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Risk factors and neonatal outcomes of late onset hyponatremia in preterm infants

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Abstract

Risk factors and neonatal outcomes of late onset hyponatremia in preterm infants

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Introduction: Late-onset hyponatremia (LOH), hyponatremia occurring after two weeks of age with the achievement of full feeding, is the result of a negative sodium balance caused by inadequate salt intake or excessive salt loss due to immature renal or intestinal function in preterm infants. *Objectives*: The aims of our study were to identify the risk factors for LOH and their influence on neonatal outcomes.

Methods: This was a retrospective cohort analysis of 161 preterm infants younger than 34 weeks of gestation who were born between June 2009 and December 2010 at Seoul National University Hospital. LOH was defined as a sodium level <132 mEq/dL or 133-135 mEq/dL with oral sodium supplementation. For the risk factor analysis, perinatal factors were compared between LOH and non-LOH groups using a multiple logistic regression analysis. For the outcome analysis, the relationships between the risk factors

and outcomes were analyzed with simple linear or logistic regressions, and the variables that correlated with the outcome variables were included in multiple linear or logistic regressions. We included gestational age at birth (GA) in all of the models.

Results: LOH occurred in 49 (30.4%) of the studied infants. A lower GA, a shorter duration of parenteral nutrition, the presence of respiratory distress syndrome, the use of furosemide, and feeding with breast milk were significant risk factors for LOH. In terms of neonatal outcomes, the infants with LOH had longer hospital stays and higher risks of bronchopulmonary dysplasia (BPD) and retinopathy of prematurity requiring surgery (ROP). LOH lasting at least seven days was significantly associated with longer hospital stays, moderate to severe BPD, periventricular leukomalacia, and extrauterine growth restriction, regardless of oral sodium supplementation.

Conclusions: LOH was commonly observed in preterm infants; it may be a risk factor for BPD or ROP; and it may be a marker of illness severity. Future research with a larger cohort is needed.

Keywords: late onset hyponatremia; risk factors; outcome; preterm; bronchopulmonary dysplasia

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Contents

List of Tables and Figures

List of Abbreviations

BPD, bronchopulmonary dysplasia

RDS, respiratory distress syndrome

ROP, retinopathy of prematurity

PVL, periventricular leukomalacia

PDA, persistent ductus arteriosus

GA, gestational age

BWT, body weight

AS, apgar score

SGA, small for gestational age

PIH, pregnancy induced hypertension

GDM, gestational diabetes mellitus

NEC, necrotizing colitis

USG, ultrasonograph

TPN, total parenteral nutrition

IVH, intraventricular hemorrhage

EUGR, extrauterine growth restriction

BM, breast milk

Introduction

Late-onset hyponatremia (LOH), hyponatremia occurring after two weeks of age with the achievement of full feeding in preterm infants, is the result of a negative sodium balance caused by a combination of inadequate sodium intake and renal or intestinal salt wasting. In contrast, early-onset hyponatremia is mainly due to excessive free water caused by perinatal factors. The incidence, severity, and duration of LOH are influenced by the maturity of the neonate's kidneys; there is a higher fractional excretion of sodium at lower gestational ages, and feeding protocols control the amount of sodium supplied to the premature baby(1-3). Because breast milk has a relatively low sodium content, feeding breast milk without a fortifier can result in LOH in premature infants. Hypoxia, drugs, and respiratory distress can also aggravate LOH associated with kidney tubular damage. However, few studies have addressed the risk factors for hyponatremia after full feeding is achieved.

The influences on LOH in growing preterm infants are also not well studied. Growth restriction has been observed in animals(4) and humans(5) with hyponatremia. Associations with impaired brain growth, poor neurodevelopmental outcomes(6), and sensory neural hearing loss have also been suggested(7). However, all of the above reports have focused on the relationship between LOH and overall hyponatremia, rather than hyponatremia after the achievement of full feeding. Very little is known about the influence of LOH on neonatal outcomes in preterm infants.

