ORIGINAL ARTICLE

Immediate oral feeding in patients with mild acute pancreatitis is safe and may accelerate recovery - a randomized clinical study.

Short title: Oral feeding in acute pancreatitis

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Non–standard abbreviations: APACHE, acute physiological and chronic health evaluation; CRP, C-reactive protein; ERCP, endoscopic retrograde cholangio-pancreatography; LOHS, length of hospital stay; VAS, visual analog scale.

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ABSTRACT

Background & Aims: In acute pancreatitis, traditional treatment has been initial fasting on purpose to avoid activation of proteolytic enzymes and pancreatic enzyme secretion. The aim of the present study was to evaluate the efficacy and feasibility of immediate oral feeding as compared to traditional fasting in patients with mild acute pancreatitis.

Methods: Sixty patients were randomized to the two treatment groups, fasting or immediate oral feeding. The inclusion criteria were pancreas amylase ≥ 3 times above normal, onset of abdominal pain within 48 hours, acute physiological and chronic health evaluation score < 8 and C-reactive protein < 150 mg/L. Outcome measures were pancreas-specific amylase, systemic inflammatory response, feasibility and length of hospital stay.

Results: The groups were comparable with respect to age, sex, etiology, acute physiological and chronic health evaluation, time from onset of pain and amylase at admission. No significant differences were seen between the groups concerning levels of amylase, C-reactive protein, leucocytes, abdominal pain or number of gastrointestinal symptoms. The length of hospital stay was significantly shorter in the oral feeding group (4 vs. 6 days; $p < 0.05$).

Conclusions: No signs of exacerbation of the disease process were seen in terms of significant differences between treatment groups for amylase or systemic inflammatory response. In mild acute pancreatitis, immediate oral feeding was feasible and safe and may accelerate recovery without adverse gastrointestinal events.

Key words: acute pancreatitis, early, oral feeding, inflammation, abdominal pain, length of hospital stay

INTRODUCTION

The initiation of acute pancreatitis is due to premature activation of digestive enzymes followed by a systemic inflammatory response mediated by cytokines. [1] In acute pancreatitis, the traditional way of initial treatment has included fasting and administration of parenteral fluids that is practicing "putting the pancreas at rest". The rational for fasting the patients has been that the presence of food in the duodenum induces a cholecystokinin release that stimulates pancreatic enzyme secretion. In the initiation of acute pancreatitis, premature activation of proteolytic enzymes, such as trypsinogen, within acinar cells might lead to autodigestion and therefore is thought to cause and exaggerate potential tissue injury. [2, 3] It has been shown, both experimentally and in humans, that the secretion of pancreatic juice and trypsin is reduced during acute pancreatitis. [4, 5]

In mild acute pancreatitis, current practice has been initial fasting until abdominal pain has resolved and levels of pancreatic and inflammatory markers have decreased. Oral refeeding has been initiated with small amounts of a diet, rich in carbohydrates and proteins and low in fat, then gradually increasing the intake during 3-7 days in order to avoid pain and pancreatitis relapse. [6, 7] However, fasting has been reported to cause atrophy of the enteric mucosa, bacterial overgrowth and decreased secretion of immunglobulin A. [8, 9] Oral feeding stimulate normal bowel function and is the natural way to provide nutrients to the intestinal lumen and should thus be the first logical route of nutritional administration whenever possible.

Immediate oral feeding in patients with acute pancreatitis has not previously been investigated in a clinical randomized study, although early, enteral feeding (nasojejunal and nasogastric) has been investigated in several randomized trials in acute pancreatitis and has been shown to

be both feasible and safe. [10-13] However, the concept from these studies have certain limitations, such as that “early” initiation of nutrition has not been defined and the time from onset of pain to initiation of nutrition has not been stated. The feeding has in general been a low fat semielemental formula that has been initiated at a slow rate and thus not comparable with intake of solid normal food.

The aim of the present study was to evaluate the efficacy and feasibility of immediate oral feeding as compared to traditional fasting in patients with mild acute pancreatitis.

