Review Article
Article de revue

Total parenteral nutrition in the surgical patient: a meta-analysis

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Objective: To examine the relationship between total parenteral nutrition(TPN) and complication and death rates in surgical patients. Data sources: A computer search of published research on MEDLINE, personal files and a review of relevant reference lists. Study selection: A review of 237 titles, abstracts or papers. Primary studies were included if they were randomized clinical trials of surgical patients that evaluated the effect of TPN (compared to no TPN or standard care) on complication and death rates. Studies comparing TPN to enteral nutrition (EN) were excluded. Data extraction: Relevant data were abstracted on the methodology and outcomes of primary studies. Data were independently abstracted in duplicate. Data synthesis: There were 27 randomized trials in surgical patients that compared the use of TPN to standard care (usual oral diet plus intravenous dextrose). When the results of these trials were aggregated, there was no effect on mortality (risk ratio = 0.97, 95% confidence intervals, 0.76 to 1.24). There were fewer major complications in patients who received TPN, although there was significant heterogeneity in the overall estimate (risk ratio = 0.81, 95% CI, 0.65 to 1.01). Because of this significant heterogeneity, several *a priori* hypotheses were examined. Studies that included only malnourished patients demonstrated a trend to a reduction in complication rates but no difference in death rate when compared with studies of patients who were not malnourished. Studies published in 1988 or earlier and studies with a lower methods score were associated with a significant reduction in complication rates and a trend to a reduction in death rate when compared with studies published after 1988 and studies with a higher methods score. There was no difference in studies that provided lipids as a component of TPN when compared with studies that did not. Studies that initiated TPN preoperatively demonstrated a trend to a reduction in complication rates but no difference in death rate when compared with studies that initiated TPN postoperatively. Conclusions: TPN does not influence the death rate of surgical patients. It may reduce the complication rate, especially in malnourished patients, but study results are influenced by methodologic quality and year of publication.

Objectif : Examiner le lien entre la nutrition parentérale totale (NPT) et les taux de complication et de mortalité chez les patients en chirurgie. Sources de données : Recherche informatique dans des recherches publiées sur MEDLINE et dans des dossiers personnels, et examen de listes de documents de référence pertinents. Sélection d'études : Revue de 237 titres, abrégés ou communications. On a inclus des études principales s'il s'agissait d'études cliniques randomisées portant sur des patients en chirurgie et qui ont évalué l'effet de la NPT (comparativement à l'absence de NPT ou aux soins normaux) sur les taux de complication et de mortalité. On a exclu les études de comparaison de la NPT à l'entéronutrition. Extraction des données : On a abrégé les données pertinentes sur la méthodologie et les résultats des études principales. Les données ont été abrégées de façon indépendante et en double. Synthèse des données : Il y avait 27 études randomisées portant sur des patients en chirurgie au cours desquelles on a comparé l'utilisation de la NPT aux soins normaux (alimentation orale habituelle et dextrose par voie intraveineuse). L'agrégation des résultats de ces études n'a révélé aucun effet sur la mortalité (risque relatif = 0,97; intervalles de confiance à 95 %, 0,76 à 1,24). Il y avait moins de complications majeures chez les patients alimentés par NPT, même si l'on a constaté une hétérogénéité importante dans l'esti-

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Accepted for publication Apr. 3, 2000.

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mation globale (RR = 0,81; IC à 95 %, 0,65 à 1,01). À cause de cette hétérogénéité importante, on a examiné plusieurs hypothèses *a priori*. Des études qui ont porté uniquement sur des patients sous-alimentés ont démontré une tendance à la réduction des taux de complication, mais aucune différence au niveau du taux de mortalité comparativement aux études portant sur des patients qui n'étaient pas sous-alimentés. Par rapport aux études publiées après 1988 et ayant obtenu un résultat méthodologique plus élevé, les études publiées en 1988 ou antérieurement et les études ayant obtenu un résultat méthodologique moins élevé affichaient une réduction importante des taux de complication ainsi qu'une tendance à une réduction du taux de mortalité. On n'a constaté aucune différence dans les études qui comportaient l'administration de lipides par NPT comparativement aux études qui n'en comportaient pas. Les études où on a entrepris la NPT avant l'intervention ont révélé une tendance à la réduction des taux de complication, mais aucune différence au niveau du taux de mortalité comparativement aux études où on a commencé à administrer la NPT après l'intervention. **Conclusions :** La NPT n'a pas d'effet sur le taux de mortalité chez les patients en chirurgie. Elle peut réduire le taux de complication, particulièrement chez les patients sous-alimentés. Les résultats des études varient cependant en fonction de la qualité de la méthodologie et de l'année de publication.

