

Original Article

Comparison of a three-in-one total nutrient mixture with conventional peripheral parenteral nutrition in children

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Background: The aim of this study was to compare clinical aspects of the application of three-in-one total nutrient mixture (TNA) for peripheral parenteral nutrition (PPN) with those of the conventional PPN (cPPN) method of providing short-term parenteral nutrition for pediatric inpatients. **Methods:** We conducted a retrospective study in children from 2 to 18 years old who were hospitalized and underwent PPN administration. We compared clinical aspects of two methods of PPN, cPPN (n=39) and TNA (n=57). **Results:** The mean age was 6.5±3.1 years in the cPPN group and 8.2±3.4 years in the TNA group ($p=0.015$). In the TNA group, there was a significantly shorter period between the day of admission and the first day of PPN or oral feeding ($p<0.0001$ & $p<0.0001$, respectively). The TNA group also fasted for a shorter period before PN after admission, and the total duration of fasting was also shorter ($p<0.0001$ & $p<0.0001$, respectively). The TNA group showed a lower glucose infusion rate and fewer daily administered total calories per weight ($p<0.0001$ & $p=0.001$, respectively). However, there was no significant difference in the amount of administered amino acids and lipids ($p=0.584$ & $p=0.650$, respectively) and PPN-related complications. **Conclusions:** When providing nutrients to hospitalized children who cannot take in enough nutrients via the enteral route, TNA formula may be an easier and faster method than cPPN.

Key Words: parenteral nutrition, peripheral, total nutrient mixture, child, standard nutrition

INTRODUCTION

Intravenous feeding systems using the central vein were introduced by Dudrick et al in the 1960s. Initially, parenteral nutrition (PN) was applied during post-operative care of adult patients.¹ Recently, however, PN has been used for countless patients who suffer from inadequate oral feeding or any medical condition which leads to gastrointestinal failure. It is also equally applicable to premature neonates and geriatric patients.²⁻⁵

PN in pediatric inpatients is significant because children are more prone to develop complications in the case of nutritional imbalance.⁵ Though PN through a central line is preferable because a greater concentration of nutrients can be provided, this invasive method may cause complications such as catheter-related infection.² Therefore, peripheral parenteral nutrition (PPN) may be a better choice for short-term pediatric inpatients who must fast for three to five days or more, or those who are admitted after poor oral intake for three to five days or more. Although PPN can only provide a limited supply of calories and volume, it is preferred for short-term nutritional supply because it is easy to administer and less likely to cause complications.⁵

Since each pediatric patient varies in terms of weight and underlying medical condition, the implementation of a nutritional support team (NST) which includes expert

physicians, pharmacists, and nutritionists is emphasized.^{6,7} Clearly, decisions made through an NST are more constructive in long term PN for patients with severe disease or chronic conditions.⁸ However, if facilities cannot maintain a multidisciplinary NST or if there is a delay in the deliberation process of the NST, standardized PN may be more efficient for patients who need short-term PN or for those who need PN as soon as possible. It also prevents complications such as contamination, nutritional and metabolic errors, or mixing errors that may occur when PN is prescribed or prepared by non-experts.⁸

Total nutrient admixture (TNA) formula, which includes glucose, amino acid, lipids, and various micronutrients, has been extensively used for standardized PN. Different TNA formulas that are on the market replace conventional peripheral parenteral nutrition (cPPN). TNA

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formula use has been studied in adult patients, as it is commonly used in adults; however, limited studies have been performed in pediatric patients.⁹

We aimed to compare clinical aspects of TNA formula use with those of cPPN in providing short-term nutritional support to children and adolescents. To the best of our knowledge, this is the first study which directly compares the application and effects of TNA formula and cPPN.

MATERIALS AND METHODS

Patients and data extraction

This study included children between 2 and 18 years of age who underwent PPN treatment for more than 5 days during hospitalization at the Seoul National University Bundang Hospital between March 2004 and December 2013.

