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Research Article

Metabolic, Electrolyte, and Hepatobiliary Complications of Parenteral Nutrition in Neonates: A Prospective Case-Series Study

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Abstract

Background: Parenteral nutrition (PN) is a life-saving intervention for neonates who are unable to meet their nutritional requirements through enteral feeding. Despite its essential role, PN is frequently associated with metabolic, electrolyte, and hepatobiliary complications. ***Objective***: To evaluate the frequency and pattern of metabolic, electrolyte, and hepatobiliary complications associated with PN administration in neonates. ***Methods***: A prospective case-series study was conducted in two tertiary neonatal intensive care units (NICUs) in Baghdad, Iraq. Term and preterm neonates who received PN for at least five days were included. PN-related metabolic, electrolyte, hepatobiliary, and hematological complications were recorded and analyzed. ***Results***: Of the 94 neonates included in the primary outcome. The incidence of hypoglycemia is 35.1%, and hyperglycemia is 31.9%. Cholestasis 11.7%, hypokalemia 20.2%, hyponatremia 18%, hypocalcemia 27.6%, and thrombocytopenia 28.7%. The mean ± standard deviation of gestational age was 32.1±3.8 weeks; for postnatal age at the start of PN, it was 9.72±17.4 days; for the duration of TPN exposure, it was 12.65±9.27 days; and for the weight of the patients at the start and end of TPN, it was 1.7±0.70 and 1.84±0.74 kg, respectively. ***Conclusions***: PN-related metabolic, electrolyte, and hepatobiliary complications are common in neonates. Close monitoring and individualized PN management are essential to improve neonatal outcomes..

Keywords: Cholestasis; Electrolyte imbalance; Metabolic complications; Neonates; Parenteral nutrition.

المضاعفات الأيضية والإلكتروليتية والكبدية الصفارية للتغذية الوريدية في حديثي الولادة: دراسة مستقبلية لسلسلة حالات

الخلاصة

الخلفية: التغذية الوريدية (PN) هي تدخل ينقذ حياة الأطفال الجدد الذين لا يستطيعون تلبية احتياجاتهم الغذائية من خلال التغذية المعوية. على الرغم من دوره الأساسي، غالبا ما يرتبط بمضاعفات الأيض والإلكتروليتات والمضاعفات الكبدية. **الهدف**: تقييم تكرار ونمط المضاعفات الأيضية والإلكتروليتية والكبدية الصفارية المرتبطة بالتغذية الوريدية لدى حديثي الولادة. **الطرائق**: أجريت دراسة حالة مستقبلية في وحدتين ثالثيتين للعناية المركزة لحديثي الولادة (NICUs) في بغداد، العراق. تم تضمين الأطفال الجدد (الولادة المبكرة) لمدة لا تقل عن خمسة أيام. تم تسجيل وتحليل المضاعفات الأيضية والكهروليت والكبد الصفراوي والدموية المرتبطة بالتغذية الوريدية. **النتائج**: من بين 94 طفلا حديث الولادة تم تضمينهم في النتيجة الأولية. معدل حدوث نقص سكر الدم هو 35.1٪ وارتفاع سكر الدم 31.9٪. الكوليستازيس 11.7٪، نقص البوتاسيوم 20.2٪، نقص ناتريميا 18٪، نقص كالسيوم 27.6٪، ونقص الصفيحات 28.7٪. كان متوسط ± الانحراف المعياري لعمر الحمل 32.1±3.8 أسبوعا؛ بالنسبة لعمر ما بعد الولادة في بداية الولادة، كان 9.72±17.4 يوما؛ وخلال فترة التعرض ل TPN، كانت 12.65±9.27 يوما؛ وبالنسبة لوزن المرضى في بداية ونهاية TPN، كان 0.70±1.7 و0.74±1.84 كجم على التوالي. **الاستنتاجات**: المضاعفات الأيضية والإلكتروليتات والكبدية الصفرافية المرتبطة بالتغذية الوريدية شائعة لدى حديثي الولادة. المراقبة الدقيقة والإدارة الفردية للتغذية الوريدية ضرورية لتحسين نتائج حديثي الولادة.

