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ORIGINAL ARTICLE

A Double-Blind, Randomised, Controlled Trial to Study the Effects of an Enteral Feed Supplemented with Glutamine, Arginine, and Omega-3 Fatty Acid in Predicted Acute Severe Pancreatitis

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ABSTRACT

Context Current best evidence is in favour of early institution of enteral feeding in acute severe pancreatitis with promising results from trials in immunonutrition on other patient groups.

Objective To identify which groups of patients and products are associated with benefit, we investigated immunonutrition in patients with predicted acute severe pancreatitis.

Design A randomised trial of a study feed containing glutamine, arginine, tributyrin and antioxidants *versus* an isocaloric isonitrogenous control feed was undertaken.

Patients Thirty-one patients with a diagnosis of acute pancreatitis predicted to develop severe disease: 15 study feeds and 16 control feeds.

Interventions Enteral feeding via nasojejunal tube for 3 days. If patients required further feeding the study was continued up to 15 days.

Main outcome measures Reduction in C-reactive protein (CRP) by 40 mg/L after 3 days of enteral feeding was the primary endpoint. Carboxypeptidase B activation peptide (CAPAP) levels were taken at regular intervals.

Results After 3 days of feeding, in the study group 2/15 (13%) of patients had reduced their CRP by 40 mg/L or more. In the control group 6/16 (38%) of patients had reduced their CRP by this amount. This difference was found to be near the statistical significant limit (P=0.220).

Conclusions The cause of the unexpectedly higher CRP values in the study group is unclear. The rise in CRP was without a commensurate rise in CAPAP or outcome measures so there was no evidence that this represented pancreatic necrosis. The contrast between the CRP and CAPAP results is of interest and we believe that specific pancreatic indices such as CAPAP should be considered in larger future studies.

INTRODUCTION

Current best evidence is in favour of early institution of enteral feeding in acute severe pancreatitis [1, 2, 3, 4]. In view of the promising results from trials in immunonutrition on other patient groups and the need to identify which patients and which

products are associated with clinical benefit, a study was designed to investigate the possible benefit of enterally fed immunonutrition in patients with predicted acute severe pancreatitis.

In the last 15 years nutrient substrates such as glutamine, omega-3 fatty acids and nucleotides thought to improve immune function have been combined to develop immune-enhancing enteral formulas in the hope of improving outcomes in high-risk or critically ill patients; many clinical trials have been carried out [5, 6, 7, 8, 9, 10, 11, 12, 13]. These benefits could be extended to patients with acute pancreatitis; for example patients with acute pancreatitis are specifically known to suffer glutamine depletion. With the evidence in favour of enteral feeding in acute severe pancreatitis there seems to be a case for enteral, immune-supplemented nutrition. The aim of the trial was to investigate whether enteral immunonutrition has beneficial effects on the acute phase and immune response in patients with severe acute pancreatitis compared to standard enteral nutrition.

PATIENTS AND METHODS

A prototype enteral feed produced by Fresenius® (Bad Homburg, Germany) containing glutamine, arginine, omega-3 fatty acids and tributyrin, vitamin C, E and beta-carotene and micronutrients zinc, selenium and chromium was used; in this article this feed is called 'I-Complete'. Fresenius® also produced the isonitrogenous, isocaloric control feed, subsequently called 'C-Complete'.

Between April 2001 and November 2002 a randomised clinical pilot study of I-Complete versus C-Complete in patients who were predicted to develop acute severe pancreatitis was undertaken in Queen Alexandra Hospital, Portsmouth, UK. Patients with a serum amylase of three times the upper limit of normal with clinical evidence of acute pancreatitis and an APACHE II score of 8 or greater were enrolled. Patients without clinical evidence of acute severe pancreatitis and those in whom enteral feed was not started within 72 hours of symptoms onset were excluded from the trial. Other exclusion criteria are listed in Table 1.

Enteral Feeding

Patients when entered into the trial had a nasojejunal tube inserted and feeding was started. 'Bengmark' self-propelling naso-jejunal tubes were used [14], which were inserted as soon as possible after admission. The use of these tubes was tested for about a year before the trial started with some success [15, 16] and there have been other reports of their use in pancreatitis by other authors [17].

If the Bengmark tube did not pass spontaneously, or if tubes became dislodged and could not be replaced by the bedside, they were replaced endoscopically in all but 4 cases who were fed with the tube placed in the stomach when felt to be clinically indicated by the pancreatic team. One patient had pancreatitis diagnosed at laparotomy, and that patient was fed via needle jejunostomy.

