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, IVH, blood transfusions, subc utaneous fat necrosis, brain injury on MRI, and mortality (Table 1)
- These findings were consistent when short-term outcomes were adjusted for birthweight (Table 2)

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
Neonatal encephalopathy stage			0.721
Mild to Moderate	19 (95.0%)	40 (100.0%)	
Severe	1 (5.0%)	0 (0.0%)	
Weeke total MRI score [a]	2.0 (1.0-6.0)	2.0 (0.0-5.0)	0.588
Weeke severity of brain injury			0.865
Normal (0 to 4)	14 (70.0%)	30 (75.0%)	
Mild (5 to 10)	3 (15.0%)	5 (12.5%)	
Moderate (11 to 15)	1 (5.0%)	3 (7.5%)	
Severe (>15)	2 (10.0%)	2 (5.0%)	
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
Brain injury on MRI	6 (30.0%)	10 (25.0%)	0.918
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

	OR	95% CI	P value	adjOR*	95% CI	P value
Seizure	0.908	[0.636 , 1.297]	0.599	1.012	[0.735 , 1.393]	0.943
IVH	1.377	[1.005 , 1.887]	0.051	1.254	[0.942 , 1.669]	0.127
Blood transfusions	1.116	[0.854 , 1.458]	0.426	0.936	[0.727 , 1.204]	0.607
Subcutaneous fat necrosis	1.188	[0.605 , 2.332]	0.618	0.914	[0.497 , 1.684]	0.775
Brain injury on MRI	1.058	[0.805 , 1.392]	0.686	1.012	[0.793 , 1.291]	0.923
Mortality	0.708	[0.362 , 1.384]	0.317	0.735	[0.406 , 1.331]	0.314

*Adjusted for birthweight
adjOR, adjusted odd ratio; CI, confidence interval; IVH, intraventricular hemorrhage.

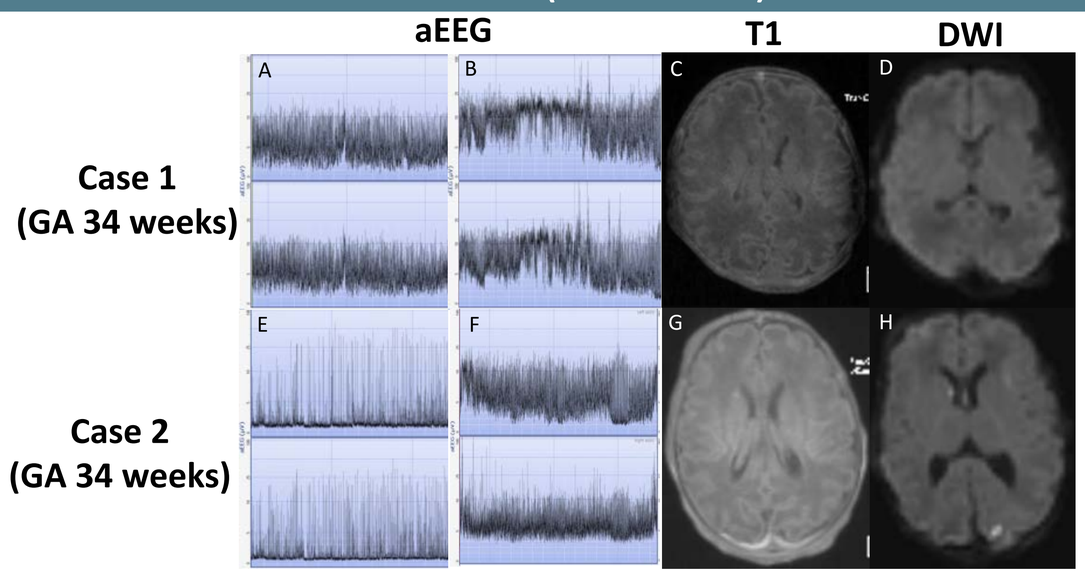
BWH Therapeutic Hypothermia Indication

- 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)

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.

