

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

Published data suggest that the gut is the best route of nutritional support in patients with an intact intestinal tract.¹ Yet total parenteral nutrition remains in widespread use, with many experts claiming equipoise between parenteral and enteral nutrition.²⁻⁶

Despite the lack of prospective data, gut rest with or without the provision of parenteral nutrition has become regarded as standard care in patients with acute pancreatitis.⁷ Recent evidence, however, suggests that enteral nutrition may be feasible (and perhaps desirable) in such patients. Animal studies have shown that if the feedings are delivered to the jejunum there are negligible increases in enzyme, bicarbonate, and volume output from the pancreas. This observation has been confirmed in humans.⁸ 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.

The most severe complication of acute pancreatitis is pancreatic infection. Many studies report that total parenteral nutrition impairs humoral and cell medi-

ated immunity, increases the vigour of the proinflammatory response, increases bacterial translocation, and increases infection rates in various critically ill patients.¹ 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. Both authors independently searched the National Library of Medicine's Medline database, Embase, the Cochrane controlled trials register, and the *Cochrane Database of Systematic Reviews* looking for relevant studies in any language published from 1966 to January 2004. See bmj.com for search terms. Bibliographies of all selected articles and review articles were reviewed for further articles, and we contacted experts in the specialty.

Study selection and data extraction

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. Disagreements were resolved by discussion and, if necessary, contact with the authors, who also supplied missing data.

We used the APACHE II (acute physiology and chronic health evaluation) score (<10 indicates mild disease), Ranson score, or Glasgow score (≥ 3 indicates severe pancreatitis) to quantify the severity of pancrea-

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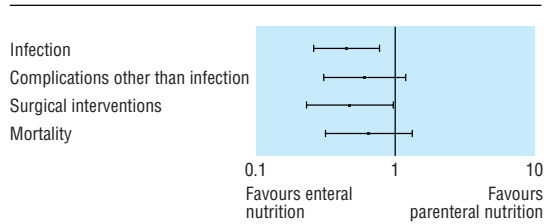


Fig 1 Risk of infection, complications other than infection, surgical intervention, and mortality; results from meta-analyses of randomised trials comparing enteral with parenteral nutrition in pancreatitis

titis. The methodological quality of the studies was scored with the Jadad composite scale,⁹ (low quality studies score ≤ 2 and high quality studies score of ≥ 3).

Data analysis

Infections, complications other than infections, operative interventions, and mortality were binary variables, and length of hospital stay was a continuous variable. The data analysis was performed using the random effects model. The relative risk and continuous data outcomes are presented with 95% confidence intervals. We tested heterogeneity between trials with χ^2 tests.

Results

The search strategy generated 117 studies. Only six randomised clinical trials fulfilled the criteria for consideration in the review. A total of 263 participants were enrolled in the six studies. Four of the six studies had a Jadad score of < 3 . See bmj.com for details.

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. 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. See bmj.com for differences between studies.

Primary outcomes

Figure 1 shows the relative risks and 95% confidence intervals for infections, complications other than infections, surgical intervention, and mortality.

Infections—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 (fig 2).

Complications other than infections—Five studies reported on complications other than infectious, 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, $P = 0.16$).

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, $P = 0.05$).

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

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.

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 results in rapid and severe atrophy of lymphoid tissue associated with the gut and increases bacterial translocation. 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. Experimental models of sepsis have shown a significantly higher mortality in animals receiving parenteral compared with enteral nutrition. These experimental data are supported by clinical studies, which have consistently shown a higher risk of infection in patients receiving total parenteral nutrition.^{16–21} Non-randomised clinical studies of use of

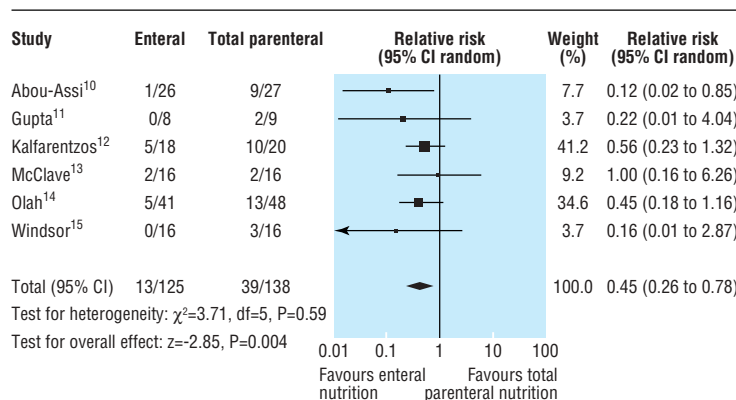


Fig 2 Random effects model of relative risk (95% confidence interval) of infections associated with enteral feeding compared with parenteral nutrition

total parenteral nutrition in patients with acute pancreatitis also suggest increased infection rates.²²⁻²⁴

Parenteral nutrition 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,²⁵ including higher concentrations of interleukin 6, interleukin 8 and C reactive protein.

