

EFFICACY OF MEDIUM-CHAIN TRIGLYCERIDES COMPARED WITH LONG-CHAIN TRIGLYCERIDES IN TOTAL PARENTERAL NUTRITION IN PATIENTS WITH DIGESTIVE TRACT CANCER UNDERGOING SURGERY

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The objectives of this prospective, randomized study were to evaluate the efficacy and tolerability of the short-term use of medium-chain triglyceride/long-chain triglyceride (MCT/LCT) fat emulsions, and to compare the hematologic and biochemical effects of MCT/LCT fat emulsions with LCT fat emulsions in gastrointestinal (GI) tract cancer patients following surgery. Thirty patients with GI tract cancer requiring total parenteral nutrition (TPN) were equally randomized to receive MCT/LCT or LCT emulsions for 7 days. After 7 days, no sign of complications directly related to administration of fat emulsions was observed and there were no marked differences in anthropometry, length of hospital stay, and surgical complication rates between the two groups. However, MCT/LCT significantly improved plasma prealbumin concentration ($p = 0.005$). Changes in complements C3 and C4, total lymphocyte count, and immunoglobulins after TPN were not significantly different between the groups. Serum triglyceride and cholesterol levels remained constant. The serum insulin level in the MCT/LCT group was higher than in the LCT group ($p = 0.048$). Our data revealed that MCT/LCT fat emulsions significantly enhanced nutritional status in patients with GI tract cancer, indicated by higher prealbumin levels, which might be partially due to the higher circulating insulin levels in the MCT/LCT group.

Key Words: medium-chain triglycerides, prealbumin, total parenteral nutrition
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Surgical intervention in gastrointestinal (GI) tract cancer patients, especially in those with serious malnutrition, induces complex physiologic changes that lead to catabolism and loss of body cell mass. To avoid severe metabolic distress, therapy with total parenteral nutrition (TPN) may be prescribed. An integral component of TPN regimens, lipid emulsions predominantly include long-chain

triglycerides (LCT) with 16–20 carbon atoms. These essential and mainly unsaturated fatty acids provide non-protein calories and, thus, reduce the caloric need for glucose and prevent fatty acid deficiency syndrome [1]. However, because LCT is involved in the metabolism of prostaglandin and leukotriene [2], and in diminishing reticuloendothelial system function [3,4], it has been fairly well documented as triggering immunosuppression and decreasing cell-mediated immunity [5–8]. In addition, much of the infused LCT is not readily oxidized, due to the relative deficiency of carnitine or inhibition of the carnitine acyltransferase system for translocating LCT across the inner mitochondrial membrane in critically ill patients [9].

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Since the 1970s, triglyceride emulsions containing medium-chain triglycerides (MCT) and LCT have been used as lipid substrates in TPN [9–12]. MCT, with 6 to 10 carbon atoms, is easily oxidized, and its entry into mitochondria is carnitine independent [12,13]. Thus, hydrolysis of MCT is faster than that of LCT and, consequently, MCT fatty acids are more rapidly made available to tissues [12–14]. Also, tissue uptake of MCT is faster due to the weaker albumin binding of MCT [15]. Because it is not involved in prostaglandin and leukotriene metabolism, MCT may also provide a better immune-system profile in these patients [8,16–19]. MCT/LCT emulsions offer significant advantages over LCT emulsions on metabolic effects *in vivo*, but this concept remains controversial in specific patient populations [20]. Therefore, this study was designed to delineate the efficacy and tolerability of short-term use of MCT/LCT emulsions, and whether or not modification of the fat composition (MCT/LCT vs LCT) in surgical GI tract cancer patients improved nutritional status by reducing protein catabolism. We also evaluated the side effects, including liver dysfunction and lipid metabolism, the impact on immunity, and the outcome by measuring the length of hospital stay and mortality rate in a homogenous group of patients.

PATIENTS AND METHODS

Patients

For this prospective randomized clinical trial at the Kaohsiung Medical University Hospital, inclusion criteria were: weight loss was greater than or equal to 10% of the usual body weight in the past 6 months, presence of histologically proven cancer, and major planned elective surgery. Patients were excluded if they were less than 18 years old; had cardiac dysfunction (New York Heart Association functional class > III, stroke history), hepatic dysfunction (Child-Pugh > 2), or renal dysfunction (serum creatinine concentration > 265 $\mu\text{mol/L}$, hemodialysis, or both); were pregnant; or had ongoing infection. The hospital's ethics committee approved the study protocol, and written informed consent was obtained from all subjects and/or guardians.

