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Papers

Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis

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Abstract

Objective To compare the safety and clinical outcomes of enteral and parenteral nutrition in patients with acute pancreatitis.

Data sources Medline, Embase, Cochrane controlled trials register, and citation review of relevant primary and review articles.

Study selection Randomised controlled studies that compared enteral nutrition with parenteral nutrition in patients with acute pancreatitis. From 117 articles screened, six were identified as randomised controlled trials and were included for data extraction.

Data extraction Six studies with 263 participants were analysed. Descriptive and outcome data were extracted. Main outcome measures were infections, complications other than infections, operative interventions, length of hospital stay, and mortality. The meta-analysis was performed with the random effects model.

Data synthesis Enteral nutrition was associated with a significantly lower incidence of infections (relative risk 0.45; 95% confidence interval 0.26 to 0.78, $P=0.004$), reduced surgical interventions to control pancreatitis (0.48, 0.22 to 1.0, $P=0.05$), and a reduced length of hospital stay (mean reduction 2.9 days, 1.6 days to 4.3 days, $P<0.001$). There were no significant differences in mortality (relative risk 0.66, 0.32 to 1.37, $P=0.3$) or non-infectious complications (0.61, 0.31 to 1.22, $P=0.16$) between the two groups of patients.

Conclusions Enteral nutrition should be the preferred route of nutritional support in patients with acute pancreatitis.

Introduction

Nutritional support has become increasing recognised as an essential component of the management of critically ill patients. The benefits of the early initiation of enteral nutrition in surgical patients has now been clearly established.[1–3] Furthermore, published data suggest that the gut is the optimum route of nutritional support in patients with an intact intestinal tract.[4] Yet despite this information, total parenteral nutrition remains in widespread use, with many experts claiming equipoise between parenteral and enteral nutrition.[5–9]

Acute pancreatitis results in a hypermetabolic, hyperdynamic, systemic inflammatory response syndrome that creates a highly catabolic stress state. Despite the lack of prospective data, gut rest (prohibiting enteral intake) with or without the provision of parenteral nutrition has become regarded as standard care in patients with acute pancreatitis.[10] Recent evidence, however, suggests that enteral nutrition may be feasible (and perhaps desirable) in such patients. Animal studies have shown that the site in the gastrointestinal tract to which feedings are delivered determines whether the pancreas is stimulated and that jejunal feedings result in negligible increases in enzyme, bicarbonate, and volume output from the pancreas.[11 12] This observation has been confirmed in humans.[13] Some experts suggest that enteral feeding stimulates lysosomal movement to the cell surface, minimising intracellular release of pancreatic enzymes, and may be therapeutic in patients with acute pancreatitis. In addition, enteral nutrition reduces production of proinflammatory mediators that may also have therapeutic potential in such patients.

The most severe complication of acute pancreatitis is pancreatic infection, which carries a mortality of up to 80%.[14–17] Many studies report that total parenteral nutrition impairs humoral and cell mediated immunity, increases the vigour of the proinflammatory response, increases bacterial translocation, and increases infection rates in various critically ill patients.[4] On the other hand, compared with total parenteral nutrition, enteral nutrition is associated with improved immune function and reduced infections. While several randomised controlled studies have been performed comparing total parenteral nutrition with enteral nutrition in patients with pancreatitis these studies have been underpowered and hence the differences were not always statistically significant. Furthermore, the magnitude of the treatment effect remains unknown. We therefore performed a meta-analysis of available studies that compared total parenteral nutrition with enteral nutrition to provide an estimate of the treatment effect on important clinical outcomes.

