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Adverse Clinical Consequences of Hyperglycemia from Total Parenteral Nutrition Exposure during Hematopoietic Stem Cell Transplantation

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ABSTRACT

Immunocompromised hematopoietic stem cell transplant (HSCT) recipients frequently receive total parenteral nutrition (TPN), a dextrose-based solution that may exacerbate the infectious risks associated with hyperglycemia. This study assessed the incidence of hyperglycemia (glucose level ≥110 mg/dL) and its effect on clinical outcomes in TPN versus non-TPN recipients who received HSCTs. A retrospective cohort of 357 adults who were admitted for initial autologous or allogeneic transplantation at 2 university-affiliated centers was examined. To discern the temporality of outcomes, "before" and "after" comparisons were made by using actual infusion times for TPN patients and using timeframes based on mean hospital days before ("before") or during ("after") parenteral infusion for non-TPN patients. Patients demonstrated similar demographic and clinical characteristics when analyzed by institution, feeding, and donor-type strata, and 57% received TPN. After attempts to equilibrate disease acuity were employed, the proportion of hyperglycemic days was equivalent before but significantly greater after in patients exposed versus unexposed to TPN (87.5% versus 8.3%, respectively; $P < .001$). Using logistic regression, the likelihood of infection doubled (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.4-3.5) after adjustment for donor type, diagnosis, age, gender, ethnicity, institution, mucositis, and obesity. This association was only slightly attenuated when patients with infections before were removed (OR, 1.9; 95%, CI, 1.1-3.3), steroid recipients were eliminated (OR, 2.1; 95% CI, 1.2-3.4), and when patients with nonablative regimens were excluded (OR, 2.1; 95% CI, 1.3-3.5), but was considerably higher for patients who were classified as normal or underweight (body mass index ≤25 kg/m^2; n = 118; OR, 4.3; 95% CI, 1.7-10.6). In addition, the effect of TPN became insignificant when glucose was added as an independent variable, thus symbolizing their collinear relation. Parenteral nutrition recipients versus nonrecipients also developed significantly greater requirements for red cell ($P = .001$) and platelet transfusions ($P = .001$) after and significant delays in granulocyte and platelet engraftment times for autologous ($P = .01$) and allogeneic ($P = .02$) subjects. The broad use of TPN in patients undergoing initial HSCT was associated with profound hyperglycemia, resultant greater morbidity, and questionable efficacy in this adult, well-nourished cohort.

KEY WORDS

Total parenteral nutrition • Hyperglycemia • Hematopoietic stem cell transplant • Nutrition • Epidemiology • Morbidity

Preliminary findings of this work were presented at the Hyperglycemia Workshop during Nutrition Week; Orlando, Florida; January 2005.

INTRODUCTION

Despite significant technologic and pharmacologic gains over the past 2 decades, infection remains the primary cause of death among hematopoietic stem cell transplant (HSCT) recipients [1]. Practices that decrease this risk are critical. Currently, there is a growing body of literature that demonstrates the negative relation between acute hyperglycemia and increased risk of infection [2-4] and other adverse outcomes. In the landmark trial by Van den Berghe et al [5], the dramatic decreases in morbidity, specifically a 46% decrease in bloodstream infections, and mortality in acutely ill patients with tight blood glucose control (80-110 mg/dL) versus conventional blood glucose levels (180-200 mg/dL) not only necessitated early termination of the study but also highlighted a potential target to improve health outcomes in hospitalized patients.

Total parenteral nutrition (TPN) has commonly been administered to HSCT patients since the early 1980s [6,7]. It is classically initiated to assist in the management of the diarrhea, nausea, vomiting, anorexia, and fluid and electrolyte disorders that accompany the transplantation process and to prevent or treat malnutrition. However, the advent of growth factors and the use of peripheral blood have significantly decreased the number of days to engraftment [8] and the consequent time of inadequate oral intake. Despite expense, its inherent risks, and lack of trials demonstrating the efficacy of TPN in this patient population, it continues to be a recommended component of transplant care [9]. As a consequence, administration of this dextrose-based solution in a population prone to infection may unknowingly compound the blood glucose aberrations associated with transplantation [10] and result in untoward rather than beneficial effects. This study assessed the incidence of hyperglycemia and its association with various clinical outcomes known to be exacerbated by acute blood glucose increases in comparable TPN versus non-TPN transplant recipients.

