



신생아 중환자실 영양요법치료에서 약사의 역할과 영향

오윤경^{1,2} · 이광섭² · 이정연^{1*}

¹이화여자대학교 약학대학, ²건국대학교병원 약제부

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Neonatal Total Nutritional Pharmacy Service at Intensive Care Unit at a University Hospital in Korea

Yun Kyoung Oh^{1,2}, Gwang Sup Lee², and Sandy Rhie^{1*}

¹College of Pharmacy, Ewha Womans University,

²Division of Pharmacy, Konkuk University Medical Center, Seoul, Korea

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Objective: The study evaluated the impact of pharmacist interventions with the implementation of pharmacist-involved nutritional support service at neonate intensive care unit in a tertiary teaching hospital. **Method:** A retrospective and observational study was carried out. The total of 58 infants in neonate intensive care unit was enrolled between January 2011 and October 2012. The pharmacist-involved total parenteral nutritional program was initiated in June of 2012. During the program, pharmacist actively participated in the multidisciplinary round with performing the interventions from reviewing the amount of combined total parenteral nutrition and enteral fluid intakes, the amount of total calories, the glucose infusion rate, and the amounts of proteins per weight in kilogram. The outcome was compared with the results from the control group which reflected the prior period of the program initiation. **Result:** The number of days of regaining birth weight was significantly shorter (14.5 vs. 19 days, $p=0.049$) and the percentage of total calorie days with >90 kcal/kg/day was increased significantly (40 vs. 13%, $p=0.008$) in intervention group compared to the values in control group. In addition, the total mean daily caloric intakes (84.78 ± 13.8 vs. 74.86 ± 15.36 kcal/kg/day, $p=0.018$) was significantly higher in intervention group than those results in control group. There were no significant differences in safety parameters between two groups related to nutritional services of necrotizing enterocolitis, intraventricular hemorrhage, proven sepsis, and also parenteral nutrition-induced hepatotoxicity. **Conclusion:** Pharmacist-involved total parenteral nutrition managed program was successfully implemented. The outcome showed the improved effectiveness of total parenteral nutrition with pharmacist interventions and no differences in adverse reactions. This could prove the positive effects of pharmacist involvement on nutritional therapy for neonate population.

□ Key words - neonate intensive care unit, pharmacist intervention, parenteral nutritional service, enteral nutrition.

INTRODUCTION

As postnatal growth is a major concern for premature or sick-born neonates, early nutritional support of pre-term infants is critical for the life-long health and well-being. Total parenteral nutrition (TPN) is one of the methods to serve the maximal nutrition in a fast and timely manner. And it prevents the complications from

the malnutrition to neonates who cannot achieve the desirable amounts of calories at the early stage of birth. Parenteral nutrient solutions mainly consist with a lipid emulsion, crystalline amino acid and dextrose as a main nutritional source. In addition, enteral feeding (EN) is another nutritional support tool via placement through the nose, esophagus, stomach, or intestines (duodenum or jejunum) once oral feeding is feasible. However, due to the immature gastrointestinal absorption capability and the potential intolerance to enteral nutrition in early stage of birth, it is often associated with several complications such as metabolic-, infectious-, and hepatobiliary prob-

Correspondence to : Sandy (Jeong Yeon) Rhie
College of Pharmacy, Ewha Womans University,
Seoul 120-750, Korea
Tel: +82-2-3277 3023, Fax: +82-2-3277-3051
E-mail: sandy.rhie@ewha.ac.kr

lems when it is inadequately managed.¹⁾ In rare cases, a possible necrotizing enterocolitis could be a concern. In clinical setting, TPN treatment requires the well-organized program with interdisciplinary management approach to achieve not only the effectiveness of treatment, but also the safety. Many studies evaluated the outcomes of the interventions on TPN management. Some of the efforts include assessing the compatibility of TPN solution with concomitantly administering intravenous medications, the solubility of calcium and phosphorus contents in the solution to prevent unwanted precipitation,²⁾ and the osmolarity to keep the osmolarity less than 850 mOsm/L³⁾ to lower the risk of phlebitis for peripheral intravenous access. Healthcare providers should be aware of signs of catheter-induced infections at the TPN needle site and contamination from the compounding process.^{4,5)} The benefits of operating a nutritional support team (NST) with the multidisciplinary members with physicians, pharmacists, nutritionists, and nurses had been assessed by optimizing the formulation. It thus demonstrated maximizing the impact of the activities of the professionals on patients' clinical prognosis and further to prevent the complications associated with TPN.⁶⁾

