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Original Communications

A Double-Blind Randomized Trial Comparing Outpatient Parenteral Nutrition With Intravenous Hydration: Effect on Resumption of Oral Intake After Marrow Transplantation

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ABSTRACT. *Background:* Outpatient parenteral nutrition (PN) is often given to marrow transplant recipients after high-dose chemoradiotherapy until the resumption of adequate oral intake; however, it may adversely prolong resumption of oral calorie intake by contributing to early satiety. *Methods:* A double-blind, randomized study compared standard PN (final concentration 25% dextrose, 5% amino acids) with a hydration solution (5% dextrose) during the first 28 days of outpatient treatment. Patients were eligible for the study if they were ≥2 years of age, <65 days posttransplant, had <70% oral caloric intake at hospital discharge, and required ≤10 U insulin/L PN. Solutions were provided until the patient's oral intake met ≥85% caloric requirements for 3 consecutive days. *Results:* Two hundred fifty-eight marrow transplant recipients (128, PN and 130, hydration solution) were studied. Age, donor type, and diagnoses were similar in the two groups. Time to resumption of ≥85% oral caloric intake was 6 days sooner in the hydration group than in the PN group (median 10 *vs* 16 days, respectively; $p = .049$). When adjusting for sex, age, donor type, total body irradiation, previous oral intake, acute graft-versus-host disease, and prednisone therapy, the hydration group resumed oral intake sooner than the PN group (relative risk = 1.51; 95% confidence interval [CI] 1.04 to 2.19; $p = .029$). The percentage of weight change from pretransplant values, adjusted for the above covariates and the number of weeks of treatment, indicated that the hydration solution group lost weight (4.63%) compared with the PN group (1.27%) after 4 weeks of therapy ($p = .004$). Rates of hospital readmissions, relapse of malignancy, and survival did not differ between the two treatment groups. *Conclusions:* We conclude that outpatient PN delays resumption of oral intake and that its replacement with hydration solution does not result in adverse patient outcome. (*Journal of Parenteral and Enteral Nutrition* **21**:157–161, 1997)

Symptoms resulting from myeloablative chemoradiotherapy and hematopoietic cell transplantation include nausea, vomiting, diarrhea, mucositis, and esophagitis.[1,2] As a result, many patients are unable to eat while these symptoms persist. Graft-versus-host disease (GVHD) and infection can further prolong the period of compromised oral intake. Because of these limitations to oral intake, parenteral nutrition (PN) is often given as standard supportive care. At many transplant centers, PN begins when the patient is unable to consume adequate calories to maintain weight and continues until 70% or more of estimated caloric requirements is taken by mouth.

Hospital discharge criteria at our institution have been reported previously.[3] In an effort to reduce the cost of care, an increasing proportion of patients are discharged at increasingly earlier dates posttransplant.[4] Many patients who meet these discharge criteria, however, are unable to sustain adequate oral intake. According to standard practice, these patients are discharged to the outpatient setting with supplemental PN, usually ≤2500 mL of a solution of dextrose plus amino acids. Specifically, 65% of patients transplanted at this Center have been discharged in this manner and continued to receive PN for a median of 15 days.[5] It is not known, however, whether this duration represents the natural course of the refeeding process or is a result of prolonged use of supplemental PN.

Both animal and human studies provide evidence suggesting that PN can adversely affect eating behavior. In rats, a continuous IV infusion of a solution containing amino acids produces marked decreases in food intake, whereas similar long-term infusions of normal saline or glucose hydration solutions produce no change in eating behavior.[6] Giner et al[7] reported that spontaneous oral calorie intake was significantly reduced in rats maintained on PN compared with saline-based hydration. In monkeys, PN significantly suppressed oral intake, but only when the infusions provided at least 50% to 60% of the animal's usual oral intake.[8,9] When parenteral supplementation was discontinued, the return to usual oral intake required 1 to 2 weeks, suggesting a residual appetite suppression by PN.[8,9]

