Published in final edited form as:

Nutr Clin Pract. 2013 December ; 28(6): 745–752. doi:10.1177/0884533613502813.

Risks and Benefits of Prophylactic Cyclic Parenteral Nutrition in Surgical Neonates

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Abstract

Background—Cyclic parenteral nutrition (PN) is used for both the treatment and prevention of parenteral nutrition-associated liver disease (PNALD). Early initiation of prophylactic cyclic PN may not be well tolerated in young neonates. Our objective was to test the hypothesis that prophylactic cyclic PN initiated prior to the onset of hyperbilirubinemia is associated with younger age at initiation, lower bilirubin levels, and similar rates of adverse events compared to therapeutic cyclic PN initiated after established cholestasis in surgical neonates.

Materials and Methods—Retrospective review of infants with gastrointestinal disorders requiring surgical intervention who received cyclic PN from 2006 to 2011.

Results—Of the 43 infants eligible for analysis, 23 received prophylactic and 20 received therapeutic cyclic PN. Infants in both groups were comparable in demographics, surgical diagnoses, and illness severity. At initiation of cyclic PN, infants with prophylactic cyclic PN were significantly younger in chronologic ($p = 0.003$) and postmenstrual age ($p = 0.029$). Prophylactic cyclic PN was associated with a significantly lower incidence of hyperbilirubinemia ($p = 0.001$), lower maximum conjugated bilirubin ($p < 0.0001$), and lower last checked conjugated bilirubin ($p = 0.032$) compared to the therapeutic cyclic PN. The incidence of hypoglycemia, hyperglycemia, and hypertriglyceridemia was similar for the two groups.

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Conflict of Interest

The authors declare no conflict of interest.

Conclusions—There may be a potential benefit to initiating cyclic PN prior to the development of hyperbilirubinemia in surgical neonates. Early initiation of prophylactic cyclic PN does not appear to increase the risk for adverse events.

Keywords

cyclic parenteral nutrition; neonates; liver disease; bilirubin

Introduction

Parenteral nutrition (PN) is one of the most common therapies for infants with intestinal failure resulting from necrotizing enterocolitis or gastrointestinal surgery. While lifesaving, prolonged PN exposure raises the risk of parenteral nutrition-associated liver disease (PNALD) that can range from mild cholestasis to cirrhosis and death.^{1–3} The incidence of PNALD is directly correlated with the duration of PN therapy^{4–6} and has been reported as high as 85% in neonates requiring prolonged PN.⁶ Morbidity and mortality increase and strongly correlate with the degree of liver dysfunction.^{7,8} Cyclic or non-continuous PN is a strategy used for both treatment of PNALD and prophylaxis of the disease to prevent development of cholestasis. The intermittent, as opposed to continuous, supply of glucose and amino acids is thought to allow more efficient substrate utilization resulting in metabolic unloading of the liver.⁹ Cyclic PN is associated with improved liver transaminases, hepatic function, and resolution of hepatomegaly in adults,^{10,11} and appears to be most effective if initiated early in mild-to-moderate liver disease.¹² In infants, cyclic PN is related to lower or stabilized serum bilirubin levels;⁹ and if used prophylactically (initiated prior to the onset of hyperbilirubinemia), may decrease the incidence of hyperbilirubinemia.^{13,14} However, the optimal time to initiate cyclic PN is unknown and despite the potential benefits of prophylactic PN cycling, early initiation of cyclic PN may not be tolerated in young infants due to immature gluconeogenic and glycogenolytic enzyme systems, limited glycogen stores, and large glucose demands that predispose to hypoglycemia.¹⁵ We conducted this retrospective study to compare the risks and benefits of prophylactic versus therapeutic cyclic PN in surgical neonates at risk for PNALD. We hypothesized that prophylactic cyclic PN initiated prior to the onset of hyperbilirubinemia is associated with younger age at initiation, lower bilirubin levels, and similar rates of adverse events compared to therapeutic cyclic PN initiated after established cholestasis.

