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Neurologic Injury in Acidemic Term Infants

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Abstract

Objective: To determine whether arterial umbilical cord gas (aUCG) pH, in anatomically normal term infants, could select infants at-risk for brain injury identified on magnetic resonance imaging (MRI).

Study Design: We performed a nested case-control within a prospective cohort of 8,580 women. Cases, with an aUCG pH < 7.10, were temporally, age, and gender matched to controls with an aUCG pH ≥ 7.20. Bivariable and multivariable analyses compared the presence and severity of brain injury. Secondary analyses estimated whether elevated arterial base excess or lactate were associated with brain injury.

Results: Fifty-five cases were matched to 165 controls. There was no statistical difference in brain injury between the groups (adjusted odds ratio [aOR]: 1.8 [95% confidence interval (CI): 0.7 – 4.4]). Base excess ≥ −8 mEq/L was not significantly associated with brain injury (p = 0.12). There was no increase in risk of injury based upon elevation of arterial lactate ≥ 4 mmol/L (p = 1.00). Cases were significantly more likely to have an abnormal score in several domains of the Dubowitz neurological exam.

Conclusion: The aUCG acid-base parameters alone are not sufficient clinical markers to identify term infants that might benefit from brain MRI to identify injury.

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Keywords

brain injury; acidemia; arterial umbilical cord gas pH; magnetic resonance imaging

Introduction

Obstetric measures of neonatal well-being immediately after birth are limited. Arterial umbilical cord gas (aUCG) acidemia measured by pH has been an obstetric cornerstone to identify infants at risk for neurologic injury, particularly at term. The evidence to support aUCG pH as an acceptable surrogate marker for clinically meaningful morbidity has varied, with some studies suggesting correlation with morbidities and others that show no association.[1–3] Infant Apgar scores have also been used as outcome measures for morbidity, with similarly inconsistent predictive ability.[4–7]

In preterm infants, gestational age at delivery alone is a sufficient risk factor for neurologic injury and adverse neurodevelopmental outcomes to make cerebral magnetic resonance imaging (MRI) an increasingly common component of routine clinical care. Similarly, term infants with hypoxic ischemic encephalopathy (HIE) routinely undergo cerebral MRI as part of clinical care. However, many children who develop cerebral palsy are neither preterm nor term infants with HIE. Rates of brain injury and its characterization among term infants without HIE are unknown, as MRI is less commonly used clinically in this population. Advances in cerebral MRI have enabled the use of diffusion-weighted imaging (DWI) along with conventional T1 and T2 sequences to identify and characterize brain injury.[8–10] Diffusion imaging enables earlier detection of brain injury and, given the predictable nature of the evolution of diffusion findings, provides insight into timing of injury.

An improved ability to identify infants at elevated risk for brain injury would allow the targeted use of diagnostic tools (*i.e.*, MRI) and, potentially, neuroprotective interventions in a manner similar to how they are used for infants born preterm or those with HIE. We hypothesized that aUCG acid-base parameters would select term-born infants with cerebral injury detected on a screening neurologic exam and brain MRI within the first 72 hours of life.

Materials and Methods

This study was a nested case-control conducted within a large, prospective cohort of 8,580 women, conducted from March 2010 to September 2014. The parent study constituted all consecutive singleton, vertex presenting non-anomalous infants live-born after the onset of labor. Participants must have had continuous electronic fetal monitoring (EFM) during labor and an aUCG pH must have been acquired, both of which are part of a universal labor management policy at our institution. Women without labor or an aUCG result were excluded. The Washington University School of Medicine Human Research Protection Office approved the study prior to participant enrollment.

For this study, *cases* were defined as infants with an aUCG pH < 7.10, and were temporally, age, and gender matched to *controls* with a normal aUCG pH ≥ 7.20. All mothers of infants

with an aUCG pH level of < 7.10 were approached for enrollment. Three controls for every case were randomly selected to be representative of the larger cohort. The study protocol included an MRI which entailed acquisition of T1-, T2- and diffusion weighted images in the first 24–72 hours of life (or immediately after rewarming in those who underwent therapeutic hypothermia), using a 3T Trio Siemens scanner, and a simultaneous Dubowitz screening neurologic exam. The trained examiner was blind to case status and MRI results. MRI sequences were anonymized, downloaded to an external hard drive and a pediatric neuroradiologist and neonatal intensivist independently interpreted the T1- and T2- weighted and DWI sequences, blind to clinical and outcome data including case-control status.

