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Benefits and Risks of Preprepared Parenteral Nutrition for Early Amino Acid Administration in Premature Infants with Very Low Birth Weight

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ABSTRACT

Purpose: Administering early parenteral amino acids to very low birth weight (VLBW) premature infants (birth body weight [BBW]<1,500 g) is challenging due to factors such as holidays, cost, and access to sterile compounding facilities. Using advance-prepared parenteral nutrition (PN) may address this issue and should be evaluated for its safety and potential benefits.
Methods: We extracted data from medical records collected between July 2015 and August 2019. VLBW infants received PN for at least seven days and were split into two groups: the traditional group (n=30), which initially received a glucose solution and then PN on workdays, and the pre-preparation group (n=16), which received advance-prepared PN immediately upon admission to the neonatal intensive care unit.
Results: The median BBWs of the traditional and pre-preparation groups were 1,180.0 vs. 1,210.0 g. In the initial two days, the pre-preparation group had a significantly higher amino acid intake (2.23 and 2.24 g/kg/d) than the traditional group (0 and 1.78 g/kg/d). The pre-preparation group exhibited greater head circumference growth ratio relative to birth (7th day: 1.21% vs. −3.57%, p=0.014; 21st day: 7.71% vs. 3.31%, p=0.017). No significant differences in metabolic tolerance were observed.
Conclusion: Advanced preparation of PN can be safely implemented in VLBW preterm infants, offering advantages such as early, higher amino acid intake and improved head circumference growth within the first 21 days post-birth. This strategy may serve as a viable alternative in settings where immediate provision of sterile compounding facilities is challenging.

Keywords: Parenteral nutrition; Amino acids; Infant, very low birth weight; Infant, premature

Conflict of Interest
The authors have no financial conflicts of interest.

INTRODUCTION

Parenteral nutrition represents a standard therapeutic approach for premature infants who are unable to derive sufficient energy through intestinal feeding, exhibit unstable vital signs, or require temporary fasting, particularly for very low birth weight (VLBW) premature infants [1,2]. Current guidelines recommend initiating amino acid supplementation on the first postnatal day, starting with at least 1.5 g/kg/d to achieve an anabolic state, followed by escalation to greater than 2 g/kg/d as soon as feasible post-birth [3,4].

The early administration of amino acids, relative to a later onset, may enhance nitrogen balance in preterm infants receiving parenteral nutrition; however, this strategy has been linked to an inconclusive increase in the risk of metabolic acidosis post-birth [5,6]. Notably, very low-quality evidence suggests that an elevated intake of amino acids could mitigate the occurrence of postnatal growth failure [7].

As a public district hospital experiencing significantly low birth rates in our country, the logistical challenge of maintaining pharmacists for the on-call production of parenteral nutrition solutions in sterile compounding facilities that adhere to United States Pharmacopeia 797 standards [8] is a substantial issue because of the cost of labor and consumables. This problem is more pronounced during holidays, when clinicians aspiring to meet guideline recommendations are compelled to resort to lower-level amino acids and parenteral nutrition solutions prepared at nursing stations. Sterile compounding and adherence to established standards are paramount to ensure patient safety. Non-sterile compounded medications can be sub-potent or contaminated, posing a substantial risk of adverse events, such as infection [8].

In an attempt to address this issue, we turned to the concept of using a “stock” amino acid and dextrose solution, a notion first introduced in seminars [9]. Despite the absence of formal literature describing this approach, it inspired our nutritional support team to reach a consensus on dispensing pre-prepared parenteral nutrition weekly, prepared by a pharmacist using aseptic techniques, and stored in the neonatal intensive care unit (NICU) refrigerator. The pre-prepared parenteral nutrition solution was prepared as follows. In a cleanroom with an ante room (ISO-Class 8), a buffer room (ISO-Class 7), and laminar airflow hoods (ISO-Class 5), the pharmacist, after disinfection, wore disposable covers for shoes, a gown, face mask, and sterile gloves. Using aseptic techniques, they combined 160 mL of 10% glucose, 21.3 mL of 50% glucose, 90 mL of 10% amino acids (infant), and 9 mL of 10% calcium gluconate in a sterile empty bottle, sequentially. Finally, 130 U of heparin was added, the bottle was sealed with parafilm, and a detailed label was affixed; the final formula content is outlined in **Table 1**. This enabled clinicians to promptly administer parenteral nutrition to premature babies upon their admittance to the NICU.