The consequences of major surgery can lead to hypermetabolism and subsequent malnutrition.[1,2] The patient's previous nutritional status, the concomitant or underlying disease, and the degree and duration of other stresses can contribute to the risk of malnutrition.[3] Malnutrition can lead to depletion of body mass, impaired tissue and organ function, compromised immunity and poor wound healing. A strong association exists between malnutrition and increased postoperative morbidity and mortality in surgical patients.[4,5]

The administration of total parenteral nutrition (TPN) can clearly prevent the effects of starvation in patients with a nonfunctioning gastrointestinal tract. However, it is unclear whether TPN can modulate the catabolic response to surgical stress and reduce complications associated with hypercatabolism.[5] Put differently, the perioperative administration of TPN may result in significant improvement in weight, nitrogen balance, prealbumin levels and other nutritional end points, but the effect on clinically important end points, such as mortality and complications, is less certain. The purpose of this paper is to systematically review, critically appraise and statistically aggregate all studies evaluating the effect of TPN on complication and death rates in surgical patients.

A number of clinical trials[6–8] and a meta-analysis[9] have suggested that preoperative administration of TPN in severely malnourished patients may be associated with a lower rate of postoperative complications. Because a number of trials have been published subsequent to the meta-analysis, we decided to conduct another meta-analysis to summarize the current literature.

Methods

Search strategy

We conducted a computerized bibliographic search of MEDLINE (including pre-MEDLINE) from 1980 to May 1999 to locate all relevant articles. The terms "randomized controlled trial," "double blind method," "clinical trial," "placebo" and "comparative study" were combined with "parenteral nutrition, total." Citations were limited to English studies reporting on adult patients. We also searched reference lists of relevant review articles and personal files.

Selection criteria

Initially, 2 investigators screened all citations and classified them into primary studies, review articles or others. We then retrieved and independently reviewed all primary studies. They were included in this overview if they met the following criteria:

- research design — randomized clinical trial
- population — adult surgical subjects
- intervention — any form of TPN (protein, carbohydrates with or without lipids) compared to no TPN
- outcome — complications, length of hospital stay and mortality.

We elected to include only randomized trials in this review because studies in which treatment is allocated by any other method than randomization tend to show larger (and frequently false-positive) treatment effects than do randomized trials.[10] Since the scope of our review was defined by our research question, we also excluded studies that compared TPN to enteral nutrition or other forms of TPN. Finally, studies that only evaluated the impact of TPN on nutritional outcomes (i.e., nitrogen balance, amino acid profile) were excluded. Although these end points may explain underlying pathophysiology, we considered them as surrogate end points,[11] and we only included papers that reported on clinically important outcomes (morbidity and mortality).

Methodologic quality of primary studies

We assessed the methodologic quality of all selected articles independently in duplicate, according to the scoring system shown in Table 1. Even in randomized trials, failure to prevent foreknowledge of treatment assignment can lead to an overestimation of treatment effect.[12] Accordingly, we scored higher those studies that reported that their randomization

schema was concealed. Given the difficulties of blinding the administration of TPN, we only awarded points for studies that blinded the adjudication of study end points. We also evaluated the extent to which consecutive, eligible patients were enrolled in the trial, whether groups were equal at baseline, if cointerventions were adequately described, whether objective definitions of infectious outcomes were employed and whether all patients were properly accounted for in the analysis (intention-to-treat analysis) (Table 1).

Data extraction

Two investigators extracted data for analysis and assessed the methodologic quality; we resolved disagreement by consensus. Not all studies reported complication rates. Some reported total complications per group not per patient. When data were missing, unclear or not reported on a per patient basis, we attempted to contact the primary investigators to provide further information if the paper had been published in the last 5 years.

Prior hypotheses regarding sources of heterogeneity

When conducting a meta-analysis, heterogeneity (major differences in the apparent effect of the interventions across studies) is often found. When present, heterogeneity weakens any inferences that can be made from the results. The possible sources of variation include the role of chance or differences across studies in population, intervention, outcome and methods. *A priori*, we developed several hypotheses that might explain heterogeneity of study results.

