

Enteral nutrition versus parenteral nutrition—the risks and benefits

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SUMMARY

The role of nutrition in patient care became a part of mainstream medicine at about the end of the 1960s, with the publication of several papers that showed a benefit of nutritional support in the prevention of complications. At that time, the emphasis was on nutrition given by the parenteral route. Since then, a series of studies that compared parenteral nutrition with enteral nutrition have suggested that the enteral route of feeding causes fewer complications than the parenteral route. A careful review of the data shows that nutritional support can increase the risk of complications when given to well-nourished, obese and hyperglycemic patients. The avoidance of overfeeding and hyperglycemia is, therefore, of paramount importance. In this context, enteral nutrition, for which gastrointestinal tolerance limits overfeeding, can protect the patient.

KEYWORDS enteral nutrition, parenteral nutrition, TPN

REVIEW CRITERIA

Full papers were selected from MEDLINE. The selected papers fulfilled the criteria of being randomized controlled trials, or reviews and meta-analyses of enteral nutrition or parenteral nutrition. In addition, papers in the author's collection were also included in this Review.

INTRODUCTION

In the late 1960s and the 1970s nutritional support became an established therapy for the management of patients with various conditions.¹ The major route of nutritional support at that time was parenteral.¹ Over the next two decades, the results of a number of small, controlled trials suggested that parenteral nutrition was harmful and promoted increased sepsis.^{1,2} Consequently, the enteral route of feeding is now recommended to be used almost exclusively for nutritional support, particularly of critically ill patients.³

This shift in the preferred route for nutritional support (from parenteral to enteral) coincided with a change in the body composition of the Western population.⁴ The incidence of obesity increased in the general population, and in particular, in patients in intensive care units (ICUs),⁵ which had a profound effect on the incidence of insulin resistance in critically ill patients. Insulin resistance is more severe in obese than nonobese patients and causes hyperglycemia,⁶ which significantly increases the risk of infection and, therefore, sepsis.^{7,8} Parenteral nutrition, by which hypertonic glucose and lipids can be infused *ad libitum*, can also result in significant hyperglycemia, which can, again, promote sepsis.^{7,8} This risk of hyperglycemia after parenteral nutrition needs to be kept in mind when considering the discussion of the relative benefits and risks of enteral versus parenteral nutrition that follows, below.

PARENTERAL NUTRITION VERSUS NO NUTRITIONAL SUPPORT

In a meta-analysis of 26 controlled clinical trials, which included a total of 2,211 patients, there was no reduction in mortality or in the incidence of major complications in patients who received parenteral nutrition, compared with those who received no nutritional support.⁹ In malnourished patients only, however, there was a significant reduction in the incidence of complications; this reduction was particularly evident in early

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studies that were also of low quality compared with the most recent studies. The authors of this meta-analysis concluded, therefore, that parenteral nutrition did not have any benefit compared with no nutritional support.

A careful analysis of the data in this meta-analysis, when considered in relation to the increase in the incidence of obesity among patients in ICUs, however, suggests that there might be an alternative explanation. The early studies included in the meta-analysis were likely to include an increased proportion of nonobese, malnourished individuals, who would benefit from parenteral nutrition. By contrast, the relatively recent studies were likely to include an increased proportion of patients who received parenteral nutrition despite the fact that they were obese and who were, therefore, significantly overfed.

This possible explanation is supported by the results of a controlled clinical trial of patients who received preoperative parenteral nutrition.¹⁰ In this trial, the patients who received parenteral nutrition had more sepsis overall than the controls, but in the subgroup of malnourished patients the relative incidence of sepsis (compared with its incidence among controls) was not increased, and noninfectious complications fell from about 40% to 20%. It should be noted that the patients in this study who were on parenteral nutrition received 1,000 calories above their metabolic requirements, which resulted in overfeeding. As discussed above, giving such an excess of calories to patients who are not malnourished increases their risk of sepsis, a finding consistent with the observed result.

In a study of Chinese patients undergoing hepatectomy, who weighed about 50 kg and had a triceps skin-fold thickness of only 10 mm, parenteral nutrition significantly reduced the incidence of complications and sepsis and the use of diuretic drugs.¹¹ The findings of this study, together with the information from the meta-analysis discussed above, suggest that if parenteral nutrition is given to patients who are malnourished, significant benefits can be observed. On the other hand, excessive calorie intake given parenterally to adequately nourished patients can increase their risk of sepsis.

