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Early Enteral Feeding in Postsurgical Cancer Patients

Fish Oil Structured Lipid-Based Polymeric Formula *Versus* a Standard Polymeric Formula

Andrew S. Kenler, M.D.,* Wendy S. Swails, R.D., C.N.S.D.,† David F. Driscoll, Ph.D.,‡,‖ Stephen J. DeMichele, Ph.D.,¶ Brian Daley, M.D.,# Timothy J. Babineau, M.D.,*,‖ Myron B. Peterson, M.D., Ph.D.,**,†† and Bruce R. Bistrian, M.D., Ph.D.§,‖

From the Department of Surgery, Nutrition Support Service,† Pharmacy,‡ and the Nutrition/ Infection Laboratory, the Department of Medicine,§ Deaconess Hospital, Boston, Massachusetts; Harvard Medical School,‖ Boston, Massachusetts; Ross Products Division, Abbott Laboratories, ¶ Columbus, Ohio; Surgical Critical Care, UMDNJ, Rutgers University,# Camden, New Jersey; New England Medical Center,** Boston, Massachusetts; and Tufts Medical School,†† Boston, Massachusetts*

Objectives
The authors compared the safety, gastrointestinal tolerance, and clinical efficacy of feeding an enteral diet containing a fish oil/medium-chain triglyceride structured lipid (FOSL-HN) *versus* an isonitrogenous, isocaloric formula (O-HN) in patients undergoing major abdominal surgery for upper gastrointestinal malignancies.

Summary Background Data
Previous studies suggest that feeding with n-3 fatty acids from fish oil can alter eicosanoid and cytokine production, yielding an improved immunocompetence and a reduced inflammatory response to injury. The use of n-3 fatty acids as a structured lipid can improve long-chain fatty acid absorption.

Methods
This prospective, blinded, randomized trial was conducted in 50 adult patients who were jejunally fed either FOSL-HN or O-HN for 7 days. Serum chemistries, hematology, urinalysis, gastrointestinal complications, liver and renal function, plasma and erythrocyte fatty acid analysis, urinary prostaglandins, and outcome parameters were measured at baseline and on day 7. Comparisons were made in 18 and 17 evaluable patients based *a priori* on the ability to reach a tube feeding rate of 40 mL/hour.

Results
Patients receiving FOSL-HN experienced no untoward side effects, significant incorporation of eicosapentaenoic acid into plasma and erythrocyte phospholipids, and a 50% decline in the total number of gastrointestinal complications and infections compared with patients given O-HN. The data strongly suggest improved liver and renal function during the postoperative period in the FOSL-HN group.

Conclusion

Early enteral feeding with FOSL-HN was safe and well tolerated. Results suggest that the use of such a formula during the postoperative period may reduce the number of infectious and gastrointesinal complications per patient, as well as improve renal and liver function through modulation of urinary prostaglandin levels. Additional clinical trials to fully quantify clinical benefits and optimize nutritional support with FOSL-HN should be undertaken.

Patients with upper gastrointestinal malignancies frequently suffer from protein-calorie malnutrition.[1,2] This is due, in large part, to a systemic anorexia, which is presumed to be cytokine-mediated in conjunction with varying degrees of local anorexia in response to obstructive symptoms. In addition, the metabolic response to injury that is seen in these patients postoperatively produces a redistribution of endogenous macronutrients, causing further depletion of body fat stores and lean body mass.[3] If the injury response persists and nutritional support is not instituted, pre-existing protein-calorie malnutrition will be exacerbated and the risk of morbidity and mortality will be increased.[4] In this setting, postoperative nutritional support serves to minimize the loss of lean body mass, thereby preserving vital organ function and maintaining immunocompetence.

Recent data suggest that the route of nutrient administration can modulate the metabolic and immunologic response to injury.[5,6] Lack of gastrointestinal feeding in animal models has been associated with intestinal mucosal atrophy and subsequent translocation of bacteria and toxins within the host via the portal and lymphatic circulations.[6] Both endotoxin and other components of bacterial cell walls activate cells of the monocyte/macrophage line to produce proinflammatory cytokines that can potentiate some of the deleterious sequelae associated with the metabolic response to injury.[7] Prospective randomized clinical trials in trauma patients have shown a significant decrease in the incidence of septic complications in patients receiving enteral feeding compared with those receiving parenteral feeding.[8,9] Recognition of the importance of gut integrity and the link between enteral feeding and maintenance of the intestinal barrier has led to the increased use of enteral feeding in patients undergoing major thoracoabdominal operations.

Current investigations in enteral nutrition have focused on the ability to modulate the metabolic response to injury via specially formulated enteral diets. Specifically, individual nutrients such as arginine, yeast RNA, and n-3 fatty acids (fish oil) have been used to alter eicosanoid synthesis, cytokine production, and immune function, in an attempt to limit the injury response and elicit more desirable physiologic adaptations during critical illness. Recent prospective, randomized clinical trials have employed enteral formulas enriched with these so-called "immunostimulatory" nutrients and have demonstrated a significant reduction in infectious and wound complications, as well as length of hospital stay in patients receiving the supplemented formula.[10,11] However, the combination of these "immunostimulants" in a single formula has obscured the individual effects of each, and it is not known whether the clinical effects observed in these trials are the result of synergism or from a specific nutrient. The specific focus of the present study was to evaluate the impact of one nutrient, n-3 fatty acids in the form of a fish oil and medium-chain triglyceride (fish oil/MCT), on the metabolic and clinical outcome in postoperative patients with cancer.

Numerous studies have shown that feeding with n-3 polyunsaturated fatty acids (PUFAs) from fish oil can alter the composition of cell membranes and their subsequent eicosanoid and cytokine production.[12,13] Specifically, n-3 PUFAs favor production of prostaglandins of the 3-series (PGE_3) and leukotrienes of the 5-series, as well as reduce production of 2-series prostaglandins (PGE_2) and 4-series leukotrienes. These changes in eicosanoid synthesis seen with n-3 PUFA feeding have been associated with an improved immunocompetence and a reduced inflammatory response to injury. In addition, several animal studies have shown an improved survival after endotoxin challenge in animals receiving fish oil.[14,15] Concern about the length of time required to alter membrane fatty acid composition to influence outcome has been addressed to some extent by studies in animals. Continuous *versus* intermittent enteral feeding dramatically shortens the time needed to incorporate n-3 PUFAs into cell membranes and subsequently produce their physiologic effects.[16] These findings suggest that the acute provision of fish oil to critically ill patients may be anticipated to influence clinical outcome.

The recognition that dietary lipids may have profound effects on inflammatory and immune responses has prompted a growing number of enteral formulas that include n-3 fatty acids. However, to date, the lipid profiles of all these products contain n-3 fatty acids in the form

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Address reprint requests to Bruce R. Bistrian, M.D., Ph.D., Chief, Nutrition/Infection Laboratory, Department of Medicine, Deaconess Hospital, 194 Pilgrim Road, Boston, MA 02215.

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of a physical mixture with other medium and long-chain triglycerides. The use of n-3 PUFAs as a structured lipid that contains medium and n-3 fatty acids on the same glycerol backbone has not been explored. Structured lipids have been shown to improve protein and energy metabolism when compared with physical mixtures,[17–20] as well as to have improved intestinal absorption.[21,22] This prospective, randomized clinical trial sought to examine the unique and singular effects of n-3 PUFAs provided as a fish oil/MCT structured lipid in a complete enteral formula without the possible confounding effects of other supplemented nutrients. We sought to examine the effects of continuously feeding such a formula on safety and metabolic parameters, and clinical outcome in patients undergoing surgical oncologic procedures involving upper gastrointestinal malignancies. Comparisons were made to its counterpart differing only in respect to the use of a conventional fat mixture.

MATERIALS and METHODS

Patients

Fifty adult patients, between 18 and 80 years of age, with upper gastrointestinal malignancies, who were scheduled for major abdominal surgery related to their cancer, were entered into the study. Patients were enrolled into the study over a 20-month period from August 1991 to April 1993. Exclusion criteria included the following: renal dysfunction defined by a serum creatinine level of >3.0 mg/dL or as dialysis-dependent; uncontrolled congestive heart failure; uncontrolled infection, defined as a temperature <101 F for ≥3 days accompanied by either a positive blood culture or signs and symptoms of intra-abdominal, urinary, or pulmonary infection; presence of acquired immune deficiency syndrome; or other chronic diseases requiring daily corticosteroid doses exceeding 15 mg of prednisone or an equivalent dose of another steroid. This prospective, randomized clinical trial was approved by the Institutional Review Board, and all patients gave written informed consent before entry into the study.

Diets

Patients were prospectively randomized to receive one of two enteral feeding formulas: Osmolite HN ([O-HN]; Ross Laboratories, Columbus, OH) or a fish oil structured lipid formula (FOSL-HN) differing from O-HN only in terms of its lipid composition (Table 1 and Fig. 1). Clinical investigators and patients were blinded to product identity. All patients had a feeding jejunostomy tube placed at the time of their abdominal surgery. Enteral feeding was initiated at 10 mL/hr in the immediate postoperative period (within 48 hours) using the designated undiluted study formula. The goal was to increase the enteral feeding infusion rate by 10 mL/hr every 12 hours so that nutritional requirements would be met by postoperative day 3 or 4. Caloric and protein needs were estimated to be 25 to 30 kcal/kg body weight and 1.2 to 1.5 g protein/kg. Oral diets were advanced by the primary surgeon, and the enteral feeding infusion rate was decreased gradually as oral intake increased. Dietary fat other than that present in the study diets was restricted and quantified.

