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Effects of parenteral structured lipid emulsion on modulating the inflammatory response in rats undergoing a total gastrectomy

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Abstract

Objectives: Structured lipid emulsion improves the nitrogen balance and is rapidly cleared from the blood of moderately catabolic patients. However, the effects of structured lipids on inflammatory reactions during major surgery are not clear. This study investigated the effect of a parenteral structured triacylglycerol emulsion on leukocyte adhesion molecule expression and inflammatory mediator production in rats undergoing a total gastrectomy.

Methods: Normal rats with internal jugular catheters were assigned to three experimental groups and received total parenteral nutrition. At the same time, a total gastrectomy was performed on the experimental groups. The total parenteral nutrition solutions were isonitrogenous and identical in nutrient compositions except for differences in the composition of the fat emulsion. Group 1 received a conventional fat emulsion with long-chain triacylglycerols (LCTs), group 2 received a physical mixture of medium-chain triacylglycerols (MCTs) and LCTs (MCT/LCT), and group 3 received structured lipids composed of MCTs and LCTs (STG). Half of the rats in each respective group were sacrificed 1 d and the other half 3 d after surgery to examine the analytical parameters.

Results: Plasma cholesterol and free fatty acid levels in the STG group were lower than those in the other groups after surgery. The STG group had lower leukocyte CD11a/CD18 expressions than the MCT/LCT group 3 d after surgery, and CD11b/CD18 expressions in the STG group were lower than those in the LCT group on postoperative days. The STG group had higher monocyte chemotactic protein-1 and macrophage inflammatory protein-2 levels in peritoneal lavage fluid than did the other two groups.

Conclusion: These results suggest that, compared with the LCT and MCT/LCT groups, rats administered STG had lower plasma lipid concentrations and leukocyte integrin expressions. In addition, STG administration may cause increased recruiting of neutrophils and monocytes at the site of injury and enhance antipathogenicity in rats undergoing a total gastrectomy.

Keywords: Gastrectomy; Structured lipids; Medium-chain triacylglycerol; Long-chain triacylglycerol; Adhesion molecule; Inflammatory mediator

Introduction

Fat emulsions containing long-chain triacylglycerols (LCTs) are the most widely used fats in parenteral nutrition. However, the use of LCTs may induce immunologic and metabolic side effects, especially in stressed patients [1,2]. To improve the tolerance and effectiveness of lipid emulsions, a combination of medium-chain triacylglycerols

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(MCTs) and LCTs has been proposed. A physical mixture of an MCT/LCT emulsion has been suggested as an alternative energy source because, compared with the LCT emulsion, partial non-carnitine transport into mitochondria with a higher oxidation rate and a decreased tendency to accumulate in the reticuloendothelial system have been found with the MCT/LCT emulsion [3,4]. A structured MCT/LCT emulsion has been developed as an alternative to physical mixtures. The structured MCT/LCT emulsion contains structured triacylglycerols (TGs) with medium- and long-chain fatty acids randomly distributed within a single TG molecule. It has been suggested that these fat emulsions may be clinically advantageous over LCT and MCT/LCT emulsions. Previous clinical studies have shown that structured MCT/LCT emulsions improve the nitrogen balance and are cleared faster from the blood, compared with LCT and physically mixed MCT/LCT emulsions, in moderately catabolic patients [5–7].

A gastrectomy is frequently undertaken for benign and malignant gastric diseases. Gastric cancer remains among the top 10 causes of cancer-related deaths in many countries, especially in Asia. A total gastrectomy has been advocated for proximal and middle stomach cancer. For most gastrectomized patients with gastric diseases, preoperative malnutrition is often administered, and artificial nutritional support is essential for these patients. Although studies have shown that early enteral feeding may be well tolerated and may be a suitable alternative to total parenteral nutrition (TPN) [8], the parenteral route is indicated for a total gastrectomy due to preoperative obstruction or postoperative ileus. Optimal parenteral formulations for patients undergoing major abdominal surgery, such as a total gastrectomy, are still being investigated.