The most severe complication of acute pancreatitis is pancreatic infection. The risk 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. 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. 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. 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. Most were stated to be in the jejunal location. Most cases of acute pancreatitis are mild and self limiting, with serum enzyme activities returning toward normal within two to four days. 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.

This systematic review has several limitations. The studies included are of relatively poor quality, with four of the six studies having a Jadad score of < 3.⁹ None of the studies were blinded and there was only small number of patients 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. 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.

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Ethical approval: Not required.

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

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Rates of caesarean section and instrumental vaginal delivery in nulliparous women after low concentration epidural infusions or opioid analgesia: systematic review

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Abstract

Objective To compare the effects of low concentration epidural infusions of bupivacaine with parenteral opioid analgesia on rates of caesarean section and instrumental vaginal delivery in nulliparous women.

Data sources Medline, Embase, the Cochrane controlled trials register, and handsearching of the *International Journal of Obstetric Anaesthesia*.

Study selection Randomised controlled trials comparing low concentration epidural infusions with parenteral opioids.

Data synthesis Seven trials fulfilled the inclusion criteria for meta-analysis. Epidural analgesia does not seem to be associated with an increased risk of caesarean section (odds ratio 1.03, 95% confidence interval 0.71 to 1.48) but may be associated with an increased risk of instrumental vaginal delivery (2.11, 0.95 to 4.65). Epidural analgesia was associated with a longer second stage of labour (weighted mean difference 15.2 minutes, 2.1 to 28.2 minutes). More women randomised to receive epidural analgesia had adequate pain relief, with fewer changing to parenteral opioids than vice versa (odds ratio 0.1, 0.05 to 0.22).

Conclusions Epidural analgesia using low concentration infusions of bupivacaine is unlikely to increase the risk of caesarean section but may increase the risk of instrumental vaginal delivery. Although women receiving epidural analgesia had a longer second stage of labour, they had better pain relief.

Introduction

Although regional anaesthesia has been associated with a reduction in anaesthesia related maternal mortality, there is continuing controversy over whether epidural analgesia impedes the progress of labour by causing dystocia and increasing operative delivery rates.¹⁻³ Previous reviews have included disparate regimens for epidural analgesia and women of mixed parity.⁴⁻⁶ We focused on epidural infusions containing low concentrations of local anaesthetic as these are

associated with a lower risk of operative delivery.⁷ To overcome the confounding effect of parity, we selected nulliparous women, who have a higher risk of dystocia. We assessed all operative deliveries (caesarean section, forceps, vacuum assisted).

Methods

We searched Medline, Embase, and the Cochrane controlled trials register for all relevant clinical reports published before June 2003, using thesaurus and MeSH terms for epidural analgesia, labour, forceps, vacuum assisted delivery, caesarean section, and instrumental delivery. We searched the bibliographies of relevant studies for other reports.

We identified potentially relevant randomised controlled trials that specifically addressed whether epidural analgesia affected the risk of instrumental delivery. We then selected trials in which epidural infusions of low concentration local anaesthetic were compared with parenteral opioids and where the epidural infusions were continued during the second stage of labour.

Trial validity was assessed by using the Scottish Intercollegiate Guideline Network checklist.⁸ We independently assessed and scored each article and independently abstracted data in duplicate and cross checked for transcription errors and discrepancies. Trials included for meta-analysis used low concentrations of bupivacaine ($\leq 0.125\%$) in continuous epidural infusions during the first two stages of labour in nulliparous women. All the trials had outcomes for caesarean section and instrumental vaginal delivery.

Results of the trials were combined in a meta-analysis. We used odds ratios and 95% confidence intervals for categorical outcomes and weighted mean differences for continuous outcomes. Random effects models were used for all analyses, and heterogeneity was assessed. Sensitivity analyses were carried out if there was heterogeneity in the outcome measures.



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