Early Parenteral Amino Acid Supplementation Reduces the Risk of Neonatal Hyperkalemia in Preterm Infants: Single-Center Retrospective Study.

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Abstract

The incidence of neonatal hyperkalemia in preterm infants was high in the early 2000s. However, the prevalence has declined recently, and the reason for the decline remains unclear. The development of neonatal hyperkalemia can be influenced by suppression of insulin secretion due to hypercatabolism; thus, early parenteral amino acid supplementation, which is now widespread for nutritional management for preterm infants, may have contributed to the decline. We conducted a single-center, retrospective cohort study with 225 preterm infants inborn between 24^{0/7} and 31^{6/7} weeks of gestation during 2009–2018. We compared the incidence of neonatal hyperkalemia between those with or without early parenteral amino acid supplementation (initiated within 24 h after birth). We included 150 infants with early AA supplementation from the first day of life and 75 controls. The incidence of neonatal hyperkalemia was significantly lower in the AA group than the control group (2.7% vs 12.4%, $p < 0.05$). In multivariate analysis, the risk of hyperkalemia increased with delivery at < 28 weeks and decreased with AA supplementation (adjusted odds ratio 0.11; 95% confidence interval 0.02–0.56, $p < 0.01$). In conclusion, early AA supplement from the first day of life might have a prophylactic effect on neonatal hyperkalemia in preterm infants.

Introduction

Neonatal hyperkalemia is a severe, acute problem that can be life-threatening due to its effect on cardiac rhythm in premature infants.¹ The ECG manifestations of hyperkalemia include peaked T waves, widened QRS duration, bradycardia, ventricular tachycardia, and ventricular fibrillation. A rapid rise in serum potassium may be seen during the first 24 h of life, especially in premature infants.² There are a few known mechanisms behind the development of hyperkalemia, including relative hypoaldosteronism, immaturity of the renal distal tubules, and low tissue K^+ intake due to low $Na^+-K^+-ATPase$ activity.^{1,3}

Although the incidence of neonatal hyperkalemia remained high (50%) until the early 2000s, its prevalence has declined recently (25%) and the reasons of this decline remain unclear.^{2,4,5} In the early 2000s, recommendations for early amino acid (AA) supplementation began,^{6,7} and this practice gradually came into widespread use. Insulin plays a role in protein synthesis, as well as in the transport of glucose and K^+ into cells; thus, the secretion of insulin decreases under conditions of increased catabolism.⁸ Conversely, infusion with parenteral AA supplementation increases insulin levels in preterm infants, which may promote K^+ shift.⁹ However, the prophylactic effect of early AA supplementation on neonatal hyperkalemia has not been elucidated yet.

Tocolytic agents improve neonatal outcome when used for extending pregnancy up to 48 hours : meanwhile, pregnant women can be transferred to facilities with a high level of perinatal care and receive antenatal steroid to accelerate fetal lung maturation¹⁰. However, in Japan, once threatened preterm labor is diagnosed, gynecologists often continue to use tocolytic agents for a longer period just before delivery.

A longer treatment with both ritodrine and MgSO_4 has recently been reported to be a risk factor for hyperkalemia in preterm infants born at 32–36 weeks of gestation.¹¹

Antenatal steroid has been regarded as a potential prophylactic strategy against hyperkalemia as well as respiratory distress syndrome.^{2,12,13} Omar et al reported that extremely low birth weight infants (ELBWI) with antenatal steroid showed significantly lower serum potassium levels than infants without one, probably because of $\text{Na}^+\text{-K}^+$ ATPase maturation.¹²

The aim of the present study was to assess the prophylactic effect of early parenteral AA supplementation on neonatal hyperkalemia in preterm infants, taking into account known risk factors and other prophylactic measures in use.

Results

During 2009–2018, a total of 261 preterm infants born at 24^{0/7}-31^{6/7} weeks of gestational age were admitted. We excluded 12 patients with congenital major malformations, 5 patients with chromosomal abnormalities, 4 with early deaths, 9 outborn patients, and 6 with missing K^+ values (Fig. 1). We included 150 preterm infants with early parenteral AA supplementation administered within the first day of life and 75 controls without early AA supplementation. Of 225 infants, 13 (5.8%) were diagnosed with neonatal hyperkalemia. Of the 225, 106 were ELBWIs, of whom 10 (9.4%) showed neonatal hyperkalemia.