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INTRODUCTION

Parenteral nutrition (PN) is an essential therapeutic modality employed for various medical conditions in both adults and pediatric patients [1]. These pertain to disorders of the gastrointestinal tract (GIT), including intestinal obstruction and inflammatory bowel disease (IBD), as well as severe malnutrition and expected prolonged deprivation [1]. In neonatal environments, parenteral nutrition is integral to delivering essential nutrients to neonates who cannot tolerate enteral feeding [2]. However, it also introduces distinct challenges in drug administration arising from complexities influenced by various factors, including gestational age and body weight, which can affect the absorption and efficacy of medications in neonates receiving parenteral nutrition [3]. The appropriate implementation of this complex therapy aims to optimize therapeutic outcomes while minimizing the risk of adverse effects. To keep patients safe during PN therapy [4,5], formulations must be sterile and made of stable, compatible ingredients, since they are injected directly into the bloodstream and have many parts. Patients may experience injury from an intravenous infusion that is incompatible, unstable, or contaminated, potentially resulting in significant morbidity and even mortality [6]. Consequently, PN formulations must be produced utilizing rigorous aseptic techniques in compliance with established pharmaceutical compounding guidelines [7]. Although PN is acknowledged as a high-alert medication, only a limited number of organizations

have established protocols to prevent dispensing errors and PN-associated patient adverse events [8]. In fact, both the PN preparations themselves and the therapy may potentially lead to complications and treatment-related issues (TRPs). Treatment-related issues, particularly in neonatal patients receiving parenteral nutrition, pose a substantial concern within healthcare environments. Administering medications to this vulnerable population necessitates the highest level of accuracy and vigilance to guarantee optimal patient outcomes [9]. Comprehending the factors that influence the occurrence of TRPs is essential for the formulation and execution of effective prevention and mitigation strategies [10]. Additionally, the frequency and nature of TRPs in this context will offer important insights into the severity of the issue among neonatal populations [3]. Identifying potential factors associated with these complications will allow healthcare professionals to customize interventions that directly address these areas for enhancement [11]. These factors may be associated with issues in medication dosing, drug interactions, or improper administration. Conversely, the issues may pertain to medication selection, inappropriate drug therapy, adverse effects, or untreated conditions [12]. Pharmacists are among the healthcare professionals who could make substantial contributions to this field. They possess medical expertise, enabling them to oversee the administration and preparation of medications [6]. As members of the PN team, they can mitigate PN-related issues by delivering nutrition support services and establishing standard operating procedures for the administration and dispensing of PN in neonatal environments [13]. Pharmacists' interventions improved nutritional support, facilitated weight gain in low birthweight neonates, and decreased healthcare costs. Interdisciplinary collaboration with other healthcare professionals, such as nutritionists, nurses, and physicians, is necessary for this process [14]. All the duties of pharmacists are encompassed within the framework of pharmaceutical care, which organizes their responsibilities to attain the optimal health outcome for the patient [15]. Furthermore, the pharmacy profession within PN contexts has evolved from traditional compounding and dispensing to a highly advanced practice that integrates artificial intelligence and modern technologies [16,17]. Therefore, addressing TRPs and comprehending the related factors can assist healthcare professionals in optimizing medication management protocols and encouraging safer practices in the administration of drugs through parenteral routes. Reducing or eliminating TRPs can enhance overall patient safety, improve treatment outcomes, and optimize resource utilization within neonatology units. This study examines the incidence and possible TRPs in neonatal patients undergoing PN. Furthermore, by identifying these factors, healthcare professionals can acquire a more profound understanding of the underlying causes of TRPs and develop interventions that address them comprehensively.

METHODS

Study design and setting

This is a prospective observational case-series study conducted in two tertiary neonatal intensive care units (NICUs), the Children's Welfare Teaching Hospital and Baghdad Teaching Hospital, in Baghdad, Iraq, from January 27, 2022, to December 15, 2022.

Patient selection

Throughout the study period, 148 preterm and term infants admitted to the NICUs of the Children's Welfare Teaching Hospital and Baghdad Teaching Hospital, necessitating specialized treatment for medical or surgical issues and requiring parenteral nutrition (PN), were deemed eligible. We adhered to the ESPEN/ESPGHAN criteria to ascertain the suitable indications for the utilization of parenteral nutrition (PN). Patient enrollment commenced with the commencement of TPN and concluded upon the conclusion of treatment.

Inclusion criteria

All preterm and term neonates required PN for various indications during admission and received PN for at least 5 days.

Exclusion criteria

Hospital discharge, death, or transfer to another unit within 4 days of starting PN. Patients who receive parenteral nutrition (PN) for less than 5 days are excluded.

