JPPT | Retrospective Study

Re-evaluating Safe Osmolarity for Peripheral Parenteral Nutrition in Neonatal Intensive Care Patients

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OBJECTIVE To reach nutrition goals for neonatal patients, institutions often exceed the American Society for Parenteral and Enteral Nutrition recommended maximum of 900 mOsm/L for peripheral parenteral nutrition (PPN). Evidence is limited regarding the safety of PPN osmolarities above this maximum, specifically in neonatal patients. The purpose of this study was to determine if PPN with osmolarities ≥ 1000 mOsm/L is associated with an increased rate of line-related complications.

METHODS This retrospective study included infants admitted to the Penn State Health Children's Hospital NICU from January 1, 2013, through July 31, 2018, who were receiving PPN, to assess if solutions with osmolarities ≥ 1000 mOsm/L versus < 1000 mOsm/L are associated with increased rates of line-related complications.

RESULTS A total of 200 patients were included in the study, and 618 individual PPN days were analyzed. Baseline patient characteristics were similar between groups. The PPN osmolarities ranged from 610 to 1267 mOsm/L. Overall, the incidence of line-related complications for PPN < 1000 (n = 342 PPN days) and ≥ 1000 mOsm/L (n = 276 PPN days) was 28.9% and 29.0%, respectively (OR 1.00 [95% CI 0.72–1.40, p = 0.99]). Irrespective of PPN osmolarity, infants weighing > 1.5 kg had significantly greater odds of experiencing line complications compared with patients < 1 kg, but showed no difference compared with patients weighing 1 to 1.5 kg.

CONCLUSIONS AND RECOMMENDATIONS There were no significant differences in the incidence of line-related complications in NICU patients receiving PPN with osmolarities 1000 to 1250 versus < 1000 mOsm/L.

ABBREVIATIONS ASPEN, American Society for Parenteral and Enteral Nutrition; CI, confidence interval; IQR, interquartile range; IV, intravenous; NICU, neonatal intensive care unit; OR, odds ratio; PN, parenteral nutrition; PPN, peripheral parenteral nutrition; REDCap, Research Electronic Data Capture; TPN, total parenteral nutrition

KEYWORDS critically ill; neonate; osmolar concentration; osmolarity; parenteral nutrition; peripheral

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Introduction

Nutrition for NICU patients is critical, especially in very low birth weight and preterm infants. Often, nutrition (parenteral nutrition [PN]) is temporarily administered through peripheral IV catheters.[1,2] Peripheral line-related complications, such as extravasations or infiltrations, in pediatrics are common, yet difficult, issues to overcome. Not only can line complications lead to cosmetic damage, but these may also cause severe functional impairment.[3]

In an attempt to reach nutrition goals for preterm NICU patients, the osmolarities of peripheral parenteral nutrition (PPN) often exceed the American Society for Parenteral and Enteral Nutrition (ASPEN) recommended maximum of 900 mOsm/L. Neonatal intensive care units frequently use higher osmolarity cutoffs (e.g., 1000 mOsm/L) than recommended by ASPEN in order to avoid placing central catheters for short-term PN administration.[4,5] Amino acids and dextrose content contribute most significantly to osmolarity in PN. Reaching goal amounts of each in PPN is often a challenge while staying within the osmolarity limits set by ASPEN.[1] Unfortunately, there is a lack of evidence regarding the safety of PPN with osmolarity >900 mOsm/L. Moreover, the European Society for Parenteral and Enteral Nutrition recommends an even more conservative cutoff (i.e., 850 mOsm/L) for PPN.[6]

Despite ASPEN recommendations and the limited safety data available in pediatric patients, many institutions, including Penn State Health Children's Hospital, use higher maximum osmolarities (i.e., < 1000 mOsm/L, < 1250 mOsm/L) for PPN to provide adequate nutrition.[4,5] We hypothesized that there would be no difference in complication rates from PPN with osmolarities below and above 1000 mOsm/L. The purpose of this study

Table 1. Intravenous Line Complication Scoring Definitions and Criteria*

Severity Score	Clinical Definition
1	Erythema at site without pain or mild edema (1%–10%†) or skin blanching
2	Pain at access site with erythema and/or edema (11%–29%†) or skin blanching
3	Pain at site with erythema, edema and/or skin blanching, with streak formation and palpable venous cord
4	Pain at site with erythema, edema and/or skin blanching, with streak formation, palpable venous cord, and purulent drainage or skin necrosis

* Adapted with permission from Penn State Health Children's Hospital line complication policy.
† Assessed edema percent measurement of effected area.