Table 1. Pre-preparation formulation of parenteral nutrition for premature infants

Component	Concentration
Carbohydrate content	9.3%
Amino acid content (brand: Aminosteril infant 10%)	3.2%
Calcium	15 mEq/L
Heparin	0.45 IU/mL
Total volume	280 mL

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We also revised the guidelines to verify that pre-prepared parenteral nutrition maintains stability and sterility for one week [10]. We expect that this strategy would facilitate the safe and rapid (within 24 hours) provision of parenteral nutrition to premature infants while ensuring a high level of amino acids in alignment with guideline recommendations. This retrospective cohort study evaluated the safety and efficacy of this treatment.

MATERIALS AND METHODS

This retrospective cohort study was conducted using medical records extracted from NICU patients over a four-year period from July 2015 to August 2019. This study was approved by the Taipei City Hospital Research Ethics Committee (reference no. TCHIRB-10810009-E).

The inclusion criteria for the study were VLBW preterm infants with a birth body weight (BBW) of 1,500 g or less, and those receiving parenteral nutrition for a minimum of seven days. The exclusion criteria included infants demonstrating good enteral nutrition tolerance (defined as consuming over 50% of the total daily calories within the first five days of birth), infants who died within 24 hours after birth, and infants with congenital anomalies. The study design and flowchart are shown in **Fig. 1**.

This study was divided into two categories of infant participants: the traditional group (n=30) from July 2015 to July 2017 and the pre-preparation group (n=16) from August 2017 to August 2019. In the traditional group, during the initial one to two days after birth, the infants typically received basic parenteral nutrition prepared at the nursing station, often consisting solely of a dextrose solution. The parenteral nutrition prescription was determined by neonatologists and prepared in a sterile room during working days, but was not available during holidays. Pharmacists prepared the parenteral nutrition prescriptions that include glucose, amino acids, electrolytes, vitamins, and trace elements. Lipids were sourced from commercial products. Over time, the medical team attempted to increase nutritional intake to align with the recommendations set out in the ESPEN guidelines [4,11,12]. Enteral feeding with either breast milk or donated breast milk was gradually introduced as tolerated by the infant, with corresponding adjustments made to parenteral feeds.

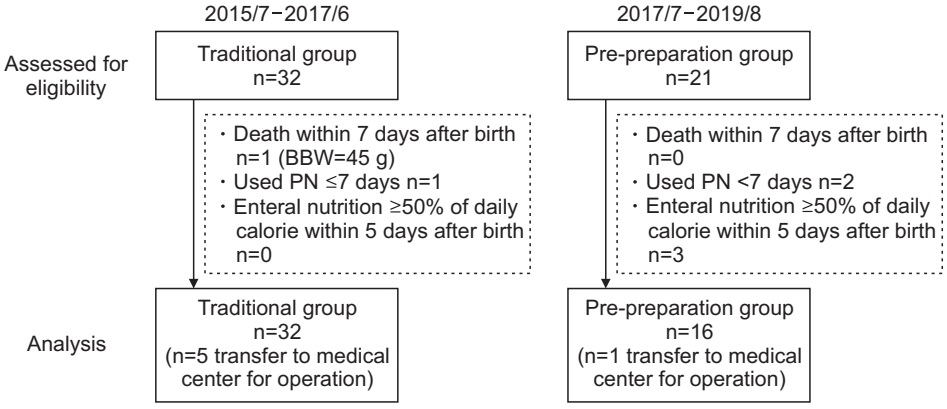

Fig. 1. Flowchart illustrating the patient selection process. Clinical data for each infant in this study were obtained from medical records.
BBW: birth body weight, PN: parenteral nutrition.

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The infants in the pre-preparation group received pre-prepared parenteral nutrition upon their immediate admission to the NICU, regardless of the time of day or holiday. The same process used in the traditional group was adopted on regular working days. If administered at 80 mL/kg/day, this formula provided 2.56 g/kg/d of amino acids and a glucose infusion rate (GIR) of 5.16 mg/kg/min.

