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Umbilical Vein White Blood Cell Count as a Marker of Acidemia in Term Neonates

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Objective: White blood cells are mobilized under both hypoxic and infectious conditions. Intrauterine hypoxia is linked to increased risk of cerebral palsy and is potentiated by the presence of infection. We hypothesized that umbilical vein white blood cell elevation in term neonates is associated with intrauterine acidemia.

Methods: We prospectively evaluated all liveborn neonates delivered at our institution for a 6-month period. Umbilical arterial blood was analyzed for pH and blood gas and venous blood for hematologic indices. Medical records of cases greater than or equal to 37 weeks' gestation were reviewed for correlative data. Student's *t*-test was used to determine difference of means and Chi-square test for goodness of fit. Pearson coefficients of correlation were applied where appropriate.

Results: A total of 1,948 liveborn, term neonates were delivered during the study period; 1,561 cases had white blood cell analysis and arterial blood gas data available. Acidemic cases had higher white blood cell (15.0 vs. 12.4 cells $\times$ 10^3/mm^3, $P < 0.001$), lymphocyte (4.43 vs. 3.59 cells $\times$ 10^3/mm^3, $P < 0.0001$), and neutrophil counts (9.08 vs. 7.71 cells $\times$ 10^3/mm^3, $P < 0.01$). As umbilical artery pH decreased, white blood cells became more prevalent. Likewise, as base deficit deepened, white blood cell counts increased.

Conclusions: This study demonstrates an association between deepening acidemia and increasing white blood cell, lymphocyte, and neutrophil counts. Although statistically different, mean white blood cell counts for acidemic and nonacidemic cases are fairly close, limiting the clinical applicability in determining whether pathology is present in an individual case. *J. Matern.-Fetal Med. 2000;9:327–329.*

Key words: white blood cells; lymphocytes; neutrophils; acidemia

INTRODUCTION

Despite advances in obstetric and neonatal care over the past several decades, the incidence of cerebral palsy attributable to intrapartum events has remained largely unchanged [1]. Intrapartum events contribute relatively less to compromised neurologic outcomes than previously thought [2]. Fetal acidemia, as reflected in cord blood gases, is believed to have an association, albeit limited, with neurologic outcomes [3]. Evaluation of neonatal acid–base status can provide some clues for understanding compromised outcomes and may rule out some other causes.

White blood cells are mobilized under both hypoxic and infectious conditions. Intrauterine hypoxia is linked to increased risk of cerebral palsy, potentiated by the presence of infection [4]. Total white blood cell and lymphocyte counts have been suggested to be possible markers of fetal hypoxic injury [5,6]. We hypothesized that umbilical vein white blood cell elevation in term neonates may be associated with acidemia and other markers of fetal hypoxia.

MATERIALS AND METHODS

This study protocol was approved by our institutional review board for human research. We prospectively evaluated all liveborn neonates delivered at our institution for a 6-month period between August 1, 1996, and February 28, 1997. Umbilical arterial blood was analyzed for pH and blood gases (ABL-520 blood gas analyzer; Radiometer America, West Lake, OH); venous blood was evaluated for hematologic indices through our hospital laboratory. Automated cell counters (Sysmex E-5000 and Sysmex F-500;

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TABLE 1. White Blood Cell Count and Acid–Base Status

	White blood cells*				Lymphocytes*				Neutrophils*			
Total cases	n	Mean	SD	*P*	n	Mean	SD	*P*	n	Mean	SD	*P*
Normal	1442	12.4	3.7	Ref.	1387	3.59	1.3	Ref.	982	7.71	2.81	Ref.
Acidemia	119	15.0	5.2	<0.001	112	4.43	1.8	<0.0001	82	9.08	4.00	<0.01
Respiratory	43	14.5	4.3	<0.01	40	4.76	1.8	<0.05	30	8.21	2.52	0.29
Mixed	7	16.0	4.5	0.051	7	4.77	1.3	<0.05	6	9.83	3.07	0.12
Metabolic	69	15.2	5.8	<0.001	65	4.20	1.8	<0.01	46	9.54	4.79	<0.05
Compensated	48	13.4	4.2	0.107	45	3.78	1.7	0.46	30	7.91	2.98	0.72
Uncompensated	21	19.6	6.7	<0.001	20	5.13	1.6	<0.0001	16	12.6	6.01	<0.01

*Cells $\times 10^3/mm^3$, Ref. = reference.

TABLE 2. White Blood Cell Count, Umbilical Artery pH, and Base Deficit

	White blood cells*				Lymphocytes*				Neutrophils*			
pH	n	Mean	SD	*P*	n	Mean	SD	*P*	n	Mean	SD	*P*
<7.0	9	15.1	8.3	0.25	7	4.64	2.34	0.18	6	9.00	3.99	0.39
7.00–09	26	16.1	4.0	<0.001	26	5.34	1.56	<0.001	22	8.96	2.62	0.01
7.10–19	144	15.4	5.3	<0.001	136	4.51	1.58	<0.001	101	9.32	4.35	<0.001
7.20–29	626	12.8	3.7	<0.001	609	3.74	1.33	<0.001	426	7.82	2.85	<0.05
7.30–39	659	11.7	3.1	Ref.	629	3.34	1.12	Ref.	443	7.45	2.57	Ref.
>7.40	97	12.0	3.2	0.39	92	3.48	0.98	0.21	66	7.45	2.36	1.0
Base excess												
<−7	144	16.3	5.1	<0.001	138	4.83	1.73	<0.001	102	9.63	4.16	<0.001
−7 to −4	578	13.0	3.8	<0.001	560	3.79	1.37	<0.001	397	8.03	2.90	<0.01
−3 to −1	707	11.7	3.0	0.53	673	3.40	1.08	<0.01	468	7.35	2.52	0.73
0 to 2	132	11.5	3.4	Ref.	128	3.13	0.90	Ref.	97	7.25	2.56	Ref.