Table 1. COMPOSITION OF ENTERAL DIETS*†

Nutrient	O-HN	FOSL-HN
Protein		
% of total calories	16.7	16.7
g/L	46.2	47.9
Source	Na, Ca-caseinates Soy protein isolate	Na, Ca-caseinates Soy protein isolate
Carbohydrate		
% of total calories	53.3	53.3
g/L	139.9	137.7
Source	Glucose polymers	Glucose polymers
Lipids		
% of total calories	30.0	30.0
g/L	38.9	39.4
Source	48.4% MCT 38.7% corn oil 9.7% soybean oil 3.2% soy lecithin	70.0% fish oil/MCT SL 20.0% canola oil 6.8% soybean oil 3.2% soy lecithin
Caloric density (kcal/mL)	1.06	1.06
Osmolality (mOsm/kg H_2O)	292	288

SL = structured lipid; FOSL-HN = fish oil/MCT structured lipid formula.

* Each liter of the formula contained the following vitamins: 4250 IU vitamin-A, 304 IU vitamin D, 37 IU vitamin E, 54.6 μg vitamin K_1, 228 mg vitamin C, 455 μg folic acid, 1.71 mg thiamin, 1.94 mg riboflavin, 2.28 mg vitamin B_6, 6.82 μg vitamin B_{12}, 22.8 mg niacin, 454 mg choline, 341 μg biotin, 11.4 mg panthothenic acid.

† Each liter of the formula contained the following trace minerals: 930 mg Na, 1570 mg K, 1440 mg Cl, 758 mg Ca, 758 mg P, 304 mg Mg, 114 μg I, 3.79 mg Mn, 1.52 mg Cu, 17.1 mg Zn, 13.7 mg Fe, 70 μg Se, 100 μg Cr, 150 μg Mo.

The fish oil/MCT structured lipid used in the experimental diet, FOSL-HN, was produced by mixing fractionated MCT and fish oil in specific proportions, allowing hydrolysis of the fatty acids, followed by random transesterification into composite triglyceride molecules. Individual triglyceride molecules may contain either two medium-chain fatty acids and one long-chain fatty acid or one medium-chain fatty acid and two long-chain fatty acid, as well as smaller quantities of pure MCT and triglycerides innate in fish oil.

Gastrointestinal Tolerance

Gastrointestinal tolerance to enteral feeding was monitored and recorded daily. If any significant adverse gas-

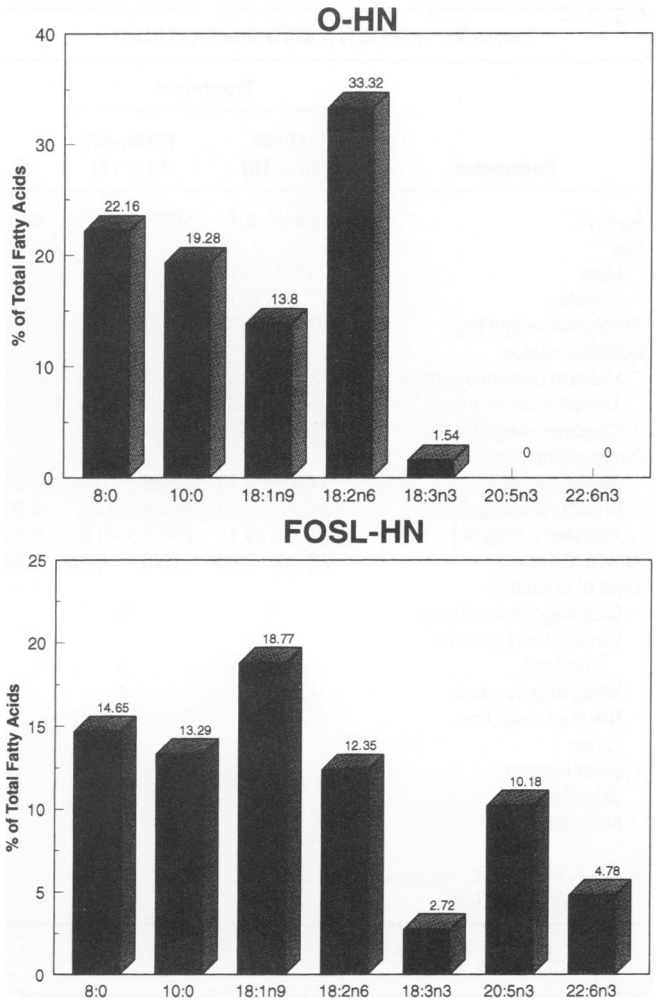

Figure 1. Fatty acid profile of the enteral diets. Values were determined by gas chromatography after lipid extraction. The n-6/n-3 ratio for the diets are 22.64 and 0.65 for Osmolite HN (Ross Laboratories, Columbus, OH) and fish oil structured lipid, respectively.

trointestinal signs or symptoms developed (*i.e.*, diarrhea, defined as greater than 3 loose stools/day; abdominal distention; nausea; and emesis), the enteral feeding infusion rate either was decreased or the tube feeds were held until they could be restarted without resumption of symptoms. When diarrhea occurred, a stool sample was sent to rule out *Clostridium difficile* infection, and all medications (particularly those containing sorbitol) that could be causing or exacerbating the diarrhea either were discontinued or administered parenterally where appropriate. If the diarrhea persisted, and stool cultures were negative, antimotility agents (Lomotil [Searle Laboratories, Chicago, IL], deodorized tincture of opium) were used to help control the diarrhea. Parenteral nutritional support (either peripheral or central) was used to supplement the tube feeding whenever gastrointestinal intolerance prevented the delivery of adequate energy and protein.

Laboratory Parameters

Preoperative evaluation consisted of a complete history and physical examination, and a nutritional assessment, including anthropometric measurements (height, weight, upper arm circumference, triceps skin fold) and creatinine height index. The following plasma and urine analyses were obtained at baseline (before surgery), whenever possible, and on study day 7: complete blood count with differential, platelet count; prothrombin and activated partial thromboplastin time; serum electrolytes; liver function tests (total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase [AST] levels, alanine aminotransferase [ALT]) levels; total protein; prealbumin levels; albumin levels; calcium; phosphorus; magnesium; iron; transferrin; triglyceride; and serum insulin levels. The following parameters also were assessed at baseline and day 7: plasma and urinary eicosanoid analyses, including 6-keto prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$) (inactive metabolite of prostacyclin I_2); thromboxane B_2 (TxB_2; inactive metabolite of thromboxane A_2); and bicyclo-PGE (cyclic derivative of 13,14-dihydro-15-keto-PGE); these were performed using methods described elsewhere.[23,24] Erythrocyte membrane, plasma triglyceride, and phospholipid fatty acid composition was determined by gas chromatography as previously described[25,26]; platelet ability to aggregate was determined using previously described methods.[27] Three consecutive 24-hour urine collections were obtained on study days 5, 6, and 7 to determine urinary urea nitrogen, total urinary nitrogen (Kjeldahl analysis), creatinine, sodium, potassium, calcium, phosphorus, chloride, and magnesium excretion.

Complications

Postoperative complications were recorded and classified as either infectious or mechanical. Infectious complications included pneumonia, defined as an abnormal chest x-ray and a positive sputum culture; intra-abdominal abscess, defined as a collection determined by either aspiration or surgical exploration; intra-abdominal infection, defined as a positive culture from a drain placed at surgery and treated with systemic antibiotics; wound infection proven by positive culture; sepsis, defined as one positive blood culture with a known pathogen or two consecutive cultures for usually nonpathogenic organisms; and the septic syndrome, defined as fever, leukocytosis, and hypotension (systolic blood pressure <90 mmHg) with or without positive blood cultures. Major mechanical complications included prolonged ileus for more than 5 days, wound dehiscence, inadvertent jejunostomy tube dislodgment or removal, and anastomotic leak radiographically or operatively confirmed.

Statistical Methodology

All statistical tests were performed as two-tailed tests. Effects were considered to be statistically significant if the obtained p value was no greater than 0.05. However, because this was an exploratory study, special attention also was given to p values greater than 0.05 but less than 0.10. All of the analyses were performed using version 6.08 of the SAS statistical package (SAS Institute, Cary, NC).

Analysis of variance was employed to determine whether a relative difference between the two diets was present in the following areas: 1) safety and tolerance, as measured by serum chemistries and electrolytes, hematology, blood coagulation parameters, urinalysis, formula tolerance and gastrointestinal complications, and nitrogen balance; 2) liver and renal function; 3) urinary prostaglandin level; 4) plasma triglyceride level; 5) plasma phospholipid and erythrocyte membrane fatty acid profile; and 6) patient outcome data. Nonparametric data (gastrointestinal complications, patient outcome data) was assessed by chi square analysis.