In neonatal intensive care unit (NICU), TPN is suggested to support all the ill and premature babies who are less than 1.5 kg, are unable to be fed at least 60 kcal/kg/day by oral or enteral route within 2~3days after birth. A direct relationship between the nutrition supply and prognosis was first described by Stephens *et al.* who showed an association between an increased protein-energy intake during the first week of life and improved neuromotor development scores in 18-month-old children.⁷⁾ This association strengthens the concept that parenteral nutrition should be started as soon as possible, preferably within the first hours after birth; this has been shown to be both safe and effective.⁸⁾ Otherwise, these neonates are at the high risk of the excessive protein loss by malnutrition in infants. It could result in the impaired neurocognitive developmental and physical growth.⁹⁻¹³⁾ Based on European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and European Society for Clinical Nutrition and Metabolism

(ESPEN) guidelines^{14,15)} to infants, children and adolescents, they justify that a premature birth should be attended to by neonatal intensive care unit (ICU) teams as a nutritional emergency.¹⁵⁾ They also note that the important role of TPN in the nutritional support for pre-term and sick-born infants in NICU, as enteral feedings does together. It allows the survival from the starvation after the reserve exhaustion for only up to four days without nutritional support which is even shorter in hypermetabolism states. Pharmacist-monitored TPN management program in neonates has provided a benefit on weight gaining by maximize the amount of nutrients²⁶⁾ and minimize the complications. In various studies, incorporating pharmacists into interdisciplinary NST team in direct patient care showed a potential solution to improve health care outcomes.¹⁷⁾ Korea is still considered as a fast growing developed country with prevalent physician-oriented practice. The pharmacist-involved TPN program in NICU has not been well investigated, yet. Thus, our study evaluated the impact of pharmacist's invention on NST program in NICU after the implementation of new program by pharmacy at a tertiary teaching hospital in Korea.

METHODS

Study design

A retrospective, observational study was carried out at NICU in Konkuk Medical Center, Seoul, Korea. The approval of study protocol from Konkuk Medical Center institutional review boards was obtained (No: KUH 1280021). We included a total of 58 infants who were born at the hospital between January 2011 and October 2012. Inclusion criterion was the neonates who were treated with parenteral nutrition (PN) at birth for 7 or more days at NICU. Exclusion criteria were the neonates who were (a) on TPN for less than 7 days, (b) transferred out of NICU while on TPN, (c) deceased on discharge, or (d) duplicated between groups. Each neonate in the control group was matched to a neonate born at similar gestational age (GA) of intervention group in order to remove the compounding effect of the gestational age

on TPN therapy outcomes. Among the control group, in case where two or more neonates with similar GA were found, one was chosen randomly and compared to the intervention group.

Intervention group: Among 60 neonates who were born during the study period, thirty-one were excluded from this study; twenty-six didn't receive PN to meet the inclusion criteria of minimum 7 or more days, three were transferred out from NICU during study period, and two were duplicated. From June 15th to October 31st in 2012, the infants in the NICU were enrolled in the Pharmacy nutritional service with TPN prescription (n=29). Besides pharmacists' participating to the daily medical round, pharmacist intervention included the assessment of nutritional intakes, patient's clinical status, complications and the report any abnormal lab results associated with PN therapy. Prior to the medical round, a pharmacist reviewed the overnight report of any unusual episodes of the patients with the laboratory results in advance. Then the pharmacist prepared for the pharmacy nutritional report to share the current information with medical team. Pharmacy nutritional report contained the amount of combined TPN and enteral fluid intakes, the amount of total calories, the glucose infusion rate, and the amounts of proteins per weight in kilogram during 24 hrs. Differently from the control group with post-order review activity, pharmacist attended to the multidisciplinary medical round for the infants with the most updated accurate information of nutrition status in intervention group. In addition, pharmacist initiated on-time intervention on the TPN management service for reviewing inappropriate TPN dosing, TPN-related complications, and checking compatibility of TPN solution.

