Continuous transcutaneous carbon dioxide monitoring in infants with neonatal encephalopathy

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Background and Aim

- Increasing evidence suggests that hypocapnia is associated with brain injury on MRI and adverse neurodevelopmental outcome in infants treated with therapeutic hypothermia (TH) for neonatal encephalopathy (NE).
- Consequently, continuous carbon dioxide (CO_2) monitoring and avoiding extreme levels of CO_2 have the potential to improve neurologic outcome.
- **Our aim was to compare changes in transcutaneous CO_2 levels during hypothermia and rewarming between infants with and without brain injury on MRI in a cohort of infants with neonatal encephalopathy.**

Methods

- **This prospective observational trial** enrolled infants, who received TH for mild to severe NE between October 2019 and June 2022 at Brigham and Women's Hospital.
- The pattern of brain injury was evaluated according to an MRI grading system developed by Weeke et al. **We identified 2 groups of patients with and without any brain injury based on the assessment of MRI after rewarming.**
- **Transcutaneous CO_2 ($tcPCO_2$) data were captured by a real-time integrated neuromonitoring system** (CNS Monitor).

Hypothermia
- Phase 1: 0-12 h
- Phase 2: >12- 24h
- Phase 3: >24- 36h
- Phase 4: >36- 48h
- Phase 5: >48- 60h
- Phase 6: >60- until the end of cooling

Phase 7: Rewarming

Phase 8: After rewarming

1. The median of $tcPCO_2$ at each hour was calculated for each infant.
2. Using these values, we calculated the mean $tcPCO_2$ in each phase of TH for all infants.
3. The association between brain injury and $tcPCO_2$ at each phase was analyzed using linear mixed models with fixed effects for group, phase, and their interaction and adjustment for correlation among repeated measurements. Differences between groups at each phase was determined using estimated marginal means

Results

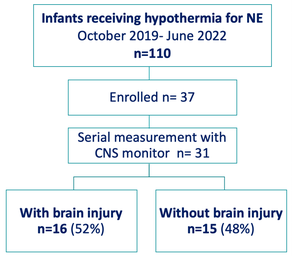


Table 1: Demographic and clinical data of the cohort

	With brain injury n= 16	Without brain injury n= 15	p values
Gestational age (week)	39 [37; 40]	40 [39; 40]	0.140
Birth weight (g)	3307 [2890; 3708]	3280 [2510; 3600]	0.358
Apgar 1 min	2 [2; 7]	1 [1; 3]	0.027
Apgar 5 min	8 [5; 8]	6 [5; 8]	0.232
Apgar 10 min	7 [6; 8]	8 [7; 8]	0.428
First postnatal pH	7.3 [7.2; 7.3]	7.3 [7.1; 7.3]	1.000
First postnatal BD (mmol/L)	8.8 [6.5; 11.7]	10.4 [6.9; 12.3]	0.560
First postnatal lactate (mmol/L)	8 [5; 9]	9 [6; 13]	0.220
Invasive ventilation, n (%)	5 (31 %)	4 (27 %)	1.000
Length of invasive ventilation (day)	1.0 [0.6; 17.0]	0.3 [0.06; 0.5]	0.003
Worst encephalopathy score within 12 h of life	7 [3; 11]	7 [4; 9]	0.870
Length of hospital stay (day)	7 [6; 11]	6 [5; 8]	0.401
MRI findings			
Age at brain MRI (day)	4 [4; 5]	4 [4; 4]	0.661
Total score of injury (min-max)	2 (2; 24)	n/a	n/a
Grey matter injury, n (%)	5 (31 %)	n/a	n/a
Cortex and white matter injury, n (%)	9 (56 %)	n/a	n/a
Cerebellar injury, n (%)	3 (19 %)	n/a	n/a

- 110 infants received TH during study period, out of those 37 infants were enrolled into this prospective study. Serial measurements from 31 patients were available for analysis. Sixteen (51.6%) infants had evidence of any brain injury on MRI.
- Integrated monitoring began at median 24 hours of life (min-max: 11-51) and ended at median 94 (min-max: 87-120) hours of life.

Trajectories of $tcPCO_2$ in infants with and without any brain injury

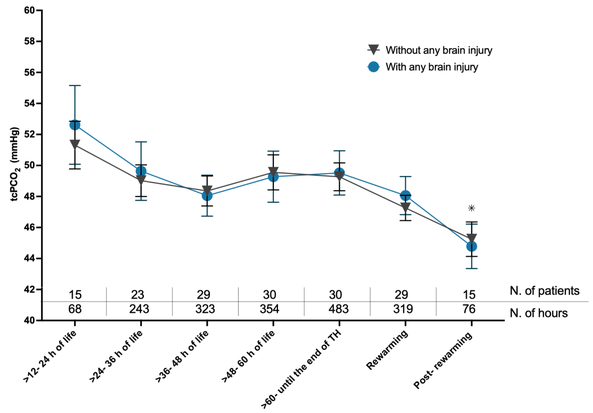


Figure 1. A linear mixed effect model was used to calculate the estimated marginal means and the association between presence of brain injury and $tcPCO_2$ values over phases.

Results

- **Results from mixed models indicated a significant effect of phases/time on mean $tcPCO_2$ level** (F =4.4, p= 0.001), **but no difference by brain injury status** (F= 0.0, p=0.304) or an interaction effect (F=1.2, p=0.304) **(Figure 1)**.

Table 2. Pairwise comparison of the post-rewarming phase (reference) to other phases

Phase (Post-rewarming phase = reference)	Mean difference	p values	95% Confidence interval	
			Lower bound	Upper bound
>12- 24 h of life	-5.67	0.032	-11.1	-0.3
>24- 36 h of life	-3.54	0.121	-7.5	0.4
>36- 48 h of life	-2.85	0.305	-6.4	0.7
>48- 60 h of life	-4.05	0.014	-7.6	-0.5
>60- until the end of TH	-3.76*	0.003	-6.7	-0.8
Rewarming	-1.68	0.676	-4.2	0.8

- **Mean levels of $tcPCO_2$ exhibited a significant decrease between the last phase of TH** (> 60 HOL) **and post-rewarming phase:** mean difference: -3.76, 95%CI -6.7; -0.8, p=0.003

Conclusions

- **This novel longitudinal study of infants with NE showed relatively stable $tcPCO_2$ levels within the normal range during hypothermia and rewarming.**
- Results from mixed models indicated **a significant effect of time on transcutaneous CO_2 levels.**
- Based on the results adjusted for multiple comparisons, the comparison that met statistical significance was the decline between the last phase of hypothermia (> 60 HOL) and post-rewarming phase.
- **The trajectories of $tcPCO_2$ did not differ between infants with and without brain injury.**
- These pilot results are needed to be interpreted with caution given study limitations that include no adjustment for potential confounding or data collection during the early hours of life.

References

- *El-Dib M, et al. 2021 Challenges in respiratory management during therapeutic hypothermia for neonatal encephalopathy. Semin Fetal Neonatal Med:101263.*
- *Lingappan K, Kaiser JR, Srinivasan C, Gunn AJ. Relationship between PCO2 and unfavorable outcome in infants with moderate-to-severe hypoxic ischemic encephalopathy. Pediatr Res. 2016;80(2):204-8.*
- *Weeke LC, et al. 2018 A Novel Magnetic Resonance Imaging Score Predicts Neurodevelopmental Outcome After Perinatal Asphyxia and Therapeutic Hypothermia. J Pediatr 192:33-40 e32.*