 - intrapartum gradually evolving or subacute hypoxia; group 3 intrapartum acute hypoxic injury. ASD – autism spectrum disorder; ASQ-3- Ages and Stages-III questionnaire; BGT - basal ganglia and thalami; BSID-III - Bayley Scales of Infant Development-III; GMFCS - Gross Motor Function Classification System; Y – yes; N – no.