Methods

Identification of trials

We aimed to identify all relevant randomised controlled clinical trials that compared enteral with parenteral nutrition in patients with acute pancreatitis. A randomised controlled trial was defined as a trial in which participants were assigned prospectively to one of two interventions by random allocation. We used a multi-method approach to identify relevant studies for this review. Both authors independently searched the National Library of Medicine's Medline database for relevant studies in any language published from 1966 to January 2004 using the MeSH headings and keywords: enteral nutrition (explode) AND parenteral nutrition (explode) or TPN, AND pancreatitis, AND randomised controlled trials (publication type) or controlled clinical trials or clinical trials, randomised. In addition we searched Embase, the Cochrane controlled trials register, and the *Cochrane Database of Systematic Reviews*. Bibliographies of all selected articles and review articles that included information on

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nutrition in pancreatitis were reviewed for other relevant articles. In addition, we reviewed our personal files and contacted experts in the specialty. This search strategy was done iteratively until we did not find any new potential citations on review of the reference lists of retrieved articles.

Study selection and data extraction

To be included in the analysis trials had to be randomised clinical trials in patients admitted to hospital with acute pancreatitis. The intervention was enteral nutrition versus parenteral nutrition, and trials had to have as a primary outcome variable at least one of the following: number of infections, total number of non-infectious complications, number of surgical interventions, length of hospital stay, and hospital mortality.

Data extraction

We independently abstracted data from all studies using standardised forms. Data were abstracted on study design, setting, and population; severity of illness; the exact methods of nutritional support; and the outcome variables listed above. In calculating each outcome variable, we used intention to treat data (including all patients randomised). Disagreements regarding values or analysis were resolved by discussion and, if necessary, contact with the primary authors. Missing data were supplied by the primary authors.[18 19]

We used the APACHE II (acute physiology and chronic health evaluation) score, Ranson score, or Glasgow score to quantify the severity of pancreatitis. APACHE II is a general purpose scoring system for severity of illness that includes 12 physiological variables, age, and a chronic health score.[20] An APACHE II score of <10 indicates mild disease with a low predicted mortality. The Ranson and Glasgow (or Imrie) scores predict the severity of pancreatitis.[21 22] The Ranson score includes 11 clinical and laboratory measurements available within 48 hours of admission.[21] The Glasgow score is a modification of the Ranson system and includes nine clinical and laboratory variables.[22] A Ranson or Glasgow score ≥ 3 indicates severe pancreatitis.[23]

The methodological quality of the studies included in the meta-analysis was scored with the Jadad composite scale.[24 25] This is a 5 point quality scale, with low quality studies having a score of ≤ 2 and high quality studies a score of ≥ 3.[25 26]

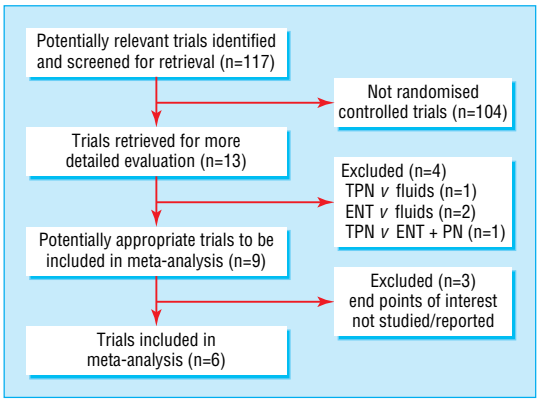


Fig 1 Process of study selection of randomised controlled trials (TPN=total parenteral nutrition; ENT=enteral nutrition; PN=parenteral nutrition)

Data analysis

Infections, complications other than infections, operative interventions, and mortality were binary variables, and length of hospital stay was a continuous variable. Study end points were calculated by intention to treat. The data analysis was performed using the random effects model with meta-analysis software (RevMan 4.1, Cochrane Collaboration, Oxford, and NCSS 2004, Kaysville, UT, USA). The relative risk and continuous data outcomes are presented with 95% confidence intervals. We tested heterogeneity between trials with χ^2 tests, with $P \leq 0.05$ indicating significant heterogeneity.[27]