Nutritional protocol and steps involved in PN

According to the aforementioned criteria, the initial stage involves the neonatologist and senior clinical pharmacist identifying the patient in need of parenteral nutrition. In the subsequent step, the neonatologist and senior clinical pharmacist devise and customize daily nutritional requirements (amino acids, lipids, and GIR) for each patient during the morning rounds, taking into account gestational age, weight, postnatal age, associated medical conditions, presence of comorbidities, and baseline biochemical profile, as per the recommendations of ESPGHAN guidelines during the study period [18,19]. In the third phase, clinical pharmacy board residents and pharmacists in the mixing unit compute the components of parenteral nutrition. Subsequent to the morning tour, they perform manual calculations and inscribe the results on a preprinted page. The document encompasses the requisite quantities of amino acids, lipids, GIR, final glucose concentration, total caloric content, osmolarity, NPC, NPC-N ratio (nitrogen balance), and total volume of parenteral nutrition, which deducts the total daily fluid requirements from the fluids utilized for antibiotics and other therapies, in addition to the volume of enteral feeding. Because vitamins and trace elements are unavailable, they are not calculated or included in the PN solution. In the fourth phase, the PN solution

is formulated by clinical pharmacy board residents and compounding pharmacists. The formula's sterility was ensured by conducting the process in the local mixing room beneath a laminar airflow hood, employing aseptic techniques in compliance with stringent aseptic protocols. The preparation step involves utilizing a sterile syringe to transfer the contents of the 3-in-1 PN bag, supplied by the hospital pharmacy or by the patients' caretakers during shortages, into a sterile bottle, which will serve as the final container for the infusion process. PN is combined and placed into the final container sequentially: glucose first, followed by amino acids, electrolytes (if applicable), and concluding with lipids. The produced PN solution had a maximum osmolarity of 900 mOsmol/L and a maximum glucose content of 12% due to the utilization of a peripheral line instead of a central line. The PN solution employed was a 3-in-1 formulation; the commercially available product utilized was Smof Kabiven Peripheral® G13%. This PN formula is not designed for neonates, yet the NICUs of both hospitals regularly employed it due to the absence of neonate-specific PN formulas. Upon preparing the 3-in-1 PN, the bottle is encased in aluminum foil to shield it from light exposure. The fifth step involves administering the prepared parenteral nutrition solution through peripheral venous access. Three specific individuals received parenteral nutrition by central line and exhibited no mechanical problems related to central intravenous access, including thrombosis and occlusion. The PN solution was continuously fed via an infusion pump for 24 hours, with interruptions occurring during the administration of antibiotics and other medications through the same IV line. The objective of halting the infusion process is to recycle the lipid infusion; hence, it contributes to the mitigation of PNALD [20]. TPN (Total Parenteral Nutrition) monitoring constitutes the sixth phase.

Management protocol and outcome assessment

The neonatologist identifies the patient who requires PN, and the plan of individualized daily nutritional requirements is individualized in cooperation with the clinical pharmacist as recommended by ESPAGHAN guidelines [21]. The pharmacist ensured the sterility of the formula by carrying out the process in the local mixing room under a laminar airflow hood using aseptic techniques in accordance with the strict aseptic rules. Due to the use of a peripheral rather than a central line, the maximum osmolarity of the prepared TPN solution was 900 mOsmol/L, and the maximum glucose concentration was 12%. Continuous infusion of the PN solution through an infusion pump for 24 hours was interrupted when antibiotics and other drugs were administered through the same IV line [22,23]. We evaluated the patients daily using a monitoring protocol for the associated certain complications such as metabolic and electrolyte abnormalities, hepatobiliary and renal complications, and hematological abnormalities.

Ethical considerations

The study protocol was approved by the Ethical Committee, Iraqi Counsel of Medical Specialties. Verbal consent was obtained from the patients' parents before participation in the Study.

Data analysis

The results were evaluated using the GraphPad Prism software (Graphpad Software, Boston, MA, USA). Numeric data were expressed as the mean ± standard deviation (SD). A Spearman correlation test was utilized to evaluate the association between the incidence of sepsis and extravasation with other patient characteristics. A *p*-value of less than 0.05 was considered significant.

RESULTS

Throughout the study period, 148 newborns were admitted to the neonatal care units of the Children's Welfare Teaching Hospital and Baghdad Teaching Hospital, where they received parenteral nutrition for various indications. They underwent screening and assessment for inclusion and exclusion criteria. Fifty-four neonates were removed from the study, resulting in a total of ninety-four neonates remaining. Table 1 presents the attributes of the 94 participants as mean ± standard deviation and percentage, encompassing gestational age (GA), gender, postnatal age (PNA), initial weight at treatment commencement, final weight at treatment conclusion, and duration of PN therapy.