MATERIALS AND METHODS

Study Design

A retrospective cohort investigation was conducted by using the medical records of patients who had an initial HSCT between September 1999 and December 2003 at 2 urban university hospitals. This design was selected because it provided an efficient, inexpensive means of examining our hypotheses with minimal risks to patients; allowed for precise documentation of exposure (initiation and termination of TPN), major outcomes (hyperglycemia, infection), and vital confounding factors (e.g., conditioning chemotherapy, quantity of $CD34^+$ cells transplanted, etc) equally for all patients; and allowed for accurate ascertainment of incidence rates, temporality of outcomes, and dose-response measurements for exposures between groups.

Study Population

All patients who were ≥18 years of age and admitted to 2 university-affiliated transplantation centers for an initial autologous or allogeneic HSCT were eligible for inclusion. This patient population was selected because it manifested several optimal characteristics: (1) a 50-60% TPN exposure rate uniformly delivered through a central line; (2) comparable baseline cardiac, pulmonary, renal, and hepatic functions; and (3) increased susceptibility to infections due to immunosuppression, thus increasing the number of observable outcomes. Individuals who had a history of home TPN administration, were admitted with a documented infection, or were <18 years old were excluded.

Data Collection

Institution-specific transplantation databases were obtained and screened for initial eligibility while working retrospectively. Computerized and hardcopy medical records were used. Baseline data were extracted from physicians' history and physical examinations. Preparative chemotherapeutic regimens were verified from the pharmacy chemotherapy dosing records. Culture results and daily blood draws were obtained from the laboratory reports. Admission height and weight and TPN dose, volume, and duration were collected from the initial nutritional evaluation and from pharmacy records. Nursing progress notes were used for daily weights, maximum temperatures, and 24-hour intake and output volumes. Documentation of mucositis was gathered from physician and/or nursing daily progress notes. Blood bank summaries were used to confirm red cell and/or platelet transfusions. Transplant records were used to verify the number of $CD34^+$ cells transplanted. Granulocyte and platelet engraftments were defined as the number of days between transplant day 0 and the first day of 3 consecutive days that the absolute neutrophil count was $>.5 \times 10^9$/L or when platelets were $>50 \times 10^9$/L, respectively. Nutritional status was assessed by using admission serum albumin level, admission body mass index (BMI), and percentage of ideal body [11].

Outcome Measurements

The primary outcome measurement was hyperglycemia, which was also analyzed as an independent variable. Glucose was recorded once per day from the first morning venous blood draw to achieve uniformity among patients, avoid measurements that occur more frequently among hyperglycemic patients, and

minimize the influence of oral intake. Total number of days and percentage of hospital days with blood glucose levels ≥110 [4] and ≥200 mg/dL were used to evaluate 2 levels of hyperglycemic events. Information on exogenous insulin administration was not collected. Secondary outcome measurements were number of infections, red cell and platelet transfusions, white blood cell (WBC) count and platelet engraftment, and hyperlipidemia. At both institutions, blood cultures were routinely procured for temperatures >38°C (100.5°F), stool cultures were sent for *Clostridium difficile* with complaints of or documentation of diarrhea, and red cells and platelets were typically transfused to maintain a hemoglobin level >8 g/dL and platelet count >10-20 × $10^3/\mu L$. To determine platelet engraftment, it was required that patients demonstrate platelet transfusion independence (ie, levels assessed 7 days after platelet transfusion) and that platelet levels decrease to $<50 \times 10^9/L$ to signify a platelet nadir. Routine surveillance cultures were not included, and culture-positive and culture-negative infections were counted only if documented and treated by the attending physician. Although triglyceride monitoring is not routine in this patient population, in an attempt to discern whether differences in hyperlipidemia occurred between TPN and non-TPN patients, a sample of 20 patients in each group who had triglyceride levels measured were examined for mean triglyceride values.