Results

The search strategy generated 117 studies. From these, we identified 12 randomised clinical trials comparing enteral and parenteral nutrition. Only six randomised clinical trials fulfilled the criteria for consideration in the review.[18 19 28–31] Articles were excluded because parenteral nutrition was compared with conventional therapy (intravenous fluids alone),[32] jejunal feeding was compared with conventional therapy,[33–35] total parenteral nutrition was compared with the combination of enteral and

Table 1 Demographic data of studies included in meta-analysis. Figures are for enteral nutrition/total parenteral nutrition, and scores are given as means (SDs)

	No of patients	Ranson criteria	Glasgow score	APACHE II	Siting of nasojejunal tube
McClave, 1997[28]	16/16	1.3 (0.35)/1.3 (0.35)	—	—	Endoscopic
Windsor, 1998[29]	16/18	—	2/2	8/9.5	Fluoroscopic*
Kalfarentzos, 1997[30]	18/20	—	4.2 (0.9)/4.6 (1.1)	12.7 (2.6)/11.8 (1.9)	Fluoroscopic
Abou-Assi, 2002[19]	26/27	3.1 (0.5)/2.5 (0.4)	—	—	Fluoroscopic/ endoscopic
Olah, 2002[18]	41/48	—	2.6 (1.2)/2.4 (1.6)	—	Fluoroscopic
Gupta, 2003[31]	8/9	—	—	8/10	Blind†

*Patients with mild disease (Glasgow score <3) received oral nutrition.
†"Blind bedside technique."

Table 2 Outcome data of studies included in meta-analysis. Figures are for enteral nutrition/total parenteral nutrition

	No of patients	Septic complications	Other complications	Surgical intervention	Length of stay	Mortality
McClave, 1997[28]	16/16	2/2	—	—	9.7/11.9	0/0
Windsor, 1998[29]	16/18	0/3	0/5	1/5	12.5/15	0/2
Kalfarentzos, 1997[30]	18/20	5/10	3/5*	2/4	40/39	1/2
Abou-Assi, 2002[19]	26/27	1/9†	13/17*	1/2	14.2/18.4	6/8
Olah, 2002[18]	41/48	5/13	3/4	5/11	16.8/23.6	2/4
Gupta, 2003[31]	8/9	0/2	0/6‡	—	7/10	0/0

*Excluding hyperglycaemia.
†All central sepsis related to venous catheter.
‡Organ failure.

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Table 3 Jadad quality score of trials included in meta-analysis[24]

	Year	Randomisation method	Blinding	Withdrawals/drop outs accounted for	Jadad score
McClave, 1997[28]	1997	Not stated	None	Yes	2
Windsor, 1998[29]	1998	Odd/even hospital number	None	Yes	1
Kalfarentzos, 1997[30]	1997	Sealed numbered envelopes	None	Yes	3
Abou-Assi, 2002[19]	2002	Not stated	None	Yes	2
Olah, 2002[18]	2002	Birth date	None	Yes	1
Gupta, 2003[31]	2003	Sealed numbered envelopes	None	Yes	3

parenteral nutrition,[36] and the end points of interest were not studied.[36–39] Figure 1 shows the search process. A review of the bibliographies of all selected articles and review articles and communication with experts in the specialty failed to identify additional relevant articles. A total of 263 participants were enrolled in the six studies included in the meta-analysis (table 1). Table 2 shows the study outcome data. Table 3 shows the quality of the included studies as assessed by the Jadad score. We did not carry out subgroup analysis according to the Jadad score.[40]

The study by Olah and colleagues included a second phase, in which early jejunal feeding was combined with prophylactic imipenem.[18] We did not include patients in this non-randomised third group in this meta-analysis. While all included studies randomised patients to enteral or parenteral nutritional support, selection of patients and study design differed somewhat between the studies. The inclusion criteria for all studies included patients admitted to hospital with acute pancreatitis characterised by abdominal pain with raised serum amylase and lipase activity. In all studies patients were enrolled within 48 hours after admission to hospital. Enteral nutrition was delivered through a nasojejunal tube that had been placed endoscopically or radiographically.