We included children who were healthy before hospital admission and who recovered fully at discharge. We excluded children who suffered from long-term nutritional imbalance due to underlying disease (i.e. neurological disease, malignancy or bed ridden state etc.), or those who had a chronic disease which leads to long-term nutritional imbalance due to extended hospitalization. We also excluded patients who received PN for less than four days, and those whose supply method was changed to a central line due to higher calorie requirements or in order to extend PN beyond the PPN period.

We retrospectively reviewed and analyzed clinical factors, nutritional factors, and complications related to PN regimens.

Subjects were classified into the cPPN group and the TNA group based on the type of PPN received. The cPPN group received mixed amino acids, lipids, and various minerals with existing glucose-based fluid. The TNA group was supplied with SMOF KabivenPeri[®] or MG TNAPERi[®] which is a commercially premixed three-in-one mixture for PPN in children and adolescents over the age of 2 (shown in Table 1). The composition of the cPPN regimen was determined and provided by the expert pediatric NST at the Seoul National University Bundang Hospital.

Patients were also categorized into an early childhood group (2-5 years), a middle childhood group (6-11 years), and an early adolescence group (12-18 years); these groups correspond to the age stages developed by the

Eunice Kennedy Shriver National Institute of Child Health and Human Development.¹⁰

This study was conducted with the approval of the Institutional Review Board of the Seoul National University Bundang Hospital.

Monitoring of PN-related complications

All patients were periodically monitored to prevent metabolic complications during PPN administration. We defined hypoglycemia as a serum glucose level or blood sugar test less than 60 mg/dL, and hyperglycemia if these levels were over 120 mg/dL. Hypertriglyceridemia was defined as a serum triglyceride level over 150 mg/dL.

We reviewed medical records during PN if patients experienced catheter-related infection or a mechanical complication, including pain or swelling of the catheter injection site such as phlebitis.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 statistical software (SPSS Inc, Chicago, IL, USA). The Student's *t*-test, the Mann-Whitney U test and Pearson's chi-square test were applied to evaluate the differences between each group. The level of statistical significance was set at $p < 0.05$.

RESULTS

Comparison of clinical factors based on PPN regimen

Clinical factors of the two PPN regimens are listed and compared in Table 2. There were 39 children in the cPPN group and 57 children in the TNA group. There was no difference between those groups in gender or body mass index (BMI), but the average patient in the TNA group was older and was hospitalized for a shorter period ($p = 0.015$ and $p = 0.002$, respectively). Table 3 shows that the TNA group included a higher percentage of adolescents than early ages, whereas the opposite was true for the cPPN group ($p = 0.015$). More patients in the TNA group required PPN due to insufficient oral intake.

More patients in the cPPN group required PPN due to the risk of acute malnutrition because they fasted during a hospital stay ($p = 0.002$, Table 2).

Comparison of clinical factors related to PPN regimen

The TNA group had a shorter time between hospital ad-

Table 1. Nutritional composition of total nutrient mixture formula for peripheral parenteral nutrition

	SMOF Kabivenperi [®]	MG TNAPERi [®]		SMOF Kabivenperi [®]	MG TNAPERi [®]
Nutrients			Electrolyte		
Glucose	103 g	65 g	Sodium	36 mEq	21.5 mEq
Amino acids	46 g	23 g	Potassium	28 mEq	16 mEq
Nitrogen	7.4 g	3.6 g	Magnesium	9.2 mEq	5.3 mEq
Lipids	41 g	34 g	Calcium	4.6 mEq	2.7 mEq
Energy			Phosphate	11.9 mEq	7 mEq
Total calories	1000 kcal	700 kcal	Sulfate	9.2 mEq	5.3 mEq
Non-protein calories	800 kcal	600 kcal	Chloride	32.0 mEq	31 mEq
Non-protein calories/nitrogen	111 kcal/g N	167 kcal/g N	Acetate	96 mEq	26 mEq
Other factors					
Total volume	1448 mL	960 mL			
Osmolarity	850 mOsm/L	750 mOsm/L			
Approximate pH	5.6	5.6			