Table 1. Exclusion criteria.

Primary exclusion criteria:
- Age below 16 or greater than 85 years
- Presentation more than 72 h post admission
- Pregnancy
- Insulin-dependent diabetes mellitus
- Parenchymal liver disease (CHILD C or greater)
- Leukocytes below 3.500/mL
- Thrombocytes below 100.000/mL
- Immunosuppression (including previous organ transplantation)
- Pre-clinical artificial kidney support
- Congestive heart failure: NYHA (New York Heart Association) IV
- Known food allergy against any ingredients of the investigational products
- Long-term glucocorticoid therapy
- Simultaneous participation in a clinical study with an investigational drug
- Known dependence to drugs and/or narcotics

Secondary exclusion criteria (post-admission and drop outs):
- Occurrence of a serious adverse reaction to the investigational products
- Interruption of protocol for longer than 24 hours
- Withdrawal of consent

The rate of feeding and protocol for enteral feeding was determined in line with local dietetic practice. The study protocol or "study period" was divided into 4 sub-periods of time.

1) An initial assessment period within 72 hours of the onset of symptoms.
2) Feeding was started on day 0, there followed a minimum of 72 hours of enteral feeding (i.e. taking the trial to day 3).
3) If further feeding was subsequently required, the study was continued up to a maximum of 15 days as long as enteral feeding was felt to be indicated. This is described as the "extension period".
4) Finally patients were assessed again on the day after feeding was finished.

Table 2 lists the outcome variables that were recorded during the study period.

Management of Acute Pancreatitis

A dedicated surgical team consisting of 2 consultant surgeons, a junior medial team and a specialist nurse looks after the patients with acute pancreatitis in Queen Alexandra Hospital. Normally patients are taken over by that team as early as possible after admission. Decisions about fluid management, medication including antibiotics, radiology and operative intervention was left to that team.

Blood cultures are taken on clinical suspicion by the surgical team, generally after a secondary rise in C-reactive protein (CRP), or any sign of systemic inflammatory response syndrome (SIRS). Antibiotics are prescribed with persistent SIRS or microbiologically proven infection on standard blood cultures. Indications for operation were verified infected pancreatic necrosis.

Laboratory Details

Carboxypeptidase B activation peptide was carried out by Professor Anders Borgström, in the Department of Surgery, Malmö University Hospital, Sweden. Muller *et al*. set out the details of their method in their 1992 paper [18]. Interleukin-6 and interleukin-10 assays were performed at Queen Alexandra Hospital, using kits obtained from R&D Systems (Abingdon, Oxon, UK). Laboratory methods are detailed in the package inserts, http://www.rndsystems.com/pdf/HS600B.pdf for IL 6 and http://www.rndsystems.com/pdf/HS100B.pdf for IL 10. Anti endotoxin antibody levels were performed by Professor G. Robin Barclay at the Edinburgh Regional Transfusion Centre of the Scottish National Blood Transfusion Service (SNBTS). Details of this assay can be found on

Table 2. Outcome variables.

Primary endpoint:
- Reduction in C-reactive protein (CRP) by 40 mg/L after 3 days of feeding

Secondary target variables:
- Carboxypeptidase B activation peptide (CAPAP) after 3 days of feeding (taken daily)
- CRP (taken daily)

Clinical outcome (all assessed daily):
- Therapeutic intervention score (TISS) [29]
- APACHE II score [30]
- Multiple organ failure (MOF) score [31]
- Sequential organ failure assessment (SOFA) score [32]
- Incidence of SIRS
- Length of hospital stay, length of time in ICU, ventilator days and need for TPN
- Time until oral feeding recommences
- Need for surgery
- Mortality

Infection rate:
- Any infection
- Sepsis
- Infected necrosis or intra-abdominal abscess

Special laboratory tests (all carried out on pre-feeding assessment period, on days 3, 5 and on the day after feeding finished):
- Plasma amino acids
- Thiobarbituric acid reactive substances (TBARS)
- Glutathione (GSH)
- Cytokines (IL-6, IL-10)
- IgM and IgG antiendotoxin antibodies
- Plasma proteins (albumin, total protein)
- Micronutrients (Se, Cr, Zn, vitamin C and E, beta-carotene)

Safety and tolerance (all carried out daily):
- Clinical chemistry, haematology, coagulation
- Gastrointestinal tolerance: vomiting, hiccups, bloating, flatulence, constipation, diarrhoea frequency (bowel movement/day), diarrhoea days, aspiration

Table 3. Patient characteristics. (Mean values±SD and frequencies).