Materials and Methods

This retrospective chart review was conducted on all infants who underwent an abdominal surgical procedure and received cyclic PN in the Children's Hospital of Wisconsin Neonatal Intensive Care Unit (NICU) from January 2006 to September 2011. Infants with hepatobiliary disease, metabolic, genetic, or endocrine abnormalities suggesting abnormal glucose or triglyceride homeostasis were excluded. The study was approved by the Institutional Review Board of Children's Hospital of Wisconsin.

Cyclic PN was defined as PN that ran for a duration of less than 24 hours per day. Orders were reviewed to identify patients who were intentionally ordered for cyclic PN while in the

NICU, and charts were reviewed to verify that infants received cyclic PN unrelated to interruptions in PN due to medication administration, loss of vascular access, or procedures. In order to be consistent with previously published work, prophylactic cyclic PN was defined as those whose PN cycling was initiated prior to developing hyperbilirubinemia (conjugated bilirubin (CB) ≥ 2 mg/dL) and therapeutic cyclic PN if cycling began after having established cholestasis (CB level > 2 mg/dL).¹⁴ During the study period, all neonates requiring PN received TrophAmine (B. Braun, Irvine, CA). Intravenous fat emulsion (IVFE) was provided as Intralipid 20%, a soybean oil-based fat emulsion (manufactured by Baxter Pharmaceuticals, Deerfield, IL prior to 2007 and by Fresenius Kabi, Uppsala, Sweden, from 2007 onward). The usual practice at our institution during the study period was to provide amino acid at a dose not to exceed 3.5 g/kg per day and IVFE not to exceed 3 g/kg per day. Parenteral nutrition was not affected by any shortages of macro- or micronutrients during the study period.

In general, the initiation, procedure, and laboratory monitoring followed a pre-established NICU guideline for cyclic PN. Clinically stable infants weighing ≥ 2 kg were candidates for cycled PN. Due to the frequent adjustments to PN at its initiation, cycling is not begun immediately on institution of PN in surgical neonates and is only initiated after reaching a stable composition of continuous PN. For patients who received cyclic PN, IVFE was delivered daily and also cycled on the same cycling schedule as PN. Cycling began with shortening of continuous 24 hour PN to 22 hours with further gradual shortening by 2 hours per day as tolerated toward the goal run-time of 18 hours depending on laboratory abnormalities. In accordance with a NICU initiative to minimize Central-line Associated Blood Stream Infections (CLABSI) by limiting changes and access to central-lines, our center's NICU guideline for cyclic PN specified that PN remain running at 1-2 mL/hr during the rest period of cyclic PN. This practice eliminated the need to unhook and re-attach PN to the central line to minimize line access and infection. Laboratory monitoring consisted of blood glucose level during the run-time for hyperglycemia and 30-60 minutes after transitioning to the rest period for hypoglycemia. Hypoglycemia is again checked with a blood glucose level halfway through the PN rest period. Additionally, a triglyceride level was obtained during the rest period after initiation of cycling to evaluate for hypertriglyceridemia. Hypoglycemia was defined as blood glucose level < 50 mg/dL, hyperglycemia as blood glucose level > 150 mg/dL, and hypertriglyceridemia as serum triglyceride level > 250 mg/dL.

Collected data consisted of patient characteristics including birth weight (BW), gestational age (GA), sex, race, surgical diagnoses, and Score for Neonatal Acute Physiology, Version II (SNAP-II) score.¹⁶ Orders were reviewed for detailed PN and enteral nutritional characteristics for each day of cycling. PN tapering was noted if the PN rate was gradually decreased during the transition from run-time to rest period. The percentage of goal enteral energy was calculated based on a goal of 110 kcal/kg per day. Because episodes of intolerance are most likely to occur during the first few days of PN manipulation, laboratory data were reviewed for all blood glucose and triglyceride values within the first 5 days of initiation of cyclic PN or within 5 days of any change in cycling interval. Birth weight z-scores were obtained from a national reference for premature infants¹⁷ while discharge weight z-scores were obtained using the WHO growth standards after correcting for

prematurity.¹⁸ All positive blood cultures, total bilirubin, and CB levels were evaluated. Bilirubin levels were chosen due to reports of their superiority in reflecting developing and resolving cholestasis in comparison to other laboratory markers of liver function.^{19–22} Sepsis was defined as a positive blood culture that was treated with antibiotics. Pre-cycling CB was the CB level closest to the day of cyclic PN initiation and within 4 days prior to starting, and post-cycling CB was the level prior to discontinuation of cycling. The daily percentage of goal enteral feeds and change in CB level were calculated over the duration of cycled PN. Medication administration records were reviewed for the administration of medications with potential bilirubin-lowering effects including ursodiol, erythromycin, and phenobarbital. Study data were collected and managed using the Research Electronic Data Capture (REDCap) system, a secure, web-based application used for data capture and management in clinical and translational research.²³