The goals of our study were to identify the risk factors for LOH in preterm

infants and to assess the influence of LOH on neonatal outcomes.

Materials and Methods

Subjects and definitions

Our retrospective cohort was composed of 196 preterm infants younger than 34 weeks of gestational age who were born and admitted to the neonatal intensive care unit of Seoul National University Children's Hospital between June 30, 2009 and December 31, 2010. Thirty-five infants were excluded (20 died, 5 underwent ileostomies, 6 had congenital anomalies, and 4 had missing data), leaving 161 infants who were enrolled as the study population (Figure 1).

The data were collected via a retrospective chart review. The collected data included the infants' perinatal histories, clinical characteristics (including LOH), and neonatal outcomes. The neonatal outcomes included the duration of hospitalization and the occurrence of bronchopulmonary dysplasia (BPD), periventricular leukomalacia, extrauterine growth restriction, rickets, and retinopathy of prematurity (ROP) requiring surgery, including laser surgery.

LOH was defined as hyponatremia that occurred more than two weeks after birth or after oral feeding had reached 120 mL/kg/day. Hyponatremia was defined as a sodium level below 132 mEq/dL or between 133 and 135 mEq/dL with oral sodium supplementation. In our unit, oral sodium supplementation is sometimes provided during the conversion from partial parenteral nutrition to full enteral feeding if the parenteral nutrition included high amounts of sodium. Three patients (1.8%) who had received supplementation with oral sodium chloride (NaCl) powder and who exhibited sodium levels between 133 mEq/dL and 135 mEq/dL were included in the

study population. We used the serum sodium level to define hyponatremia; however, if only a capillary sodium level measured with an i-STAT® Portable Clinical Analyzer(PCA; Abbott, Princeton, NJ, USA)® kit was available, we used that level in the analysis. Ten of the 49 patients had only a capillary sample. The duration of hyponatremia was defined as the length of time when the sodium level was ≤132 mEq/dL.

Oligohydramnios was defined as the single deepest pocket of less than 2.0 cm. Maternal pregnancy-induced hypertension, chronic hypertension, preeclampsia, and eclampsia were all categorized as maternal hypertensive disorders. Patent ductus arteriosus was defined by the necessity of medical or surgical treatment. BPD was identified using a definition suggested by Alan H. Jobe et al. in a National Institute of Child Health and Human Development (NICHD) workshop(8). The use of antibiotics was limited to aminoglycoside and vancomycin because these medications were known to cause nephrotoxicity. Rickets was defined as a serum alkaline phosphatase level over 800 IU/L or evidence of rickets in an X-ray. Extrauterine growth retardation was defined as a body weight below the 10th percentile at a gestational age of 35 weeks. We analyzed the data from kidney ultrasonograms that were performed at least once before discharge as part of a separate, concurrent study. Metabolic acidosis was defined a as base deficit of less than 6 or a bicarbonate level of less than 18 mmol/L.

Statistical analysis

All the numerical data are expressed as the means ± standard deviation. The

t-test or the Mann-Whitney test was used for continuous variables. The χ^2 test or Fisher's exact test was used for the analysis of categorical variables.

To evaluate the risk factors for LOH, we compared the perinatal factors of the LOH and non-LOH groups during the study period. A multiple logistic regression using a stepwise selection was employed, and we included significant variables (those with p-values below 0.05) in a univariate analysis.

To assess the influence of LOH on neonatal outcomes, the relationships between perinatal factors and neonatal outcomes were first analyzed with a simple linear regression or a simple logistic regression due to the possibility of multicollinearity among the prenatal risk factors (explanatory variables) and the measures of neonatal outcomes (outcome variables). Each explanatory variable that was correlated with the outcome variables was also analyzed using multiple linear regression or multiple logistic regression. Because gestational age can influence the entire perinatal outcome, we applied a statistical correction for this factor. We also assessed the influence of LOH that persisted for at least seven days on neonatal outcomes using the same statistical methods. The statistical analysis was conducted using SPSS Statistics version 20 and R version 2.15.1.

