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Research Article

Parenteral Nutrition-Associated Sepsis and Extravasation in Iraqi Neonates: A Case-Series Prospective Study

Dalya Abdul Kareem Mohammed[1]*, Yasir Ibrahim Abdulridha[1], Mustafa Ghazi Alabbassi[2], Saad Abdulrahman Hussain[3]

[1]*Neonatal Intensive Care Unit, Children Welfare Teaching Hospital, Medical City, Baghdad, Iraq;* [2]*Department of Pharmacology and Toxicology, College of Pharmacy, University of Alkafeel, Al-Najaf, Iraq;* [3]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Al-Rafidain University College, Baghdad 10052, Iraq*

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Abstract

Background: Extravasation and sepsis are two of the many side effects linked to the use of intravascular devices during parenteral nutrition (PN). ***Objective***: To assess the incidence of sepsis and extravasation in Iraqi neonates receiving PN in the critical care unit. ***Methods***: From January 27, 2022, to January 15, 2023, a case-series prospective study was carried out in two tertiary neonatal intensive care units (NICUs) in Children Welfare Hospital and Baghdad Teaching Hospital, Baghdad, Iraq. The study reports the rate of sepsis and extravasations and correlates their occurrence to other neonatal features. ***Results***: Of the 94 newborns examined, 24 patients (25.5%) experienced 35 instances of stage IV extravasation, and 34.04% of them experienced 40 episodes of sepsis in total. They have a strong and significant correlation with the newborns' body weight, treatment duration, gestational age, and postnatal age. ***Conclusions***: The administration of PN to neonates in Iraq has been linked to severe side effects such as sepsis and extravasation.

Keywords: Extravasation, Intensive care, Neonates, Parenteral nutrition, Sepsis.

الإنتان المرتبط بالتغذية الوريدية والتسرب الوريدي عند حديثي الولادة العراقيين: دراسة مستقبلية لسلسلة حالات

الخلاصة

الخلفية: التسرب والإنتان هما من الآثار الجانبية العديدة المرتبطة باستخدام الأجهزة داخل الأوعية الدموية أثناء التغذية بالحقن (PN). **الهدف**: تقييم حالات الإنتان والتسرب لدى حديثي الولادة العراقيين الذين يتلقون التغذية بالحقن في وحدة العناية المركزة. **الطريقة**: من 27 يناير 2022 إلى 15 ديسمبر 2022، تم إجراء دراسة مستقبلية لسلسلة حالات في وحدتين للعناية المركزة لحديثي الولادة (NICU). في مستشفى رعاية الأطفال ومستشفى بغداد التعليمي، بغداد، العراق. وتبحث الدراسة في معدلات حدوث الإنتان والتسرب الوريدي وتربط حدوثها بسمات أخرى لحديثي الولادة. **النتائج**: من بين 94 مولودا جديدا تم فحصهم، عانى 24 مريضا (25.5٪) من 35 حالة من تسرب المرحلة الرابعة، و 32 منهم (34.04٪) عانوا من 40 نوع من الإنتان في المجموع. واتضح وجود علاقة متبادلة قوية وعلاقة كبيرة مع وزن جسم الأطفال حديثي الولادة ، ومدة العلاج ، وعمر الحمل، وعمر ما بعد الولادة. **الاستنتاجات**: تم ربط إعطاء التغذية الوريدية لحديثي الولادة في العراق بآثار جانبية شديدة مثل الإنتان والتسرب الوريدي.

* ***Corresponding author***: Dalya A. Mohammed, Neonatal Intensive Care Unit, Children Welfare Teaching Hospital, Medical City, Baghdad, Iraq; Email: dalya.pharmacist@gmail.com

