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Original Article

Risk Factors for Cholestasis in Neonates Receiving Total Parenteral Nutrition: Single Center Cross Sectional Study

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Abstract

Background: Parenteral nutrition (PN) is vital treatment intended to provide patients who cannot meet their nutritional demands enterally with nutrients. It's given to very low birth weights newborns. primary problem of prolonged PN is cholestasis, which incidence ranges from 15.7% to 60.9%. **Aim**: identifying critical variables thought to be main contributor to cholestasis in neonates receiving PN. **Patients and Methods:** cross sectional study of 114 neonates admitted to our university neonatal intensive care unit (NICU) was done from 1/3/2022 to 28/2/2023. **Results:** newborns were divided into group 1 (cholestatic group) &2 (non-cholestatic group) according to direct bilirubin level if ≥ 2 mg/dL or ≥ 1 mg/dL when total bilirubin level is ≤ 5 mg/dL, those neonates were included in cholestatic group. total incidence of cholestasis was13%. gender, gestational age, age at PN commencement, and PN length did not significantly differ between groups 1 and 2. according to bowel resection and necrotizing enterocolitis (NEC), there were substantial differences between group 1and group 2. Additionally, subgroup analysis revealed that PN length varied significantly across the subgroups that based on gestational age and PN duration. Demonstrated that probability of developing parenteral nutrition-associated cholestasis (PNAC) increased with PN length using multivariate logistic regression mode. PN administered for longer than cut-off points of 17.5 days had a high sensitivity and specificity for cholestasis, according to receiver operating characteristic curve (ROC) study. **Conclusion**: significant risk variables of PNAC in newborns were prolonged PN length, NEC incidence, and bowel resection.

Key words: Risk factors, cholestasis, neonates, parenteral nutrition

Introduction

Parenteral nutrition (PN), which includes macronutrients like dextrose, fat, and protein as well as micronutrients like calcium and potassium, has been used extensively as a therapeutic technique for nutritional assistance to newborns who are unable to feed themselves or who are intolerant of enteral nutrition [1]. Because preterm infants have lower nutritional stores compared to non-preterm infants, preterm neonates are more likely to experience postnatal malnutrition. Additionally, infants born before 28 weeks of gestation have lower stores of glycogen, minerals, and vitamins, and their growth and nutrition during the early years of life have a significant impact on the long-term health of premature babies. Consequently, nutritional care for preterm neonates is a challenge in clinical practice [2]. Cholestasis refers to the accumulation of toxic levels of bile acids in the liver due to defective bile secretion [3]. Parenteral nutrition-associated cholestasis (PNAC) significantly limits the safety of intravenous parenteral nutrition [4].

parenteral nutrition-associated cholestasis is defined as PN lasting more than 14 days with light colored stool and/or yellow skin staining, and a direct bilirubin level of ≥ 34 µmol/L (2 mg/dL) or ≥ 17 umol/L (1 mg/dL) when total bilirubin level is ≤ 85 umol/L(5 mg/dL) at any given time, excluding any infections , biliary tract developmental malformations, and other causes[5]. There is still much to find out about the mechanism underlying parenteral nutrition associated cholestasis (PNAC). It was proposed that the proteins, lipids, and trace components in PN solutions could start an inflammatory chain reaction. Cholestasis development in PN may be significantly influenced by lipid solutions in particular. An inflammatory response has been linked to an increase in a number of cytokines, including

interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor alpha. The development of cholestasis was proposed to be linked to a reduction in bile flow due to higher cytokine concentrations [6]. Low birth weight, preterm, long-term PN use, lack of enteral feeding, enzyme deficiencies, hereditary causes, anatomical factors, and PN-specific characteristics are risk factors for PNAC. Increasing enteral caloric intake while weaning off PN is the most successful therapy for PNAC. Another risk factor is the possibility of severe infections because PN requires a central line for infusion. Bacterial overgrowth is caused by enteral starvation and undeveloped immune function. Reversal of PNAC has been shown in multiple publications and clinical studies when typical soy-based parenteral lipid emulsion is substituted with fish oil-based lipid emulsion [7].

Patients and Methods

Study settings

This was descriptive cross-sectional study carried out in the NICU at xx University Children Hospital during the period from 1/3/2022 to 28/2/2023,

Inclusion and exclusion criteria

a. Inclusion criteria: Neonates who received PN for ≥14 days.

