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Neonatal and Pediatric Peripheral Parenteral Nutrition: What Is a Safe Osmolarity?

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Abstract

Background: To reach nutrition goals, peripheral parenteral nutrition (PPN) often exceeds an osmolarity (Osm) of 900 mOsm/L. Evidence suggesting PPNs with Osm > 900 mOsm/L are safe in adults. However, some pediatric data suggest the PPN Osm limit should be 500-700 mOsm/L, yet A.S.P.E.N. recommends a limit of 900 mOsm/L. *Materials and Methods*: This is a retrospective cohort study from January 1, 2005, to December 31, 2007, to determine if PPNs with an Osm > 900 mOsm/L result in an increased rate of line-related events in neonatal and pediatric patients. Patients from birth to 21 years were included and grouped based on the final Osm of the PPN. The exposed group included patients with Osm > 900 mOsm/L and the nonexposed (NE) group Osm ≤ 900 mOsm/L. *Results*: Baseline demographic data were similar. The mean Osm for neonatal PPNs was 856 and 944 mOsm/L for pediatric PPNs. For neonatal PPNs, the incidence of line-related events was 50 per 100 patient days and 52 per 100 patient days for PPNs ≤ 900 and > 900 mOsm/L (RR = 1.02, 95% CI 0.88-1.18). For pediatric PPNs, the incidence of line-related events was 49.5 per 100 patient days and 42.6 per 100 patient days for PPNs ≤ 900 and > 900 mOsm/L (RR = 0.94, 95% CI 0.77-1.15). *Conclusion*: The final Osm of PPN did not effect the rate of line-related events. Prospective studies assessing the development of line-related events, as a result of PPN Osm, are warranted to confirm the data presented in this analysis. (*Nutr Clin Pract*. 2014;29:118-124)

Keywords

neonatal; pediatrics; osmolarity; infant, newborn; osmolar concentration; parenteral nutrition

Background

After birth, extremely low birth rate (ELBW) and very low birth weight (VLBW) infants are dependent on externally administered nutrients as a result of decreased lipid, dextrose, and protein stores. Catabolism is a particular problem of the VLBW infant who may have minimal nutrition reserves. Furthermore, newborn infants who do not receive adequate protein after birth rapidly develop a negative nitrogen balance.[1] Therefore, without adequate nutrient delivery, protein breakdown will increase resulting in a catabolic state. The current standard for postnatal nutrition in preterm infants is one that duplicates normal in utero fetal growth rates.[2] The American Academy of Pediatrics (AAP) established this recommendation in 1985, and it remains the nutrition guideline to which most neonatologists adhere.[3]

Protein accretion more appropriately reflects nutrition status than weight gain. Neonates are known to have very high rates of protein turnover, synthesis, catabolism, and deposition. Several studies have shown that neonates who receive only supplemental glucose will approximately lose 1.2 g/kg/day of protein.[2,4-7] Therefore, without exogenous protein intake, protein synthesis rates remain high and breakdown rates further increase.[4] Te Braake and colleagues[8] reported that administration of 3 g/kg/day of amino acids in the immediate postnatal period (within 4 hours starting on day of life 0) was safe, effective, and improved outcomes. As a result of this work, many institutions have adopted this practice. In an attempt to reach nutrition goals (amino acids 3-4 g/kg/day) and maintaining a glucose concentration sufficient to meet glucose infusion rates necessary for anabolism often times results in an osmolarity > 900 mOsm/L for the parenteral nutrition (PN) solution.

Peripheral parenteral nutrition (PPN) is also utilized outside of the neonatal period in infants and children for many different reasons (short gut, postoperative ileus, etc). Again, in an attempt to deliver an appropriate level of nutrition to these patients, osmolarities often exceed 900 mOsm/L for the PN solution. Now, there is some evidence demonstrating administration of PPNs with osmolarities > 900 mOsm/L is safe and effective in the adult population.[9-11] However, some of the data in the neonatal and pediatric population suggests the PPN osmolarity limit should be between 500-700[12] even though the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recommends a limit of 900 mOsm/L for PPNs.[13]

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Table 1. Definitions and Grading Schemata for Intravenous Line-Related Events in Pediatric Patients.

