Supplementary parenteral nutrition in patients with malignant disease

Guidelines to patient selection

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Much of the morbidity and mortality of malignant disease is due to the profound nutritional depletion caused by the disease. This is particularly true of gastrointestinal related malignancies. Recently Dudrick[1] described weight gain, increase in strength and activity, and positive nitrogen balance in patients with malignancies treated with supplementary parenteral nutrition. Schwartz et al[2] have also shown parenteral nutrition to be of significant value when combined simultaneously with chemotherapy in the treatment of patients with disseminated carcinoma. However, serious complications can occur which preclude indiscriminate application of parenteral nutrition, especially in patients weakened by malignant disease. This paper reports results of a prospective clinical study undertaken specifically to establish guidelines for the use of total or supplemental parenteral nutrition as an adjunct to the treatment of cancer patients.

Clinical material and methods

Twenty-three patients are included in the study. All patients had malignant disease and received either supplemental or total parenteral nutrition during hospitalization at the Cleveland

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Table 1. Tumor site

Site	No. patients
Colon	7
Stomach	6
Pancreas	4
Cervix	4
Ovary	1
Lung	1
Total	23

Table 2. Indications for parenteral nutrition

Indication		No. patients
Preoperative: weight loss, weakness, hypoalbuminemia		7
Postoperative complications		16
Ileus, sepsis, poor wound healing	3	
"High output" fistula and sepsis	4	
Postoperative pancreatitis	2	
"Low output" fistula	2	
Disseminated carcinoma with progressive weakness	4	
Gastric outlet obstruction	1	

Clinic or at St. Vincent Charity Hospital, Cleveland, Ohio. *Table 1* lists the patients according to site of tumor. As indications for parenteral nutrition all patients had (1) a 20% weight loss from predisease weight, with marked weakness or significant hypoalbuminemia; or (2) a prolonged postoperative course complicated by poor wound healing, wound dehiscence, or fistula formation (*Table 2*). An operative procedure confirmed the diagnosis of malignancy in all 23 patients. The seven patients selected for treatment preoperatively were given supplemental parenteral nutrition in addition to oral feedings. The 16 patients treated in the postoperative period were treated with total parenteral nutrition.

The catabolic state induced by malignant tumors, particularly gastrointestinal malignancies, is well known. It is also well known that sepsis and trauma produce significant, additional loss of nitrogen. The patients in this study were divided into four groups based on the extent of the malignancy and the degree of sepsis: Group I—nutritional depletion secondary to the tumor manifested by severe weight loss, without disseminated disease or sepsis; Group II—nutritional depletion complicated by mild to moderate sepsis; Group III—patients with severe sepsis; and Group IV—patients with disseminated malignancy.

Solutions for parenteral nutrition. Positive nitrogen and calorie balance was achieved with hypertonic parenteral solutions.[3, 4] To achieve this goal, large amounts of carbohydrate calories were given simultaneously with nitrogen to spare amino acids for utilization in protein synthesis. A ratio of 100 to 150 carbohydrate calories to 1 g nitrogen is required to achieve a positive nitrogen balance. In this study the nitrogen source was protein hydrolysate* or crystalline amino acid.† Dextrose was the sole source of carbohydrate calories. The parenteral solution formulas are listed in *Table 3*.

The schedule for administration of parenteral fluids is listed in *Table 4*. Blood glucose, serum osmolality, and electrolyte determinations were obtained daily; reductions of urine excre-

* *Hyprotigen 10%, McGaw Laboratories, Glendale, California.*

† *FreAmine 8.5%, McGaw Laboratories, Glendale, California.*

Table 3. Hyperalimentation solution

Basic solution
1. 500 cc 10% Hyprotigen (6.7 g N) or 8.5% FreAmine (6.25 g N)
2. 300 cc 50% dextrose in water
3. 40 mEq NaCl
4. 25 mEq KCl
5. Sterile H_2O to 1,000 ml

