Digestive Diseases and Sciences, Vol. 50, No. 8 (August 2005), pp. 1467–1470 (© 2005)
DOI: 10.1007/s10620-005-2863-7

Enteral Nutrition as a Primary Therapy for Intestinal Lymphangiectasia: Value of Elemental Diet and Polymeric Diet Compared with Total Parenteral Nutrition

KUNIHIKO AOYAGI, MD, MITSUO IIDA, MD, TAKAYUKI MATSUMOTO, MD, and SHOTARO SAKISAKA, MD

Intestinal lymphangiectasia (IL) is a rare disease requiring oral fat restriction. The aim of this study was to evaluate the efficacy of enteral nutrition compared to that of total parenteral nutrition (TPN). We retrospectively reviewed nine patients with IL presenting with protein-losing enteropathy. Of these, seven patients not responding to a low-fat diet were treated with elemental diet (ED), polymeric diet (PD) containing medium-chain triglycerides, or TPN. Improvement in serum total protein was observed in two of three on ED and in one of two on PD, compared with three of three on TPN. Enteric protein loss was improved in two of two on ED, one of two on PD, and two of two on TPN. Outpatients who continued to receive enteral nutrition maintained a total protein level. Enteral nutirition appears to be as effective as TPN for patients with IL, and it may provide a valid and safe alternative therapy.

KEY WORDS: intestinal lymphangiectasia; protein-losing enteropathy; nutritional therapy.

Intestinal lymphangiectasia (IL) is a congenital or acquired disorder characterized by dilated lymphatics. IL is more often complicated clinically by protein-losing enteropathy (PLE). IL has been treated with a low-fat diet (1), medium-chain triglycerides (MCTs) (2–4), and steroids (5). Restriction of fat intake is a theoretically established therapy for IL (6). Total parenteral nutrition (TPN) has also been reported to improve hypoproteinemia (7, 8). However, little has been written about the efficacy of enteral nutrition with either an elemental diet (ED) or a polymeric diet (PD), which are both chemically defined as low-fat or MCT-rich diets. We herein describe the value of enteral nutrition with ED or PD and compare it with that of TPN.

Manuscript received July 30, 2004; accepted November 9, 2004.

From the Third Department of Medicine, School of Medicine, Fukuoka University, and Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Address for reprint requests: Kunihiko Aoyagi, MD, Third Department of Medicine, School of Medicine, Fukuoka University, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan; kaoyagi@fukuoka-u.ac.jp.

MATERIALS AND METHODS

Patients. We retrospectively reviewed nine consecutive patients with PLE due to IL between 1985 and 2000. All patients were diagnosed as having IL according to endoscopic findings together with the histology of intestinal biopsy specimens, radiographic features, and increased enteric protein loss (9, 10). The enteric protein loss was evaluated using the fecal α-1-antitrypsin clearance test (11) or the ^{131}I- or ^{123}I-polyvinylpyrrolidone test (12). The clinical features are listed in Table 1. At diagnosis, a marked reduction was observed in the concentrations of serum total protein (mean, 3.7 g/dl; range, 3.0–5.0 g/dl) and albumin (mean, 2.0 g/dl; range, 1.6–3.0 g/dl) in all nine patients. Three of the five patients who underwent lymphangiography showed abnormal dilated lymphatics. Excluding two patients

TABLE 1. PATIENT CHARACTERISTICS

Age, mean (range)	44. 8 yr (16–69 yr)
Gender (no.)	
Female	5
Male	4
Serum total protein at diagnosis, mean (range)	3.7 g/dl (range, 3.0–5.0 dl)
Dilated lymphatics on endoscopic histology (no.)	
Present	9
Not present	0
Intestinal protein loss (no.)	
Present	9
Not present	0
Complications (no.)	
Pulmonary or colonic tuberculosis	2
Constrictive pericarditis	1
Churg–Strauss syndrome	1
No complications	5
Low-fat diet and/or medium-chain triglycerides (no.)	
Response	2
No response	7

who responded to a low-fat diet and/or MCTs, the remaining seven patients were treated with enteral nutrition or TPN and then analyzed.

Nutritional Therapy. As for enteral feeding, two types of liquid formula diets of known composition, which were chemically defined and nutritionally complete, were used in this study. The ED used was Elental (Ajinomoto Pharma, Tokyo), which is composed of free amino acids as the protein source, dextrin, and a very small quantity of fat (soy oil). Elental is comparable to Vivonex T.E.N. (Novartis Nutrition, Minneapolis, MN). The PD used was Besvion (Fujisawa Pharmaceutical, Osaka, Japan), which contains milk protein as the protein source and MCTs whose quantity is half that of the total fat. Besvion is similar to Lipisorb Liquid (Novartis Nutrition) in that MCTs are a major component of fat. Table 2 shows the nutrient composition of ED and PD. ED or PD was supplied orally or through a nasoduodenal tube during the daytime. Enteral feeding of ED was started at an isotonic concentration, and the concentration was increased gradually to a level of 1 kcal/ml. The patients received 40.1–42.7 kcal/kg/day as the sole nutrition. Patients on TPN received 40.5–42.4 kcal/kg/day with a protein:calorie ratio of 1:9 and were placed on complete restriction of oral fat intake. In patients treated with ED or TPN, fat was administered once weekly as a 10% solution to prevent essential fatty acid deficiency.