Table 1: Characteristics of the enrolled neonates (n= 94)

Variable		n(%)	Mean ± SD	Range
Gestational age (week)	< 37	79(84)	32.1±3.8	24.0-40.0
	≥ 37	15(16)		
Gender	Male	53(56.4)		
	Female	41(43.6)		
Weight at start of PN (kg)	< 2.5	76(81)	1.7±0.70	0.6-3.0
	≥ 2.5	18 (19)		
Weight at end of PN (kg)			1.84±0.74	0.6-3.8
Age at time of PN initiation (day) (PNA)			9.72±17.4	1.0-90.0
Duration of PN exposure (day)			12.65±9.27	5-45
Death rate		26(27.7)		

PN: parenteral nutrition, PNA: post-natal age.

The subjects were admitted to the NICU and commenced parenteral nutrition at an average age of 9.72 days; their mean weights at the initiation and conclusion of parenteral nutrition were 1.7 kg and 1.84 kg, respectively (Figure 1).

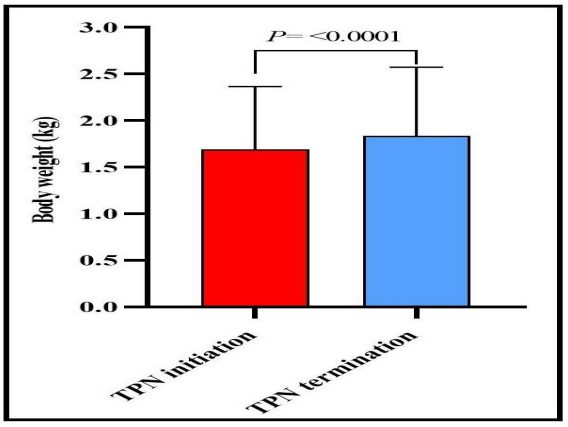

Figure 1: Changes in bodyweight after PN treatment. Paired *t*-test: Significantly different at $p< 0.05$.

The mean and standard deviation of PN exposure duration are 12.65 ± 9.27 days, respectively. Male patients exceeded female patients by a ratio of 53 to 41 (56.4% to 43.6%). Table 2 presents the quantity and percentage of PN complications observed in neonates during the administration period. Hypoglycemia was the predominant metabolic problem, occurring in 35.1% of cases, whereas hyperglycemia was observed in 31.9% of newborns. Elevated blood urea was observed in 11.7% of the newborns examined, whereas metabolic acidosis was detected in 7.4% of the subjects. Thrombocytopenia impacted 28.7% of patients, while hypertriglyceridemia affected 3.1%. Cholestasis impacted 11.7% of neonates. Hypocalcemia (27.6%), hypokalemia (20.2%), and hyponatremia (18%) were the predominant electrolyte imbalances. The prevalence of hyperkalemia was 11.7%, while hypernatremia was 2.1%. Figure 1 illustrates the variation in body weight from the commencement to the conclusion of PN, revealing a statistically significant difference at $p< 0.0001$. The mean weight at the commencement of parenteral nutrition is 1.7 kg with a standard deviation of 0.70. Final weight (kg) following PN treatment: mean ± SD 1.84 ± 0.74 kg. The weight difference is 0.14 kg, indicating a substantial weight gain.

Table 2: Frequency and percentage of PN-related complications in 94 studied neonates during PN administration period (n=94)

Type of Complication		Observed complications
Metabolic complications	Elevated blood urea	11(11.7)
	Hypoglycemia	33(35.1)
	Hyperglycemia	30(31.9)
	Metabolic acidosis	7(7.4)
Hepatobiliary complications	Cholestasis	11(11.7)
Electrolyte disturbances	Hypokalemia	19(20.2)
	Hyperkaliemia	11(11.7)
	Hyponatremia	17(18)
	Hypernatremia	2(2.1)
	Hypercalcemia	2(2.1)
	Hypocalcemia	26(27.6)
Hematological abnormality	Thrombocytopenia	27(28.7)
Hypertriglyceridemia	Hypertriglyceridemia	3(3.1)

Values are expressed as frequency and percentage.

Table 3 illustrates alterations in serum electrolytes, blood urea and creatinine concentrations, liver function indicators, serum triglycerides, random blood glucose levels, and arterial blood gases throughout parenteral nutrition (PN) administration, contrasting the levels at PN initiation and cessation (biochemical marker blood samples were collected within 1–3 days of initiation or cessation). No substantial alteration in serum potassium and calcium levels is seen. A notable variation in serum Na^+ levels exist; however, it remains within the normal range ($p= 0.012$). Table 3 additionally illustrates the variations in blood urea and serum creatinine concentrations with parenteral nutrition therapy.