Table 2. Baseline Patient Demographics (N = 200 patients)

Demographics	Results
Postmenstrual age, mean ± SD, wk	32.3 ± 4.7
Birthweight, median (IQR), kg	1.6 (1.1–2.3)
Weight on day 1 of PPN, median (IQR), kg	1.8 (1.3–2.4)
Male, n (%)	114 (57.0)
Race, n (%)	
White	134 (67.0)
Hispanic	30 (15.0)
Other	24 (12.0)
African American	12 (6.0)

PPN, peripheral parenteral nutrition

was to determine if PPN with osmolarities ≥ 1000 versus < 1000 mOsm/L are associated with increased rates of line-related complications in NICU patients using osmolarity cutoffs based on current clinical practice at our institution.

Materials and Methods

This is an institutional review board approved, single-center, retrospective chart review from January 1, 2013, through July 31, 2018, at Penn State Health Children's Hospital with a 42-bed, Level IV NICU. Parenteral nutrition is ordered by the medical team providers, with assistance from nutrition and pharmacy. Our average custom neonatal PN usage is 218 PNs per month. Patients were included if they were admitted to the NICU and received ≥ 1 day of PPN. Patients were excluded if their PN was administered only through a central venous catheter, rather than peripherally. If there was a break in PPN therapy > 36 hours, each administration was recorded as separate PPN sessions.

At our institution, patient-specific PPN is outsourced through Central Admixture Pharmacy Services, Inc (Allentown, PA). If PPN is required outside of the proper time window, premixed, ready-to-use, starter PN is begun. All starter PN solutions have an osmolarity < 900 mOsm/L, and patients who received these products peripherally, as well as the individual days on this therapy, were included in the study (see the Supplemental Table for components of the starter PN). Starter PN is initiated for any patient < 1.5 kg at birth until a custom PN solution can be ordered.

The primary outcome of this study was the incidence of line-related complications for infants receiving PPN with osmolarities ≥ 1000 versus < 1000 mOsm/L (osmolarity calculation based on Central Admixture Pharmacy Services, Inc, label). Line complications were defined and scored on a severity scale of 1 through 4 according to institution-specific policies (see Table 1). Secondary outcomes included complication severity and time to line event (after beginning PPN) for each osmolarity group, as well as concurrent lipid therapy, PPN components, and patient weight. Fat emulsion was administered over 20 to 24 hours by means of a Y connector to the PN. The type of lipid emulsion used was Intralipid (Baxter, Deerfield, IL) before August 20, 2018, and SMOF (Fresenius Kabi USA, Lake Zurich, IL) lipid beginning August 20, 2018, until the end of the study timeframe.

Study data were collected and managed using Research Electronic Data Capture (REDCap) tools (Vanderbilt University, Nashville, TN) hosted at Penn State Health Milton S. Hershey Medical Center and Penn State College of Medicine. REDCap is a secure, web-based application designed to support data capture for research studies. Data analysis was performed using SAS software, version 9.4 (SAS Institute, Inc, Cary, NC). Differences between groups were considered significant when p values were < 0.05. Analyses were performed based on PPN days, instead of patient numbers, using generalized estimating equations, as many patients received both higher and lower osmolarity PPN. Generalized estimating equation analyses are similar to binomial logistic regressions, but they account for the correlation between observations in the same patient. An ordinal logistic regression analysis was performed for the line complication severity outcome.