	I-Complete: Study feed (n=15)	C-Complete: Control feed (n=16)	P value
Age (years)	63.2±18.0	73.2±7.2	0.205
Gender			0.029
- Male	12 (80.0%)	6 (37.5%)	
- Female	3 (20.0%)	10 (62.5%)	
Height (cm)	172.1±8.5	165.3±9.4	0.028
Weight (kg)	81.4±15.0	71.4±12.2	0.030
BMI (kg/m^2)	27.3±3.2	26.1±3.9	0.358

http://www.endocab.com/. Measurement of plasma amino acids, thiobarbituric acid reactive substances (TBARS), glutathione (GSH) and micronutrients (Se, Cr, Zn, Vitamin C and E, beta-carotene) were performed at the Department of Nutrition, University of Bonn, Germany.

To monitor inflammatory response as an indirect indication of systemic inflammatory response or immune activation we used CRP as the primary endpoint. CRP is a widely available assay that is cheap to perform and gives rapid results [3, 19, 20, 21]. As an indicator of pancreatic damage we used carboxypeptidase activation peptide (CAPAP). Although we initially intended to use trypsinogen activation peptide (TAP) the assay was not felt to be reliable enough; the small TAP molecule is only present in very low concentrations in the urine and is rapidly cleared [22, 23, 24]. As a result CAPAP was used; this is a larger molecule than TAP and has a longer half life in blood and urine [25].

Randomisation

The trial was double-blind. Randomisation was undertaken by Fresenius® Kabi Clinical Research Department (Bad Homburg, Germany), generated by means of personal computer according to the principle of randomly permuted blocks, before the study began (program RANCODE, version 3.6, IDV, Gauting, Germany). Each patient who qualified for entry into the study was assigned a patient number (consecutively in chronological order). This number corresponded to the randomisation number and allocated the patient to one of the treatment groups.

ETHICS

The local ethics committee approved the study, and written informed consent was obtained from all participants.

STATISTICS

The primary endpoint was set as a drop in CRP by 40 mg/L after 3 full days of enteral feeding, representing a drop from at least 150 mg/L to 110 mg/L or less. This should therefore correlate in larger studies with a reduction in mortality. It was calculated using StatsDirect (StatsDirect Ltd.®, Sale, Cheshire, UK) that a sample size of 17 controls *vs*. 17 experimental subjects would detect a reduction in CRP of 40 mg/L with a 95% confidence interval of less than 40 mg/L, a power of 0.8 and a P value of less than 0.05. Data are reported as means±SD, while APACHE II and therapeutic intervention score (TISS) scores were reported as median values and ranges. The two groups were compared by means of the Mann-Whitney and the Fisher's exact tests, while the Wilcoxon matched-pairs and the McNemar tests were used for the within-subject analyses. StatsDirect (StatsDirect Ltd.®, Sale, Cheshire, UK) statistical software was used.

RESULTS

Thirty-two patients were recruited: 15 received study feed, and 17 received control feed. The study did not achieve the intended number of patients due to time constraints. The nasojejunal tubes were generally well tolerated, and no patients gave this as a reason for withdrawal from the study. One patient of the control group withdrew from the study on day 2 without giving a reason. This patient was not included in any of the analyses; therefore data are reported in 31 patients: 15 study feed and 16 control feed. Patient characteristics are listed in Table 3. Males

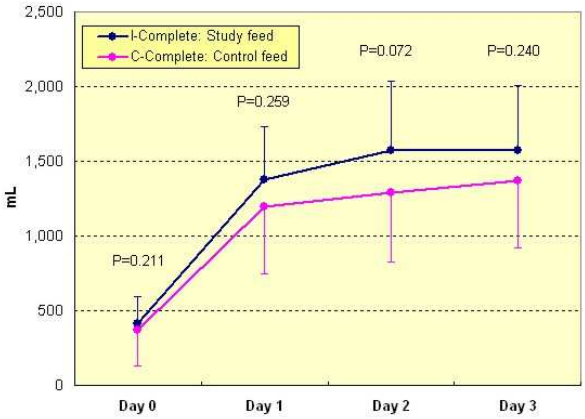

Figure 1. Daily volume of enteral feed (mL). (Mean values±SD).

