Limited long-term survival after in-hospital intestinal failure requiring total parenteral nutrition1–3

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ABSTRACT

Background: Total parenteral nutrition (TPN) is an invasive and advanced rescue feeding technique that has acceptable short-term survival although at costs of substantial risks. Survival after the clinical use of TPN >6 mo is unknown.

Objective: We determined long-term survival after clinical TPN use in a consecutive cohort who were attending an academic hospital.

Design: The study included a prospective cohort with a retrospective analysis of all 537 consecutive episodes of TPN in 437 patients between January 2010 and April 2012. Follow-up was until October 2013 with a total follow-up of 608 patient-years. Survival was analyzed by using Kaplan-Meier and Cox regression.

Results: Survival was 58% in 437 patients with a first-time use of TPN at an average of 1.5 y after the initiation of TPN. The mortality rate was 30 deaths/100 patient-years. Older age, admission at an intensive care unit or a nonsurgical department, lower body mass index, and an underlying malignancy were positively associated with mortality.

Conclusion: TPN use, if correctly indicated, is a clinical sign of intestinal failure and a surrogate marker for markedly increased risk of mortality even >1.5 y after TPN use. This trial was registered at clinicaltrials.gov as NCT02189993 with protocol identification name TPN-01. Am J Clin Nutr 2014;100:1102–7.

INTRODUCTION

Total parenteral nutrition (TPN)4 is the last resort to feed patients with clinically important intestinal failure who cannot be sufficiently fed via the enteral route. The application of TPN has developed since the 1970s. TPN is currently widely used in intensive care units (ICUs), surgical and nonsurgical wards, and even in a home setting. By means of TPN, nutrients are delivered when this supply is impossible, contraindicated, or inadequate via the usual enteral route. It is well known that malnutrition is associated with a poor outcome in almost any severe disease (1). Therefore, TPN is thought to benefit patient outcomes when there is a just indication for the initiation of TPN (2).

Patients with upper gastrointestinal cancer might benefit in terms of a lower number of major complications. This absolute risk difference implied that one such complication could be avoided for every 5.5 patients treated (95% CI: 3.2, 16.7 patients) (2). However, these results have come from low-quality trials, which could have overestimated the actual beneficial effect (3). In contrast, 2 meta-analyses of randomized controlled trials did not show that the use of TPN compared with no (enteral) feeding was associated with a lower mortality rate (3, 4). Specifically, in patients with protein-energy malnutrition, TPN seemed beneficial in terms of lower risk of mortality or infections compared with that for standard care with enteral feeding. In particular, in well-nourished patients, the benefit of TPN is doubted (4).

Conceptually, it has been argued that an experiment to prove the benefit of TPN cannot be performed because TPN should be started in individuals who are thought to truly benefit, namely those with true intestinal failure. Other authors have argued that it is unethical to initiate an unproven and potentially dangerous therapy in patients (3).

The clinical therapeutic benefit of TPN has not been fully established. Therefore, it is important to evaluate TPN because TPN is associated with morbidity and even mortality. Complications associated with TPN use in the short term include water and electrolyte disorders, (eg, the refeeding syndrome) and complications related to the insertion and care of a central venous catheter, including pneumothorax or infections (5). As mentioned before, there is also a substantial mortality in patients who use TPN, although the exact relation with TPN remains to be clarified. A prospective study from England reported 20% mortality within 28 d (6). Short-term mortality rates have been reported between 2–43% in (randomized) clinical trials. However, results from these clinical trials are difficult to extrapolate to the actual, regular clinical use of TPN because of the strictly defined and specific populations in these trials (7–10).

Follow-up in most studies has been limited to 4–6 mo, and less is known about long-term survival after TPN use. Because of the relatively high short-term mortality, an investigation of the...
long-term survival is of critical clinical importance to assess the clinical value of this invasive and advanced feeding technique. Therefore, we analyzed the long-term survival in clinical TPN use in a cohort of consecutive TPN-using patients in an academic hospital setting.

SUBJECTS AND METHODS

The VU University Medical Center is a tertiary referral, academic hospital. For this study, all consecutive patients who were using TPN from 1 January 2010 to 30 April 2012 were analyzed with the exclusion of patients from the Pediatric and Haematological Departments because of different department-specific TPN protocols. In total, 437 patients with 537 episodes of TPN were included in this study. TPN was initiated by the treating physician usually after consultation with the Nutrition Support Team.

Nutrition Support Team

Patients who initiated TPN were monitored by a dedicated Nutrition Support Team consisting of dietitians (SMID and SDWdG), a TPN nurse (WA), and a gastroenterologist with a specific nutritional background (AAvB). If necessary, a pharmacist or ICU physician was consulted. All patients who were using TPN were discussed in a weekly meeting attended by the Nutrition Support Team. Details of all patients who were receiving TPN were prospectively recorded by the Nutrition Support Team.