Exclusion criteria: newborns who had a significant congenital defect, cholestasis from birth, or cholestasis-related disorders (such as inborn metabolic errors, viral hepatitis, cystic fibrosis, and any main cholestatic liver diseases) that were discovered during hospitalization. Potential surgical explanations for conjugated hyperbilirubinemia, including choledochal cysts detected on abdominal ultrasonography, hepatobiliary scintigraphy, and biliary atresia.

Data collection

Data were collected through the clinical interpretation and investigations of the patients at presentation and follow up of them during admission period.

Medical data collection sheet

1- History: gestational age , weight at birth, gender, symptoms that point to necrotizing enterocolitis (NEC) and

sepsis (septic patients were confirmed by blood cultures) , gastrointestinal tract abnormalities, history of bowel resection, day of life at PN initiation, length of PN, parenteral dosage in g/kg/d of protein, carbs, and lipids, intake of vitamins and minerals, and day of life (DOL) at which enteral feeds were initiated.

2- Examination: thorough clinical examination with particular emphasis on: hepatomegaly, jaundice and signs of liver cell failure.

3- Laboratory investigation done at the start of parenteral nutrition and after 14 day of PN included: Complete blood count, Liver functions including alanine transaminase, aspartate transaminase and alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin level, hepatic synthetic function included albumin and coagulation tests.

3- Imaging: abdominal ultrasonography, and hepatobiliary scintigraphy

Statistical analysis

Version 22 of SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) used for all statistical calculations. When applicable, data were statistically reported using the mean ± standard deviation (±SD), median, and range, as well as frequencies (number of cases) and relative frequencies (percentages). Quantitative variables were compared using the independent samples t-test, and further suitable tests carried out as needed. The Chi square ($\chi 2$) test was used to compare categorical data; the P-value is always two-tailed and set significant at the 0.05 level. Multivariate logistic regression analysis was utilized to determine the most significant risk factors to remove interactions between these components. Subsequently, the best cut-off points for statistically significant risk factors were identified using receiver operating characteristic (ROC) curve analysis in order to predict PNAC. The area under the ROC curve for different risk factors was also calculated.

Ethical considerations: The protocol of the study had been approved from Medical Ethical Review Board (IRB) No (17101964) in accordance with Helsinki Declaration.

Clinical trial number.gov identifier; NCT05163145

Written informed consents were obtained from all the study participants. Confidentiality of the data of the study participants was ensured.

Data management and analysis:

Before the data were imported into IBM SPSS, a statistical program for social science research, version 27, they were inputted, amended, coded, and updated. For quantitative data that was not parametric, the means, standard deviations, and ranges were given; for parametric data, these were the median and inter-quartile range (IQR). Quantitative data was also displayed using numbers and percentages. The independent t-test, the Chi-square test, or the Fisher exact test were used to evaluate the qualitative data between groups: the Mann-Whitney test was used for non-parametric distributions. The Wilcoxon Rank test was used to compare the quantitative data from two paired groups with a non-parametric distribution, while the Paired t-test was used to analyze the parametric data from two groups. Within the same group, a relationship between two quantitative parameters was established using Spearman correlation coefficients. To determine the optimal cut off point, the investigated marker's area under the curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value were analyzed using the receiver operating characteristic curve (ROC). We examined the factors that contribute to an inadequate weaning process using both univariate and multivariate logistic regression analysis. A 95% confidence interval and a 5% allowable margin of error were established. As a result, a p-value of less than 0.05 was regarded as significant.

Results

Table 1 shows that the study included 114 patients on total parenteral nutrition for at least 14 days the mean gestational age of the studied participants was 33.88±3.66 week and ranged from 26.00-38.00 weeks. Out of 114 neonates 69 cases (60.5%) were males versus 45 cases (39.5%) were females .The mean birth weight was 1.93±.81 kg and ranged from (.70-4.00)kg, and the mean duration of PN was 19.32 ±7.04 day and ranged from (14 -45) day and the age at initiation of PN ranged from (1-35)day. Bowel resection is done for neonates with surgical conditions such as (complicated gastroschisis, severe jejunoileal atresia, massive small bowel resection caused by NEC or malrotation about 25% of the cases had surgical conditions for which bowel resection done. NEC incidence in our study group was 18.4% while sepsis occurred in 53.5% of the study group.