- We considered that the premorbid nutritional status of study patients was a possible cause of variation in results. Whenever possible we grouped the results of studies that included only patients who were malnourished and compared them to the results of studies that included patients who were not malnourished at the time of entry into the study. When possible, we used the definition of malnourished provided in each individual study. If no definition was provided, we assumed patients who had greater than 10% weight loss to be malnourished.
- We hypothesized that study results may be related to the methodologic quality of the study. We planned a separate analysis comparing the effect of studies with an overall methodologic quality of 7 and greater to those with a score of less than 7 (median score = 7).
- Since the practice of providing nutritional support and the management of surgical patients has evolved over time, we divided the studies into groups comparing studies published in 1988 or earlier with studies published since 1989 (halfway point of this study period).
- There are several randomized trials of surgical patients that examine the effect of amino acid infusion alone or in combination with a carbohydrate source of calories (without the addition of lipids) on clinical outcomes. We hypothesized that there may be some adverse effects from the use of lipids.[13,14] Accordingly, we separated trials into those that included lipids and those that did not.
- We speculated that differences in the timing of the intervention may account for different results. To test this hypothesis we planned a separate analysis comparing studies that initiated TPN preoperatively to studies that started TPN postoperatively.

Table 1

Criteria Used to Assess Methodologic Quality

	Score		
Criterion	0	1	2
Randomization		Not concealed or not sure	Concealed
Blinding	Not blinded		Adjudicators blinded
Analysis	Other		Intention-to-treat
Patient selection	Selected patients or cannot tell	Consecutive eligible patients	
Comparability of groups at baseline	No or not sure	Yes	
Extent of follow-up	<100%	100%	
Treatment protocol	Poorly described	Reproducibly described	
Cointerventions*	Not described	Described but not equal or not sure	Well described and all equal
Outcomes	Not described	Partially described	Objectively defined

*The extent to which antibiotics, enteral nutrition, ventilation, oxygen and transfusions were applied equally across groups. For questions 1 to 3 and 8 and 9, possible score 0, 1 or 2. For questions 4 to 7, possible score 0 or 1. Total possible score is 14.

Analysis

The primary outcome was perioperative death (death within 30 days of operation) or death in hospital. The secondary outcome was major complications. We defined major complications as pneumonia, intra-abdominal abscess, sepsis,catheter-related infection, myocardial infarction, pulmonary embolism, heart failure, stroke, renal failure, liver failure and anastomotic leak. Minor complications were defined as wound infection, phlebitis, urinary tract infection and atelectasis. In 5 studies, the data were not portrayed in a fashion that allowed us to report major complication rates so we reported total complications[8,15,16] and total infectious complications.[17,18] There were some studies in which their reporting

methods did not allow us to disaggregate infectious from noninfectious complications. One study randomized patients to 3 groups (control versus standard TPN versus TPN with branched-chain amino acids).[19] We only included data from the control group and the standard TPN group. Two other studies randomized patients to 3 groups (control versus TPN without lipids versus TPN with lipids) and we included both experimental groups in the analysis.[7,20,21] We also reported on the duration of hospital stay, although these data were not aggregated owing to infrequent and variable reporting methods. Agreement between reviewers on the inclusion of articles was measured by weighted kappa.

We combined data from all studies to estimate the common relative risk of death and complications and associated 95% confidence intervals (CIs). We summarized the treatment effect using risk ratios (RRs). To avoid the problem with bias and instability associated with RR estimation in sparse data, we added one-half to each cell.[22] In the meta-analysis, we used maximum likelihood methods of combining RRs across all trials and examined the data for evidence of heterogeneity within groups.[23] The Mantel–Haenzel method was used to test the significance of treatment effect.[24] We used a random effects model to estimate the overall RR.[25,26] For the test of heterogeneity across subgroups, the *t*-test for the difference between the 2 subgroups was used. We considered a *p* value of less than 0.05 to be statistically significant.

Results

Study identification and selection

In all 187 citations were identified from the MEDLINE databases. Our personal files and review of reference lists yielded 57 additional articles for consideration. Initial eligibility screening resulted in 47 articles selected for further evaluation. Of these potentially eligible papers, 27 met the inclusion criteria.[6-8,15–21,27–43]

There was 100% agreement on the inclusion of articles for this overview. Reasons for excluding relevant randomized studies included studies evaluating different kinds of TPN,[44–46] pseudorandomized studies,[47–52] duplicate publications,[53,54] studies not reporting clinically important outcomes,[55–57] a study available in abstract form only[58] and a study that also randomized patients to anabolic steroids.[59]

Impact of total parenteral nutrition on death and complication rates

The 27 randomized trials, involving 2907 patients, compared the use of TPN to standard care (usual oral diet plus dextrose given intravenously) in patients who underwent surgery.[6–8,15–21] The details of each study are described in Table 2.[6–8,15–21,27–43] When the results of these trials were aggregated, there was no effect on mortality (RR = 0.97, 95% CI, 0.76 to 1.24) (Fig. 1). The test for heterogeneity was not significant although a visual inspection suggests that the treatment effect of some of the studies was significantly different from other studies. Twenty-two studies reported major complications. When these results were aggregated, TPN was associated with a reduction in complication rates (RR = 0.81, 95% CI, 0.65 to 1.01, p = 0.06) (Fig. 2). The test for heterogeneity was significant (p = 0.01).