Few studies have investigated the effects of PN on appetite and eating behavior in humans. Smyth et al[10] reported a progressive loss of appetite in healthy men who received short-term administration of amino acid mixtures, with a delay in the return of normal eating; Sriram et al[11]

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observed that reducing the amount of PN was associated with an increase in voluntary food intake in patients with transient dysfunction of the gastrointestinal tract. A long-term infusion study compared the effects on food intake of infusions of fat, glucose, or amino acid solutions, given singly or in combination to healthy volunteers. Results showed that subjects simultaneously given all three nutrients reduced daily voluntary food intake by an amount approximating the PN calories provided.[12]

The hypothesis that PN delays refeeding has not been studied in the marrow transplant population. In addition to its expense, PN also has possible adverse medical consequences. Prolonged PN has been associated with liver, gallbladder, and other serious gastrointestinal dysfunction. Adverse metabolic consequences of PN include elevations in liver function tests, particularly alkaline phosphatase and transaminases, cholelithiasis, and bone disease.[13,14] Physiological consequences of PN include slowed gastric emptying, early satiety, anorexia, and nausea.[10,15]

The purpose of the present study was to evaluate the effect of PN on time to resumption of oral intake in addition to medical outcome. We conducted a double-blind, randomized clinical trial comparing PN with IV hydration after hospital discharge of patients undergoing marrow transplantation.

MATERIALS AND METHODS

Patients

Informed consent was obtained in accord with the Institutional Review Board. Patients were prepared for marrow transplant with high-dose chemotherapy with or without total body irradiation.[16,17] Day 0 was denoted as the day of transplant. Patients were followed with daily nutrient intake analysis. PN was instituted before the marrow infusion and continued during the inpatient transplant course. The volume of PN was decreased as the patient's oral intake increased.

Eligibility criteria for the study included the following: (1) oral intake <70% of caloric requirements at time of hospital discharge; (2) patient age ≥2 years; (3) discharge before day 65 posttransplant; (4) insulin requirement of ≤10 U; and (5) toleration of at least a GVHD-II (low-lactose, low-fat, low-fiber) oral diet.[18] Individual baseline calorie requirements, as a percentage of basal energy expenditure, were estimated at 130% for adults and 140% for children, as described by Harris and Benedict.[19] Two hundred fifty-eight marrow transplant recipients were enrolled in the study between January 1989 and June 1993 (Table I).

TABLE I
Patient characteristics

	Parenteral nutrition	Hydration solution
Number of patients	128	130
Age (y)		
<10	14	14
10–20	16	13
20–30	52	60
>40	46	43
Age range (y)	2.7–64.2	2.1–63.1
Median age	34.6	34.8
Sex		
Male	69	70
Female	59	60
Donor type		
Autologous	30	23
Syngeneic	3	2
Allogeneic		
HLA-compatible related donor	67	70
Unrelated donor	35	35
Diagnosis		
Aplastic anemia	0	2
Acute lymphoblastic leukemia	18	14
Acute nonlymphoblastic leukemia	28	21
Chronic myelogenous leukemia	46	58
Congenital disorders	1	2
Hodgkin's disease	2	3
Myelodysplastic syndrome	4	9
Multiple myeloma	6	4
Non-Hodgkin's lymphoma	17	11
Solid tumors	6	6

Treatment Plan

There were two stratification factors for the study. The first was age (<12 *vs* ≥12 years) to assure a balance in the exposure among the pediatric patients. The second factor was corticosteroid administration (yes *vs* no) at the time of randomization because this therapy is associated with hyperphagia. Patients were randomized to receive either PN composed of a 25% dextrose and 5% (4.25% for pediatric patients) amino acid solution or IV hydration fluid composed of a 5% dextrose solution. Initial IV support was calculated to supplement oral intake to provide at least 100% of the patient's estimated calorie requirements in total, assuming that all patients received PN.