Stata Version 12.0 (Stata Corporation, College Station, TX, USA) was used for statistical analysis. Unless otherwise stated, the data are expressed as medians (interquartile ranges). Data were not normally distributed and univariate analysis was carried out using Mann-Whitney test, categorical data were compared using Fisher's exact test, and repeated measures were compared using Wilcoxon signed-rank test. All tests were conducted as two-tailed tests with a p-value < 0.05 considered statistically significant.

Results

Sixty-one patients were identified as having a gastrointestinal anomaly requiring surgical intervention and had orders to receive cyclic PN. Of these, 18 patients were excluded (4 did not actually receive cyclic PN, 11 received cyclic PN outside of the NICU, 1 had Beckwith-Wiedemann syndrome, 1 had metabolic liver disease, and 1 had biliary atresia). The remaining 43 infants were included in the analysis.

All patients initially received continuous PN and subsequently converted to cyclic PN. Overall, patients received PN for a median of 8.6 weeks (IQR 5.1 - 16 weeks) and median cyclic PN duration of 1.4 weeks (IQR 0.7 – 4.3 weeks). Of the qualifying infants, 23 received prophylactically cycled PN and 20 received therapeutically cycled PN. Demographic, perinatal, and clinical characteristics of the two cyclic PN groups are presented in Table 1. Infants in both groups were comparable in gestational age, birth weight, sex, race, surgical diagnoses, and SNAP-II score.

Nutritional, clinical, and adverse event comparisons associated with cyclic PN are shown in Table 2. At initiation of cyclic PN, infants in the prophylactically cycled group had significantly lower median age ($p = 0.003$), lower median PMA ($p = 0.029$), and were receiving higher median IVFE dose ($p = 0.014$) as compared to the therapeutic group. There were no differences in infant weights, percentage of goal enteral energy, glucose infusion rate (GIR), amino acid dose, and PN energy between the groups at the time cycling was started. Although both groups received cyclic PN for similar lengths of time, infants in the therapeutic group had a longer median duration of PN compared to the prophylactic group (13.7 (IQR 6.6 – 18.6) weeks vs 7.7 (IQR 3.3 – 10.9) weeks, respectively, $p = 0.022$).

During the cyclic PN period, both groups received lipid restriction and the proportion of infants with lipid restriction to an IVFE dose < 3 gm/kg per day during the cyclic PN period were similar between the two groups (61% of the prophylactic group vs 85% of the therapeutic group, $p=0.203$). The incidence of sepsis was similar between the two groups and all cases of sepsis were of late-onset. More infants in the therapeutic group received a medication with potential bilirubin-lowering effects both during the cycling period ($p < 0.001$) and during the entire hospitalization as well (85% vs 43%, therapeutic and prophylactic group respectively, $p = 0.010$). The frequency of use for each of the medications during the cyclic PN period is shown in Table 2.

Overall, 23% (10/43) of patients developed hypoglycemia, 7% developed hyperglycemia, and 7% developed hypertriglyceridemia. PN tapering during the transition from run-time to rest period was done in only 4 patients, none of whom had hypoglycemia. Infants who experienced hypoglycemia with cyclic PN had lower median weight at the time PN cycling was initiated compared to those who did not have hypoglycemia (2.33 (IQR 2.11 - 2.57) kg vs 2.95 (IQR 2.48 - 3.80) kg, respectively, $p = 0.006$). Infants with hypoglycemia were also of lower median post-menstrual age (PMA) when the therapy was started compared to those who did not have hypoglycemia (36.4 (IQR 35 - 37.4) weeks vs 40.7 (36.9-43.3) weeks, respectively, $p = 0.005$). Gestational age, birth weight (BW), sex, surgical diagnosis, SNAP-II score, weight, postnatal age, PMA, and percentage of goal enteral intake at the time of initiation of PN cycling were not significantly associated with hyperglycemia or hypertriglyceridemia (data not shown). There was no difference in the incidence of adverse events between the prophylactic and therapeutic groups (Table 2).