In the study by Gutpa et al, a dual lumen weighted nasojejunal tube was passed into the stomach at the bedside, with the position being verified radiographically.[31] The study by Kalfarentzos et al included only patients with an Imrie score of ≥ 3 or an APACHE II score of ≥ 8.[30] The study by Abou-Assi randomised patients with moderate to severe pancreatitis who had not improved clinically by 48 hours and were unable to tolerate resumption of normal feeding.[19] In the study by Windsor et al patients were stratified according to their admission Imrie score.[29] In this study patients with mild/moderate disease (<3 Imrie points) received enteral feeding in the form of oral nutritional supplements, while patients with an Imrie score of ≥ 3 received enteral nutrition through a nasojejunal tube. McClave and coworkers compared early enteral versus parenteral nutrition in patients with mild pancreatitis.[28] In three studies nutritional support was initiated within 48 hours of admission to hospital.[18 28 30] In two studies a 48 hour enrolment period was followed by the nutritional support period.[19 29] Indications for operative intervention in all studies included persistent or deteriorating organ failure despite maximal intensive care, verified infected pancreatic necrosis, and large symptomatic or infected pseudocyst formation.

Primary outcomes

Figure 2 shows the relative risks and 95% confidence intervals for infections, complications other than infections, surgical intervention, and mortality.

Infections—Information on the incidence of infections was available for all the studies included in the meta-analysis. Infections recorded included pneumonia, abdominal abscess, pancreatic abscess, wound infections, and blood stream infection. Overall, there was a significantly lower risk of infection in the patients who received enteral nutrition compared with those who received parenteral nutrition (relative risk of 0.45, 95% confidence interval 0.26 to 0.78, P = 0.004, fig 3). The test result for heterogeneity between the studies was not significant (P = 0.59).

Complications other than infections—Five studies reported on complications other than infections, including adult respiratory distress syndrome, multi-organ failure, acute pseudocysts, and pancreatic fistula. There was no significant difference in the incidence between the enteral and total parenteral nutrition group (0.61, 0.31 to 1.22, P = 0.16).

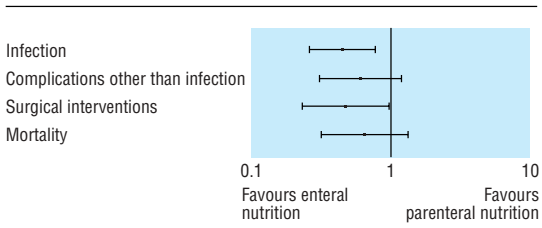


Fig 2 Risk of infection, complications other than infection, surgical intervention, and mortality; results from meta-analyses of randomised trials comparing enteral with parenteral nutrition in pancreatitis

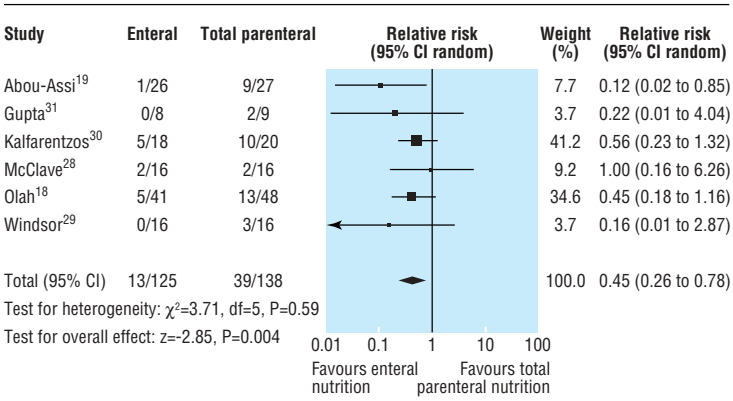


Fig 3 Random effects model of relative risk (95% confidence interval) of infections associated with enteral feeding compared with parenteral nutrition

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Surgical interventions—Four studies reported on the need for surgical intervention for the management of pancreatitis. The requirement for surgery was significantly lower in the patients fed enterally (0.48, 0.23 to 0.99, P = 0.05). The test result for heterogeneity was not significant ($\chi^2 = 0.62$, P = 0.89).