Table 3: Changes in serum electrolytes, blood urea and creatinine levels, liver function markers, serum triglycerides, random blood glucose levels and arterial blood gases during PN administration (n = 94)

Variable	PN initiation n=94	PN termination n=94	P-value*
K^+ (meq/L)	4.5±0.9	4.61±0.94	0.373
Na^+ (meq/L)	135.6±5.7	137.0±5.6	0.012
Ca^{++} (mg/dl)	8.75±0.9	9.52±0.62	0.348
blood Urea (mg/dl)	34.4±19.2	45.92±24.6	0.0001
Serum Creatinine (mg/dl)	0.467±0.34	0.45±0.24	0.634
AST (U/L)	87.2±276.8	75.12±246.1	0.934
ALT (U/L)	31.22±75.26	33.17±100.1	0.863
ALP (IU/L)	194.4±150.4	215.4±132.4	0.035
DB (mg/dl)	0.511±1.53	0.785±1.47	0.649
Serum Triglycerides (mg/dL)	78.72±21.1	95.25±35.6	0.0004
Random Blood Glucose (mg/dL)	113.9±73.7	95.41±21.18	0.022
pH	7.39±0.07	7.38±0.06	0.412
$PaCO_2$ (mmHg)	39.38±14.02	37.79±10.84	0.275
PaO_2 (mmHg)	103.5±29.16	93.71±25.47	0.002
HCO_3 (mEq/L)	23.82±6.21	22.87±4.83	0.146
Anion Gap (mEq/L)	12.23±5.23	12.57±5.06	0.441

Values are presented as mean±SD. *Paired *t*-test.

The average blood urea level in the initial week of administration was 34.4 ± 19.2 mg/dL, whereas in the last week it was 45.92 ± 24.6 mg/dL, indicating a statistically significant difference with a *p*-value of 0.0001. A non-significant disparity exists in AST, ALT, and DB levels. Nonetheless, a notable disparity exists in ALP levels between the initial and final week of administration. A notable disparity exists in serum triglyceride levels (p= 0.0004); however, it remains within the normal reference range. A notable variation in random blood glucose exists between the commencement and conclusion of PN therapy (p= 0.022), although it remains within the normal reference range. An insignificant variation in pH, $PaCO_2$, HCO_3, and anion gap. A notable change in PaO_2 exists (p= 0.002). Figure 2 shows that there is a significant decrease in platelet count between PN initiation and termination (p= 0.003) but still within the normal reference range. Table 4 indicates that twenty-six deaths (27.7%) transpired throughout the study period. Among 69 patients who underwent parenteral nutrition for fewer than 14 days, 27.5% succumbed. Out of 25 patients who received parenteral nutrition for over 14 days, seven (28%) succumbed, demonstrating a non-significant correlation between mortality rate and duration of parenteral nutrition administration (p= 0.999).

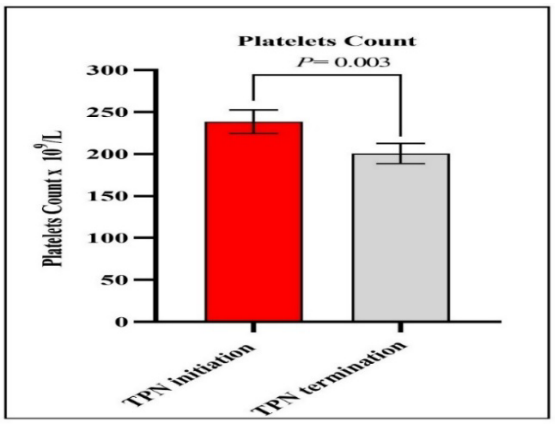

Figure 2: Change in platelets count during PN administration. Paired *t*-test: significantly different at $p< 0.05$.

Eight (27.5%) of the 29 surgery patients succumbed. Furthermore, there were eighteen (27.6%) fatalities among the 65 medical patients. The correlation between the death rate and PN indication is not significant (p= 0.999). Table 4 indicates a non-significant correlation between mortality rate and gestational age (p= 0.766). Of the seventy-nine infants with a gestational age of less than 37 weeks, 24 (30%) succumbed. Only two (13.3%) fatalities occurred among the fifteen infants with a gestational age beyond 37 weeks.