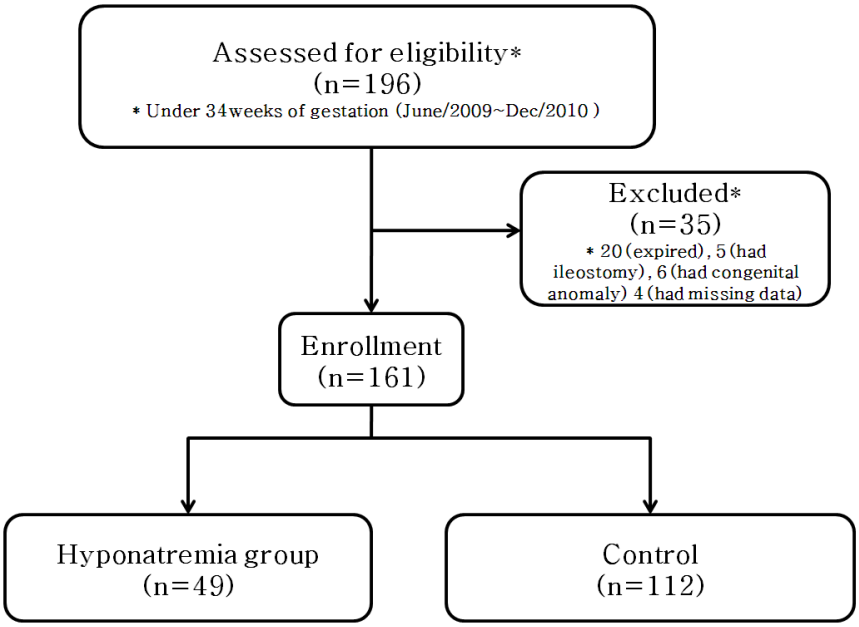

Figure 1. Flowchart of participants

Results

Clinical Characteristics of the LOH group

There were 49 infants who had LOH, accounting for 30.4% of the infants enrolled in the study. The mean gestational age of the LOH group was 28.0 ± 2.6 weeks (23.4-33.3 weeks), and their mean birth weight was 989.3 ± 362.7 g (420-2050 g). The mean onset of LOH was 24.3 ± 10.2 days after birth (14-51 days), and the mean duration of LOH was 5.31 ± 3.89 days (1-17 days). Of the 49 infants with LOH, 17 (34.7%) experienced an LOH duration of at least seven days. Oral NaCl supplementation was provided to 37 of the hyponatremic patients (75.5%), including 14 of the 17 neonates whose LOH persisted at least seven days. The mean replacement duration was 16.8 ± 11.9 days (3-45 days).

Risk factors of hyponatremia

Late onset hyponatremia group had lower gestational age and lower birth weight than no late onset hyponatremia group($p<0.05$). Premature rupture of membrane over 18 hours, use of prenatal antibiotics, presence of respiratory distress syndrome, patent ductus arteriosus which needed medical or surgical treatment, postnatal culture proven sepsis, and use of postnatal antibiotics and furosemide within 2 weeks after birth were significantly more frequent in late onset hyponatremia group($p<0.05$). Breast milk feeding was more common and mean duration of parenteral nutrition was longer in late onset hyponatremia group($p<0.05$)(Table1).

In multiple logistic regression analysis, lower gestation and shorter duration

of parenteral nutrition was independently associated with increased risk of late onset hyponatremia. Respiratory distress syndrome, use of furosemide, and breast milk feeding also independently associated with the development of late onset hyponatremia(Table2).

Table1. Univariate analysis of perinatal and neonatal outcomes between late onset hyponatremia group or late onset hyponatremia for more than 7 days group and no late onset hyponatremia group.

