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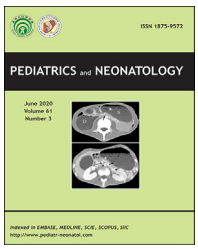

Original Article

Use of sodium glycerophosphate in neonatal parenteral nutrition solutions to increase calcium and phosphate compatibility for preterm infants

Hsueh-Ju Wang [a], Ya-Ting Hsieh [a], Ling-Yu Liu [a], Chih-Fen Huang [a], Shu-Chiao Lin [a], Po-Nien Tsao [b], Hung-Chieh Chou [b], Ting-An Yen [b], Chien-Yi Chen [b,*]

[a] *Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan*
[b] *Department of Pediatrics, National Taiwan University Children's Hospital, National Taiwan University College of Medicine, Taipei, Taiwan*

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calcium;
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organic phosphate;
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Background: Preterm infants require higher calcium and phosphate intake than term infants to facilitate adequate bone growth, but this is rarely met in parenteral nutrition (PN) solution because of the limited solubility of calcium and phosphate. This study aimed to evaluate the solubility of organic phosphate with calcium gluconate in neonatal PN solutions, simulating its clinical use.

Methods: PN solutions were composed of calcium gluconate at 50 mEq/L and sodium glycerophosphate (NaGP) at 25 mmol/L. Another component included 1% or 4% amino acid and 10% or 20% dextrose. For comparison, PN solution composed of potassium phosphate was also evaluated. Each solution was evaluated using the following methods: visual inspection, light obscuration particle count test, and pH measurement. To simulate the clinical condition, the solution was tested after compounding, after being stored at 25 °C for 24 h, and after being stored at 2°C-8°C for 2 or 9 days and subsequently at 25 °C for 24 h.

Results: There was no visual deposition in PN solution using NaGP in any of the concentrations and under any stored condition. The solution fulfilled the criteria of physical compatibility as $<$ 25 particles/mL measuring $\geq$10 μm in diameter and $<$3 particles/mL measuring $\geq$25 μm in diameter. On the contrary, visual deposition was evidently noted in PN solution using potassium phosphate after its formulation, and the particle count significantly exceeded the range of physical compatibility.

* Corresponding author.
E-mail address: chienyichen@ntu.edu.tw (C.-Y. Chen).

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Conclusion: NaGP and calcium gluconate have significantly good compatibility in PN solution. The use of NaGP in neonatal PN prevents calcium and phosphorus precipitation, hence increasing their supply to preterm infants in meeting their growth requirement.

1. Introduction

With the advancement in neonatal care, the survival rates of very-low-birth-weight (VLBW) preterm infants increased significantly in recent decades.[1] Hence, aggressive nutrition support is one of the key factors that improve the survival rates of VLBW preterm infants.[2–4] Preterm infants require higher nutrient intake than term infants to meet their rapid intrauterine growth rate. Moreover, adequate calcium and phosphate supplement is of paramount importance because of the infants' rapid bone growth rate. If VLBW infants have inadequate calcium and phosphate to maintain appropriate bone accretion, metabolic bone disease of prematurity may develop, which leads to osteomalacia, fracture, and impaired linear growth.[5] However, with an immature gastrointestinal tract, infants' enteral nutrition is generally limited; thus, early parenteral nutrition (PN) is usually required in VLBW infants to meet their nutritional demands.

