PDA Treatment and Hydrocortisone Exposure in Extremely Preterm Infants: A Secondary Analysis of the Hydrocortisone Trial

NICHD Neonatal Research Network

Meera Sankar MD[1], Valerie Chock MD, MS Epi[1], Faith Myers MD[1], Alexis Davis MD, MS Epi[1], Scott McDonald, BS[2], Matthew Rysavy MD, PhD[3], Matthew Laughon MD, MPH[4], Shazia Bhombal MD[5], Krisa P. Van Meurs MD[1], Abhik Das PhD[2], William E. Benitz MD[1], Kristi Watterberg MD[6] for the NICHD Neonatal Research Network

[1] Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA • [2] RTI International, Research Triangle Park, NC • [3]Department of Pediatrics at UT Health Houston and McGovern Medical School, Houston, TX • [4]The University of North Carolina at Chapel Hill, Chapel Hill, NC • [5]Emory University/Children's Healthcare of Atlanta, Atlanta, GA • [6]University of New Mexico Health Sciences, Albuquerque, NM

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Introduction

- Although prior trials of early hydrocortisone (HC) supplementation for preterm infants found reduction in both moderate to severe BPD or death and in treatment for patent ductus arteriosus (PDA), neither of these effects were observed with HC treatment initiated at 14-28 days of age in the NICHD Neonatal Research Network (NRN) Hydrocortisone Trial. (Watterberg K, et al. NEJM 2022).
- Heterogeneity in patient characteristics, such as cortisol insufficiency, have been suggested as explanations for failure of PDA treatment to reduce BPD or death
- Whether later HC exposure in preterm infants who received PDA treatment decreases BPD or death has not been examined

Objective

- We hypothesize that combined exposure to HC and PDA treatment will decrease the outcome of moderate to severe BPD or death compared to infants who received only PDA treatment in the HC Trial

Methods

- We performed a secondary analysis of infants enrolled in the NICHD NRN Hydrocortisone Trial
- The primary outcome was moderate to severe BPD or death
- Secondary outcomes included moderate to severe BPD, death, moderate to severe cerebral palsy (CP), neurodevelopmental impairment (NDI), necrotizing enterocolitis (NEC), late onset sepsis (LOS), days of mechanical ventilation, oxygen supplementation, z-scores for growth, home oxygen, and any grade of BPD
- Robust Poisson, linear and cumulative logistic regression analyses adjusted for center and gestational age were performed
- Separate analyses adjusting for prophylactic indomethacin or for interaction between PDA treatments and hydrocortisone were performed for the primary and secondary outcomes

Results

Table 1: Perinatal and Infant Characteristics

Characteristics	PDA Rx+/HC+ N=198	PDA Rx+/HC- N=197	PDA Rx-/HC+ N=199	PDA Rx-/HC- N=205
Maternal age (years)	29.4 ± 6.37	28.6 ± 6.39	27.7 ± 5.94	27.8 ± 6.38
Mother's ethnicity (n, %)				
Hispanic or Latino	33 (17%)	25 (13%)	33 (17%)	35 (17%)
Not Hispanic or Latino	162 (83%)	171 (87%)	163 (83%)	166 (83%)
Mother's racial category (n, %)				
Black	73 (38%)	86 (45%)	65 (33%)	82 (41%)
White	110 (57%)	98 (51%)	121 (62%)	108 (54%)
Other	9 (4.7%)	8(4.2%)	9 (4.6%)	9 (4.5%)
Mother's education (n, %)				
Less than High School Diploma	33 (17%)	25 (13%)	36 (18%)	34 (17%)
High School Diploma	51 (26%)	55 (28%)	50 (25%)	53 (26%)
Partial College	40 (20%)	39 (20%)	38 (19%)	46 (23%)
College degree or more	32 (16%)	39 (20%)	34 (17%)	30 (15%)
Unknown	41 (21%)	38 (19%)	41 (21%)	38 (19%)
Received any antenatal glucocorticoids? (n, %)	172 (87%)	172 (87%)	170 (86%)	185 (90%)
Gestational age (weeks)	24.8 ± 1.51	24.9 ± 1.38	24.9 ± 1.50	24.9 ± 1.59
Maternal chorioamnionitis (n, %)	32 (16%)	28 (14%)	32 (16%)	37 (18%)
Birth weight (grams)	717 ± 165	726 ± 165	704 ± 161	715 ± 179
Male sex (n, %)	92 (46%)	125 (63%)	93 (47%)	110 (54%)
Small for gestational age (n, %)	21 (11%)	19 (9.6%)	25 (13%)	25 (12%)
Multiple birth (n, %)	52 (26%)	53 (27%)	42 (21%)	49 (24%)
5-min Apgar score (median, IQR)	6 (4-8)	6 (5-8)	6 (4-7)	6 (4-7)
Postnatal days at randomization (median, 5th-95th %ile)	21 (15-28)	22 (14-28)	21 (14-28)	21 (15-28)
Highest mode of support at trial entry (n, %)				
High frequency ventilator	60 (30%)	61 (31%)	71 (36%)	58 (28%)
Conventional ventilator	138 (70%)	136 (69%)	126 (63%)	146 (72%)
Nasal IPPV	0 (0%)	0 (0%)	2 (1.0%)	0 (0%)
FiO2 at trial entry	0.49 ± 0.20	0.50 ± 0.20	0.54 ± 0.22	0.50 ± 0.20
Respiratory severity score* at trial entry	568 ± 337	587 ± 329	625 ± 362	552 ± 310
PDA Diagnosis	198 (100%)	197 (100%)	73 (37%)	68 (33%)
Prophylactic indomethacin (n, %)	43 (22%)	43 (22%)	109 (55%)	114 (56%)
Proven NEC** (n, %)	6 (3.0%)	3 (1.5%)	4 (2.0%)	8 (3.9%)
SIP** without proven NEC	4 (2.0%)	3 (1.5%)	9 (4.5%)	6 (2.9%)
Late onset sepsis** (n, %)	41 (21%)	30 (15%)	21 (11%)	32 (16%)