Length of hospital stay—All studies included in the meta-analysis provided information on length of hospital stay, which was significantly shorter in the enteral nutrition group (mean reduction of 2.9 days, 1.6 days to 4.3 days; P < 0.001). There was, however, significant heterogeneity between studies ($\chi^2 = 16.5$, P = 0.0056).

Mortality—All studies reported on hospital mortality. There was no significant difference in hospital mortality between the enteral and total parenteral nutrition groups (relative risk 0.66, 0.32 to 1.37, P = 0.3).

Discussion

This meta-analysis shows that in patients with acute pancreatitis, total parenteral nutrition, as compared with enteral nutrition, significantly increases the risk of infective complications, increases the likelihood of a surgical intervention (to control pancreatic infection), and increases the length of hospital stay. The detrimental effects of total parenteral nutrition were associated with a trend towards increased complications other than infections and a higher mortality. Importantly, the results are internally consistent and all outcomes favour the enterally fed groups.

Parenteral nutrition and infections

The finding that parenteral nutrition increases infections in patients with pancreatitis is not unexpected and is supported by a large body of experimental and clinical data. Experimental studies show that total parenteral nutrition (enteric starvation) results in rapid and severe atrophy of lymphoid tissue associated with the gut (GALT) and increases bacterial translocation.[41–44] Lymphoid tissue associated with the gut is the source of most mucosal immunity in humans. In addition, total parenteral nutrition is associated with impaired B and T cell lymphocyte function, altered leucocyte chemotaxis, impaired phagocytosis, and impaired bacterial and fungal killing.[45–49] Experimental models of sepsis have shown a significantly higher mortality in animals receiving parenteral compared with enteral nutrition.[50–53] These experimental data are supported by clinical studies, which have consistently shown a higher risk of infection in patients receiving total parenteral nutrition.[19 54–59] Non-randomised clinical studies of use of total parenteral nutrition in patients with acute pancreatitis also suggest increased infection rates.[60–62]

Parenteral nutrition enhances the proinflammatory response

While parenteral nutrition is associated with impaired innate and acquired immunity, predisposing patients to infection, it is also associated with a more pronounced proinflammatory response. Clinical and experimental studies have shown higher levels of both local and systemic proinflammatory mediators with parenteral compared with enteral nutrition.[29 53] Lin and coworkers found higher concentrations of interleukin 6 and interleukin 8 after colorectal surgery in patients receiving total parenteral nutrition compared with those fed enterally.[63] Similarly Gianotti and coworkers found higher concentrations of interleukin 6 in patients undergoing major abdominal surgery for malignant neoplasms who received total parenteral nutrition compared with enteral nutrition.[59] Fong and colleagues challenged healthy volunteers with endotoxin after they had received enteral feedings or total parenteral nutrition (without oral intake) for seven days.[64] In this study, circulating concentrations of tumour necrosis factor α and C reactive protein were significantly higher in the total parenteral nutrition group. In the study by Windsor et al, included in our meta-analysis, there was a significant fall in the serum concentration of C reactive protein after enteral nutritional support, while there was no significant change in this variable in the parenterally fed group.[29] An enhanced proinflammatory response in patients receiving total parenteral nutrition may partly explain the associated increased morbidity we observed.