Brain injury was assessed in both hemispheres using a validated scoring system.[11] The scoring system consisted of evaluation of five regions: the sub-cortical region (caudate nucleus, globus pallidus and putamen, thalamus and posterior limb of the internal capsule), cortex, white matter, cerebellum and brainstem. Injury in each region except the brainstem was scored from 0 to 3, with 0 delineating no injury, 1 signifying mild focal injury (<25% of region), 2 representing moderate multifocal injury (25–50% of region) and 3 defining severe, widespread injury to the brain (>50% of region).[11] The brainstem was scored from 0–2 given the smaller size of the region. The scores from each hemisphere were then combined to reach a final global score (GS) for brain injury. Per the global scoring system, 0 indicated no brain injury, 1–11 was mild, 12–32 moderate and any score of 33 or more severe brain injury. Differences were reconciled with arbitration.

All infants underwent a neurological examination on the same day as the MRI scan using the Dubowitz neurological exam.[12] Infants with two or greater abnormalities in the screening exam underwent a re-evaluation by a co-investigator. The screening evaluates domains of muscle tone, body movements, tremors and startles, Moro reflex, auditory and visual orientation, alertness and presence or absence of abnormal eye movements, fisting and clonus. The combination of neuroimaging and neurological screening improves the likelihood of detecting infants with neurological injury.

Descriptive bivariate analyses, Fisher's exact test, Chi-square, Mann-Whitney *U* test or Student's *t* test, were used to compare presence and severity of brain injury between cases and controls. Conditional logistic regression was applied to adjust for mode of delivery and prostaglandin exposure to refine the odds of injury among those with acidemia compared to a normal pH. Day of life at MRI, infant gender, gestational week at delivery and race did not remain in the final model. Secondary analyses were performed to estimate whether elevated arterial base excess (≥ −8 mEq/L) or lactate level (≥ 4.0 mmol⁄L) were associated with brain injury.

During the study period, therapeutic hypothermia became part of clinical practice for treatment of infants with moderate-severe encephalopathy based on neurological examination and abnormal aUCG pH<7.1, base excess ≥ −12 mEq/L or 10minute Apgar scores ≤ 5 due to evidence demonstrating improved neurodevelopmental outcomes in this population [11,13]. Therefore, additional analyses were completed excluding the 14 infants who underwent therapeutic hypothermia treatment. All analyses were performed using STATA Version 12 (STATA Corp., College Station, TX).

Results

Of the 8,580 term-born, non-anomalous infants, 220 participated in the nested case-control study. Fifty-five cases with an aUCG pH < 7.10 were matched to 165 controls with an aUCG pH level ≥ 7.20. The mean pH for cases was 7.03 ± 0.06 and 7.29 ± 0.04 for controls. Maternal age, gestational age at delivery, parity and history of prior cesarean were not statistically different between the groups. Labor type was not different between the groups, although prostaglandin exposure was significantly more common among cases. Cesarean and operative deliveries were also more common among those with aUCG pH < 7.10 when compared to the controls (Table 1). When correlating aUCG pH with clinical neurologic screening results, infants with an aUCG pH < 7.10 were significantly more likely to have an abnormal score in several domains of the Dubowitz neurological exam compared to those infants with an aUCG pH level ≥ 7.20 (Table 2).

Severity of MRI injury

Comparing the MRI injury scores between the two groups, 83.6% of the cases and 90.3% of the controls had a Global Score of zero (or no injury). For the cohort with MRI injury, scores ranged from 1 to 60. Nine of the 55 cases had evidence of brain injury on MRI; seven were mild, one was moderate and one was severe. The cases of moderate and severe brain injury had aUCG pH of 7.05 and 6.91, respectively. Additionally, 16 controls had MRI injury categorized as mild based on the Global Score. There was no statistical difference in the rate of brain injury among cases compared to controls, and this remained true after adjusting for mode of delivery and prostaglandin exposure (Table 3). When a sensitivity analysis was performed excluding the 14 infants who underwent therapeutic hypothermia to eliminate the potential impact of this treatment on the study findings, there remained no difference in risk of injury between cases and controls (Table 4).