	No-hyponatremia group (n=112)	Hyponatremia group (n=49)	P-value
GA at birth	31.2±2.5	28.0±2.6	<0.01
Birthweight	1461.5±481.2	989.3±362.7	<0.01
M:F ratio	1:1.07	1:1.04	0.67
5 minute AS<7	36 (32.1%)	25 (51.0%)	0.02
SGA	31 (27.7%)	13 (26.5%)	0.88
Oligohydramnious	14 (12.5%)	8 (16.3%)	0.52
Maternal hypertensive disorders	27 (24.1%)	8 (16.3%)	0.27
GDM	17 (15.2%)	5 (10.2%)	0.4
PROM>18hr	33 (29.5%)	26 (53.1%)	<0.01
Chrioamnionitis	34 (31.8%)	19 (40.4%)	0.3
Prenatal antibiotics	41 (36.6%)	29 (59.2%)	<0.01
Prenatal steroid	87 (77.7%)	36 (73.5%)	0.56
RDS	15 (13.4%)	24 (49%)	<0.01
PDA	39 (34.8%)	39 (79.6%)	<0.01
NEC	9 (8.0%)	3 (6.1%)	1
Sepsis	12 (10.7%)	13 (26.5%)	<0.05
IVH >Gr2	6 (5.4%)	7 (14.3%)	0.06
Antibiotics use	75 (67.0%)	46 (93.9%)	<0.01
Furosemide use	15 (13.4%)	26 (53.1%)	<0.01
BM feeding	37 (33.0%)	33 (67.3%)	<0.01
Kidney sono abnormalities	20 (26.7%)	15 (36.6%)	0.27
TPN duration	10.7±13.9	18.5±11.7	<0.05
Metabolic acidosis	15 (13.4%)	4 (8.2%)	0.433
BPD	26 (23.2%)	39 (79.6%)	<0.01
Moderate to Severe BPD	10 (8.9%)	20 (40.8%)	<0.01
PVL	6 (5.4%)	5 (10.2%)	0.26
ROP with surgery	3 (2.7%)	13 (26.5%)	<0.01
Rickets	20 (18.0%)	22 (44.9%)	<0.01
EUGR	60 (53.6%)	34 (69.4%)	0.06
Hospital day	41.2±29.1	79.43±33.2	<0.01

Table 2. Multivariate logistic regression analyses about risk factors of late onset hyponatremia

	Odds Ratio	p-value	95% CI for Estimate (OR)	
			Lower	Upper
GA(per week)	0.654	0.000	0.438	0.870
TPN duration(day)	0.943	0.034	0.888	0.997
RDS	3.092	0.020	2.143	4.041
Furosemide use	4.081	0.008	3.043	5.118
BM feeding	2.546	0.041	1.652	3.444

LOH and neonatal outcomes

BPD, ROP, rickets, a longer duration of ventilation, and a longer hospitalization occurred more frequently in the LOH group, according to the univariate analyses(Table 1). After the multiple linear or logistic regression was performed, including all the perinatal factors found to be significantly associated with LOH, LOH was found to be independently associated with a longer hospitalization (*beta*=8.279, p=0.009, 95% confidence interval 2.140-14.418) and with increased rates of BPD (odds ratio 16.9, p=0.029, 95% confidence interval 1.329-214.873) and ROP (odds ratio 4.9, p=0.028, 95% confidence interval 1.186-20.053, Table 3). LOH tended to be associated with the development of extrauterine growth restriction, although the relationship was not statistically significant (p=0.079)

The multiple linear and multiple logistic regression analyses of the influence of LOH lasting at least seven days on neonatal outcomes revealed correlations with a longer hospital stay and with higher rates of periventricular leukomalacia, moderate to severe BPD, and extrauterine growth restriction (Tables 4 and 5).