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INTRODUCTION

When neonates are unable to receive adequate oral or enteral nutrition due to intestinal failure or an intolerance to enteral feeds, parenteral nutrition (PN) may prove to be a lifesaving intervention [1,2]. Pediatric patients are particularly susceptible to the energy and protein restrictions that occur during critical illness episodes. Inadequate nutrition is linked to negative clinical outcomes in critically ill neonates, including an extended mechanical ventilation duration, an elevated risk of acquiring infections in the hospital, and an increased mortality rate [3,4]. Parenteral nutrition (PN) can only be administered via venous access, which may

be achieved through the use of peripheral or central venous catheters, in neonates who are hospitalized. Among the numerous adverse effects associated with intravascular device use during PN were extravasation and sepsis [5]. Sepsis can happen in a number of ways, including when microbes get into the area where the catheter was inserted, on the hub of the catheter, or in the solution that was infused [2]. Preterm births have increased in the majority of nations across the globe in recent years [6]. Particularly vulnerable to healthcare-associated infections (HAIs) are these patients, as are neonates born at extremely low birth weight and very low birth weight [7]. Neonatology centers administer specialized care, such as parenteral nutrition (PN), and subject these patients to more invasive medical devices. Evidence suggests that the use of PN during neonatal care is linked to bloodstream infections (BSI). BSIs account for the majority of nosocomial infections among neonates, constituting over three-quarters of all HAI [8]. Parenteral nutrition for prolonged durations is more prevalent among critically ill and most vulnerable patients, increasing the risk of developing PN-associated sepsis [9]. Catheter use, specifically central lines like peripherally inserted central catheters (PICC) and umbilical lines, is linked to the majority of BSIs [10]. Infections of the central line-associated bloodstream (CLBI) cause an average seven-day increase in the duration of hospitalization and a rise in costs attributable to each infection. Parenteral nutrition-associated nosocomial BSI is a potentially fatal complication in neonates, with an attributable mortality rate of 11% [11]. Due to the high incidence and mortality rates of late-onset sepsis and central line-associated bloodstream infections (CLABSI), every effort must be made to minimize this risk [12,13]. PN is identified as a risk factor in part because of the contamination of the infused solution; nevertheless, catheter contamination or improper handling can occur at any moment during catheterization and result in the infection of the catheter. Moreover, complications associated with catheters can manifest in two ways: technically, such as extravasation, or infectiously, such as sepsis [14]. Furthermore, extravasation injuries are a common and challenging condition among neonates who are hospitalized. In premature neonates, inadvertent infusion leakage into the adjacent tissues can often result in skin necrosis, which poses a significant threat to both aesthetic and functional integrity [15]. Additionally, skin-based pathogens have the potential to penetrate the insertion site, increasing the risk of localized cellulitis and potentially systemic bacteremia. Frequent complications associated with peripheral intravenous lines (PIVLs) were restraint infiltration and extremity injuries [16]. There is a scarcity of data in Iraq concerning the frequency and structure of sepsis and extravasation associated with PN. The current study aimed to provide insight into the frequency of sepsis and extravasation associated with PN in the neonate intensive care unit of the Medical City, Baghdad.

METHODS

Study design and setting

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

Patient selection

During the study period, 148 preterm and term neonates admitted to the NICUs of the Children's Welfare Teaching Hospital and the Baghdad Teaching Hospital who required specialized care for medical or surgical problems, as well as those who required parenteral nutrition (PN), were considered eligible. We followed the ESPEN/ESPGHAN guidelines to determine the appropriate indications for the use of PN. Enrollment of patients occurred from the initiation of PN until the completion of treatment.

Inclusion and exclusion criteria

All preterm and term neonates requiring PN for various indications during admission and receiving PN for at least 5 days were included. Meanwhile, we excluded those discharged within 4 days of starting PN, death cases, those transferred to another unit within 4 days of initiating PN, and those receiving PN for less than 5 days.

Management protocol and outcome assessment

According to ESPAGHAN guidelines [17], the neonatologist recognizes the patient who needs PN and collaborates with the clinical pharmacist to develop an individualized plan of daily nutritional requirements. 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 PN 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 [18]. To minimize distress and ensure a low risk of adverse events, we conducted the monitoring protocol for certain biochemical data once per week, with the exception of the daily assessment of a random glucose level and other biochemical markers in the event of biochemical abnormalities. Extravasation was monitored daily, while blood culture was performed on admission and when required based on clinical observation.

Data analysis

The collected data were analyzed in a descriptive manner 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

During the study period, the neonatal care units of the Children Welfare Teaching Hospital and the Baghdad Teaching Hospital admitted 148 neonates who received PN for various indications. We excluded fifty-four neonates from the study due to early death or the unavailability of full details in the case sheets, resulting in a final sample size of ninety-four neonates. Table 1 displays the characteristics of the participants as mean±SD and/or percentage.