The results of another meta-analysis of seven randomized, controlled trials that compared standard care with parenteral nutrition are in

line with this relationship of nutritional status to the outcome of parenteral nutrition.¹² Although, on the whole, patients who received parenteral nutrition had more infectious complications than those who received standard care, in populations with a high degree of protein–energy malnutrition, standard care was associated with increased mortality compared with parenteral nutrition, as well as a trend towards an increased incidence of sepsis.¹²

ENTERAL NUTRITION VERSUS PARENTERAL NUTRITION

In a meta-analysis of 30 controlled clinical trials that compared early enteral nutrition with parenteral nutrition in patients with a critical (admitted to an ICU) or noncritical illness, there was no difference in mortality between patients on enteral nutrition compared with those on parenteral nutrition.¹³ The same result was observed in another meta-analysis of 12 controlled clinical trials that compared enteral nutrition with parenteral nutrition in ICU patients only:³ in this meta-analysis, which included a total of 748 patients in ICUs, there was no difference in mortality between the two forms of nutritional support.³ By contrast, a third meta-analysis of nine trials in ICU patients showed a significant reduction of mortality in favor of patients who received parenteral nutrition compared with those who received enteral nutrition started after 24 h, but not when compared with those given early enteral nutrition.¹⁴ This third meta-analysis¹⁴ (unlike the other two) included only studies in which 95% of the patients had completed follow-up. In addition, a sensitivity analysis showed that this benefit of parenteral nutrition was robust, and persisted after the inclusion of two further studies in which less than 95%, but more than 90%, of patients had completed follow-up.

The incidence of sepsis in all three meta-analyses was statistically greater in the patients who received parenteral nutrition^{3,13,14} than in those who received enteral nutrition or standard care. On the basis of this difference in septic complications, the authors of one of the meta-analyses³ have strongly recommended enteral nutrition over parenteral nutrition. The authors of the two other studies did not make such an emphatic recommendation, and concluded that further good-quality studies were required.^{13,14} The authors of one of these meta-analyses also questioned the significance

of the increase in infectious complications, because mortality was reduced.¹⁴ The authors of the other meta-analysis concluded that "... the impact of [parenteral nutrition] on infective complications may in fact be more apparent than real", because the increased infection rate seen in patients given parenteral nutrition could have been caused by controllable factors such as hyperglycemia.¹³

These meta-analyses all included several of the same trials. On careful examination of the ICU-based data, however, only six of these trials included a comparison of the incidence of sepsis. In three of the six studies there was no difference in the incidence of sepsis, and in the other three there was an increased incidence of sepsis in patients who received parenteral nutrition. A detailed analysis of the studies in which the incidence of sepsis was increased in patients given parenteral nutrition,^{15–17} shows that there was significant hyperglycemia in patients who received parenteral nutrition compared with those who received enteral nutrition. Despite the difference in the incidence of sepsis in two of the studies,^{16,17} there was no difference between patients who received parenteral or enteral nutrition, respectively, in relation to their requirements for antibiotics, ventilation time and need for dialysis.^{16,17} Whether the difference in the incidence of sepsis between patients given parenteral and enteral nutrition in these two studies actually resulted in any clinical harm remains unclear.

In summary, the aggregate information from these meta-analyses suggests that parenteral nutrition might not alter mortality when compared with enteral nutrition, and that parenteral nutrition might be beneficial when enteral nutrition cannot be started within 24 h or for nonobese malnourished patients.¹⁴ Parenteral nutrition also seems to be associated with hyperglycemia. Despite the increased incidence of sepsis in parenterally versus enterally fed patients, however, these studies showed no differences in antibiotic use or in other complications related to sepsis, such as ventilation requirements and the need for dialysis. In addition, although the third meta-analysis¹⁵ revealed an increased incidence of sepsis in patients given parenteral nutrition, comparison of the intent-to-treat populations showed no differences in the duration or cost of patients' hospital stay.

HYPERGLYCEMIA AND OUTCOME

In a controlled clinical trial of 1,458 patients who received nutritional support (either enteral or parenteral) in ICUs,¹⁸ the use of intensive insulin therapy to maintain blood sugar levels between 4.4 mmol/l and 6.1 mmol/l reduced mortality by 50% compared with that of patients whose blood sugar levels were maintained by conventional insulin therapy between 10.0 mmol/l and 11.1 mmol/l. This study showed that maintenance of euglycemia had a much more profound effect on outcome than enteral nutrition per se. Euglycemia in ICU patients was associated with reduced mortality, whereas enteral nutrition did not result in reduced mortality compared with parenteral nutrition. The reduction in mortality seen with the control of blood sugar to euglycemic levels was observed irrespective of the severity of the illness or whether the patient received enteral or parenteral nutrition. This study was criticized because it involved only surgical patients treated in the ICU. The same authors have subsequently shown that patients treated in a medical (i.e. nonsurgical) ICU also had fewer major complications when euglycemia was strictly maintained as defined above.¹⁹ Although on an intent-to-treat basis mortality was no different between patients treated with tight control of blood glucose to euglycemic levels and those were not so treated, complications were reduced in euglycemic patients.