Comparability of TPN and Non-TPN Participants

Several steps were taken to demonstrate comparable disease acuity between the TPN and non-TPN groups before TPN exposure. First, patients who typically develop higher rates of transplant-related complications and mortality were not eligible for inclusion (eg, matched unrelated donor, tandem, or subsequent transplants), thereby eliminating potentially sicker or atypical transplant candidates. Second, vital clinical characteristics were compared between groups and patients who seemed principally different were removed. Specifically, to minimize the risk of undiagnosed diabetes mellitus or underlying acute illness, patients with consistently elevated blood glucose values, temperatures, or WBC counts on admission were eliminated. Third, nutritional status at admission was compared across groups because depleted serum albumin and BMI have been shown to be valid indicators of unfavorable hospital outcomes [12]. Fourth, to determine temporal changes in hyperglycemia, infections, and blood product support, standardized timeframes, referred to as "before" and "after" TPN exposure, were created. In patients who received TPN, actual days before TPN and during TPN infusion were used and categorized as "before" and "after." Because the non-TPN group did not actually receive TPN, the before and after intervals were created for these patients as follows: "before" (pre-TPN time) indicated the transplant-specific mean number of days before TPN initiation as assessed for TPN patients (10 days for autologous, 13 days for allogeneic) and "after" (post-TPN time) indicated the transplant-specific mean number of TPN infusions days as assessed in patients who received TPN (11 days for autologous, 16 days for allogeneic).

Data Quality

To assure reproducible and accurate data points, a routine data collection procedure was used to identify, locate, and verify data within the medical record (eg, physician documentation of infection confirmed by laboratory reports). Quality assurance was performed by having an individual who was not involved in the study examine 2-4 records per month, and discrepancies were resolved by consensus and developing methods to prevent future errors. All data were double-entered and cleaned in Epi Info 6 [13]. This study was approved by the institutional review boards at both centers.

Statistical Analyses

Means, medians, SDs, and ranges were used to examine and describe the distribution of data and Student *t*, chi-square, and Wilcoxon rank-sum tests were used to compare clinical and demographic characteristics between institutions, feeding strata, and donor types. Subsequent analyses concentrated on the main effects of TPN exposure on outcomes, with stratification by donor type when applicable. Multiple logistic regression analysis was conducted to ascertain odds ratios (ORs) and 95% confidence intervals (CIs) for the association between TPN exposure and infection. Statistical analysis was conducted with SAS 9.1 [14].

RESULTS

Study Population

A total of 380 patients qualified based on donor type and initial transplant. Of these, 23 patients were excluded (15 were admitted with an active infection that required treatment, 7 had insufficient medical record documentation or atypical admissions, and 1 was on home TPN), leaving 357 for analyses. Overall, TPN exposure occurred in 57% of the cohort, with only minimal variations in exposure rates by study year. When TPN was analyzed according to attending physician use, exposure patterns ranged from 20% to 77%, symbolizing within-physician practice variations. Institutional differences were reflected in patient demographics, admission albumin level, length of stay, and preparative chemotherapeutic regimens, specifically with regard to the use of rituximab, total

Table 1. *Baseline Patient Characteristics by Institution and by TPN Status (n = 357)**

	Hospital A	Hospital B	P†	TPN	No TPN	P
Patients	250	107		202	155	
Male	152 (61)	56 (52)	.14	115 (57)	93 (60)	.56
Female	98 (39)	51 (48)		87 (43)	62 (40)	
Age, y	48.4 ± 13.1	49.6 ± 12.7	.67	47.6 ± 13.2	50.3 ± 12.6	.06
Race						
White	152 (61)	40 (37)	<.001	115 (57)	77 (49)	.17
AA	52 (21)	40 (37)	.001	46 (23)	46 (30)	.14
Hispanic	35 (14)	22 (21)	.12	29 (14)	28 (18)	.34
Other	11 (4)	5 (5)	.91	12 (6)	4 (3)	.20
Primary disease						
Multiple myeloma	85	43	.26	60	68	.006
Non-Hodgkin lymphoma	69	22	.16	61	30	.02
Acute myeloid leukemia	18	12	.21	18	12	.69
Hodgkin lymphoma	21	6	.36	16	11	.77
Other diagnosis‡	57	24	.94	47	34	.77
Type of transplant						
Autologous	171 (68)	74 (69)	.89	129 (64)	116 (75)	.03
Allogeneic	79 (32)	33 (31)		73 (36)	39 (25)	
Karnofsky score	92 ± 5	92 ± 5	.57	92 ± 5	92 ± 5	.84
Preparative chemotherapy - n						
Carmustine, etopside, cytarabine, melphalan ± rituximab	35/31	23/0	.08/<.001	36/23	22/8	.36/.04
Melphalan ± fludarabine	75/26	42/18	.09/.09	52/29	65/15	<.001/.18
Total body irradiation ± cyclophosphamide§	75	17	.005	51	41	.80
Other chemotherapy‖	8	7	.15	11	4	.29
History of DM	29 (12)	17 (16)	.27	19 (9)	27 (17)	.03
Insulin requirement	13	4	.21	8	9	.54
Oral agents	13	10	.36	9	14	.76
Diet controlled	3	3	.66	2	4	.99
Admission glucose, mg/dL	116 ± 53	115 ± 37	.82	116 ± 57	115 ± 36	.80
Steroid use, %	12	15	.38	19	4	<.001
Nutritional status						
Body mass index, kg/m^2	28.0 ± 6.2	29.1 ± 7.1	.15	27.6 ± 6.2	29.3 ± 6.6	.02
Albumin, g/dL	3.3	3.5	<.001	3.3	3.4	.06
Ideal body weight, %	126	133	.06	125	132	.04
Admission temperature, °F	98.7 ± 0.8	98.1 ± 0.9	<.001	98.6 ± 0.9	98.5 ± 0.8	.29
Admission WBC, ×10^3/μL	7.3 ± 8.1	7.1 ± 7.1	.59	8.3 ± 11.9	6.5 ± 5.1	.05
Length of stay, d	24 ± 8	22 ± 7	.02	27 ± 9	20 ± 4	<.001
Alive at discharge	244 (98)	97 (91)	.004	187 (93)	154 (99)	.001