Procedures

All patients who fulfilled the selection criteria were randomly assigned to receive TPN with MCT/LCT or LCT. All patients had a central venous catheter placed during the operation. At the time of admission, we recorded the patient's age and gender, co-morbidity, actual and usual body

weight, hemoglobin concentration, serum glucose, serum creatinine, serum electrolytes, urine urea nitrogen (UUN), serum total protein, serum albumin and prealbumin, and total lymphocyte count (TLC). Duration of surgery, operative blood loss, the frequency and amount of homologous blood transfusions, and duration of postoperative hospital stay were also recorded. The nutritional regimen was designed to be isocaloric and isonitrogenous over 1 week, and to deliver, for an average individual with a weight of 70 kg, 1.2 g amino acid/kg/day and 26 kcal/kg/day. Patients received 0.88 g fat/kg/day, the MCT/LCT group from Lipofundin 20% (200 g/L fat emulsion containing 100 g/L soybean oil LCT and 100 g/L MCT; B. Braun, Melsungen, Germany) and the LCT group from Intralipid 20% (200 g/L LCT; Otsuka, Tokushima, Japan). Parenteral nutrition included electrolytes, vitamins, and trace elements according to current standards. TPN was started on the afternoon after surgery (at 6:00 pm) and was continued for 1 week. All patients received concurrent prophylactic antibiotics. Surgical staff diagnosed any postoperative complications, both infectious and noninfectious. All infectious complications were demonstrated by microbiologic analysis and positive culture. Re-laparotomy, complications requiring transfer of the patient to the intensive care unit during the postoperative course, or percutaneous drainage of deep infected collections by interventional radiologic procedures were defined as major complications. The primary endpoint was occurrence of postoperative complications. Length of postoperative stay, adverse effects, and treatment switchover were secondary endpoints.

Nutrition assessment

Nutritional status was assessed by trained nutrition nurses within 24 hours of admission (Day 0) and after 7 days (Day 7). Nutritional status was determined from anthropometric and biochemical measurements and from medical records. Anthropometric measurements included height and weight on admission, triceps skinfold thickness (TSF), and mid-arm circumference (MAC). The mid-arm muscle circumference was calculated as:

$$\text{Mid-arm muscle circumference (mm)} = \text{MAC (mm)} - (\text{TSF [mm]} \times 3.14)$$

Biochemical measurements included serum albumin and prealbumin and TLC. A 24-hour urine collection was obtained to measure UUN and creatinine. The nitrogen balance was derived from:

$$\text{Nitrogen balance (g/day)} = \text{nitrogen intake} - (\text{UUN} + 4 \text{ g obligatory loss})$$

The following values were considered normal for our laboratory: serum albumin, 3.5–5.0 g/dL; prealbumin, 18–43 mg/dL; and TLC greater than 1500/mm³.

Statistical analysis

Results are expressed as mean ± standard deviation. All data were analyzed using the Statistical Package for the Social Sciences version 8.0 software (SPSS Inc., Chicago, IL, USA). The Chi-squared test was used to compare clinical characteristics in the two groups, while Student’s *t* test was used to compare parameters. A probability of less than 0.05 was considered statistically significant.

RESULTS

Between January 1997 and March 1999, 30 patients with GI tract cancer were enrolled in this study, 15 in the MCT/LCT group with an average age of 63.7 years, and 15 in the LCT group with an average age of 71.0 years. The two groups were well balanced for baseline characteristics (Table 1). Both emulsions were well tolerated by all patients, and no-one left the study due to adverse reactions. The use of different lipid emulsions had no effect on overall complications and mortality (all *p* > 0.05) (Table 1). Length of hospital stay did not differ significantly between the two groups, at 26.8 days for the MCT/LCT group and 27.6 days for the LCT group (*p* > 0.05). In-hospital mortality was 6.7% for each group. Comparison of the anthropometry profiles showed no difference between the groups (*p* > 0.05) (Table 2). However, a marked improvement in the prealbumin level was found in the MCT/LCT group after 7 days of TPN (*p* = 0.005) (Table 3). Changes in transferrin and nitrogen balance were not significantly different.