Characteristics of growth, hospitalization, and conjugated bilirubin levels are compared in Table 3. Although average weight gain during the cyclic PN period and discharge weight z-scores were similar for both groups, infants in the therapeutic group had significantly longer median length of hospitalization compared to the prophylactic group ($p = 0.007$). By definition, all infants in the therapeutic group had hyperbilirubinemia prior to initiating cyclic PN. In contrast, 57% of the prophylactic group developed hyperbilirubinemia during their hospitalization ($p = 0.001$). The maximum CB and last CB obtained prior to discharge were lower for the prophylactic group ($p < 0.0001$ and $p = 0.032$, respectively).

Thirty-four patients had CB levels both at the beginning and end of the cycling period (16 prophylactic, 18 therapeutic), and only these were used in the analysis of pre- and post-cycling CB levels shown in Figure 1. In looking at the effect of cycling on CB for each group, the prophylactic group had a significantly lower median CB before compared to after cycling (0.6 (IQR 0 - 1.35) mg/dL vs 1.15 (IQR 0.2 - 2.9) mg/dL, respectively, $p = 0.006$) and had a median increase of 0.03 (IQR 0 - 0.05) mg/dL per day in CB during the cycling period. Only 38% of the prophylactic group had hyperbilirubinemia at the end of the cycling period. Therapeutic group median CB levels tended to be higher before compared to after cycling, although this did not reach statistical significance (pre-cycling CB 4.4 (IQR 3.2 - 5.4) mg/dL vs post-cycling CB 3.4 (IQR 2.6 - 5.3) mg/dL, $p = 0.050$). During therapeutic PN cycling, CB levels decreased by a median of 0.05 (IQR - 0.01–0.14) mg/dL per day. The change in CB during the PN cycling period was statistically different between the two groups ($p = 0.004$).

Discussion

This is the first study to directly compare the risks and benefits of prophylactic versus therapeutic cyclic PN in surgical neonates. Despite earlier initiation of cyclic PN in the prophylactic group when infants were approximately 1 month younger and less mature, we found no difference in the incidence of hypoglycemia, hyperglycemia, or hypertriglyceridemia between the two groups. Prophylactic cyclic PN was associated with lower incidence of hyperbilirubinemia and lower CB levels; less frequent use of bilirubin-lowering medications; and shorter hospitalization. These findings suggest a potential benefit for early initiation of cyclic PN prior to the development of hyperbilirubinemia with no increased risk for adverse events compared to later initiation of PN cycling.

These findings are important since PNALD has an incidence of up to 85% in neonates requiring prolonged PN,⁶ and significantly increased morbidity and mortality are seen in patients with potentially irreversible, severe cholestasis and advanced liver disease.^{24,25} Although PNALD has long been recognized as a significant complication of prolonged PN,²⁶ it has also been associated with prematurity, low birth weight, male gender, excessive energy intake, absence of enteral feeding, sepsis, bowel surgery and length of remaining bowel, necrotizing enterocolitis, and PN-specific factors.^{24,26–30}

Cyclic PN was initially introduced to decrease the duration of daily PN to improve lifestyle,³¹ and has been associated with preservation or recovery of liver function in adults.^{10–12} The theory underlying the proposed benefits of cyclic PN is its relation to fuel utilization and hormonal secretion resembling normal, physiologic patterns seen with oral feedings. This has been demonstrated in terms of glucose and amino acid utilization, lipid and carbohydrate storage and oxidation, energy expenditure, and growth hormone and insulin secretion.^{32–35}