PATIENTS AND METHODS

This prospective randomized study was conducted at the Department of Surgery, Lund University Hospital, between March 2003 and August 2005. The inclusion criteria were clinical signs of mild acute pancreatitis, pancreas amylase ≥ 3 times above normal, onset of abdominal pain within 48 hours, acute physiological and chronic health evaluation score (APACHE) II < 8 and C-reactive protein (CRP) < 150 mg/L. Patients were excluded if acute pancreatitis was caused by surgery, trauma or cancer and if inflammatory bowel disease, stoma, short bowel, pregnancy or chronic pancreatitis with exacerbation were present and if the age was below 18 years. 112 consecutive patients were evaluated for the study. Of these patients, 44 did not fulfill the inclusion criteria (mainly because of longer duration of abdominal pain than 48 hours), 4 patients refused entry (psychological reasons), 1 patient was pregnant, 2 patients had chronic pancreatitis and 1 patient had inflammatory bowel disease. Finally, sixty patients were included and all had provided written informed consent. The local ethics committee of the South Region of Sweden approved the study protocol.

Protocol

The randomization consisted of fasting and intravenous fluids or immediate oral feeding and intravenous fluids when necessary. The patients in the fasting group had oral fluids and diet reintroduced in a traditional stepwise manner as tolerated and the patients in the oral feeding group were immediately allowed to drink and eat freely as tolerated. In both groups, intravenous fluids were administered in amounts that were individually required. All patients were monitored daily for administration of fluids, intake of liquids and food, urinary output, gastrointestinal symptoms (nausea, vomiting, gripes and diarrhea) and pain by visual analog scale (VAS) performed at rest. Patients were treated according to clinical routine, including

analgesia and supportive treatment of organs when indicated. The criterias for discharge were decreased levels of abdominal pain and amylase. A follow-up was conducted after 3 months.

Assignment

Randomization was done by means of opening sealed, numbered opaque envelopes and the assignment was balanced with the use of blocks of four. It was not possible to blind the present study due to the nature of the intervention. In an attempt to minimize bias, the investigators who evaluated the outcome did not participate in the monitoring or discharge of the patients.

Endpoints

Outcome measures were pancreas-specific amylase, systemic inflammatory response, feasibility and length of hospital stay (LOHS). Concentrations of CRP and leucocytes were used as markers for systemic inflammation. Feasibility was evaluated by abdominal pain and frequency of gastrointestinal symptoms. Based on an average LOHS of 7 days (calculated from previous patient records), a sample size calculation showed that 50 patients would be required to demonstrate a difference between groups of 1 day in length of hospital stay at the 5% level of significance with a power of 80%.

Data collection

Biochemical data, such as CRP and leucocytes were collected after the inclusion in the study and after 2, 3 and 7 days. Pancreas-specific amylase was collected after the study inclusion and daily thereafter. The samples were analysed by the local laboratory at the Lund University Hospital. Clinical data recorded were age, gender, etiology, time from onset of pain to baseline, APACHE II by day 1, intravenous fluids administered, gastrointestinal symptoms,

abdominal pain, days until intake of solid food, hyperglycemia (defined as blood glucose ≥ 10 mmol/L), pain relapse, interventions (such as surgery and endoscopic retrograde cholangio-pancreatography), complications, mortality, LOHS, readmissions and compliance to protocol.

Statistical analysis

Data are presented as median and interquartile range. Comparisons between groups were performed using the χ^2 tests for binary data or Fisher's exact test for small samples. Continuous variables were compared using the Mann-Whitney *U* test. P-values of less than 0.05 were considered significant. Statistical analyses were performed with SPSS version 12.0.2. (SPSS, Chicago, Illinois, USA). Analysis by intention-to-treat was used.

RESULTS

Thirty patients in the fasting group and 29 patients in the oral feeding group completed the study protocol. The determination of eligibility for inclusion was made too quickly in one patient in the oral feeding group. In this patient, organ failure developed during the screening and randomization procedure and the patient never managed to start immediate oral feeding and was therefore excluded from analysis. Three patients, one in the fasting group and two in the oral feeding group, developed severe acute pancreatitis, according to the Atlanta classification system, but continued treatment per protocol. [14] Acute fluid collections were diagnosed before day 3 in these patients. At inclusion, the groups were comparable with respect to clinical characteristics such as age, sex, etiology, APACHE II score, time from onset of pain to baseline and pancreas-specific amylase at admission (Table 1).