Calcium phosphate precipitation is the major problem that is observed when PN is performed in preterm infants, and some equations and graphs have been developed to guide practitioners in preventing calcium phosphate precipitation.[6–8] As a result, calcium and phosphate intake is seldom sufficient to meet the infants' requirement for bone mineralization. For growing preterm infants, the updated European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines have recommended PN administration of calcium 1.6—3.5 mmol/kg/day (64—140 mg/kg/day) and phosphate 1.6—3.5 mmol/kg/day (50—108 mg/kg/day), with a molar calcium:phosphate ratio around 1.3 (mass ratio around 1.7).[9] For example, in our institution, the average supplementation of calcium and phosphate are 19.8 $\pm$ 11.3 mg/kg/day and 20.1 $\pm$ 10.9 mg/kg/day, respectively, for LBW infants (internal data). As a result, a preterm infant who cannot tolerate enteral feeding well is usually at risk of metabolic bone disease after long-term PN. A systematic review has demonstrated that PN predisposes the infant to metabolic bone disease and suggested the administration of PN solutions with high-dose calcium and phosphorus supplementation.[10] Increasing calcium and phosphate concentrations without increasing the risk of precipitation is an important issue that enhances bone health in preterm infants.

There are several factors, including temperature, pH of the solution, the composition and concentration of amino acid and glucose, presence of lipid, length of storage, and the nature of calcium and phosphate (organic or inorganic), affecting calcium phosphate solubility in PN solution.[11] Most of these factors, such as the use of amino acid, glucose, and lipid, are already unchangingly determined when providing PN to individualized patients. The most promising intervention to prevent precipitation is to change the type of salts. Compared to inorganic salts, organic calcium and phosphate have higher compatibility and lower propensity to precipitate.[12–15] Organic calcium salts such as calcium gluconate have been widely used in neonatal PN, whereas organic phosphate such as sodium glycerophosphate (NaGP) or sodium glucose-1- phosphate is still not available in many countries.

In our hospital, aggressive PN policy, including early PN with starter solution and high protein supplement, has established as a routine care for VLBW infants since 2013. However, since then, early hypophosphatemia has also been observed because of low phosphate intake. To increase calcium and phosphate intake in preterm infants, we plan to introduce NaGP to the current PN program in our hospital. Several reported studies have shown the high compatibility of organic phosphate with both organic and inorganic calcium salts and different concentrations of protein and glucose.[13–17] However, neonatal PN is formulated with different components, concentrations, and conditions in Taiwan. Since the previous reports did not provide sufficient reference to evaluate the risk of precipitation under our usual conditions, we conducted a series of studies to assess the compatibility of inorganic phosphate and calcium gluconate in neonatal PN, simulating its clinical practice.

2. Methods

2.1. Formulation of parenteral nutrition

All PN solutions were aseptically prepared in a horizontal laminar airflow hood using an automated compounding machine (Baxa Exacta-Mix 2400 compounder). The components of PN are listed in Table 1. After reviewing the past formulation of PN in our neonatal intensive care unit (NICU), the minimum and maximum concentrations of dextrose (10% and 20%) and amino acid (1% and 4%) were chosen for testing. The final concentrations of other components included the following: calcium at 25 mmol/L, phosphate at 25 mmol/L, sodium at 50 mEq/L, potassium at 40 mEq/L, and magnesium at 5 mEq/L. Each concentration was formulated as 250 mL per bag and in 3 repetitions.

Precipitation may take time to form. In the clinical condition, PN solution may be stored at different temperatures for different periods before or during infusion. To assess the compatibility of formulated PN solution under different clinical conditions, PN solution composed of NaGP was stored under several conditions before analysis (Fig. 1).

Table 1 Composition of parenteral nutrition solution.

Component	Product	Manufacturer	Concentration	Added volume
Dextrose	Glucose	Y.F. (Taiwan)	50%	50 or 100 mL
Amino acid	Aminosteril Infant	Fresenius Kabi (Austria)	10%	25 or 100 mL
Calcium	Calgon (calcium gluconate)	Y.F. (Taiwan)	10%	27 mL
Organic phosphate	Glycophos	Fresenius Kabi (Norway)	Na: 2 mEq/mL P: 1 mmol/mL	6.25 mL
Inorganic phosphate	Potassium phosphate	U-Liang (Taiwan)	K: 4.4 mEq/mL P: 3 mmol/mL	2.08 mL
Sodium chloride	3% sodium chloride	Y.F. (Taiwan)	Na: 0.513 mEq/mL Cl: 0.513 mEq/mL	0 or 17.8 mL
Na acetate	Na acetate	Kingdom (Taiwan)	Na acetate: 4 mEq/mL	0 or 0.85 mL
Potassium chloride	Potassium chloride	C.C.P.C. (Taiwan)	K Cl: 2 mEq/mL	0.45 or 5 mL
Magnesium sulfate	Magnesium sulfate	C.C.P.C. (Taiwan)	10%	1.55 mL
Water	Water for injection	Y.F. (Taiwan)		0.27—135.2 mL