TNA, total nutrient mixture

Table 2. Comparison of clinical features according to regimens of peripheral parenteral nutrition

Variable	cPPN group (n=39)	TNA group (n=57)	p value
Mean age (years)	6.5±3.1	8.2±3.4	0.015*
Male gender	21 (53.8%)	32 (56.1%)	0.838
Duration of admission (days)	9.1±2.9	7.4±2.2	0.002*
BMI (kg/m ²)	15.6±2.5	16.7±2.8	0.065
PN indication			
Insufficient oral intake	8 (20.5%)	30 (52.6%)	0.002*
At risk of acute malnutrition due to fasting	31 (79.5%)	27 (47.4%)	

* $p < 0.05$. cPPN: conventional peripheral parenteral nutrition; TNA: total nutrient mixture; PN: parenteral nutrition.

Table 3. Distribution of age groups according to regimens of peripheral parenteral nutrition

Age group	cPPN group (n=39)	TNA group (n=57)
Early childhood (2.0 ~ 5.9 years)	18 (46.2%)	14 (24.6%)
Middle childhood (6.0 ~ 11.9 years)	17 (43.6%)	29 (50.9%)
Early adolescence (12.0 ~ 18.9 years)	4 (10.3%)	14 (24.6%)

* $p = 0.015$. cPPN: conventional peripheral parenteral nutrition; TNA: total nutrient mixture.

mission and the first day of PN or oral feeding (2.6±1.7 vs. 1.4±1.1, $p < 0.0001$ and 5.2±3.2 vs. 2.5±2.5, $p < 0.0001$, respectively, Figure 1). The TNA group also fasted for a shorter period before PN after admission, and the total duration of fasting was also shorter in this group compared with the cPPN group (2.2±1.4 vs. 0.9±0.9, $p < 0.0001$ & 5.3±3.2 vs. 2.7±2.6, $p < 0.0001$, respectively, Figure 2). There was no significant difference in PN duration between those groups (5.8±2.0 vs. 5.4±1.7, $p = 0.385$, Figure 2).

There was only one case each of hypoglycemia and hyperglycemia. Three patients in the cPPN group and one patient in the TNA group developed hypertriglyceridemia. No patients developed infectious complications. 31 out of 39 (79.5%) patients in the cPPN group and 47 of 57 patients (82.5%) in the TNA group had a mechanical complication related to PPN ($p = 0.714$). There was no significant difference in the incidence of mechanical complication per day between the groups (0.44±0.43 vs. 0.34±0.27, $p = 0.215$). A body weight comparison after five days between the groups revealed no significant difference (0.12±0.80 vs. 0.18±1.04, $p = 0.785$).

Comparison of nutritional factors related to regimens of PPN

Table 4 shows the comparisons of nutritional factors related to regimens of PPN. In the TNA group, the glucose infusion rate (GIR) and the number of daily administered calories per weight (kg) were significantly lower, compared with the cPPN group (4.7±1.6 vs. 2.9±1.1 mg/kg·min, $p < 0.0001$ and 43.6±13.2 vs. 34.8±10.9 kcal/kg·day, $p = 0.001$, respectively). However, there was no significant difference in the amount of administered amino acids and lipids (1.2±0.4 vs. 1.3±0.4 g/kg·day, $p = 0.584$ and 1.3±0.5 vs. 1.3±0.4 g/kg·day, $p = 0.650$, respectively).

Comparison of clinical and nutritional factors related to regimens of PPN in the same age category

When the two PPN groups were compared in the same age category, there was no significant difference in days

between the admission and first day of PN or oral feeding. In addition, there was no significant difference in fasting duration before PN after admission, total duration of fasting, and hospitalization period.