The data collected included demographic and anthropometric data, maternal disease and medication around the time of birth, enteral and parenteral nutrition status within the first five days of birth, length of NICU stay, duration of parenteral nutrition, and time taken for infants to regain their BBW. Physical examination data were collected on the 1st, 7th, 14th, and 21st days of life, and changes in body weight and head circumference were compared with birth values and presented as percentages. The Score for Neonatal Acute Physiology, Version II (SNAP II) and Score for Neonatal Acute Physiology, Perinatal Extension, Version II (SNAPPE II) scores were calculated based on the data collected from the medical records [13].

This study hypothesized that early life amino acid intake would be higher in the pre-preparation group owing to pre-prepared parenteral nutrition. Possible adverse reactions were monitored and metabolic tolerance was assessed by measuring blood urea nitrogen (BUN), pH, and $PaCO_2$ [14]. In an effort to minimize bias, data were also collected on intestinal nutrition, and intake data were split into total and intravenous categories. Within the carbohydrate data, the GIR was specifically highlighted because of its dependence on individual variations in blood sugar levels, energy demand, and postnatal weight loss [12].

Statistical analysis

Nutritional data and sequential changes are presented as mean and standard deviation and were then tested using an independent sample *t*-test. The characteristics and outcomes are expressed as medians with the first quartile (Q1) and third quartile (Q3), as these variables were not normally distributed. Continuous variables were tested using the Mann-Whitney *U*-test, while categorical variables were analyzed using Fisher's exact test and the chi-square test. Statistical significance was set at a 2-tailed *p*-value of <0.05, and all analyses were conducted using the SPSS 22 software (IBM Co.).

RESULTS

The clinical characteristics of the infants are summarized in **Table 2**. The traditional group consisted of 30 premature infants, whereas the pre-preparation group included 16 infants. Following a normal distribution analysis, the data are presented as medians (Q1 and Q3) or quantities (percentages). The gestational age (GA) was 29.0 (27.0, 31.0) weeks in the traditional group versus 28.9 (28.5, 32.1) weeks in the pre-preparation group. The BBW in the traditional and pre-preparation groups were 1,180.0 (835.0, 1,310.0) g and 1,210.0 (943.8, 1,315.0) g, respectively. Both head circumference and length at birth were proportional to the GA, showing no significant difference between the two groups. Additionally, there was no observed sex imbalance or inconsistency in the proportion of twins among groups. High rates of cesarean sections were noted in both groups (76.6% vs. 87.5%), which may be associated with lower mortality in extremely premature infants, as indicated in the literature [15].

Disease severity and risk of death were assessed using the Apgar, SNAP, and SNAPPE II scores [13,16]. The first- and fifth-minute Apgar scores showed no significant differences between

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Table 2. Clinical characteristics

	Traditional (n=30)	Pre-preparation (n=16)	*p*-value*
BBW (g)	1,180.0 (835.0–1,310.0)	1,210.0 (943.8–1,315.0)	0.800
Sex, male	15 (50.0)	7 (43.8)	0.686
GA (wk)	29.0 (27.0–31.0)	28.9 (28.5–32.1)	0.253
Birth head circumference (cm)	26.6 (24.5–28.0)	26.6 (24.8–27.4)	0.094
Birth length (cm)	36.5 (33.4–39.1)	39.0 (36.3–40.0)	0.908
Twins	4 (13.3)	2 (12.5)	>0.999
Cesarean section	23 (76.7)	14 (87.5)	0.463
Apgar 1˚ min	5.0 (4.0–7.0)	6.0 (4.0–7.0)	0.727
Apgar 5˚ min	8.0 (6.0–8.5)	7.5 (6.3–8.0)	0.733
SNAP II	5.0 (0.0–12.0)	8.0 (5.0–15.0)	0.185
SNAPPE II with 1 min Apgar	23.0 (14.25–30.0)	31.5 (9.75–37.0)	0.386
SNAPPE II with 5 min Apgar	12.0 (5.0–22.3)	14.0 (5.0–32.5)	0.719
Maternal disease	21 (70.0)	15 (93.8)	0.130
Any prenatal steroid	23 (76.7)	15 (93.8)	0.230
Any prenatal antibiotics	17 (56.7)	11 (68.8)	0.424
PDA	14 (46.7)	5 (31.3)	0.393
RDS	30 (100.0)	15 (93.8)	0.348