Grade	Clinical Criteria
1	Pain at site
	Patient crying with flushing of IV
	Difficulty with flushing of IV
	No redness or swelling
2	Pain at site
	Redness at site, no blanching
	Slight swelling at site (0%-20% above baseline)
	Good pulses below site
	Brisk capillary refill below site
3	Pain at site
	Marked swelling (30%-50% above baseline)
	Blanching of area
	Skin cool to touch
	Good pulses and brisk capillary refill below site
4	Pain at site
	Very marked swelling (>50% above baseline)
	Blanching of area
	Skin cool to touch
	Area of skin necrosis or blistering
	Decreased or absent pulses below site

Adapted from the Alfred I. duPont Hospital for Children line-related event policy. IV, intravenous.

As such, there is much debate about what the osmolarity limit should be for PPNs. The specific aim of this study was to determine if administering PPNs to neonatal and pediatric patients with an osmolarity > 900 mOsm/L results in an increased incidence of line-related events in neonatal and pediatric patients.

Methods

Study Design and Patient Population

This was a single-center, retrospective cohort study that was conducted at the Alfred I. duPont Hospital for Children (AIDHC), a 200-bed free-standing children's tertiary care teaching hospital that is also a Level II Pediatric Trauma and Emergency Department with a 23-bed general intensive care unit (ICU), a 14-bed cardiac intensive care unit (CICU), and a 14-bed neonatal intensive care unit (NICU). Children from birth to 21 years of age admitted to AIDHC from January 1, 2005, to December 31, 2007, that received PN via a peripheral line were eligible for inclusion. The site of peripheral access was confirmed in all patients and those patients that were ordered PN but received it through a central access site were excluded. A line-related event was defined as any episode of an infiltrate, extravasation, or thrombophlebitis (Table 1). Due to the inherent nature of retrospective analyses, deciphering between a grade 1 and grade 2 infiltrate is difficult solely from a medical record. As a result, grades 1 and 2 line-related events were grouped together for analysis in this investigation. The primary outcome was the incidence of any event for patients receiving a PPN with an osmolarity > 900 mOsm/L compared with the incidence of any event for patients receiving a PPN with an osmolarity ≤ 900 mOsm/L. The exposed group (E) consisted of patients receiving PPNs with osmolarities > 900 mOsm/L via a peripheral line and the nonexposed group (NE) received PPNs with osmolarities ≤ 900 mOsm/L, also via a peripheral line. Since the individuals ordering PPN differ whether a patient is in the NICU (NICU group) or outside (non-NICU group) of the NICU, therefore, for analysis, patients that received PPN while residing in the NICU were separated from those patients receiving PPN outside of the NICU.

Statistical Analysis

Demographic and clinical characteristics were compared between groups with a student's t test for continuous variables and a chi-square, Fisher's exact test or Mann–Whitney *U* test for noncontinuous variables, respectively. A 2-sided significance level of $\alpha = .05$ was used to determine statistical significance. Line-related events were stratified by gestational age (GA) and peripheral access site to remove any potential confounding that could be introduced by either of these variables. Simple linear regression was used to test the association between osmolarity and a line-related event. Next, a correlational analysis was conducted to determine statistically significant variables ($P < .05$) to be included in the multivariate logistic regression analysis. Variables determined to be statistically significant were then included in a multivariate logistic regression analysis to determine clinical variables that represent potential predictors of line-related events and their corresponding relative risks and correlational coefficients are presented. Assuming a rate of line-related events of 10% at AIDHC, with an $\alpha = .05$, a power of 80%, and a 10% confidence interval range, 200 days of PPN per group are needed to detect a 10% difference in the rate of line-related events. All analyses were performed using SPSS Version 18 (SPSS Inc, Chicago, IL, USA). This study was approved by the Nemours/Alfred I. duPont Hospital for Children Institutional Review Board.