Results

A total of 803 neonatal patients were ordered TPN solutions in the electronic health record from January 1, 2013, through July 31, 2018. The original patient list was randomized in Excel and data were collected into REDCap until 200 patients met inclusion criteria. Three hundred seven patients were evaluated, and 107 patients were excluded because the PN was administered

Table 3. Baseline Patient Demographics by Osmolarity Group (N = 618 PPN days)

Demographics	<1000 mOsm/L (n = 342*)	≥1000 mOsm/L (n = 276*)
Postmenstrual age, mean ± SD, wk	33.6 ± 4.3	33.4 ± 5.1
Weight on day 1 of PPN, mean ± SD, kg	1.9 ± 0.8	1.8 ± 0.9
Male, n (%)	192 (56.1)	153 (55.4)
Race		
White, n (%)	226 (66.1)	204 (73.9)
African American, n (%)	21 (6.1)	18 (6.5)
Hispanic/Latino, n (%)	44 (12.9)	30 (10.9)
Other, n (%)	51 (14.9)	24 (8.7)

PPN, peripheral parenteral nutrition

* Ninety-two of two hundred patients contributed to both PPN osmolarity groups; 81/200 had only PPN < 1000 mOsm/L and 27/200 had only PPN ≥ 1000 mOsm/L.

Table 4. Components of Peripheral Parenteral Nutrition (PPN) Solutions (N = 618 PPN days)

PPN Component	Line Event, Mean ± SD (n = 179)	No Line Event, Mean ± SD (n = 439)
Dextrose, %	11.0 ± 1.1	10.8 ± 1.2
Amino acids, %	3.2 ± 0.7	3.4 ± 1.2
Sodium, mEq/L	36.2 ± 24.3	31.2 ± 22.4
Potassium, mEq/L	17.2 ± 9.4	15.2 ± 9.9
Calcium, mEq/L	25.3 ± 6.2	24.2 ± 7.4
Phosphate, mEq/L	12.0 ± 4.2	10.9 ± 5.2

only via central access. Therefore, 200 patients were included in the study resulting in assessment of 618 days of PPN (n = 276 days for ≥1000 mOsm/L group; n = 342 days for <1000 mOsm/L group).

Baseline patient characteristics were not different between the groups (Tables 2 and 3). About half of the patients contributed to both osmolarity groups (92/200, 46.0%). For the 618 individual PPN days, osmolarities ranged from 610 to 1267 mOsm/L (see Figure 1). There were 122 PPN days with osmolarities > 1100 mOsm/L, and 39/122 PPN days had osmolarities ≥ 1200 mOsm/L. Of the 618 PPN days evaluated, 76 (12.3%) PPN days used starter PN; the remaining 542 PPN days comprised a custom PN solution. For the primary outcome, there was no significant difference in the incidence of line-related complications for PPN with osmolarities ≥ 1000 mOsm/L (29.0%) versus < 1000 (28.9%) (OR 1.00 [95% CI 0.72–1.40, p = 0.99]). The median infusion rate of PPN for the line event group (6.5 mL/hr [IQR 4.6–11.3 mL/hr]) was similar to the group without line events (5.5 mL/hr [IQR 4.0–9.1 mL/hr]). The components of the PPN solutions are displayed in Table 4.

The most common peripheral IV catheter locations were in the hands and wrists (see Figure 2). Patients with antecubital IV catheters had lower odds of developing line complications compared with those with hand IV catheters (OR 0.49 [95% CI 0.32–0.77], p = 0.002). Overall, the median time from PPN initiation to the time of the line complication was 56 hours for ≥ 1000 mOsm/L (IQR 31–91 hours), and 24 hours for < 1000 mOsm/L (IQR 13–54 hours). The median age of the IV catheter at the time of the line complication was 28 hours (IQR 14–53 hours) and 20 hours (IQR 7–40 hours), respectively.

Of the documented line complications, 97.2% had a severity score of 1 or 2, which consisted of mild edema, erythema, or skin blanching. There were no significant differences in the severity of line complications between the 2 PPN osmolarity groups (OR 1.32 [95% CI 0.65–2.71], p = 0.443). However, 2 patients in the ≥ 1000 mOsm/L group had a complication severity score of 4, whereas there were none in the < 1000 mOsm/L group (see Tables 5 and 6).

Infants weighing > 1.5 kg had significantly greater odds of experiencing line complications (severity score 1 or 2) compared with patients < 1 kg (OR 2.20 [95% CI 1.03–4.67], p = 0.040). Moreover, the > 1.5 kg subgroup had more line complications overall, whereas infants < 1.5 kg had more severe (i.e., scores of 3 or 4) line complications (1/367 [0.27%] versus 4/251 [1.59%]).