AA indicates African American; DM, diabetes mellitus.

*Values are numbers (%) of patients or mean ± SD.

†*P* values were determined with the use of Student *t* test, Wilcoxon rank-sum test, chi-square test, or Fisher exact test, as appropriate.

‡Other diagnoses included smaller clusters of chronic myelogenous leukemia (n = 20), acute lymphocytic leukemia (n = 9), chronic lymphocytic leukemia (n = 13), renal cancer (n = 8), breast cancer (n = 6), myelodysplastic syndrome (n = 6), aplastic anemia (n = 2), testicular cancer (n = 2), myelofibrosis (n = 5), and other diagnoses (n = 10).

§Chemotherapy included a combination of 1 or both of these agents with or without others.

‖Various combinations of busulphan, carmustine, etoposide, fludarabine, melphalan, and/or rituximab.

body irradiation, and/or cyclophosphamide (Table 1). Disparities between TPN strata were detected for primary disease (significantly more patients with non-Hodgkin lymphoma and fewer with multiple myeloma received TPN), which reflected preparative chemotherapeutic differences.

Most patients were well nourished at admission, with a clinically insignificant trend toward higher levels of albumin in the non-TPN than in the TPN group. Using BMI classifications from the Centers for Disease Control and Prevention [15], the average transplant recipient was overweight (BMI ≥25 kg/m^2), with 35% meeting obesity qualifications (BMI ≥30 kg/m^2), regardless of institution, TPN grouping, or diagnosis, and only 7 patients were classified as underweight (BMI ≤18.5 kg/m^2). Significantly more non-TPN patients had diabetes mellitus (Table 1). In addition, significantly more TPN patients received steroids during hospitalization compared with non-TPN patients ($P < .001$), beginning typically on hospital day 24 and ending on hospital day 33. Although all allogeneic patients received graft-versus-host disease (GVHD) prophylaxis using methotrexate, acute GVHD was documented in 22 patients (19 received TPN and 21 received steroids) and significantly larger proportions of hospital days with mucositis were ex-

Table 2. *Total Parenteral Nutrition Practices by Institution and Donor Type**

	Hospital A	Hospital B	*P*	Autologous	Allogeneic	*P*
No. patients	149/250	39/107		118/245	70/112	
TPN initiation day	12 ± 4	13 ± 3	.08	11 ± 3	14 ± 5	<.001
TPN duration, d	13 ± 7	12 ± 7	.74	11 ± 5	16 ± 9	<.001
Total kilocalories	1813 ± 306	1727 ± 350	.13	1796 ± 306	1794 ± 336	.97
Kilocalories†	26 ± 3	26 ± 5	.82	26 ± 4	26 ± 4	.33
Protein‡	1.2 ± 0.2	1.2 ± 0.3	.48	1.3 ± 0.2	1.2 ± 0.2	.29
Lipid emulsion§	98%	97%	.99	98%	97%	.99