After 7 days of the study, we observed significant alteration in liver function tests, including cholestasis enzymes (γ -glutamyltranspeptidase and alkaline phosphatase) and bilirubin level, in both groups, but the modifications were similar in both groups (Table 4). Insulin levels were increased in the MCT/LCT group (*p* = 0.048) (Table 5). Four patients in each group received exogenous insulin and were, therefore, excluded from the analysis of insulin concentrations. Needs for exogenous insulin were similar in both groups. We further analyzed the immunologic profiles including lymphocytes, immunoglobulins (IgG, IgM, IgA) and complements (C3, C4) before and after use of TPN. Our data showed that, after 7 days of parenteral nutrition, lymphocyte counts declined in both groups, C3 and C4 levels decreased in the LCT group, while IgG, IgM, and IgA markedly

increased in both groups, and C3 and C4 increased in the MCT/LCT group. However, the differences between groups did not reach statistical significance (Table 6).

Table 1. Patient and clinical characteristics in the two groups

	MCT/LCT (n = 15)	LCT (n = 15)
Age, mean (yrs)	63.7	71.0
Gender		
Male	10	14
Female	5	1
Gastric cancer		
Stage		
II	0	1
III	1	6
IV	4	3
Colon cancer		
Dukes’ stage		
B1	1	1
B2	6	0
C2	1	4
D	2	0
BT (U)	1.06	1.5
LOS, mean (d)	26.8	27.6
Complications (n)	2	5
Mortality (n)	1	1

MCT = medium-chain triglycerides; LCT = long-chain triglycerides; BT = blood transfusion; LOS = length of stay.

Table 2. Comparison of anthropometry profiles in the two groups (mean ± standard deviation)

	MCT/LCT	LCT	<i>p</i> *
Body weight (kg)			
Day 0	53.6 ± 11.4	54.6 ± 14.2	
Day 7	52.5 ± 11.0	53.5 ± 13.0	0.496
TSF (mm)			
Day 0	12.4 ± 8.1	12.0 ± 4.2	
Day 7	12.9 ± 8.1	12.5 ± 4.7	0.848
MAC (cm)			
Day 0	23.6 ± 3.4	24.4 ± 3.7	
Day 7	23.4 ± 3.2	23.8 ± 3.9	0.262

MCT = medium-chain triglycerides; LCT = long-chain triglycerides; TSF = triceps skinfold thickness; MAC = mid-arm circumference.

*Paired *t* test.

Table 3. Comparison of nutrition parameters in the two groups (mean ± standard deviation)

	MCT/LCT (n = 15)	LCT (n = 15)	p*
Albumin (g/dL)			
Day 0	3.6 ± 0.2	3.3 ± 0.1	0.911
Prealbumin (mg/dL)			
Day 0	11.9 ± 0.9	15.3 ± 1.8	
Day 7	20.1 ± 1.5	15.0 ± 1.8	0.005
Transferrin (mg/dL)			
Day 0	150.6 ± 13.6	161.7 ± 14.6	
Day 7	166.9 ± 14.4	147.8 ± 16.6	0.167
Nitrogen balance (g/D)			
Day 0	-2.1 ± 1.2	-4.8 ± 1.7	
Day 7	-1.6 ± 2.5	-0.4 ± 1.7	0.139

MCT = medium-chain triglycerides; LCT = long-chain triglycerides.
*Paired t test.

Table 4. Comparison of biochemistry and liver function tests in the two groups (mean ± standard deviation)

	MCT/LCT	LCT	p*
GOT (IU/L)			
Day 0	33.6 ± 6.2	29.2 ± 3.0	
Day 7	51.2 ± 7.1	59.5 ± 16.8	0.496
GPT (IU/L)			
Day 0	20.3 ± 3.4	19.4 ± 2.8	
Day 7	47.0 ± 9.0	43.0 ± 12.6	0.848
ALP (IU/L)			
Day 0	242.0 ± 80.2	194.3 ± 17.4	
Day 7	420.7 ± 67.9	374.2 ± 39.7	0.986
γ-GT (IU/L)			
Day 0	30.3 ± 54.1	22.7 ± 18.4	
Day 7	164.2 ± 152.1	110.1 ± 88.5	0.248
T-Bil (mg/dl)			
Day 0	0.7 ± 0.2	0.7 ± 0.1	
Day 7	0.9 ± 0.2	1.5 ± 0.4	0.137
Prothrombin time			
Day 0	11.4 ± 0.2	11.8 ± 1.0	
Day 7	11.3 ± 1.4	12.3 ± 0.3	0.112

MCT = medium-chain triglycerides; LCT = long-chain triglycerides; GOT = glutamyl oxaloacetic transaminase; GPT = glutamyl pyruvic transaminase; ALP = alkaline phosphatase; γ-GT = γ-glutamyltranspeptidase; T-Bil = total bilirubin.
*Paired t test.