C.C.P.C.: China Chemical and Pharmaceutical Co., Ltd.
Kingdom: Synpac-Kingdom Pharmaceutical Co., Ltd.
U-Liang: U-Liang Pharmaceutical Co., Ltd.
Y.F.: Y F CHEMICAL CORP.

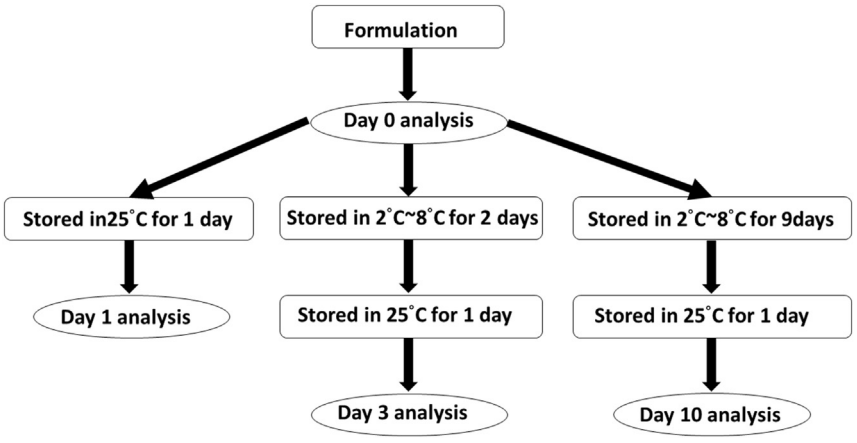

Figure 1 The parenteral nutrition solution composed of NaGP was stored under several conditions before analysis.

For comparison, PN composed of inorganic phosphate (potassium phosphate), 10% or 20% dextrose, and 1% or 4% amino acid was also formulated and analyzed after formulation.

2.2. Analysis

Each solution was visually inspected and then analyzed by light obscuration particle count test using the United States Pharmacopeia (USP) 788 standards.[18] A suitable apparatus (APS 2000 Particle Measuring Systems, Boulder, CO, USA) based on the principle of light blockage was used, which allows an automatic determination of the size of the particles and the particle count according to size. The test was performed in a laminar flow cabinet, and particle count $\geqq$10 μm and $\geqq$25 μm in each sample was counted. Particle counts were assessed by a mean of 3 counts of 10 mL of PN solution for each sample. Solutions are considered physically compatible if the average particle count $<$25 particles/mL measuring $\geq$10 μm in diameter and $<$3 particles/mL measuring $\geq$25 μm in diameter. Measurements of pH were performed in each bag using a validated pH meter (Radiometer PHM210, Lyon, France). The pH was assessed by a mean of 3 counts of PN solution for each sample.

2.3. Statistical analysis

The result of the pH value and particle count in each group was presented as mean $\pm$ standard deviation. Since the aim of the study is to evaluate the condition of precipitation in each preparation and the criteria to pass are well defined in the above method, comparisons between groups were not performed because no further information would be provided.

3. Results

There was no visual deposition in the PN solution using NaGP in 10% and 20% dextrose or 1% and 4% amino acid after formulation. Lower pH value was noted in the solution with 4% amino acid compared to 1%, but the particle counts were within the normal range (Table 2). Nearly no large particles

Table 2 pH value and particle counts after formulation in parenteral nutrition solution composed of inorganic or organic phosphate.