The relationship among renal function (creatinine and urea clearance), urinary prostaglandins (6-keto-$PGF_{1\alpha}$ and TXB_2), and liver function parameters was established through two separate analyses. First, a principal components analysis was performed on the aforementioned variables to extract the primary factors. That is, a principal components analysis was performed to reduce renal function, urinary prostaglandins, and liver function parameters to a smaller number of primary dimensions (called factors). The resulting factors then were used in a multivariate analysis of variance as dependent variables to simultaneously explore the differences among the diet groups on factors underlying the outcome parameters under study. Second, stepwise regression was performed to explain urinary TXB_2 to 6-keto-$PGF_{1\alpha}$ ratio as a linear function of creatinine clearance, urea clearance, urinary TXB_2, urinary 6-keto-$PGF_{1\alpha}$, alkaline phosphatase, ALT, AST, direct bilirubin, and total bilirubin. The variable entry criterion for the stepwise regression model was set at the 0.10 level of significance.

RESULTS

Patient Demographics

A total of 50 patients (25 for the O-HN group and 25 for the FOSL-HN group) were entered into the study. There were, however, 18 and 17 evaluable patients (based on their ability to reach a tube feeding rate of more than 40 mL/hr) who were fed O-HN and FOSL-HN, respectively. The mean age was similar for patients fed O-HN and those fed FOSL-HN—64 ± 3 years and 63 ± 3 years, respectively (Table 2). The preoperative diagnosis of the two groups were not substantially different. Two patients (one in each study group) had a presumptive preoperative diagnosis of cancer, but were found to have benign disease at the time of surgery.

Table 2. PATIENT DEMOGRAPHICS*

Parameter	Treatment: O-HN (n = 18)	Treatment: FOSL-HN (n = 17)	p
Age (yr)	64.4 ± 3.4	62.8 ± 2.7	0.71
Sex			
Male	11 (61.1%)	15 (88.2%)	
Female	7 (38.9%)	2 (11.8%)	
Admission weight (kg)	70.9 ± 3.0	73.8 ± 4.4	0.58
Nutritition status			
Mid-arm circumference (mm)	272.0 ± 9.4	275.8 ± 8.3	0.77
Triceps skinfold (mm)	15.7 ± 1.8	13.7 ± 1.4	0.39
Creatinine height index	72.6 ± 6.2	71.4 ± 4.3	0.88
Preoperation status			
Albumin (g/dL)	3.63 ± 0.18	3.59 ± 0.16	0.87
Prealbumin (mg/dL)	18.05 ± 2.23	14.59 ± 1.36	0.20
Transferrin (mg/dL)	208.4 ± 15.1	212.7 ± 11.8	0.82
APACHE II score	7.92 ± 0.85	7.73 ± 0.86	0.88
Type of operation			
Esophagogastrectomy	3	10	
Gastrectomy (total or subtotal)	2	0	
Whipple procedure	9	4	
Bile duct resection	2	1	
Other	2	2	
Type of feeding			
Jejunostomy	17	17	
Nasoduodenal	1	0	

FOSL-HN = fish oil/MCT structured lipid formula.
* Values are mean ± SEM.

There were no significant differences between groups in terms of baseline nutritional status based on admission body weight; preoperative serum albumin levels, prealbumin levels, and transferrin levels; anthropometric measurements (mid-arm circumference, triceps skin fold); and creatinine height index. Twelve of 25 patients in each group had a mid-arm muscle circumference less than the tenth percentile, reflecting moderate to severe protein-calorie malnutrition. The type of operations performed were similar between groups except for 9 of 18 patients who underwent Whipple procedures in the O-HN group and 10 of 17 patients who underwent esophagogastrectomies in the FOSL-HN group. Although both operations are severe, injury severity as quantified by APACHE II score was similar between the two groups.

Nutritional Intake Parameters

All patients except one in the O-HN group had jejunostomies placed during surgery. The one exception was

Table 3. AVERAGE DAILY ENTERAL AND PARENTERAL INTAKES*

Parameter	Treatment		p
	O-HN (n = 18)	FOSL-HN (n = 17)	
Enteral formula			
Calories (kcal/day)	812.6 ± 55.1	936.5 ± 67.9	0.16
Lipid (g/day)	29.82 ± 2.02	34.81 ± 2.52	0.13
ΣEPA (g/day)	0	3.27 ± 0.22	
ΣDHA (g/day)	0	1.48 ± 0.10	
Protein (g/day)	35.41 ± 2.40	42.32 ± 3.07	0.08
TPN			
Calories (kcal/day)	161.6 ± 62.5	44.0 ± 33.7	0.11
Lipid (g/day)	0.32 ± 0.32	0	
Protein (g/day)	14.13 ± 5.29	3.98 ± 2.90	0.11
Total			
Calories (kcal/day)	1049.6 ± 78.0	1102.9 ± 78.7	0.63
Lipid (g/day)	30.14 ± 2.03	34.81 ± 2.52	0.16
Protein (g/day)	52.27 ± 5.42	50.69 ± 4.45	0.82

FOSL-HN = fish oil/MCT structured lipid formula; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; TPN = total parenteral nutrition.
* Values are mean ± SEM.

nasoduodenally fed for the study period. On review of eligibility criteria, patients in each group were subdivided into those who were able to reach a tube feeding rate of more than 40 mL/hr (18 in the O-HN group *vs.* 17 in the FOSL-HN group) and those who remained at an infusion rate of less than 40 mL/hr (7 patients in the O-HN group compared with 8 patients in the FOSL-HN group). No patients were dropped because of safety concerns or adverse experiences related to either formula. Conclusions from this study are based on patients who met all eligibility criteria and achieved an infusion rate of more than 40 mL/hr.

Analyses of the enteral feeding parameters indicated that no significant differences existed between groups with respect to volume of study formula delivered. This allowed for similar daily intakes of calories, lipids, and protein (Table 3). The average daily calorie and protein intake supplied by total parenteral nutrition (TPN) was slightly higher for the O-HN group compared with the FOSL-HN group ($p = 0.11$). This difference was due to the fact that more patients in the O-HN group (7/18) required TPN during the course of the study compared with the FOSL-HN group (2/17; $p = 0.07$). The overall nutrition intake (enteral and parenteral) was very similar and not statistically different between the groups for daily intakes of total calories, lipids, and protein. The amount of oral intake, in terms of calories, protein, and nitrogen consumed by the patients in both the O-HN and FOSL-HN groups, was not significant and did not affect enteral feeding analyses. Patients receiving more than 40 mL/hr of FOSL-HN received a moderate daily intake of 3.27 ± 0.22 g of eicosapentaenoic acid and 1.48 ± 0.10 g of docosahexaenoic acid.

Safety and Tolerance Parameters

Safety and tolerance issues pertaining to the feeding of FOSL-HN were assessed by measurements of serum chemistries, serum electrolytes, hematology (Table 4), blood coagulation parameters, urinalysis, formula tolerance and gastrointestinal complications (Table 5), and nitrogen balance.

Serum Chemistries and Electrolytes

At baseline (day 0), the O-HN and FOSL-HN groups had similar mean values for serum albumin, blood urea nitrogen, creatinine, glucose, prealbumin, and transferrin levels. After 7 days of feeding, similar changes were observed for these parameters in both groups, with no statistically significant differences noted (data not shown).

There were no significant differences at either day 0 or day 7 between the groups for serum calcium, potassium, chloride, magnesium, and sodium. There were no clinically significant changes after 7 days of feeding, with all electrolytes remaining within or close to the normal range (data not shown).

Hematology and Blood Coagulation Parameters

Hematologic parameters measured were hemoglobin, hematocrit, erythrocyte and leukocyte count, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration (Table 4). No statistically significant differences on day 0 or day 7 were observed for erythrocyte count, leukocyte count, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Statistically significant differences at day 0 and day 7 were found with measurements of hemoglobin and hematocrit. A statistical difference was noted because the variability of the tests between patients was very small. These differences were not viewed as clinically significant because the changes were similar for both groups and remained either within or close to the normal range. There were no clinically significant changes after 7 days of feeding, with all hematologic parameters remaining within or close to the normal range.

There was no significant difference between the diets in platelet aggregation using either adenosine diphosphate or epinephrine (data not shown). There were increases in platelet aggregation in response to adenosine

Table 4. HEMATOLOGY DATA*

Parameter†	Day	Treatment O-HN (n = 18)	Treatment FOSL-HN (n = 17)	p
Hemoglobin (g/dL) [12–18]	0	12.01 ± 0.51	13.54 ± 0.41	0.03
	7	10.61 ± 0.34	11.62 ± 0.29	0.03
Hematocrit (%) [36–51]	0	35.48 ± 1.48	39.66 ± 1.16	0.04
	7	31.46 ± 0.97	34.11 ± 0.91	0.05
RBC (10^6/mm^3) [3.8–5.7]	0	4.12 ± 0.21	4.22 ± 0.14	0.72
	7	3.55 ± 0.12	3.76 ± 0.10	0.20
WBC (10^3/mm^3) [4–10]	0	8.14 ± 0.51	9.46 ± 1.00	0.24
	7	11.26 ± 0.60	13.64 ± 1.78	0.20
MCV (μm^{-3}) [28–34]	0	88.69 ± 2.03	91.88 ± 1.22	0.20
	7	88.83 ± 1.71	90.84 ± 1.06	0.33
MCH (UUG) [28–34]	0	30.21 ± 0.80	31.38 ± 0.48	0.22
	7	29.96 ± 0.70	31.00 ± 0.43	0.22
MCHC (%) [32–36.5]	0	33.97 ± 0.18	34.12 ± 0.16	0.56
	7	33.82 ± 0.18	34.08 ± 0.18	0.30

FOSL-HN = fish oil/MCT structured lipid formula; RBC = red blood cells; WBC = white blood cells; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration.
* Values are mean ± SEM.
† Values in brackets indicate the normal range.

diphosphate and collagen postoperatively in the O-HN and FOSL-HN groups. These changes were viewed as reflecting the effect of injury. At baseline (day 0), the O-HN and FOSL-HN groups had similar mean values for platelet count, prothrombin time, and partial thromboplastin time. After 7 days of feeding, similar changes within the normal range were observed for these parameters in both groups, with no statistically significant differences.