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

Variable	*n*(%)		mean±SD	Range
Gestational age (weeks)	< 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)		
Age (days)	9.72±17.4			(1.0-90.0)
Duration of PN exposure (day)			12.65±9.27	(5-45)

The mean gestational age of the participants was 32.1±3.8 weeks. At the mean age of 9.72 days, the participants were admitted to the NICU and initiated PN; their mean weights at the start of PN were 1.7 kg. The average PN exposure time is 12.65±9.27 days. Male patients outnumbered females by a margin of 53 to 41 (56.4% to 43.6%). Figure 1A shows the incidence rate of stage IV extravasation. Of the 94 neonates studied, 24 patients (25.5%) had 35 episodes of stage IV extravasation, as follows: nineteen patients had one episode of extravasation, two patients had two episodes, one patient had three episodes, one patient had four episodes, and only one patient had five episodes of stage IV extravasation. Figure 1B shows the incidence of sepsis events in the studied group.

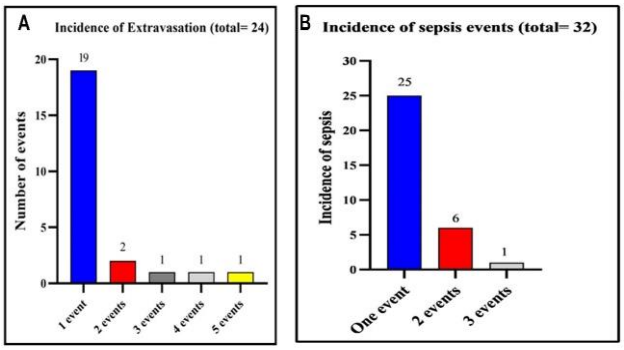

Figure 1: Incidence rate of extravasation (A) and sepsis (B) in neonates during PN administration.

Thirty-two patients (34.04%) had a total of 40 sepsis episodes. Twenty-five patients had only one sepsis episode. Six patients had two episodes of sepsis during their admission, and only one patient had three episodes of culture-proven sepsis. Table 2 shows the types of pathogens identified. Gram-negative bacteria (57.5%) were responsible for the majority of the 40 noted episodes of sepsis. Gram-positive bacteria accounted for 35% (n=14) of all culture-proven sepsis, while fungal infection accounted for only 7.5% (n=3) of the total episodes.

Table 2: Types of pathogens identified from positive blood culture during PN administration.

Pathogen	No (%) Total 40 episodes
Virus	0(0)
Fungi	3(7.5)
Gram positive bacteria	14(35)
Gram negative bacteria	23(57.5)
Total	40(100)

Treating these patients involved administering appropriate antibiotics and antifungal agents. Table 3 shows the causative organisms isolated from blood cultures. It was found that there were 9 cases of *Acinetobacter baumannii*, 7 cases of *Klebsiella* spp., 3 cases of *Enterobacter* spp., 2 cases of pseudomonas aeruginosa, 1 case of *E. coli*, and 1 case of Burkholderia cepacia. Seven cases of coagulase-negative Staphylococci were found, with Staphylococcus epidermis being the most common. There were also four cases of coagulase-positive *Staphylococcus aureus*, one Diphtheroid spp., one *Staphylococcus hominis*, and one *Staphylococcus haemolyticus*. The fungi identified were *Candida albicans* and *Cryptococcus laurentii*.

Table 3: Causative organisms in bacteriologically confirmed sepsis cases of neonates receiving PN therapy

Pathogen	*n*(%)
Klebsiella spp.	7(17.5)
Coagulase positive *Staphylococcus aureus*	4(10)
Coagulase negative staphylococci	7(17.5)
Acinetobacter baumannii	9(22.5)
Diphtheroid spp.	1(2.5)
Pseudomonas aeruginosa	2(5)
Staphylococcus hominis	1(2.5)
E. coli	1(2.5)
Enterobacter spp.	3(7.5)
Burkholderia cepacia	1(2.5)
Staphylococcus haemolyticus	1(2.5)
Cryptococcus laurentii	1(2.5)
Candida albicans	2(5)
Total	40 (100)

Table 4 shows the correlation between the rates of extravasation and sepsis with body weight, treatment duration, gestational age, and post-natal age. There is a significant but weak positive correlation between sepsis, extravasation, and body weight, with p= 0.0003 and p= 0.0003, respectively. Sepsis, extravasation, and treatment duration showed a moderate but significant correlation, with a p-value of 0.0001 for each.