When the two PPN groups were compared in the same age category, the TNA group showed significantly lower GIR and calories in early childhood ($p = 0.001$, $p = 0.013$, respectively), which were similar to those in all age groups combined. In middle childhood and early adolescence, however, there was no significant difference in GIR and calories between the two groups ($p = 0.067$, $p = 1.000$, in middle childhood; $p = 0.082$, $p = 0.082$ in adolescence, Table 5). There was no significant difference in the amount of administered protein and lipid in same age category ($p = 0.653$ and $p = 0.166$ in early childhood; $p = 1.000$ & $p = 0.222$ in middle childhood; $p = 0.576$ and $p = 0.576$ in adolescence).

DISCUSSION

In general, calculation of each component of PN in pediatric inpatients depends on the daily requirements for dextrose, amino acids, and lipids based on body weight, age, and disease status. Prescription and preparation of an individualized PN mixture is time-consuming, leading to inevitable delay in supplying inpatients with appropriate PN. In addition, there is a high risk of contamination or infection because different fluids must be administered through the limited peripheral line.

TNA formula may be a good alternative for these situations. According to a study by Colomb et al¹¹ TNA formula was more manageable and easier to administer. TNA is also more cost-effective and requires less nursing time than cPPN does.⁴ As a more immediate way to provide nutrients, TNA is more applicable to patients who possess a preexisting nutritional imbalance and are at risk for acute malnutrition if they need to fast during a hospital stay.³

We showed that PPN through TNA required a shorter time period than cPPN between hospital admission and the first day of PN. Fasting duration before PN in the hospital as well as the total duration of fasting can be

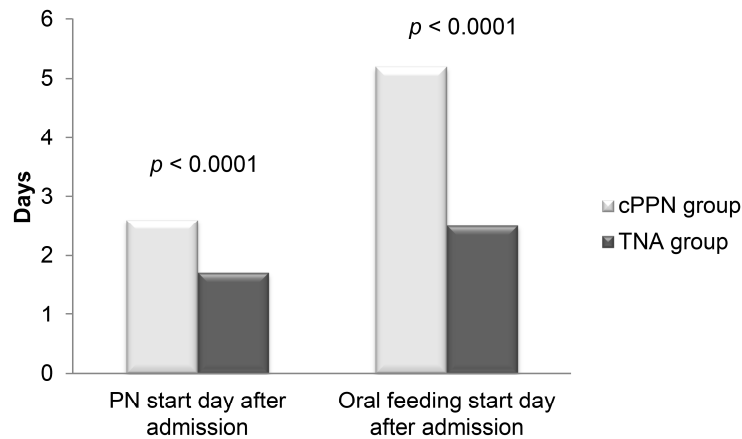


Figure 1. Comparisons of factors related to regimens of peripheral parenteral nutrition. The total nutrient mixture (TNA) group had a shorter time between hospital admission and the first day of parenteral nutrition (PN) or oral feeding when compared with the conventional peripheral parenteral nutrition (cPPN) group.

