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고영양수액제의 안정성에 대한 트리글리세라이드의 측쇄 길이의 영향

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Effect of Triglyceride Chain Length on the Stability of Total Nutrient Admixtures

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Background : 긴 측쇄의 트리글리세라이드(long chain triglyceride, LCT)는 대두 또는 홍화씨로부터 제조된 지방유제의 주요 성분이다. 중 측쇄 트리글리세라이드(medium chain triglyceride, MCT)는 LCT와 다른 물리적 성질을 가지고 있다. MCT의 지방산은 LCT의 지방산 보다 작은 분자량을 가지기 때문에 물에 더 잘 녹으며 다른 경로를 통하여 더 빨리 대사된다. **Objectives & Methods :** 본 연구에서는 지방산의 길이에 따른 고영양수액제(total nutrient admixture, TNA)의 안정성을 비교하기 위하여 서로 다른 LCT와 MCT 조성을 가지는 4 가지 TNA 처방의 안정성을 실온 및 냉장 조건에서 측정하였다. **Results :** 그 결과 MCT와 LCT의 혼합 조성의 TNA는 LCT 단독 조성의 TNA 와 유사한 안정성을 나타내었다. MCT와 LCT 혼합 TNA는 LCT 단독 TNA에 비하여 작은 입자크기를 보였지만 외관, 산도, 과산화수소가, 삼투농도, 아연 농도, 니코틴아미드 및 리보플라빈 농도에서는 의미 있는 차이를 보이지 않았다. **Conclusion :** 따라서 MCT와 LCT의 혼합 TNA는 LCT 단독 조성 TNA에 상응하는 안정성을 가지고 LCT단독 TNA을 대체제로 사용할 수 있다. 결론적으로, TNA의 2가지 타입 모두 3일 동안 실온과 냉장에서 안정하고, MCT와 LCT의 혼합 TNA는 LCT 단독 조성 TNA보다 생리화학적으로 더 안정하므로 환자들에게 좀 더 효과적인 에너지원이 될 것으로 전망된다.

□ Key words - LCT, MCT, TNA, Stability, pH

Total nutrient admixtures (TNAs) are formulas providing patients with much needed calories by placing sugars, amino acids, lipids, electrolytes, and other important nutrients in one container and are also called TIO (three -in-one) or AIO (all-in-one). The use of TNAs instead of the previous IVH can reduced the chances of infection due to simpler manipulation, is effective even in patients who would show hyperglycemia at the time of IVH administration, and can reduce the occurrence of refeeding syndrome that could occur in patients with severe weight loss since it reduces osmolarity compared with IVH.[1-3] TNAs have been formulated with long chain triglyceride (LCT) and administered until now. Although LCT lipid emulsion is safe and effective, an issue has been raised with stability since hypertriglyceridemia, fat accumulation into tissue, and lowering of immune function can occur when administered fast or when administering into those patients with LCT metabolism difficulty, and emulsification of lipids is induced as lipids in TNAs become physically unstable when mixed with high concentrations of glucose solution and electrolytes.[4-8] Therefore, studies have been conducted on stability on TNAs in hospitals using TNA.[9] Total nutrient admixture was made using medium chain triglyceride (MCT) thinking that the side effect and stability of LCT could be supplemented to

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supply patients with more safe TNA formula. MCT is a triglyceride composed of medium chain fatty acids, and is an effective energy source[10,11] in malnourished patients, hepatic failure patients, diabetic patients, new-born infants, postoperative sepsis patients and ICU patients since it oxides fast and completely compared with LCT due to its smaller molecular weight and size.[11,12]. TNAs containing MCT are used in many cases in countries with active use of TNAs such as the United States. Since stability can differ according to pharmaceutical company, we used the products, IntraMCT and Intralipose and conducted the present study using TNAs made with IntraMCT containing MCT and LCT at 1:1 ratio and TNAs made with the LCT lipid emulsification, Intralipose, to determine and compare stability of these two TNAs.

MATERIALS AND METHODS

Study Subjects

According to the following formula table (Table 1), TNAs containing LCT (Intralipose) and LCT/MCT (IntraMCT) were prepared in two types, i.e., Peripheral and Central types; observations were made on appearance, particle distribution, pH, osmolarity, hyperoxide value, Zn content, and vitamin contents at room temperature and at refrigerated state for 3 days to compare the stability of the TNAs. TNA formulas were prepared at an amount applicable to 6 lots using 1 L TNA bags according to composition, and after placing glucose, amino acids, fats, and electrolytes in the order, the mixtures were shaken thoroughly. After preparation, TNAs were stored according to the storing condition, and a sample was taken from each TNA every day, and examinations were done on the applicable items. The study results were obtained by calculating an average from 3 measurements made per each lot.