Urinalysis

Twenty-four hour urine volumes were collected at baseline, and on study days 5, 6, and 7 (data not shown). The total daily volume of urine output was not significantly different between groups on day 0 or day 7. In addition, pooled urine volumes for study days 5 through 7 were not different between the O-HN and FOSL-HN groups. Twenty-four hour urinary excretion of calcium,

Table 5. FORMULA TOLERANCE AND GASTROINTESTINAL COMPLICATION*†

Parameter‡	Treatment O-HN (N = 18)	Treatment FOSL-HN (n = 17)	p
Serum triglycerides (mg/dL) [50–181]			
Day 0	189.5 ± 21.0	155.1 ± 22.2	0.27
Day 7	177.8 ± 19.2 (−6.1%)	128.6 ± 23.4 (−17.1%)	0.11
Gastrointestinal functions			
Total patients with GI complications	15/18	9/17	0.05
Cramping	3	1	
Diarrhea	6	5	
Distention	6	2	
Nausea/vomiting	9	5	
No. of days with complications	39	23 (−40%)	0.036
No. of actual reported complications	54	27 (−50%)	0.004

FOSL-HN = fish oil/MCT structured lipid formula.
* Values are mean ± SEM.
† Values in parentheses indicate the percent change of the mean day 7 value from the mean baseline (day 0) value.
‡ Values in brackets indicate the normal range.

chloride, magnesium, and sodium was similar for both groups on day 0 and day 7. Daily urinary creatinine and potassium excretion levels were similar between groups on day 0, but were significantly higher on day 7 for patients fed FOSL-HN compared with those receiving O-HN ($p = 0.01$).

Formula Tolerance and Gastrointestinal Complications

One assessment of formula tolerance is to measure the ability of patients to clear lipids that were infused continuously on a 24-hour basis, from their circulation. Therefore, an analysis of serum triglycerides on day 0 and after 7 days of feeding was undertaken. Day 0 serum triglyceride values (Table 5) were not statistically different between the O-HN and FOSL-HN groups. Serum triglycerides on day 7 decreased by 17.1% in patients fed FOSL-HN compared with a 6.1% decrease in patients receiving O-HN.

Eighty-three percent (15/18) of the patients receiving O-HN experienced gastrointestinal complications (Table 5) compared with 53% (9/17) in the FOSL-HN group ($p = 0.053$). Increases in the number of patients reporting cramping, diarrhea, distention, and nausea/vomiting accounted for this difference. There was a 40% reduction in the total number of days with reported gastrointestinal complications (39 *vs.* 23; $p = 0.036$) and a 50% reduction in the total number of actual reported gastrointestinal complications (54 *vs.* 27; $p = 0.004$) for patients fed FOSL-HN *versus* O-HN. The incidence of mechanical complications was similar for both diets. There were two incidents of small bowel ileus and one incident of biliary leakage in the O-HN group compared with two incidents of anastomotic leakage in the FOSL-HN group.

Nitrogen Balance

Nitrogen balance (apparent and calculated) for both groups was not different on day 0 (data not shown). These values are difficult to interpret, given the difference in immediate postsurgical condition and variation in feeding schedules. Therefore, to obtain a better reflection of nitrogen excretion in critically ill patients, nitrogen balance calculations (apparent and calculated) were made from analyses of urine obtained on study days 5 through 7 (pooled value for days 5–7). There was no significant difference between the two diets with respect to pooled total nitrogen intake, total urinary nitrogen, and total urea nitrogen outputs. Calculated nitrogen balance (total nitrogen intake − [urinary urea nitrogen + 4 g nitrogen]) and apparent nitrogen balance (total nitrogen intake − total urinary nitrogen) in patients receiving either O-HN or FOSL-HN were not different between groups for pooled study days 5 through 7. Apparent and calculated nitrogen balances were negative for both groups on day 0, but improved substantially to closely reflect zero nitrogen balance on study days 5 through 7.

Metabolic Efficacy and Outcome Parameters

Metabolic efficacy and outcome parameters were assessed by measurements of liver function (Table 6), renal function (Table 7), urinary prostaglandins (Table 8), plasma prostaglandins (Table 9), plasma triglyceride fatty acid profile (Table 10), plasma phospholipid fatty acid profile (Table 11), erythrocyte membrane fatty acid profile (Table 12), and patient outcome data (Table 13).

Liver Function Data

Table 6 lists liver function data on day 0 and day 7 for patients fed either O-HN or FOSL-HN. Measurements of alkaline phosphatase, AST, ALT, direct bilirubin levels, and total bilirubin levels were elevated above the normal range in both groups on day 0, but were not significantly different between the diets. After 7 days of enteral nutrition, patients in the O-HN group showed a small decrease in alkaline phosphatase and AST levels, and an increase in ALT measurements. Patients that were fed FOSL-HN, however, showed substantial reductions in alkaline phosphatase, AST, and ALT (−36.6%, −14.1%, and −23.1%, respectively) levels, allowing for the elevated baseline liver enzymes to return toward their normal range. Patients given either diet showed substantial decreases in direct and total bilirubin measurements, because of surgical relief of biliary obstruction, which were not statistically different between the groups.

Renal Function Data

Renal function was assessed by calculating creatinine and urea clearance based on 24-hour measurements of urine volume, urinary creatinine, and blood urea nitrogen (Table 7). Creatinine clearance was calculated using the following equation: 24-hour urine volume (mL) × urinary creatinine (mg)/serum creatinine (mg %) × 100. Urea clearance was calculated by the following equation: 24-hour urine volume (mL) × urinary urea nitrogen (mg)/(blood urea nitrogen (mg %) × 100. There were no significant differences between the two groups in 24-hour urine volume collected on either day 0 or day 7. Urea and creatinine clearance was calculated on day 7, rather than on pooled days 5 through 7, because serum measurements of blood urea nitrogen and creatinine were obtained only on day 7. Renal function declined in patients fed O-HN, as evidenced by a 12.9% reduction in creatinine clearance, a 14.3% decline in urea clearance, and an overall 13.3% reduction for the mean urea and

Table 6. LIVER FUNCTION DATA*†

Parameter‡	Day	Treatment O-HN (n = 18)	Treatment FOSL-HN (n = 17)	p
Alkaline phosphate (mIU/mL) [16–106]	0	202.6 ± 54.7	213.4 ± 52.0	0.89
	7	185.3 ± 45.1 (−8.6%)	135.4 ± 23.2 (−36.6%)	0.34
ALT (mIU/mL) [0–35]	0	73.3 ± 21.3	59.0 ± 14.1	0.58
	7	81.4 ± 14.6 (+11.0%)	50.7 ± 7.1 (−14.1%)	0.07
AST (mIU/mL) [10–35]	0	54.6 ± 12.6	49.9 ± 9.7	0.77
	7	53.9 ± 9.7 (−1.3%)	38.4 ± 3.6	0.15
Bilirubin (mg/dL)				
Direct [0–0.8]	0	4.36 ± 1.72	2.07 ± 1.15	0.27
	7	1.48 ± 0.59 (−66.0%)	1.02 ± 0.48 (−50.5%)	0.55
Total [0.2–1.2]	0	4.52 ± 1.61	2.84 ± 1.45	0.44
	7	2.30 ± 0.72 (−49.1%)	1.46 ± 0.55 (−48.3%)	0.37

FOSL-HN = fish oil/MCT structured lipid formula, ALT = alanine aminotransferase; AST = aspartate aminotransferase.
* Values are mean ± SEM.
† Values in parentheses indicate the percent change of the mean day 7 value from the mean baseline (day 0) value.
‡ Values in brackets indicate the normal range.

creatinine clearance. After 7 days of enteral nutrition, patients fed FOSL-HN demonstrated a considerable increase in creatinine (+28.9%, p = 0.07) and urea (+15.5%, p = 0.11) clearances, as well as the mean of urea and creatinine clearances (+ 24.8%, p = 0.07) compared with patients receiving O-HN.