Results

NICU

There were no differences in the baseline demographic data between groups for the NICU cohort (Table 2). For the time period January 1, 2005, through December 31, 2007, there was a total of 236 patients that received PPN in the NICU which accounted for 668 days of PPN therapy. The median GA age in the NE group was 34 weeks (range 22-42 weeks) and 32 weeks in the E group (range 22-42). The median days of PPN in the NE group was 2 days (range 1-14) and 2 days (range 1-11) in the E group. There was a statistically significant difference in

Table 2. Baseline Demographic Information for the NICU Cohort Receiving PPN.

NICU	≤900 mOsm/L (n = 159)	>900 mOsm/L (n = 77)
Median GA (weeks), range	34 (22-42)	32 (22-42)
Mean weight (kg), range	3 (0.71-7)	3 (0.89-7)
Mean age (days), range	26 (0-185)	37 (0-186)
Female (%)	49	51.8
Median days of PPN, range	2 (1-14)	2 (1-11)
Events by IV site (%)		
Arm	121 (26.2)	53 (25.9)
Foot	144 (31.2)	52 (25.5)
Hand	179 (38.8)	81 (39.7)
Scalp	17 (3.6)	18 (8.8)

There were no statistically significant differences between groups. GA, gestational age; IV, intravenous; NICU, neonatal intensive care unit; PPN, peripheral parenteral nutrition.

Table 3. Intravenous Line-Related Events by Grade for the NICU Cohort Receiving PPN.

Grade	≤900 mOsm/L	>900 mOsm/L
1/2	230	107
3	0	0
4	1[a]	0

There were no statistically significant differences between groups. NICU, neonatal intensive care unit; PPN, peripheral parenteral nutrition.
[a]812 mOsm/L.

Table 4. Rate of IV Line-Related Events per 100 Patient Days Stratified by GA for the NICU Cohort Receiving PPN.

GA (weeks)	≤900 mOsm/L	>900 mOsm/L	*P* Value
<32	45.8	48.5	.71
32-37	41.9	51.5	.19
>37	53.3	44.9	.33

GA, gestational age; IV, intravenous; NICU, neonatal intensive care unit; PPN, peripheral parenteral nutrition.

the mean osmolarity between the NE and E groups, 804 (range 400-899) vs 981 (range 900-1425) mOsm/L, $P < .001$. In the NE group there was a total of 159 patients that accounted for 464 days of PPN and the overall incidence of line-related events was 50 per 100 patient days. In the E group there was a total of 77 patients that accounted for 204 days of PPN and the overall incidence of line-related events was 52 per 100 patient days. When comparing the NE group to the E group, there was no difference in the overall incidence of line-related events ($\chi^2 = 0.07$, $P = .79$). The relative risk (RR) for developing a line-related event was 1.02 (95% confidence interval [CI] 0.88-1.18). The grading of line-related events is shown in Table 3. No line-related events resulted in a compartment syndrome and antidotes were not used for any line-related event.

To determine whether GA had an impact on the incidence of line-related events, analyses were also conducted after stratification by GA: <32, 32-37, and >37 weeks GA (Table 4). Again, there was no difference in the incidence of line-related events between the E and NE group after stratification by GA. The rate of line-related events per 100 patient days for the <32 weeks GA group was 45.8 in the NE group and 48.5 in the E group, $P = .71$ (RR = 1.06, 95% CI 0.82-1.37). The rate of line-related events per 100 patient days for the 32-37 weeks GA group was 41.9 in the NE group and 51.5 in the E group, $P = .19$ (RR = 1.23, 95% CI 0.91-1.65). The rate of line-related events per 100 patient days for the >37 weeks GA group was 53.3 in the NE group and 44.9 in the E group, $P = .33$ (RR = 0.84, 95% CI 0.6-1.19).