Decreasing Time to NIRS Application for Infants Born < 28 Week's Gestation

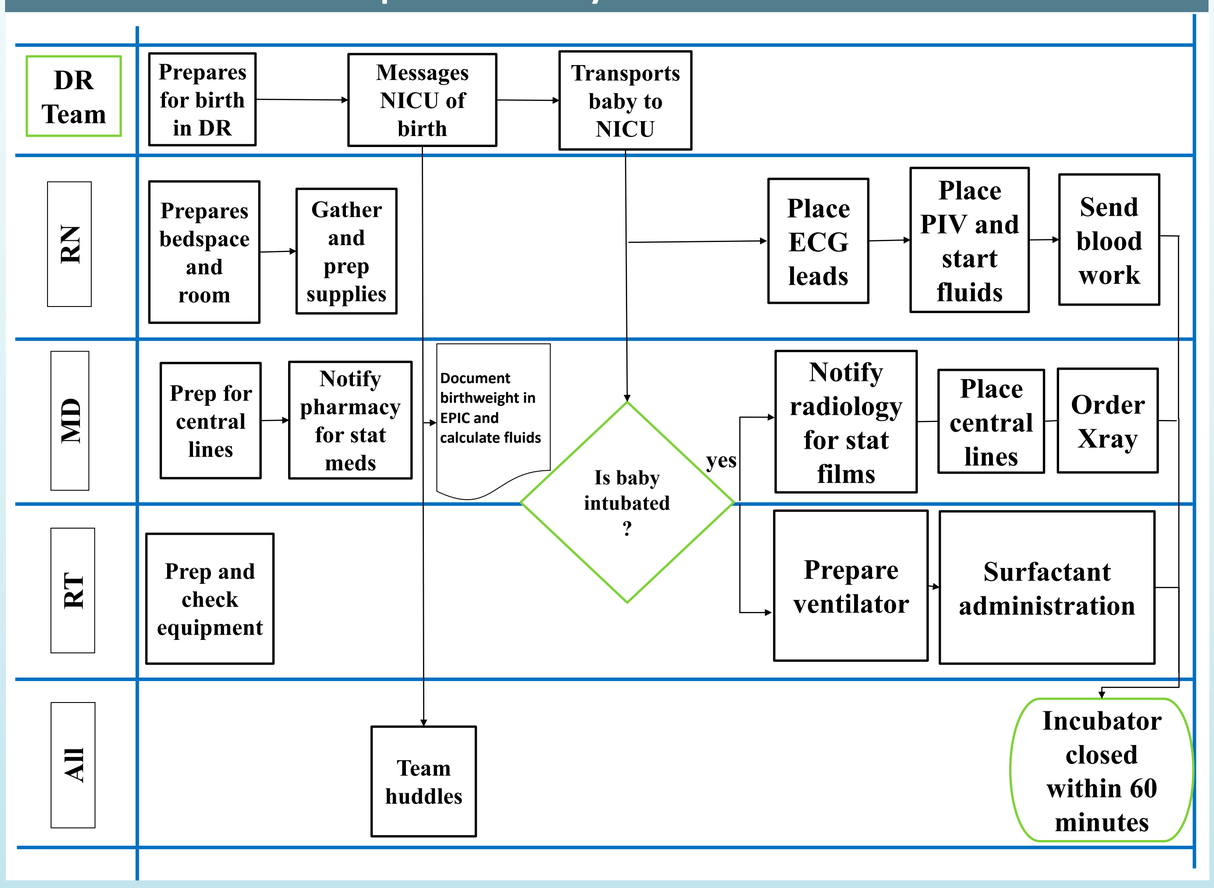
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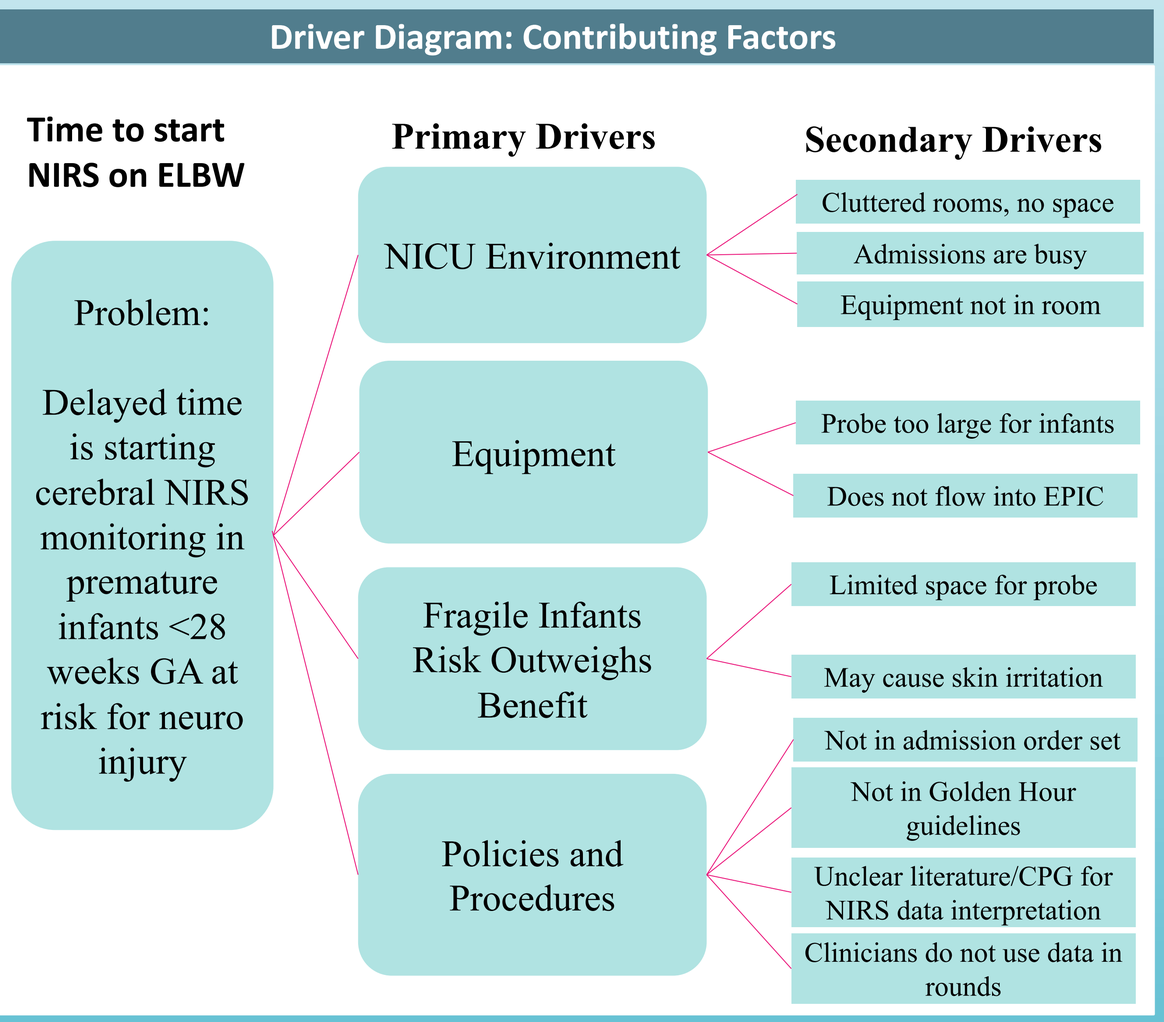
Problem Statement

- Near-Infra Red Spectroscopy (NIRS) has been used clinically in BWH NICU since January 2018. It is indicated in all neonates < 28 weeks gestation in the first 3 days of life. Early application of NIRS allows for early monitoring of cerebral oxygenation in the critical first few hours of life.