When frequency and severity of brain injury were examined between groups categorized by arterial base excess and lactate, the findings were similar. Two infants were excluded due to missing base excess and lactate values. Forty-nine infants with base excess ≥ −8 mEq/L were compared to the 169 infants who had a base excess < −8 mEq/L. The mean base excess in the elevated group (≥ −8 mEq/L) was −11.95 ± 3.07 mEq/L and was −2.34 ± 2.00 mEq/L in the low base excess (< −8 mEq/L) group. There was no statistically significant relationship between base excess ≥ −8 mEq/L and rate or severity of brain injury (Table 5). Additionally, when excluding the 14 who underwent therapeutic hypothermia treatment, the differences in rate and severity of brain injury by base excess were not statistically affected (Table 6). In the high versus low lactate group, defined as arterial lactate of ≥ 4 mmol/L versus < 4 mmol/L, the mean lactate was 7.43 ± 2.79 mmol/L and 2.46 ± 0.64 mmol/L, respectively. Eight of the 74 infants with an elevated lactate and 16 of the 144 infants with a lactate < 4 mmol/L were identified to have brain injury, which was not statistically different between the groups, even when those who underwent hypothermia were excluded (Tables 7 & 8).

Patterns of MRI injury

MRI abnormalities were detected in 25/220 (11.4 %) infants in the study. Of those detected, there were 20 (80%) MRI abnormalities that consisted of mild white matter signal abnormalities. Further, of the detected abnormalities, nine were within the cases and 16 within the controls. Five infants had evidence of white matter and cortical signal abnormality suggestive of “border-zone” hypoxic-ischemic injury. Of these, three were in the mild category while one each was in the moderate and severe category. One infant had severe global injury on MRI while one infant mild cerebellar injury. Six of 14 (42.9%) that underwent therapeutic hypothermia had evidence of MRI injury. Four had border-zone injury, one had global injury involving the white matter, cortex, deep nuclear gray matter and brain stem and one had cerebellar injury.

Discussion

Among anatomically normal infants born at or beyond 37 weeks, cerebral injury identified by MRI was not significantly more common among infants with an aUCG pH < 7.10 compared to controls. Injury was similarly not more common among those with an elevated arterial base excess or lactate. However, abnormalities on screening Dubowitz neurologic clinical exam were more common among those with acidemia compared to those with a normal pH, likely indicating a transient clinical impact of a compromised metabolic milieu.

Acidosis develops when there is decrease in arterial oxygen exchange between the mother and fetus and carbon dioxide accumulates, thus becoming detrimental to the brain.[14–16] In a nonhuman primate study, conclusions suggested umbilical cord occlusion and subsequent acidemia could lead to severe, acute birth asphyxia and neurocognitive delays.[17] In a sheep model, Prout and colleagues reported repetitive umbilical cord occlusions with near-term fetal sheep resulted in an inflammatory response within the brain and increased risk of brain injury.[18] In affected infants, two principal patterns of brain injury have been reported. These include injury to the deep nuclear gray matter following acute catastrophic events leading to profound acidosis and parasagittal or “borderzone” injury, which results from prolonged partial hypoxia due to intermittent compromise of umbilical blood flow.

In this cohort, all the MRI abnormalities seen in infants with a pH ≥ 7.20 were mild and located in the white matter. This finding of white matter abnormalities in this non-acidotic, cohort of full term infants has not been described in prior literature and warrant further investigation. They may represent mild, clinically inconsequential findings with no long-term impact or contribute to the normal variation in childhood neuro-development. White matter abnormalities are more prevalent in the preterm population.[9] However, mild injury correlates poorly with neurodevelopmental outcome even in that group. In contrast, infants in the acidotic group had a higher prevalence of MRI abnormality. Only 25% of this group had moderate-severe encephalopathy and underwent therapeutic hypothermia, reiterating the poor correlation of aUCG pH and neonatal encephalopathy with brain injury.[19] The proportion of infants who underwent therapeutic hypothermia and had MRI injury (42.9%) is similar to that described in the NICHD therapeutic hypothermia trial.[20]

Currently, term-born infants at risk of neurologic morbidity must be identified by surrogate measures. The aUCG pH has received the most focus, and data has suggested it to be superior to Apgar scores in identifying infants at risk.[3,5,7] Recent studies have suggested that arterial base excess or lactate may be additional surrogates for identifying infants at risk for injury.[21–23] In order for cerebral MRI to become established as a biomarker and guide for clinical intervention for neuroprotection in term infants, more effective clinical variables must be identified to select patients for imaging. In our study, moderate to severe MRI injury was seen rarely, which is not surprising given that term infants without anomalies were sampled based upon aUCG pH alone, but this remains consistent with published literature.[24–26] In contrast, the number of infants with mild MRI injury was greater than anticipated, but because this population has never been studied before, the clinical relevance of these findings remains unclear. To our knowledge, this is the first report of brain MRI findings in a cohort of anatomically normal term-born neonates.