Patients who undergo a major operation may develop an inflammatory reaction and postoperative immunosuppression, which increases the susceptibility to infection [9,10]. Because previous studies have reported greater body weight gain, a greater positive nitrogen balance, and higher albumin levels with structured MCT/LCT formulations compared with physical mixtures or LCTs in stressed conditions [11,12], structured MCT/LCT formulations seem to be a better fuel source for patients undergoing a major operation. Therefore, in this study, we parenterally infused structured MCT/LCT to investigate whether it had beneficial effects on attenuating inflammatory reactions. The β2 integrins (CD18) are surface proteins expressed on leukocytes and are important in the adhesion of leukocytes to activated endothelium [13]. Integrins are reported to be good markers of leukocyte activation in the inflammatory mechanism [14]. Cytokine-induced neutrophil chemoattractant-1 (CINC-1) and macrophage inflammatory protein-2 (MIP-2) play important roles in mediating neutrophil recruitment to the site of injury [15,16]. Monocyte chemotactic protein-1 (MCP-1) is a chemotactic and activating factor for mononuclear phagocytes. MCP-1 is also involved in recruiting peripheral blood leukocytes to the peritoneal cavity [17]. To determine the possible roles of different fat emulsions in modulating inflammatory mediators in a surgical condition, the levels of these inflammatory-related cellular adhesion molecules and cytokines were measured in this study.

Materials and methods

Animals

Male 7-wk-old Wistar rats weighing 180~210 g at the beginning of the experiment were used. All rats were housed in temperature- and humidity-controlled rooms and were allowed free access to standard rat chow for 7 d before the experiment. The care of the animals followed standard experimental animal care procedures. This study was approved by the National Taiwan University Hospital animal care committee.

Study protocol and operative procedures

Rats were randomly assigned to three experimental groups, with each group containing 20 rats. The average weights among groups were adjusted to be as similar as possible. After overnight fasting, all rats were anesthetized with intraperitoneal pentobarbital sodium (50 mg/kg), and the right internal jugular vein was cannulated with a Silastic catheter (Dow Corning, Midland, MI, USA) under sterile conditions. At the same time, a total gastrectomy was performed as described by Ohta et al. [18] in the experimental groups. Briefly, the stomachs of the rats were removed after ligation of most of the blood vessels around the stomach that supplied blood, and an end-to-side anastomosis was carried out between the cut edge of the esophagus and the upper jejunum, 5 cm distal from the ligament of Treitz. The cavity was closed by sewing. Half of the rats ($n = 10$) in each experimental group ($n = 20$) were sacrificed 1 d and the other half 3 d (days 1 and 3 of TPN) after surgery. TPN was begun immediately after the operation and was maintained for 1 or 3 d in the different groups according to the sacrifice schedule of the rats. All basal TPN solutions were isonitrogenous (6.82 mg/mL) and identical in nutrient composition except for the composition of the fat emulsion. Group 1 (LCT) received a soybean oil emulsion (Lipovenous 20%; Frensenius Kabi, Bad Homburg, Germany) with LCTs, group 2 (MCT/LCT) received a physical mixture of MCTs and LCTs (Lipovenous MCT 20%; Frensenius Kabi), and group 3 (STG) received a structured TG emulsion composed of MCTs and LCTs (Structolipid; Frensenius Kabi). The TPN provided 270 kcal/kg of body weight per day, and the energy (kilocalories):nitrogen (grams) ratio was 118:1. The calorie density was 0.93 kcal/mL. The energy distribution of the TPN solutions in the

groups was 58% from glucose, 22% from protein, and 20% from fat (Table 1). The TPN solution was refilled daily and infused for 24 h at room temperature. Two milliliters per hour was administered on the first day, and then the rats received 48~57 kcal/d according to their individual body weights. The infusion rate was maintained with a Terufusion pump (model STC-503; Terumo, Tokyo, Japan). The TPN solution without fat was prepared every other day in a laminar flow hood, and the fat emulsion was added daily just before use.