*Values are means ± SD. These totals exclude patients with <4 days of TPN exposure.
†Number of kilocalories per kilogram of body weight adjusted for obesity, when applicable.
‡Number of grams of protein per kilogram of body weight adjusted for obesity, when applicable.
§Percentage of patients who received lipid emulsion as a component of TPN.

perienced by TPN patients compared with non-TPN patients (25.8 ± 22.8% versus 14.4 ± 19.7%, respectively; $P < .001$). When triglyceride levels were analyzed in a subset of TPN (n = 20) and non-TPN (n = 20) subjects, similar values were found (156 versus 154 mg/dL, respectively). Number of hospital days until TPN initiation, TPN duration, total kilocalories, and grams of protein were not significantly different by institution but were markedly different by donor type (Table 2).

Blood Glucose Control

Blood glucose values were plotted longitudinally for all patients throughout hospitalization (ie., average blood glucose for all participants each hospital day when n ≥ 50). Figure 1 shows that all patients developed increases in blood glucose during the first few days of hospitalization due to the catabolic nature of conditioning chemotherapy, with a return to lower levels in subsequent days. A clear divergence between curves is noted by hospital day 10 as a reflection of TPN initiation; however, this did not change when steroid recipients, patients with diabetes mellitus, or those who died at discharge were removed (Figure 2) or when plotted by donor type. When dichotomized, the median proportion of hyperglycemic days for all patients was not statistically different before (40.0% of TPN subjects versus 38.4% of non-TPN subjects; $P = .77$) but was markedly different after (87.5% of TPN subjects versus 12.5% of non-TPN subjects; $P < .001$); this difference remained when stratified by donor type and after patients who received steroids were removed. In addition, when conventional hyperglycemia definitions were used (>200 mg/dL, or 11.1 mmol/L), only 11% of TPN patients (n = 22) and 1% of non-TPN patients (n = 1) were classified as hyperglycemic (mean blood glucose level, 237 mg/dL, or 13.2 mmol/L).

Morbidity

Total infections and blood product support were analyzed according to the before and after periods as

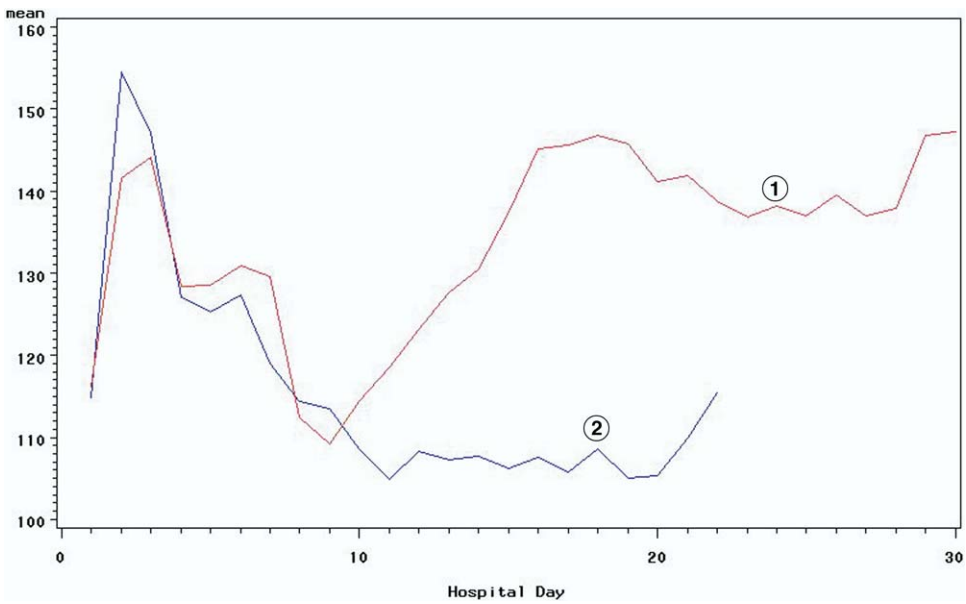

Figure 1. Glucose across time as stratified by TPN for all patients (n ≥ 50). TPN = line 1, Non-TPN = line 2.