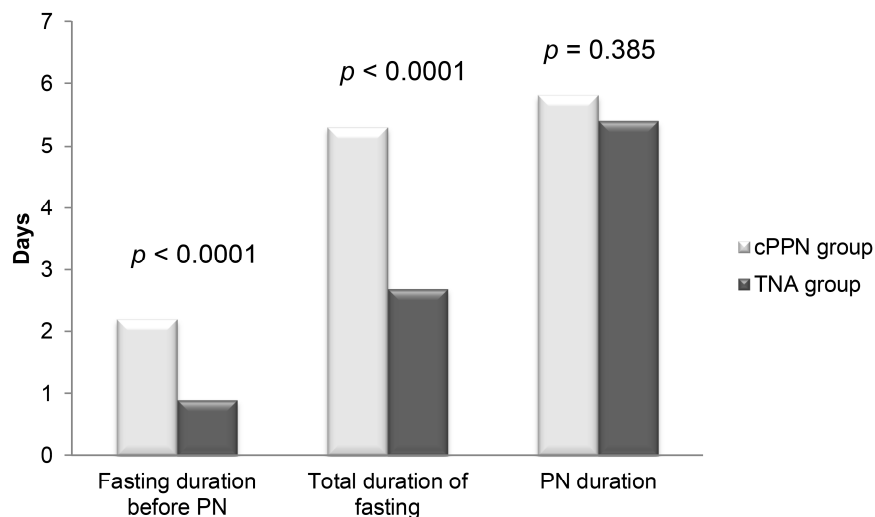


Figure 2. Comparisons of factors related to regimens of peripheral parenteral nutrition. The total nutrient mixture (TNA) group fasted for a shorter period before parenteral nutrition (PN) after admission, and the total duration of fasting was also shorter in this group when compared with the conventional peripheral parenteral nutrition (cPPN) group. There was no significant difference in PN duration between those groups.

minimized via the provision of standardized TNA. This is consistent with previous studies showing that TNA formula is more effective and controllable by non-experts; therefore, it can be utilized for early initiation of oral feeding and early recovery of patients in facilities without an NST.^{4,8,11}

Rapid initiation of PN, of course, may not be the only factor for early initiation of oral feeding. It is unclear whether the short hospitalization period in the TNA group resulted from the rapid supply of PN; it may also be because TNA formula was more frequently administered to older age groups, or because different underlying diseases and health conditions led to different choices regarding which PPN regimen was chosen. However, previous studies reported that early and appropriate administration of PN led to rapid recovery and hospitalization period.^{4,8,11} Further study is warranted in this matter.

TNA formula can be adapted preferentially in place of cPPN when a hospitalized patient of older age group requires PPN due to insufficient oral intake.³ The mean age

in the TNA group was higher than that of the cPPN group, suggesting easy accessibility of TNA formula in an older age group. Priority consideration can also be given to TNA formula in cases where fasting is expected during a hospital stay due to underlying disease.

There is a possibility that TNA formula without any additional regimens may cause inadequate GIR or calorie provision to pediatric patients whose weight or BMI are variable. Thus, we recommend that physicians consider an extra calorie supply supplemented with addition dextrose or condensed amino acid solution, based on age, body weight, or BMI. For patients supplied with PN only who are null per os, 20% protein and 10% dextrose can be provided in addition to TNA formula to overcome its limitations, if present, under the supervision of an NST. This modified TNA method may deserve further research.

Even though GIR and calorie supply for the TNA group were low compared with those in cPPN group and generally recommended guidelines, the amount of administered protein and lipid were not deficient in either PPN

Table 4. Comparisons of nutritional factors related to regimens of peripheral parenteral nutrition

	cPPN group (n=39)	TNA group (n=57)	<i>p</i> value
GIR (mg/kg·min)	4.7±1.6	2.9±1.1	<0.0001*
Proteins (g/kg·day)	1.2±0.4	1.3±0.4	0.584
Lipids (g/kg·day)	1.3±0.5	1.3±0.4	0.650
Calories (kcal/kg·d)	43.6±13.2	34.8±10.9	0.001*

**p*<0.05. cPPN: conventional peripheral parenteral nutrition; TNA: total nutrient mixture; GIR: glucose infusion rate.

Table 5. Comparison of factors related to regimens of peripheral parenteral nutrition

Age group	Variable	cPPN group (n=39)	TNA group (n=57)	<i>p</i> value
Early childhood	GIR (mg/kg·min)	5.85 (2.04~8.10)	4.10 (3.25~5.90)	0.001*
	Calories (kcal/kg·day)	55.28 (25.0~72.2)	46.8 (42.9~59.3)	0.013*
	Amino acid (g/kg·day)	1.53 (0.70~1.90)	1.50 (1.00~1.95)	0.653
	Lipid (g/kg·day)	1.50 (0.96~2.50)	1.70 (1.40~2.88)	0.166
Middle childhood	GIR (mg/kg·min)	4.10 (2.33~6.50)	2.70 (1.44~4.50)	0.067
	Calories (kcal/kg·day)	34.8 (24.6~62.9)	34.9 (19.6~45.3)	1.000
	Amino acid (g/kg·day)	1.20 (0.54~1.50)	1.30 (0.64~2.34)	1.000
	Lipid (g/kg·day)	1.01 (0.00~2.15)	1.29 (0.74~2.00)	0.222
Early adolescence	GIR (mg/kg·min)	3.87 (2.68~4.20)	1.55 (0.97~2.10)	0.082
	Calories (kcal/kg·day)	37.2 (24.1~54.0)	22.5 (12.0~32.3)	0.082
	Amino acid (g/kg·day)	1.12 (0.70~1.20)	0.84 (0.50~1.42)	0.576
	Lipid (g/kg·day)	1.02 (0.70~1.30)	0.90 (0.52~1.57)	0.576