Since a line-related event is considered a binary outcome, for univariate analysis it was regressed on the outcomes of interest: osmolarity, gender, GA, postnatal age (PNA), post-menstrual age (PMA), and site of peripheral line placement (Figure 1). Osmolarity was not found to increase the incidence of the primary outcome, of line-related events (odds ratio [OR] = 0.96, 95% CI 0.89-1.04, $P = .79$). For the remainder of the univariate analysis, none of the other outcomes of interest were found to have an effect on the incidence of a line-related event: site of peripheral line placement (OR = 1.01, 95% CI 0.99-1.04, $P = .86$), gender (OR = 0.96, 95% CI 0.89-1.04, $P = .36$), GA (OR = 1.02, 95% CI 0.97-1.06, $P = .51$), PNA (OR = 0.99, 95% CI 0.95-1.04, $P = .81$), or PMA (OR = 1.02, 95% CI 0.97-1.07, $P = .51$).

Before multivariable analysis, a correlational analysis was conducted to determine variables associated with line-related events for inclusion in the multivariable model. Similar to the univariate linear regression, none of the outcomes of interest were found to be correlated with the primary outcome. As a result, each of the factors was then entered into the multivariable model. Again, none of the outcomes of interest were found to have influenced the incidence of a line-related event with multivariable logistic regression: osmolarity (OR = 1.06, 95% CI 0.76-1.49, $P = .73$), site of peripheral line placement (OR = 1, 95% CI 0.87-1.17, $P = .95$), gender (OR = 0.85, 95% CI

Table 5. Baseline Demographic Information for the Non-NICU Cohort Receiving PPN.

Outside	≤900 mOsm/L (n = 50)	>900 mOsm/L (n = 53)
Age, mean	9 yrs (44 days-19 years)	11yrs (47 days-20 years)
Weight (kg), mean	28 (2.4-83)	38 (2.4-77)
Female (%)	44.9	28.2
Median days of PPN, range	1.5 (1-7)	2 (1-13)
Events by IV site (%)		
Arm	19 (35.8)	21 (30.4)
Foot	2 (3.8)	4 (5.8)
Hand	32 (60.4)	44 (63.8)

There were no statistically significant differences between groups. IV, intravenous; NICU, neonatal intensive care unit; PPN, peripheral parenteral nutrition.

Table 6. Intravenous Line-Related Events by Grade for the Non-NICU Cohort Receiving PPN.

Grade	≤900 mOsm/L	>900 mOsm/L
1/2	53	66
3	0	1[a]
4	0	2[b]

There were no statistically significant differences between groups. NICU, neonatal intensive care unit; PPN, peripheral parenteral nutrition.
[a]914 mOsm/L.
[b]959 mOsm/L.

Table 7. Rate of IV Line-Related Events per 100 Patient Days Stratified by Age for the Non-NICU Cohort Receiving PPN.

Age	≤900 mOsm/L	>900 mOsm/L	*P* Value
0-<6 yrs	36.2	31.4	.81
6-12 yrs	60.9	52.9	.62
>12 yrs	59.5	40.3	.07

IV, intravenous; NICU, neonatal intensive care unit; PPN, peripheral parenteral nutrition.

0.63-1.17, *P* = .32), GA (OR = 1, 95% CI 0.66-1.5, *P* = 1), PNA (OR = 0.97, 95% CI 0.7-1.34, *P* = .83) or PMA (OR = 1.1, 95% CI 0.72-1.7, *P* = .65).