Table 2 shows the demographic and clinical data of both studied groups (n=114), There were no significant differences between group1 and group 2 in terms of gender, GA, age at initiation of PN and duration of PN , there were significant differences between group1 and group 2 in terms of bowel resection & NEC &sepsis p. value < 0.001.

To reduce biases given by not specified subgroups of preterm neonates and different durations of PN, we further analyzed the patients in relation to the length of PN.

Subgroup analysis in table 3 showed that duration of PN was significantly different between the group1 and group 2 groups ($P < 0.05$), while gestational age was not of significant difference between the group 1 and group 2 ($P > 0.05$).

Table 4 shows that the daily average total PN caloric intake were lower and Trace elements were higher in the PNAC group than in the non-PNAC group (p. value = 0. 021 AND < 0.001) respectively).

Table 5: Multivariate logistic regression analysis for possible predictive risk factors of PNAC.

We studied these six statistically significant variables (duration of parenteral nutrition bowel resection before onset of PNAC, septic episodes, necrotizing enterocolitis before onset of PNAC, and average energy intake and average trace element intake) by a multivariate logistic regression mode the most important risk factor associated with PNAC was the duration of parenteral nutrition ($p = 0.003$). An increase in duration of parenteral nutrition, increased the risk for development of PNAC by 5.85-fold (95% confidence interval -.02−.00) compared with patients without PNAC. Also, occurrence of NEC is an important risk factor associated with PNAC ($p = 0.035$) that increased the risk for development of PNAC by 6.5 -fold (95% confidence interval -.155−.047) compared with patients without PNAC.), and gastrointestinal operation (OR 2.4, 95% CI -.23-.0258 ($p < 0.001$). Table 6 shows that parenteral nutrition for more than the cut-off point of 17.5 days had a high sensitivity (1) and specificity (0.67) with P Value < 0.001 also higher trace element intake more than the cut-off point of 1.95 g/kg/day had a high sensitivity (.8) and specificity (0.8) with P Value < 0.001 more than any of the other variables evaluated.

Table 1: Clinical characteristics and potential risk factors in study population

Variable	Cases (n=114)	Percent
Gender		
Male	69	60.5(%)
Female	45	39.5(%)
Gestational age (weeks)		
Mean ±SD	33.88±3.66	
Median	35.00	
Min.-Max.	(26.00-38.00)	
Duration of PN		
Mean ±SD	19.32 ±7.04	
Median	16.00	
Min.-Max.	(14.00-45.00)	
Birth weight(kg)		
Mean ±SD	1.93±.81	
Median	1.90	
Min.-Max.	(.70-4.00)	
Bowel resection before onset of PNAC		
yes	29	25.4(%)
no	85	74.6(%)
NEC before onset of PNAC		
yes	21	18.4(%)
No	93	81.6(%)
Sepsis before onset of PNAC		
yes	61	53.5(%)
no	53	46.5(%)
Day of life at initiation of PN		
Mean ±SD	5.8±.8.9	
Median	1	
Min.-Max.	1-25	

NEC: necrotizing enterocolitis .PN: Parenteral nutrition.

Table 2 Demographic and clinical data of both studied groups (n=114)

Variables	**group1** (cholestatic group) **(n=15) 13%**	**group 2** (non-cholestatic group) **(n=99)87 %**	**p-value**
Gender Male, n (%) Female, n (%)	 10 (66.6%) 5 (33.4%)	 59 (59.6%) 40 (40.4%)	0.60
Gestational age (wks.)	31.93± 3.30	34.12± 3.57	.146
Parenteral nutrition duration (day)	23.2± 4.95	18.73 ±7.13	.571
Birth weight (kg)	1.52± 0.62	2.06± 0.82	.129
Bowel resection before onset of PNAC (n)	12/15 (80%)	17/99 (17.1%)	< 0.001*
Necrotizing enterocolitis before onset of PNAC (n)	12/15 (80%)	18/99 (18.1%)	< 0.001*
Sepsis before onset of PNAC (n)	15/15 (100%)	44/99 (44.4%)	< 0.001*

Table 3 Subgroup analysis in neonates with and without parenteral nutrition-associated cholestasis (PNAC).