Type of phosphate	K_3PO_4				NaGP			
Dextrose	10%	20%	10%	20%	10%	20%	10%	20%
Amino acid	1%	1%	4%	4%	1%	1%	4%	4%
pH	6.07 ± 0.02	6.02 ± 0.02	6.11 ± 0.01	6.05 ± 0.02	6.79 ± 0.01	6.66 ± 0.02	6.39 ± 0.02	6.34 ± 0.01
≧10 μm particle (per mL)	7793.5 ± 1309.8	11134.2 ± 2168.6	481.2 ± 156.3	415.3 ± 429.1	5.2 ± 2.1	7.3 ± 1.8	8.2 ± 3.6	9.1 ± 3.5
≧25 μm particle (per mL)	8892.6 ± 4391.8	814.6 ± 770.1	11.7 ± 8.5	29.0 ± 45.2	0.2 ± 0.2	0.1 ± 0.1	0.2 ± 0.2	0.3 ± 0.3
Compatibility	Exceeding compatible range				Within compatible range			

K_3PO_4, tripotassium phosphate; NaGP, sodium glycerophosphate.

Table 3 pH value and particle count in parenteral nutrition solution after storage.

	Day 1				Day 3				Day 10			
Dextrose	10%	20%	10%	20%	10%	20%	10%	20%	10%	20%	10%	20%
Amino acid	1%	1%	4%	4%	1%	1%	4%	4%	1%	1%	4%	4%
pH	6.73 ± 0.01	6.64 ± 0.01	6.40 ± 0.01	6.31 ± 0.01	6.77 ± 0.01	6.67 ± 0.01	6.44 ± 0.02	6.34 ± 0.01	6.78 ± 0.01	6.68 ± 0.01	6.44 ± 0.00	6.36 ± 0.01
≧10 μm particle (per mL)	3.1 ± 2.7	0.8 ± 0.7	1.6 ± 0.8	1.4 ± 0.6	1.7 ± 1.4	0.9 ± 0.4	0.3 ± 0.3	0.5 ± 0.3	0.7 ± 0.4	0.5 ± 0.5	0.8 ± 0.4	0.7 ± 0.6
≧25 μm particle (per mL)	0.2 ± 0.2	0.1 ± 0.1	0.1 ± 0.2	0.2 ± 0.2	0.2 ± 0.2	0.2 ± 0.2	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	0.2 ± 0.3	0.1 ± 0.2
Compatibility	Within compatible range											

(≧25 μm) were found, and few smaller particles (≧10 μm) were noted. On the contrary, visual deposition was evidently noted in PN solution using tripotassium phosphate (K_3PO_4) after its formulation in both 10% and 20% dextrose and 1% amino acid. PN solution containing K_3PO_4 was more acidic compared to PN solution containing NaGP. The particle counts, both ≧25 μm in diameter and ≧10 μm in diameter particles, significantly exceeded the USP limits.

Table 3 shows the pH value and particle counts in PN containing NaGP with 10% or 20% dextrose and 1% or 4% amino acid after several conditions of storage as a simulating clinical condition. PN solution was administered to infants by continuous infusion for 24 h after formulation. To assess the compatibility of organic phosphate in PN solution during infusion, a set of PN solution was stored at 25 °C for 1 day and was subsequently analyzed. According to the result on the Day 1 group, the pH value did not change after storage in all test concentrations. Particle count ≧10 μm decreased more compared to the particle count after formulation. Particle count ≧25 μm remained at low level.

For the infants who need PN support during weekends, PN solution is formulated on Friday and stored in the refrigerator before use. To simulate the clinical condition, PN solution was stored at 2°C-8°C for 2 days after preparation (mixed on Friday for use on Sunday) and subsequently stored at 25 °C for an additional day before analysis (infusion for 24 h). The pH value was still unchanged in the Day 3 group, and the particle counts remained low in different dextrose and amino acid concentrations.