Non-NICU

There were no differences in the baseline demographic data between groups for the non-NICU cohort (Table 5). For the time period January 1, 2005, through December 31, 2007, there was a total of 103 patients that received PPN in the non-NICU group which accounted for 269 days of PPN therapy. The mean age in the NE group was 9 years (range 44 days-19 years) and in the E group was 11 years (range 47 days-20 years). The median days of PPN in the NE group was 1.5 days (range 1-7) and 2 days (range 1-13) in the E group. There was a statistically significant difference in the mean osmolarity between the NE and E groups, 835 (range 623-896) vs 1013 (range 902-1348) mOsm/L, p<0.001. In the NE group there were 50 patients that accounted for 107 days of PPN and the incidence of line-related events was 49.5 per 100 patient days. In the E group there were 53 patients that accounted for 162 days of PPN and the incidence of line-related events was 42.6 per 100 patient days. When comparing the E group to the NE group, there was no difference in the incidence of line-related events (χ^2 = 0.39, *P* = .54). The RR for developing a line-related event was 0.94 (95% CI 0.77-1.15). The grading of line-related events is shown in Table 6. No line-related events resulted in a compartment syndrome and antidotes were not used for any line-related event.

To determine whether age had an impact on the incidence of line-related events, analyses were also conducted after stratification by age: 0 days-<6 years, 6-12 years, and >12 years (Table 7). Again, there was no difference in the incidence of line-related events between the E and NE group after stratification by GA. The rate of line-related events per 100 patient days for the 0 days-<6 years group was 36.2 in the NE group and 31.4 in the E group, *P* = .81 (RR = 0.87, 95% CI 0.47-1.61). The rate of line-related events per 100 patient days for the 6-12 year group was 60.9 in the NE group and 52.9 in the E group, *P* = .62 (RR = 0.87, 95% CI 0.57-1.32). The rate of line-related events per 100 patient days for the >12 years group was 59.5 in the NE group and 40.3 in the E group, *P* = .07 (RR = 0.68, 95% CI 0.46-1.01).

Since a line-related event is considered a binary outcome, for univariate analysis, it was regressed on the outcomes of interest: osmolarity, gender, age and site of peripheral line placement (Figure 2). Osmolarity was not found to increase the incidence of the primary outcome, of line-related events (OR = 0.96, 95% CI 0.85-1.09, *P* = .96). For the remainder of the univariate analysis, none of the other outcomes of interest were found to have an effect on the incidence of a line-related event: site of peripheral line placement (OR = 1.07, 95% CI 0.97-1.1, *P* = .29), gender (OR = 0.93, 95% CI 0.82-1.05, *P* = .23) or age (OR = 1.03, 95% CI 0.94-1.09, *P* = .69).

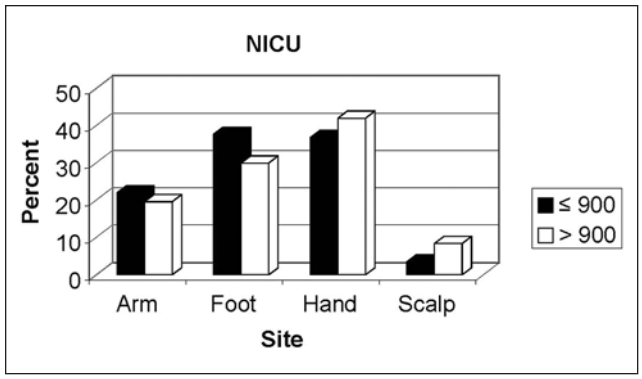

Figure 1. Percentage of patients' IV line-related events stratified by the site of IV catheter placement and osmolarity of peripheral parenteral nutrition for the NICU cohort. IV, intravenous; NICU, neonatal intensive care unit.