Determination of efficacy was assessed after 4 to 6 weeks, when the serum protein concentration reached a constant level. In six treatments, enteric protein loss was also identified.

TABLE 2. COMPOSITION AND OSMOLARITY OF NUTRITIONALLY COMPLETE LIQUID FORMULA DIETS

	Elemental diet	*Polymeric diet*
Calorie composition		
% protein	16.9	17.7
% fat (g/L)	1.5	29.9
MCTs/fat (%)	0	56
% carbohydrate	81.6	52.4
Osmolarity (mOsm/L)	838	493

Note. Each diet contains all known required minerals and vitamins. MCT, medium-chain triglycerides.

After discharge from hospital, six patients continued to receive enteral nutrition (21.2–25.3 kcal/kg/day) in addition to a low-fat diet from the outpatient department. ED or PD was taken orally two or three times a day as part of the total necessary diet.

RESULTS

Comparison of Nutritional Managements. Seven patients underwent a total of nine treatments (four received ED, two received PD, and three received TPN). Serum total protein in one patient remained unchanged with ED, but the same patient achieved a good response with PD. Another patient did not respond to PD but did respond to TPN. The remaining five patients received one treatment each (three received ED, and two received TPN).

Table 3 shows the changes in serum total protein and enteric protein loss before and after therapy. An increase in serum total protein (more than 1 g/dl) was identified in three of three on TPN, three of four patients on ED, and one of two on PD. Enteric protein loss was assessed in six of the treatments. While the presence of excessive enteric protein loss was evident in all patients on admission, normalization or improvement in enteric protein loss was observed in two of two on TPN, two of two patients on ED, and one of two on PD. These results suggest that enteral nutritions are comparable to TPN in the treatment of IL, while ED may be more effective than PD. No patients developed complications of the enteral and parenteral nutritions.

Maintenance Therapy by Supplementation with Enteral Nutrition. Figure 1 shows the serum total protein levels of six outpatients who continued to receive enteral nutrition as well as a low-fat diet. Serum total protein at hospital discharge was 5.8 ± 0.3 g/dl, while that 6 months after discharge was 5.7 ± 0.6 g/dl. Thus clinical improvement was maintained by supplementation with enteral nutrition.

TABLE 3. EFFECTS OF NUTRITIONAL MANAGEMENT ON SERUM TOTAL PROTEIN AND ENTERIC PROTEIN LOSS

	Increase in serum total protein (g/dl)				*Enteric protein loss†*			
*Therapy**	n	*<1*	*1–2*	*>2*	n	*Unchanged*	*Improved*	*Normalized*
TPN	3		1	2	2			2
ED	4	1	2	1	2		1	1
PD	2	1		1	2	1		1

*TPN, total parenteral nutrition; ED, elemental diet; PD, polymeric diet.
†Enteric protein loss was evaluated by α-1-antitrypsin clearance test (upper limit of normal range, 13 ml/day) or radiolabeled polyvinylpyrrolidone test (upper limit of normal range, 3%).

DISCUSSION

PLE includes a variety of disorders such as inflammatory bowel disease, systemic lupus erythematosus, Whipple's disease, and malignant diseases, as well as IL (8). The characteristic endoscopic and radiographic features of IL have been documented, thereby greatly facilitating an accurate diagnosis (9, 10). Steroid therapy is often useful in the treatment of PLE associated with inflammatory conditions, such as systemic lupus erythematosus (13). In contrast, the treatment of IL differs greatly from that of these other diseases.

The mechanisms for enteric protein loss in IL are not well understood, although an increase in the pressure of the lymph channels has been suggested to be a possible cause of protein loss (1, 14). Because partial block of the intestinal lymphatic system produces lymph loss into the lumen upon a high-fat diet, dietary fat restriction is considered to be the first choice of treatment in IL (6, 8, 14). In practice, reduction of the intestinal lymph flow through fat restriction has been reported (1, 2, 14). Likewise, a diet containing MCTs as a substitute for long-chain triglycerides is of benefit, because MCTs are absorbed directly into the portal vein rather than the lymphatics, thereby reducing the pressure of the lymph channels (3, 4).