Variables	**group 1 (n=15)**	**group 2 (n=99)**	**p-value**
Gestational age >37	3	18	
33:37	9	43	0.338
<32	3	38	
Duration of PN			
14-28	5	94	
29–42	7	5	0.001
≥43	3	0	

Table 4 Daily average intravenous macronutrients as a function of PN–associated cholestasis (PNAC).

Variables	group 1 (n=15)	group 2 (n=99)	p-value
Daily average IV protein intake, g/kg/day	3.04±.55	2.86±.58	.29
Daily average IV dextrose intake, g/kg/day	22.2±1.2	20.67±3.6	.11
Daily average IV lipid intake, g/kg/day	2.60±.50	2.64±.56	.97
Daily average total PN caloric intake, kcal /kg	72.60±3.68	86.76±1.87	.021
Trace elements	2.3±.78	.86±1.07	< 0.001*

Table 5: Multivariate logistic regression analysis for possible predictive risk factors of PNAC.

Variables	Odds ratio	95%CI for B		P. value
		lower	upper	
Necrotizing enterocolitis before onset of PNAC	6.565	.155	.047	0.035
Sepsis before onset of PNAC	4.945	.040	.006	0.015
Bowel resection before onset of PNAC	2.397	.236	.025	<0.001*
Duration of PN	5.859	.021	.000	0.003
Trace element	2.132	.004	.021	<0.001*
Daily average total PN caloric intake	.849	.093	.178	<0.001*

CI, confidence interval; PN, parenteral nutrition. PNAC: parenteral nutrition-associated cholestasis.

Table 6: Cutoff points; sensitivity and specificity, for the predictive risk factors of PNAC

Variables	Cut-off	Sensitivity	Specificity	AUC (SE)	P. value
Parenteral nutrition duration (day)	17.5	1	.67	.798	< 0.001*
Trace element	1.95	.8	.8	.849	< 0.001*
Daily average total PN caloric intake kcal/kg/day	92.5	.6	.616	.473	0.734

AUC: Area under curve, SE: Standard error, PNAC: parenteral nutrition associated cholestasis. AUC=0.5 represents prediction no better than chance; AUC=1 represents perfect prediction.

Discussion

PNAC has been researched for a long time, but its exact cause is still unknown. The pathophysiology is thought to be complex, and its cause is still up for discussion [8]. According to a research by Ah-Young Kim et al., a prolonged administration of PN has also been linked to hyperinsulinemia, which causes glucose to be converted into fat and causes hepatic fatty infiltration and cholestasis [8]. Variations in the annual incidence of PNAC could be attributed to modifications in practice throughout time. Our reported incidence is 13.2 % consistent with Lee et al., Y. Wang et al., Hsieh et al. studies [1,9,15]. However, the higher incidence of transitory cholestasis than in other studies (N. Wang et al., where the incidence was 9.5%) could be attributed to the higher prevalence of prematurity and survival of sicker and premature neonates, as well as a rise in the number of referrals to our tertiary centre. The modest number of smaller infants included in our analysis compared to previous studies may be the cause of this tiny variation in the incidence. The goal of the current study was to investigate the aspects and risk factors connected to the onset of PNAC.

We discovered that the PNAC group and the non-PNAC group did not significantly differ in terms of gender, GA, age at PN commencement, PN duration, lipid, amino acid, and glucose dose. A study conducted by N. Wang et al. produced a similar outcome [9].

However, research by Alkharfy et al. and Y. Wang et al. indicates that there are notable variations in gestational age between the PNAC group and the non-PNAC group, which runs counter to our findings. As Gestational age also had an impact on the occurrence of cholestasis; research has indicated that a lower gestational age is associated with a higher direct bilirubin concentration [5,10]. This connection may be explained by the neonatal liver's physiological immaturity, which results in poor hepatic transport and bile acid metabolism. In our study, the PNAC group's parenteral nutrition duration was marginally longer

than that of the non-PNAC group., P. value 0.571; this comes in concordance with and N. Wang et al., and Gupta et al. studies [9,11]. This can be explained by first, the PN duration (19.3 days, range: 14–45 days) of the study group was different from previous studies [13].