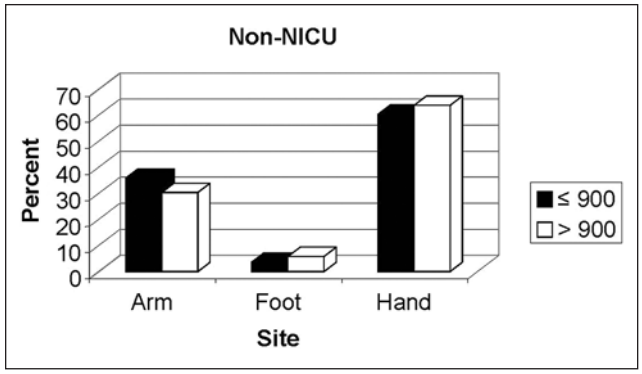

Figure 2. Percentage of patients' IV line-related events stratified by the site of IV catheter placement and osmolarity of peripheral parenteral nutrition for the non-NICU cohort. IV, intravenous; NICU, neonatal intensive care unit.

Before multivariable analysis, a correlational analysis was conducted to determine variables associated with line-related events for inclusion in the multivariable model. Similar to the univariate linear regression, none of the outcomes of interest were found to be correlated with the primary outcome. As a result, each of the factors was then entered into the multivariable model. Again, none of the outcomes of interest were found to influence the incidence of a line-related event with multivariable logistic regression: osmolarity (OR = 0.9, 95% CI 0.54-1.52, P = .69), site of peripheral line placement (OR = 1.2, 95% CI 0.91-1.58, P = .2), gender (OR = 0.71, 95% CI 0.42-1.2, P = .21) or age (OR = 1.07, 95% CI 0.79-1.46, P = .66).

Discussion

One of the main concerns with hyperosmolar solutions is thrombophlebitis. Many studies have attempted to determine the effects of osmolarity on the rate of thrombophlebitis.[14-18] Gazitua and colleagues[18] found thrombophlebitis was universal when osmolarity exceeded 600 mOsm/L in adult patients. They also found thrombophlebitis occurred more commonly with the use of solutions that contained amino acids. The important factors in the production of thrombophlebitis by amino acid solutions were osmolarity and the amount of potassium infused per day.

Bodoky and colleagues[19] demonstrated that parenteral solutions containing amino acids and carbohydrates with an osmolarity of 1,100 m0sm/L exhibited no difference in peripheral venous thrombosis after 48 hours compared to parenteral solutions such as lactated ringer's, dextrose 5% in water, and other electrolyte solution with osmolarities ranging from 280-407 m0sm/L in adult patients. Comberg and colleagues[20] concluded that a hyperosmolar standard nutrition solution (806 mOsm/L) does not cause a higher rate of peripheral venous irritation in adult patients when compared with an iso-osmolar electrolyte solution, and hyperosmolar solutions should be administered to patients with an expected infusion time of not longer than 4 days.

Daly and colleagues[21] evaluated 80 adult patients in 4 groups receiving infusions with osmolarities of 630-983 mOsm/L. There was no difference in the rates of thrombophlebitis between patients who received peripheral infusions with a high osmolarity solution compared to low osmolarity solution. Kane and colleagues[22] randomized 36 adult patients to either "high" (1700 mOsm/L) or "standard" (1200 mOsm/L) osmolarity peripheral parenteral solutions, with heparin added. Patients who received the 1200 mOsm/L solutions showed a mean duration of line survival of 6.8 days with 8 cases of thrombophlebitis as compared to a mean duration of line survival of 6.3 days with only 4 cases of thrombophlebitis in the 1900 mOsm/L group. The difference between groups was not statistically significant in either line duration or number of cases of thrombophlebitis. Kane et al concluded that increasing osmolarity therefore, did not affect the rate of thrombophlebitis or the duration of line survival.

Currently, A.S.P.E.N. recommends a 900 mOsm/L limit for PN administered via a peripheral line.[13] This is based on a 1977 study by Isaacs et al,[23] which compared solutions with and without lipids at various concentrations with and without heparin and hydrocortisone. Several adult reports listed previously have suggested that increasing osmolarity is 1 major determinant to the risk of thrombophlebitis.[18,23] Despite these recommendations, national organizations such as the Infusion Nurses Society (INS) have developed their own, more conservative guidelines that recommended only solutions with an osmolarity < 600 mOsm/L are appropriate for peripheral administration.[24] The European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines state that an osmolarity < 850 mOsm/L can be used.[25] However, some clinical investigations on short-term PN with increasing osmolarity did not increase episodes of thrombophlebitis and did not affect the success rate of catheters as mentioned above.