ENERGY INTAKE AND OUTCOME IN OBESE ICU PATIENTS

A pseudorandomized trial investigated whether early (within 48 h) or late (after 4 days) enteral feeding alters the outcome of ICU patients.²⁰ The authors' hypothesis was that delayed (late) feeding would significantly increase complications from malnutrition. In this trial, 150 patients were randomly allocated to receive either 25 kcal/kg of body weight daily from the start of the study (so that their caloric intake met their metabolic requirements) or to receive only 20% of their energy requirements for the first 4 days, subsequently followed by the full amount of 25 kcal/kg daily.²⁰ The patients in the delayed enteral feeding group received an average of 9 kcal/kg daily, in contrast to the other group who actually received about 20 kcal/kg daily. The patients in this study were distinguished by the fact that their mean BMI was 29 kg/m² and they were hyperglycemic. The obese, hyperglycemic

patients who were fed approximately 9 kcal/kg daily had a lower complication rate in terms of pneumonia, number of days on a ventilator, and requirements for antibiotic use than those patients who received sufficient calories to meet their metabolic requirements from the study start. In short, hypocaloric feeding of these obese patients was better than providing them with an optimal energy intake.

ENTERAL VERSUS PARENTERAL NUTRITION: SPECIFIC CONDITIONS

Pancreatitis

Most patients with mild pancreatitis can eat within 5 days of hospitalization and parenteral nutrition has no clinical benefit in this setting.²¹ Most controlled clinical trials of enteral versus parenteral nutrition in patients with pancreatitis have, therefore, included very few patients: on average, 30–40 patients, who were randomly allocated almost equally to receive either enteral or parenteral nutrition.^{22,23} The power of these studies is, therefore, extremely low. Two studies that included patients who had moderately severe pancreatitis did not show any difference in clinical outcomes between enterally fed and parenterally fed patients.^{22,23}

In one study of 38 patients who had severe pancreatitis, the incidence of sepsis was higher in those patients who received parenteral nutrition.¹⁷ Patients who received parenteral nutrition were also hyperglycemic, however, in contrast to those who received enteral nutrition. Furthermore, despite the difference in the incidence of sepsis, there was no difference between these patients' requirements for antibiotic use, number of days on a ventilator or the need for dialysis. In a study published in 2003, hypocaloric enteral nutrition was shown to shorten the duration of hospital stay compared with parenteral nutrition.²⁴

Head injury

One randomized clinical trial of enteral nutrition versus parenteral nutrition that included 51 patients with head injury showed that total parenteral nutrition allowed more calories to be administered and resulted in a better increase in the Glasgow Coma Score than enteral nutrition.²⁵ Another controlled clinical trial showed no difference in outcome for patients with head injury who were assigned to enteral nutrition compared with those assigned to parenteral nutrition.²⁶

Trauma

Moore *et al.* randomly allocated 29 trauma patients to receive enteral nutrition and 30 trauma patients to receive parenteral nutrition.¹⁵ Patients on parenteral nutrition received significantly more calories than those on enteral nutrition, and they also had higher glucose levels and higher insulin levels. The incidence of major sepsis was increased in the patients who received parenteral nutrition.

Kudsk *et al.* randomly allocated a total of 98 trauma patients to receive either enteral nutrition or parenteral nutrition.¹⁶ The patients on parenteral nutrition received significantly more calories than those on enteral nutrition. In patients who had an injury severity score of less than 20 or an abdominal trauma index score of less than 24, the incidence of sepsis was similar for patients on enteral nutrition or parenteral nutrition. For patients who had an injury severity score greater than 20 or an abdominal trauma index score greater than 24, however, the incidence of sepsis was higher in patients on parenteral nutrition than in those on enteral nutrition. In this trial, and despite the increased incidence of sepsis in trauma patients who received parenteral nutrition, there was no difference between the groups in the requirement for antibiotic use, the duration of hospital stay or the number of antibiotics used.

CAUSES OF SEPSIS IN PATIENTS ON PARENTERAL NUTRITION

The theory traditionally used to explain the increased incidence of sepsis in patients on parenteral nutrition is based on the observation that the mucosa of the intestine atrophies in animals on parenteral nutrition, because the intestine does not receive food and enters a resting state.²⁷ Intestinal atrophy is thought to promote translocation of bacteria into the bloodstream, which causes sepsis.²⁸

Although this theory is attractive, a number of flaws become evident when it is applied to human patients. In humans, intestinal atrophy does not occur unless the gastrointestinal tract is kept at rest for very prolonged periods of time (Table 1).^{29–32} Intestinal biopsies taken after an individual has been without oral food intake for several weeks have shown surprisingly few abnormalities (Table 1). To show that bacterial translocation occurs, it is necessary to demonstrate that intestinal bacteria can be cultured from the bowel lumen, mesenteric lymph

Table 1 Total parenteral nutrition and intestinal atrophy in humans.