Control group: Control group was represented by the infants (n=29) who TPN order was processed without the pharmacy nutrition services in the NICU from January 1st, 2011 to June 14th, 2012. During this period, one-hundred-twenty-five infants were born. However, ninety-six were excluded; sixty were on PN for less than 7 days, three were transferred out, two were duplicated, two were deceased upon discharge and twenty-

nine were not matched with the intervention group.

Once the TPN order was entered by physicians in the order entry system, pharmacists initiated to review the TPN order with consideration of the relevant lab results, a line accessibility for TPN administration, and a progress note on electronic medical chart. With any problems on TPN prescription, pharmacist tried to resolve the issues collaboratively with the physicians. On the contrary, in control group, pharmacists didn't prepare for the nutritional report including other additional activities, so that physicians' TPN prescriptions were processed mainly according to TPN dosing protocols and guidelines.

Whether pharmacists intervention was considered or not, for both groups, it was the physicians who determine the composition of TPN formulations every morning based on the individual's daily serum chemistry results (sodium, potassium, BUN, creatinine, glucose, etc) and clinical status of the patients. The basic work-up of calculation of the solubility of Ca-P product and the osmolarity of TPN solution were performed by embedded instruments using TPN ordering computer based-program in both intervention and control group.

Data were collected from the medical records of each infant of the both groups and were compared. This included the chemical parameters of serum glucose (mg/dl), blood urine nitrogen (mg/dl), creatinine (mg/ml), pH, bicarbonate, sodium, potassium, magnesium and ionized calcium. The safety outcomes were evaluated by investigating clinical prognosis records and lab results after the discontinuation of TPN, such as necrotizing enterocolitis (\geq stage 2b), intraventricular hemorrhage (\geq grade 3), proven sepsis, PN-induced hepatotoxicity, ALT (IU/L), AST (IU/L), ALP (IU/L) and direct bilirubin level (Table 2).

Statistical analysis

Data were analyzed using SPSS version 17 (SPSS Inc., Chicago, IL, USA). The program employed the unpaired student t-test to the data sets that were normally distributed. Mann-Whitney test was used to analyze the data sets that were non-normally distributed. χ^2 -test and Fisher's exact tests were used for nominal

variables. Depending on distribution and the type of test, values are expressed as mean±standard deviation, median (min-max), or percentage, respectively. Multiple variables were considered to be statistically significant at $P<0.05$.

RESULTS

Demographic and perinatal variables

Matching the infants in the intervention with those in control groups based on GA was appropriate, as the median GA and the range (min-max) of both groups were not significantly different. Mean±SD of the birth weight for both groups were similar ($p=0.716$). Besides, it didn't show any significant differences between the two groups; sex, delivery methods, 5-min APGAR score, percentage of congenital heart disease, the presence of heart functional disorder, respiratory distress syndrome, patent ductus arteriosus, antenatal steroid medications and maternal diabetes. These variables were listed in Table 1.

Nutrition composition during TPN

On the 7th day of TPN administration, the compositions (fluid volume, caloric intake, amino acid, glucose,

sodium, potassium, calcium, magnesium) with or without EN were compared between intervention group and control group. There were no significant differences between both groups in; TPN composition, the rate of TPN administration, the initiation of the enteral feeding and treatment duration of both TPN and enteral nutrition. However, intervention group results were preferable. The day of regaining birth weight was significantly shorter (14.5 days vs. 19 days, respectively, $p=0.049$) and the percentage of the number of days with total calories >90 kcal/kg/day over the total duration of TPN administration was significantly higher (40% vs. 13%, respectively, $p=0.008$) in intervention group compared to the values in control group. In addition, the total mean daily caloric intakes (84.78 ± 13.8 kcal/kg/day vs. 74.86 ± 15.36 kcal/kg/day, respectively, $p=0.018$) were significantly higher in intervention group than those results in control group, that would be explained the adding effect of TPN and enteral feeding calories. A lower amount of the median magnesium was found in the intervention group (Table 2), which was explained by the impact of one of the pharmacist-interventions on magnesium content in TPN solution for the babies who showed hypermagnesemia due to their mother use of

Table 1. Demographic and clinical characteristics of the infants in the study.