Urinary and Plasma Prostaglandins

Urinary (Table 8) and plasma (Table 9) prostaglandins measured were bicyclo-PGE (cyclic derivative of 13, 14-dihydro-15-keto-PGE), 6-keto-$PGF_{1\alpha}$ (stable metabolite of prostacyclin I_2), and TXB_2 (stable metabolite of thromboxane A_2). Plasma levels of bicyclo E, 6-keto-$PGF_{1\alpha}$, TXB_2, and the ratio of TXB_2/6-keto-$PGF_{1\alpha}$ were not significantly different between patients fed either O-HN or FOSL-HN at baseline (day 0) and on day 7. Twenty-four hour urinary levels of the aforementioned prostaglandins were not different on day 0, but did show substantial changes between the two diets after 7 days of enteral feeding. Patients fed FOSL-HN showed a 16.4% increase in 6-keto-$PGF_{1\alpha}$ and a 21.7% reduction in TXB_2, whereas patients fed O-HN showed a 46.0% reduction in 6-keto-$PGF_{1\alpha}$ and a 26.1% reduction in TXB_2. These results were reflected in opposite changes in the ratio of TXB_2/6-keto-$PGF_{1\alpha}$; a 49.5% increase for patients fed O-HN and a 61.1% decrease for those fed FOSL-HN (p = 0.06). No significant differences were observed between the two groups for 24-hour urinary output of bicyclo E for either day 0 or day 7.

Plasma Triglyceride Fatty Acid Profile

The fatty acid composition of plasma triglycerides is outlined in Table 10. As expected, modulation of plasma triglyceride fatty acids by enteral feeding tended to reflect the fatty acid composition of the enteral formulations. There were no significant differences in the levels of 18:2n6, 20:4n6, and total n-6 fatty acids after 7 days on either O-HN or FOSL-HN diets. Although the level of 18:3n3 on day 7 was not significantly different between the two diet groups, a significant difference at baseline (day 0) did exist. Thus, the change from day 0 to day 7 reflected an increase in 18:3n3 for the FOSL-HN group and a reduction from baseline for the O-HN group. Significant increases in 20:5n3, 22:5n3, 22:6n3, and total n-3 fatty acids and significant decreases in 18:1n9 and total n-9 fatty acids were observed in patients fed FOSL-HN compared with those fed O-HN. These changes in

Table 7. RENAL FUNCTION DATA*†

Parameter	Treatment		p
	O-HN (n = 18)	FOSL-HN (n = 17)	
Urine volume (mL/24 hr)			
Day 0	1656 ± 218	1566 ± 257	0.79
Day 7	1002 ± 230	1204 ± 146	0.46
Urinary creatinine (mg/24 hr)			
Day 0	952 ± 128	955 ± 75	0.99
Day 7	658 ± 97	1043 ± 107	0.01
	(−30.9%)	(+9.3%)	
Creatinine clearance (mL/min)			
Day 0	73.53 ± 8.90	70.56 ± 5.38	0.78
Day 7	64.04 ± 11.36	90.93 ± 9.01	0.07
	(−12.9%)	(+28.9%)	
Urea clearance (mL/min)			
Day 0	29.43 ± 3.37	31.42 ± 2.80	0.66
Day 7	25.21 ± 5.48	36.30 ± 4.02	0.11
	(−14.3%)	(+15.5%)	
Urea and creatinine clearance (mL/min)			
Day 0	51.48 ± 5.76	50.99 ± 3.79	0.95
Day 7	44.63 ± 8.05	63.62 ± 5.87	0.07
	(−13.3%)	(+24.8%)	

FOSL-HN = fish oil/MCT structured lipid formula.
* Values are mean ± SEM.
† Values in parentheses indicate the percent change of the mean day 7 value from the mean baseline (day 0) value.

plasma triglyceride fatty acids resulted in an approximate 64% reduction ($p < 0.001$) in the n-6/n-3 ratio via a significant increase ($p < 0.001$) in the total n-3 fatty acids in patients fed FOSL-HN. In addition, the ratio of 20:5n3/20:4n6 increased substantially from baseline (day 0) to day 7 in the FOSL-HN group.

Table 8. URINARY PROSTAGLANDINS*†

Parameter	Treatment		p
	O-HN (n = 18)	FOSL-HN (n = 17)	
Urinary bicyclo E (ng/24 hr)			
Day 0	1950 ± 568	1214 ± 323	0.31
Day 7	974 ± 214	867 ± 147	0.67
Urinary 6-keto-$PGF_{1\alpha}$ (ng/24 hr)			
Day 0	9451 ± 1675	7125 ± 1884	0.37
Day 7	5108 ± 1942	8293 ± 1519	0.20
	(−46.0%)	(+16.4%)	
Urinary thromboxane B_2 (ng/24 hr)			
Day 0	1646 ± 419	1044 ± 264	0.27
Day 7	1217 ± 289	818 ± 112	0.19
	(−26.1%)	(−21.7%)	
Urinary thromboxane B_2/6-keto-$PGF_{1\alpha}$			
Day 0	0.24 ± 0.05	0.42 ± 0.19	0.30
Day 7	0.35 ± 0.10	0.16 ± 0.04	0.06
	(+49.5%)	(−61.5%)	

FOSL-HN = fish oil/MCT structured lipid formula.
* Values are mean ± SEM.
† Values in parentheses indicate the percent change of the mean day 7 value from the mean baseline (day 0) value.

Table 9. PLASMA PROSTAGLANDINS*

Parameter	Treatment		p
	O-HN (n = 18)	FOSL-HN (n = 17)	
Plasma bicyclo E (pg/mL)			
Day 0	98.4 ± 9.7	94.4 ± 8.2	0.76
Day 7	85.6 ± 10.2	87.7 ± 7.2	0.87
Plasma 6-keto-$PGF_{1\alpha}$ (pg/mL)			
Day 0	123.3 ± 24.3	146.6 ± 37.3	0.60
Day 7	123.6 ± 28.4	94.3 ± 9.8	0.35
Plasma thromboxane B_2 (pg/mL)			
Day 0	367.9 ± 59.6	254.7 ± 39.9	0.13
Day 7	257.6 ± 67.1	269.7 ± 56.1	0.89
Plasma thromboxane B_2/6-keto-$PGF_{1\alpha}$			
Day 0	4.04 ± 0.83	2.35 ± 0.44	0.09
Day 7	3.02 ± 1.14	2.81 ± 0.40	0.87

FOSL-HN = fish oil/MCT structured lipid formula.
* Values are mean ± SEM.

Plasma Phospholipid and Erythrocyte Membrane Fatty Acid Profiles

The fatty acid composition of plasma phospholipids is outlined in Table 11, and that of erythrocyte membranes is outlined in Table 12. Incorporation of specific fatty acids into the phospholipids of plasma and erythrocyte membranes occurred in patients fed the FOSL-HN diet for 7 days. There were small, insignificant changes in the

Table 10. PLASMA TRIGLYCERIDE FATTY ACID PROFILE*

Fatty Acid	Day	% of Total Fatty Acids		p
		O-HN (n = 18)	FOSL-HN (n = 17)	
Oleic [18:1n9]	0	35.7 ± 1.4	37.8 ± 2.4	0.44
	7	36.0 ± 1.2	28.3 ± 3.0	0.02
Linoleic [18:2n6]	0	23.2 ± 1.6	21.4 ± 1.4	0.41
	7	21.8 ± 1.0	22.1 ± 3.1	0.92
Arachidonic [20:4n6]	0	1.95 ± 0.20	2.15 ± 0.30	0.58
	7	1.66 ± 0.16	2.48 ± 0.61	0.19
α-Linolenic [18:3n3]	0	1.01 ± 0.18	0.53 ± 0.14	0.05
	7	0.72 ± 0.09	0.69 ± 0.14	0.86
Eicosapentaenoic [20:5n3]	0	0.18 ± 0.05	0.12 ± 0.05	0.42
	7	0.18 ± 0.09	5.50 ± 1.17	0.00
Docosapentaenoic [22:5n3]	0	0.26 ± 0.05	0.12 ± 0.04	0.05
	7	0.18 ± 0.05	0.79 ± 0.14	0.00
Docosahexaenoic [22:6n3]	0	0.90 ± 0.36	0.37 ± 0.11	0.18
	7	0.34 ± 0.07	2.03 ± 0.41	0.00
Total n-3	0	2.35 ± 0.15	1.14 ± 0.27	0.05
	7	1.42 ± 0.18	9.01 ± 1.58	0.00
Total n-6	0	25.66 ± 1.63	24.19 ± 1.60	0.53
	7	23.90 ± 1.09	25.39 ± 3.06	0.64
Total n-9	0	35.96 ± 1.47	38.49 ± 2.18	0.34
	7	36.26 ± 1.18	28.92 ± 2.97	0.03
n-6/n-3 ratio	0	13.95 ± 1.56	14.31 ± 2.54	0.90
	7	14.83 ± 3.98	5.20 ± 1.30	0.02
[20:5n3]/[20:4n6]	0	0.11 ± 0.03	0.09 ± 0.04	0.76
	7	0.14 ± 0.06	3.37 ± 2.70	0.43

FOSL-HN = fish oil/MCT structured lipid formula.
* Values are mean ± SEM.