Indications and TPN protocol

TPN was started according to the local protocol when there was intestinal failure present for 5 d or clinically likely to persist >5 d. Intestinal failure was defined as an insufficient oral or enteral diet in terms of energy or protein demands. Furthermore, TPN was considered before an operation in the case of malnutrition according to Dutch guidelines of preoperative nourishment (11). However, treating physicians could initiate TPN at their own discretion. Indications for the start TPN were classified into the following 4 categories: 1) enteral feeding was not possible, 2) enteral feeding was contraindicated, 3) enteral feeding was inadequate, and 4) an inadequate use of TPN (as defined by the hospital protocol and judged by the Nutrition Support Team). The discontinuation of TPN was decided by the treating physician, usually after consultation with the Nutrition Support Team. A suspicion of a central venous catheter infection was judged by the treating physician or the Nutrition Support Team. A suspicion of a central venous catheter infection was judged by the treating physician or the Nutrition Support Team. A suspicion of a central venous catheter infection was judged by the treating physician or the Nutrition Support Team.

Data collection

With all patient records addressed, we recorded the duration of hospital admission and overall survival. Follow-up was retrieved up to October 2013. The duration of follow-up was defined as the interval in years between the date of starting TPN and follow-up defined as the date of mortality or last known date of contact. The outcome of TPN therapy was analyzed by retrieving patients’ files according to hospital and national regulations regarding investigational conduct.

Statistical analysis

Analyses were performed with SPSS version 19.0 software (IBM SPSS Inc). Parametric variables are given as means ± SDs, and nonparametric variables are given as medians (IQRs). The normal distribution was tested by using the Kolmogorov-Smirnov test. Differences in parametric variables were tested by using a t test, and differences between dichotomous variables were tested by using a chi-square test. A survival analysis was performed in the following predefined manner. Initially, a univariate analysis was performed with a log-rank test and Kaplan-Meier curves with the following variables: sex, BMI (in kg/m²) (in 2 groups: BMI <25 and ≥25), malignancy (present or not present), surgical or nonsurgical departments, ICU admission, indication for TPN (1) enteral feeding was not possible, 2) enteral feeding was contraindicated, 3) enteral feeding was inadequate, or 4) an inadequate use of TPN), and TPN use <5 d. This latter analysis was performed only in patients with survival ≥5 d and in all patients with survival ≥30 d. A Cox-regression analysis was performed with the previously named variables and age. In the Cox-regression analysis, age and BMI were used as continuous variables.

Ethics and study registration

This research was performed in accordance with the ethical standards of the responsible institutional committee on human experimentation (Medical Ethical Commission, VU University Medical Center). This trial was registered at clinicaltrials.gov as NCT02189993 with protocol identification name TPN-01.

RESULTS

We analyzed 437 patients with 537 episodes of TPN. The average age was 60 ± 16 y when TPN was started for the first time. In 240 cases, TPN was started in men (55%). Mean BMI was 24.0 ± 4.8. The median duration of TPN was 7 d (4–13 d). Most patients were admitted by surgical specialties. Forty-three percent of patients required a hospital admission because a malignancy as an underlying disease. In 70% of patients, enteral feeding was not possible mainly because of an ileus. Inadequate enteral feeding was the second most-important indication. Only 20 patients (5%) did not have an adequate indication for TPN. Additional details are shown in Table 1.

Patient details are shown in Table 2 according to nonsurgical and surgical departments or an ICU admission. Patients admitted to nonsurgical departments were younger and had a longer duration of admittance than did patients admitted to surgical departments. Moreover, there were more ICU admissions in the nonsurgical group. Durations of the use of TPN and malignancy
Reason to stop TPN 

- Morbidity and mortality
- Inadequate use of TPN
- Normal distribution was tested by using the Kolmogorov-Smirnov test. CABS1, central line-associated bloodstream infection; CIP, chronic intermittent intestinal pseudoobstruction; ENT, Ear, Nose, and Throat; TPN, total parenteral nutrition.
- Mean ± SD (all such values for parametric variables).
- Median; IQR in parentheses (all such values for nonparametric variables).
TABLE 2
Characteristics of patients who started TPN for the first time according to nonsurgical, surgical, or ICU admission