	Intervention (Min-max)	Control (Min-max)	p-value
‡Gestational age (weeks)	35(26-40)	35(26-40)	0.931
preterm (≤ 37), n	18	18	
term (>37), n	11	11	
†Body weight (kg)	2.224±0.952	2.313±0.8984	0.716
‡Apgar score, 5 min	8(6-10)	8(4-10)	0.936
Male gender, n (%)	17(58.62%)	17(58.62%)	1.0
Diagnosed PDA, n (%)	21(72.41%)	19(65.51%)	0.570
Diagnosed RDS, n (%)	18(63.97%)	22(75.86%)	0.256
Congenital heart disease, n (%)	13(44.82%)	11(37.93%)	0.594
PROM >6 hr (%)	6(20.69%)	5(17.24%)	0.738
Caesarean delivery, n (%)	22(75.86%)	22(75.86%)	1.000
§Prenatal steroid, n (%)	1(3.45%)	7(24.14%)	0.053
§GDM, n (%)	5(17.24%)	0(0%)	0.052

† Values are expressed as mean±SD and tested by *t*-test

‡ Values are expressed as median (min-max) and tested by Mann-Whitney test.

* Values are expressed as percentage and tested by χ^2 test

§ Values are expressed as percentage and tested by Fisher's exact test.

* Statistically significant; $P<0.05$

Abbreviation> RDS: respiratory distress syndrome, PDA: patent ductus arteriosus, PROM: premature rupture of membranes, GDM: gestational diabetes

Table 2. Nutritional composition during 7 days on TPN.

	Intervention group (Min-Max)	Control group (Min-Max)	P-value
The duration of TPN (days)	14(7-47)	13(7-56)	0.262
The initiation of EN (day)	6(0-28)	6(1-18)	0.845
The duration on both TPN and EN (days)	10(2-28)	7(3-42)	0.126
Maximum percentage of weight loss after birth ^{a)} (%)	0.0993(0-0.192)	0.113(0.016-0.178)	0.234
The time of regaining the birth weight (day)	14.5(0-39)	19(6-34)	0.049*
The number of days of total calorie intake >90 kcal/kg/day on TPN (%)	40(0-71)	13(0-75)	0.008*
†Total TPN volume (ml/kg/day)	92.23±40.85	90.97±37.18	0.903
†Calories in TPN (kcal/kg/day)	61.55±25.52	58.23±19.78	0.582
‡Feeding Calories (kcal/kg/day)	14.11(0-72.19)	8.17(0-73.68)	0.417
†Total Calories (kcal/kg/day)	84.80±13.8	74.82±15.4	0.018*
‡Amino acid in TPN (g/kg/day)	2.4(0.22-5.02)	1.76(0-4.76)	0.981
‡ amino acid in Feeding (g/kg/day)	0.12(0-2.51)	0.2(0-1.74)	0.776
†Total amino acid (g/kg/day)	2.69±0.6425	2.61±0.9443	0.71
‡TPN glucose (g/kg)	11.27(1.76-18.23)	10.14(2.8-16.3)	0.213
†IV lipid (g/kg/day)	1.608±1.19	1.495±0.825	0.675
‡TPN sodium (mEq/kg)	3(1.0-9.0)	3(2-5)	0.933
‡TPN potassium (mEq/kg)	2(0-3.5)	2(1.0-4.5)	0.308
‡TPN calcium (mEq/kg)	2.1(1.0-3.2)	2.1(1.1-2.9)	0.784
‡TPN magnesium (mEq/kg)	0.5(0-0.5)	0.5(0-0.6)	0.011*

Values are expressed as median (min-max) and tested by Mann-Whitney test

a) (Birth weight – minimum weight after birth)/birth weight

b) (Days of total calories >90 kcal/kg/day)/TPN duration, (%), if total calories didn't reached to 90 kcal/kg/day over TPN duration, recorded "0"

†Values are expressed as mean±SD and tested by Student *t*-test

‡Values are expressed as median (min-max) and tested by Mann-Whitney test.

Nutritional and electrolyte composition of the solution was measured in units per kilogram

* Statistically significant; P<0.05

Abbreviation>TPN: total parenteral nutrition, EN: enteral nutrition

magnesium sulfate during delivery.