Reports of cyclic PN in young infants are limited. In a study of 10 infants less than 6 months age, Collier *et al* described an association between cycled PN over a maximum of 18 hours with decreased or stabilization of direct bilirubin in the majority of infants.⁹ We found similar effects with primarily moderation of CB levels with prophylactic cycling and a combination of CB stabilization and reduction with therapeutic cycling. Takehara *et al* described 10 surgical neonates who underwent successful alternations of PN and non-PN solutions every 4 hours without development of cholestatic jaundice or abnormal serum transaminases.¹³ However, the burden and potential for central venous line infections with frequent fluid changes complicate this cyclic PN regimen. In a retrospective review of infants with gastroschisis comparing 36 infants with prophylactic cyclic PN to 72 infants with continuous PN, Jensen *et al* found continuous PN associated with a 2.86 higher likelihood of developing hyperbilirubinemia compared to prophylactically cycled PN, but the difference was not statistically significant (95% confidence interval, 0.86 - 9.53, $p = 0.088$).¹⁴ The authors concluded that prophylactic cyclic PN is associated with a decreased incidence and prolonged time to onset of hyperbilirubinemia, but the study lacked information regarding potential adverse events with early PN cycling. In a recent prospective, randomized controlled study, Salvador *et al* found no significant difference in cholestasis between very low birth weight infants who received cyclic compared to

continuous PN.³⁶ Risks and benefits are difficult to assess as only the amino acid component of PN was cycled in the study.

Our study extends the findings of earlier studies by comparing cyclic PN initiated prior to developing hyperbilirubinemia with cyclic PN initiated after established cholestasis. We believe that many centers attempt to cycle PN for infants with prolonged PN requirements, but the optimal time for its use is unknown. Despite starting PN cycling significantly earlier than the therapeutic cyclic PN group, we found that prophylactic PN cycling was not initiated until approximately 3 weeks of age even though 60% of the group had GI anomalies (atresia, gastroschisis, TEF, CDH) that would likely have required initiation of PN shortly after birth. Jensen *et al* found a similar delay in starting prophylactic cyclic PN in infants with gastroschisis at their center where the mean age was 23 days (range 7-89 days) when prophylactic PN cycling began.¹⁴ We hypothesize that several factors contribute to this delay in implementing prophylactic PN cycling in surgical neonates. First, because frequent adjustments are needed after PN initiation, cycling is not begun immediately on institution of PN in neonates and is only initiated after reaching a stable composition of continuous PN. Second, clinical stability is essential for infants to tolerate PN cycling as stress will alter metabolic demands and can predispose to hypoglycemia, hyperglycemia, and hypertriglyceridemia. Because the majority of patients in the prophylactic group were premature at birth, we suspect that the higher risk for respiratory distress and other complications of prematurity could have played a role in a delay in reaching clinical stability after birth. Lastly, we suspect that the variability in the time of surgical intervention and time to reach clinical stability post-operatively likely influences the later initiation of prophylactic cyclic PN. In contrast to the prophylactic group, therapeutic cyclic PN was initiated significantly later, at approximately 9 weeks of age. We speculate that this is likely due to the general criteria of reaching a conjugated bilirubin > 2 mg/dL to initiate therapeutic PN cycling used at our center. There may be considerable variability in the time to reach this level with some infants developing cholestasis much later than others. We suspect that this variability in time to develop cholestasis contributes to the relatively late initiation of therapeutic PN cycling.

Decisions regarding when to initiate cyclic PN therapy must balance benefits with adverse events related to discontinuous PN infusion. This is important since hyperglycemia, hypoglycemia, and hypertriglyceridemia have all been associated with increased infant morbidity and mortality.³⁷⁻⁴¹ Our study found no difference in the incidence of adverse events between the prophylactic and therapeutic cyclic PN groups despite the prophylactic group initiating cyclic PN at significantly earlier age and younger PMA. Consistent with prior studies,⁴²⁻⁴⁴ we found hypoglycemia to be the most frequently experienced adverse event. Younger PMA and lower weight at the time of initiation were identified as risk factors for hypoglycemia with cyclic PN. PN tapering was used in only 9% of our study patients but was not done in any of the patients with hypoglycemia. Importantly, none of the hypoglycemic episodes were associated with clinical manifestations or symptoms. These episodes of asymptomatic hypoglycemia underscore the considerable vigilance required to monitor and manage hypoglycemia in neonates undergoing cyclic PN. At our center, NICU guidelines specify checking for hypoglycemia by obtaining a blood glucose level 30-60 minutes after transitioning from the PN run-time to the PN rest period and again halfway

through the PN rest period. If hypoglycemia is detected, it is our clinical practice to restart the PN, and thereby decrease the PN rest period. If hypoglycemia is seen, the PN rest period is not advanced and if hypoglycemia persists despite decreasing the PN rest period, then cyclic PN is discontinued.