The relationship of concurrently running lipids with PPN and line adverse events was also analyzed. In the group with line complications, the percentage of patients with lipids running concurrently with PPN was higher (151/179, 84.4%) versus those without line complications (334/439, 76.1%) (OR 1.70 [95% CI 1.07–2.69], p = 0.026). We also evaluated other concurrently administered medications (as potential vesicants) during PPN infusion through the same IV site, including nafcillin, gentamicin, vancomycin, acyclovir, calcium gluconate, sodium bicarbonate, 3% sodium chloride, and potassium chloride, and found no significant differences in the incidence of line complications for patients who did and did not concomitantly receive these medications.[7]

Discussion

Although line-related complications are associated with many factors, PPN osmolarity may be an important cause.[1,2,6] There is much debate regarding the safest osmolarity limits for PPN solutions, especially in infants who have significant nutritional requirements. Currently, ASPEN recommends a maximum osmolarity limit of 900 mOsm/L for PPN, but many institutions have had to adopt higher limits (i.e., 1000 mOsm/L) to provide adequate nutrition.[4,5] Our study found no significant difference in

Table 5. Line Complication Severity (n = 179)

Severity Score*	< 1000 mOsm/L, n (%) (n = 99)	≥ 1000 mOsm/L, n (%) (n = 80)
1	77 (77.8)	60 (75.0)
2	21 (21.2)	16 (20.0)
3	1 (1.0)	2 (2.5)
4	0	2 (2.5)

* Severity of line complications were scored according to the institution's policy (see Table 1).

Table 6. Peripheral Parenteral Nutrition (PPN) Osmolarity for Severe Line Complications (n = 5)

Severity Score	PPN Osmolarity (mOsm/L)
3	929 1112 1250
4	1128 1242

the incidence of line-related complications between PPN with osmolarities 1000 to 1250 versus < 1000 mOsm/L.

Prior to our study, evidence regarding PPN osmolarity and line complications has been limited and conflicting, and various osmolarity cutoffs have been studied. In a prospective analysis of 14,167 infants who received ready-to-use PPN formulations, osmolarities up to 800 mOsm/L were determined to be safe.[8] Another study in 352 pediatric patients found increased infiltration and phlebitis when PPN osmolarity was > 1000 mOsm/L versus ≤ 1000 mOsm/L.[4] Lastly, in a study of 236 infants, there was no difference in line complications between PPN with osmolarities > 900 mOsm/L versus ≤ 900 mOsm/L.[9]

Theoretically, as PPN osmolarity increases far beyond the recommended limit, it is expected that patients would have higher risk of line complications. This study analyzed an osmolarity limit higher than recommended by ASPEN, and the data would be expected to be more applicable to those facilities, which currently use a maximum of 1000 mOsm/L, or higher, for PPN solutions. Despite our institution's current PPN osmolarity cutoff of 1250 mOsm/L, evidence addressing PPN osmolarity and line complications in infants is especially lacking for high PPN osmolarities (>1200 mOsm/L). In our cohort, there were 39 PPN days with osmolarities ≥ 1200 mOsm/L. Importantly, a study comparing line complications between PPN with high osmolarities (>1200 mOsm/L) versus osmolarities 901 to 1200 mOsm/L, reported no difference.[9] In this study, there was 1 PPN with osmolarity over our institution's limit of 1250 mOsm/L (1267 mOsm/L), which was an error.

Previous literature has been mixed with regard to the effect of co-infusion of lipids on the incidence of line complications. Several studies have found a protective effect of co-infused lipids on peripheral line patency and by inference, decreased risk of line-related complications.[10-12] In fact, in 1 study, co-infusion of high lipid concentration appeared to have a vascular protective effect resulting in longer line patency.[10] Although our study results showed a higher odds of having a line event with concurrently running lipids, the line complications occurred almost 11 hours later than in those without lipid co-infusion. Based on the conflicting results, the evidence supporting this concept is still unclear.

