# Therapeutic Hypothermia for Preterm Infants 34-35 weeks Gestational Age with Neonatal Encephalopathy

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## Background and Aim

- Therapeutic hypothermia (TH)
  - Gold standard treatment of moderate and severe neonatal encephalopathy
  - Numerous centers provide TH to infants born at 36 weeks or more of gestation due to the lack of recommendations of TH in preterm infants at younger gestation
  - Our center has routinely provided TH for infants as young as 34 weeks gestation
- This study aims to evaluate the short-term outcomes and safety of TH in preterm infants at 34-35 weeks of gestation who received TH

## Methods

- Matched retrospective cohort study
- 20 preterm infants at 34-35 weeks of gestation who received TH and 40 infants at 36 weeks of gestation or more who received TH between the years 2015-2021.
- Case and controls were matched by Apgar score at 5 min, the worst base deficit on blood gas, and the worse neonatal encephalopathy score within a calendar year.

## Results

- Seven infants were cooled at 34 weeks gestation, and 13 were cooled at 35 weeks' gestation
- Short-term outcomes of preterm infants at 34-35 weeks of gestation who received TH were comparable with infants at 36 weeks or more of gestation who received TH regarding seizures, blood transfusions, subcutaneous fat necrosis, mortality and IVH (Table 1)
- These findings were consistent when short-term outcomes were adjusted for birthweight (Table 2)

## BWH Therapeutic Hypothermia Indication

- A. ≥ 34 weeks gestation

  AND

- B. Any one of the following:
  1) Sentinel event prior to delivery such as uterine rupture, profound bradycardia or cord prolapse
  2) Low Apgar scores → ≤ 5 at 10 minutes of life
  3) Prolonged resuscitation at birth → chest compressions and/or intubation and/or mask ventilation at 10 minutes
  4) Severe acidosis → pH ≤ 7.1 from cord or patient blood gas within 60 minutes of birth
  5) Abnormal Base Excess → ≤ - 10 mEq/L from cord or patient blood gas within 60 minutes of birth

  AND

- C. Any one of the following:
  1) Seizure or any clinical event concerning for seizure
  2) Neonatal encephalopathy (defined as the presence of abnormal neurological behavior on the Neonatal Encephalopathy Scale of ≥4)

## Table1. Clinical characteristics and outcomes of study population

| | 34-35 weeks gestation (n=20) | 36 weeks gestation or more (n=40) | p value |
|---|---|---|---|
| GA (week) [a] | 35.3 (34.5-35.5) | 39.5 (37.3-40.3) | <0.001 |
| Birthweight (gram) [b] | 2373.5 ± 715.9 | 3150.6 ± 663.0 | <0.001 |
| Male | 14 (70.0%) | 19 (47.5%) | 0.169 |
| Outborn | 5 (25.0%) | 12 (30.0%) | 0.919 |
| Maternal age (years) [b] | 32.7 ± 5.9 | 30.7 ± 5.0 | 0.171 |
| 5 min Apgar score [a] | 6.0 (3.5-7.0) | 6.0 (4.0-7.0) | 0.366 |
| Worst base deficit (mEq/L)[b] | 11.5 ± 6.5 | 10.5 ± 5.3 | 0.525 |
| Worst encephalopathy score [a] | 8.0 (6.0-11.0) | 6.0 (4.0-10.0) | 0.088 |
| Seizures | 2 (10.0%) | 6 (15.0%) | 0.893 |
| IVH | 6 (30.0%) | 4 (10.0%) | 0.111 |
| Blood transfusion | 7 (35.0%) | 10 (25.0%) | 0.613 |
| Subcutaneous fat necrosis | 1 (5.0%) | 1 (2.5%) | 1.000 |
| Mortality | 0 (0.0%) | 2 (5.0%) | 0.799 |

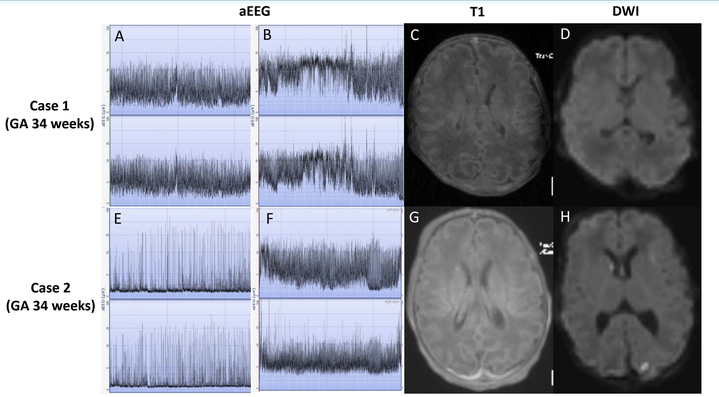
GA, gestational age; IVH, intraventricular hemorrhage.
Values are expressed as N (%) except [a] median (interquartile range) and [b] mean ± SD.

## Table2. Multivariate regression analyses for 34-35 weeks gestation cooled

| | adjOR* | 95% CI | | | | P value |
|---|---|---|---|---|---|---|
| Seizures | 1.012 | [ | 0.730 | , | 1.403 | ] | 0.943 |
| IVH | 1.254 | [ | 0.936 | , | 1.679 | ] | 0.127 |
| Blood transfusions | 0.936 | [ | 0.723 | , | 1.211 | ] | 0.607 |
| Subcutaneous fat necrosis | 0.911 | [ | 0.490 | , | 1.694 | ] | 0.765 |
| Mortality | 0.735 | [ | 0.401 | , | 1.348 | ] | 0.314 |

IVH, intraventricular hemorrhage.
*Adjusted for birthweight.

## Fig 1: MRI and aEEG of Case 1 (GA 34 weeks) and Case 2 (GA 34 weeks)




**Case 1**: Male infant was born at 34$^{+1}$ weeks of gestation by cesarean section for abnormal fetal heart tracing. Apgar scores at 1 and 5 minutes were 1 and 6. On blood gas analysis, worst pH was 6.76 and base deficit was 15.9 mEq/L. Neonatal encephalopathy score was 11. Therapeutic hypothermia was started at first day of life.
aEEG at first day of life showed discontinuous pattern (A) and was improved at 4$^{th}$ days after birth (B). MRI at 4$^{th}$ days after birth showed normal (C and D).

**Case 2:** Female infant was born at 34$^{+4}$ weeks of gestation by vacuum assisted vaginal delivery. Pregnancy was complicated by preterm labor and chronic placental abruption. Delivery was assisted via vacuum due to fetal bradycardia. Apgar scores at 1 and 5 minutes were 8 and 8. On blood gas analysis, worst pH was 7.07 and base deficit was 9.5 mEq/L. Neonatal encephalopathy score was 13. Therapeutic hypothermia was started at first day of life.
aEEG at first day of life showed burst suppression pattern (E) which was improved at 4th days after birth (F). MRI at 5$^{th}$ days after birth showed small amount of intraventricular hemorrhage within the lateral ventricles, left greater than right. There was several foci of T1 shortening within the periventricular white matter representing nonspecific areas of white matter injury (G). Also, there was small acute infarcts within the left occipital lobe and right caudate head (H).

Abbreviations: MRI, Magnetic resonance imaging; EEG, electroencephalogram.

## Conclusions

- TH in preterm infants at 34-35 weeks of gestation is feasible in our study population.
- Results of randomized controlled trials are still needed to confirm safety as well as efficacy at younger gestation.