Given that we found significant heterogeneity and in an attempt to better explain our findings, we examined our *a priori* hypotheses. We compared those trials that included only malnourished patients with other trials. TPN was not associated with any difference in mortality (Fig. 3) in studies of malnourished patients (RR = 1.13, 95% CI, 0.75 to 1.71) or in studies of normally nourished patients (RR = 0.90, 95% CI, 0.66 to 1.21, p = 0.38 for differences between subgroups). In studies of malnourished patients, TPN was associated with a significant reduction in complication rates (RR = 0.52, 95% CI, 0.30 to 0.91). The RR of major complications in studies of patients who were not malnourished was 0.95 (95% CI, 0.75 to 1.21). When we compared the complication rates associated with TPN in studies of patients who were not malnourished with the rate in studies of malnourished patients, the differences were just short of statistical significance (p = 0.066).

We compared trials with a methods score of less than 7 to trials with a score of 7 or better (Fig. 3). Trials with the higher methods score demonstrated no effect of TPN on mortality (RR = 1.08, 95% CI, 0.81 to 1.43), whereas trials with a score of 7 or less suggested a trend toward a reduction in mortality associated with the use of TPN (RR = 0.75, 95% CI, 0.47 to 1.19). The test for heterogeneity across subgroups was not significant (p = 0.21). With respect to complication rates, in studies with a higher methods score there was no effect of TPN on major complications (RR = 1.07, 95% CI, 0.86 to 1.32). In studies with a lower methods score, there was a significant reduction in complication rates (RR = 0.50, 95% CI, 0.32 to 0.76). The test for heterogeneity across subgroups was significant (p = 0.005).

We next compared trials published in 1988 or earlier with studies published since 1989 (see Fig. 3). Trials published in 1988 or earlier were associated with a trend toward a decrease in death rates associated with the use of TPN (RR = 0.68, 95% CI, 0.43 to 1.10). Trials published since 1989 were consistent with no treatment effect associated with TPN (RR = 1.11, 95% CI, 0.83 to 1.48). The test for heterogeneity across subgroups was short of conventional levels of significance (p = 0.10). With respect to complication rates, in studies published in 1988 or earlier there was a significant reduction in major complications associ-