In term born infants, studies have described the predictive ability of cerebral MRI injury, even if mild, for neurodevelopmental outcomes. Coleman and colleagues assessed the relationship between brain injury and neurocognitive delays on MRI in 68 encephalopathic newborns after therapeutic hypothermia treatment.[27] Of the term infants with neurocognitive delays, as assessed by the neonatal intensive care unit (NICU) network neurobehavioral scale (NNNS), 22% had associated MRI evidence of brain injury.[27] Barnette and colleagues conducted a large, multicenter study of 4,171 term infants from 2006 to 2010 in whom a variety of neuroimaging modalities were used, including MRI, cranial ultrasound and computed tomography (CT).[28] Their findings indicated MRI scans were superior to CT scans and cranial ultrasounds in detecting nuclear gray matter and cerebellar injury that correlated with adverse outcomes.[28]

Interventions that may be explored for term infants with injury not otherwise diagnosed include therapeutic hypothermia, as current evidence has demonstrated reduction in long-term neurocognitive disabilities among infants with HIE undergoing therapeutic hypothermia.[11,29] Recent data also suggests that magnesium sulfate therapy may be another intervention to consider, as initial studies have yielded favorable outcomes among infants with HIE.[30,31] Due to the paucity of data for term-born infants without such clinical findings, cerebral MRI remains a tool infrequently utilized in this population as its clinical application has yet to be determined.

Our study has potential limitations for consideration in the context of our results. There is inherent subjectivity, which can be introduced by the human interpretation of MRI. However, we attempted to minimize this effect by having two expert blinded independent readers use a validated scoring system. Introduction of clinical therapeutic hypothermia treatment during the study period may have influenced the estimated relationship between pH and MRI injury. However, sensitivity analyses excluding those who underwent therapeutic hypothermia treatment it did not affect our results. While therapeutic hypothermia decreases brain tissue injury on MRI in infants with HIE, the predictive value of MRI for subsequent neurological impairment is not affected by therapeutic hypothermia.[32] Finally, while this is the largest known study to date to examine the use of aUCG pH to

select non-anomalous term infants for cerebral MRI, and to describe the distribution of injury, the number of infants demonstrating injury remained limited.

Additional strengths of our study include an institutional universal aUCG policy, which decreases the inherent selection bias introduced when aUCG sampling is completed at the discretion of the obstetric provider. The selection of the sample increased representativeness of the larger unselected cohort of infants without anomalies born at or beyond 37 weeks and thus generalizability.

In conclusion, we found neither aUCG pH, base excess nor lactate alone were sufficient markers to identify term infants that might benefit from cerebral MRI for the detection of injury. Increased utilization of MRI has enabled the early and improved detection of brain injury. In this study, the most common injury type was mild, though the resultant phenotype remains unknown and requires exploration. Further work needs to be completed to detect clinical factors, alone or in combination, which identify term infants who would benefit most from cerebral MRI during the neonatal period, to enable early intervention and additional neurodevelopmental follow-up.

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Table 1.