Additives
1. Salt poor albumin 12.5 g to 25 g/liter if serum albumin is less than 2.5 g/100 ml
2. Calcium 5 mEq/liter
3. Magnesium 0.5 g to 1 g/liter, added as indicated
4. Dextroferon 3 mg to 6 mg/liter as indicated
5. Vitamin B_{12} 5 mEq/liter added in cases of prolonged hyperalimentation
6. Folic acid 4 mg to 5 mg/liter
7. K_2PO_4 5 mEq to 10 mEq added only when 8.5% FreAmine is used

Table 4. Ideal schedule for delivery of parenteral solutions

Day	Nitrogen g	Carbohydrate calories	Volume infused
First to second	21	1,800	3,000 cc
Second to third	21	2,400	3,000 cc
Third to fourth	21	3,000	3,000 cc

tion were monitored every 6 hours. Most patients who had loss of protein from fistulas or severe malnutrition causing low serum proteins and hypoalbuminemia were given, in addition, serum albumin supplements intravenously. The ability of some patients to maintain serum albumin despite losses by fistulas will be discussed later. Patients usually received from 12.5 to 25 g salt-poor albumin added to each liter of parenteral fluid for 3 to 5 days.

Subclavian catheterization. An infraclavicular, subclavian approach was used in all patients, with one exception. The infraclavicular region is shaved and prepared with an iodine compound. The patient is placed in a slight Trendelenberg position to distend the subclavian veins. A local anesthetic is injected into the area of the middle third of the clavicle. A 14-gauge needle is then directed toward the suprasternal notch, hugging the underneath border of the clavicle, and slight negative pressure is kept on the syringe. The needle is never moved haphazardly once it is beneath the clavicle. If this approach fails, the needle must then be removed from beneath the clavicle, but this time it should be aimed between the two heads of the sternocleidomastoid muscle.

When the needle is in the subclavian vein, the syringe is removed and a finger is placed over the hub of the needle to prevent air embolus. An 18-gauge polyethylene catheter is inserted. The catheter is then fixed to the skin with no. 4-0 nylon suture. A topical antibiotic, usually gentamicin, is applied to the catheter, and the catheter is covered with a sterile dressing. A chest x-ray film should be obtained to check on placement of the catheter in the superior vena cava and to check for a pneumothorax.

The amount of fluid infused was related to the patient's basic maintenance requirements or cardiac status. All solutions were administered by intravenous drip; millipore filters and pump infusions were not used. The infusion was maintained at a constant rate over a 24-hour period to insure effective utilization. Blood transfusions were given only in accordance with the patient's need for blood replacement. The intravenous tubing was changed daily. The intravenous system was maintained as a closed system

to reduce the possibility of outside contamination.

Results

The usefulness of parenteral nutrition in patients with malignant disease was judged by: weight gain or loss, increase or decrease of serum albumin, glucose metabolism, healing of fistulas, improvement in general well-being, increased strength, and increased energy for activity. Nitrogen balance studies were not done in this study, but several investigators have shown weight gain to reflect a positive nitrogen balance, providing the blood urea nitrogen remains normal and water retention is not present.[5]

Weight gain and glucose metabolism. The weight response in various groups is summarized in *Table 5.* Weight gain was recorded in most of the patients in Groups I and II. This indicates the ability of most patients in Group II to overcome the increase in metabolic demand of mild to moderate sepsis. Patients from both Group I and Group II showed less weight gain and less adequate glucose metabolism with advancing age. Other investigators have noted similar limitations in parenteral nutrition with advancing age.[1] The inability of older patients to regain weight is, in part, a result of a relative glucose intolerance. The three patients in Group III, all of whom had severe sepsis, progressively lost weight despite supplementary parenteral nutrition. Hyperosmolality and glucose intolerance developed in all patients despite the addition of moderate amounts of added regular insulin. Cultures of the catheters in these patients revealed staphylococcus coagulase positive infections and candida albicans septicemia. The *Candida albicans* septicemia was associated with severe hyperosmolality and glucose intolerance.