Table 4: The relationship between death rate and gestational age, duration of PN exposure, and indication of PN

Death Rate	GA (week)		Indication		Duration (day)	
	<37	≥ 37	Surgical	Medical	≤14	>14
Death	24	2	8	18	19	7
No death	55	13	21	47	50	18
Total	79	15	29	65	69	25
Chi square test	p= 0.766		p= 0.999		p= 0.999	

Table 5 illustrates the association among the examined parameters and body weight, treatment duration, gestational age (GA), and postnatal age (PNA). A notable albeit modest positive connection exists between, percentage change in sodium level, percentage change in triglyceride level, and body weight (p= 0.0003, 0.0003, 0.012, and 0.028, respectively). A non-significant link existed among renal function, liver function tests, metabolic acidosis, alterations in serum electrolytes (K^+ and Ca^{2+}), glucose abnormalities, platelet count, and body weight. Treatment duration exhibited a moderate yet significant connection, with *p*-values of 0.0001 for each variable. A notable albeit weak positive connection existed between Na and TG levels and treatment duration (p= 0.032 and 0.007, respectively). Table 5 also indicates a substantial, albeit modest, negative connection, with a *p*-value of 0.032, between random blood glucose and treatment duration. As the length of treatment extends, the percentage variation in random blood sugar diminishes. A non-significant link existed between treatment time and blood urea, serum creatinine, DB, AST, ALT, ALP, pH, HCO_3, potassium, calcium, and platelet count. A notable albeit slight positive connection exists between gestational age, and serum sodium level (p= 0.010, 0.011, and 0.010, respectively). A non-significant link existed between gestational age and blood urea, serum creatinine, DB, AST, ALT, ALP, pH, HCO_3, K^+, Ca^{+2}, TG, random blood sugar, and platelet count. A notable, albeit trivial, positive connection exists between PNA and serum creatinine (p= 0.022). Postnatal age shows a substantially weak negative connection with the percentage change in direct bilirubin levels (p= 0.001) and the percentage change in platelet levels (p= 0.022), indicating that as postnatal age grows, the percentage change in both direct bilirubin and platelet levels diminishes. A notable, albeit slight, positive connection exists between PNA and TG levels (p= 0.019). A non-significant association exists between PNA and blood urea, liver function tests, pH, bicarbonate, sodium, potassium, calcium, and random blood sugar.

DISCUSSION

The current study offers a brief overview of the better management of neonates on PN and calls for more research in this area. Interestingly, despite the occurrence of PN-related complications, there is a significant increase in body weight from the first day of treatment until full enteral feeding is achieved or PN is discontinued. Neonates in this study received either PN alone or in combination with enteral feeding or oral feeding.

Table 5: Spearman's correlation results the percentage changes of the studied markers with Bodyweight, PN treatment duration, Gestational age, and post-natal age of neonates received PN therapy

Markers (% changes)	Bodyweight (kg)	Treatment duration (day)	Gestational age (week)	Post-natal age (day)
Blood urea	*r* = - 0.001 *p* = 0.336	*r* = - 0.031 *p* = 0.766	*r* = - 0.068 *p* = 0.510	*r* = - 0.119 *p* = 0.252
S. Creatinine	*r* = - 0.037 *P* = 0.723	*r* = 0.138 *p* = 0.184	*r* = - 0.021 *p* = 0.837	*r* = 0.084 *p* = 0.022
DB	*r* = - 0.201 *p* = 0.051	*r* = - 0.072 *p* = 0.492	*r* = - 0.091 *p* = 0.379	*r* = - 0.325 *p* = 0.001
AST	*r* = - 0.074 *p* = 0.474	*r* = 0.042 *p* = 0.685	*r* = - 0.006 *p* = 0.953	*r* = - 0.012 *p* = 0.906
ALT	*r* = - 0.143 *p* = 0.171	*r* = - 0.003 *p* = 0.977	*r* = - 0.091 *p* = 0.378	*r* = - 0.145 *p* = 0.163
ALP	*r* = - 0.158 *p* = 0.128	*r* = 0.143 *p* = 0.168	*r* = - 0.081 *p* = 0.378	*r* = - 0.058 *p* = 0.575
pH	*r* = 0.119 *p* = 0.054	*r* = - 0.080 *p* = 0.442	*r* = 0.092 *p* = 0.378	*r* = 0.137 *p* = 0.185
HCO3	*r* = 0.025 *p* = 0.810	*r* = 0.067 *p* = 0.521	*r* = 0.119 *p* = 0.253	*r* = - 0.002 *p* = 0.829
Na	*r* = 0.257 *p* = 0.012	*r* = 0.220 *p* = 0.032	*r* = 0.262 *p* = 0.010	*r* = 0.137 *p* = 0.186
K	*r* = - 0.047 *p* = 0.652	*r* = 0.124 *p* = 0.235	*r* = - 0.012 *p* = 0.901	*r* = - 0.063 *p* = 0.544
Calcium	*r* = - 0.011 *p* = 0.911	*r* = 0.129 *P* = 0.214	*r* = 0.072 *p* = 0.490	*r* = - 0.021 *p* = 0.834
Triglycerides	*r* = 0.226 *p* = 0.028	*r* = 0.275 *p* = 0.007	*r* = 0.085 *p* = 0.415	*r* = 0.240 *p* = 0.019
RBS	*r* = - 0.041 *p* = 0.692	*r* = - 0.221 *p* = 0.032	*r* = - 0.119 *p* = 0.252	*r* = 0.006 *p* = 0.954
Platelets	*r* = - 0.192 *p* = 0.063	*r* = - 0.022 *p* = 0.830	*r* = - 0.214 *p* = 0.234	*r* = - 0.234 *p* = 0.022