Table 2

Randomized Studies Evaluating Total Parenteral Nutrition in Surgical Patients

Study	Methods score (max 14)	Patients (no.)	Intervention	Major complications		Mortality		Hospital stay, d	
				TPN	Control	TPN	Control	TPN	Control
Muller et al, 1982[6]	3	GI surgery (125) 60% malnourished	10 d preop; no lipids	11/66	19/59	3/66	11/59	n/a	
Veterans Affairs Total Parenteral Nutrition Cooperative Study Group, 1991[7]	10	Thoracoabdominal surgery (395) 100% malnourished	7–15 d preop; lipids	49/192	50/203	31/231	24/228	n/a	
Bellantone et al, 1988[8]	6	GI surgery (100) 100% malnourished	7 d preop; lipids	8/54	22/46	1/54	1/46	n/a	
Fan et al, 1989[15]	10	Surgery for esophageal cancer (40) 75% malnourished	14 d preop; lipids	17/20	15/20	6/20	6/20	15*	16*
Figueras et al, 1989[16]	7	GI surgery (49) 0% malnourished	5 d postop; no lipids	4/25	5/24	0/25	0/24	13 (6)	11 (3)
Sandstrom et al,1993[17]	10	Major surgery/trauma (300) 22% malnourished	7–10 d postop; lipids	n/a		12/150	10/150	n/a	
Hu et al, 1998[18]	3	Spinal surgery (40) 0% malnourished	7 d postop; lipids	7/16	8/19	0/16	0/19	n/a	
Reilly et al, 1990[19]	7	Liver transplantation (18) 100% malnourished	7 d postop; lipids	n/a		0/8	2/10	67 (29)	47 (19)
Hwang et al,1993a[20]	5	Gastric surgery (42) ?% malnourished	7 d postop; lipids	0/12	0/16	0/12	0/16	n/a	
Hwang et al, 1993b[20]	5	Gastric surgery (42) ?% malnourished	7 d postop; no lipids	0/14	0/16	0/14	0/16	n/a	
Muller et al, 1986[21]	4	GI surgery (105) ?% malnourished	10 d preop; lipids	17/46	19/59	10/46	11/59	n/a	
Garden et al, 1983[27]	6	GI surgery (20) ?% malnourished	4 d postop; no lipids	n/a		0/10	1/10	14 (4)	18 (10)
Hogbin et al, 1984[28]	7	GI surgery (43) ?% malnourished	5 d postop; no lipids	n/a		n/a		n/a	
Doglietto et al, 1996[29]	10	GI surgery (678) ?% malnourished	5 d postop; no lipids	66/338	71/340	16/338	12/340	n/a	
Jimenez et al, 1995[30]	5	GI surgery (75) 100% malnourished	5 d postop; no lipids	6/60	3/15	4/60	1/15	9 (6)	12 (8)
Brennan et al, 1994[31]	8	Pancreatic resection (117) ?% malnourished	? d postop; lipids	27/60	13/57	4/60	1/57	16 (7–72)*	14 (6–88)*
Askanazi et al, 1986[32]	3	Radical cysectomy (35) ?% malnourished	? d postop; lipids	1/22	2/13	0/22	2/13	17*†	24*†
Thompson et al, 1981[33]	4	GI surgery (21) 100% malnourished	5 d preop; no lipids	2/12	1/9	0/12	0/9	n/a	

Table 2 continued

Study	Methods score (max 14)	Patients (no.)	Intervention	Major complications		Mortality		Hospital stay, d	
				TPN	Control	TPN	Control	TPN	Control
Fan et al, 1994[34]	7	Surgery for hepatocellular cancer (124) 26% malnourished	7d preop and postop; lipids	22/64	33/60	5/64	9/60	n/a	
Abel et al, 1976[35]	4	Cardiac surgery (44) 100% malnourished	5 d postop; no lipids	n/a		4/20	3/24	19 (6)	18 (6)
Smith and Hartemink, 1988[36]	7	GI surgery (34) 100% malnourished	10 d preop; no lipids	3/17	6/17	1/17	3/17	44 (13)	38 (10)
Holter and Fischer, 1977[37]	5	GI surgery (56) 100% malnourished	3 d preop; no lipids	4/30	5/26	2/30	2/26	n/a	
Meguid et al, 1988[38]	4	GI surgery (64) 100% malnourished	9 d preop; lipids	n/a		1/32	0/34	10 (6–30)*	14 (9–30)*
Woolfson and Smith, 1989[39]	10	Thoracoabdominal surgery (122) ?% malnourished	6 d postop; lipids	6/62	4/60	8/62	8/60	14 (9–64)*	13 (9–95)*
Von Meyenfeldt et al, 1992[40]	7	GI surgery (101) 29% malnourished	10 d preop; lipids	6/51	7/50	2/51	2/50	36 (17)	32 (22)
Yamada et al, 1983[41]	3	Gastric surgery (62) ?% malnourished	18 d postop; lipids	0/29	5/28	0/29	1/28	n/a	
Gys et al, 1990[42]	7	Colorectal surgery (20) 0% malnourished	6 d postop; lipids	1/10	1/10	0/10	0/10	n/a	
Freund et al, 1979[43]	8	GI surgery (35) 0% malnourished	5 d postop; no lipids	0/25	0/10	0/25	0/10	17 (2.3)	19 (2.9)

*Median (range) otherwise reported as mean (standard deviation).
†No range specified.
n/a = not available, GI = gastrointestinal.

ated with TPN (RR = 0.42, 95% CI, 0.26 to 0.68). The aggregated results of studies published since 1989 were consistent with no treatment effect (RR = 1.09, 95% CI, 0.91 to 1.31). The test for heterogeneity across subgroups was statistically significant ($p = 0.002$).

We then compared studies that provided intravenous lipids as a component of TPN administration to those studies that did not include lipids. There was no difference in mortality associated with TPN with lipids (RR = 1.05, 95% CI, 0.79 to 1.40) or without lipids (RR = 0.80, 95% CI, 0.50 to 1.28). The test for heterogeneity across subgroups was not statistically significant ($p = 0.35$). There was a trend toward a reduction in complications associated with TPN without lipids (RR = 0.80, 95% CI, 0.63 to 1.02), but this did not differ significantly from the effect of TPN with lipids (RR = 0.86, 95% CI, 0.63 to 1.19). The test for heterogeneity across subgroups was not statistically significant ($p = 0.72$).

