Total parenteral nutrition in the critically ill patient: a meta-analysis

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Authors' objectives
To examine the relationship between total parenteral nutrition (TPN) and complication and mortality rates in critically ill patients.

Searching
MEDLINE and pre-MEDLINE (1980 to 1998) were searched using the search terms: "randomised controlled trial", "double blind method", "clinical trial", "placebo", and "comparative study", combined with "explode parenteral nutrition, total". Citations were limited to English language studies. Reference lists of relevant review articles and personal files were also searched.

Study selection
Study designs of evaluations included in the review
Only randomised clinical trials (RCTs) were included.

Specific interventions included in the review
Any form of total parenteral nutrition (TPN; protein, source of non-protein energy with or without lipids) compared with standard care (oral diet plus intravenous fluids).

Participants included in the review
Participants were surgical or critically ill (defined as those who would be cared for in a critical care environment) adults. The patient population consisted of people undergoing: thoracoabdominal surgery, esophageal cancer surgery, gastrointestinal surgery, major surgery/trauma, liver transplant, gastric surgery, pancreatic resection, radical cystectomy, hepatocellular cancer surgery, cardiac surgery, colorectal surgery. Other studies involved patients: with pancreatitis, in neurology intensive care, and with burns to greater than 50% of their body. Studies of paediatric or neonatal patients were excluded. The age and sex of participants was not reported.

Outcomes assessed in the review
The primary outcome was perioperative mortality (death within 30 days of operation) or mortality reported at discharge from hospital. The secondary outcome was the rate of major complications. Major complications were defined as: pneumonia, intra-abdominal abscess, sepsis, line sepsis, myocardial infarction, pulmonary emboli, heart failure, stroke, renal failure, liver failure and anastomotic leak. Minor complications were defined as wound infection, phlebitis, urinary tract infection, and atelectasis.

Length of hospital stay was also an outcome.

How were decisions on the relevance of primary studies made?
Initially, two reviewers screened all citations and classified them as primary studies, review articles, or other. The two reviewers then independently assessed all primary studies. Agreement between reviewers was measured by K with quadratic weights and 100% agreement was reached.

Assessment of study quality
Methodological quality was assessed using a previously used scoring system (see Other Publications of Related Interest). This involved an assessment of: concealment of randomisation, blinding of adjudicators to the study end points, the extent to which consecutive, eligible patients were enrolled in the trial, equality of groups at baseline, adequate description of co-interventions, use of objective definitions of infectious outcomes, and whether intention-to-treat analysis was undertaken. Given the difficulties of blinding the administration of TPN, this was not assessed. Two reviewers independently assessed the methodological quality of studies, and disagreements were resolved by consensus.
**Data extraction**
Two reviewers independently extracted data for analysis and disagreements were resolved by consensus.

Data were extracted on patient population, percentage of malnourished patients, and the outcomes listed above (see "Outcomes Assessed in the Review").

When data were missing, unclear, or not reported on a per-patient basis, the authors attempted to contact the primary investigators and requested them to provide further information if the article had been published in the last 5 years.

Data were combined from all studies to estimate the common relative risk of mortality and complications and associated 95% confidence intervals. The treatment effect was summarised using risk ratios. One half was added to each cell to avoid the problem with bias and instability associated with relative risk estimation in sparse data.

**Methods of synthesis**
How were the studies combined?
Maximum likelihood methods were used to combine risk ratios across all trials. The Mantel-Haenszel method was used to test the significance of treatment effect. A random-effects model was used to estimate the overall risk ratio.

Data on length of hospital stay was not aggregated because of infrequent and variable reporting methods.

How were differences between studies investigated?
A test of heterogeneity was performed across subgroups using the t-test for the difference between 2 subgroups. Subgroup analyses (on malnourished verses adequately malnourished patients, quality score, year of publication, provision of intravenous lipids, critically ill versus surgical patients) were performed in an attempt to explain the heterogeneity present.

**Results of the review**
Twenty-six studies involving 2211 patients were included.

Total parenteral nutrition (TPN) had no effect on mortality compared with standard care (risk ratio (RR), 1.03; 95% CI: 0.81, 1.31). The test for heterogeneity for these studies was not significant, but the authors state that a visual inspection of the individually plotted risk ratios suggests that treatment effects are variable.

Patients who received TPN tended to have a lower complication rate, but this result was not statistically significant (RR, 0.84; 95% CI: 0.64, 1.09). The test for heterogeneity was significant (p = 0.003).

Subgroup analyses: For the following subgroup analyses, TPN is always compared with usual care. Differences between subgroups will only be noted when they are significant.

No difference between TPN and usual care mortality rates occurred for studies of malnourished or adequately nourished participants. The rate of major complications was significantly lower for TPN compared to usual care in malnourished patients (RR, 0.52; 95% CI: 0.30, 0.91). This difference did not exist for adequately nourished patients. The difference in complication rates between these subgroups was of borderline significance (p=0.05).

Mortality rates for those receiving TPN did not differ from usual care for studies published in 1988 or before, or studies published after 1989. Complications for TPN did not differ from usual care for studies published since 1989. However, there were significantly fewer major complications associated with TPN compared with usual care reported in studies published in 1988 or earlier (RR, 0.49; 95% CI: 0.29, 0.81). The difference between subgroups was significant (p<0.005).

There was no difference in mortality rates for TPN versus usual care for studies with a methodological quality score greater than 7, or studies with a methodological score less than 7. Studies with a lower methods score showed a significant reduction in complication rates associated with TPN (RR, 0.54; 95% CI: 0.33, 0.87). This difference did not
occur in studies with higher methodological quality scores. The difference between these subgroups was significant (p=0.02).

There was no difference in mortality rates for TPN versus usual care for patients receiving lipids, or not receiving lipids. Complication rates for TPN were lower than for usual care in studies that did not use lipids (RR, 0.59; 95% CI: 0.38, 0.90). This difference was not present for studies involving no lipids.

Mortality was significantly higher in critically ill patients receiving TPN than usual care (RR, 1.78; 95% CI: 1.11, 2.85). This difference was not apparent in surgical patients. The difference between subgroups was significant (p=0.03). Studies limited to critically ill patients showed no difference in complication rates (only 2 studies reported complication rates) for TPN compared to usual care. Studies of surgical patients were associated with lower complication rates (RR, 0.76; 95% CI: 0.48, 1.0). The difference between subgroups reached borderline significance (p=0.05).

Authors' conclusions
Total parenteral nutrition may have a positive effect on nutritional end points and on even minor complications, but there is no evidence to support a benefit of TPN on overall mortality or major complication rates, particularly in critically ill patients. It may reduce the complication rate, especially in malnourished patients, but study results are influenced by patient population, use of lipids, methodological quality and year of publication.

CRD commentary
The review focuses on a well defined review question. Inclusion and exclusion criteria were appropriate. The validity of the included studies was adequately assessed and the authors performed further analyses to compare outcomes in trials with a methodological quality a score of less than 7 with trials with a score of 7 or better.

The literature search could have been extended to include other databases such as EMBASE. An attempt could also have been made to identify unpublished material and grey literature. Publication bias can not be ruled out. Some details of the individual studies were presented, but it would also have been useful to report the length of treatment and follow-up time. The primary studies were combined despite the presence of heterogeneity in most of the comparisons.

The conclusions follow from the results, but both should be interpreted with caution due to the heterogeneity present.

Implications of the review for practice and research
Practice: The authors suggest that the economics of providing TPN to critically ill patients needs to be carefully studied to facilitate future practice guidelines.

Research: The authors state that future research needs to define the role of TPN in critically ill patients who cannot tolerate any enteral intake.

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