Measurements and analytical procedures

Rats in the respective groups were sacrificed 1 or 3 d after surgery. Animals were anesthetized with intraperitoneal sodium pentobarbital (50 mg/kg; Sigma, St. Louis, MO, USA) [illegible] middle abdominal incision was made, and 10 mL of phosphate buffered saline was intraperitoneally injected to elute the peritoneal cells. After harvesting the peritoneal lavage fluid (PLF), rats were killed by drawing arterial blood from the aorta. Blood samples were collected in tubes containing heparin and were immediately centrifuged for further measurements. Plasma TG, total cholesterol, and non-esterified fatty acids (NEFAs) were determined by colorimetric methods after enzymatic reaction with peroxidase (Randox, Antrim, Ireland).

Analysis of intracellular interleukin-4 and interferon-γ expressions

Populations of lymphocyte interleukin (IL)-4 and interferon-γ (IFN-γ) expressions in fresh blood were analyzed by flow cytometry (Coulter, Miami, FL, USA). After sacrificing the rats, 50 μL of fresh blood was immediately incubated with 100 μL of Leucoperm (Serotec, Oxford, United Kingdom) reagent A for 15 min at room temperature to fix the leukocytes, and then 5 mL of phosphate buffered saline was added and centrifuged for 5 min at 300 × *g*. After discarding the supernatants, 100 μL of Leucoperm reagent B was added to the cell pellets to penetrate the leukocytes, and then 10 μL of fluorescein-conjugated mouse monoclonal anti-rat IFN-γ (Serotec) and 5 μL phycoerythrin-conjugated mouse monoclonal anti-rat IL-4 (Serotec) were incubated together for 30 min at room temperature. Leukocytes were washed with phosphate buffered saline. After removing the supernatant and resuspending cells in the sheath fluid, lymphocytes were gated on the basis of their forward- and side-scatter profiles. Lymphocytes capable of IL-4 and IFN-γ expressions were assessed using dual intracellular cytokine staining and flow cytometry (Coulter). The results are presented as a percentage of cytokine-producing cells in 1×10^5 lymphocytes.

Analysis of CD11a/CD18 distributions in lymphocytes and polymorphonuclear neutrophil expressions of CD11b/CD18

One hundred microliters of fresh blood was incubated with 10 μL of fluorescein isothiocyanate–conjugated mouse monoclonal anti-rat CD11a and phycoerythrin-conjugated mouse anti-rat CD18 (Serotec) for 15 min at 4°C. Afterward, red blood cells were lysed with lysing buffer (Serotec). The proportions of CD11a/CD18 expression on lymphocytes were analyzed by flow cytometry (Coulter). Fluorescence data were collected, and the results are presented as a percentage of CD11a-presenting cells in 1×10^5 lymphocytes. To determine the CD11b/CD18 expressions on polymorphonuclear neutrophils (PMNs), fluorescein isothiocyanate–conjugated mouse monoclonal anti-rat CD11b and phycoerythrin-conjugated mouse anti-rat CD18 (Serotec) were added to 100 μL of the PMN suspension. Fluorescence data were collected on 1×10^5 viable cells and

kits (BioSource, Camarillo, CA, USA). Monoclonal antibodies specific for rat MCP-1, MIP-2, and CINC-1 were precoated onto a microplate. Standards and samples were pipetted into the wells, and MCP-1, MIP-2, and CINC-1 present in the wells were bound by the immobilized antibodies. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for the proteins was added to the wells. After washing to remove any us antibodies. After

Table 4
Leukocyte CD11a/CD18 and CD11b/CD18 expressions among experimental groups 1 and 3 d after surgery