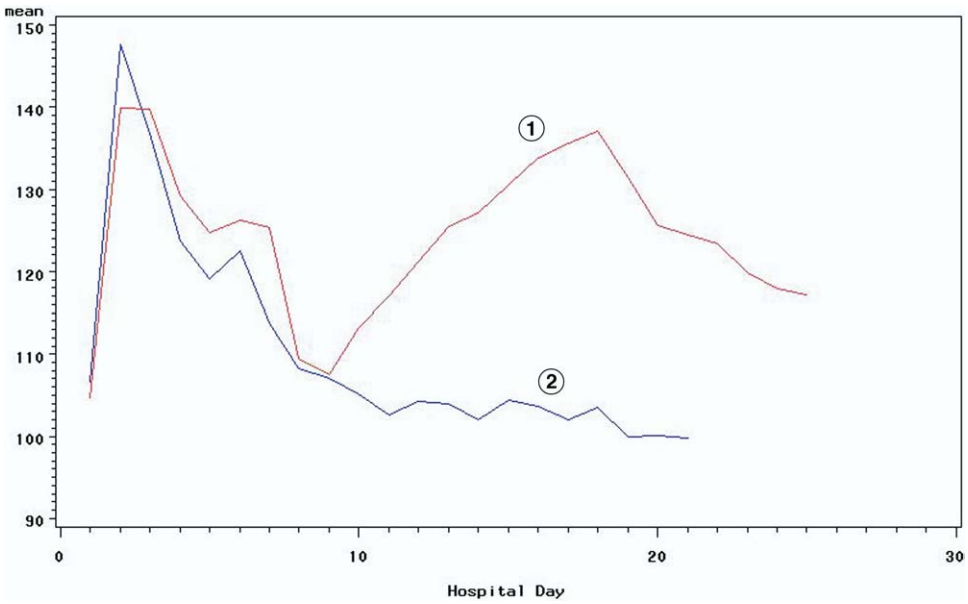

Figure 2. Glucose across time as stratified by TPN with exclusions (n ≥ 50). TPN = line 1; Non-TPN = line 2.

stratified by TPN exposure. To control further for severity of illness, patients were eliminated if they were infected before. Regardless, total infections after were .8 ± 1.0 versus .4 ± .6 in TPN versus non-TPN subjects, respectively. Red cell and platelet supports did not differ in the TPN groups before, but considerable differences were detected after when comparing TPN with non-TPN subjects (Table 3). When further stratified by donor type, no significant variations occurred before, but significant differences across TPN strata were detected after in allogeneic patients with regard to total infection ($P = .001$) and red cell ($P < .001$) and platelet ($P < .001$) transfusions and in autologous patients with regard to red cell and platelet transfusions. In a multiple logistic regression model, TPN recipients were ≥2 times more likely to become infected than were non-TPN recipients (OR, 2.2; 95% CI, 1.4-3.5) for the entire cohort, after controlling for donor type, diagnosis, age, gender, ethnicity, institution, mucositis, and obesity. This association decreased only slightly when patients with infections before were removed (OR, 1.9; 95% CI, 1.1-3.3), steroid recipients were eliminated (OR, 2.1; 95% CI, 1.2-3.4), and when patients with nonablative regimens were excluded (OR, 2.1; 95% CI, 1.3-3.5). However, when the analysis was restricted to patients who had normal weight or were underweight (BMI ≤25 kg/m^2; n = 118), the odds of infection increased considerably (OR, 4.3; 95% CI, 1.7-10.6).

Next, TPN subjects were categorized according to mean glucose values during TPN infusion (Table 4). The incidence of infection increased as mean glucose values increased, which was more pronounced in subjects without an infection before. To examine the odds of infection by length of time exposed to TPN, a tertile-split TPN variable was created (0 = no TPN, 1 = 1-7 days, 2 = 8-12 days, 3 = >12 days). Using a simple logistic regression model, crude ORs (95% CIs) for the association between infection and length of time exposed to TPN were 1.0 (referent), 1.5 (1.2-1.8) for 1-7 days, 2.2 (1.5-3.1) for 8-12 days, and 3.2 (1.8-5.5) for >12 days; these values were only slightly attenuated after controlling for glucose.