Values are presented as median (Q1–Q3) or number (%).
BBW: birth body weight, GA: gestational age, SNAP II: Score for Neonatal Acute Physiology, Version II, SNAPPE II: Score for Neonatal Acute Physiology, Perinatal Extension, Version II, PDA: patent ductus arteriosus, RDS: respiratory distress syndrome.
*Tested using the Mann–Whitney *U* and chi-square tests.

the groups. The scores in the first minute were lower than those in healthy infants (usually a score of 7 to 10) (5.0 [4.0, 7.0] vs. 6.0 [4.0, 7.0]), but the fifth-minute scores (8.0 [6.0, 8.5] vs. 7.5 [6.3, 8.0]) did not appear to correlate with mortality [17]. Despite individual variations in SNAP and SNAPPE II scores, consistency was noted between the groups.

There were no significant differences in medication use (steroids and antibiotics) or maternal diseases between the two groups. Maternal diseases included preeclampsia, preterm premature rupture of membranes, placental abruption, placental thrombosis, placenta previa, intrauterine growth restriction, gestational hypertension, gestational diabetes mellitus, and antepartum hemorrhage. The incidences of patent ductus arteriosus and respiratory distress syndrome were also not significantly different between the two groups [18,19]. Overall, baseline characteristics were similar between the groups.

Carbohydrates, proteins (amino acids), and fats (lipids) were the primary macronutrients analyzed because of the modification in pre-preparation parenteral nutrition within the first two days post-birth. Consequently, we focused on the daily intake of amino acids, carbohydrates, and lipids during the initial five days of life, as summarized in **Table 3**.

Consistent with expectations, the administered amount of amino acids was significantly greater in the pre-preparation group than in the traditional group during the first two days of life (Day 0: 2.23±0.20 vs. 0 g/kg/d, $p<0.001$; Day 1: 2.24±0.36 vs. 1.78±0.48 g/kg/d, $p=0.002$). Significant differences persisted over the subsequent four days.

In the carbohydrate analysis, prior to the era of advanced preparation, the medical team utilized a commercial intravenous glucose infusion as the primary solution.

Lipid analysis revealed that neither group received lipids on the day of birth. However, on the first and second days, the pre-preparation group displayed a greater total intake (Day 1: 0.23±0.35 vs. 0.0 g/kg/d, $p=0.018$; Day 2: 0.65±0.44 vs. 0.35±0.34 g/kg/d, $p=0.014$).

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Table 3. Sequential changes in parenteral and daily total nutrition during the first five days after birth in premature infants

Day	Traditional (n=30)		Pre-preparation (n=16)		*p*-value*	
	Amino acids (g/kg/d)					
	Total	Parenteral form	Total	Parenteral form	Total	IV
D0	0.0	0.0	2.23±0.20	2.23±0.20	<0.001	<0.001
D1	1.78±0.48	1.72±0.58	2.24±0.36	2.23±0.36	0.002	0.002
D2	2.08±0.37	2.00±0.52	2.58±0.44	2.56±0.43	<0.001	0.001
D3	2.46±0.51	2.33±0.66	2.75±0.44	2.70±0.42	0.062	0.047
D4	2.60±0.40	2.47±0.61	2.91±0.40	2.85±0.39	0.016	0.026
D5	2.65±0.46	2.50±0.65	3.06±0.48	2.97±0.47	0.007	0.016

Day	Carbohydrates, CHO (g/kg/d)				*p*-value*	
	Total	Parenteral form	Total	Parenteral form	Total	IV
D0	6.71±0.90	6.71±0.90	6.62±0.60	6.62±0.60	0.724	0.724
D1	7.15±1.50	7.15±1.50	6.94±0.75	6.86±0.72	0.607	0.489
D2	7.87±1.35	7.82±1.33	7.45±0.89	7.32±0.91	0.279	0.187
D3	8.85±1.39	8.72±1.40	8.27±1.28	7.99±1.20	0.175	0.086
D4	9.27±1.42	9.07±1.40	8.99±1.87	8.66±1.86	0.568	0.399
D5	9.35±1.61	9.08±1.57	9.48±2.01	8.99±2.02	0.810	0.868

