Does the Use of Hypothermia Therapy Improve Outcomes for Newborns with Hypoxic Ischemic Encephalopathy?

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**Summary statement:**

Perinatal asphyxia leading to hypoxic ischemic encephalopathy (HIE) is a major cause of death and disability worldwide. There are no specific treatments proven to decrease brain damage from HIE. Experimental studies have demonstrated that if the perinatal asphyxia is severe, there may be immediate primary neuronal death that is related to primary energy failure. After a latent period of at least six hours, there is a secondary phase leading to delayed neuronal death. The delayed phase is associated with encephalopathy. (1-3) Deep hypothermia has been shown to be valuable for neuroprotection during cardiac arrest for open-heart and neurosurgical procedure. Hypothermia therapy may modify cells programmed for apoptosis, leading to their survival. (4) Two methods are being evaluated in newborn infants with HIE: whole body cooling and selective head cooling. Rationale for selective head cooling is to minimize the adverse effects of systemic cooling. Relevant studies were identified from the Cochrane database, PubMed (using the Mesh terms (“Infant, Newborn” and “Hypoxic ischemic encephalopathy” and “hypothermia”), Web of Knowledge (using topic terms (“ischemic encephalopathy” and “cooling or hypothermia”) and Trip database (using terms “hypoxic-ischemic encephalopathy” and “cooling or hypothermia”). The methodological quality of the studies was assessed according to whether they used randomization and blinding to the intervention and on the basis of completeness of follow-up.

**Clinical Bottom Line:**

There is sufficient evidence to support the use of hypothermia therapy in infants with moderate and severe hypoxic ischemic encephalopathy resulting in clinical and statistical reduction in the composite outcome of mortality and degree of neurodevelopmental disability at 18 months of age. In addition there is sufficient evidence that hypothermia therapy decreases mortality, without increasing major neurodevelopmental disability in survivors. (5-10)

Further studies are needed to look at to better define the ideal cooling temperature, clarify the interaction between disease severity and treatment effect and method of hypothermia therapies. In addition, further studies are needed to evaluate the impact of hypothermia therapy on HIE and neurodevelopment beyond 18 months of age including cognitive and adaptive behavioral function, speech and language disorders, and attention and psychosocial health. (11-12)

**Summary of Studies Evaluated (5-10):**

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| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Enrollment criteria | Method | Duration of cool | N | Time of Follow-up | Results | Notes |
| Jacobs et al (2008)*Cochrane* | <6hpH <7.1, BE >12Apgar <5 at 10’Clinical enceph | WBC, SHC | >48 h33.5-34.5°C rectal | 8 RCT327 (H)330 (N) | 18 mth | Death or severe disability:RR 0.76\*; NNT=7Mortality:RR 0.74\*; NNT=11Severe neuromotor disability:RR 0.68\*Adverse effects:Bradycardia, thrombocytopenia | -Ongoing studies not included in meta-analysis |
| Azzopadi et al (2009)*TOBY* | <6 hpH <7.0, BE>16 Apgar <5 at 10’Abnl aEEG | WBC | 72h33-34°C rectal | 163 (H)162 (N)LTF:1 (H)1 (N) | 18 to 21 mth | Death or severe disability:53% (N) vs 45% (H); NNT=13Mortality:27% (N) vs 26% (H); NNT=72Survival without neuromotor disability:28% (N) vs 44% (H)\*; NNT=6Multiple neurodevelopmental disabilities:30% (N) vs 19% (H)\*; NNT=9Cerebral palsy:41% (N) vs 28% (H)\*; NNT=7 | -Analyzed according to intention to treat-Neurodevelopmental assessments at 18 months may not reliably predict later outcomes |
| Simbruner et al (2010) *neo.nEURO* | <6hpH <7.0, BE>16Apgar <5 at 10’Abnl aEEG | WBC | 72 h33-34°C rectal | 62 (H)63 (N)LTF:9 (H)5 (N) | 18 to 21 mth | Death or severe disability:83% (N) vs 51% (H)\*; NNT=4Severe neuromotor disability:57% (N) vs 21% (H)\*; NNT= 3Disabling cerebral palsy:48% (N) vs 13% (H)\*; NNT = 4 | -Analyzed using OR and did not use intention to treat-Large percentage of mortality-Neurodevelopmental assessments at 18 months may not reliably predict later outcomes |
| Jacobs et al (2011) | <6 hpH<7.0, BE >12Apgar <5 at 10’Clinical enceph | WBC | 72h33-34°C rectal | 110 (H)111 (N)LTF:3 (H)10 (N) | 18 to 21 mth | Death or severe disability:66% (N) vs 52% (H)\*; NNT=7Mortality:39% (N) vs 25% (H)\*; NNT=7Survival without neuromotor disability:23% (N) vs 40% (H)\*; NNT=7Multiple neurodevelopmental disabilities:42% (N) vs 35% (H); NNT=14Cerebral palsy:28% (N) vs 27% (H); NNT=4 | -Analyzed not according to intention to treat-Neurodevelopmental assessments at 18 months may not reliably predict later outcomes |
| Shankaran et al (2008) | <6hpH<7.0, BE>16Clinical enceph | WBC | 72h33-33.5°C esophageal | 102 (H)106 (N) |  | Acute outcome looking at adverse effects: Not statistically or clinically significant  | -Transient decreases in esophageal temperature to <32˚C |
| Sarkar et al (2009) | <6hpH <7.0, BE >16Apgar <5 at 10’Abnl aEEG or clinical enceph | WBC vs SHC | 72 h34-35°C(esophageal in WBC group; rectal in SHC group) | 28 (WBC)31 (SHC) | 4, 8, 12, 24, 48, 72 hours | Acute outcome looking at adverse effects: Not statistically or clinically significant  | -Not randomized |

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