Demographic data and potential risk factors for neonatal hyperkalemia between AA supplement and controls

AA supplement group included more pregnant women aged >35 (33.3% vs. 20.0%) and primipara women (58.7% vs 38.7%) and less multiple pregnancy (21.3% vs. 34.7%) than controls (Table 1). There was no significant difference in obstetric complications between the two groups. Maternal use of ritodrine alone was less frequent (19.3% vs. 42.7%), and the use of both MgSO_4 and ritodrine use was higher in the AA supplement group (47.3% vs. 20.0%). Gestational weeks at delivery was significantly earlier (28 vs. 30 w; median) and birth weight was lower (953 vs. 1248 g; median) in the AA supplement group. Early AA supplement increased from 53.1% in 2009-2013 to 84.5% in 2014-2018. The median peak serum K^+ level was significantly lower in the AA supplement group than the controls (4.6 vs. 5.0 mEq/l) ($p < 0.01$) (Table 2). Na^+ , pH, and ionized calcium (iCa^{2+}) were significantly lower in infants with hyperkalemia. The peak K^+ was observed between 10 and 30 h (median, 14.5 h) of life. The incidence of neonatal hyperkalemia was significantly lower in infants with early AA supplementation (2.7% vs 12.0%, $p < 0.05$) (Table 2). The complications (bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA) requiring ligation, and retinopathy of prematurity (ROP) requiring treatment), mortality (7.3% vs. 6.7%), and neurological impairments (5.3% vs. 10.7%) were not statistically significantly different between the two groups.

The effects of various risk factors for and prophylactic management on hyperkalemia occurrence

We performed logistic regression with hyperkalemia occurrence as the dependent variable and risk factors and prophylactic management as the explanatory variables (Table 3). Both univariate analysis (crude odds ratio (OR) and multivariate analysis (adjusted odds ratio (aOR)) are presented. In multivariate analysis, independent risk factors and prophylactic management for hyperkalemia that were shown to be statistically significant were delivery at < 28 weeks of gestation (aOR: 10.93 (95% CI:1.78-66.79)) and AA supplementation from the first day of life (aOR: 0.11 (95%CI 0.02-0.56, $p<0.01$)), adjusted for maternal aged>35, primipara, multiple pregnancy, antenatal steroid, tocolytic agents, cesarean section, infant sex, small for gestational age (SGA), non-reassuring fetal status (NRFS), Apgar score<3 at 1min, and calendar year. AA supplementation on the first day of life was associated with an 89% risk reduction and may be protective against neonatal hyperkalemia.

Discussion

This retrospective cohort study showed that parenteral AA supplementation on the first day of life was associated with reduced risk of hyperkalemia in preterm infants.

Blanco et al reported that a small randomized controlled study did not show a significant association between serum insulin levels and the incidence of hyperkalemia among preterm infants when a higher AA supplementation group (2 g/kg/day) was compared with a lower AA supplementation group (0.5 g/kg/day) ⁵. However, they described the incidence of hyperkalemia as lower than expected, which may have reduced the statistical power needed to show intervention effects. We also suggested that any AA supplementation (i.e., both lower and higher levels) could help prevent catabolism as compared to no supplementation at all. Bonsante et al. conversely reported that early AA supplementation strongly reduced neonatal hyperkalemia among preterm infants in a prospective observational study.¹⁴

Tocolytic agents did not affect the development of neonatal hyperkalemia in this study. We think that in preterm infants before 32 weeks of gestation, the effects of prematurity on hyperkalemia appeared to be greater than those of tocolytic agents.

In multivariate analysis, antenatal steroid did not show a significant effect in preventing hyperkalemia. One of the reasons was that the use of antenatal steroid in the present study was quite lower than that of previous reports (42 % vs. 80–90 %) ¹⁵. This is because long-term tocolysis and bed rest masked the threatened preterm labor, and the obstetricians in our hospital did not administer antenatal steroid for pregnant women with hypertension disorder and infection. Also, even with maternal steroids, the continuous tocolytics often result in a significant delay in labor and might reduce the effect of maternal steroid.

A key limitation in this study is long-term enrolment. Early AA supplement increased in 2014–2018 compared to 2009–2013. Despite multivariate analysis using set with calendar year, epoch effects could not be zero. Changes in management, i.e., respiratory management, postnatal steroid use, and anti-vascular endothelial growth factor therapy for ROP might have affected the results for mortality or

morbidity.^{16,17} Potential confounders that were not included as variables might have affected the incidence of neonatal hyperkalemia. Therefore, multicenter observational studies are required to confirm the present findings.