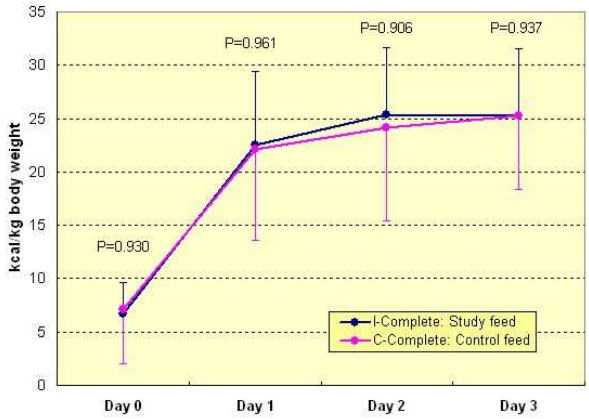

Figure 2. Daily amount of enteral feed in kcal/kg body weight. (Mean values±SD).

were prevalent in the study group and females in the control group. Therefore, there were differences in height and weight, however, there was no significant difference in body mass index between the groups.

Nasojejunal tube insertion was successful in 23 (77%) out of the 30 patients (one patient had acute pancreatitis diagnosed on laparotomy and was fed via needle jejunostomy) which corresponded to the rate attained in our previous experience [15]. Three patients had a nasojejunal tube placed endoscopically and 4 were fed nasogastrically (with the Bengmark tube in the stomach). Three patients had the tubes dislodged and so required resiting, and it w as possible to do so in a 'blind' fashion without endoscopy in all three. None of the patients who were fed via the nasogastric route developed adverse symptoms or other adverse events.

When retrospectively analysed 12 of the study feed group (80%) and 13 of the control group (81%) developed severe acute pancreatitis according to the Atlanta criteria [26].

Patients in both groups received similar amounts of both feed, both in terms of volume (Figure 1) and calories (and therefore nitrogen) (Figure 2).

Both feeds were well tolerated, with no statistically significant difference in the days x patients complained of aspiration, nausea, diarrhoea, bloating, flatulence, or constipation; on the other hand, vomiting was significantly more frequent in the study fed than in control fed patients (P=0.029), (Table 4). Related (meaning documented as either definitely, probably or possibly related to feed) severe and non-severe adverse events occurred in 9/15 (60%) of the I-Complete patients and 10/16 (63%) of the C-Complete patients (Table 5; P=1.000; Fisher's exact test). Non-serious related adverse events were: diarrhoea (1 patient), vomiting (2 patients), and hypernatraemia (2 patients) in the I-Complete group, while the serious adverse events observed in the C-Complete patients were both episodes of severe diarrhoea.

Table 4. Feed tolerance during the study period (day 0-3). Data are reported as days x patients.

	I-Complete: Study feed (Out of 60 days x patients)	C-Complete: Control feed (Out of 64 days x patients)	P value[a]
Aspiration	2 (3.3%)	1 (1.6%)	0.610
Nausea	11 (18.3%)	7 (10.9%)	0.310
Vomiting	7 (11.7%)	1 (1.6%)	0.029
Diarrhoea	7 (11.7%)	11 (17.2%)	0.450
Bloating	17 (28.3%)	10 (15.6%)	0.127
Flatulence	2 (3.3%)	4 (6.3%)	0.681
Constipation	1 (1.7%)	3 (4.7%)	0.620

[a] Fisher's exact test

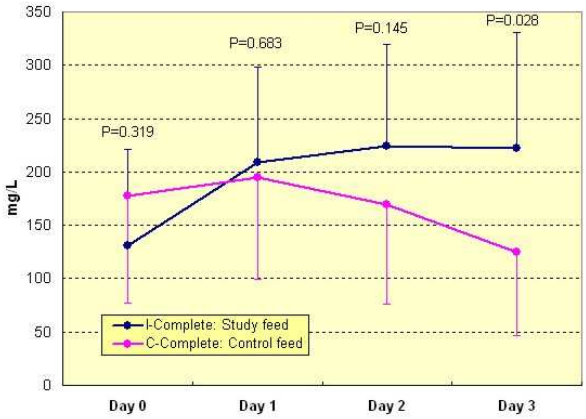

Figure 3. CRP values during the trial. (Mean values±SD; reference range: 0-5 mg/L).