Associations by Arterial Umbilical Cord Gas pH in Clinical Characteristics

	pH < 7.10 (N = 55)	pH ≥ 7.20 (N = 165)	OR[a] (95% CI)	P[a]
Maternal age, years	24.7 ± 6.1	24.7 ± 5.8	1.00 (0.95–1.05)	0.96
Maternal age ≥ 35 years	4 (7.3)	11 (6.7)	1.01 (0.34–3.54)	0.88
Gestational age delivered, weeks	39.3 ± 1.1	38.9 ± 1.2	1.42 (1.08–1.87)	0.01
Body mass index, kg/m^2	35.7 ± 9.0	33.1 ± 7.6	1.04 (1.00–1.07)	0.06
Any gestational hypertension or preeclampsia	8 (14.6)	22 (13.3)	1.11 (0.46–2.68)	0.82
Gestational diabetes mellitus	0 (0.0)	3 (1.8)	---	---
Pregestational diabetes mellitus	2 (3.6)	0 (0.0)	---	---
Nulliparous	22 (40.0)	46 (27.9)	1.77 (0.92–3.41)	0.09
Prior cesarean	9 (16.4)	15 (9.1)	1.84 (0.79–4.26)	0.16
Labor type				
Spontaneous	15 (27.3)	52 (31.5)	*Ref*	
Augmented	10 (18.2)	44 (26.7)	0.81 (0.32–2.03)	0.65
Induction	30 (54.6)	69 (41.8)	1.54 (0.72–3.28)	0.26
Prostaglandin	15 (27.3)	24 (14.6)	2.29 (1.07–4.89)	0.03
Foley bulb	8 (14.6)	20 (12.1)	1.25 (0.50–3.14)	0.63
Oxytocin	36 (65.5)	108 (65.5)	1.00 (0.52–1.92)	1.00
Birthweight, grams	3299 ± 523	3215 ± 453	1.00 (1.00–1.00)	0.25
Birthweight >4000 grams	6 (10.9)	10 (6.1)	1.80 (0.65–4.95)	0.26
Birthweight <1800 grams	0 (0.0)	0 (0.0)	---	---
Mode of delivery				
Vaginal	13 (23.6)	129 (78.2)	*Ref*	
Operative vaginal	6 (10.9)	7 (4.2)	6.58 (1.80–24.13)	<0.001
Cesarean	36 (65.5)	29 (17.6)	10.74 (4.77–24.21)	<0.001
Maternal fever				
At delivery	3 (5.5)	4 (2.4)	2.25 (0.50–10.05)	0.29
Post-partum	2 (3.6)	5 (3.0)	1.20 (0.23–6.19)	0.83

Data are mean ± standard deviation or n(%)

[a]Odds ratios and *P* values derived from simple conditional logistic regression models

Table 2.

Associations with Neurological Exam by pH < 7.10 vs. pH ≥ 7.20

	pH < 7.10 (N = 55)	**pH ≥ 7.20 (N = 165)**	**aOR[a] (95% CI)**
Posture	5 (9.1)	10 (6.2)	1.52 (0.50–4.69)
Arm Traction	8 (14.6)	8 (4.9)	3.28 (1.17–9.20)
Leg Traction	14 (25.5)	15 (9.3)	3.35 (1.49–7.50)
Head Control 1	9 (16.4)	8 (4.9)	3.77 (1.38–10.33)
Head Control 2	10 (18.2)	7 (4.4)	4.89 (1.76–13.59)
Head Lag	9 (16.7)	13 (8.1)	2.28 (0.92–5.70)
Ventral Suspension	11 (20.0)	12 (7.5)	3.11 (1.28–7.55)
Body Movements	11 (20.0)	7 (4.3)	5.59 (2.04–15.35)
Tremors/Startles	11 (20.0)	7 (4.3)	5.78 (2.08–16.07)
Moro	14 (25.9)	30 (18.6)	1.53 (0.74–3.16)
Auditory	5 (9.3)	7 (4.4)	2.25 (0.68–7.51)
Visual	6 (11.3)	16 (10.4)	1.10 (0.41–2.98)
Alertness	2 (3.7)	7 (4.5)	0.82 (0.16–4.07)
Facial Palsy	2 (3.6)	0 (0.0)	---
Abnormal Eye Movements	6 (10.9)	2 (1.3)	9.73 (1.87–50.64)
Sunset Sign	2 (3.7)	3 (1.9)	1.97 (0.32–12.16)
Fisted Hand	9 (16.7)	6 (3.7)	5.19 (1.76–15.37)
Clonus	7 (13.0)	1 (0.6)	23.98 (2.88–199.96)

Data are n(%)

[a]Adjusted for gender

Table 3.

Global Score Injury and Severity > 0 Based on Fetal Acidemia

	pH < 7.10 (N = 55)	pH ≥ 7.20 (N = 165)	P[a]	aOR[b] (95% CI)
Global Score			0.09	
None	46 (83.6)	149 (90.3)		---
Mild (1–11)	7 (12.7)	16 (9.7)		---
Moderate (12–32)	1 (1.8)	0 (0.0)		---
Severe (33–136)	1 (1.8)	0 (0.0)		---
Global Score > 0	9 (16.4)	16 (9.7)	0.22	1.82 (0.76–4.40)

Data are n(%)

[a] *P* values based on X^2 or Fisher's exact test

[b] Adjusted for mode of delivery and prostaglandin use

Table 4.