Results of randomization were unknown to the patient and all medical staff except for the research pharmacist who prepared the study solutions. Blinding included use of identical solution containers and tubing. Both study solutions contained electrolytes according to standard procedures. All patients received daily oral multivitamins and trace element supplements. Fluid volumes ranged from 500 to 2500 mL/d at hospital discharge and were based on the patient's weight according to the following standard: <20 kg: ≤1000 mL/d; 20 to 35 kg: ≤1500 mL/d; 35 to 70 kg: ≤2000 mL/d; ≥70 kg: ≤2500 mL/d.

Study parameters were followed for 4 weeks after study entry. Patients were seen by the study dietitian once weekly for a routine clinic visit with another weight check conducted 4 days later. Daily self-reported food intake records were maintained by all study patients and reviewed for accuracy by the study dietitian. The volume of study solution infused was reduced in accordance with increasing oral calorie intake levels. For patients >35 kg, when the sum of infused study solution (assuming 1000 kcal/L) and oral calories exceeded estimated energy requirements by an average of 300 calories for 3 days, the volume of study solution was reduced by 500 mL. For patients ≤35 kg, when the sum of infused calories and oral intake exceeded estimated requirements by 150 calories for 3 days, the volume of study solution was reduced by 250 mL. Oral intake was evaluated in this manner every 3 days and the study solution was reduced in 500- or 250-mL increments. The volume of the solution was increased by similar increments as oral intake decreased by 150 or 300 calories below estimated requirements for any 3-day period.

Study Endpoint

The major endpoint of the study was successful refeeding, defined as an oral intake ≥85% of estimated energy requirements sustained for 3 consecutive days. When patients achieved this oral intake level, the study solution was discontinued. Patients meeting the study criteria for weight loss (adults: loss to ≤80%; children: loss to ≤90%, of either ideal body weight or of hospital admission weight) or those requiring hospital readmission were removed from the study and received PN.

Data Collection

Daily food and fluid intake records were collected through study day 28. The patient or caregiver recorded daily intake of food and liquids. Before a patient entered the study, a dietitian instructed the record keeper in the procedures, using standard measuring utensils and plastic food models for illustration. The dietitian reviewed the initial 3-day records with the record keeper to verify accuracy. Patients submitted daily food records three times weekly to assure timely adjustments of the volume of study solution. The food records were evaluated for caloric content using the Food Processor II Nutritional Data Base (ESHA Research, Salem, OR).

Frequency of hospital readmissions, treatment failures, and protocol violations were also recorded. Weight comparisons were made for values obtained pretransplant, at study entry, at the end of the study, and at discharge home from the transplant center at approximately day 90 posttransplant.

Statistical Analysis

The primary endpoint of the study was time to resumption of oral intake. Secondary endpoints were readmission to the hospital during the study period, percentage weight change from pretransplant values to last weight on study and to last weight before discharge home, and relapse and survival to day 150 posttransplant. The following variables were examined to determine their effect on the association between outcome and study treatment: sex, age, donor type, acute GVHD, total body irradiation, prednisone therapy, and time posttransplant of randomization. All variables were included in the multivariate models except days posttransplant at time of randomization, which was not found to be a confounding factor.

A logrank test comparing time to resumption of oral intake between study arms was conducted and Kaplan-Meier plots were generated.[20] Resumption of oral intake was evaluated using a multivariate Cox regression model that adjusted for the factors listed above. Prednisone was incorporated as a time-dependent covariate.[20] Additional models were tested stratifying for oral intake before the time of randomization. In a subset of the study in patients ≥19 years old, the analysis was stratified by volume of study solution.

Secondary analyses examining weight change were conducted with a Wilcoxon rank-sum test. Analysis of the relationship between study solution and percentage weight change was conducted with analysis of variance (ANOVA), adjusting for the same variables included in the Cox regression analysis.[21] Percentage weight change was also studied by ANOVA, controlling for the length of time the patient received the study solution. Other secondary endpoints, hospital readmission, disease relapse before day 150 posttransplant, and death before day 150 posttransplant, were evaluated with the Pearson χ^2 test.[22]

An interim analysis, using a logrank test, was conducted when 50% of the study population had been enrolled. The significance level for the primary endpoint required at the interim analysis was .001 and was not attained. Consequently, at the final analysis, the significance level for the logrank test was ≤.049.