Mean serum biochemical parameters on the 7th day of TPN

Table 3 shows the mean values of serum biochemical parameters on the 7th day of TPN. Compared to the control group, intervention group didn't show significant differences in serum glucose, blood urine nitrogen, creatinine, serum sodium, serum potassium, serum ionized calcium, serum pH, serum bicarbonate and base excess. However, we found a significant decrease in the level of sodium in serum (135.96±2.77 mmol/L vs. 139.01±4.03 mmol/L, p=0.001) in intervention group, although it was still in the normal range. Therefore the results may indicate that the pharmacist's recommendation to increase the calorie supply, in many cases, didn't cause

the metabolic complications.

Safety parameters

There were no significant differences in safety parameters between the two groups related to nutritional services of necrotizing enterocolitis (≥ stage 2b), intraventricular hemorrhage (≥ grade 3), proven sepsis, and also PN-induced hepatotoxicity in the abnormal liver function enzymes level like AST, ALT and ALP (Table 4).

DISCUSSION

Preterm and sick-born neonates who cannot be fed with appropriate calories by oral and enteral routes within 3~5 days at birth are subjected to a high risk of development of malnutrition status due to the low nutri-

Table 3. Blood gas analysis and mean serum biochemical parameters on the 7th day of TPN.

	Intervention group (n=29)	Control group (n=29)	P-value
‡Serum glucose (mg/dl)	90(49-169)	102(56-306)	0.186
‡Blood urine nitrogen (mg/dl)	13.3(4.1-39.1)	17.8(6.2-92)	0.189
†Creatinine (mg/dl)	0.632±0.3943	0.5741±0.26381	0.513
†Serum sodium (mmol/L)	135.962±2.772	139.014±4.0267	0.001*
‡Serum potassium (mmol/L)	4.66(3.34-6.9)	4.67(3.28-5.7)	0.686
†Serum ionized calcium (mmol/L)	1.1717±0.1040	1.1335±0.10529	0.238
†Serum PH	7.38579±0.084	7.37917±0.08034	0.761
‡Serum bicarbonate (mmol/L)	21.5(11.6-35.4)	19(15.2-30.9)	0.202
‡Base excess (mmol/L)	-3.5(-11.5-11.0)	-4.8(-12.8-7.1)	0.419

† Values are expressed as mean±SD and tested by Student *t*- test

‡Values are expressed as median (min-max) Statistically significant; P<0.05

Table 4. Complications and laboratory results related to TPN.

	Intervention group (n=29)	Control groups (n=29)	P-value
Necrotizing enterocolitis (≥ stage 2b), n (%)	0/29(0%)	0/29(0%)	NS
§Intraventricular hemorrhage (≥ grade 3), n(%)	4/29(13.79%)	5/29(17.24%)	1.0
†Proven sepsis, n(%)	10/29(34.48%)	7/29(24.14%)	0.387
†PN induced hepatotoxicity, n (%)	6/29(20.69%)	9/29(31.034%)	0.368
*AST (IU/L)	27(16-104)	35(17-203)	0.091
*ALT (IU/L)	13(6-86)	14(5-162)	0.427
*ALP (IU/L)	262(137-714)	283(115-868)	0.219
*d-bilirubin (mg/dl)	1.2(0.3-3.6)	0.9(0.2-4.9)	0.129

§ Values are expressed as No. of patients and percentage and tested by Fisher's exact test

† Values are expressed as No. of patients and percentage and tested by χ^2 test

* Values are expressed as median (min-max) and tested by Mann-Whitney test.