Nutritional outcome and pain relapse

All patients received intravenous fluids upon admission. The duration of intravenous fluids was shorter in the oral feeding group than in the fasting group, the patients in the oral feeding group were fasting less days and started intake of solid food earlier than those treated by fasting (Table 2). By the time when oral food was reintroduced, 17 (57%) patients in the fasting group and 21 (72%) patients in the oral feeding group still had limited abdominal pain ($p = 0.28$). Because of pain relapse 4 (13 %) patients in the fasting group and 1 (3%) patient in the oral feeding group interrupted their oral feeding ($p > 0.30$).

Pancreas-specific amylase and systemic inflammatory response

On day 3, the median values for pancreas-specific amylase were 66 (48 - 120) IU/L in the fasting group and 84 (36 - 318) IU/L in the oral feeding group, the CRP values were 81 (45 -

139) mg/L in the fasting group and 61 (26 - 127) mg/L in the oral feeding group and the leukocyte values were 7.7 (6.4 - 10.8) 10^9/L in the fasting group and 6.6 (6.3 - 10.2) 10^9/L in the oral feeding group. On the day of discharge the values for pancreas-specific amylase had decreased in both groups; 48 (36 – 108) IU/L in the fasting group and 72 (42 – 252) IU/L in the oral feeding group. There was no significant difference between groups in any of those biochemical markers for amylase or systemic inflammatory response on any of the days evaluated.

Feasibility

Overall, 30 gastrointestinal symptoms in the fasting group and 22 in the oral feeding group were noted, thus without statistical difference between the groups ($p > 0.30$). Details of the gastrointestinal symptoms are given in Table 3. Abdominal pain, evaluated by VAS, was in median 3 (1 - 6) in the fasting group and 2 (0 - 4) in the oral feeding group on day 3. On the day of discharge, the VAS values were 1 (0 - 2) in the fasting group and 0 (0 - 2) in the oral feeding group and did not significantly differ on any day when comparing fasting and orally fed patients.

Clinical outcome

The number of complications was 4 in the fasting group and 3 in the oral feeding group and these are specified in Table 4. There was no mortality encountered. No significant difference was seen between groups concerning the frequency of interventions performed (cholecystectomy and endoscopic retrograde cholangio-pancreatography) carried out during hospital stay (7/30 vs. 6/29; $p > 0.30$). Nine patients underwent cholecystectomy at the same hospital stay (6 in the fasting group and 3 in the oral feeding group; ns). The incidence of hyperglycemia (blood glucose ≥ 10 mmol/L) at any time point during the study was 12 (48%)

patients in the fasting group and 8 (27%) patients in the oral feeding group ($p = 0.25$). Five patients in the fasting group had diabetes mellitus prior to admission and were therefore excluded in the calculations of hyperglycemia.

Length of hospital stay and follow-up

The length of hospital stay was significantly shorter in the oral feeding group as compared to the fasting group; 4 versus 6 days; $p = 0.047$ (Fig 1). By the time of follow-up after 3 months, 3 (10%) patients in the fasting group and 2 (7%) patients in the oral feeding group had been readmitted due to another attack of pancreatitis ($p > 0.30$). The etiology in those that developed a recurrent attack was alcohol in one and biliary in two patients in the fasting group and alcohol in one and idiopathic in one patient in the oral feeding group. No mortality or pancreatic complications such as necrosis, abscess or pseudocysts were noted.

DISCUSSION

The goals of fasting, as a traditional therapy in acute pancreatitis, has been to "put the pancreas at rest" by reducing pancreatic secretion of enzymes and minimize the stress on the pancreatic gland and thereby theoretically decrease autodigestion of the pancreas and exacerbation of tissue injury. Although initial fasting is standard and in general accepted in patients with mild acute pancreatitis, the concept has not truly been evaluated and challenged previously in a clinical randomized study. In the present study, no signs of exacerbation of the disease process, increased abdominal pain or number of gastrointestinal symptoms were seen as a result of immediate oral feeding. The only form of feeding that avoids stimulation of pancreatic secretion is intravenous feeding and jejunal feeding with a mid-distal placement of the tube. [17-19] Although immediate oral feeding compared to fasting has not previously been investigated, several randomized clinical trials have been carried out that favours enteral feeding to parenteral feeding. [20] The tolerance for gastric feeding, might be explained by the hypothesis that pancreas is in a state of unresponsiveness during an attack of acute pancreatitis. [4]