Table 11. PLASMA PHOSPHOLIPID FATTY ACID PROFILE*

Fatty Acid	Day	% of Total Fatty Acids		p
		O-HN (n = 18)	FOSL-HN (n = 17)	
Oleic [18:1n9]	0	11.1 ± 0.8	10.9 ± 0.5	0.87
	7	9.9 ± 0.5	10.0 ± 0.6	0.95
Linoleic [18:2n6]	0	21.4 ± 0.8	20.1 ± 0.5	0.19
	7	21.4 ± 1.1	14.1 ± 0.9	0.00
Arachidonic [20:4n6]	0	9.8 ± 0.5	11.4 ± 0.7	0.08
	7	8.2 ± 0.3	8.7 ± 0.5	0.40
α-Linolenic [18:3n3]	0	0.09 ± 0.02	0.07 ± 0.03	0.53
	7	0.09 ± 0.02	0.11 ± 0.04	0.63
Eicosapentaenoic [20:5n3]	0	0.76 ± 0.14	0.60 ± 0.15	0.44
	7	0.57 ± 0.08	11.33 ± 1.37	0.00
Docosapentaenoic [22:5n3]	0	0.86 ± 0.08	0.70 ± 0.10	0.21
	7	0.68 ± 0.09	1.03 ± 0.07	0.004
Docosahexaenoic [22:6n3]	0	3.56 ± 0.34	3.10 ± 0.23	0.28
	7	5.73 ± 2.80	3.62 ± 0.22	0.47
Total n-3	0	5.27 ± 0.44	4.47 ± 0.36	0.17
	7	7.07 ± 2.79	16.09 ± 1.58	0.01
Total n-6	0	34.0 ± 0.8	34.4 ± 1.0	0.71
	7	32.9 ± 1.2	25.0 ± 0.9	0.00
Total n-9	0	12.5 ± 0.8	12.4 ± 0.5	0.92
	7	11.3 ± 0.4	11.8 ± 0.5	0.52
n-6/n-3 ratio	0	7.32 ± 0.78	8.65 ± 0.81	0.25
	7	8.98 ± 0.51	2.37 ± 0.61	0.00
[20:5n3]/[20:4n6]	0	0.08 ± 0.02	0.06 ± 0.02	0.26
	7	0.07 ± 0.01	1.32 ± 0.17	0.00

FOSL-HN = fish oil/MCT structured lipid formula.
* Values are mean ± SEM.

levels of 18:1n9, 18:3n3, 20:4n6, 22:6n3, and n-9 fatty acids after 7 days in plasma phospholipids of the patients receiving either O-HN or FOSL-HN diets. Significant increases in 20:5n3 (Fig. 2), 22:5n3, and total n-3 fatty acids and significant decreases in 18:2n6 and total n-6 fatty acids were observed in the plasma phospholipids of the patients fed FOSL-HN compared with those fed O-HN. Similar changes were observed in erythrocyte membrane fatty acid profile, except that total n-6 fatty acids did not show significant changes. These changes in plasma phospholipid and erythrocyte membrane fatty acids resulted in an approximate 60% to 70% reduction ($p < 0.001$) in the n-6/n-3 ratio via a significant increase ($p < 0.001$) in the total n-3 fatty acids in patients fed FOSL-HN. In addition, the 20:5n3/20:4n6 ratio (Fig. 3) significantly increased in both plasma phospholipid and erythrocyte membranes from the baseline (day 0) to day 7 in the FOSL-HN group.

Patient Outcome Data

The patient outcome data are summarized in Table 13. Although this study was not designed as an outcome study, the following variables were compiled to assess the effects of the two dietary treatments: total number of infections, total number of positive cultures, total number of days in the hospital, total number of patients and days on TPN, and the incidence of mortality. Postoperative complications were classified as infectious (pneumonia, wound, abdominal, urinary, or systemic infection) complications. There was no statistical difference in the number of patients with any infection in each group; however, there were approximately 50% reductions in the total number of infections in patients fed FOSL-HN compared with those fed O-HN. In addition, the number of infected patients with more than one infection was substantially higher in patients receiving O-HN (5/7) compared with those fed FOSL-HN (1/6) ($p = 0.037$), as was the number of patients with more than one infection (5/18 *vs.* 1/17; $p = 0.090$). The number of patients requiring total parenteral nutrition along with their enteral nutrition was higher for the O-HN group (7/18) than the FOSL-HN group (2/17). This increase was reflected in a greater than twofold increase in the total number of days patients fed O-HN received TPN compared with the FOSL-HN group (29 and 11 days, respectively; $p = 0.004$). The average number of days in the hospital was similar for both groups.

Table 12. RED BLOOD CELL MEMBRANE FATTY ACID PROFILE*

Fatty Acid	Day	% of Total Fatty Acids O-HN (n = 18)	FOSL-HN (n = 17)	p
Oleic [18:1n9]	0	13.8 ± 0.9	14.8 ± 0.9	0.46
	7	14.9 ± 0.6	13.3 ± 0.7	0.09
Linoleic [18:2n6]	0	11.1 ± 1.0	9.9 ± 0.9	0.36
	7	11.8 ± 0.6	9.1 ± 0.6	0.003
Arachidonic [20:4n6]	0	11.3 ± 1.3	10.0 ± 1.3	0.49
	7	12.2 ± 0.9	11.4 ± 1.0	0.57
α-Linolenic [18:3n3]	0	0.01 ± 0.01	0.34 ± 0.22	0.14
	7	0.13 ± 0.12	0.01 ± 0.01	0.35
Eicosapentaenoic [20:5n3]	0	0.42 ± 0.11	0.31 ± 0.12	0.49
	7	0.40 ± 0.11	2.59 ± 0.39	0.00
Docosapentaenoic [22:5n3]	0	1.55 ± 0.29	1.45 ± 0.26	0.78
	7	1.86 ± 0.19	2.75 ± 0.73	0.23
Docosahexaenoic [22:6n3]	0	3.44 ± 0.45	2.52 ± 0.39	0.13
	7	3.41 ± 0.43	3.29 ± 0.43	0.85
Total n-3	0	5.43 ± 0.78	4.61 ± 0.71	0.44
	7	5.78 ± 0.66	8.64 ± 0.78	0.01
Total n-6	0	24.7 ± 1.7	22.4 ± 1.8	0.35
	7	25.7 ± 1.3	22.7 ± 1.3	0.11
Total n-9	0	16.7 ± 1.2	17.7 ± 1.2	0.56
	7	17.8 ± 0.8	15.9 ± 0.8	0.09
n-6/n-3 ratio	0	4.88 ± 0.56	7.96 ± 1.99	0.16
	7	5.71 ± 1.09	3.17 ± 0.43	0.04
[20:5n3]/[20:4n6]	0	0.03 ± 0.01	0.08 ± 0.06	0.44
	7	0.03 ± 0.01	0.21 ± 0.03	0.00

FOSL-HN = fish oil/MCT structured lipid formula.
* Values are mean ± SEM.

Table 13. SUMMARY OF PATIENT OUTCOME DATA

Parameter	Treatment O-HN	FOSL-HN	p
Total no. of infections	13	7	
Pneumonia	2	2	
Line sepsis	1	0	
Intra-abdominal sepsis	0	1	
Wound infection	3	1	
Intra-abdominal infection	4	2	
Urinary tract infection	3	1	
No. of patients with any infection	7/18	6/17	
No. of infected patients with >1 infection	5/7	1/6	0.037
No. of days in hospital	19.8	20.5	
No. of days on TPN	29	11	0.004
Patients on TPN	7/18	2/17	
Mortality	1/18	0/17	

FOSL-HN = fish oil/MCT structured lipid formula; TPN = total parenteral nutrition.

DISCUSSION

This study describes for the first time the safety and tolerance of jejunal feeding of an oil blend containing a structured lipid composed of fish oil and MCT (FOSL-HN) to postsurgical patients. Both the control (O-HN) and FOSL-HN groups were very similar, as outlined by comparable demographics and APACHE II scores at study entry. Most importantly, the overall nutritional intake (enteral and parenteral) was similar and not statistically different between groups for daily intakes of total calories, lipid, and protein. This allowed for direct assessment of the metabolic effects of FOSL-HN without the confounding effect of different levels of macronutrients (*e.g.*, proteins, lipids, and calories).

It was clearly established in this trial that jejunal administration of FOSL-HN was safe (compared with feeding a standard formula, O-HN), as evidenced by similar changes observed in serum chemistries, hematology, most urinalysis parameters, and nitrogen balance after 7 days of feeding. Provision of n-3 fatty acids from fish oil has raised concerns of exacerbating blood glucose, prolonging platelet aggregation, and negatively affecting blood coagulation parameters. Daily administration of