Recent clinical guidelines published by the American Society for Enteral and Parenteral Nutrition (ASPEN) emphasize special considerations for neonates receiving PN to reduce clinical complications of hypo- and hyperglycemia. Our definition of hyperglycemia were consistent with those from ASPEN however, insufficient data precluded the ASPEN committee from identifying a precise value for hypoglycemia.⁴⁵ Other sources have advocated blood glucose values of above 45 mg/dL in the first 24 hours of life, 40-50 mg/dL beyond 24 hours of age, and 45-50 mg/dL in sick term or preterm infants.^{46,47} Our choice of blood glucose level < 50 mg/dL for hypoglycemia incorporated these recommendations in order to cover the spectrum of gestational ages and possible clinical scenarios for infants receiving cyclic PN and may be conservative.

Compared to CB levels at the beginning of cycling, we found significantly higher post-cycling CB levels in the prophylactic group and a trend toward lower post-cycling CB levels in the therapeutic group. This difference may be partially due to the significantly higher IVFE dose at initiation of prophylactic PN cycling as several studies have shown an increased risk for liver disease with greater doses of soybean-based lipid emulsions.^{48,49} Of note, the median IVFE dose at the time therapeutic cyclic PN was initiated was 2 gm/kg per day. While lipid restriction to 1 gm/kg per day has been associated with decreased bilirubin levels in patients with established cholestasis,⁴⁸⁻⁵⁰ lipid restriction is typically done cautiously in neonates due to the critical role of fat in energy supply and neural development, as well as the vital function of essential fatty acids in the developing brain and visual system.⁵¹ Notably, Cober *et al* found mild essential fatty acid deficiency in 26% of neonates with PNALD who underwent lipid restriction to 1 gm/kg per day twice weekly.⁴⁹ There are no studies that report on the long-term implications of lipid restriction in infants and thus, the impact of lipid restriction on future growth and neurodevelopment is unknown. Given that these concerns are particularly relevant for premature infants, aggressive lipid restriction was not done in premature infants in our NICU during the study period. We recognize the possibility that CB levels may have been lower in our therapeutic group if IVFE restriction was more aggressive however, we found that the majority of infants in both cycling groups were premature and we suspect the cautious lipid restriction needed in preterm infants underlies the finding that IVFE was not restricted to 1 gm/kg per day in either group. Although there is evidence for lipid restriction in ameliorating established cholestasis, far fewer studies have examined the impact of lipid restriction on the prevention of PNALD. In a recent retrospective study by Nehra *et al*, lipid reduction of soy-based lipid emulsion to 1 gm/kg per day did not prevent cholestasis in neonates. Moreover, investigators found no difference in the incidence of cholestasis or time to onset of cholestasis in infants who consistently received 1 gm/kg per day compared to those who received 2-3 g/kg per day of soy-based lipid emulsion.⁵² Larger, prospective studies designed to include long-term neurodevelopmental follow-up are greatly needed to evaluate the safety of lipid restriction in preterm and term infants at risk for PNALD. The effects of therapeutic cyclic PN seen in our study should also be interpreted with caution because significantly more infants in the

therapeutic group received a medication with bilirubin-lowering effects and the relative contributions of cyclic PN and bilirubin-lowering medications on CB levels cannot be determined with this study.

Although both groups had similar diagnoses and illness severity at birth, infants in the prophylactic group had lower pre-cycling, maximum, and last CB levels; less frequent use of medications with bilirubin-lowering effects; and shorter hospitalization compared to the therapeutic group. Some of these findings may be due to the shorter PN duration in the prophylactic group, but the combination of results support a potential benefit of cyclic PN use prior to the development of hyperbilirubinemia over its use after having established cholestasis.