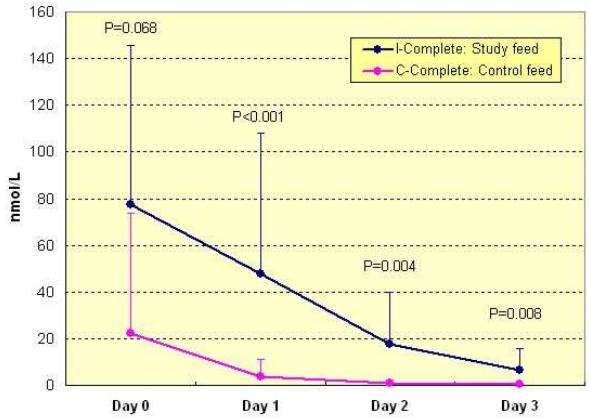

Figure 4. CAPAP values during the trial. (Mean values±SD; reference range: 0-1.5 nmol/L).

Primary Endpoint: CRP

Regarding the primary endpoint of a reduction in CRP of 40 mg/L after 3 days of feeding, in the study gro up 2/15 (13%) of patients had reduced their CRP by 40 mg/L or more. In the control group 6/16 (38%) patients had reduced their CRP by this amount or more. Using the Fisher's exact test this difference was found to be near the statistical significant limit (P=0.220). This is probably due to the low number of cases: in fact, few cases than those required by the power analysis were recruited. CRP values during the trial are illustrated in Figure 3. During the extension period, CRP decreased in C-Complete group and at day 3 was significantly lower when compared to the I-Complete group (P=0.028).

Table 5. Number of patients with related adverse events and documented perceived severity.

	I-Complete: Study feed (n=15)	**C-Complete: Control feed (n=16)**
Mild	**3 (20.0%)**	**4 (25.0%)**
- Related	2 (13.3%)	-
- Not related	1 (6.7%)	4 (25.0%)
Moderate	**4 (26.7%)**	**2 (12.5%)**
- Related	3 (20.0%)	-
- Not related	1 (6.7%)	2 (12.5%)
Severe	**2 (13.3%)**	**4 (25.0%)**
- Related	-	2 (12.5%)
- Not related	2 (13.3%)	2 (12.5%)
Total	**9 (60.0%)**	**10 (62.5%)**
- Related	5 (33.3%)	2 (12.5%)
- Not related	4 (26.7%)	8 (50.0%)

Secondary Outcome Measures

CAPAP

After 3 days of feeding, mean CAPAP levels in the study group decreased from 77.4±68.3 to 6.6±9.2 nmol/L (P=0.003), with a smaller decrease found in the control group from 22.4±51.4 to 0.3±0.4 nmol/L (P=0.011). The differences between the two groups were found to be significant starting from the first day of feeding (Figure 4).

Scoring Systems

APACHE II (pre-fed: P=0.992; after 3 days: P=0.640) and TISS (pre-fed: P=0.381; after 3 days: P=0.974) were not significantly different in the 2 groups during the study period. In the study group APACHE II dropped from a median pre-feed of 9 (range: 8-19) to 6 (range: 0-18) after 3 days (P=0.035). In the control group these figures dropped from 9.5 (range: 8-16) to 6 (range: 5-15) (P=0.002). TISS values dropped from 9 (range: 4-22) pre-feed to 7 (range: 4-32) after 3 days in the study group (P=0.288), and from 7 (range: 4-22) to 6 (range: 3-22) in the control group (P=0.703).
The mean multiple organ failure (MOF) score decreased in the course of the study from day 0 to day 3 in the immunonutrition group only (I-Complete: from 0.8±1.0 to 0.6±1.1, P=0.496; C-Complete: from 0.4±0.7 to 0.4±0.4, P=0.512). MOF score was not significantly different in the 2 groups during

the study period (day 0: P=0.234; day 3: P=0.309). The mean sequential organ failure assessment (SOFA) score did not significantly change in the immunonutrition group (from 1.9±1.8 to 2.1±2.5; P=0.880) and significantly decreased in the study group from 2.6±1.5 to 1.3±1.2 (P=0.002) during this period. No significant differences of SOFA score were found in the two groups (day 0: P=0.192; day 3: P=0.143). The modifications of MOF, SOFA, and TISS scores were not significantly different between the two groups (P=0.086, P=0.985, and P=0.557, respectively).
The percentage of patients with SIRS was not significantly different between the two groups (day 0: P=1.000; day 3: P=0.722) and decreased in both groups almost identically from day 0 until day 3: I-Complete from 10 (67%) to 6 (40%) cases (P=0.630) and C-Complete from 10 (63%) to 8 (50%) cases (P=0.814).