Day	Glucose infusion rate, GIR (mg/kg/min)		*p*-value*
	Parenteral form	Parenteral form	IV
D0	4.63±0.70	4.59±0.42	0.850
D1	5.00±1.01	4.86±0.60	0.633
D2	5.40±0.94	5.17±0.74	0.394
D3	6.04±0.98	5.51±0.80	0.068
D4	6.31±0.98	6.01±1.29	0.381
D5	6.24±1.08	6.22±1.31	0.961

Day	Lipids (g/kg/d)				*p*-value*	
	Total	Parenteral form	Total	Parenteral form	Total	IV
D0	0.0	0.0	0.0	0.0		
D1	0.0	0.0	0.23±0.35	0.21±0.34	0.018	0.027
D2	0.35±0.34	0.32±0.32	0.65±0.44	0.59±0.43	0.014	0.018
D3	0.73±0.40	0.65±0.36	0.99±0.46	0.84±0.42	0.057	0.107
D4	0.98±0.38	0.87±0.34	1.23±0.42	1.04±0.42	0.051	0.141
D5	1.32±0.47	1.20±0.43	1.52±0.54	1.27±0.59	0.206	0.627

Values are presented as mean±standard deviation.
*Tested with Student's *t*-test.

Thereafter, no significant differences emerged between the two groups over the next three days.

Table 4 illustrates the daily sequential changes in energy, fluid, and enteral nutrition ratio across the first five days of life. The total daily fluid target administered to premature infants in the intensive care unit remained consistent over a period of four years.

On the day of birth, a significant difference in total daily energy was observed (35.42±3.22 vs. 26.48±4.38 kcal/kg/d, $p<0.001$), primarily due to the administration of parenteral amino acids. However, no significant differences were found on the subsequent days.

In line with recent recommendations [20], the pre-preparation group endeavored to provide enteral nutrition on the day of birth. Notably, this practice can influence growth and other outcomes. Consequently, we included the ratio of the daily caloric intake in our analysis.

Several infants were transferred to higher-level hospitals for specialized treatments such as cardiac surgery when stable, potentially introducing bias into our data. After adjusting for

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Table 4. Sequential changes in total energy, fluid, and enteral nutrition ratios

Day	Traditional (n=30)	Pre-preparation (n=16)	*p*-value*
	Energy (kcal/kg/d)		
D0	26.48±4.38	35.42±3.22	<0.001
D1	35.65±6.25	38.71±4.87	0.097
D2	43.03±7.53	45.87±8.13	0.242
D3	52.31±9.06	53.52±8.72	0.665
D4	57.65±7.00	58.96±9.09	0.590
D5	61.27±9.70	64.74±9.24	0.245
	Fluid (mL/kg/d)		*p*-value*
D0	66.59±11.07	69.58±6.33	0.325
D1	81.74±10.04	78.43±6.59	0.242
D2	91.04±9.79	91.14±9.30	0.973
D3	99.18±11.95	98.64±9.52	0.878
D4	105.71±11.07	107.38±12.97	0.649
D5	108.66±13.28	113.73±14.61	0.240
	Enteral nutrition ratio of daily calorie (%)		*p*-value*
D0	0.00	0.36±1.46	0.333
D1	0.00	0.99±2.82	0.179
D2	1.33±3.19	2.74±2.82	0.147
D3	2.32±3.71	4.53±3.18	0.049
D4	3.42±5.77	5.85±4.71	0.155
D5	5.22±8.43	7.80±7.91	0.319

Values are presented as mean±standard deviation.
*Tested with Student's *t*-test.

this, we found no significant differences between the two groups in the length of NICU stay, duration of parenteral nutrition, or time required to regain birth weight (**Table 5**).