According to the regulation of the United States Pharmacopeia chapter 797, a pharmacy-prepared PN formulation stored under refrigeration has a beyond-use date of up to 9 days after preparation. To evaluate the stability of organic phosphate after maximum storage days, PN solution was analyzed after it was stored at 2°C-8°C for 9 days and then at 25 °C for 1 day. The particle count and pH value were still in normal range in this Day 10 group in all test concentrations.

4. Discussion

Administration of neonatal PN is significantly complicated because large amounts of nutrients are required to be supplied in a limited volume of solution. It is particularly challenging to supply adequate calcium and phosphate in such highly concentrated solution since it is often near the calcium phosphate saturation point. Some factors, such as higher concentration of glucose, lower temperature, and lower pH, may improve calcium and phosphate solubility.[11] Hyperglycemia is one of the common complications in preterm infants treated with PN, limiting the concentration of glucose in the solution. The temperature of PN solution during infusion depends on the environment, which is usually not low because of possible hypothermia in preterm infants. The pH value of PN solution is determined by the additive, and one of the important components is the amino acid. Higher concentrations of amino acid lead to more acidic solution, which allows higher calcium phosphate compatibility. The maximum allowable calcium and phosphate concentration in PN solution is usually dependent on the manufacturer of different amino acid products. Although aggressive protein intake is highly recommended in the current nutritional care of preterm infants, the appropriate supplementary doses of calcium and phosphate are still not achieved even in PN solution with relatively high amino acid concentration.

Several studies outlined the improved solubility of PN when organic phosphate is used in place of inorganic phosphate, which allows practitioners to provide adequate calcium and phosphorus to meet the needs of preterm infants.[13–17] Most of these studies use NaGP as the source of organic phosphate, but the composition of PN solution and the timing to test the compatibility differed among studies (Table 4). Although NaGP has been approved for use in Europe, there is no Food and Drug Administration approval of NaGP in Taiwan, and NaGP is only temporarily imported during a national shortage of inorganic phosphate. Most of the pharmacists and neonatologists in Taiwan are hesitant to use NaGP to increase calcium and phosphate levels because guidelines on the use of organic phosphate are not yet established. The published studies of compatibility as shown in Table 4 were conducted in definite standard PN solutions of their institution, which differ from the PN solutions produced in Taiwan. Therefore, this study aimed to assess the risk of precipitation when NaGP was used instead of potassium phosphate in the usual compounding component and concentration in our NICU. Compared to other reports, our study is the only one study to use Aminosteril Infant as preparation for amino acid, to check the compatibility in higher dextrose concentration (20%), and to test at different timing in the clinical scenario. All of these factors are important for clinical practitioners in Taiwan, because they represent the difference between our daily practices and reported reference. The result of our study demonstrated that the use of NaGP significantly increased the compatibility of calcium and phosphate when neonatal PN was composed of the commonly used components and concentrations in our hospital even after its 10-day storage. Using NaGP as the source of phosphate would eliminate the need to use calcium phosphate solubility curves when administering PN and increase the final calcium and phosphate concentration in solution.

Optimal ratio of calcium:phosphate is also an important issue for adequate retention of mineral for bone accretion.[19,20] Since 2005, the ESPGHAN guideline recommended a calcium:phosphate ratio (mol/mol) in the range of 1.3—1.7.[21] However, early hypophosphatemia emerged as a new problem since the introduction of early aggressive nutrition.[22,23] Very low birth weight and small for gestational age infants are especially at risk for early hypophosphatemia owing to their high P needs for growth.[20,24,25] Mulla et al.[26] reported that reverting from a PN calcium:phosphate molar ratio of 1.3—1.5:1 to a ratio of 1.0:1 was associated with a lower incidence and severity of hypophosphataemia and hypercalcaemia in preterm infants given higher concentrations of amino acids from postnatal day one. Therefore, the recently published ESPGHAN guideline recommended use of a molar calcium:phosphate ratio below 1 (0.8—1.0) to reduce the incidence of early postnatal hypercalcaemia and hypophosphataemia in early PN with low calcium and phosphorus intakes and optimized protein and energy.[9] In the present study, the concentration of calcium in PN preparation is 50 mEq/L, and the phosphate is 25 mmol/L. The molar ratio of

Table 4 List of study for physical compatibility in neonatal parenteral nutrition.