ST: aspartate aminotransferase; ALT: alanine transaminase; ALP: alkaline phosphatase; DB: direct bilirubin; RBS: random blood glucose.

Waffa *et al*. [24] found that there was a significant increase in weight gain from baseline achieved during overall parenteral management in ELBW preterm neonates. However, there were no significant differences in overall weight gain from baseline in VLBW and LBW. One report [25] has shown that pharmacist monitoring of an individualized program of parenteral nutrition in low-birth-weight neonates provided a greater mean daily weight gain and allowed a greater amino acid and energy intake compared with the use of a standardized solution without pharmacist monitoring. This current study proved that the rate of hypoglycemia was 35.1%, which is higher than Suganuma *et al*. [26]; it also shows that the incidence of change in random blood sugar between PN initiation and termination is inversely correlated with the treatment duration. Another study reported that the occurrence of hypoglycemia is higher in developing nations, which may be explained by a high percentage of low birth weight or intrauterine growth retardation (IUGR) and poor feeding/nursing practices [27]. Newborns at risk for developing hypoglycemia are premature or post-mature neonates; small for gestational age neonates (SGA); large for gestational age neonates (LGA); IUGR; neonates with perinatal stress (birth asphyxia/ischemia); twins; neonates born to diabetic mothers; hypothermic neonates; and neonates whose mothers received high-glucose infusions before birth [27]. Possible causes of hypoglycemia, especially when the neonate has been normoglycemic and then suddenly becomes hypoglycemic, include intravenous line issues such as abrupt cessation of high-glucose infusion or extravasation, an underlying disorder like infection or sepsis, and delayed feeding. Neonates receiving no or minimal enteral nutrition had the highest risk for developing hypoglycemia [20]. It appears that the occurrence of hypoglycemia is not only related to the characteristics of neonatal glucose metabolism since hypoglycemia has occurred in term neonates and neonates of normal weight, but it is also related to its primary diseases, including infection [28], feeding issues, acidosis, high bilirubin factors, and hyperlipidemia [27]. Hyperglycemia affected 31.9% of the evaluated neonates in the current study. The percent change in blood glucose level negatively correlated with PN duration, implying that more glucose disturbances occurred during the PN initiation phase. This finding contradicts that of Mantegazza *et al*. [29], who found only 10.45% of newborns have hyperglycemia. During acute injury states, excessive production of glucagon, epinephrine, and cortisol can induce hyperglycemia as a counter-regulatory response. These mechanisms are important promoters of hyperglycemia during acute injury states. The second cause of hyperglycemia is the supplement of extra calories, particularly during PN delivery [30]. Another important complication of IV lipid administration is thrombocytopenia [20]. However, some people were concerned about the effect of ILEs on platelet aggregation. Long-term administration of PN containing pure SO-derived ILEs resulted in monocyte-macrophage hyperactivation and hematological abnormalities, including recurrent thrombocytopenia due to decreased platelet lifespan and hemophagocytosis in the bone marrow [31]. The incidence of thrombocytopenia in the current study was 28.7%, which is higher than Hammerman *et al*. [32]. In other studies on VLBW and ELBW infants [32,33], it has been reported that there was no