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonsurgical (n = 107)</th>
<th>Surgical (n = 330)</th>
<th>P-difference</th>
<th>Non-ICU (n = 306)</th>
<th>ICU (n = 131)</th>
<th>P-difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>56 ± 16</td>
<td>62 ± 16</td>
<td>&lt;0.01</td>
<td>60 ± 16</td>
<td>60 ± 18</td>
<td>0.9</td>
</tr>
<tr>
<td>Male sex [n (%)]</td>
<td>53 (50)</td>
<td>187 (57)</td>
<td>0.2</td>
<td>165 (54)</td>
<td>75 (57)</td>
<td>0.5</td>
</tr>
<tr>
<td>Weight</td>
<td>71 ± 20</td>
<td>72 ± 15</td>
<td>0.6</td>
<td>71 ± 15</td>
<td>74 ± 18</td>
<td>0.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23 ± 96.2</td>
<td>24.1 ± 4.3</td>
<td>0.7</td>
<td>23.7 ± 4.7</td>
<td>24.7 ± 5.5</td>
<td>0.07</td>
</tr>
<tr>
<td>≥25 [n (%)]</td>
<td>35 (33)</td>
<td>119 (36)</td>
<td>0.3</td>
<td>113 (37)</td>
<td>41 (31)</td>
<td>0.2</td>
</tr>
<tr>
<td>Duration of TPN (d)</td>
<td>7 (3–11)</td>
<td>7 (4–12)</td>
<td>0.6</td>
<td>8 (5–13)</td>
<td>4 (3–9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TPN duration ≤5 d [n (%)]</td>
<td>46 (43)</td>
<td>115 (39)</td>
<td>0.1</td>
<td>88 (29)</td>
<td>73 (56)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration admitted in hospital (d)</td>
<td>33 (18–58)</td>
<td>20 (14–37)</td>
<td>0.01</td>
<td>19 (14–32)</td>
<td>38 (16–68)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Intensive care admission [n (%)]</td>
<td>50 (47)</td>
<td>81 (25)</td>
<td>&lt;0.01</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nonsurgical admission</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>57 (19)</td>
<td>50 (38)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Malignancy [n (%)]</td>
<td>39 (36)</td>
<td>148 (45)</td>
<td>0.1</td>
<td>142 (46)</td>
<td>45 (34)</td>
<td>0.02</td>
</tr>
<tr>
<td>Complications [n (%)]</td>
<td>9 (8)</td>
<td>37 (11)</td>
<td>0.5</td>
<td>43 (14)</td>
<td>5 (4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Central line dysfunction [n (%)]</td>
<td>2 (2)</td>
<td>9 (3)</td>
<td>0.9</td>
<td>10 (3)</td>
<td>1 (1)</td>
<td>0.2</td>
</tr>
<tr>
<td>Suspicion of central line infection [n (%)]</td>
<td>8 (8)</td>
<td>31 (9)</td>
<td>0.7</td>
<td>35 (11)</td>
<td>4 (3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CABSI (/1000 catheter days)</td>
<td>4.4</td>
<td>3.1</td>
<td>0.2</td>
<td>4.1</td>
<td>1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mortality within 30 d [n (%)]</td>
<td>26 (24)</td>
<td>31 (9)</td>
<td>&lt;0.01</td>
<td>18 (6)</td>
<td>39 (30)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total mortality [n (%)]</td>
<td>64 (60)</td>
<td>119 (36)</td>
<td>&lt;0.01</td>
<td>101 (33)</td>
<td>82 (63)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

1 Normal distribution was tested by using the Kolmogorov-Smirnov test. Differences in parametric variables were tested by using a t test, and differences between dichotomic variables were tested with a chi-square test. CABSI, central line-associated bloodstream infection; ICU, intensive care unit; TPN, total parenteral nutrition.

2 P values of the difference between nonsurgical and surgical patients.

3 P values of the difference between patients not admitted and admitted to the ICU.

4 Mean ± SD (all such values for parametric variables).

5 Median; IQR in parentheses (all such values for nonparametric variables).

mortality and nonsurgical department admission. Furthermore, mortality was not different between nonsurgical patients admitted to a regular ward and nonsurgical patients admitted to the ICU (log-rank test: P = 0.2).

DISCUSSION

The survival rate was 58% in 437 patients with a first-time use of TPN at an average of 1.5 y after the initiation of TPN. Older age, admission at an ICU, admission to a nonsurgical department, lower BMI, and an underlying malignancy were positively associated with mortality. In our study, there were 56 TPN-related complications in 537 episodes of TPN use, mainly during non-ICU admissions.

To our knowledge, mortality after TPN use has only been reported up to a maximum of 6 mo and in specific patient categories (6–10). Mortality within the first 6 mo has been reported to be between 2% and 43%. For comparison, the mortality rate of 30 deaths/100 patient-years after clinical TPN use in our study was higher than that in patients in need of dialysis because of renal failure (mortality rate: 16 deaths/100 patient-years [12] or heart failure [mortality rate: 12 deaths/100 patient-years (13)]. Patients receiving dialysis who have heart failure and are admitted to an ICU have dedicated medical treatment by numerous medical providers. Studies that investigated the role of a nutrition support team indicated a reduced inappropriate TPN use, less catheter-related sepsis, and even improved survival (14–19). The improved efficacy of TPN use resulted in reduced costs in most studies (14–16).