Given the small sample size of preterm infants, the ratio of body weight change from birth is presented as the median (Q1, Q3) in **Fig. 2**. A statistically significant difference was observed on the 7th day, with the pre-preparation group experiencing less body weight loss (−6.74 [−10.38, −3.94]% vs. −11.11 [−15.09, −7.27]%, p=0.030).

The pre-preparation group also showed an advantage in the ratio of head circumference change from birth, starting from the 7th day (1.21 [−1.85, 4.00]% vs. −3.57 [−5.19, 0.36]%, p=0.014) and persisting to the 21st day (7.71 [3.03, 13.10]% vs. 3.31 [0.00, 6.52]%, p=0.017). This trend is illustrated in **Fig. 3**.

Table 5. Growth performance of preterm infants

	Traditional (n=30)		Pre-preparation (n=16)		*p*-value§
	n	Median (Q1, Q3)	n	Medium (Q1, Q3)	
Length of NICU stay (d)*	24	55.55 (42.23, 67.65)	15	60.80 (39.07, 74.92)	0.773
Days to regain birth weight (d)†	29	14.00 (10.00, 16.00)	16	13.25 (10.70, 15.15)	0.785
Duration of PN (d)‡	27	19.00 (14.00, 27.00)	16	22.5 (13.25, 27.00)	0.840
7th day: body weight difference compared to birth (%)	29	−11.11 (−15.09, −7.27)	15	−6.74 (−10.38, −3.94)	0.030
7th day: head circumference difference compared to birth (%)	29	−3.57 (−5.19, 0.36)	15	1.21 (−1.85, 4.00)	0.014
14th day: body weight difference compared to birth (%)	29	1.45 (−4.20, 5.12)	16	0.35 (−1.66, 6.77)	0.767
14th day: head circumference difference compared to birth (%)	29	0.00 (−1.81, 2.12)	15	2.84 (0.00, 8.00)	0.011
21st day: body weight difference compared to birth (%)	26	13.87 (6.99, 19.26)	16	14.65 (9.17, 26.10)	0.623
21st day: head circumference difference compared to birth (%)	26	3.31 (0.00, 6.52)	14	7.71 (3.03, 13.10)	0.017

NICU: neonatal intensive care unit, PN: parenteral nutrition.
*Excludes patients who were transferred to a medical center because of illness but were still in the NICU.
†Excludes patients who were transferred to the medical center due to illness but whose body weight is still under BBW.
‡Excludes patients who were transferred to the medical center due to illness but still under parenteral nutrition.
§Tested using the Mann-Whitney *U*-test.

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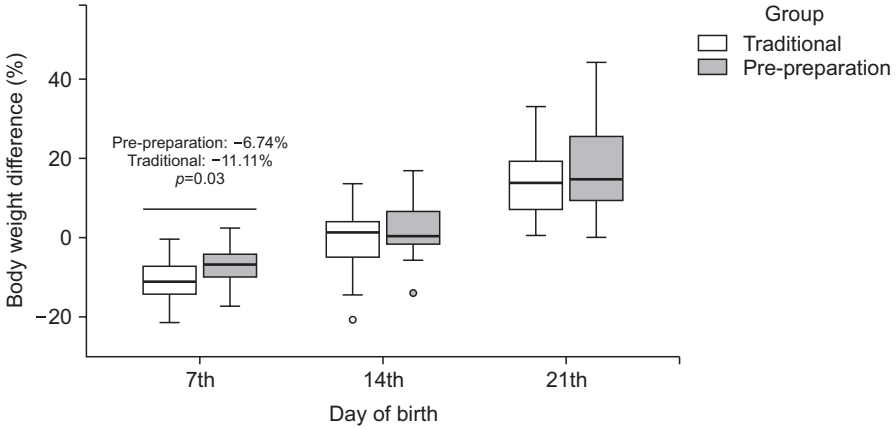

Fig. 2. Changes in body weight difference compared to weight at birth.