Table 5. Comparison of plasma glucose and insulin concentrations in the two groups (mean ± standard deviation)

	MCT/LCT	LCT	p*
Glucose (g/dL)			
Day 0	126.4 ± 8.2	129.4 ± 9.1	
Day 7	142.7 ± 12.6	145.3 ± 10.2	0.964
Insulin (IU/mL)			
Day 0	14.1 ± 2.6	22.5 ± 5.2	
Day 7	20.7 ± 7.0	18.3 ± 1.9	0.048
C-peptide			
Day 0	4.5 ± 5.2	4.7 ± 3.2	
Day 7	5.8 ± 4.4	5.6 ± 4.0	0.946

MCT = medium-chain triglycerides; LCT = long-chain triglycerides.
*Paired t test.

DISCUSSION

Our data revealed that, after 7 days of administration of TPN with either MCT/LCT or LCT emulsions, there was no difference in overall postoperative complications and length of hospital stay (Table 1) or in anthropometry profiles (Table 2). However, further evaluation in a larger patient population with long-term follow-up is needed because the number of patients in this study was relatively small, and the duration of TPN administration was only 7 days.

The greater improvement of serum prealbumin level in the MCT/LCT group (11.9 ± 0.9 to 20.1 ± 1.5 vs 15.3 ± 1.8 to 15.0 ± 1.8 in the LCT group; *p* = 0.005) documented a better recovery of nutritional status (Table 3), even with a lower initial prealbumin level. Although the serum prealbumin level can be altered by systemic inflammatory status, prealbumin is recognized as the most sensitive measure and the test of choice for early assessment and intervention to enhance the care of hospitalized individuals [21,22]. The randomization and similar complication rate and length of hospital stay indicated that inflammatory status was comparable in the two groups, so the smaller increase in prealbumin in the LCT group might reflect poorer nutritional status.

The nitrogen balance and plasma transferrin level in our series did not change in both groups. Nitrogen balance is the most common clinical method for assessing protein turnover and the primary aim of nutritional support should be the achievement of a positive nitrogen balance [23,24]. The beneficial effects on protein metabolism exhibited by

Table 6. Comparison of the immunologic profiles in the two groups (mean \pm standard deviation)

	Day 0	Day 7	ΔE	p^*
Total lymphocyte count				
MCT/LCT	16.8 \pm 12.4%	14.3 \pm 5.5%	-2.6%	0.356
LCT	18.3 \pm 7.8%	11.9 \pm 6.2%	-6.4%	
IgG (mg/dL)				
MCT/LCT	1,189.9 \pm 509.2	1,445.7 \pm 506.9	+255.9%	0.515
LCT	1,290.9 \pm 228.6	1,475.8 \pm 315.8	+184.9%	
IgA (mg/dL)				
MCT/LCT	287.4 \pm 145.3	344.0 \pm 143.1	+56.6%	0.771
LCT	319.4 \pm 157.2	385.3 \pm 187.5	+65.9%	
IgM (mg/dL)				
MCT/LCT	105.2 \pm 58.3	140.9 \pm 79.9	+35.7%	0.107
LCT	91.4 \pm 34.8	103.9 \pm 52.1	+12.5%	
C3 (mg/dL)				
MCT/LCT	94.8 \pm 18.3	122.3 \pm 30.7	+27.5%	0.223
LCT	160.3 \pm 271.2	103.4 \pm 32.5	-56.9%	
C4 (mg/dL)				
MCT/LCT	27.1 \pm 9.9	29.0 \pm 10.5	+1.9%	0.172
LCT	21.7 \pm 5.2	20.5 \pm 7.3	-1.1%	

*Paired *t* test. ΔE = % difference; MCT = medium-chain triglycerides; LCT = long-chain triglycerides; Ig = immunoglobulin; C3 = complement 3; C4 = complement 4.

MCT are not well understood and different nitrogen-sparing mechanisms may be involved. MCTs are hydrolyzed and cleared faster than LCTs in normal volunteers, surgical patients, and critically ill subjects [25–27]. Moreover, the oxidation rate of medium-chain fatty acids (MCFAs) is considered higher than that of long-chain fatty acids (LCFA). Nevertheless, the lipid emulsion did not affect nitrogen balance after a short period of nutritional support in some studies [20,28,29].