Process Map of Extremely Preterm Infant Admission



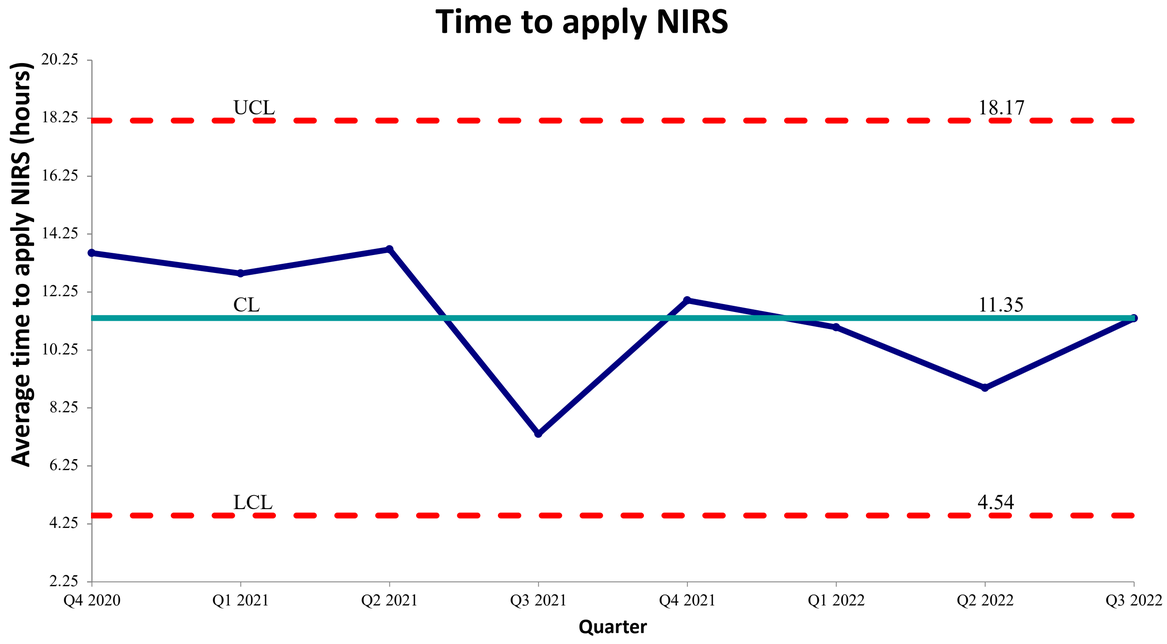
Driver Diagram: Contributing Factors



Diagnostic Data

- Barriers to using NIRS in extremely preterm infants in BWH NICU, Staff survey N=68 (21.5%)