This study has limitations. The most significant is the small size of the study population primarily due to the low prevalence of surgical neonates and strict selection criteria. Therefore, results should be interpreted with caution as this could impact the significance of our findings. Second, the retrospective nature of the study prohibits analysis of other clinical factors at initiation, during, and after cycling, making it difficult to elucidate reasons for discontinuation of cyclic PN. Similarly, we are unable to determine all of the factors that led one group to receive prophylactic cyclic PN and another to receive therapeutic cyclic PN. The retrospective nature of this study precludes our ability to determine if prophylactic cyclic PN can prevent PNALD. Larger, prospective studies are warranted to more definitively determine if prophylactic PN cycling is protective against PNALD. Lastly, because prior studies have compared cyclic to continuous PN, we chose to focus on the effects of initiating cyclic PN before versus after developing cholestasis. We believe that many centers utilize both approaches to cyclic PN but no previous studies have compared their relative risks and benefits. This lack of a third continuous PN comparison group limits the ability to detect any true advantage of cyclic PN over continuously administered PN.

Despite the limitations, the strengths of the study are that cyclic PN therapy followed established NICU guidelines with a protocol for gradually transitioning surgical neonates from continuous to cyclic PN and procedures for the careful monitoring and management of adverse events. Also, all patients were managed by a team experienced in the management of cyclic PN in young surgical neonates. We believe this study contributes important information regarding a practice that is frequently used with little data. It provides valuable, previously unreported information regarding the influence of cyclic PN initiation time on the development of associated adverse events and PNALD and in young surgical neonates.

In conclusion, these findings suggest a potential benefit of early initiation of cyclic PN prior to the development of hyperbilirubinemia in surgical neonates at risk for PNALD. Earlier initiation of prophylactic cyclic PN does not appear to increase the risk for adverse events associated with cyclic PN compared to later initiation of the therapy. However, the overall moderately high incidence of hypoglycemia with non-continuous PN warrants careful monitoring and consideration should be given to PN tapering. The small study size, retrospective design, and lack of continuous PN comparison group limit definitive conclusions regarding the true risks and benefits of cyclic PN and highlights the need for a prospective, multicenter randomized study that is currently being planned.

Acknowledgments

No financial support was provided for this research.

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Figure 1.
Conjugated bilirubin levels before and after cyclic PN

Table 1

Demographic, perinatal, and clinical characteristics of the 43 surgical neonates in this study

	Prophylactic Cyclic PN (n=23)	Therapeutic Cyclic PN (n=20)	P-value
Gestational age (weeks)	34 (31.3 – 36)	32.2 (26.5 – 35.3)	0.267 ^a
Birth weight (kg)	2.25 (1.31 – 2.48)	1.74 (0.91 – 2.44)	0.913 ^a
Birth weight z-score	−0.27 (−0.95 – 0.25)	−0.05 (−1.03 – 0.61)	0.706 ^a
Sex			
Male	14 (61)	8 (40)	0.227 ^b
Race			0.082 ^b
White	12 (52)	8 (40)	
African-American	1 (4)	6 (30)	
Other	10 (44)	6 (30)	
Diagnosis			0.692 ^b
NEC	5 (22)	7 (35)	
Small Bowel Atresia	4 (17)	3 (15)	
Gastroschisis	7 (30)	3 (15)	
TEF	2 (9)	2 (10)	
CDH	1 (4)	2 (10)	
Volvulus	2 (9)	0 (0)	
Other	2 (9)	3 (15)	
SNAP-II score	14 (5 – 18)	12 (0 – 25.5)	0.344 ^a

Abbreviations: NEC, necrotizing enterocolitis; TEF, tracheoesophageal fistula; CDH, congenital diaphragmatic hernia; SNAP-II, Score for Neonatal Acute Physiology Version II; PN, parenteral nutrition.

Data are presented as median (interquartile range) or n (%).