Authors, publication year	Dextrose	Amino acid	Calcium	Phosphate	Analysis method	Timing
Bouchoud, 2010.[13]	3%	Vaminolact: 0.4%	Calcium chloride/ calcium glubionate: 10—50 mmol/L	G1P: 10—50 mmol/L	Visual inspection Particle counts	4 °C for 2 d then 32 °C for 1 d
MacKay, 2015.[14]	15%	TrophAmine: 1.5%, 4%	Calcium gluconate: 10, 20, 30, 40, 50 mEq/L	NaGP: 10, 20, 30, 40, 50 mmol/L	Visual inspection Particle counts Turbidimeter	37 °C for 1 d
Anderson, 2016.[15]	15%	TrophAmine: 1.5%, 4%	Calcium chloride: 10, 20, 30, 40, 50 mEq/L	NaGP: 10, 20, 30, 40, 50 mmol/L	Visual inspection Particle counts Crystal count	37 °C for 1 d
Thowladda, 2016.[16]	10%	Aminoven Infant: 2%	Calcium gluconate: 20, 30 mmol/L	NaGP: 20, 50 mmol/L	Visual inspections Spectrophotometry Particle size	1. After mixing 2.30 °C for 1 d 3.4 °C for 1 d 4.4 °C for 7 d
Lee, 2017.[17]	7.1%	Vaminolact: 2%	Calcium gluconate: 15, 20, 25, 30 mmol/L	NaGP: 12, 15, 19, 23 mmol/L	laboratory of Fresenius Kabi	2°C-8°C for 7 d, then 25 °C for 1 d, then 37 °C for 4 h
Our study	10%, 20%	Aminosteril Infant: 1%, 4%	Calcium gluconate: 50 mEq/L	NaGP: 25 mmol/L	Visual inspections Particle counts	1. After mixing 2.25°C for 1 d 3.2°C-8°C for 2 d, then 25°C for 1 d 4.2°C-8°C for 9 d, then 25°C for 1 d

G1P, disodic glucose-1-phosphate (Phocytan) (Aguettant, Lyon, France); NaGP, sodium glycerophosphate.

calcium:phosphate was 1.0, which is compatible for use in early PN in the current guideline.

This study has several limitations. First, we assessed the solubility in limited groups. The concentration of dextrose in this study was chosen from the starter (10%) to the most common upper limit (20%). In some extreme conditions, PN containing <10% or >20% dextrose may be required, but these were not included in this study. According to previous reports, precipitation may not exit under such extreme concentrations of dextrose.[13,17] Most neonatal PN contains amino acid of between 1% and 4% concentration, which was included in the current study. Second, some other factors affecting the solubility were not included in this study. Several studies have reported that the presence of cysteine in PN solution improves the compatibility of calcium phosphate.[27,28] Since cysteine is not used in our hospital, we did not include it in the current study.

In conclusion, NaGP and calcium gluconate have significantly good compatibility in neonatal PN with 10% or 20% dextrose and 1% or 4% amino acid even after 10-day storage. In contrast to inorganic phosphate, the use of NaGP in PN may be more compatible with the nutritional requirement of extremely preterm infants than the nutritional requirement of term infants. Hence, further study of the long-term outcomes and clinical impacts of NaGP to current practice is required.

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The authors have no personal financial relationships relevant to this article to disclose.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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