Finally, we compared studies that initiated TPN preoperatively to studies that initiated TPN postoperatively. With respect to mortality, TPN did not seem to have any treatment effect when administered preoperatively (RR = 0.85, 95% CI, 0.61 to 1.20) or postoperatively (RR = 1.08, 95% CI, 0.73 to 1.58). The test for heterogeneity across subgroups was not statistically significant ($p = 0.39$). In studies that initiated TPN preoperatively, there was a significant reduction in complication rates associated with the use of TPN (RR = 0.70, 95% CI, 0.52 to 0.95), but in studies that initiated TPN postoperatively there was no such effect (RR = 1.01, 95% CI, 0.70 to 1.46). The difference between the complication rates of these 2 groups was not statistically significant ($p = 0.15$).

Only 13 studies reported the impact of TPN on duration of hospital stay, 5 reporting median stay and 8 reporting mean stay. In 7 studies, the duration of stay in hospital was

shorter in the control group. Due to the variability in duration of stay and variability of reporting methods, we did not attempt to aggregate these results, but they are displayed in Table 2.

Discussion

Although meta-analyses have recently come under scrutiny,[60] they are potentially useful tools to help evaluate the efficacy of medical interventions. In the last 2 decades, there have been 27 randomized trials examining the effect of TPN on the morbidity and mortality of surgical patients. These studies ranged in size from 18 to 678 patients, with the majority of studies including fewer than 100 patients. The death rate in these studies ranged from 0% to 30%, with an overall average death rate of 8.6%. Individually, the majority of these studies were underpowered to demonstrate a significant treatment effect with TPN. The advantage of a meta-analysis is that it provides a method of aggregating similar studies to determine the best estimate of overall treatment effect.

For this meta-analysis, we defined a specific research question, conducted a comprehensive literature search and used explicit criteria for study selection and methodologic quality assessment.[61] In the overall analysis, there was no effect on mortality and no significant reduction in complication rates when comparing the use of TPN to standard care (usual oral diet plus intravenous dextrose). The degree of heterogeneity of the results weakens the inferences we can make from the overall results and makes the results of the prespecified subgroups more compelling. Furthermore, it is the exploration of why this heterogeneity exists that sheds light on the potential benefits or risks of TPN.

Our subgroup analysis, based on our *a priori* hypotheses, showed that the significant reduction in complication rates associated with the use of TPN was found only in those studies that were published in 1988 or earlier or those with a methodologic quality score less than 7. This treatment effect was systematically different from the effect observed in studies since 1989 and in studies of higher methodologic quality. Indeed, if we accept the more recent, high-quality studies as providing the best estimate of the current treatment effect, TPN is associated with no proven benefit in surgical patients. Finally, we found no difference in outcome in comparing studies that used lipids versus studies that did not use lipids in TPN administration. There were no significant differences in mortality associated with TPN in any of the subgroups explored in this meta-analysis.