Table 5. Weight response of Groups I through IV

Group	Change in weight (lb)	
	Range	Average
I (7 patients)	+20 to −10	+5
II (6 patients)	+20 to −7	+3
III (3 patients)	−8 to −5	−6
IV (6 patients)	+12 to −12	0

Patients in Group IV tolerated glucose loads well. However, despite this, these patients either lost weight or gained weight which was complicated by edema. Interestingly, patients with large pancreatic tumors tolerated 3,000 calories in 24 hours.

Serum albumin. Eighteen patients had hypoalbuminemia, a serum albumin of 2.5 g or less. Four patients were dropped from the study because they received parenteral nutrition for only 5 days. Of the 14 remaining patients, 12 had extra-body losses of serum protein. Most patients with extra-body losses of serum protein were given from 25 g to 75 g of salt-poor albumin per day for 3 to 5 days to try to bring the serum albumin level into the normal range. Patients who could not maintain a serum albumin between 2.5 g to 3.0 g/100 ml after 3 to 5 days of therapy were given additional supplements. Of the 14 patients with hypoalbuminemia, 8 required additional protein supplements to maintain serum albumin levels. The mean age of these eight patients was 59.1 years; the mean length of parenteral nutrition was 12.1 days. Two of the eight patients were in Group II,

three were in Group III, and the remaining three patients were in Group IV.

Six patients improved or maintained their serum albumin levels between 2.5 g and 3.0 g/100 ml without additional supplements. All but one of these six patients had extra-body losses of protein. The mean age of this group of patients was 44.8 years; the mean duration of parenteral nutrition was 22.5 days. Two of these six patients were in Group I and the remaining four were in Group II.

Fistula and wound healing. Eight patients had fistulas and one had a slowly granulating, open wound. In four of the eight patients who were receiving hyperalimentation the fistulas closed promptly. Of these four in whom the fistulas closed, only one had irradiation previously; of the four in whom the fistulas did not close, three had had irradiation previously. Wound healing problems were directly related to prior tissue irradiation and not to an inability to handle parenteral nutrition.

All patients in Group I and Group II exhibited some increase in strength, activity, and sense of well-being while receiving parenteral nutrition. Group III patients with profound sepsis were moderately to severely obtunded and difficult to evaluate. Group IV patients noted little change in well-being and most patients continued to deteriorate gradually.

Complications. Sepsis and hyperosmolality were the most frequent complications of supplementary parenteral nutrition. Catheters were cultured at least once, and often up to three times, in 19 of 23 patients. One catheter tip was positive (staphylococcus coagulase positive) in a patient with fulminating sepsis prior to the start of parenteral nutrition. Candida albicans septicemia developed in another patient. Complications are listed in *Table 6*.

Table 6. Complications of parenteral nutrition in 23 patients with malignant disease

Complications	No.
Hyperosmolality without coma	3
Catheter sepsis	1
Candida albicans septicemia	1
10% pneumothorax	1
Caval thrombosis	1

Discussion

The metabolic response of patients with malignancy to supplemental parenteral nutrition decreased progressively with increasing age. Younger patients appeared to have a better glucose tolerance, more energy reserve, and were better prepared to deal with stress. They were generally able to gain weight, increase or maintain their serum albumin levels above 2.5 g/100 ml, and increase their levels of activity. Older patients showed relative glucose intolerances, had less energy reserve, and were less prepared to deal with their catabolic states.