Additionally, there is a significant but weak positive correlation between gestational age and sepsis and extravasation, with *p*-values of 0.010 and 0.011, respectively. The age at PN initiation demonstrated a moderately significant positive correlation with the incidence of sepsis and extravasation, with a *p*-value of 0.0001 for both parameters.

Table 4: Spearman's correlation of percent changes of extravasation and sepsis rates with bodyweight, PN treatment duration, gestational age, and post-natal age of neonates received PN therapy

Markers	Bodyweight (kg)	Treatment duration (day)	Gestational age (wk)	Postnatal age (day)
Sepsis	*r*=0.368	*r*=0.478	*r*=0.263	*r*=0.467
	p=0.0003	*p*<0.0001	*p*=0.010	*p*<0.0001
Extravasation	*r*=0.368	*r*=0.478	*r*=0.262	*r*=0.466
	p=0.0003	*p*<0.0001	*P*=0.011	*p*<0.0001

Data represent the percent changes in the studied parameters.

Figure 2 depicts a significant and very strong positive correlation between the incidence of sepsis and extravasation using a Spearman correlation. The coefficients are r = 1.0 and p= 0.0001, respectively, which explains why the incidence of extravasation and sepsis rises.

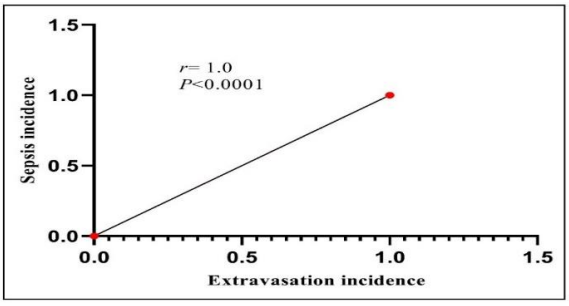

Figure 2: Spearman's correlation between incidence of sepsis and Extravasation in neonates received PN therapy.

DISCUSSION

Given the facility's constrained resources, the neonatal nutrition service has become firmly entrenched. Through our steadfast dedication and fruitful interdisciplinary cooperation, we successfully administered healthcare of exceptional quality, notwithstanding the limited resources of the practice. We included in the present study all neonates who were admitted to the NICU as a result of medical or surgical complications requiring the administration of PN. The findings revealed a significant prevalence of sepsis and extravasations linked to PN among the neonates that were the subject of the inquiry. Drawing upon the information at hand, this study constitutes an initial endeavor to enumerate the diverse complications associated with the implementation of neonatal PN in Iraq. The results of the study revealed a significant correlation between sepsis and treatment duration, gestational age, postnatal age, body weight, and treatment duration in 34% of neonates who received PN. Contrary to the findings displayed here, Saeedi *et al*. investigated a cohort of 82 premature neonates that received PN for an average of 13.29 days [19]. A Turkish study found that the prevalence of infection was greater among patients who utilized PNs for an extended period of time and remained in ICU for an extended period of time [20]. Sepsis incidence was found to be correlated with the duration of PN use [21]. Furthermore, a correlation between PN and BSI was identified. Neonates are at risk of death from nosocomial BSIs associated with PN, with an attributable mortality rate of 11% [19]. In a number of investigations, PN has been identified as a risk factor, including contamination of the PN solution. Coagulase-negative staphylococci (CoNS) are the most commonly identified pathogen in neonatal central line-associated bloodstream infections. This finding provides evidence that catheter handling contamination can lead to infection at any stage of the procedure [19]. Additional evidence for this finding is presented in the current study, which demonstrates that CoNS is the second most frequently identified pathogen, accounting for 17.5% of all positive blood cultures. There is concern among certain individuals that intra-lipid emulsions administered to premature neonates may increase their susceptibility to coagulase-negative staphylococcal bacteremia [22]. Additionally, complex transfers of medium from vials and ampoules to intravenous bags indicate that compounding increases the risk of contamination. Despite strict adherence to aseptic procedures, the estimated rate of contamination is approximately 5.2%. Twenty-four hours after being operated under laminar flow by trained personnel in a pharmacy, transfer sets for compound pumps continued to accumulate skin contaminants [10]. Due to the lack of readily available standard formulations, personalized packs were administered to the neonates on a daily basis, taking into consideration their specific requirements, in order to facilitate this research undertaking. The packs are manufactured in the mixing room using rigorous aseptic techniques while being encased in a laminar airflow hood. As the catheter was not used exclusively for PN administration, establishing a definitive correlation between catheter-associated infections and PN would be difficult; furthermore, such infections can occur even in the absence of this therapy [23]. It was evident that both the duration of PN use and sepsis and the use of PN were associated with sepsis [21]. The peripheral PN solution employed in this study was in accordance with the ESPGHAN/ESPEN/ESPR/CSPEN peripheral administration guidelines [10]. In order to reduce the likelihood of extravasation injuries, it is advised against the use of hyperosmolar solutions exceeding 900 mOsmol/L, as stated in these guidelines. To achieve the intended osmolarity reduction and facilitate the introduction of amino acids, the glucose concentration was reduced to below 12%. Because of the increased risk of extravasation, electrolytes were