* P-value < 0.05

^a Mann-Whitney (Wilcoxon rank-sum)

^b Fisher's exact

Table 2

Comparison of nutritional, clinical, and adverse event data for the 43 surgical neonates based on cyclic PN therapy

	Prophylactic Cyclic PN (n=23)	Therapeutic Cyclic PN (n=20)	P-value
<i>At Initiation of Cyclic PN</i>			
Age (weeks)	3.9 (1.1 – 5.7)	9.2 (4.4 – 12.7)	0.003 ^{*a}
PMA (weeks)	37 (35.1 – 40.7)	41.1 (37.6 – 43.9)	0.029 ^{*a}
Weight (kg)	2.55 (2.32 – 2.98)	3 (2.36 – 3.84)	0.252 ^a
Percent of goal enteral energy (%)	0 (0 – 6)	0 (0 – 10)	0.599 ^a
GIR (mg/kg per min)	11.8 (8.8 – 12.6)	11.9 (10.3 – 13)	0.387 ^a
AA dose (g/kg per day)	3.5 (3 – 3.5)	3 (3 – 3.5)	0.355 ^a
IVFE dose (g/kg per day)	3 (2 – 3)	2 (1.5 – 3)	0.014 ^{*a}
PN energy (kcal/kg per day)	92.7 (75.4 – 97.9)	86.2 (72.1 – 92.2)	0.318 ^a
<i>During the Cyclic PN Period</i>			
Duration of cycled PN (weeks)	1.3 (0.3 – 4.3)	1.4 (0.9 – 3.6)	0.742 ^a
Daily percentage of goal enteral energy (%)	15 (0 – 28)	22 (6 – 36)	0.326 ^a
IVFE dose < 3 g/kg per day	14 (61)	16 (80)	0.203 ^b
Sepsis	3 (13)	3 (15)	1.000 ^b
Bilirubin-lowering medication	2 (9)	13 (65)	<0.001 ^{*b}
Ursodiol	1 (4)	7 (35)	0.017 ^{*b}
Erythromycin	1 (4)	1 (5)	1.000 ^b
Phenobarbital	0 (0)	5 (25)	0.016 ^{*b}
<i>Adverse Events During Cyclic PN</i>			
Hypoglycemia	6 (26)	4 (20)	0.728 ^b
Hyperglycemia	1 (4)	2 (10)	0.590 ^b
Hypertriglyceridemia	1 (4)	2 (10)	0.590 ^b

Abbreviations: PN, parenteral nutrition; PMA, post-menstrual age; GIR, glucose infusion rate; AA, amino acid; IVFE, intravenous fat emulsion.

Data are presented as median (interquartile range) or n (%).

* P-value < 0.05

^a Mann-Whitney (Wilcoxon rank-sum)

^b Fisher's exact

Table 3

Comparison of growth, hospitalization, and conjugated bilirubin for the 43 surgical neonates based on cyclic PN therapy

	Prophylactic Cyclic PN (n=23)	Therapeutic Cyclic PN (n=20)	P-value
<i>Growth and Hospitalization</i>			
Average daily weight gain during cyclic PN (g/day)	22 (13 – 33)	26 (16 – 33)	0.635 ^a
Discharge weight (kg)	3.36 (3 – 4.77)	4.35 (3.23 – 4.88)	0.158 ^a
Discharge weight z-score	–1.07 (–2.27 – –0.01)	–1.73 (–2.82 – –0.77)	0.223 ^a
Length of stay (days)	63 (29 – 83)	102 (70 – 158)	0.007 ^{*a}
<i>Conjugated Bilirubin Levels</i>			
Pre-cycling CB (mg/dL)	0.6 (0 – 1.3)	4.4 (3.3 – 5.2)	<0.0001 ^{*a}
Maximum CB (mg/dL)	2.4 (0.8 – 4.1)	6.1 (4.9 – 7.6)	<0.0001 ^{*a}
Last CB (mg/dL)	1.5 (0.2 – 2.8)	2.4 (1.9 – 3.4)	0.032 ^{*a}

Abbreviations: PN, parenteral nutrition; CB, conjugated bilirubin.

Data are presented as median (interquartile range) or n (%).

* P-value < 0.05

^a Mann-Whitney (Wilcoxon rank-sum)

^b Fisher's exact