PDA Rx+ Any treatment for PDA (indomethacin, ibuprofen, acetaminophen, ligation, catheter-based closure)

PDA Rx– No treatment for PDA

HC+ Received hydrocortisone

HC– Placebo (no hydrocortisone)

* Respiratory severity score was calculated as mean airway pressure x FiO2 x 100
** Pre-randomization only

Table 2: Hydrocortisone and PDA treatment - Regression Analyses

Outcome	HC treatment		PDA treatment		Interaction term p-value †
Poisson regressions	**RR (95% CI)**	**p-value**	**RR (95% CI)**	**p-value**	
Moderate to severe BPD or Death at 36 weeks PMA	0.96 (0.91-1.01)	0.14	1.10 (1.04-1.17)	0.001	0.93
Moderate to severe BPD at 36 weeks PMA	0.96 (0.91-1.02)	0.18	1.11 (1.04-1.18)	0.001	0.92
NDI	1.02 (0.90-1.16)	0.72	1.04 (0.91-1.20)	0.53	0.85
SIP Without Proven NEC	N/A (0 infants with outcome)				
Home Oxygen at Discharge	0.93 (0.83-1.03)	0.17	1.15 (1.02-1.31)	0.03	0.82
Death or moderate-severe CP *	PDARx+: 0.89 (0.65-1.23) PDARx-: 1.33 (0.93-1.90)	0.48 0.11	HC+: 1.13 (0.84-1.52) HC-: 1.69 (1.24-2.31)	0.41 0.0008	0.051 ††
Death or NDI	1.01 (0.91-1.13)	0.83	1.06 (0.95-1.19)	0.31	0.69
Death at 36 weeks PMA *	0.68 (0.45-1.04)	0.08	0.89 (0.54-1.47)	0.66	0.51
Moderate to severe CP *	PDARx+: 0.92(0.55-1.53) PDARx-: 1.80 (0.97-3.32)	0.74 0.06	HC+: 1.03 (0.63-1.67) HC-: 2.02 (1.18-3.46)	0.91 0.01	0.07 ††
Death before discharge *	0.88 (0.57-1.35)	0.54	1.12 (0.74-1.70)	0.59	0.16
Proven NEC *	0.67 (0.41-1.08)	0.10	0.63 (0.39-1.00)	0.052	0.57
Late onset sepsis *	PDARx+: 0.61 (0.39-0.98) PDARx-: 1.89 (1.23-2.90)	0.04 0.003	HC+: 0.65 (0.43-0.98) HC-: 2.00 (1.19-3.37)	0.04 0.009	0.003 ††
Linear regressions	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Interaction term p-value †**
Days of mechanical ventilation to 36 weeks¶	-2.00 (-4.63, 0.64)	0.14	3.91 (1.01, 6.82)	0.008	0.37
Days of oxygen supplementation to 36 weeks	-0.46 (-3.70, 2.78)	0.78	4.53 (0.95-8.11)	0.01	0.63
Length of hospital stay among survivors to 36 weeks	5.27 (-3.44, 14.0)	0.24	1.77 (-7.89, 11.4)	0.72	0.57
Z score for weight for age at 36 weeks	-0.04 (-0.17, 0.10)	0.6	-0.20 (-0.34, -0.05)	0.009	0.92
Z score for height for age at 36 weeks	-0.12 (-0.28, 0.04)	0.14	-0.16 (-0.34, 0.02)	0.07	0.57
Z score for head circumference for age at 36 weeks	0.06 (-0.11, 0.24)	0.47	-0.14 (-0.33, 0.05)	0.15	0.89
Cumulative logistic (Ordinal outcomes)	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**Interaction term p-value †**
Grade of BPD (None, Grade 1, Grade 2, Grade 3)	0.997 (0.76-1.31)	0.98	1.50 (1.11-2.03)	0.009	0.96
NDI (None/Mild, Moderate, Profound)	1.02 (0.76-1.39)	0.88	1.25 (0.89-1.74)	0.2	0.98
Death/Grade of BPD (None, Grade 1, Grade 2, Grade 3, Death)	0.92 (0.71-1.19)	0.52	1.38 (1.04-1.85)	0.03	0.89
Death/NDI (None/Mild, Moderate, Profound, Death) ‡	0.995 (0.76-1.30)	0.97	1.19 (0.90-1.58)	0.22	0.45