Statistically significant; P<0.05.

tional reserve. TPN is an essential nutritional supporting tool and it is indicated for the cases.²⁹⁾ The energy used for the maintenance of the body metabolism and the growth in gestational age has to be obtained by nutritional support. Calorie requirements in an infant should be carefully balanced not to be overfed which can result in hyperglycemia, hyperlipidemia, fatty liver, and PN-related liver toxicity, whereas malnutrition can cause an impaired immune function, an imbalance of nutrition, and a failure of catching up growth.^{21,22)} The design of the individual nutrition should consider the clinical status of the patients and the energy expenditure, while monitor continuously the complications associated with TPN.²³⁾

A numerous quantity of articles reporting the benefits of the involvement of a pharmacist as a member of the interdisciplinary team has been written. The clinical interventions of the pharmacists have played an impor-

tant role in identifying medication errors, increasing drug safety. Hence it is likely to be the most effective way of improving drug therapy.¹⁷⁾ The pharmacist in clinical nutritional support management, for example, advocates the safe use of nutritional therapy, the assessment of the nutritional and fluid requirements accurately with the actual nutrient intakes with adjusting the composition and compounding of parenteral feeding to avoid toxicities/complications.^{25,26)} That can highlight the pharmacist-managed nutritional service on NICU. However, there is only a minimum research proving the outcomes in Korea, yet.

Cox *et al.* investigated the application of the on-line TPN calculator on clinical practice and found that it prevented the medical errors and saved the working hours of the healthcare providers on TPN.²⁸⁾ Another study also claimed that a nutritional program improved

the body composition, the amount of nutrition intake, and the growth rates of very low birth weight infants by developing the guidelines and algorithms reflecting the demands of each ingredient for the infants. Nevertheless of the efforts to perform the better practice in TPN management, Kairamkonda *et al.* suggested the diversity and unstandardized practices of neonatal PN prescription are still common in current practice. They claimed the urgent need to modify and improve the practice during early postnatal life.³¹⁾

The NICU at Konkuk Medical Center has been using a computer-based TPN program to calculate the volume of each ingredient preparing TPN solution and to generate the recipe labels. It has the algorithms embedded to check osmolarity and calcium-phosphorous solubility of each TPN solution. With pharmacists involved in the TPN management, new protocol to manage the nutritional treatment was developed and rebuilt in the system in 2011. It focused on individual infants needs and the each necessary request was intervened by pharmacists in the multidisciplinary team members. It was readily accepted to the neonatologists.

This pilot study is designed to evaluate the efficacy of pharmacist's intervention on nutritional therapy in NICU. Pharmacist's intervention includes the assessment of nutritional intakes, clinical status of the patients, any complications or the abnormal lab results associated with PN therapy during the daily medical round. In many occasions, pharmacist could prevent the possible interactions in TPN solutions from the ionic interactions, the destabilizing problems, and the metabolic complications. On the other hand, the control group was managed by mainly the post-review after the TPN order was placed in the system. The majority of interventions by pharmacists in the control group were often based on the laboratory results only despite of the patient's concurrent changes.

Our results show that the pharmacist's intervention can make significant improvements in the total amount of calories intake from the nutritional therapy compared with control group. We also found that the time to regain the birth weight was significantly reduced ($p=0.049$). And at the

same time, the duration of the calorie intakes over 90 kcal/kg/day while on TPN was longer in intervention group ($p=0.007$). The criterion of the caloric cutoff of over 90 kcal/kg/day was set according to pediatric TPN Calories guidelines.³¹⁾ Moreover, it seems that pharmacist's intervention prevented hypermagnesemia in babies, especially when their mothers were administered magnesium sulfate during delivery. However, additional studies are required to clarify the benefit of pharmacist intervention on electrolyte imbalances further in detail. Although our pilot study had small number of subjects, the results showed some benefits of the pharmacist intervention on nutritional service in NICU. Moreover, no significant differences in mean biochemical parameters, metabolic imbalances and PN related complications in the study. That may suggest that the advantage of pharmacist's intervention assures the best possible nutrition and biochemical control.

The limitations of the present study include the single-center, retrospective design of the study, so there are some data missed of as ionized calcium in the control group. Maternal records were not available when they were transferred from other facilities. Due to the new transplant initiative program during the study period, the beds turnover was poor for the pending surgery patients. The enrollment of the subject was very limited.

CONCLUSION

Pharmacist-involved TPN managed program was successfully implemented in the hospital. Pharmacist's intervention improved the total amount of calories from intravenous and enteral nutrition ($p=0.018$) without significant differences in serum glucose level and adverse effects between two groups. This could prove the favorable effects on pharmacist's interventions on nutritional therapy. The results of this study will need to be confirmed with a prospective, randomized trial involving a larger number of infants.

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