Engraftment

Within this cohort, 99% (n = 352) of patients had peripheral blood as the sole source of stem cells, all were treated with colony-stimulating factors according to predetermined institution protocols, and the

Table 3. *Incidence and Temporality of Infection and Blood Product Support Stratified by TPN* (n = 258)*

	TPN		Non-TPN		
	Before	After	Before	After	P†
Total infection	0	0.8 ± 1.0	0	0.4 ± 0.6	.03
Red cell support	1.2 ± 1.4	3.3 ± 3.2	1.2 ± 1.5	1.5 ± 1.8	<.001
Platelet support	0.7 ± 1.9	5.7 ± 6.6	0.4 ± 1.0	2.3 ± 2.7	<.001

*Values are means ± SD; n = 258 after elimination of infected patients before.
†TPN after versus. non-TPN after.

Table 4. *Dose-Response Relation between Blood Glucose and Infections for TPN Subjects* (n = 200)*

	≤109 mg/dL	110-135 mg/dL	136-160 mg/dL	>160 mg/dL	P†
No. patients	**28**	**69**	**47**	**56**	**.08**
Total infections	**0.6 ± 1.0**	**0.6 ± 0.8**	**0.7 ± 0.8**	**1.0 ± 1.3**	
No. patients	**23**	**46**	**33**	**86**	
Total infections‡	**0.4 ± 0.7**	**0.7 ± 0.8**	**0.8 ± 0.9**	**1.2 ± 1.5**	**.04**

*Values are means ± SD.
†*P* for trend.
‡TPN subjects without infection before (n = 138).

number of infused $CD34^+$ cells for TPN and non-TPN patients were not significantly different, regardless of donor type. Despite these similarities that directly influence engraftment time, significant differences were detected in posttransplant days until WBC engraftment for autologous (11.9 ± 2.4 versus 11.2 ± 1.9 days; $P = .01$) and allogeneic (14.8 ± 4.8 versus 12.3 ± 2.5 days; $P < .001$) patients who received TPN compared with those who did not.

According to criteria similar to those of Cetin et al. [16], platelet levels decreased to $<50 \times 10^9$/L in 346 subjects, with most patients exhibiting levels $<20 \times 10^9$/L (n = 304). Because 237 patients were not independent of transfusions and an additional 17 subjects did not achieve levels $>50 \times 10^9$/L, 92 subjects remained for analyses. Of these, significantly longer periods until platelet engraftment were found for autologous (16.6 ± 4.9 versus 12.9 ± 2.6 days; $P = .004$; n = 51) and allogeneic (19.8 ± 5.1 versus 15.3 ± 4.8 days; $P = .02$; n = 41) patients who received TPN versus those who did not.

DISCUSSION

We determined that there were profound differences in the incidence of hyperglycemia in TPN versus non-TPN recipients, and that hyperglycemia as a consequence of TPN exposure was associated with more infections, blood product support, and delayed granulocyte engraftment and platelet engraftments in a cohort of HSCT recipients. Several previous investigators have demonstrated the importance of short-term glycemic control on clinically important outcomes in hospitalized patients [2-5,17-22]; however, to our knowledge, no one has directly assessed the influence of hyperglycemia and its resultant morbidities a priori in TPN versus non-TPN patients.

The early studies by Weisdorf et al. [6,7] associated prophylactic versus ad libitum TPN with earlier engraftment and prolonged survival. Although these investigations are widely cited as the rationale behind TPN use during transplantation, changes in patient population and clinical management methods since the 1980s have made them increasingly difficult to apply to modern practice. In addition, considering that 73% [6] and 60% [7] of control patients in the studies by Weisdorf et al. actually received TPN, the groups' treatments were homogeneous, making determination of TPN exposure on outcomes difficult to evaluate and diminished the rationale for its routine use unsubstantiated. To date, TPN administration has been shown to be beneficial for patients who are severely malnourished [23]. By using comparable BMI cutpoints as a crude measurement of nutritional status (underweight, BMI ≤18.5 kg/m^2), we found that only 2% (n = 7/357) of our cohort was classified as malnourished, although 44% of all TPN recipients were overweight or obese (n = 89/202). Although this generalization is limited by the lack of information on weight history or oral intake, it does support the observations of Muscarotoli et al. [24] that TPN is often provided during transplantation irrespective of nutritional status. Considering the paucity of studies that support the efficacy of TPN during transplantation and the fact that infection remains their leading cause of death [1], the concept of permissive underfeeding and its effect of transplantation outcomes warrants further investigation.