When examining just studies of malnourished patients and studies

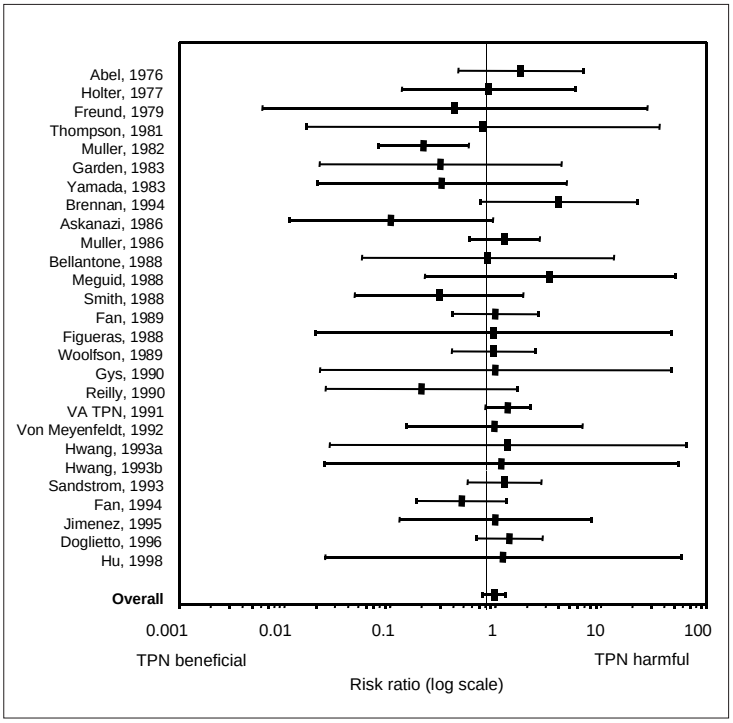

FIG. 1. Risk ratios and associated 95% confidence intervals for mortality reported in 27 randomized trials of total parenteral nutrition (TPN) in surgical patients. VATPN = Veterans Affairs Total Parenteral Nutrition Cooperative Study Group.

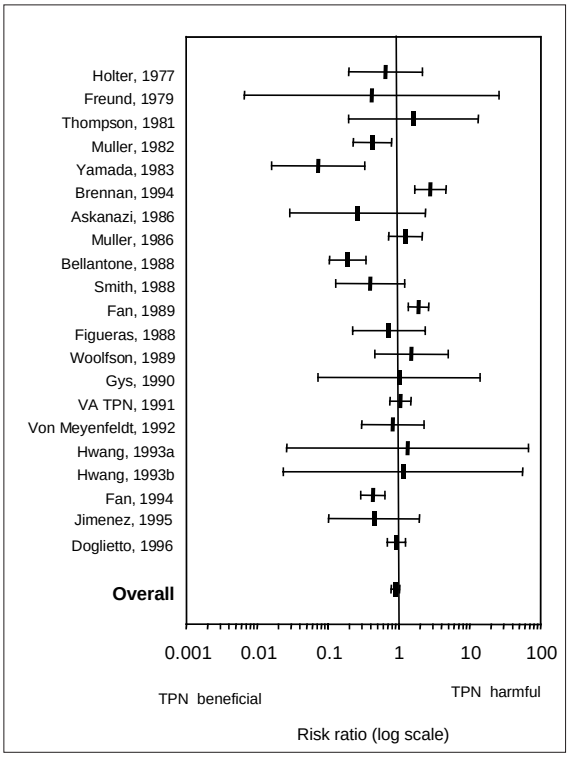

FIG. 2. Risk ratios and associated 95% confidence intervals for major complications reported in 21 randomized trials of total parenteral nutrition (TPN) in surgical patients. VATPN = Veterans Affairs Total Parenteral Nutrition Cooperative Study Group.

that initiated TPN preoperatively, one finds a significant reduction in complication rates associated with the use of TPN. However, the test of heterogeneity across these subgroups was not statistically significant, suggesting that the differences across these subgroups (malnourished versus normally nourished, preoperative versus postoperative) may be due to chance alone. This weakens any inference that TPN is beneficial in malnourished patients or preoperatively. If nutrition support is indicated in malnourished surgical patients, there are preliminary data that enteral supplementation may significantly reduce complication rates.[62–65]

There are a number of strengths to this meta-analysis. First, we included only randomized controlled trials and did not include pseudorandomized studies in the data analysis. Second, unlike previous reviews of the use of TPN in surgical patients, our study provided a thorough analysis of heterogeneity of the data. By exploring the heterogeneity of the various studies, we have come to a better understanding about the observed treatment effects (or lack thereof). Third, our updated data set included many recent studies.

A previous meta-analysis on perioperative parenteral nutrition published in 1987 aggregated the results of 18 trials of surgical patients.[9] Similar to our findings, no overall effect of TPN on morbidity and mortality and an inverse correlation between better quality studies and treatment effect of TPN was shown. That is, the more methodologically rigorous studies demonstrated less treatment effect with TPN. Following this meta-analysis, the results of a large randomized trial of preoperative TPN in surgical patients were published.[8] In this study of 395 patients, overall death and complication rates were similar in the group receiving TPN preoperatively and in the control group. There were, however, more infectious complications in the TPN group (14.1% versus 6.4%, p = 0.01). Again, consistent with our findings, in a subgroup analysis, these investigators found that TPN was associated with a trend to a lower rate of major complications in patients who were considered to be severely malnourished (25.8% versus 47.4%, p = 0.12).

Recently, another critical review of the medical literature appraising the use of nutritional support was conducted by a panel of experts recruited from the National Institutes of Health, the American Society for Parenteral and Enteral Nutrition and the American Society for Clinical Nutrition.[66] They synthesized data from 33 trials involving over 2500 surgical patients. They did not describe the search strategy they used to find relevant articles, nor did they do a methodologic quality assessment of primary studies included in the review process. Consistent with our findings, they found that the preoperative use of TPN was associated with a 10% risk reduction in complication rates. Unlike our findings, they noted a 10% increase in complications associated with the use of TPN postoperatively.