To reduce biases given by not specifying subgroups of pre-term neonates and different durations of PN, we further analysed the patients in relation to the length of PN. Subgroup analysis showed that and duration of PN was significantly different between the PNAC and non-PNAC groups ($P < 0.05$) similar to N. Wang et al. study [9]. Additionally, there were significant differences between the PNAC group and non-PNAC group in terms of bowel resection & NEC & sepsis p. value < 0.001, and this is in agreement with M. Crill et al., Alkharfy et al. and Y. Wang et al [5,10,12]. Sepsis, a common complication during TPN infusion, may be associated with cholestasis. The direct hepatotoxicity caused by endotoxins, because of intestinal bacterial overgrowth, might be a possible mechanism of injury [10]. The potential correlation between liver toxicity and TPN duration and the development of PNAC could be the cause. Liver damage may be exacerbated by the lack of physiological enteral intake, as in the cases of bowel resection and NEC. Early enteral feeding can stop the onset of liver dysfunction that results in cholestasis, preserve intestinal integrity, and sustain the production of hormones and enzymes within the gut [10]

A number of studies have demonstrated the involvement of TPN components, such as lipids, in the pathophysiology of both PNAC and hepatic steatosis; amino acids were also thought to be a potential contributor in the induction of liver dysfunction [14].

This is consistent with studies by Gupta et al. and Ah-Young Kim et al., but it differs from a study by N. Wang et al. that found there was no significant difference in daily average total PN calorie intake or trace element intake between the PNAC group and the non-

PNAC group. The PNAC group's daily average total PN caloric intake was lower, and its trace element intake was significantly higher. After that, a logistic regression analysis was done to assess the statistically significant variables shown as risk factors in Tables 2 through 4. The purpose of the analysis was to identify the roles of particular elements that might have an impact on PNAC and to eliminate interactions between the predicted factors of PNAC. The duration of parenteral nutrition, bowel resection prior to the onset of PNAC, septic episodes, necrotizing enterocolitis prior to the onset of PNAC, average energy intake, and average trace element intake are the six statistically significant variables that we examined and included in a multivariate logistic regression model, as indicated in table 5. After controlling for these variables, the most important risk factor associated with PNAC was the duration of parenteral nutrition (p = 0.003). An increase in duration of parenteral nutrition, increased the risk for development of PNAC by 5.85 -fold (95% confidence interval –0.02−.00) compared to patients without PNAC. Also occurrence of NEC is an important risk factor associated with PNAC (p = 0.035) that increased the risk for development of PNAC by 6.5 -fold (95% confidence interval -.155−.047) compared with patients without PNAC.), and bowel resection (OR 2.4, 95% CI -.23-.0258 (p < 0.001) similar to Ah-Young Kim et al. study[8].

The optimal cut-off values for illness prediction were found using ROC curve analysis of these factors. Table 6 displays the results of the computation of the areas under the ROC curves, which were used to assess the predictability of these variables. Parenteral nutrition administered for a duration greater than 17.5 days demonstrated a high level of specificity (0.67) and sensitivity (1), with a P value < 0.001..Also higher trace element intake more than the cut-off point of 1.95 g/kg/day had a high sensitivity (0.8) and specificity (0.8) with P Value < 0.001* more than any of the other variables evaluated , nearly similar

to Hsieh et al. and Alkharfy et al. studies.in which Parenteral nutrition for more than the cut-off point of 61 days had a higher sensitivity (0.91) and specificity (0.86) Hsieh et al. study. Also receiving TPN for more than the cut-off point of 38.5 days had a sensitivity of 96% and a specificity of 89% in Alkharfy et al. study [10] and Hsieh study [15].

Conclusions

To wrap up, it has been determined that prolonged PN length, NEC incidence, and intestinal resection are risk factors for PNAC in newborns. Therefore, active EN and short-term PN will be required to reduce the incidence of PNAC. Additionally, TPN components like calories and trace elements have a strong relationship with PNAC. The findings of this study could assist health care administrators in managing and ultimately getting rid of PNAC.

Data availability

The dataset used in the current study is available from the corresponding author on request.

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Author's contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by: ME, MA and NH. The first draft of the manuscript was written by MA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

Conflict of interest

The authors declare that they have no conflict of interest

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