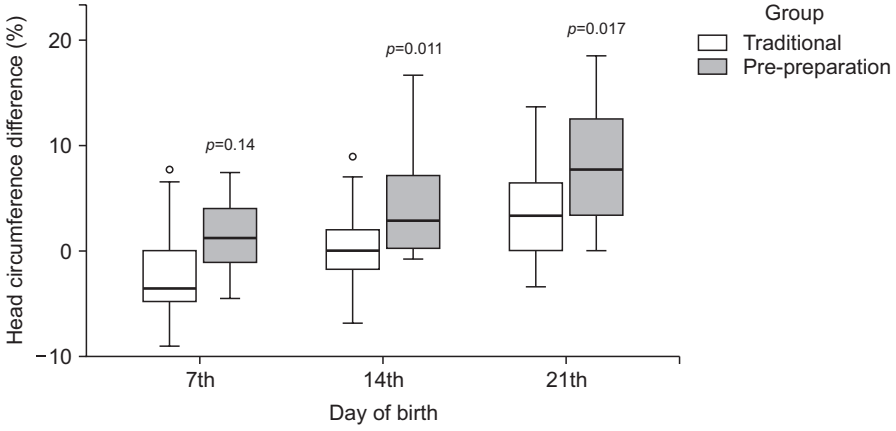

Fig. 3. Changes in head circumference difference compared to circumference at birth.

Finally, the attending neonatologist determined the frequency and timing of laboratory tests, including arterial blood gas and biochemistry tests. As there were limited data after the first two days of birth, we compared these variables during the initial two days. We were concerned that severe acidosis could be disregarded; hence, even with the somewhat scattered data from the initial five days postpartum, we scrutinized cases with a pH <7.1 for comparison. When blood was drawn, this usually indicated suspicion of acidosis by the clinician at that time. We found no significant difference in pH and $PaCO_2$ values between the two groups; however, there was a marked increase in BUN in the pre-preparation group within the first two days after birth (7.50 [6.26, 9.07] mmol/L vs. 6.07 [4.75, 7.03] mmol/L) (**Table 6**).

Table 6. Acid–base parameters and outcomes

	Traditional (n=30)	Pre-preparation (n=16)	*p*-value*
Blood pH on D0	7.21 (7.18, 7.28)	7.2 (7.14, 7.27)	0.413
Blood pH on D1	7.36 (7.30, 7.39)	7.34 (7.29, 7.42)	0.987
Blood pH <7.1 within 5 days of birth	2 (6.70)	3 (18.80)	0.325
$PaCO_2$ (mm Hg) on D0	53.40 (48.98, 57.50)	52.40 (33.00, 58.40)	0.406
$PaCO_2$ (mm Hg) on D1	37.10 (32.00, 45.70)	38.20 (29.05, 45.85)	0.962
Blood urea (mmol/L) on D0 or D1	6.07 (4.75, 7.03)	7.50 (6.26, 9.07)	0.009

Values are presented as medians (Q1, Q3) or number (%). D0: day 0, D1: day 1.
*Tested using the Mann-Whitney *U* and Fisher's exact tests.

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DISCUSSION

The strengths of this study lie in the meticulous collection of data on daily nutrient and fluid intake within the first five days after birth for each case. The detailed presentation of oral and enteral contributions helps negate the potential confounding influence of enteral nutrition. Moreover, the study carefully gathered and analyzed data regarding medications and disease conditions between the two groups, thereby confirming the comparable severity of diseases in both groups.

One notable finding was the inability of the traditional group to supply parenteral amino acids on day 0, potentially resulting in delays if the infant was born at night or during a holiday, when a sterile compounding room might not be immediately available. Despite the clinicians' attempts to supplement carbohydrates, the total caloric intake remained relatively low on day 0. Of note, although the intake of amino acids in both groups over the first five days was lower than the current standards [4], pre-preparation nutrition ensured that premature infants received parenteral amino acids within 24 hours of birth. This approach significantly expedited the time needed to reach the amino acid intake target of 3 g/kg/d, which is particularly important for small hospitals, and provides a clear endorsement of pre-preparation nutrition initiatives.

These results further suggest that pre-preparation nutritional regimens may benefit from adjustments to allow for higher amino acid concentrations, thereby aligning more closely with the clinical guidelines.

The nutritional compositions of the two groups over the five days following birth were assessed and found to be similar in terms of carbohydrate content, GIR, and daily fluid intake.