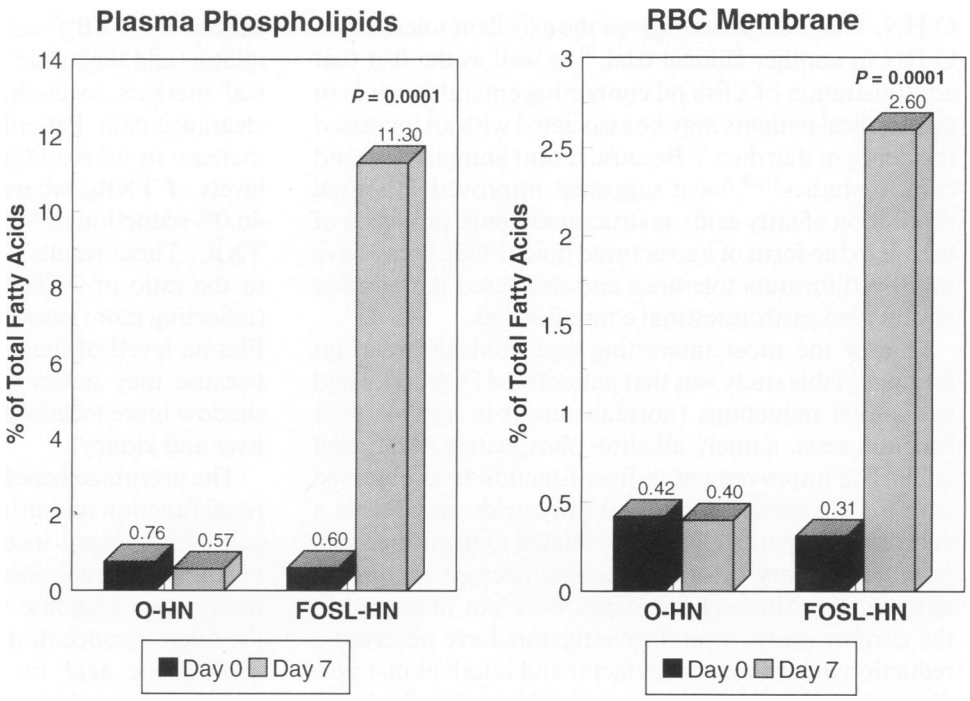

Figure 2. Eicosapentaenoic acid (20:5n3) levels in plasma phospholipids and erythroctye membrane. Values are means ± standard error of the mean for 18 patients in the Osmolite HN ([O-HN]; Ross Laboratories, Columbus, OH) group and 17 patients in the fish oil structured lipid (FOSL-HN) groups. P values on day 7 for the FOSL-HN group are significantly different *vs.* O-HN.

4.5 to 5.0 g of eicosapentaenoic acid plus docosahexaenoic acid for 7 days to patients in the FOSL-HN group produced no untoward side effects and did not raise blood glucose levels or prolong blood clotting parameters, compared with the control formula.

An additional significant finding was that patients given FOSL-HN appeared able to clear circulating lipid and experienced fewer gastrointestinal complications compared with those given O-HN. This was evidenced by a 17% reduction in serum triglycerides, a 40% reduction in the total number of days with reported gastrointestinal complications (39 *vs.* 23), and a 50% decline in the total number of actual reported gastrointestinal complications (54 *vs.* 27) for patients fed FOSL-HN *versus*

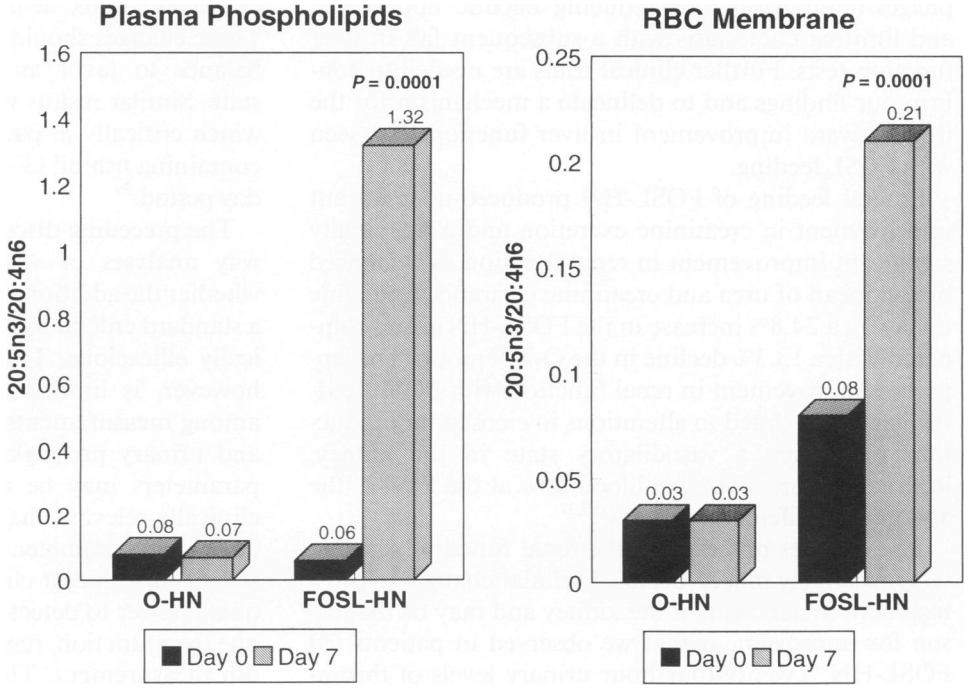

Figure 3. 20:5n3/20:4n6 (eicosapentaenoic acid/arachidonic acid) ration in plasma phospholipids and erythrocyte membrane. Values are means ± standard error of the mean for 18 patients in the Osmolite HN ([O-HN]; Ross Laboratories, Columbus, OH) and 17 patients in the fish oil structured lipid (FOSL-HN) groups. P values on day 7 for the FOSL-HN group are significantly different *vs.* O-HN.

O-HN. This is surprising, given the excellent tolerance of O-HN in another clinical trial,[10] as well as the fact that administration of a fish oil containing enteral formula to postsurgical patients may be associated with an increased incidence of diarrhea.[10] Because recent animal[20,22,28] and clinical studies[21,29] have suggested improved intestinal absorption of fatty acids as structured lipids, provision of fish oil in the form of a structured lipid (FOSL) may have improved formula tolerance and decreased the number of observed gastrointestinal complications.

One of the most interesting and clinically relevant findings of this study was that patients fed FOSL-HN had substantial reductions (normalization) in specific liver function tests, namely alkaline phosphatase, AST, and ALT. The improvement in liver function tests observed with the enteral feeding of n-3 fatty acids may reflect a decrease in hepatic lipogenesis, related to the decrease in proinflammatory cytokines (tumor necrosis factor, interleukin-1). Although cytokines were not measured in the current study, several investigators have observed a reduction in tumor necrosis factor and interleukin-1 production by monocytes in human subjects fed moderate amounts of fish oil.[30,31] Tumor necrosis factor and interleukin-1 have been shown to produce an increase in serum triglyceride levels as well as an increase in *de novo* hepatic lipogenesis.[32–34] Furthermore, n-3 fatty acids have a direct effect on reduction of hepatic triglyceride synthesis.[35] Increased hepatic lipogenesis may contribute to the "cholestatic" picture commonly encountered during the inflammatory response to injury. Feeding an enteral formula containing FOSL may reduce tumor necrosis factor and interleukin-1 production by macrophages/monocytes, thus reducing hepatic lipogenesis, and limiting cholestasis with a subsequent fall in liver function tests. Further clinical trials are needed to confirm our findings and to delineate a mechanism for the trend toward improvement in liver function tests seen with FOSL feeding.

Enteral feeding of FOSL-HN produced a significant improvement in creatinine excretion and a marginally significant improvement in renal function as evidenced by the mean of urea and creatinine clearances (baseline to day 7); a 24.8% increase in the FOSL-HN group compared with a 13.3% decline in the O-HN group. This apparent improvement in renal function with FOSL feeding has been related to alterations in eicosanoid production promoting a vasodilatory state in the kidney, leading to more favorable blood flow at the level of the afferent and efferent arterioles.[36,37]

The changes observed in the renal function parameters most likely reflect localized cellular changes in prostaglandin metabolism at the kidney and may be the reason for improvement that we observed in patients fed FOSL-HN. Twenty-four hour urinary levels of thromboxane B_2 (TXB_2; vasoconstrictor), 6-keto-$PGF_{1\alpha}$ (vasodilator) and their ratio were assessed to serve as biochemical markers to complement the urea and creatinine clearance data. Patients fed FOSL-HN showed a 16.4% increase in 6-keto-$PGF_{1\alpha}$ and a 21.7% reduction in the levels of TXB_2, whereas patients fed O-HN showed a 46.0% reduction in 6-keto-$PGF_{1\alpha}$ and a 26.1% decline in TXB_2. These results were reflected in opposite changes in the ratio of TXB_2/6-keto-$PGF_{1\alpha}$—a 49.5% increase (reflecting more vasodilation) for those given FOSL-HN. Plasma levels of these prostaglandins often are variable because they reflect one point in time and can overshadow more localized effects at specific tissue sites (*i.e.*, liver and kidney).