Admission to a nonsurgical department was associated with a higher mortality rate than that for admission to a surgical department (50 compared with 26 deaths/100 patient-years). We could not relate this higher mortality rate to age or an underlying malignancy; nonsurgical patients were younger than surgical patients. However, compared with surgical patient, nonsurgical patients had almost twice the number of ICU admissions. Other possibilities for a higher mortality in nonsurgical patients could have been differences in patient selection of those receiving TPN or differences in physicians’ discretion between nonsurgical and surgical departments. It is possible that patients with reversible intestinal failure, such as an ileus amened by a surgical intervention, were predominantly admitted by surgical specialties.

TABLE 3
Mortality of patients with multiple admissions with TPN (n = 437)

<table>
<thead>
<tr>
<th>Admissions with TPN</th>
<th>Patients</th>
<th>30-d mortality patients</th>
<th>Total mortality patients</th>
<th>Total mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>No. of deaths/100 patient-years</td>
</tr>
<tr>
<td>1 time</td>
<td>369 (85)</td>
<td>56 (15)</td>
<td>145 (39)</td>
<td>28</td>
</tr>
<tr>
<td>2 times</td>
<td>50 (11)</td>
<td>10 (20)</td>
<td>30 (60)</td>
<td>42</td>
</tr>
<tr>
<td>≥3 times</td>
<td>18 (4)</td>
<td>2 (11)</td>
<td>8 (42)</td>
<td>26</td>
</tr>
</tbody>
</table>

1TPN, total parenteral nutrition.
Besides mortality, our study also highlights the considerable complication rate of 11%. Complications were mainly due to the suspicion of a central line infection. In our study, the CABSI rate was 1.1/1000 catheter days in the ICU and 4.1 in non-ICU wards. These rates are comparable to data in the literature. In 55 ICUs, the median CABSI was 2.7/1000 catheter days, with an IQR of 0.6–4.8 (20). In 4 non-ICU medical wards, CABSI had a range between 4.3 and 8.0/1000 catheter days (21).

Another finding was that higher BMI was associated with a better survival. We did not show that a very low BMI was associated with a poor survival. This was also seen in patients with peritoneal carcinomatosis (22). Perhaps patients with higher BMI have greater reserves, but unfortunately, we did not have reliable information on nutritional status (and fat-free mass in particular) to further investigate this relation.

Our study had several limitations, most notably the retrospective character of assessing the long-term outcome. However, all patients had at least follow-up during admission, and the greatest majority of patients were seen at our outpatient clinics. Also, the retrospective follow-up could only underestimate the long-term mortality. We were not informed of comorbidity or underlying disease that required the admission of the patient. Finally, not all patients had an appropriate indication for TPN, and 37% of patients received <5 d of TPN. However, the fact that some patients had an inappropriate indication for TPN reflects actual TPN use, and inappropriate indications have also been often noted in other studies of actual TPN use (6, 23). Furthermore, an inappropriate use of TPN was not associated with excess mortality. A strength of our study was the long follow-up of an average of 1.5 y and 608 patient-years of follow-up.

In conclusion, our study underlines that complete intestinal failure, for which the clinical use of TPN is necessary, is associated with a remarkably high, long-term mortality rate of 42%. This outcome was particularly observed in nonsurgical patients. TPN should not be regarded as a simple dietary measure but as a high complex medical intervention. TPN requires an appropriate indication, a dedicated, knowledgeably team, and thorough nutritional and clinical follow-up. TPN use is a clinical sign of intestinal failure and a surrogate marker for markedly increased risk of mortality.

The authors’ responsibilities were as follows—LHO and AAvB: designed the research protocol and had primary responsibility for the final content of the manuscript; LHO, SMtD, SDWdG, and WA: conducted the research; SMtD, SDWdG, and WA: provided essential materials; LHO: performed the statistical analysis; and LHO, SMtD, SDWdG, WA, and AAvB: wrote drafts of the manuscript. None of the authors had a conflict of interest.

### TABLE 4

Multivariate cox-regression analysis for total mortality for 437 patients who used total parenteral nutrition for the first time.

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\beta$ (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per year</td>
<td>1.03 (1.02, 1.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intensive care admission</td>
<td>2.6 (1.9, 3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonsurgical specialty</td>
<td>2.2 (1.6, 3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>0.95 (0.91, 0.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Present malignancy</td>
<td>1.6 (1.2, 2.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.8 (0.7, 1.3)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*For 437 patients who used total parenteral nutrition for the first time.*

A Cox-regression analysis was performed with age and BMI as continuous variables.
REFERENCES