Global Score Injury and Severity > 0 Based on Fetal Acidemia and Excluding those with Therapeutic Hypothermia Treatment

	pH < 7.10 (N = 41)	pH ≥ 7.20 (N = 165)	P[a]	aOR[b] (95% CI)
Global Score			0.09	
None	38 (92.7)	149 (90.3)		---
Mild (1–11)	2 (4.9)	16 (9.7)		---
Moderate (12–32)	1 (2.4)	0 (0.0)		---
Severe (33–136)	0 (0.0	0 (0.0)		---
Global Score > 0	3 (7.3)	16 (9.7)	0.77	0.74 (0.21–2.68)

Data are n(%)

[a] *P* values based on X^2 or Fisher's exact test

[b] Adjusted for mode of delivery and prostaglandin use

Table 5.

Global Score Injury and Severity > 0 Based on Base Excess Levels[a]

	Base Excess ≥ −8 mEq/L (N = 49)	Base Excess < −8 mEq/L (N = 169)	P[b]	aOR[c] (95% CI)
Global Score			0.04	
None	40 (81.6)	153 (90.5)		---
Mild (1–11)	7 (14.3)	16 (9.5)		---
Moderate (12–32)	1 (2.0)	0 (0.0)		---
Severe (33–136)	1 (2.0)	0 (0.0)		---
Global Score > 0	9 (18.4)	16 (9.5)	0.12	2.15 (0.89–5.23)

Data presented as n(%)

[a]Two infants excluded due to missing base excess value

[b]*P* values based on X^2 or Fisher's exact test

[c]Adjusted for mode of delivery and prostaglandin use

Table 6.

Global Score Injury and Severity > 0 Based on Base Excess Levels and Excluding those with Therapeutic Hypothermia Treatment[a]

	Base Excess ≥ −8 mEq/L (N = 35)	Base Excess < −8 mEq/L (N = 169)	P[b]	aOR[c] (95% CI)
Global Score			0.07	
None	32 (91.4)	153 (90.5)		---
Mild (1–11)	2 (5.7)	16 (9.5)		---
Moderate (12–32)	1 (2.9)	0 (0.0)		---
Severe (33–136)	0 (0.0)	0 (0.0)		---
Global Score > 0	3 (8.6)	16 (9.5)	1.00	0.90 (0.25–3.26)

Data presented as n(%)

[a] Two infants excluded due to missing base excess value

[b] *P* values based on X^2 or Fisher's exact test

[c] Adjusted for mode of delivery and prostaglandin use

Table 7.

Global Score Injury and Severity > 0 Based on Lactate Levels[a]

	Lactate ≥ 4 mmol/L (N = 74)	Lactate < 4 mmol/L (N = 144)	P[b]	aOR[c] (95% CI)
Global Score			0.23	
None	66 (89.2)	128 (88.9)		---
Mild (1–11)	6 (8.1)	16 (11.1)		---
Moderate (12–32)	1 (1.4)	0 (0.0)		---
Severe (33–136)	1 (1.4)	0 (0.0)		---
Global Score > 0	8 (10.8)	16 (11.1)	1.00	0.97 (0.39–2.38)

Data presented as n(%)

[a] Two infants excluded due to missing lactate value

[b] *P* values based on X^2 or Fisher's exact test

[c] Adjusted for mode of delivery and prostaglandin use

Table 8.

Global Score Injury and Severity > 0 Based on Lactate Levels Excluding those with Therapeutic Hypothermia Treatment[a]

	Lactate ≥ 4 mmol/L (N = 61)	Lactate < 4 mmol/L (N = 144)	P[b]	aOR[c] (95% CI)
Global Score			0.06	
None	58 (95.1)	128 (88.9)		---
Mild (1–11)	2 (3.3)	16 (11.1)		---
Moderate (12–32)	1 (1.6)	0 (0.0)		---
Severe (33–136)	0 (0.0)	0 (0.0)		---
Global Score > 0	3 (4.9)	16 (11)	0.20	0.41 (0.12–1.48)

Data presented as n(%)

[a]Two infants excluded due to missing lactate value

[b]*P* values based on X^2 or Fisher's exact test

[c]Adjusted for mode of delivery and prostaglandin use