RESULTS

Patient Characteristics

As shown in Table I, characteristics of the two treatment groups were similar.

Length of Outpatient Parenteral Therapy

As shown in Figure 1, the median time to resumption of oral intake for hydration patients was 10 days compared with 16 days for PN recipients ($p = .049$). The relative risk for a longer duration of administration of the study solution for the PN group was 1.47 compared with the hydration group ($p = .038$). To account for any subtle differences in tolerance of an oral diet at the time of randomization, we conducted a multivariate analysis of time to resumption of 85% oral intake, stratified for initial level of oral intake. This confirmed that the hydration group resumed oral intake sooner than the PN group (relative risk = 1.51; 95% confidence interval [CI] 1.04 to 2.19; $p = .029$). Fluid volumes may be a surrogate for the number of hours per day on IV support because most solutions were infused at a rate of 100 to 125 mL/h. To determine the relation of solution volume to resumption of oral intake, a multivariate Cox regression analysis was conducted in a subset of adult patients ≥19 years old (n = 203), stratifying by volume of study solution. This analysis indicated that fluid volume did not alter the association between treatment group and resumption of oral calorie intake.

Weight Loss

The percentage of change in weight from pretransplant to study day 28 and to the last weight before return home

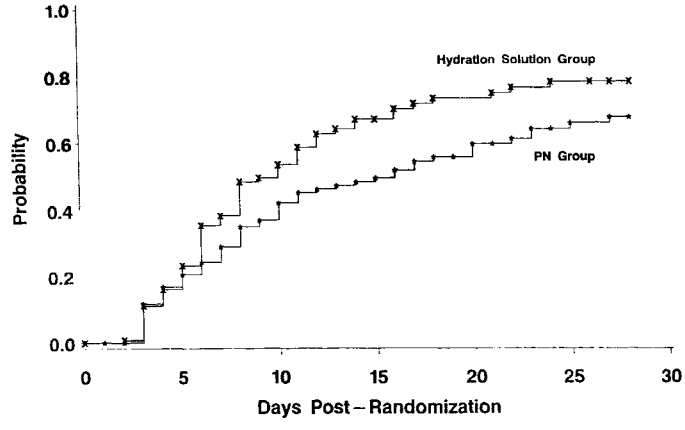

FIG. 1. Kaplan-Meier estimate of the probability of resuming >85% of estimated energy intake by study arm.

was calculated in 249 evaluable patients. Tables II and III provide the frequency distributions for percentage of weight loss to day 28 and to the last weight, respectively, stratified for the amount of time a subject actually received the study solution. As shown, patients who received parenteral therapy for a longer duration experienced a decrease in weight, regardless of the treatment group.

A Wilcoxon rank-sum test, comparing percentage of weight change from pretransplant to the last weight during the study, indicated that subjects in the hydration solution group lost more weight compared with the PN group ($p = .026$). In an ANOVA, controlling for the number of weeks that patients received the study solution as well as the other covariates included in the Cox regression, the hydration group had a higher percentage of weight loss compared with the PN group ($p = .004$).

Outcomes

There were no significant differences between treatment groups for hospital readmission ($p = .38$), relapse before day 150 ($p = .92$), or death before day 150 posttransplant ($p = .83$)(Table IV). At our Center, the average patient charges for 2 L/d of hydration, without electrolyte additives, for 10 days were $300 compared with $4,160 for 2 L/d of PN for 16 days.