Table 1. Composition of four TNA formulations.

Contents \ Formulation		P I	P II	C I	C II
Dextrose	50%			400	400
	20%	400	400		
Solgreen 12.5%		250	250	500	500
Emulsion	Intralipose 20%		250		250
	IntraMCT 20%	250		250	
Multivitamin		5	5	5	5
Frutman		0.2	0.2	0.5	0.5
Heparin		1000 IU	1000 IU	1000 IU	1000 IU
KH_2PO_4 (13.6%)		5	5	10	10

*IU (international units); P I (peripheral I); P II (Peripheral II); C I (Central I); C II (Central II)

Samples

IntraMCT (Fresenius Kabi Corp.), 20% Intralipose (Fresenius Kabi Corp.), Solgreen (Fresenius Kabi Corp.), 50% Dextrose (Choongwae Pharma Corporation), 20% Dextrose (Choongwae Pharma Corporation), Multivitamin (MVH, Whanin Pharm Co. Ltd.), Frutman (Choongwae Pharma Corporation), KH_2PO_4 (K-phos, Choongwae Pharma Corporation).

Appearance

The prepared TNA formulas were stored at room temperature and at a refrigerated state for 3 days, a sample was taken from each TNA formula to observe the presence of absence of coalesscence under 1000 lux, visual observation on color change, picture taking, and picture taking under optical microscope at 0, 1, 2, and 3 days of storage.

Particle distribution

After diluting each sample in distilled water by 1000 folds, the samples were kept at room temperature out of refrigeration and the molecular distribution was measured with the dynamic light scattering (DLS) method using a laser particle analyzer (Otsuka electronics, Japan) for 3 days. The measurement was measured for 3 times per each sample and the average of the 3 measurements was calculated.

pH

After adjusting the temperature of each sample using cold water to 20°C, pH was measured using Horiba pH meter F-113. The measurements were made 3 times for each sample, and the average was calculated.

Hyperoxide value

Each sample was measured 3 times using a methrom

682 titroprocessor, and the average was calculated.

$$\text{hyperoxide value (mEq/L)} = \frac{(EP1\text{-}CO1)\times 10\times \text{titration factor}}{CO_0}$$

EP1 = sample titrate amount (mL)
CO1 = blank titrate amount (mL)
CO_0 = sample amount (mL)

Osmolarity

After diluting the sample by 2 folds using distilled water, the measurement was made using Fiske one-ten osmometer. The average of 3 measurements for each sample was calculated.

Measurement of Zn content

In order to observe changes in the Zn content in the Central I type, the TNA was stored in dark, samples were taken on 0, 1, 2, and 3 day, diluted by 5 folds with absolutely distilled water, and analyzed according to the atomic spectrophotometric method. As the standard solution, pure Frutman was diluted by 10,000 folds and prepared into the concentrations of 0.25, 0.5, and 0.75 ug/ml, and a calibration curve was prepared.

$$\text{Zn } (\mu\text{mol/L}) = \frac{\text{measured value}\times\text{dilution folds}}{\text{Zn molecular weight}\times 100}$$

Measurement of vitamin (nicotinamide, riboflavine) contents

A sample was taken and diluted by 2 folds on 0, 1, 2, and 3 days after storing the TNA Central I type formula in dark, the samples were filtered with a 0.2 um filter and nicontinamide and riboflavine contents were measured using HPLC, and compared with the vitamin contents in multivitamin tablets.

$$\text{nicotinamide content } (\mu\text{mol/L}) = std.conc(mg/mL)\frac{\text{area of sample peak}\times 2}{\text{area of std. peak}}$$

$$\text{riboflavine content } (\mu\text{mol/L}) = std.conc(mg/mL)\frac{\text{area of sample peak}\times 2}{\text{area of std. peak}}$$

Statistical analysis

To evaluate the significance in the change of each measurement, statistical analysis was done using t-test (GraphPad Prism 4). P values less than 0.05 were considered to be statistically significant.