Length of Stay

There was no significant difference between the two groups in length of stay in hospital, or length of stay on ICU (Table 6). There were 3 deaths in the control group (19%) and no deaths in the study group, and one emergency operation in the control group (6%) with none in the study group. Neither of these differences was statistically significant. There was only a trend towards starting earlier oral feeding with the study feed (P=0.332), with large standard deviations; the study group started oral feeding at a mean of 10.7±6.8 days and the control group at a mean of 13.3±5.7 days.

Table 6. Length of stay, mortality and need for abdominal surgery. (Mean values±SD and frequencies).

	I-Complete: Study feed (n=15)	C-Complete: Control feed (n=16)	P value
Length of stay (days)			
- Hospital	19.1±14.4	13.4±11.1	0.347
- ICU	11.0±9.5	4.0±3.6	0.150
Mortality	0	3 (18.8%)	0.226
Surgery	0	1 (6.3%)	1.000

Cytokines

The results for IL-6 and IL-10, together with IgG and IgM antiendotoxin antibodies, vitamin C, E, and beta carotene, are reported in Table 7. Mean IL-6 levels decreased significantly in both groups, while mean IL-10 levels decreased in the study group and increased in the control groups; however these results were not statistically significant.

Anti-Endotoxin Antibodies

IgG antiendotoxin antibodies were significantly higher in the control group after 3 days of feeding, and the overall comparison of the effect of the feeds was statistically significant also. However, this effect was not seen in the IgM antiendotoxin antibodies; the explanation for this effect is not entirely clear (Table 7).

Vitamins

As shown in Table 7, vitamin C levels increased significantly in the immunonutrition group but not in the control group and the differences between the two groups after 3 days of feeding, and the overall differences between the two groups were also statistically significant. As the study feed contained high levels of Vitamin C this is unsurprising, but confirms absorption of the study feed in this group. This effect lasted until the last day of enteral feeding into to extension period. Vitamin E increased significantly in both groups, but the differences between the two groups were not significant. Beta carotene levels showed a similar behaviour, but the statistical significance was not reached.

Other Special Laboratory Tests

There were no statistically significant differences in the level of thiobarbituric acid reactive substances (TBARS) (day 0: P=0.408; day 3: P=0.112), glutathione (day 0: P=0.536; day 3: P=0.281), total protein (day 0: P=0.645; day 3: P=0.186) or other micronutrients: Se (day 0: P=0.291; day 3:

Table 7. Details of cytokines, antiendotoxin antibodies and vitamins tested.

	I-Complete: Study feed n=15	C-Complete: Control feed n=16	P value
Interleukin-6 (pg/mL)			
Day 0	418.8±617.1	299.9±396.7	0.704
Day 3	24.6±43.8	43.8±85.2	0.748
	P=0.003	P=0.002	0.796[a]
Interleukin-10 (pg/mL)			
Day 0	24.4±36.9	23.9±42.0	0.992
Day 3	10.8±6.7	33.8±90.4	0.799
	P=0.682	P=0.617	0.845[a]
IgG antiendotoxin Ab (mU/mL)			
Day 0	53.6±25.9	107.6±99.5	0.098
Day 3	57.8±30.5	166.0±138.7	0.035
	P=0.809	P=0.253	0.004[a]
IgM antiendotoxin Ab (mU/mL)			
Day 0	43.4±30.5	23.1±15.0	0.128
Day 3	38.0±23.6	34.2±17.1	0.705
	P=0.903	P=0.222	0.206[a]
Vitamin C (µmol/L)			
Day 0	10.0±8.1	10.4±6.3	0.532
Day 3	71.5±57.5	18.0±18.6	0.001
	P<0.001	P=0.447	<0.001[a]
Vitamin E (µmol/L)			
Day 0	20.9±8.7	22.5±5.1	0.269
Day 3	38.0±13.3	33.6±14.2	0.779
	P=0.001	0.009	0.807[a]
Beta carotene (µmol/L)			
Day 0	0.218±0.109	0.274±0.115	0.267
Day 3	0.254±0.107	0.390±0.193	0.168
	P=0.226	P=0.134	0.095[a]

P=0.201), Cr (day 0: P=0.578; day 3: P=0.410), Zn (day 0: P=0.822; day 3: P=0.444) (data not shown).