DISCUSSION

High-dose chemoradiotherapy is associated with several complications that inhibit normal eating. Although efforts to institute refeeding and discontinue PN begin before hospital discharge, 65% of patients at our institution are unable to eat sufficient quantities at discharge.[5] Because PN has been associated with symptoms that inhibit oral feedings (delayed gastric emptying, early satiety, anorexia, and nausea), the possibility exists that PN itself prolongs poor intake after marrow transplantation.[10,15]

Our randomized, double-blind study found a significant delay in time to resumption of oral intake in marrow transplant patients maintained on PN compared with IV hydration. Even when accounting for confounding factors such as sex, age, donor type, total body irradiation, acute GVHD grade, and prednisone, the hydration solution group met treatment endpoint 6 days sooner than the PN group.

Other investigators have found similar results in other patient populations.[10–12] Smyth et al[10] investigated the influence of short-term administration of amino acid mixtures on voluntary food intake in eight healthy men. The mixture that most consistently and markedly depressed voluntary intake was a casein hydrolysate enriched with tryptophan, which reduced food intake by an average of 61% of normal. This infusion led to a progressive loss of appetite and a delay in the return of normal eating. To determine whether reducing the amount of PN infusion results in an increase in voluntary food intake, Sriram et al[11] studied 10 stable patients receiving PN for transient dysfunction of the gastrointestinal tract. After a 3-day observation period to establish baseline oral intake, parenteral calories were reduced without the patients' knowledge and the calories consumed during the subsequent 3 days were measured. When PN calories were reduced by half, the mean oral calorie intake increased significantly, suggesting that PN depressed voluntary food intake.

The mechanism by which PN affects oral intake is unknown. MacGregor et al[15] reported the rate of gastric emptying of solid food among five patients with cancer who served as their own controls. During PN infusions, the emptying rate was significantly slower than during the noninfusion control period. Humoral mechanisms of regulating food intake, such as circulating levels of substrates, have also been investigated. Correlation of circulating levels of glucose[23–25] or amino acids[10,26] with the onset of hunger or oral intake has been inconsistent, and regulation of eating behavior remains poorly understood.

Modest weight loss was seen in both treatment groups of the current study despite an earlier return to refeeding in the hydration solution group. Because marrow transplant patients frequently experience fluid weight shifts posttransplant, as a result of organ toxicities or steroid therapy, weight loss may be due, in part, to diuresis. Although the difference in the percentage of weight change between the PN group and hydration solution group was statistically significant, the actual difference in mean percentage of weight lost for the hydration solution group was <5% of baseline. This degree of weight loss did not appear to result in an increase in adverse patient outcome, such as more frequent readmissions or increased mortality. The average savings in charges for 10 days of hydra-

TABLE III
Percent weight change: pretransplant to discharge home (last weight)

Weeks of parenteral therapy	Parenteral nutrition	Hydration solution
0–1	3.26 ± 1.30	0.19 ± 1.07
1–2	0.62 ± 1.87	−2.15 ± 1.02
2–3	0.50 ± 2.10	−2.89 ± 2.75
3–4	−1.27 ± 1.84	−4.63 ± 1.05
Total	1.41 ± 0.86	−1.14 ± 0.71*

The analysis was controlled for the number of weeks on the study solution. Values are means ± SE.
*$p = .004$.

TABLE II
Percent weight change: pretransplant to last weight on study (day 28)

Weeks of parenteral therapy	Parenteral nutrition	Hydration solution
0–1	1.98 ± 0.95	0.14 ± 0.82
1–2	2.08 ± 1.51	−0.91 ± 1.08
2–3	−0.20 ± 0.93	−1.58 ± 2.44
3–4	−1.56 ± 1.43	−3.84 ± 0.91
Total	0.87 ± 0.61	−0.23 ± 0.58*

Values are means ± SE.
*$p = .026$.

TABLE IV
Patient outcomes

	Parenteral nutrition	Hydration solution
Readmission while on study		
Yes	46	40
No	82	90
Disease relapse before day 150		
Yes	22	23
No	106	107
Death before day 150		
Yes	27	26
No	101	104

tion support was $3,860 compared with PN charges for the same time period. Others have also shown that PN did not reduce medical costs.[27,28] In summary, the results suggest that outpatient PN should be reserved for transplant recipients with evidence of severe gastrointestinal dysfunction.

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