The AIDHC utilizes a limit of 1050 mOsm/L for PPN solutions and while guidelines exist for maximum limits, clinical

practice varies. In addition to the data presented above, there are other reasons why institutions may utilize a higher osmolarity limit. For example, sodium bicarbonate 4.2%, which is 0.5 mEq/mL, has an osmolarity of 1000 mOsm/L. The 4.2% sodium bicarbonate is often used in the neonatal population and has been infused over periods ranging from 4-24 hours with minimal reports of thrombophlebitis or other adverse reactions.[11] Hypertonic saline, 0.513 mEq/mL, has an osmolarity of ~1050 mOsm/L and is also often administered via a peripheral line for periods exceeding 24 hours. Our data, exclusively in neonatal and pediatric patients, suggest the final osmolarity did not have an effect on the rate of thrombophlebitis or line-related events. Other risk factors have been suggested as reasons for line-related events and thrombophlebitis such as amino acid concentration, potassium and calcium concentrations, catheter time in situ, catheter type, filter type and the type of skin disinfectant used prior to line insertion.[26-28] Some or all of these factors may have played a role in the rate of line-related events in this investigation. Due to the inherent limitations with retrospective analyses, many of these data elements were unable to be collected and analyzed, but with a prospective analysis it would be paramount to include these data elements.

There is no national benchmark regarding what is an acceptable rate of line-related events. In this investigation, the data suggest that a line-related event will happen at least every other day for individuals receiving PPN, depending on the age group in question. The ideal number would be zero. The national benchmark for hospital-acquired infections (HAIs) is not zero and the Centers for Disease Control and Prevention (CDC) estimate that 1 out of every 20 hospitalized patients will acquire an HAI.[29] With the advent of peripherally inserted central catheters (PICCs), the rate of line-related events from PPN should continue to decrease. However, scenarios still exist and patients will still continue to receive PPN, such as the short-gut patient with a central line infection who has the central line removed and needs to have sterile blood prior to having a new central line placed. As clinicians continue to push the envelope on clinical practice, no therapy is without risk. To safely administer PPN, conditions or factors thought to increase the risk of throbmophlebitis should be minimized and monitoring of the access site is essential.

Prior to data collection, a power calculation was conducted assuming a baseline rate of line-related events of 10% at AIDHC, the analysis suggested that 200 days of PPN would be needed per group. After data collection and analysis, a power analysis was completed to determine what the power of this study was with 204 days of PPN in the NICU E group and 162 days of PPN in the non-NICU E group. For the NICU group, the power was determined to be 88% and for the non-NICU group the power was determined to be 81%. Therefore, there was a sufficient sample size in this cohort to detect a 10% difference in the rate of line-related events due solely to osmolarity.

There are several limitations to this study. First, the data presented here were collected as part of a single-center, retrospective study and have all the attendant limitations, such as causation cannot be demonstrated and the influence of factors not reviewed cannot be excluded. Second, our results could be due to a sampling error. Third, factors such as filter type and catheter type were not analyzed and could have played a role in the rate and development of thrombophlebitis. Fourth, other PPN contents such as electrolytes were not analyzed and could have affected the rate of line-related events. Fifth, heparin is not used in PPNs at AIDHC, and, as such, its impact could also not be evaluated. As with all retrospective, single-center studies, these findings need to be interpreted with caution and verified in a prospective trial.

Conclusion

In our neonatal and pediatric cohort, the final osmolarity of a PPN solution did not have an effect on the rate of line-related events. Prospective studies assessing the development of line-related events, as a result of PPN osmolarity, are warranted to confirm the data presented in this retrospective analysis.

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