Baseline Data



- BWH NICU, Infant born less than 28 weeks
- April. 2020 ~ Sep. 2022

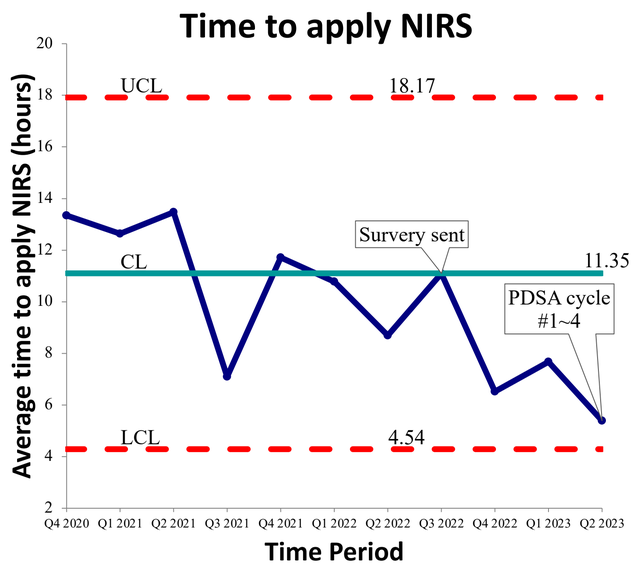
Aim Statement

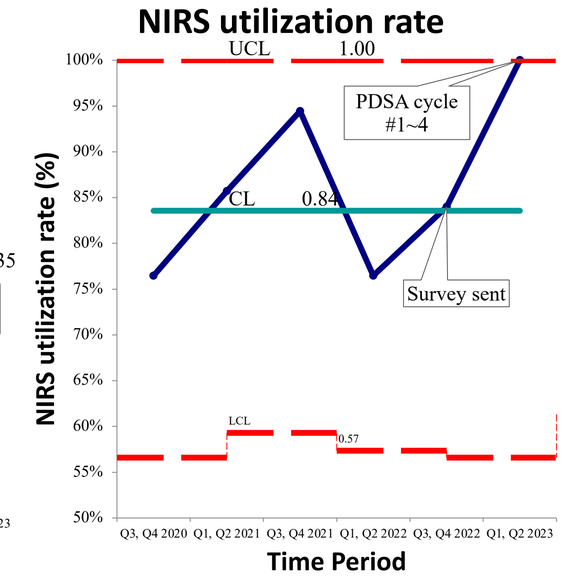
- To reduce the time for placement of NIRS probes on infants born at <28 weeks gestation from 11 hours to less than 2 hours after admission by July 30, 2023.

PDSA Plan

Date	Description of Intervention (PLAN/DO)	How will you track this intervention? (STUDY)	What happened with the test? (STUDY)	What are your next steps? (ACT)
4/2/2023	Nursing Email Re; NIRS application on admission	Nurses asking questions about utilization of NIRS	Email went out to entire nursing staff (~200 RNs)	Continued nursing education
4/5/2023	NIRS application signage at teaming stations	MD/LIP team ensuring NIRS monitoring is happening	NIRS application signage was posted at teaming stations	Talking about importance of NIRS for ELGA infants
5/15/23	NIRS application added to Golden hour checklist	Monitor checklist	NIRS application was successfully added into the golden hour checklist	Meet with team
5/25/23	NIRS info added to Unit Info screens	Monitor screens	NIRS info was added into the unit info screens	Update the NIRS info

Result





- The average time to apply NIRS was slowly decreased from 11 hours to about 5 hours after admission.

Conclusions

- Early application of NIRS is feasible and the time to apply NIRS following the birth of infants < 28 weeks could be reduced. Ongoing education regarding the value of NIRS and how to incorporate in clinical practice is needed.

Association between heart rate variability, brain injury, and hemodynamic medications in extremely preterm infants

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Background and Aim

- Heart rate variability (HRV)
  - The variation of time intervals between each subsequent heartbeat
  - Controlled by the autonomic nervous system, which may be affected by hypoxia and compromised blood flow
  - The association between HRV, brain injury, and hemodynamic medications in extremely preterm infants is not well established

- This study aims to evaluate the correlation between HRV, brain injury, and hemodynamic medications in extremely preterm infants

Methods

- Prospective observational study
- 24 Extremely preterm infants (<28 weeks gestation) admitted to Brigham and Women's Hospital NICU between July 2022 and June 2023
- The electrocardiogram data was captured by a real-time integrated neuromonitoring system
- The analysis involved the examination of the relative power of:
  - High-frequency (HF)
  - Low-frequency (LF)
  - Very-low-frequency (VLF)
- HF, LF, VLF are indicators of autonomic nervous system regulation of HRV
- HRV patterns in extremely preterm infants of below groups were compared:
  - Brain injury (n=10)
  - The use of a sedative agent (n=10)
  - The use of an inotrope agent (n=5)
  - Patent ductus arteriosus (PDA) treatment (n=10)

