From: Effect of Depth and Duration of Cooling on Deaths in the NICU Among Neonates With Hypoxic Ischemic Encephalopathy: A Randomized Clinical Trial

Hypothesis & Study Design

• Deeper (32°C vs 33.5°C) and longer (120 hrs vs. 72 hrs) could improve the efficacy of TH and is as safe as the current standard of care (33.5°C for 72 hrs)
• Factorial design – 4 groups
  – 33.5°C x 72 hrs
  – 33.5°C x 120 hrs
  – 32°C x 72 hrs
  – 32°C x 120 hrs
Study Design

• Sample size based on assuming the following rates of Death or Disability
  – 33.5°C x 72 hrs – 45%  \((\text{what was previously observed in the RCTs})\)
  – 33.5°C x 120 hrs – 30%
  – 32°C x 72 hrs – 30%
  – 32°C x 120 hrs – 25%
Interim Analyses

• Done to ensure safety – look for increased risk of death or morbidity in study arms compared to standard of care arm

• After 8 interim analyses trial stopped due to concern for safety and low likelihood of demonstrating a benefit compared to standard of care arm

• Only 364 of planned 726 were enrolled and randomized
Outcome

• Death in each group
  – 33.5°C x 72 hrs – 7% (*much less than anticipated*)
  – 33.5°C x 120 hrs – 16%
  – 32°C x 72 hrs – 14%
  – 32°C x 120 hrs – 17%

• Death was observed to occur less frequently in the standard arm compared to previous RCTs
• Would have <2% chance of showing deeper and longer treatment reduced the risk of death
• Increased report of death due to multi-organ failure
• Multiple safety concerns
During the intervention there was an increase in the number of patients with arrhythmias that required treatment.
Increased PPHN, iNO and ECMO in 32°C vs 33.5°C group

Increased Arrhythmia in 120 hrs vs 72 hours

Increased frequency of sustained Bradycardia in 32°C vs 33.5°C
Take Home Points

• Always include the current standard of care when testing a variation of the current intervention
  – Mortality decreased from prior RCTs – patient selection, improved clinical care
  – Must prove variation does not cause harm

• Not everything that works in animals works in humans
Take Home Points, Cont.

• Maximal point of effectiveness for hypothermia?
  – Colder and deeper may confer no additional benefit and may increase risk
  – Metabolism $\downarrow \approx 8\%$ for each $1^\circ\downarrow$ in body temp – perhaps further reduction is detrimental to cellular function

• Efficacy of Primary Outcome pending
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Figure Legend:
Survival for the Hypothermia Groups
Dotted lines represent day 3 (72 hours) and day 5 (120 hours).
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Figure Legend:
Mean (SD) Esophageal Temperatures During the Intervention Period