Derangement of liver function is a common untoward effect in patients receiving TPN with or without lipids. Because it is not stored in the liver, does not interfere with bile acid composition, and produces ketone bodies as fuel for the enterocyte to diminish bacterial translocation, some investigators have hypothesized that MCT might reduce the hepatic dysfunction caused by TPN [30]. Some clinical trials have confirmed this hypothesis [31,32], whereas others, including this study, have not [33,34]. The hepatic enzymes and cholestasis enzymes were markedly elevated in both groups in this study, as was the bilirubin level. Nevertheless, our short-term use of fat emulsions might not be long enough to demonstrate any differences.

The finding of higher levels of circulating insulin on Day 7 in the MCT group was compatible with previous observations [25,33]. Serum ketone bodies increased in both normal and diabetic rats after an MCT diet for 3 days, and the serum insulin levels of MCT-fed rats tended to be higher than in normal animals [35]. MCT feed caused an enhancement of fatty acid synthetase and malic enzyme in the liver of normal rats. The elevated levels of insulin might be explained by the direct effect of MCFAs or ketone bodies on pancreatic cells to stimulate the release of insulin [25,33]. However, despite higher plasma insulin levels in the MCT group, plasma glucose and insulin requirements were similar in both groups. Rett et al suggest that the inhibition of muscular glucose uptake by infusion of MCT may explain the neutral influence on glucose levels when using MCT/LCT [36]. Insulin is the major endogenous anabolic hormone in the body, and several studies have found reduced nitrogen loss with insulin administration in injured patients [37]. This elevation of plasma insulin levels could be another factor explaining the MCT promotion of nitrogen retention in these patients.

Excess use of LCT fat emulsions might cause overproduction of prostaglandins and Th1-type cytokines,

subsequently inducing immunosuppression and decreasing cell-mediated immunity [2]. In our study, there was no difference in immunologic profiles between the two groups, which might be explained by less-stressed patients with elective surgery in our series. Furukawa et al found an amplified level of interleukin-6 and a decreased level of concanavalin A- or phytohemagglutinin-stimulated lymphocyte proliferation with LCT fat emulsion in severely stressed patients undergoing esophagectomy, but not in moderately stressed patients who underwent gastrectomy or colectomy [38].

In conclusion, our results indicated that modification of the fat composition (MCT/LCT vs LCT) of TPN for GI tract cancer patients improved nutritional status, as indicated by a higher prealbumin level, which might be partially due to the higher circulating insulin levels in the MCT/LCT group.

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胃腸道癌症病患術後接受七天中/長鏈 脂肪酸脂肪乳劑的臨床效益

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本篇前瞻隨機性研究目的在評估，針對胃腸道癌症病患，術後接受七天的中/長鏈脂肪酸脂肪乳劑的臨床效益；並比較在血液學檢查及生化指標方面，使用中/長鏈脂肪酸脂肪乳劑與長鏈脂肪酸脂肪乳劑的差異。共有 30 位接受胃癌及大腸癌手術，且需要全靜脈營養治療的病患，被隨機分配成兩組：一組使用中/長鏈脂肪酸脂肪乳劑，另一組使用長鏈脂肪酸脂肪乳劑。經七天治療後，兩組均未產生與脂肪乳劑相關的併發症，且兩組病患在體位測量、住院天數與手術併發症發生率均相同。但是使用中/長鏈脂肪酸脂肪乳劑的病患，血清前白蛋白值有顯著的改善 ($p = 0.005$)。另外，兩組病患在補體 C3、C4、血液全淋巴球數及免疫球蛋白值等免疫功能指標，並未達到統計上的差異。兩組病患在使用脂肪乳劑後，血清膽固醇值及三酸甘油脂值同樣無明顯差異。但血清胰島素值在使用中/長鏈脂肪酸脂肪乳劑的病患中，有較明顯上升 ($p = 0.048$)。本研究顯示，與接受長鏈脂肪酸脂肪乳劑相比較，病患接受七天中鏈長鏈脂肪酸脂肪乳劑，可以更明顯改善營養狀態，有較高的血清前白蛋白值。而造成此一現象的部分原因，可能與接受中/長鏈脂肪酸脂肪乳劑，可產生較高的血清胰島素值有關。

關鍵詞：中鏈脂肪酸，前白蛋白，全靜脈營養
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