Table3. Multivariate linear or logistic regression analysis models about the influences of late onset hyponatremia on neonatal outcomes

Outcome	Odds Ratio	p-value	95% CI for Estimate (OR)	
			Lower	Upper
Hospital Day[a]		0.009	2.140	14.418
BPD[b]	16.896	0.029	1.329	214.873
PVL[b]	0.732	0.745	0.111	4.804
ROP with surgery[b]	4.873	0.028	1.186	20.024
Rickets[b]	1.232	0.674	0.466	3.260
EGUR[b]	2.414	0.079	0.903	6.453

[a]multiple linear regression, [b]multiple logistic regression

Table4. Univariate analysis of perinatal and neonatal outcomes between late onset hyponatremia for more than 7 days group and no late onset hyponatremia group *P-value <0.05 when compared to no late onset hyponatremia group

	No-hyponatremia group (n=112)	Hyponatremia longer than 7 days group (n=17)
GA at birth	31.2±2.5	27.9±2.8*
Birthweight	1461.5±481.2	902.1±370.0*
M:F ratio	1:1.07	1:1.03
5 minute AS<7	36 (32.1%)	12 (70.6%)*
SGA	31 (27.7%)	5 (29.4%)
Oligohydramnious	14 (12.5%)	6 (35.3%)*
Maternal hypertensive disorders	27 (24.1%)	2 (11.8%)
GDM	17 (15.2%)	2 (11.8%)
PROM>18hr	33 (29.5%)	12 (70.6%)*
Chrioamnionitis	34 (31.8%)	5 (29.4%)
Prenatal antibiotics	41 (36.6%)	12 (70.6%)*
Prenatal steroid	87 (77.7%)	11 (64.7%)
RDS	15 (13.4%)	8 (47.1%)*
PDA	39 (34.8%)	14 (82.4%)*
NEC	9 (8.0%)	1 (5.9%)
Sepsis	12 (10.7%)	4 (23.5%)
IVH >Gr2	6 (5.4%)	4 (23.5%)*
Antibiotics use	75 (67.0%)	16 (94.1%)
Furosemide use	15 (13.4%)	11 (64.7%)*
BM feeding	37 (33.0%)	11 (64.7%)
Kidney sono abnormalities	20 (26.7%)	7 (41.2%)
TPN duration	10.7±13.9	23.0±15.2*
Metabolic acidosis	15 (13.4%)	2 (11.8%)*
BPD	26 (23.2%)	14 (82.4%)*
Moderate to Severe BPD	10 (8.9%)	11 (64.7%)*
PVL	6 (5.4%)	5 (29.4%)*
ROP with surgery	3 (2.7%)	4 (23.5%)
Rickets	20 (18.0%)	10 (58.8%)
EUGR	60 (53.6%)	15 (88.2%)*
Hospital day	41.2±29.1	87.65±34.2*

Table5. Multivariate linear or logistic regression analysis models about the influences of late onset hyponatremia longer than 7 days on neonatal outcomes

Outcome	Odds Ratio	p-value	95% CI for Estimate (OR)	
			Lower	Upper
Hospital Day[a]		0.005	4.554	24.635
BPD[b]	9.736	0.152	0.432	219.569
Moderate to severe	7.224	0.002	2.008	25.990
PVL[b]	6.881	0.007	1.684	28.119
ROP with surgery[b]	1.319	0.7	0.322	5.397
Rickets[b]	2.272	0.194	0.658	7.846
EGUR[b]	6.395	0.018	1.370	29.851

[a]multiple linear regression [b]multiple logistic regression

Discussion

In our study, 30.4% of preterm infants younger than 34 weeks of gestational age were affected by LOH. The significant risk factors for LOH were a lower gestational age at birth, a shorter duration of total parenteral nutrition, the presence of respiratory distress syndrome, furosemide use, and feeding with breast milk. LOH was also significantly associated with a longer hospital stay and the development of BPD and ROP. In addition, LOH lasting for more than seven days was significantly associated with a longer hospital stay and the development of moderate to severe BPD, periventricular leukomalacia, and extrauterine growth restriction.