added to the PN bag whenever an imbalance occurred. It may be necessary to supply electrolytes using different solution. [15]. Danski *et al*. looked at the growth rate of preterm babies born at 30 to 33 weeks gestation and compared the effects of peripheral intravenous 10% glucose versus a low-osmolarity PN solution [24], but in this study there were 24 cases (25.5%) of stage 4 extravasation PN. This discrepancy may be due to the difference between the report of Suganuma *et al*. (5.9 days and below 700 mOsmol/L) and our study's mean duration (12.6 days) and osmolarity below 900 mOsmol/L [23]. An additional factor contributing to the elevated extravasation rate documented in our research is the supplementation of the PN bag with additional electrolytes. None of the 78 term neonates enrolled in an additional study by Worth *et al*., who administered PN through a central venous catheter (CVC), exhibited extravasation injuries [25]. Due to the known risk of extravasation associated with the peripheral catheter utilized in this study, this result could be attributed to the CVC utilized in the study by Ratchagame *et al*. [8]. The associations between extravasation risk and body weight, gestational age, postnatal age, and postnatal age were identified in the present study. Furthermore, neonates exhibit a heightened vulnerability to extravasation due to their physiological attributes, including the delicate nature of their capillaries. Extravasation is more prevalent in neonates, according to some authors, due to the fragility of their subcutaneous tissue, which expands easily in the presence of liquid, and the fragility of their veins, which facilitate capillary leakage [26]. These characteristics are positively associated with the outcomes that result in neonates being admitted to the NICU, including preterm birth, low birth weight, or premature birth during pregnancy, all of which contribute to their clinical instability and intensive care requirements [27]. Significant and robust positive correlations were observed between sepsis events and extravasation, according to the study. An inverse correlation was observed between the duration of treatment, the gestational age of the neonate, and both complications. Regardless of the catheter connection, Danski *et al*. discovered that a blood infection on the day of the perforation was a significant risk factor for developing sepsis [24]. Therefore, the presence of infections at the site of injection heightened the probability that bacterial proliferation would occur in the peripheral catheters of the neonates. Additionally, the adoption of health-educational practices for nursing personnel can function as a proactive strategy to mitigate a range of healthcare-related issues that are linked to the increase in infection rates [27].

Study Limitations

The present investigation is not without its constraints. We utilize only individualized PN solutions due to the lack of standardized PN solutions; the study comprises a single treatment arm. Additionally, the provision of daily blood test results for certain neonates was restricted because the tests were requested on an as-needed basis, thereby impeding PN monitoring. The unavailability of the central line was an additional constraint resulting from logistical and resource limitations. In addition, the small sample size is noteworthy because a considerable number of cases were excluded as a result of mortality or a brief duration of PN administration.

Conclusion

Prolonged administration of PN to neonates has been linked to severe complications, such as sepsis and extravasation. Consequently, it is imperative that all PN recipients remain closely monitored of their clinical status so that prompt adjustments to the PN regimen can be made in response to unforeseen circumstances.

Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

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

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