RESULTS

Appearance

Each lot was light yellow due to the effect of vitamins, and during the study period, no changes such as creaming, flocculation, breakage, and oiling out were observed.

pH

Although about 0.1 larger change was seen in TNAs containing LCT compared with TNAs containing MCT/LCT, no significance was present (P>0.05), and no changes in pH were present during the study period (Table 2).

Osmolarity

The Peripheral preparation at about 1000 mOsm, and Central preparation at about 1850 mOsm showed no changes, and lthough a minute change was present between LCT, Intralipose preparation and MCT:LCT=1:1, IntraMCT, no significance was present (P>0.05) (Table 3).

Particle distribution

No significant change was present by maintaining the ini-

Table 2. pH change at room temperature (RT) and refrigerator (CT).

Formulation \ Day	Day 0		Day 1		Day 2		Day 3	
	RT	CT	RT	CT	RT	CT	RT	CT
P I	5.85	5.85	5.85	5.85	5.85	5.85	5.85	5.85
P II	5.82	5.82	5.82	5.83	5.81	5.84	5.81	5.83
C I	5.95	5.95	5.94	5.94	5.90	5.90	5.84	5.84
C II	5.81	5.81	5.80	5.81	5.80	5.82	5.78	5.80

P I (peripheral I); P II (Peripheral II); C I (Central I); C II (Central II)

Table 3. Osmolarity change at room temperature (RT) and refrigerator (CT).

Formulation \ Day	Day 0		Day 1		Day 2		Day 3	
	RT	CT	RT	CT	RT	CT	RT	CT
P I	1071	1068	1070	1064	1065	1060	1073	1067
P II	1006	1013	1009	1007	1014	1003	1010	1016
C I	1892	1885	1878	1883	1892	1890	1878	1874
C II	1723	1727	1710	1720	1711	1711	1737	1713

P I (peripheral I); P II (Peripheral II); C I (Central I); C II (Central II)

tial particle size between about 150 nm to 230 nm according to each preparation, but about 40 nm smaller particle size was seen with MCT:LCT (1:1, IntraMCT) TNAs compared with LCT (Intralipose) TNAs but with no significance (P>0.05) (Table 4).

Hyperoxide value

The results of measuring hyperoxide value at each lot according to the storage condition showed no significant changes (P>0.05) (Table 5).

Zn content

When Zn content was measured in the Central I type TNAs for 3 days while keeping the sample in dark, the results showed a slight change about 0.6 umol/L around 36.6 umol/L, but no significance was present (P>0.05) (Fig. 1).

Vitamin contents

During the study period, Nicotinamide showed almost no change but riboflavine showed a slight decrease of ±0.44 ug/ml without significance (P>0.05) (Fig. 2, 3).

DISCUSSION

As a preparation that supplies patients with sugars, amino acids, lipids, electrolytes, and required nutrients in one container, TNA is a preparation that requires caution at the time of mixing since the stability of the preparation changes according to the mixing order.[13] Especially, since a physicochemically unstable lipid state can be induced when lipids are mixed with high concentrations of glucose solution, many studies were conducted on stability of TNAs.[14] TNAs using LCT have been used in 8 hospitals in Korea, and studies on stability were also conducted.

Table 4. Changes in particle distribution at room temperature (RT) and refrigerator (CT).

Formulation \ Day	Day 0		Day 1		Day 2		Day 3	
	RT	CT	RT	CT	RT	CT	RT	CT
P I	180	181	178	172	171	170	171	174
P II	224	225	219	229	218	225	232	235
C I	166	176	152	154	149	160	164	157
C II	227	233	237	229	228	233	235	228

P I (peripheral I); P II (Peripheral II); C I (Central I); C II (Central II)

Table 5. Changes in hyperoxide value at room temperature (RT) and refrigerator (CT).

Formulation \ Day	Day 0		Day 1		Day 2		Day 3	
	RT	CT	RT	CT	RT	CT	RT	CT
P I	0.07	0.05	0.16	0.15	0.18	0.17	0.21	0.15
P II	0.14	0.12	0.16	0.13	0.18	0.11	0.17	0.13
C I	0.11	0.10	0.11	0.11	0.11	0.11	0.12	0.13
C II	0.03	0.03	0.06	0.05	0.07	0.05	0.17	0.05

P I (peripheral I); P II (Peripheral II); C I (Central I); C II (Central II)

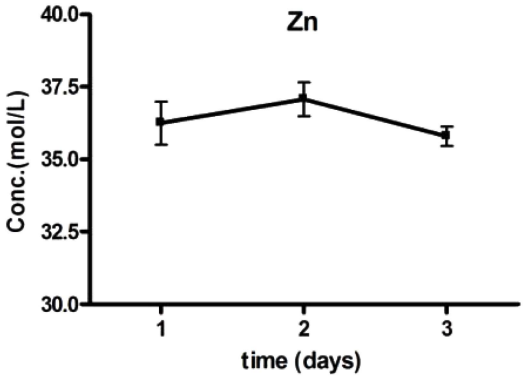

Fig. 1. Zn content changes in Central I type preparation at temperature lower than room temperature.