Table1. Clinical characteristics of study population

Characteristic	
Gestational age (weeks) [a]	26.7 (25.7-28.0)
Birthweight (gram) [a]	880.0 (665.0-1015.0)
Female gender	9 (37.5%)
Cesarean section	16 (66.7%)
1 min Apgar score[a]	4.5 (3.0-7.0)
5 min Apgar score[a]	7.5 (6.0-9.0)
Brain injury	10 (41.7%)
Sadative agent use	10 (41.7%)
Inotrope use	5 (20.8%)
PDA treatment	10 (41.7%)

Values are expressed as N (%) except [a] median (interquartile range)

Results

- This study included 24 extremely preterm infants
- Extremely preterm infants with brain injury had lower relative HF variability on day 3 of life (p=0.045) and higher relative VLF variability on day 3 of life (p=0.042) compared to the control
- The use of sedative agents was associated with higher relative HF variability on day 2 of life (p=0.016), lower relative LF variability on day 4 of life (p=0.039), and lower relative VLF variability on day 2 of life (p=0.024)
- The use of inotrope agents was associated with higher relative HF variability on day 2 of life (p<0.001), lower relative LF variability on day 3 of life (p=0.01), and lower relative VLF variability on day 2 of life (p=0.049)
- PDA treatment group was associated with higher relative HF variability on day 1 (p=0.041) and 2 of life (p=0.001), and lower relative VLF variability on day 2 of life (p=0.013)