**p*<0.05. cPPN: conventional peripheral parenteral nutrition; TNA: total nutrient mixture; GIR: glucose infusion rate.

group.¹² The TNA group was also not deficient in amino acid or lipid supply in each age group. Furthermore, even with GIR and calories lower than those in the cPPN group, there were no significant differences in the middle childhood group and early adolescence group. Calorie deficiency associated with the TNA method did matter in early childhood, from 2 to 6 years of age. Thus, supplementary dextrose may be needed to replenish a calorie shortage in early childhood, but is not routinely recommendable in middle childhood or adolescence.

There are various limitations in applying adult formulas to pediatric patients. They might lead to overdose in pediatric patients, and remaining formula must be discarded after use. Because nutritional requirements for pediatric patients are different from those for adults, TNA designated for children and adolescents is more suitable for providing adequate PPN to these age groups¹³. Further development of pediatric TNA formula and further research are required.

With respect to TNA-related complications, Colomb et al reported that there were 17 adverse events in 10 out of 18 children and adolescents related to the administration of TNA. None were serious, and 4 adverse events were either hypertriglyceridemia or hyperglycemia.¹¹ Our study also revealed that the incidence of metabolic, infectious or mechanical complications in TNA group was not higher than that of the cPPN group supported by an expert NST. Though TNA formula, including our formula, has relatively low osmolarity, the incidence of mechanical complications such as phlebitis was similar between the TNA and cPPN groups. Therefore, effort is required to reduce PPN-related phlebitis regardless of which regimen is chosen in pediatric patients who are vulnerable to mechanical complication.

Despite its limitations, TNA formula is a good alternative to traditional cPPN for short-term PPN of pediatric inpatients who need prompt PN administration. It is considered as an initial treatment of choice for the pediatric patients who require PPN due to insufficient oral intake.

In conclusion, TNA formula may be an easier and faster way than cPPN administration to provide a short period of nutrient supply to hospitalized children and adolescents who cannot take enough nutrients via an enteral route.

AUTHOR DISCLOSURES

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儿童三效合一的全营养混合液与传统肠外营养比较

背景：本研究的目的是为儿科住院病人提供短期三合一的全营养混合液(TNA)与采用外周静脉营养(PPN)的传统肠外营养(cPPN)的临床应用进行比较。
方法：我们对2到18岁的住院并接受肠外营养的儿童进行回顾性研究。对PPN和cPPN(39例)与TNA(57例)两种营养的方法进行临床效果比较。
结果：cPPN组和TNA组的平均年龄分别为 6.5 ± 3.1 岁和 8.2 ± 3.4 ($p=0.015$)岁。在TNA组中，入院当天到开始PPN或者口服的第一天时间明显缩短($p<0.0001$ 、 $p<0.0001$)。TNA组还缩短了入院后肠外营养前的时间，总的空腹时间也缩短了($p<0.0001$ 、 $p<0.0001$)。TNA组的结果显示较低的葡萄糖输液率，更少的每日单位体重总热量摄入($p<0.0001$ 、 $p=0.001$)。但是，氨基酸和脂类摄入量与PPN相关并发症之间无显著差异($p=0.584$ 、 $p=0.650$)。
结论：当为那些不能通过肠内途径摄取足够营养的住院儿童提供营养时，TNA比cPPN更简便快捷。

关键词：肠外营养、外周、全营养混合液、儿童、营养标准