In conclusion, our results indicate that early AA supplementation from the first day of life may have a prophylactic effect on neonatal hyperkalemia in preterm infants, in addition to the known benefit as nutritional support.

Methods

Ethics

All aspects of the study were approved by the ethics committee of Tokushima University (approval number 3755) and were carried out in accordance with the approved guidelines. Because this is a retrospective study, it was difficult to obtain appropriate informed consents from each subject. Therefore, we gained consents using opt-out, which is a way for investigators to give subjects an opportunity for all participants or their guardians to refuse to participate in this study by announcing the detail of this study on the Tokushima University website (http://www.tokushima-hosp.jp/about/disclosure_document.html). The review board of ethics committee of Tokushima University Hospital has approved the way of opt-out consent in this retrospective study.

Enrollment

Inclusion criteria for this study were preterm infants who were inborn at 24^{0/7}-31^{6/7} weeks of gestation and were admitted between 2009 and 2018 to the neonatal intensive care unit (NICU) at Tokushima University Hospital. Patients were excluded if any of following was applicable: chromosomal abnormalities, congenital major malformations, outborn, or death prior to 48 h of life. Basic clinical information was extracted from the database in the NICU, and individual medical records were reviewed by multiple authors (MT, ST, OT, and SM).

Fluid therapy starting from the first day of life

Fluid therapy was principally determined based on the judgment of attending physician. Early parenteral AA supplementation was defined as having started within 24 h after birth. Controls were infants supplied with parenteral AA after 24 h of life. The other regimen of fluid therapy on the first of life was also obtained including glucose and gluconate calcium.

Neonatal hyperkalemia

The primary outcome was the occurrence of neonatal hyperkalemia. Peak K⁺ levels during the first 72 h were recorded, and neonatal hyperkalemia was defined as K⁺ > 6.5 mEq/l with urine output ≥1 ml/kg/h

.^{2,18} Other data for blood examinations were also obtained at the time of the highest serum K⁺ concentration.

Neurological impairments and morbidities

Neurological impairments were cerebral palsy, mental retardation, attention deficit hyperactivity disorder, autism spectrum disorder, and learning disorder. These neurological impairments were adjudicated by senior pediatricians who were not otherwise involved in this study. Neonatal morbidities were also recorded, including BPD, IVH, PVL, NEC, ligation of PDA, and ROP requiring treatment. BPD was defined as oxygen or respiratory support at a corrected age of 36 weeks. IVH above grade 2 according to the Papile classification was extracted in this study.¹⁹

Statistical analysis

Continuous variables are shown as medians and interquartile ranges, and categorical variables are shown as counts and percentages. The chi-squared test and Fisher's exact test were used to compare categorical variables appropriately, and the Wilcoxon rank-sum test was used to compare continuous variables, because all continuous variables were determined to be nonparametric by the Shapiro-Wilk normality test. $p < 0.05$ was considered the threshold for statistical significance. Multivariate analysis were performed with the following explanatory variables: AA supplementation that started within 24 h after birth, risk factors and possible prophylactic management for the occurrence of hyperkalemia determined by clinical relevance and the settings used in previous reports ^{2,11}. These included maternal age, primipara, multiple pregnancy, antenatal steroid, tocolytic agents, cesarean section, delivery before 28 weeks of gestation, non-reassuring fetal status, infant sex, small for gestational age (defined as an infant with weight below the 10th percentile for gestational age and height below the 10th percentile for gestational age),²⁰ Apgar score at 1 min after birth < 3 , and calendar year (in 5 year intervals). JMP version 15.2 (SAS Institute, Cary, NC) was used for all statistical analyses.

Data availability

Data and materials used in this study are available upon reasonable request to the corresponding author and under a collaboration agreement.

Abbreviations

AA: amino acid

OR: odds ratio

aOR: adjusted odds ratio

CI: confidence interval

NRFS: non-reassuring fetal status

SGA: small for gestational age

NICU: neonatal intensive care unit

BPD: bronchopulmonary dysplasia

IVH: intraventricular hemorrhage

PVL: periventricular leukomalacia

NEC: necrotizing enterocolitis

ROP: retinopathy of prematurity

WQ: water quantity

ELBWI: extremely low birth weight infants

Declarations

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Author contributions

KS wrote the first draft and revised the manuscript, YW advised on statics and methodology, MT, ST, OT, and SM collected and analyzed data, RN and SK supervised the research, and all authors revised the manuscript and agreed to submit.