Parenteral nutrition has proved to be life-saving in humans with permanent gastrointestinal failure, but it has inherent risks, most appreciably, a greater risk of infection when compared with enteral tube feeding [25-31] or standard oral diets [32]. Some have speculated that this increased risk is due to bacterial translocation after atrophy of the gut mucosa and gut-associated lymphoid tissue [33,34]. We hypothesized that the higher incidence of infection among those initially free of infection was a result of TPN-induced hyperglycemia, which impaired granulocyte adherence [35], chemotaxis [36], phagocytosis [37], and microbicidal cell functions [38]. In our simple logistic regression model, TPN exposure and hyperglycemia remained significant predictors for infection, suggesting that other attributes of TPN administration may contribute to the observed increased risks. Further, because pancytopenia occurred around the average time of TPN initiation, it is biologically plausible that the hyperglycemic environment may have delayed neutrophil recovery, impeded nascent neutrophil function, and ultimately promoted greater infections and prolonged engraftment times.

We specifically selected a retrospective study de-

sign due to its strengths of efficiency and speed. However, because of its retrospective nature, it was imperative for us to demonstrate comparability in those exposed versus unexposed to TPN for valid outcome comparison. To this end, less common donor types and patients with differences in baseline admission characteristics known to predict adverse outcomes were eliminated, thus collectively minimizing patients who are predisposed to increased morbidity. Next, intensive efforts to discover differences between feeding strata were employed. Nominal variations at baseline for demographic and transplant characteristics were revealed, and crude measurements of nutritional status and the incidence of hyperglycemia before appeared equivalent for TPN versus non-TPN subjects, thus reflecting an overall comparability between groups. Traditionally, prospective trials are cited as the gold standard for the determination of causality; however, they have to be adequately powered for equal randomization of known and unknown confounders. Because an illness acuity scoring system is lacking for this patient population, there is no currently available method to evaluate the effectiveness of randomization. Thus a large sample would be required to decrease the risks of unbalanced distribution of unknown confounders, thus necessitating a multicenter trial or a long investigation period. Therefore, despite the expanded understanding of the role of TPN on hyperglycemia and hyperglycemia-related morbidities that a prospective clinical trial could offer, the negative outcomes that were found from its exposure and the continued inability to assess severity of disease between TPN and non-TPN patients has limited our enthusiasm for this type of investigation in this population.

The limitations of this study should be noted. First, although we believe our efforts were successful in equilibrating disease acuity between TPN and non-TPN patients, the potential for these groups to be fundamentally different remains. Consistent clinical triggers of TPN initiation were not apparent. When we analyzed within-physician patterns of TPN exposure, these ranged from 20% to 77%. Therefore, we concluded that TPN administration was largely dictated by physician clinical judgment, which served as a form of randomization. Further, to eliminate confounding effects the sickest patients may have had on the outcomes and strengthen our findings, during data analysis patients with infections in the time preceding TPN (n = 94) or those with a history of diabetes mellitus, intensive care unit admission, or death at discharge (n = 57) were eliminated. Despite these exclusions, disparities in blood glucose control with regard to incidence, temporality, and dose-response and disparities in blood product support remained significant between TPN and non-TPN patients, even after stratification by donor type. Differences in infection after were not significant in the autologous patients due to inadequate statistical power, but significant differences in infection after remained for allogeneic patients ($P = .02$). Second, because mucositis is associated with conditioning chemotherapy and often methotrexate use, it can be a major predictor of TPN initiation and predispose individuals to infection, making it difficult to discern its direct influence on the outcomes of interest. However, despite controlling for conditioning chemotherapy and the uniform use of methotrexate in those who required GVHD prophylaxis, mucositis was not a significant predictor of infection and it did not attenuate the associations observed when added to the regression models. Third, although we found equivalent triglyceride levels between TPN and non-TPN recipients, we were unable to determine the true effect of hypertriglyceridemia on infectious risk because these values are not routinely and uniformly collected for all transplant recipients. Fourth, although we cannot account for the potential effect of insulin administration on outcomes, we believe this was minimal because most of the blood glucose values were <200 mg/dL, which do not typically prompt exogenous insulin support.

Globally, the use of TPN was significantly associated with hyperglycemia and untoward events in a heterogeneous group of patients who received initial HSCTs and when examined by donor type. Further studies are needed to address the overall efficacy of TPN use in well-nourished, adult transplant populations; and until experimental evidence is available, blood glucose levels should be frequently monitored during TPN administration and should not exceed 150 mg/dL.

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