Adjusted for center and stratum (gestational age)
* Due to sparse data, center was adjusted for as a cluster effect
† Interaction term p-values are from separate regressions except as noted; p-values and RRs/Estimates/ORs in the table do not account for the interaction term
‡ Due to sparse data, center adjusted for as a random effect

¶ Mechanical ventilation: use of conventional or high-frequency ventilator
†† Results shown from analyses adjusted for interaction term

All linear regressions provide estimates for mean difference (95% CI)

BPD: Bronchopulmonary dysplasia, graded according to method of Jensen et al.
CP: Cerebral palsy; definite abnormalities observed in the neuromotor examination, with functional challenges classified by GMFCS level (II-III = moderate, IV-V = severe).
NEC: Necrotizing enterocolitis
SIP: Spontaneous intestinal perforation

NDI: Neurodevelopmental impairment, as indicated by one or more of: Bayley Scales of Infant and Toddler Development–III (Bayley-III) cognitive score < 85 (standardized mean [±SD], 100±15; range, 55 to 145) or a Bayley-III motor score < 85 (standardized mean, 100; range, 45 to 155), with lower scores indicating greater impairment; a Gross Motor Function Classification System (GMFCS) level ≥ II (on a scale from level I to V, with I indicating normal and higher levels indicating greater impairment); severe vision impairment in both eyes (consistent with a visual acuity of <20/200); or bilateral hearing impairment with or without amplification (on the basis of observation during the trial visit; report by the parent, guardian, or primary caregiver; or chart review). According to the protocol of the follow-up study, NDI could be determined if a component of a binary indicator in the NDI definition was known as "Yes," but the severity level could be determined only when all components of level of severity were known.

Results

- Treatments for PDA were used in 198 infants who received HC and in 197 who received placebo (Table 1)
- The interaction between PDA treatment and HC was not statistically significant for moderate-severe BPD or death (p=0.93)

Discussion

- HC did not modify the effect of PDA treatment on these outcomes
- PDA treatment alone was associated with a significant increase in moderate-severe BPD or death at 36 weeks, moderate-severe CP or death, home oxygen, duration of ventilatory support, oxygen supplementation at 36 weeks, and BPD severity, and with decreased weight-for-age z-score at 36 weeks
- Late onset sepsis was less frequent among those who received HC and PDA treatment and more frequent among those who received only HC or only PDA treatment (p=0.003, Table 2)

Conclusions

- In preterm infants in the NICHD NRN Hydrocortisone Trial, the relationship between PDA treatment and BPD or death was not altered by HC exposure after the second postnatal week as mandated in the treatment arm
- PDA treatment remained a significant risk factor for several adverse neonatal outcomes regardless of HC exposure

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RTI INTERNATIONAL

NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development