The presumed beneficial changes observed in liver and renal function and urinary protaglandins may be the result of significant incorporation of n-3 fatty acids into hepatic and renal phospholipids. The immune and inflammatory response to injury is influenced greatly by the relative concentrations of eicosapentaenoic acid and arachidonic acid in macrophages, lymphocytes, and polymorphonuclear cells.[38] In the clinical setting, excessive production of eicosanoids may promote the hypermetabolic inflammatory response that accompanies sepsis or injury.[3] Provision of FOSL-HN significantly increased 20:5n3, 22:5n3, and total n-3 fatty acids, and significantly decreased 18:2n6 and total n-6 fatty acids in plasma phosholipids, and erythrocyte membranes from baseline (day 0) to day 7 in the FOSL-HN group. Arachidonic acid levels in plasma triglyceride, phospholipid, and erythrocyte membranes, however, remained virtually unchanged after 7 days of feeding FOSL-HN (4.7 g eicosapentaenoic acid plus docosahexaenoic acid/day). These changes should foster a shift in the prostaglandin balance to favor an anti-inflammatory, vasodilatory state. Similar results were observed in a recent study in which critically ill patients received an enteral formula containing fish oil (3–4 g EPA plus DHA/day) for a 14-day period.[39]

The preceding discussion is based on a series of one-way analyses of variances performed to determine whether the addition of an oil blend containing FOSL to a standard enteral formula, which was safe and metabolically efficacious. This traditional analysis of the data however, is limited in showing possible interactions among measurements of liver function, renal function, and urinary prostaglandins. Interactions among these parameters may be more biologically important and clinically relevant than separate interpretations of each individual parameter. In addition, the available sample size of this modest clinical study may not provide adequate power to detect a difference between diets on any one liver function, renal function, or urinary prostaglandin measurement. Therefore, two additional statistical

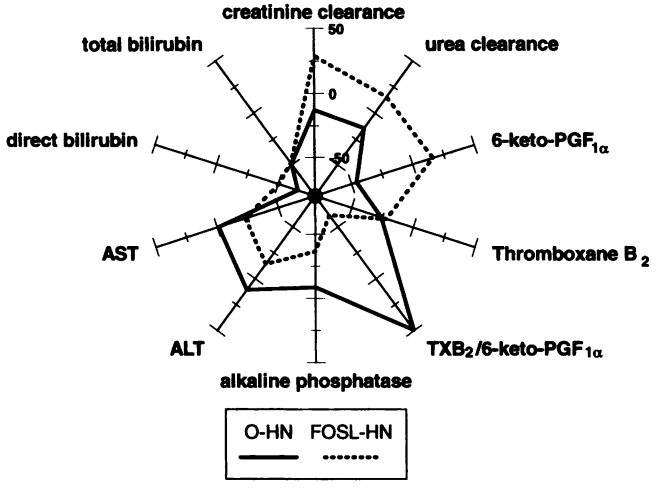

Figure 4. Relationship between changes in the ratio of urinary TXB_2/6-keto prostaglandin $F_{1\alpha}$ and liver function (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin levels), renal function (creatinine and urea clearances), urinary TXB_2 and 6-keto prostaglandin $F_{1\alpha}$. Points on figure indicate percent changes between day 0 and day 7.

analyses were performed in this study; a principal component analysis followed by multivariate analysis of variance and a stepwise regression analysis.

The principal component analysis was conducted using liver function (alkaline phosphatase, ALT, AST, direct bilirubin, and total bilirubin levels), renal function (creatinine and urea clearances) and urinary prostaglandins (TXB_2, 6-keto-$PGF_{1\alpha}$, and their ratio).

A set of four independent factors, which are composite scores that interrelate the ten variables, captured approximately 90% of the information inherent in the correlations among all ten parameters. These factors then were submitted to a multivariate analysis of variance to simultaneously compare the diet groups on the factors. The multivariate analysis of variance was statistically significant ($p = 0.0387$) primarily because of a markedly significant difference on factor 2 ($p = 0.0025$), which was only one of the four factors that was significant on univariate analysis. Figure 4 provides a graphic representation of the changes between day 0 and day 7 for factor 2. Factor 2 is a composite score developed from the principal component analysis described in the Methods section. Clearly, the FOSL-HN group has all parameters shifted to a more favorable direction (*i.e.*, lower liver enzymes and TXB_2/6-keto-$PGF_{1\alpha}$ ratio, and higher urinary clearances) overall from unfavorable positions of the O-HN group. It is these dynamic and interrelated changes among liver, renal, and prostaglandin measurements that was found to be statistically significant by the multivariate analysis of variance.

The results of the stepwise regression model are found in Table 14. More than 90% of the variance in the urinary TXB_2:6-keto-$PGF_{1\alpha}$ ratio can be explained as a function of creatinine clearance, urinary TXB_2 and 6-keto-$PGF_{1\alpha}$, alkaline phosphatase, direct bilirubin levels, and total bilirubin levels ($R^2 = 0.93$). Therefore, it appears that urinary TXB_2:6-keto-$PGF_{1\alpha}$ ratio could serve as a primary end point in future clinical studies, provided that adequate statistical power is available.

Compilation of the patient outcome data revealed no statistical difference in the number of patients with any infection or positive culture in each group. There was, however, approximately a 50% reduction in the total number of infections and positive cultures in patients fed FOSL-HN compared with those fed O-HN. This is in agreement with the recent work by Daly et al.,[10] who found a significant decrease in the incidence of infectious and wound complications in patients fed the supplemented diet, Impact, compared with those receiving the standard enteral formula, O-HN (11% *vs.* 37%, respectively; $p = 0.02$). In our study, although the number of patients experiencing infectious complications was not significantly different between groups, there were significantly fewer infected patients with more than one infection (1/6 *vs.* 5/7) and fewer patients with multiple infections in the FOSL-HN group (1/17) *versus* the O-HN group (5/18). This may suggest an improved immunocompetence in the FOSL-HN group by its ability to prevent further infection once a primary infection has occurred.

Although we did not observe any significant difference in length of stay between the two feeding groups, length

Table 14. STEPWISE REGRESSION ANALYSIS PREDICTING THROMBOXANE B_2 TO 6-KETO-$PGF_{1\alpha}$ RATIO AS A FUNCTION OF VARIOUS RENAL AND LIVER FUNCTION PARAMETERS

	df	Mean Square	F	p
ANOVA				
Regression	6	0.8361	12.31	0.0038
Error	6	0.0679		
Total	12			

Variable	Coefficient	F	p
Linear Regression Model ($R^2 = 0.925$)			
Intercept	+0.30909	8.58	0.0263
Creatinine clearance	+0.00725	6.58	0.0426
Thromboxane B_2	+0.00052	57.28	0.0003
6-Keto-$PGF_{1\alpha}$	−0.00004	33.73	0.0011
Alkaline phosphatase	−0.00083	4.14	0.0881
Direct bilirubin	−0.80588	22.43	0.0032
Total bilirubin	+0.71701	17.05	0.0062

of stay was similar to that observed in the Daly study.[10] The level of illness and subsequent care provided at Deaconess Hospital (a tertiary care referral institution) may be uniquely high, thereby preventing a further reduction in length of stay by supplemented enteral nutritional support alone. In comparison, Daly's work[10] demonstrated a 22% reduction in length of stay for the supplemented group (16 ± 5 days *vs.* 20 ± days in the standard diet group; p = 0.01). However, nutritional intakes of protein, arginine, RNA, and n-3 fatty acids were higher in the experimental group of Daly's study, which could have had a positive metabolic effect on those patients.

In many respects, the current study is similar in its experimental design and aims as three previous outcome trials.[10,40,41] One criticism of these trials, which cannot be made of this study, is that the study groups received significantly more nitrogen and other key macronutrients compared with their control groups. Thus, it is difficult to discern whether the observed beneficial effects were because of immune-enhancing nutrients administered to the study group or because of unrecognized protein malnutrition in the control group. The study described herein had appropriate controls because the FOSL-HN diet was designed nearly identical to the control diet (O-HN) in its nutrient composition except for the source of lipid. The one difference between our study and the aforementioned three outcome studies is the fact that some patients received TPN without lipids to supplement enteral intake, as deemed medically necessary. This also could be a factor in the failure to see a change in length of stay because both groups were fed the same amount of combined nutrition. The number of patients requiring TPN along with their enteral nutrition was higher with O-HN (7/18) *versus* FOSL-HN (2/17). This increase was reflected in a greater than twofold increase in the total number of days O-HN patients received TPN compared with the FOSL-HN group (29 *vs.* 11 days, respectively). Statistical analyses revealed that the inclusion of TPN did not affect the results or interpretation of study data.

CONCLUSIONS

It was clearly established in this trial that jejunal administration of FOSL-HN could be administered safely in the early postoperative period with excellent tolerance in patients with upper gastrointestinal malignancies. Fish oil structured lipid was safe, as evidenced by similar changes observed in serum chemistries, hematology, most urinalysis parameters, and nitrogen balance after 7 days of feeding compared with a standard enteral formula, O-HN. Patients fed the FOSL-HN formula experienced a 40% reduction in the total number of days with reported gastrointestinal complications (39 *vs.* 23 days; p = 0.036) and a 50% decline in the total number of actual reported gastrointestinal complications (54 *vs.* 27; p = 0.004) compared with those fed O-HN. In addition, those patients in the FOSL-HN group who required TPN received it for a significantly shorter period of time compared with those requiring TPN in the O-HN group (11 *vs.* 29 days). Daily administration of 4.5 to 5.0 g eicosapentaenoic acid plus docosahexaenoic acid for 7 days to patients in the FOSL-HN group produced no untoward side effects and did not raise blood glucose levels or prolong clotting parameters compared with the control formula.

Moreover, physiologic data suggest that the use of n-3 fatty acids in the form of a structured lipid may improve renal and liver function during the postoperative period through modulation of tissue prostaglandin levels. Assessment of patient outcome data showed a 50% reduction in the total number of infections and positive cultures in patients receiving FOSL-HN compared with those fed O-HN. Although the number of patients experiencing infectious complications was not significantly different between the two groups, there were significantly fewer infected patients with multiple infections (1/6 *vs.* 5/7) and fewer patients with multiple infections in the FOSL-HN group (1/17) as compared with the O-HN group (5/18).

The aforementioned clinical benefits were observed with a modest sample size, suggesting that an additional randomized trial with similar outcome parameters should be undertaken to fully quantify clinical benefits and to optimize nutritional support with FOSL.

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