Pancreatic infections and bacterial translocation

The most severe complication of acute pancreatitis is pancreatic infection.[14–17] The risk of pancreatic infection is related to the extent of pancreatic necrosis and therefore the severity of the disease. The finding that the microorganisms causing pancreatic infection are common enteric pathogens implies that bacterial translocation from the intestinal tract to pancreas may have a role in the pathogenesis of sepsis induced by pancreatitis.[14–17 65–67] Lack of enteral feeding results in atrophy of the gastrointestinal mucosa, bacterial overgrowth, increased intestinal permeability, and translocation of bacteria or bacterial products into the circulation.[68–76] Total parenteral nutrition may therefore promote bacterial translocation in patients with pancreatitis. In an experimental model of pancreatitis, compared with total parenteral nutrition, enteral nutrition reduced systemic plasma endotoxin, bacterial translocation to the portal and systemic blood, and bacterial colony counts in the mesenteric lymph nodes, pancreas, and lung.[77] In addition, changes in enteral nutrient supply, osmolality, or pH with total parenteral nutrition may induce bacteria to express virulence genes that enhance bacterial adhesion and translocation or the production of local toxins that may act locally or systemically.[78–81] Enteral nutrition, on the other hand, may switch off these virulence genes.

The studies reported in this analysis provided enteral nutrition through feeding tubes in the small bowel. Although the exact location of all tubes was not reported, most were stated to be in the jejunal location. It is known that pancreatic stimulation from enteral nutrients decreases as the feeding site moves down the bowel. Thus, it is unclear whether similar results would occur with more proximal feeding sites such as the stomach.

Most cases of acute pancreatitis are mild and self limiting, with serum enzyme activities returning toward normal within two to four days. Indeed, in the study by Abou-Assi et al, 87% of patients with pancreatitis admitted to their hospital over a 12 month period had mild pancreatitis (< 3 Ranson criteria), with 75% of patients being able to resume oral feeding within 48 hours after admission.[19] We suggest placement of a jejunal feeding tube and the initiation of early enteral feeding in patients with moderate and severe pancreatitis (> 3 Ranson criteria). In patients with mild pancreatitis placement of a jejunal feeding tube and the initiation of enteral feeding should be considered in those patients who are unable to resume oral feeding after 48 hours of conservative therapy. Previously well nourished patients with mild pancreatitis who can resume oral intake within a few days may not benefit from enteral tube feeding. On the other hand, it is likely that previously malnourished patients and patients unable to resume oral intake within a few days would benefit from nutritional support.

Limitations of study

This systematic review has several limitations. The studies included are of relatively poor quality, with four of the six studies

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What is already known on this topic

Gut rest, with or without parenteral nutrition, is considered to be the standard care in patients with acute pancreatitis

In patients with an intact gastrointestinal tract, enteral nutrition is the preferred route of nutritional support

Parenteral nutrition is immunosuppressive and proinflammatory and may be deleterious in patients with pancreatitis

What this study adds

Compared with enteral nutrition, parenteral nutrition significantly increases the risk of infections and the requirement for surgical interventions in patients with acute pancreatitis

The early initiation of enteral nutrition should be considered as standard in patients with severe pancreatitis

having a Jadad score of <3.[24] None of the studies included in this meta-analysis were blinded. Studies with inadequate concealment of allocation may overestimate the intervention effect.[82] However, it would be extremely difficult, if not impossible, to conceal the route of nutritional support even if placebo formulations were used. An additional limitation is the small number of patients that were included in the analysis (n = 263). The overall small sample size led to wide confidence intervals. Furthermore, the included studies had differing inclusion and exclusion criteria (and therefore differing severity of illness). The difference in severity of disease may explain the heterogeneity in the length of stay between studies. Furthermore, it is possible that studies with negative results, which showed no trend in favour of either intervention, may remain unpublished, leading to publication bias. The limitations of the individual included studies restrict the strength of the conclusion that can be drawn from this review. However, our results are supported by an extensive body of experimental and clinical data, which has shown the adverse effects of parenteral compared with enteral nutrition (such as immune compromise, increased risk of infections, exaggerated proinflammatory response, metabolic complications, depletion of antioxidants, gut atrophy).[29 41–53 63 68–76]

In conclusion, although the available data are limited in terms of numbers and methodological quality, the best available evidence does not support the use of total parenteral nutrition in patients with acute pancreatitis. This conclusion is supported by a large body of experimental and clinical data and with the underlying pathophysiology of pancreatitis.

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Competing interests: None declared.

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