The enteral nutrition ratio demonstrated a somewhat conservative approach to early enteral nutrition in the traditional group. Notably, most infants in both groups were either fasting or were administered water only on days 0 and 1 post-birth.

The increasing number of studies over the last decade confirming the safety of early enteral nutrition may account for this trend [2,21]. Nevertheless, the administration of low-volume feed was necessitated by enteral intolerance and apprehensions about potential complications such as necrotizing enterocolitis, thereby eliminating significant differences between the two groups.

Another disparity concerns the lipid intake on days 1 and 2. With the safety of lipid emulsions now confirmed, current guidelines recommend starting lipid emulsions immediately after birth or, at the latest, on the second day after birth [11].

Despite these minor variations, the principal impact was on the total calorie intake on the first day after birth. The main variation in the subsequent five days was related to the delivery of amino acids. Based on these similarities, we investigated the additional disparities in outcomes. The pre-preparation group was able to offer higher concentrations of parenteral amino acids (>2 g/kg/d) to extremely low-birth-weight premature infants within 24 hours of birth. This rendered the cohorts analyzed in this study more akin to groups characterized by differences in the administration of high concentrations of amino acids in the early and late stages (>24 hours), as shown in **Tables 3** and **4**.

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However, the growth advantages of early administration of parenteral amino acids remain uncertain [6,7]. No discernible differences were observed in the duration of NICU stay or the duration of parenteral nutrition between the two groups. This lack of variation is likely attributable to the influence of other factors, corroborating findings from other studies [22, 23].

A previous study reported a positive correlation between increased intake of calories and protein and head circumference growth [24]. However, systematic reviews have not corroborated this finding [6]. Our study demonstrated that early administration of parenteral amino acids led to a significant increase in head circumference growth over a span of three weeks, which aligns with previous studies [7]. Although the initial lipid intake discrepancy might have influenced this outcome, the similarities in the total caloric intake lend credibility to our results. A significant difference in weight was apparent only in the first week of life, which subsequently disappeared. This pattern is consistent with the majority of studies regarding timeframes for regaining birth weight. In previous reports, growth effects at different time points varied. Statistically significant findings were often observed in analyses based on grams but less frequently in percentage-based analyses. However, in this study, we chose to present the data in percentage terms because we believe that this is more significant. However, the limited number of cases may have reduced the statistical power concerning weight [7].

The group that received pre-prepared parenteral nutrition exhibited a significant upward trend in BUN levels, which may be associated with the early administration of higher parenteral amino acids [5,25,26]. The observed BUN elevation was consistent with the findings of another study [14]. There was no significant difference in blood pH between the two groups within the initial 48 hours after birth, which is consistent with previous research [6]. Furthermore, no difference was detected in the incidence of severe acidosis (pH<7.1) within the first five days after birth. These findings help to reduce concerns regarding the potential onset of metabolic acidosis due to the use of pre-preparation parenteral nutrition.

Limitations

The primary limitation of this retrospective study pertains to data completeness, potentially stemming from the fragile health conditions of premature infants, which occasionally results in missing physical examination data. The study spanned a long enrolment period, with variations in attending clinicians and pharmacists between subjects. Although this variation may have affected the two groups, parenteral nutrition prescriptions were always discussed with the same NICU intensivists, and pharmacists consistently followed the same guidelines when assessing parenteral nutrition. Our findings regarding head circumference growth warrant further investigation in future studies with larger sample sizes and more comprehensive tracking. Our initial aim was to analyze the daily changes in blood gas and biochemical values during the first week after birth. However, routine tests were conducted only 48 hours after birth. Consequently, we presented the most comprehensive data possible for the initial two-day period. Furthermore, the COVID-19 pandemic affected data collection efforts, leading to a reduced number of participants in the pre-preparation group.

Conclusion

In summary, this investigation substantiates that pre-preparation parenteral nutrition in extremely low-birth weight premature infants can serve as a safe and efficacious source of intravenous nutrition within the first 24 hours after birth. Notably, this intervention appeared to promote head circumference growth during the initial 21 days following birth without

causing serious adverse reactions. Therefore, this strategy may be a promising option for hospitals operating in regions with relatively limited medical resources.

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