Albumin levels decreased in the study group from a mean of 33.7±8.0 g/L to 29.4±4.8 g/L (P=0.053) and increased in the study group from 33.8±6.4 g/L to 35.2±4.2 g/L (P=0.480). The differences between the groups were not significant at day 0 (P=0.646) but at day 3 the difference was statistically significant (P=0.003).

DISCUSSION

This trial showed an increase in CRP after 3 days of feeding in the immunonutrition-fed group compared to the isonitrogenous, isocaloric control. There was also a significantly lower albumin in the immunonutrition group, but a significantly lower CAPAP in the study group when compared to control. The increase in CRP was a surprising finding. The primary endpoint (i.e., the number of patients with a drop in CRP of at least 40 mg/L) did not reach the statistical significance possibly because of the lower number of cases than hoped for; fewer cases than those required by the power analysis were recruited. The possibility that this increase in CRP in the study group is a "true" effect, rather than one that has happened by chance, is supported by the significantly different mean CRP levels at day 3, and additionally the significantly different albumin levels on day 3 (which could be interpreted as showing an increase in capillary permeability as a result of the more severe inflammatory response in the study

group). The cause of the unexpectedly higher CRP values in the study group is unclear, but is worthy of further investigation. Although the constituents of the feed in the trial presented were devised with the best available evidence at the time, one of the ingredients, arginine, particularly has been the subject of some debate since then [27], with one metanalysis hinting that enteral immunonutrition with diets containing arginine may be associated with a worse outcome compared to patients receiving parenteral nutrition [28]. The rise in CRP in our study was associated with a commensurate reduction in CAPAP and without a worsening in other clinical outcome measures so there was no evidence that this was likely to represent pancreatic necrosis, or clinical deterioration in the patients fed with the arginine-containing feed.

CAPAP has been used as a marker for the diagnosis of acute pancreatitis and to predict pancreatic necrosis [18]. It is thought that active pancreatic enzymes such as phospholipase A2, pancreatic elastase and carboxypepitidases contribute to the development of necrosis in acute pancreatitis (the 'autodigestion concept'). This could be the explanation for why markers for proenzyme activation such as CAPAP levels correlate with the degree of necrosis in acute pancreatitis. The correlation between CAPAP values and maximum CRP values during the course of the disease in the paper by Muller *et al*. [18] showed that many attacks of mild pancreatitis are accompanied by CRP levels in the range 100-200 mg/L but low levels of CAPAP. Again the inference from that study is that CAPAP correlates better with necrosis than inflammation.

We are encouraged by the fact that the both feeds were well tolerated. This validates our approach in enteral feeding patients with predicted severe acute pancreatitis in the trial, by feeding jejunally where possible, but not putting patients with critical illness through the additional risk of a procedure in order to do so if they are tolerating gastric feeding. This is a practice which is now widespread in many specialist centres, but in practice only 4 out of 31 patients were fed nasogastrically in any case and the vast majority were fed jejunally. There is little evidence on the optimal route for nutrition (nasogastric, nasojejunal, gastrostomy or jejunostomy) in acute pancreatitis, as has been discussed previously, so a pragmatic approach was taken.

This is the first trial of this type to use a marker specific to pancreatic damage or necrosis, such as CAPAP to monitor outcome. We believe its use in applications such as this should be increased. We suggest that more studies are needed to investigate the correlation between CRP and inflammatory response, CAPAP and markers of pancreatic necrosis and inflammation. This study has shown a significant worsening of CRP but a non-significant reduction in mortality. It is conceivable that the rise in CRP may represent a healthier immune system.

Further trials are still needed, with greater numbers, to investigate the benefit of enteral immunonutrition in acute severe pancreatitis as a whole.

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Keywords Arginine; carboxypeptidase B activation peptide; Enteral Nutrition; Fatty Acids, Omega-3; Glutamine; Pancreatitis, Acute Necrotizing

Abbreviations CAPAP: carboxypeptidase B activation peptide; CRP: C-reactive protein; GSH: glutathione; MOF: multiple organ failure; NYHA New York Heart Association; SNBTS: Scottish National Blood Transfusion Service; SOFA: sequential organ failure assessment; TAP: trypsinogen activation peptide; TBARS: thiobarbituric acid reactive substances; TISS: therapeutic intervention score

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