Author, year and reference	Number of patients	Nutritional support	Presence or absence of intestinal atrophy
Guedon <i>et al.</i> (1986) ²⁹	7	NPO	No atrophy after 21 days
Rossi <i>et al.</i> (1993) ³⁰	7	NPO	Atrophy after 9 months
Pironi <i>et al.</i> (1994) ³¹	2	TPN	Atrophy after 2–3 months
Sedman <i>et al.</i> (1995) ³²	203	TPN or enteral nutrition	No atrophy after ≥10 days

Abbreviations: NPO, *nulla per os* (nothing by mouth); TPN, total parenteral nutrition.

nodes and the blood. Moore and colleagues³³ took blood from 132 patients and showed that most cultures were of bacteria not found in the intestine. In addition, in only two patients were the same bacteria cultured from the intestine, mesenteric lymph nodes and blood. Sedman *et al.*³⁴ used the criteria described above to demonstrate that bacterial translocation occurred in about 10% of patients who underwent laparotomy for various conditions. The proportion of patients in whom bacterial translocation occurred was no different for patients on enteral nutrition and those on parenteral nutrition. In conclusion, it is very unlikely that parenteral nutrition in humans increases sepsis because of intestinal atrophy or bacterial translocation.

Another theory has been advanced to explain the increased incidence of sepsis in patients who receive parenteral nutrition: that parenterally administered lipids promote bacterial infection, perhaps by blocking the reticulo-endothelial system. In a controlled clinical trial that involved recipients of bone marrow transplants on nutritional support, 253 patients were randomly allocated to receive 30% of their energy intake as fat and 259 patients were randomly allocated to receive only 6% of their energy intake as fat.³⁵ Both groups of patients received one to five times their daily requirements (based on the resting metabolic rate) for total energy, through the parenteral route. Care was taken to give the patients enough insulin to prevent hyperglycemia from developing. There was no difference in the incidence of bacteremia or fungal infections between the high-fat-intake group and the low-fat-intake group. There was also no difference in the time to the first infection or any infection over the next 60 days between the patients who received 30% lipid and those who received only 6% lipid. In fact, some patients in the low-fat-intake group

developed essential fatty acid deficiency. This trial, in patients who were markedly immunosuppressed, indicates that parenterally administered lipids do not increase the incidence of bacterial infection.

CONCLUSIONS

There is no doubt that parenteral nutrition can be life-saving for patients who cannot eat and/or absorb nutrients. In addition, parenteral nutrition is not likely to cause hyperglycemia in nonobese, insulin-sensitive patients. By contrast, obese, insulin-resistant patients are easily overfed via the parenteral route, which results in hyperglycemia; these patients consequently become prone to infection. It is, however, very difficult to feed an excessive amount of calories to patients via the enteral route, and for this reason enteral feeding is safer than parenteral feeding for patients who are obese and insulin-resistant.

The route of nutritional support does not seem to alter the risk of infection because of either intestinal atrophy or bacterial translocation. The selection of enteral versus parenteral nutrition should depend on the availability of the gastrointestinal tract for feeding and the patient's tolerance levels. In addition, it should be remembered that nasogastric tubes can cause fluid aspiration and pneumonia. On the basis of the available evidence and irrespective of the route used to administer nutritional support, it is important to avoid the development of hyperglycemia and hyperlipidemia, as well as the feeding of an excessive amount of calories to obese patients.

In the future, the metabolic effects of nutrients rather than the route of administration need to be emphasized. Trials that compare the role of reduced energy intake with an adequate intake of protein, minerals, trace elements and vitamins should be undertaken in obese, diabetic and hyperglycemic patients.

KEY POINTS

- Parenteral nutrition is lifesaving for all patients who are unable to eat and/or absorb an oral diet
- The demographics of the Western population have resulted in an increased incidence of obesity in the general population and in patients in intensive care units
- Obese, hyperglycemic and diabetic patients are prone to develop infection as a result of hyperglycemia
- Parenteral nutrition is more likely to cause hyperglycemia and increased sepsis than enteral nutrition
- Strict glucose control has been shown to reduce the incidence of sepsis and mortality in patients in intensive care units
- In avoidance of the complications associated with nutritional support, the most important consideration is not the route of administration but the avoidance of excessive energy intake and hyperglycemia

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Competing interests

The author declared he has no competing interests.