	CD11a/CD18 (%)	CD11b/CD18 (%)
Postoperative day 1		
LCT	13.04 ± 1.55	16.9 ± 1.45*
STG	14.78 ± 1.80	11.53 ± 1.56
MCT/LCT	12.02 ± 1.76	10.25 ± 1.63
Postoperative day 3		
LCT	7.68 ± 1.52†	10.75 ± 1.14‡
STG	8.78 ± 1.73†	7.43 ± 1.58†
MCT/LCT	11.32 ± 1.68*	9.02 ± 1.60

LCT, long-chain triacylglycerol; MCT, medium-chain triacylglycerol; STG, structured triacylglycerol emulsion composed of medium-chain and long-chain triacylglycerols

* Significantly different from the other groups on the same postoperative day.

† Significantly different from the same group on postoperative day 1.

‡ Significantly different from the STG group on postoperative day 3.

Discussion

This investigation showed that administration of TPN containing a structured lipid emulsion affected several aspects of plasma lipids and the immune response that differed from those seen with MCT/LCT- and LCT-based TPN. In this study, we did not include a sham-operation control group because major surgery is known to result in metabolic alteration and inflammation. However, this study design was not able to assess whether STG administration restored plasma lipid profiles and inflammatory responses comparable to the control rats.

Under stress conditions such as major surgery, lipid metabolism is altered and plasma NEFA levels are elevated as a result of increased lipolysis. However, the rate of NEFA oxidation for fuel is not much; approximately 70% of plasma NEFAs are undergoing re-esterification in the liver to resynthesize TGs [19]. Although the exogenous fat that can be used as an energy substrate is limited, a certain amount of administered fat influences plasma lipid profiles after surgery. The effects of STG on plasma lipids reported in previous studies are conflicting. Some studies reported no difference, whereas others indicated lower TGs in the structured lipid infusion group compared with other fat emulsions [5,6,20,21]. In this study we found that plasma cholesterol and NEFA levels were lower in the STG group than in the other two groups postoperatively. Although there were no differences in TG levels among the groups after surgery, we did observe that the TG levels were lower on postoperative day 3 than on postoperative day 1 in the STG group, whereas no such alteration was noted in the other two groups. These results may indicate that STG administration reduced lipolysis after surgery when compared with MCT/LCT and LCT-based TPN.

Chemokines are proteins that exhibit activities associated with inflammatory, immune, and tissue repair processes. Chemokines play important roles in mediating inflammatory cell recruitment in tissues in response to endotoxin and bacterial challenges. CINC and MIP-2 are mediators of stimulant-induced neutrophilic inflammation in tissues. MCP-1 is known to contribute to monocyte/macrophage recruitment [22]. Inflammatory mediators produced by immune cells serve to regulate the whole-body response to infection and injury. Standiford et al. [23], using a murine model of acute bacterial pneumonia, found that the depletion of MIP-2 is associated with higher early mortality. A study performed by Matsukawa et al. [17] found that endogenous MCP-1 protected mice in a model of septic peritonitis. MCP-1 blockade with anti–MCP-1 antiserum decreased the survival rate after cecal ligation and puncture [17]. In this study, we found that that MCP-1 and MIP-2 levels in PLF were higher in the group with STG than with LCT or MCT/LCT administration 1 d postoperatively. This finding may indicate that more neutrophils and monocytes were recruited to the site of injury when STG was administered after surgery.

CD11a/CD18 are exclusively expressed on leukocytes, whereas CD11b/CD18 are abundant in PMNs [24]. The binding of these integrins to cellular adhesion molecules expressed on endothelial cells is important for firm attachment to and migration across the endothelium [25]. Excessive expression of these integrins induces an inflammatory response and tissue injury [24,26]. A previous study showed that the expressions of CD11b/CD18 were significantly increased in patients with septic shock [27]. In this study, we found that the percentages of CD11a and CD11b decreased on postoperative day 3 compared with postoperative day 1 in the LCT and STG groups. The STG group had even lower CD11b percentages than the LCT group after surgery. Our findings suggest that LCT and STG emulsion administration may attenuate leukocyte adhesion and migration, and the effect was more obvious when STG was administered in a surgical condition. The physical mixture of MCT/LCT had