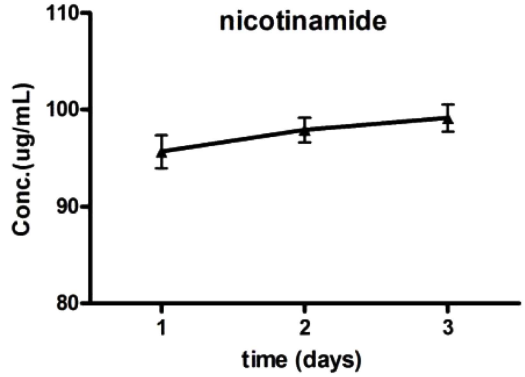

Fig. 2. Content change in nicotinamide contained in Central I type.

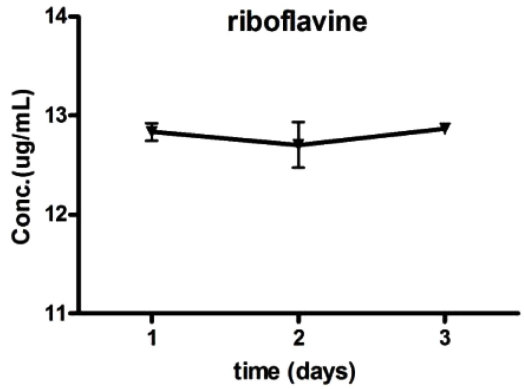

Fig. 3. Changes in riboflavine content contained in Central I type.

The results of the study conducted by Suh et al on stability of TNA prepared using LCT showed that TNAs containing LCT should be used within 1 day and 3 days when kept refrigerated to prevent the phenomena such as creaming, flocculation, coalescence, and breakage. In the present study, coalescence was shown in all samples left at room temperature within 24 h, and increases in pH, particle size, and hyperoxide value were seen. We developed a TNA formula using MCT/LCT (1:1, IntraMCT) that could overcome the problem of TNAs prepared with LCT, and compared appearance, pH, osmolarity, particle size, and hyperoxide value with TNAs prepared with LCT. The results of the present study showed that when the TNAs were kept at room temperature and in refrigeration for 3 days each, no signifiant changes were present in appearance, pH, osmolarity, hyperoxide value, Zn content, and nicotinamide content ($P>0.05$), but riboflavine showed a decrease of about 0.4 ug/ml ($P>0.05$), and the particle size of TNAs containing MCT/LCT was maintained about 40 um smaller compared with TNAs containing only LCT. Although we concluded that the two type of TNAs all maintained stability during the 3 day study period according to the study results, we think that TNAs containing MCT/LCT would be more physicochemically stable compared with TNAs containing LCT. These results agree with the study results of Jiang, J. M., M.D. and fast hydrolysis occurs with small particle size with MCT rather than LCT, suggesting a higher utilization as an energy source.[15] Conclusively, the stability of TNAs prepared with MCT/LCT (1:1, Intra MCT) was maintained for 3 days at room under 25°C temperature and refrigeration, and we think that it can be more effective energy source than TNAs prepared with LCT.

In conclusion, when we examined the stability of TNAs prepared with Intra MCT with MCT: LCT= 1:1, the results showed that the appearance of the formula was light yellow due to the vitamins present but no change in color was observed during the study period. During the study period, pH was decreased about 0.1, which was higher than the TNAs prepared with LCT, but at no significance. No significant changes were observed in osmolarity and hyperoxide value during the study period, and smaller particle distribution was shown compared with TNAs prepared with LCT, confirming that our TNAs can be more effective physiologic energy source compared with TNAs prepared with LCT. Thus,

TNAs prepared with Intra MCT at MCT:LCT= 1:1 can maintain stability for 3 days at room temperature lower than 25°C and refrigeration as more effective energy source than the existing TNAs prepared with LCT.

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