Some of the suggested pathophysiological causes of LOH in premature babies are inadequate sodium intake and increased natriuresis, which can cause increased vasopressin. Our risk factor analysis supports these pathophysiological factors as causes of LOH. In preterm infants, the immaturity of the proximal renal tubule can cause the decreased reabsorption of sodium. Numerous factors affecting the proximal tubule can aggravate hyponatremia, including hypoxia, respiratory distress, and the administration of drugs with tubular toxicity. Our study showed that the infants' gestational age at birth and birth weight tended to be lower in the LOH group and that respiratory distress syndrome was a significant risk factor for LOH. Another significant risk factor was furosemide, a well-known diuretic that affects kidney tubules, causing massive natriuresis. Regarding inadequate sodium supplementation, a shorter duration of parenteral nutrition and feeding with breast milk were significant risk factors. Although the mean total parenteral

nutrition duration was longer in the LOH group, the multiple logistic regression showed that a shorter duration of total parenteral nutrition was a risk factor for LOH. In our unit, the amount of sodium supplementation in parenteral nutrition is decided based on the serum sodium level, and it sometimes increases by up to 8-9 mEq/kg/day. However, when oral feeding without sodium supplementation begins, the amount of sodium intake suddenly decreases to 2-3 mEq/kg/day during the conversion from parenteral nutrition to enteral feeding. A shorter duration of parenteral nutrition can therefore lead to less sodium administration, which can initiate LOH. Although we used fortified breast milk, feeding with breast milk was found to be associated with the development of LOH. This finding may suggest that the current fortification of breast milk is not sufficient for the sodium intake needs of preterm infants.

In the present study, the incidence of LOH was high, reaching 30.4%. It will therefore be of great importance to clarify the clinical consequences of a low serum sodium level in premature babies. Some preliminary data have already indicated that neonatal sodium deficiency may have unfavorable consequences for later cognitive functions(6, 9). Furthermore, hyponatremia has been documented to be a risk factor for cerebral palsy in severely premature babies(10). In our data, there was no significant association between the presence of LOH and periventricular leukomalacia during hospitalization. However, in infants with LOH that lasted longer than seven days, LOH was significantly associated with the development of periventricular leukomalacia.

In our study, LOH influenced the development BPD and ROP. There have been reports that excessive fluid and water balance with hyponatremia within one week after birth were associated with the development of BPD(11), and restricted water intake tended to reduce the risk of BPD(albeit not to a statistically significant extent)(12). In preterm infants, increased natriuresis due to renal tubular immaturity can lead to protracted volume contraction, which can stimulate aldosterone and arginine vasopressin release, allowing further water retention and late hyponatremia to progress(1, 13, 14). The elevation of plasma arginine vasopressin levels in BPD infants both during the fourth week of life and as a chronic condition has also been reported(15). Although an impaired renal response to arginine vasopressin in hyponatremic patients prevents the further worsening of hyponatremia(1), elevated arginine vasopressin levels in BPD patients can cause the pulmonary fluid to accumulate and pulmonary edema to increase; therefore, LOH can be a significant risk factor for BPD. In our results, LOH lasting longer than seven days was significantly associated with only moderate to severe BPD. This result may indicate that a longer duration of LOH is associated with the development of more severe BPD.

Postnatal growth restriction related to hyponatremia has also been reported(5). Sodium is a significant growth factor that stimulates cell proliferation and plays a significant role in protein turnover(16). NaCl deprivation inhibits growth, which is manifested in reductions in body weight, brain weight, body length, muscle and brain protein and RNA content, and brain lipid content (compared with controls). Subsequent NaCl

supplementation restores the growth velocity; however, it does not induce catch-up growth(17). Additionally, tubular injury, which can be combined with LOH, can be associated with impaired growth. In our study, extrauterine growth restriction was not related to LOH, with a marginally significant p-value. However, in infants with LOH lasting longer than seven days, LOH was significantly associated with the development of extrauterine growth restriction.

We performed an outcome analysis to examine the influence on neonatal outcomes of not only LOH in general but also LOH lasting for more than seven days because we feel that the duration of hyponatremia is a highly critical factor that can affect neonatal outcomes. Among the infants who had experienced LOH for more than seven days, 14(14/17, 82.4%) were supplemented with oral sodium. Although it may be a mild form of hyponatremia, a longer duration of LOH can affect many neonatal outcomes, including the development of moderate to severe BPD, periventricular leukomalacia, and extrauterine growth retardation. More aggressive treatment is needed if the LOH persists for long periods despite a lack of acute symptoms.