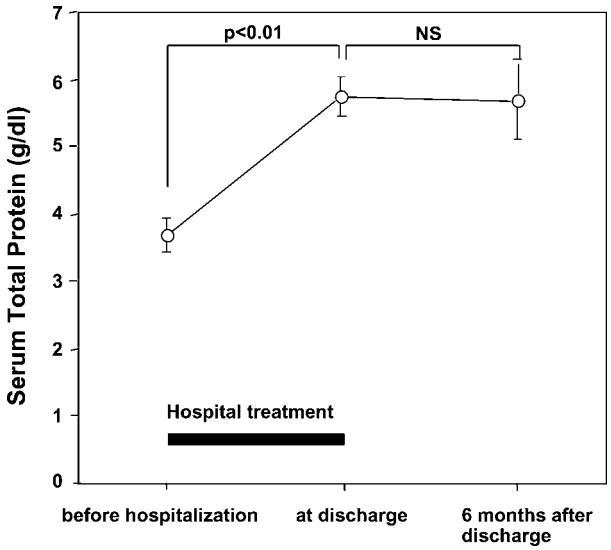

Fig 1. Effects of maintenance treatment on serum total protein level in patients with intestinal lymphangiectasia. Six patients received hospital treatment (four received elemental diet, one received polymeric diet, and one received total parenteral nutrition), followed by ambulatory treatment with enteral nutrition as a supplement to a low-fat diet (four received elemental diet, and two received polymeric diet). Serum total protein levels showed no significant change following discharge for up to 6 months. Data are shown as mean ± SE. Parameters were compared using a paired *t*-test. $*P < 0.05$. NS, not significant.

TPN has been shown to resolve protein-losing enteropathy in IL because with TPN, oral fat intake becomes zero (7, 8). Recently, chemically defined liquid formula diets such as ED and PD have been developed for widespread use (15, 16). ED contains little fat, while the PD used in the current study included MCTs whose quantity was half that of the total fat. These diets can be administered orally, or through a nasoduodenal tube when oral intake is not possible. They would seem to have an advantage over a conventional low-fat solid diet because of the smaller quantity of long-chain triglycerides. On the basis of our data, it is considered that enteral nutrition is an effective treatment in patients with IL and that ED may be more effective than PD, probably due to the difference in fat content. Because of the limited number of patients in this study it was hard to perform a detailed statistical analysis. One patient did not improve with ED but did respond to PD. This may have been because hypertonic ED induces a greater quantity of diarrhea compared with isotonic PD (17). However, a comparison between ED and PD still needs to be fully elucidated.

TPN is valuable for patients who are refractory to enteral nutrition. When enteral nutrition is not so effective, or when symptoms are severe, TPN should be given. Since TPN provides complete restriction of oral fat intake, it would seem to be a much more useful nutritional treatment for IL than enteral nutrition and/or MCTs. However, the relative merits of enteral nutrition versus TPN are its cost advantage and safety.

There has been no specific therapy for this condition, although fat restriction can successfully reduce

gastrointestinal protein loss in most patients with IL. Surgery may be successful when fibrotic entrapment of the small bowel causes partial mechanical bowel obstruction (18). Antiplasmin therapy has been applied in patients who respond poorly to other therapies (19). Alternatively, octreotide has been documented to improve protein-losing enteropathy in IL by speculative mechanisms including reduction in lymph flow and immunomodulatory action (20, 21). When patients do not respond to fat restriction, these medical therapies should be considered. However, controversy still remains over whether or not patients with IL do in fact respond to antiplasmin and octreotide (22, 23).

Following discharge with an improvement in hypoproteinemia, prevention of recurrent enteric protein loss is important for outpatients. The need for fat restriction has been described as permanent, because of frequent clinical relapse upon relaxation of the regimen (24). It is considered that, when treating outpatients with IL, enteral nutrition should be continued as long as hypoproteinemia is present.

In summary, enteral nutrition as well as TPN may be a useful therapy in patients with IL. Continuation of enteral nutrition once the serum protein level has recovered appears to be valuable in preventing relapse. Compared with TPN, ED and PD are ideal maintenance therapies because they are safer, cheaper, and more convenient to prepare at home.

ACKNOWLEDGMENTS

The English used was revised by Miss K. Miller (Royal English Language Centre, Fukuoka, Japan).