*Cells $\times 10^3/mm^3$, Ref. = reference.

Baxter, Long Grove, IL) performed the initial analysis and trained hematology technicians evaluated peripheral smears and corrected white blood cell counts for nucleated red blood cells. Medical records, including our perinatal database (Paradox; Borland, Scotts Valley, CA) of cases ≥37 weeks gestation were reviewed for correlative data. We used published American College of Obstetricians and Gynecologist's guidelines for acid–base definitions, utilizing the mean and standard deviations from our blood gas data [7]. Student's *t*-test was used to determine difference of means and Chi-square test for goodness of fit. Pearson coefficients of correlation were used where appropriate. Significance was defined as $P < 0.05$.

RESULTS

A total of 1,948 live-born, term neonates were delivered during the study period. The cord blood specimen was of insufficient quantity or quality for analysis in 166 cases and either the arterial or venous specimen, or both, were absent in an additional 221 cases. Thus, 1,561 term cases had data available for arterial blood gas and blood cell analysis. These cases were analyzed further for this report.

The mean gestational age of our study population was 39.1 ± 1.2 completed weeks, with a mean birthweight of 3,289 ± 476 g. The racial composition of our population was: Black, n = 1,066 (68.3%); White, n = 222 (14.2%); Hispanic, non-Black, n = 179 (11.5%); Asian, n = 83 (5.3%); and Native American n = 11 (0.7%). The mean pH for our population was 7.28 ± 0.08, range 6.84–7.51. Using two standard deviations from a mean of 51.67 mm Hg (SD 10.92), our high normal P_{CO2} was 73.31 mm Hg. For HCO_3, mean value 23.43 meq/L (SD 2.26), and lower normal 18.91 meq/L. These values concur with normative data from other studies [8–10].

We found acidemic cases (>2 SD below the mean) to have higher white blood cell counts than normals (15.0 ± 5.2 vs. 12.4 ± 3.7 cells $\times 10^3/mm^3$, $P < 0.001$). This relationship held for both respiratory and metabolic acidosis (see Table 1). Analysis of lymphocyte and neutrophil subsets found elevation of both in cases of acidemia compared with normals (3.59 ± 1.26 vs. 4.43 ± 1.75 cells $\times 10^3/mm^3$, $P < 0.001$, and 7.71 ± 2.81 vs. 9.08 ± 4.00 cells $\times 10^3/mm^3$, $P < 0.01$), respectively). As umbilical artery pH decreased, white blood cells became more prevalent ($r = -0.29$, $P < 0.001$). Likewise, as base excess deepened circulating white blood cells increased ($r = -0.36$, $P < 0.0001$) (Table 2). Both lymphocyte and neutrophil counts were inversely proportional to pH and base excess. The correlation between lymphocyte count and pH was stronger than that between neutrophil counts and pH (Pearson coefficient -0.30 vs. -0.19, respectively; $P < 0.001$).

DISCUSSION

Both lymphocyte and neutrophil counts have been demonstrated to increase in response to hypoxia in human adults and in animal models [11,12]. Lymphocytosis is associated with hypoxia in neonates [5]. Infection, including chorioamnionitis, may increase neonatal neutrophil counts. To further complicate the relationship between hematologic indices and acid–base status, infection alters oxidative stress, contributing to hypoxia, and oxidative stress impairs cellular response to infection [13,14]. In a rat model, interleukins act as a stimulus for myelopoeisis and erythropoeisis, producing changes in the number of neutrophils, lymphocytes, and red blood cells [15]. The neutrophil response itself is suggested to contribute to hypoxic-ischemic brain injury in a separate neonatal rat model [16]. How and why infection and hypoxia interact in a particular intrauterine environment to manifest clinically as neurologic deficit in some human individuals and not others remains unclear.

This study demonstrates the relationship between deepening acidemia and increasing white blood cell, lymphocyte, and neutrophil counts. The cases with lowest pH's of <7.00 showed a trend toward higher white blood cell and white blood cell subset counts. This trend did not reach statistical significance due to the relatively few cases of severe acidemia that occurred during this 6-month study. Several factors limit the clinical applicability of white blood cell counts as markers of acidemia. We studied umbilical cord blood, which reflects the intrauterine state. It may not be feasible to obtain cord blood for hematologic analysis outside of a study protocol. Both neutrophil and lymphocyte counts change rapidly in the neonatal period [6,17]. The longer after delivery the specimen is obtained, the greater the potential influence of neonatal events. Also, the mean white blood cell counts for acidemic and nonacidemic cases are quite close, with overlapping ranges. We conclude that elevated umbilical vein white blood cell counts in term neonates are associated with both respiratory and metabolic acidemia.

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