This was a retrospective, observational study; therefore, it had several limitations. First, our unit has a relatively general policy of sodium supplementation and the treatment of hyponatremia, rather than a strict, uniform protocol. We therefore had to include in the LOH group some neonates whose sodium levels did not reach 132 mEq/dL with oral sodium supplementation. Second, because we usually provided sodium

supplementation if there was any chance of hyponatremia, we could not determine the natural course of untreated mild hyponatremia(with serum sodium levels between 130 mEq/dL and 132 mEq/dL). Third, we included in the LOH group ten infants with only a capillary sample to confirm the hyponatremia. In a clinical situation, the clinicians might not be not concerned about the sodium levels of these neonates because they was not extremely low, and there were no acute symptoms. Fourth, only 161 patients were included in the analysis, which could influence the statistical outcome. Indeed, the confidence interval for the BPD analysis was wide, which may have been influenced by our small sample size. Therefore, the possibility remains that LOH may be only a marker of disease severity in preterm infants, although we attempted to correct for all of the possible confounding factors in the analysis. Further large cohort studies are needed.

In our study, LOH occurred at a relatively high frequency. The risk factors for LOH were a lower gestational age at birth, a shorter duration of parenteral nutrition, feeding with breast milk, and respiratory distress syndrome. LOH may also be a risk factor for BPD and ROP, and LOH lasting longer than seven days was associated with the development of periventricular leukomalacia, moderate to severe BPD, and extrauterine growth restriction. Because the underlying pathophysiological mechanisms are not apparent, especially for ROP, further larger clinical studies should be performed. The close monitoring and correction of LOH is warranted, especially when LOH persists for more than seven days.

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국 문 초 록

조산아에서 발생하는 후기 저 나트륨 혈증은 미숙한 신장 기능으로 인한 과도한 나트륨의 배출이 원인이다. 조산아에서 저 나트륨 혈증의 영향에 대한 내용은 아직 논란의 여지가 있으나, 나쁜 신경학적 예후들이 보고된 바 있다. 본 연구에서는 조산아의 후기 저 나트륨 혈증의 위험 인자 및 이의 조산아의 예후에 미치는 영향에 대한 연구이다. 연구는 후향적 의무기록 검증으로 이루어 졌으며 2009년 6월 30일부터 2010년 12월 31일까지 서울대학교 병원 신생아 중환자실에 입원하였던 34주 미만의 조산아를 대상으로 이루어 졌다. 총 161명의 환아가 검색 되었으며 이들의 주산기 인자 및 신생아 예후에 대한 내용이 조사되었다. 조사된 내용은 후기 저 나트륨 혈증이 있었던 환자 군과 없었던 환자 군으로 나누어 비교하였다. 후기 저 나트륨 혈증은 전체의 30.4%에서 발견되었으며 주수가 어릴수록, 정맥 영양의 기간이 짧을 수록 신생아 호흡곤란 증후군 및 이뇨제의 사용, 모유 수유가 관련성이 있는 것으로 나타났다(p<0.05). 또한 후기 저 나트륨 혈증은 기관지폐형성이상, 미숙아망막증의 수술 여부와 관련이 있는 것으로 나타났다(p<0.05). 7일 이상 저 나트륨 혈증이 지속되었던 환아는 중등도 이상의 기관지폐형성이상, 뇌백질연화증, 자궁외 성장지연과 관련이 있는 것으로 나타났다. 후

기 저 나트륨 혈증은 조산아에서 흔히 관찰되는 현상이며, 상기 질환들과의 이환과 관련성을 보이고 있으므로 면밀히 경과 관찰 하며 이의 교정이 고려된다.

주요어: 후기 저 나트륨 혈증; 위험인자; 영향; 미숙아; 기관지폐이형성증

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↑
2cm
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Risk factors and neonatal outcomes of late onset hyponatremia in preterm infants

2013

김윤주

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4cm
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3cm
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