Competing interests

The authors have no conflicts of interest relevant to this article to disclose.

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Tables

Table 1. Demographic data and possible risk factors for neonatal hyperkalemia between infants with versus without hyperkalemia

	AA supplement n=150	Control n=75	Missing value	p value
Maternal characteristics and obstetric complications				
Maternal age (years)	33 (28-38)	31 (27-34)	0	<0.05
Maternal age >35	33.3% (n=50)	20.0% (n=15)	0	<0.05
Primipara	58.7% (n=88)	38.7% (n=29)	0	<0.01
Multiple pregnancy	21.3% (n=32)	34.7% (n=26)	0	<0.05
DM/GDM	6% (n=9)	4.0% (n=3)	0	0.75
pPROM	6.0% (n=9)	10.7% (n=8)	0	0.28
HDP/HELLP/AFLP	14.0% (n=21)	18.7% (n=14)	0	0.36
Placental abruption	0.0% (n=0)	2.7% (n=2)	0	0.11
Placenta previa/ Low-lying placenta	2.7% (n=4)	0.0% (n=0)	0	0.30
Maternal management				
Antenatal steroid	46.7% (n=70)	33.3% (n=25)	0	0.06
No tocolysis	27.3% (n=41)	36.0% (n=27)	0	0.18
Ritodrine alone	19.3% (n=29)	42.7% (n=32)	0	<0.01
MgSO ₄ alone	6.0% (n=9)	1.3% (n=1)	0	0.17
MgSO₄ and ritodrine	47.3% (n=71)	20.0% (n=15)	0	<0.0001
Cesarean section	66.0% (n=99)	74.7% (n=56)	0	0.19
Possible neonatal risk factors for hyperkalemia				
NRFS	34.0% (n=51)	29.3% (n=113)	0	0.48
GW at delivery	28 (26-30)	30 (27-31)	0	<0.01
Delivery at <28 w	45.3% (n=68)	29.3% (n=22)	0	<0.05
Birth weight (g)	953 (772.5-1258)	1248 (916-1476)	0	<0.001
SGA	16.7% (n=25)	12.0% (n=9)	0	0.43
ELBWI	53.7% (n=82)	32.0% (n=24)	0	<0.01
Male	48.0% (n=72)	61.3% (n=46)	0	0.06
Apgar score at 1 min <3	24.0% (n=36)	12.0% (n=9)	0	<0.05

Apgar score at 5 min <6	8.0% (n=12)	2.7% (n=2)	0	0.15
Calendar year range				
2009-2013	53.1% (n=68)	46.8% (n=60)	0	<0.0001
2014-2018	84.5% (n=82)	15.5% (n=15)	0	

Continuous variables are shown as the median (interquartile range), and categorical variables are shown as % (n). Statistical differences between the 150 infants with early amino acid supplement and the 75 infants of control were tested using the Wilcoxon test, χ^2 test, or Fisher's exact test. Those variables for which differences are significant are in bold font.

DM: diabetes mellitus, GDM: gestational diabetes mellitus, pPROM: preterm premature rupture of membranes, HDP: hypertension disorder of pregnancy, HELLP: hemolysis, elevated liver enzyme, low platelets syndrome, AFLP: acute fatty liver of pregnancy, NRFS: non-reassuring fetal status, GW: gestational week, SGA: small for gestational age, ELBWI: extremely low birth weight infant.

Table 2. Neonatal data, management, complications and outcomes between infants with versus without early amino acid supplement.