Both these review articles included nonrandomized studies, weakening any inferences one can make from their results. In addition, neither review assessed or explained the heterogeneity across studies included in their review. As previously stated, in our meta-analysis, the tests for heterogeneity suggest that the treatment effect was only observed in studies published in 1988 or earlier and in those with methodologic quality scores less than 7. Such findings further weaken any inferences that can be made by previous review articles.

There are a number of limitations to the methods used in our meta-analysis. First, our computerized literature search was restricted to studies published in English. Second, we were not able to assess whether the composition and amount of TPN influenced study outcomes since included studies did not consistently report these data. We could not assess

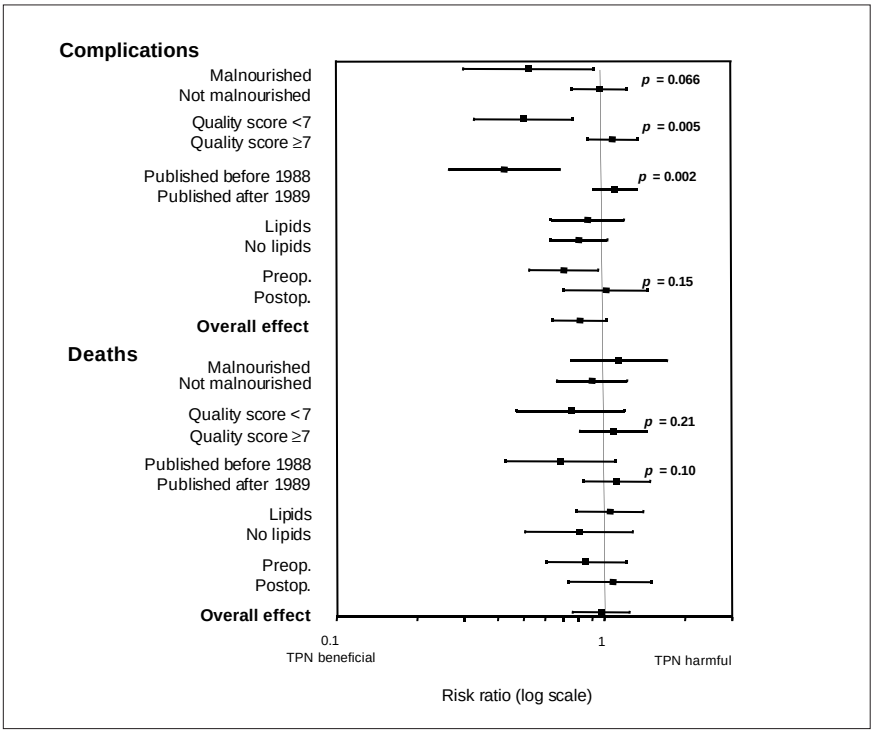

FIG. 3. Results of subgroup analysis, examining the effect of total parenteral nutrition (TPN) on death and complication rates in surgical patients. *p* values represent tests of heterogeneity across subgroups.

the extent to which the adverse or neutral effects of TPN may be due to hyperglycemia or overfeeding in certain studies.[67,68] In addition, we were not able to assess whether the effect of TPN varied across different surgical populations. We were unable to classify patients according to severity of illness and degree of comorbid illnesses present at baseline. With the exception of 3 studies,[18,32,35] all studies included patients who underwent major gastrointestinal surgery. Perhaps the treatment effect is different in other subgroups of surgical patients not well characterized or represented in the current literature. Finally, the definition of malnourished was not standard across studies. We had to rely on the investigators' definition, which may vary across studies.

Conclusions

The results of this meta-analysis suggest that, overall, there is no advantage to using TPN perioperatively in surgical patients. The apparent reduction in complication rates with TPN is associated with a significant degree of heterogeneity across studies. Possibly the treatment effect is strongest in malnourished patients. However, the beneficial effects of TPN in surgical patients are only seen in those studies done prior to 1988 and studies of low methodological quality. Given the potential for increased costs and complications associated with the use of TPN in the surgical patients (with no apparent reduction in mortality or length of stay), further studies are needed to confirm the benefits of TPN in this patient population.

Acknowledgements: We thank Dr. David Spain who reviewed earlier versions of this manuscript.

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