Table 5
Concentrations of CINC-1, MCP-1, and MIP-2 in peritoneal lavage fluid among experimental groups 1 and 3 d after surgery

	CINC-1	MCP-1	MIP-2
Postoperative day 1			
LCT	109.2 ± 57.1	63.1 ± 21.3	23.3 ± 6.7
STG	80.7 ± 25.2	105.5 ± 43.9†	47.2 ± 11.1†
MCT/LCT	64.2 ± 36.6*	75.3 ± 36.2	17.2 ± 2.9
Postoperative day 3			
LCT	87.5 ± 57.8	47.7 ± 20.1	72.9 ± 24.4
STG	62.6 ± 18.1	37.6 ± 15.3‡	80.4 ± 31.6‡
MCT/LCT	42.6 ± 16.3*	35.6 ± 15.1‡	50.7 ± 22.9†

CINC-1, cytokine-induced neutrophil chemoattractant; LCT, long-chain triacylglycerol; MCP-1, monocyte chemotactic protein-1; MCT, medium-chain triacylglycerol; MIP-2, macrophage inflammatory protein-2; STG, structured triacylglycerol emulsion composed of medium-chain and long-chain triacylglycerols

* Significantly different from the LCT group on the same postoperative day.

† Significantly different from the other two groups on the same postoperative day.

‡ Significantly different from the same group on postoperative day 1.

a higher CD11a percentage than the other groups 3 d after surgery. This result is consistent with a report by Wanten et al. [28], which found that a physical mixture of MCT/LCT expresses higher integrins than do LCT and STG emulsions in neutrophils isolated from healthy volunteers.

Cytokines are produced by various cells of the immune system and act as mediators of the immune response. Cytokine profiles are related to the severity of different types of infection. The cytokine profiles are determined by two functional subsets of T lymphocytes, T-helper (Th) type 1 and Th2. Th1 cytokines, including IL-2 and IFN-γ, enhance cell-mediated immunity, whereas Th2 cytokines, including IL-4 and IL-10, enhance humoral immunity. The effects of Th1 and Th2 lymphocytes are counter-regulatory [29]. Studies have shown that a marked depression in cellular immunity occurs after an operation, and overexpression of the Th2 cytokine, IL-4, is responsible for the immunosuppression associated with surgery [30]. In this study, we directly measured intra-lymphocyte IFN-γ and IL-4 productions to investigate the effects of different fat emulsions on Th1- and Th2-type responses with a gastrectomy. The results showed that, compared with the LCT group, Th1- and Th2-type responses in the STG group were suppressed. Because the overexpression of IL-4 is associated with operation-induced immunosuppression [30], determining whether a lower IL-4 distribution observed after STG feeding will have a favorable effect with a gastrectomy requires further investigation.

A previous study showed that the positional specificity of lipoprotein lipase on TG hydrolysis favors the metabolism of structured lipids [31]. The faster hydrolysis and oxidation of STG indicate a preference for STG as a substrate for the energy source. Eicosanoids derived from ω-6 fatty acids enhance prostaglandin E_2 production and promote inflammatory reactions [32]. A study reported that STG did not stimulate eicosanoid production [33]. It is possible that, when STG is administered, more energy is available for use and fewer inflammatory-related eicosanoids are produced under the stress of operation and thus attenuates the severity of the inflammatory reaction.

In summary, this study showed that, compared with the LCT and MCT/LCT groups, rats administered STG had lower plasma lipid concentrations and leukocyte integrin expressions. STG administered after surgery resulted in higher MCP-1 and MIP-2 levels, which may result in more neutrophils and monocytes being recruited to the site of injury and enhanced antipathogenicity in rats with a total gastrectomy.

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