	AA supplement n=150	Control n=75	Missing value	p value
Neonatal data				
Urination at 0 days of life (ml/kg/h)	2.6 (1.8-3.5)	2.3 (1.6-3.1)	1	0.06
PH	7.42 (7.35-7.49)	7.37 (7.23-7.45)	2	<0.01
HCO₃⁻ (mmol/l)	19.6 (17.5-21.5)	20.5 (19.4-22.5)	3	<0.01
Glucose (mg/dl)	83 (59-103)	81.5 (61-96)	3	0.77
Na⁺ (mEq/l)	140 (136-145)	137 (135-142)	0	<0.01
K⁺ (mEq/l)	4.6 (4.1-5.3)	5.0 (4.5-5.7)	0	<0.01
iCa ²⁺ (mmol/l)	1.23 (1.14-1.34)	1.23 (1.13-1.33)	0	0.76
Infusion at 0 days of life				
WQ (ml/kg/day)	70 (62-82)	65 (60-70.5)	0	<0.01
GIR (mg/kg/min)	4.8 (4.4-5.3)	4.2 (4-4.4)	0	<0.001
Ca⁺ (mEq/kg/day)	2.2 (1.8-2.7)	1.2 (0-3.3)	0	0.11
AA (g/kg/day)	2.4 (2.1-2.8)	0	0	<0.0001
Neonatal complications and outcomes				
Neonatal hyperkalemia	2.7% (n=4)	12.0% (n=9)	0	<0.05
BPD	49.3% (n=74)	41.3% (n=31)	0	0.25
IVH	8.0% (n=12)	5.3% (n=4)	0	0.59
PVL	4.0% (n=1)	0.7% (n=3)	0	0.11
NEC	0.7% (n=1)	1.3% (n=1)	0	1.00
PDA ligation	3.3% (n=5)	2.7% (n=2)	0	1.00
ROP treatment	12.7% (n=19)	10.7% (n=8)	0	0.82
Mortality	7.3% (n=11)	6.7% (n=5)	0	1.00
Neurological impairment	5.3% (n=8)	10.7% (n=8)	0	0.17

Continuous variables are shown as the median (interquartile range), and categorical variables are shown as % (n). Statistical differences between the 150 infants with early amino acid supplement and the 75 infants of control were tested using the Wilcoxon test, χ^2 test, or Fisher's exact test. Those variables for which differences are significant are in bold font.

WQ: water quantity, GIR: glucose infusion rate, AA: amino acid, BPD: bronchopulmonary dysplasia, IVH: intraventricular hemorrhage, PVL: periventricular leukomalacia, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, ROP: retinopathy of prematurity.

Table 3. Effects of various risk factors for hyperkalemia and potential prophylactic strategies against neonatal hyperkalemia

Risk factors	Univariate analysis			Multivariate analysis		
	Crude odds ratio		p value	Adjusted odds ratio		p value
	(95%CI)			(95%CI)		
Maternal characteristics and management						
Maternal aged>35	1.10	(0.29-3.52)	0.87	1.10	(0.25-4.76)	0.89
Primipara	1.51	(0.48-5.14)	0.48	2.72	(0.56-13.17)	0.21
Multiple pregnancy	1.30	(0.34-4.17)	0.67	0.40	(0.06-2.90)	0.37
Antenatal steroid	2.30	(0.74-7.83)	0.15	2.64	(0.57-12.17)	0.21
MgSO ₄ alone ^a	3.67	(0.42-14.54)	0.34	3.30	(0.06-188.03)	0.83
Ritodrine alone ^a	2.95	(0.61-21.12)	0.18	1.93	(0.22-17.09)	0.55
MgSO ₄ and ritodrine ^a	2.04	(0.43-14.54)	0.39	0.76	(0.06-8.90)	0.83
Cesarean section	1.02	(0.32-3.86)	0.98	3.21	(0.42-24.91)	0.26
Neonatal characteristics and management						
Male	2.12	(0.64-7.12)	0.22	2.56	(0.58-11.32)	0.21
Delivery at <28 weeks	5.50	(1.63-25.07)	<0.01	10.93	(1.78-66.79)	<0.01
SGA	1.02	(0.15-4.04)	0.98	0.98	(0.15-6.67)	0.98
NRFS	0.92	(0.27-3.10)	0.89	0.46	(0.07-2.79)	0.39
Apgar score <3 at 1 min	1.85	(0.54-6.32)	0.32	2.13	(0.41-10.87)	0.36
AA supplement	0.20	(0.05-0.64)	<0.01	0.11	(0.02-0.56)	<0.01
Calendar year						
2009-2013	1	-	-	1	-	-
2014-2018	0.38	(0.08-1.27)	0.12	0.77	(0.11-4.93)	0.78

Those variables for which differences are significant are in bold font.

CI: confidence interval, NRFS: non-reassuring fetal status, SGA: small for gestational age, WQ: water quantity, AA: amino acid

Figures

Figure 1

Enrollment flowchart

Supplementary Files

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