significant difference in platelet count between early and no early lipid infusion. However, delay in intravenous lipid emulsion infusion (Vitrum soybean oil) to VLBW and ELBW infants caused essential fatty acid deficiency, especially linoleic acid deficiency, which is associated with low platelet count [32,33]. The current study found that platelet count decreased significantly between the PN initiation and termination but remained within the normal reference range and found a correlation between platelet count and body weight, treatment duration, and postnatal age. The low content of essential fatty acids in the lipid formulation used in this study (SMOF lipid) could be one cause of this decrease. In this study, the frequency of hypokalemia was 20.2%, which was higher than the rate reported by Waffa *et al*. (13.4%) [24]. This study included both normal-weight and low birth weight neonates, while Waffa *et al*. only included low birth weight neonates. The higher rate of hypokalemia in this study may be attributed to the fact that potassium supplementation is not routinely added unless there is hypokalemia in the lab result or the patient is not receiving enteral or oral nutrition. The primary cause of hypokalemia in PN was thought to be an insufficient and inadequate potassium supply. The current study's rate of hyperkalemia is lower than that reported by Iacobelli *et al*. (20%) [25], who compare fluid and electrolyte balance in preterm neonates receiving individualized PN versus standardized PN in the first week of life. Hypocalcemia was the most common electrolyte disturbance in the current study, with a rate of 27.6%, which is higher than the rate reported by Waffa *et al*. (13.4%) [24]. Early hypocalcemia develops rapidly in newborns due to a relative immaturity of hormonal control (a delayed PTH surge) caused by a disruption in placental transfer at birth. In the current study, the incidence of hyponatremia was 18%, which is lower than Waffa *et al*. (25.6%) [24]. In the first week of life, Iacobelli *et al*. [25] compare fluid and electrolyte balance in preterm neonates receiving ITPN versus STPN; hyponatremia occurred at a rate of 5.0% in the ITPN group versus 10.4% in the STPN group. When compared with this study, which used individualized PN solutions, a higher incidence of hyponatremia than in Iacobelli *et al*. was noted (18% *vs*. 5%). It can also occur as a result of receiving too much free water (diluted formula milk) or not getting enough sodium in the infusion fluids [20]. In this study, the incidence of cholestasis was 11.7%, which was lower than the 20.7% reported by Dahel *et al*. [34] in a retrospective study of newborns admitted to the NICU who received PN for more than 14 days and were evaluated for PN-induced cholestasis. Aggravating factors such as sepsis and duration of bowel rest have also been described [34]. The current study revealed a significant difference in serum ALP levels between PN initiation and termination, with the last week being higher and falling within the normal reference range. This finding was in line with that reported by others [35], who studied the effect of different oil emulsions on short-term clinical outcomes. The current study revealed a rise in blood urea similar to that previously reported in patients under PN [36]. This elevation may be caused by inadequate caloric intake or high-protein catabolism. In preterm infants on routine PN, blood urea is considered a marker of protein intake adequacy and amino acid oxidation. However, in unstable preterm neonates on PN during the first days of life, it may be affected by several clinical factors such as renal function, hydration status, the severity of illness, and others [37]. The current study showed a 3.1% incidence of hypertriglyceridemia, which was lower than the rate reported by Al-Lawama *et al*. [38]. The reason for this difference could be due to the fact that the majority of the neonates in Al-Lawama *et al*. were ELBW and VLBW, which carries a higher risk of hypertriglyceridemia [39], and received a nutritional protocol consisting of enteral feeding with formula milk fortifier and PN, whereas in this study some neonates did not receive enteral feeding due to gastrointestinal surgeries and other causes, and the milk fortifier was not available at the time of this study. In this study the blood sample for serum TG level was drawn after 12 hours of lipid fasting; however, Correani *et al*. didn't mention the timing of the blood sample or lipid fasting since the study was retrospective [39], which raises the question about the perfect timing of blood sampling and the optimum duration of lipid fasting before blood sampling for serum TG level. More studies are needed in this respect.

Study limitations

Unavailability of specialized neonatal PN formula. The central intravenous line's unavailability due to resource constraints and logistics. Small sample size, which is due in part to the fact that many cases were excluded due to death or a short duration of PN administration. The lack of a computerized system for calculation and preparation.

Conclusion

Parenteral nutrition is well tolerated by the neonates despite the occurrence of some complications, with a lower incidence of cholestasis and hypertriglyceridemia associated with the administration of SMOFlipid®. However, we reported a higher than predicted incidence of electrolyte abnormalities, particularly low serum potassium and sodium levels.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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