The addition of sepsis to malignant disease apparently represents a profound metabolic expenditure. Mild to moderate sepsis did not significantly increase this expenditure. Patients with fulminating sepsis, however, appear to be limited by a significant degree of glucose intolerance, not overcome by added insulin. The glucose intolerance was especially severe in one patient with candida albicans septicemia. Other observers have also noted the onset of glucose intolerance

with the development of candida septicemia.[6] Some investigators have related candida septicemia to prolonged use of intravenous catheterization.[7] We agree that patients with chronic sepsis are more prone to complications; adherence to strict aseptic conditions should reduce the incidence of infection secondary to parenteral nutrition.[8, 9]

Patients with widespread, disseminated malignancies did poorly on adjunctive parenteral nutrition. These patients continued to deteriorate and lose weight. With one exception, weight gain was associated with water retention. There was no increase in strength or level of activity. In some instances, it appeared that the rate of growth of metastases actually increased with improved nutrition. Animal studies have demonstrated an increase in the rate of growth of hepatic metastases when protein intake is increased. Although some investigators have observed marked improvement in patients with disseminated malignancy when chemotherapy and adjunctive parenteral nutrition are given simultaneously, we no longer have enthusiasm for supplementary parenteral nutrition in this group of patients. We believe that adjunctive parenteral nutrition has little advantage in patients with far advanced malignancy.

Complications are an ever present fact of parenteral nutrition. Proper sterile technique for catheter placement, maintenance, and fluid preparation is stressed. In our experience, the elderly and the patient with sepsis are more prone to develop the problem of hyperosmolality. By careful monitoring of serum osmolality, urine reductions, and daily blood sugars, severe hyperosmolality can be avoided. Caval thrombosis has also been reported as a complication of parenteral nutrition.[4] One death in this series was related to multiple, septic pulmonary emboli from a thrombosis in the subclavian vein extending into the superior vena cava. Even subclavian vein catheterization, which we prefer, does not guarantee against subclavian or superior vena cava thrombosis.

Summary

A prospective study was undertaken of 23 patients with malignant disease who were given supplementary parenteral nutrition while undergoing treatment of malignancy. An effort was made to establish guidelines in selecting patients for parenteral nutrition. Results were based on the ability to gain or sustain weight, to raise or maintain serum albumin above 2.5 g/100 ml, to heal wounds and fistulas; and on an increase in the sense of well-being and the level of activity.

The best results were obtained in relatively young patients without severe sepsis or disseminated disease. Older patients, particularly those over age 70, and patients with severe sepsis had a limited metabolic response, were unable to handle large glucose loads, and were more susceptible to serum hyperosmolality. Patients with widely disseminated carcinoma progressively lost weight and showed no increase in the level of activity. We believe that supplementary parenteral nutrition is of limited value in the elderly patient, seems to be poorly tolerated by the patient with severe sepsis, and is of no value in patients with disseminated disease. Sterile technique, subclavian catheterization, careful monitoring, and appropriate patient selection are

all essential to avoid or minimize complications of supplementary parenteral nutrition.

References

1. Dudrick SJ: Intravenous feeding as an aid to nutrition in disease. CA **20:** 198–211, 1970.
2. Schwartz GF, Green HL, Bendon ML, et al: Combined parenteral hyperalimentation and chemotherapy in the treatment of disseminated solid tumors. Am J Surg **121:** 169–173, 1971.
3. Dudrick SJ, Wilmore DW, Vars HM, et al: Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. Surgery **64:** 134–142, 1968.
4. Rush BF Jr, Richardson JD, Griffen WO Jr: Positive nitrogen balance immediately after abdominal operations. Am J Surg **119:** 70–75, 1970.
5. Freeman JB, MacLean LD: Intravenous hyperalimentation: a review. Can J Surg **14:** 180–194, 1971.
6. Ashcraft KW, Leape LI: Candida sepsis complicating parenteral feeding. JAMA **212:** 454–456, 1970.
7. Curry CR, Quie PG: Fungal septicemia in patients receiving parenteral hyperalimentation. N Engl J Med **285:** 1221–1225, 1971.
8. Fischer JE, Abbott WM, Abel RM: Fungal septicaemia complicating intravenous hyperalimentation. Lancet **1:** 640, 1972.
9. Shils ME: Guidelines for total parenteral nutrition. JAMA **220:** 1721–1729, 1972.