Fig 1. Comparison of relative HF variability

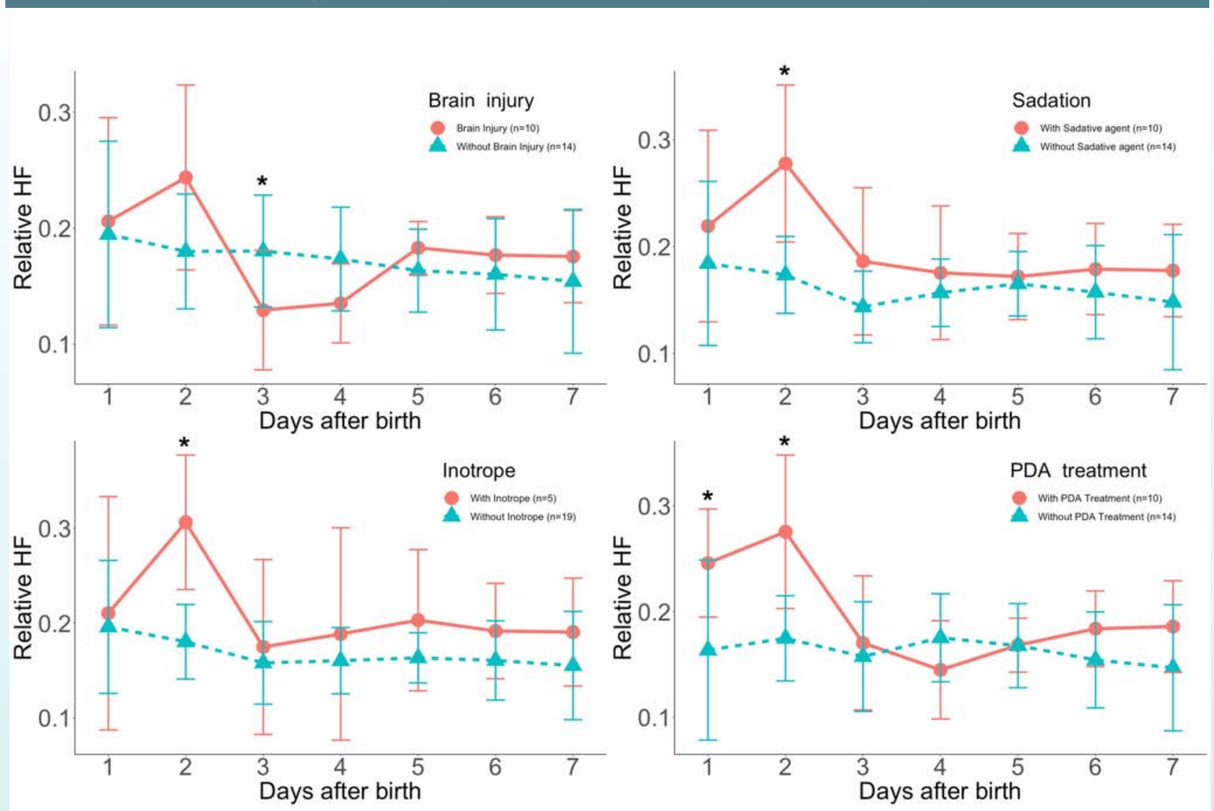


Fig 2. Comparison of relative LF variability

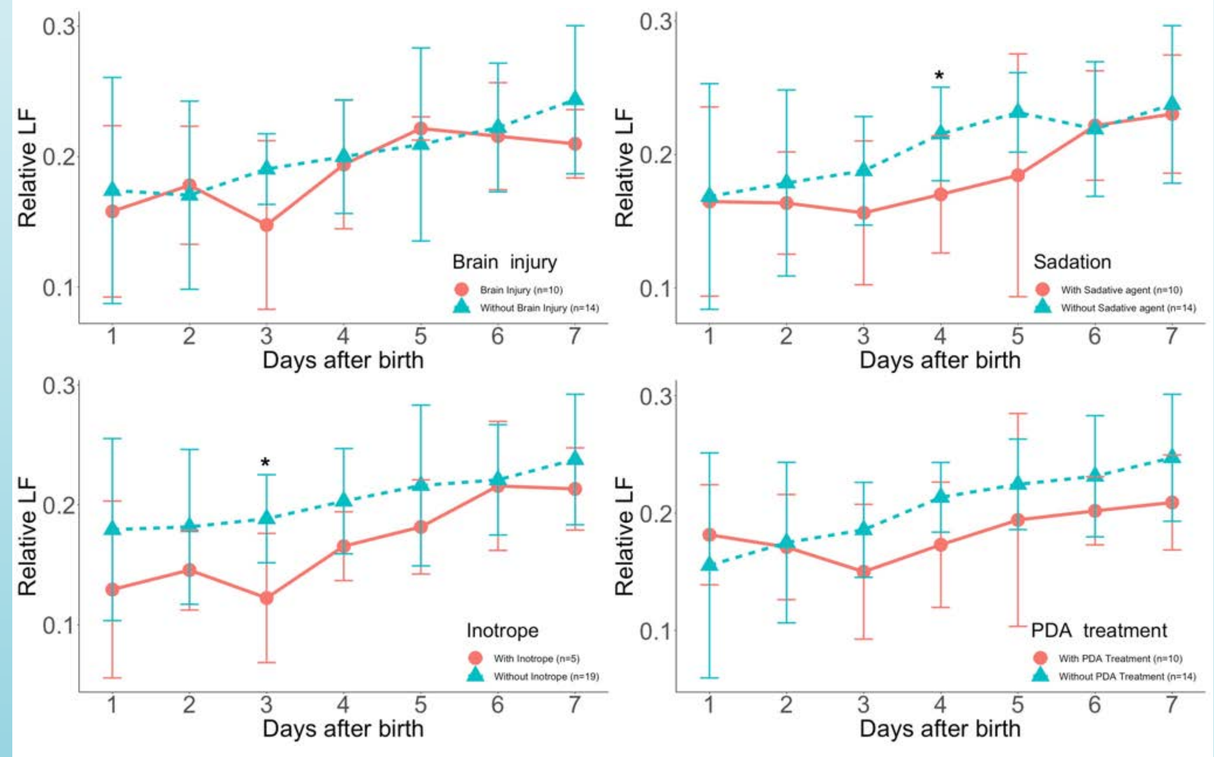
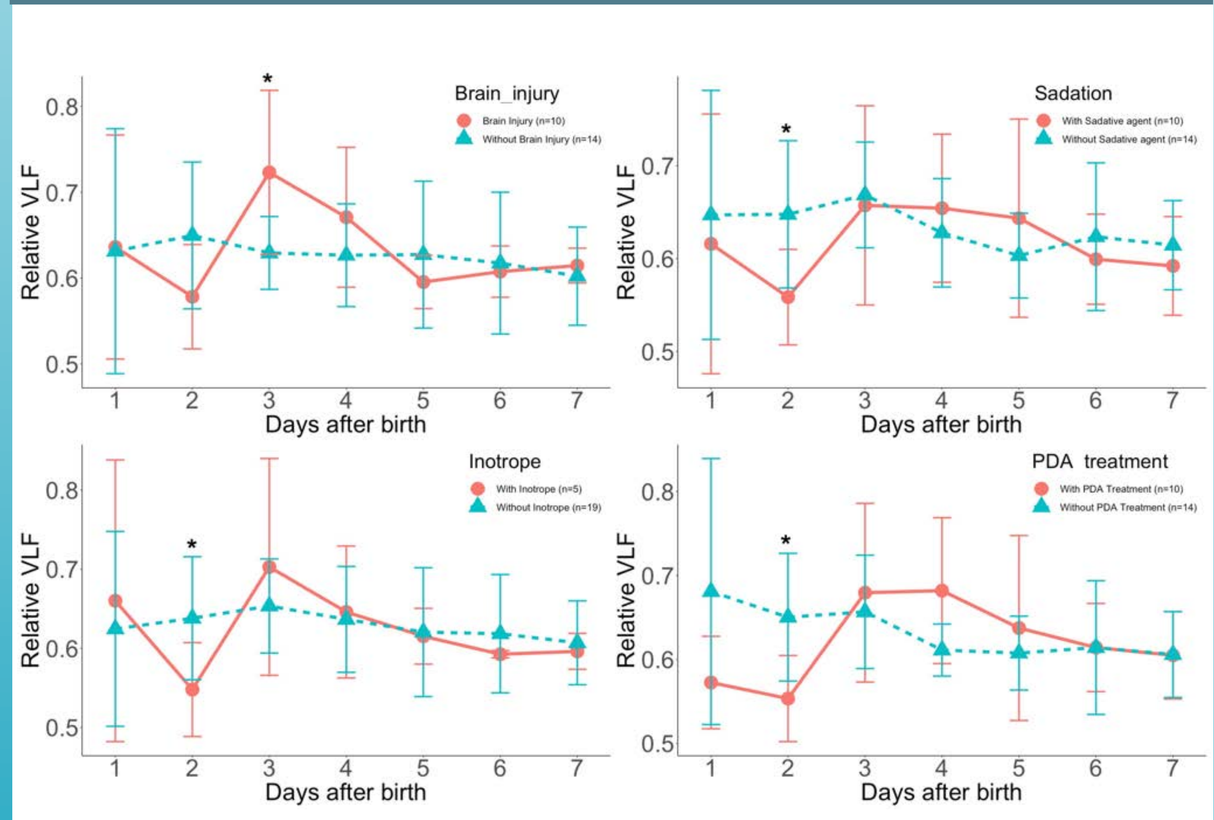


Fig 3. Comparison of relative VLF variability



Conclusions

- HRV components were different in extremely preterm infants with brain injury and hemodynamic medications significantly during the initial 3 days of life.
- This physiological biomarker holds promise for detecting infants who may benefit from additional neuroprotective treatments.
- These discoveries call for more extensive research involving a larger cohort of extremely premature infants.