Ideally all line-related complications should be prevented, but the risk is nearly impossible to eliminate completely using current technology. In the meantime, attention should be focused on preventing the most severe line complications, such as those with high severity scores leading to purulent drainage or skin necrosis necessitating plastic surgery repair. In our 5 patients with high severity scores of 3 and 4, the average dextrose concentration was 11.8%, with 2 infants having dextrose concentrations ≥ 12%. Although the accepted maximum glucose concentration for peripheral IV catheters is 12.5%, perhaps, according to our study results, maximum glucose concentration should be limited to 11% when providing PPN, irrespective of osmolarity. Mean calcium concentrations in patients with severe line complications (28.2 ± 2.5 mEq/L) were similar to both the patients with less severe line complications (25.3 ± 6.2 mEq/L) and the patients without line events (24.1 ± 7.4 mEq/L). Since the completion of this study, our institution has implemented a limit of 20 mEq/L for calcium in PPN to minimize line complications and comply with current best practices.[13,14]

This study also found that NICU patients weighing > 1.5 kg had significantly greater odds of experiencing line complications (severity score 1 or 2) compared with patients < 1 kg (OR 2.20 [95% CI 1.03–4.67], p = 0.040). However, there was no clinically significant difference in mean osmolarity between the groups (<1 kg [n = 19] 975 mOsm/L versus > 1.5 kg [n = 131] 979 mOsm/L). The mean dextrose concentration was 10.1 ± 1.85% in the < 1 kg group compared with 10.97 ± 0.98% in the > 1.5 kg group. Mean calcium concentrations also did not differ between the 2 groups (<1 kg 23.9 ± 7.33 mEq/L versus >1.5 kg 25.1 ± 6.75 mEq/L). Moreover, the > 1.5 kg subgroup had more line complications overall, whereas infants < 1.5 kg had more severe (i.e., scores of 3 or 4) line complications (1/367 [0.27%] versus 4/251 [1.59%]).

Our study was limited, in that it was a single-center, retrospective study design. The patients in both osmolarity groups were not initially matched, and our results may be confounded due to the potential for sampling error. However, we did account for this during our analysis. Additionally, due to the nature of retrospective data collection via chart review, inaccurate or incomplete documentation is possible and may have introduced error, especially during the analysis of line event severity

Figure 1. Distribution of peripheral parenteral nutrition (PPN) osmolarities (N = 618 PPN days).

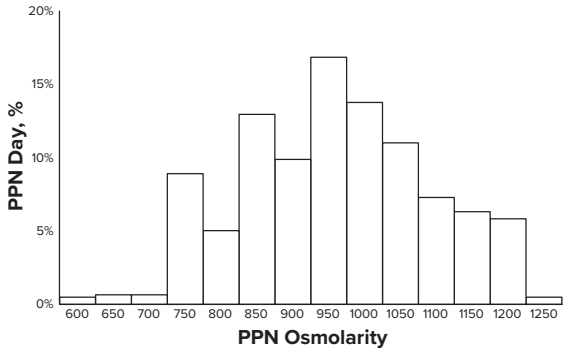
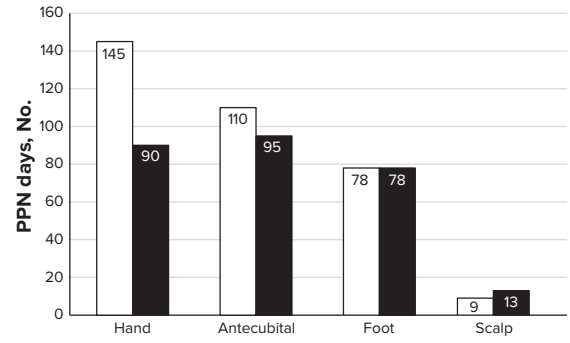


Figure 2. Peripheral intravenous line location for each individual peripheral parenteral nutrition (PPN) according to osmolarity group (N = 618 PPN days).



and co-infused lipids or vesicant medications in patients with multiple peripheral IV lines.

Currently there are only a few studies assessing the relationship between PPN osmolarity and line complications, and they have shown mixed results. Our study was unique in that it focused on the neonatal population and included PPNs with osmolarities significantly above ASPEN recommendations. To date, there is only 1 other study of similar size specifically assessing line complications associated with PPN in NICU patients.[9]

Conclusion

Our retrospective study found no significant difference in the incidence of line-related complications between PPN with osmolarities < 1000 mOsm/L versus ≥ 1000 mOsm/L. Providing temporary, yet adequate nutrition in infants can be a challenge, especially with limited evidence supporting the administration of PPN with osmolarities beyond the ASPEN recommended maximum of 900 mOsm/L. Our study results suggest that neonatal patients with PPN osmolarity 1000 to 1250 mOsm/L are not associated with an increase in line complications.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. Given the nature of this study, the project was exempt from informed consent.

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