REFERENCES

1. Jeffries GH, Chapman A, Sleisenger MH: Low-fat diet in intestinal lymphangiectasia. Its effects on albumin metabolism. N Engl J Med 270:761–766, 1965
2. Yssing M, Jensen H, Jarnum S: Dietary treatment of protein-losing enteropathy. Acta Paediatr Scand 56:173–181, 1967
3. Alfano V, Tritto G, Alfonsi L, Cella A, Pasanisi F, Contaldo F: Stable reversal of pathologic signs of primitive intestinal lymphangiectasia with a hypolipidic, MCT-enriched diet. Nutrition 16:303–304, 2000
4. Amirhakimi GH, Samloff M, Bryson MF, Forbes GB: Intestinal lymphangiectasia. Metabolic studies. Am J Dis Child 117:178–185, 1969
5. Fleisher TA, Strober W, Muchmore AV, Broder S, Krawitt EL, Waldmann TA: Corticosteroid-responsive intestinal lymphangiectasia secondary to an inflammatory process. N Engl J Med 300:605–606, 1979
6. Rubin DC: Small intestine: anatomy and structural anomalies. Lymphangiectasia. *In* (ed) Textbook of Gastroenterology, 3rd ed. Yamada T, ed. Philadelphia, Lippincott Williams & Wilkins, 1999, pp 1578–1579
7. Vardy PA, Lebenthal E, Shwachman H: Intestinal lymphangiectasia: a reappraisal. Pediatrics 55:842–851, 1975
8. Goldberg RI, Calleja GA: Protein-losing gastroenteropathies. *In* Boccus Gastroenterology, 5th ed. Haubrich WS, Schaffner F, Berk JE (eds). Philadelphia, WB Saunders, 1995, pp 1072–1086
9. Aoyagi K, Iida M, Yao T, Matsui T, Okada M, Oh K, Fujishima M: Characteristic endoscopic features of intestinal lymphangiectasia: correlation with histological findings. Hepatogastroenterology 44:133–138, 1997
10. Aoyagi K, Iida M, Yao T, Matsui T, Okada M, Fujishima M: Intestinal lymphangiectasia: value of double-contrast radiographic study. Clin Radiol 49:814–819, 1994
11. Florent C, L'Hirondel C, Desmazures C, Aymes C, Bernier JJ: Intestinal clearance of alpha 1-antitrypsin. A sensitive method for the detection of protein-losing enteropathy. Gastroenterology. 81:777–780, 1981
12. Tsuchiya M, Oshio C, Asakura H, Ishii H, Aoki I, Miyairi M: Budd–Chiari syndrome associated with protein–losing enteropathy. Gastroenterology. 75:114–117, 1978
13. Edworthy SM, Fritzler MJ, Kelly JK, McHattie JD, Shaffer EA: Protein-losing enteropathy in systemic lupus erythematosus associated with intestinal lymphangiectasia. Am J Gastroenterol 85:1398–1402, 1990
14. Mistilis SP, Stephen DD, Skyring AP: Intestinal lymphangiectasia. Mechanism of enteric loss of plasma-protein and fat. Lancet 1:77–81, 1965
15. Giaffer MH, North G, Holdsworth CD: Controlled trial of polymeric versus elemental diet in treatment of active Crohn's disease. Lancet. 335(8693):816–819, 1990
16. Verma S, Brown S, Kirkwood B, Giaffer MH: Polymeric versus elemental diet as primary treatment in active Crohn's disease: a randomized, double-blind trial. Am J Gastroenterol. 95:735–739, 2000
17. Thompson JM, Brett A, Rose SJ: Dietary management of intestinal lymphangiectasia complicated by short gut syndrome. Hum Nut Appl Nutr 40:136–140, 1986
18. Rust C, Pratschke E, Hartl W, Kessler M, Weibecke B, Sauerbruch T, Paumgartner G, Beuers U: Fibrotic entrapment of the small bowel in congenital intestinal lymphangiectasia. Am J Gastroenterol 93:1980–1983, 1998
19. Mine K, Matsubayashi S, Nakai Y, Nakagawa T.: Intestinal lymphangiectasia markedly improved with antiplasmin therapy. Gastroenterology 96:1596–1599, 1989
20. Bac DJ, Van Hagen PM, Postema PT, ten Bokum AM, Zondervan PE, van Blankenstein M: Octreotide for protein–losing enteropathy with intestinal lymphangiectasia. Lancet 24(345):1639, 1995
21. Ballinger AB, Farthing MJ: Octreotide in the treatment of intestinal lymphangiectasia. Eur J Gastroenterol Hepatol 10:699–702, 1998
22. Kuroiwa G, Takayama T, Sato Y, Takahashi Y, Fujita T, Nobuoka A, Kukitsu T, Kato J, Sakamaki S, Niitsu Y: Primary intestinal lymphangiectasia successfully treated with octreotide. J Gastroenterol 36:129–132, 2001
23. MacLean JE, Cohen E, Weinstein M: Primary intestinal and thoracic lymphangiectasia: a response to antiplasmin therapy. Pediatrics 109:1177–1180, 2002
24. Tift WL, Lloyd JK: Intestinal lymphangiectasia. Long-term results with MCT diet. Arch Dis Child 50:269–276, 1975