In the present study, indirect measures of the disease process, such as pancreas-specific amylase and systemic inflammatory response were used and there were no indications that immediate oral feeding influenced on the inflammation in the pancreas. Only a limited number of studies in acute pancreatitis have dealt with the impact of gastric feeding on the pancreatic tissue per se. In an experimental study comparing early oral feeding with parental feeding in acute pancreatitis, it was reported that the histopathological changes in pancreatic tissue were less pronounced in the group of rats that were fed orally. [21] The result was explained by the hypothesis that oral feeding stimulates the production of enteral hormones

(for example cholecystokinin, motilin, serotonin) and that might have positive effects on the inflammatory process in the pancreas such as trophic effect on the pancreatic tissue, increased pancreatic blood flow and gastrointestinal motility. In the present study, a direct measure such as collection of histological samples from pancreatic tissue was not possible from an ethical point of view in this patient group with mild acute pancreatitis.

The optimal timing and diet for refeeding patients in acute pancreatitis is scarcely investigated. The mode of refeeding (drinking and eating immediately and monitoring of the daily intake) as used in the oral feeding group seems to be well tolerated in patients with mild acute pancreatitis. In the present study, most of the patients still had some abdominal pain when oral feeding was commenced, but in most cases pain resolved by itself without the need of interrupting the feeding. In the fasting group, the incidence of pain relapse that required interruption of oral feeding and thereby prolonged hospital stay was comparable to what has been reported in a study by Levy et al. [7] In that study, 16% interrupted their oral feeding to be compared with 13% as reported in the fasting group in the present study. The refeeding regimes used in the fasting group and in the study by Levy et al were similar. In the oral feeding group, a low number (4%) interrupted oral feeding because of pain relapse and this implies that immediate oral feeding does not increase the incidence of pain relapse in patients with mild acute pancreatitis.

In severe acute pancreatitis it is crucial to treat patients with initial aggressive fluid resuscitation in order to maintain intravascular circulatory volume, renal function and microcirculation, thereby minimizing the extent of the ischemia and reperfusion injury. [22, 23] The majority of acute pancreatitis patients will have mild disease according to the Atlanta classification. [14] Since this classification cannot fully be conducted at admission, it is

important to ensure that all patients with potential severe disease receive sufficient initial and well-monitored fluid resuscitation until the true severity of the disease can be established. [24] In the present study, all patients thus received initial fluid resuscitation and were carefully monitored concerning circulation, respiration, administration of fluids, oral intake and urinary output.

In our study, hospital stay was shortened by 1 / 3 from an already quite short hospital stay (6 days). Taking the incidence of acute pancreatitis in Sweden into account [15, 16], about 85 % being mild according to the Atlanta classification [14], the saving for reduction of hospital stay by immediate oral feeding corresponding to about 0.22 million € per million inhabitants (Sweden).–It should though be emphasized that earlier discharge from hospital should not be the primary objective per se for health care. In the present study, no evidence was found suggesting that earlier feeding and earlier discharge subjected the patients to unnecessary risks. It is also to be taken into consideration that it might be an improvement in patient comfort just by being allowed to eat and drink instead of fasting and parenteral nutrition.

A limitation of the present study is that the design did not include blinding. The nature of the intervention (oral intake versus fasting) makes it obvious that the patients and staff are informed of the groups. In the present study, the discharge criteria were decreased levels of abdominal pain and amylase and that was seen in both groups. One possibility of reducing the risk for bias would have been to set criteria for discharge to specific levels of the biochemical markers or VAS, but that might have prolonged hospitalization and would not have reflected the true clinical management of the control group. The need for readmission was assessed at 3 months. If data on the decision to discharge patients had been biased, it may have been anticipated that a difference in readmission rate would exist and this was not the

case. The potential positive placebo effect of the feeding information given to the patients in the oral feeding group might though influence on the nutritional outcome. However, it is possible that the number of pain relapses would increase if the patients were encouraged to initiate oral food intake too early and this was not the case.

In conclusion, the present study in patients with mild acute pancreatitis shows that immediate oral feeding was feasible and safe and may accelerate recovery without adverse gastrointestinal events. The present study is a small clinical trial and other larger studies will be needed to confirm the results. However, the implementation of this concept in mild acute pancreatitis seems safe.

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All authors have been involved in the design of the study. Gunilla E Eckerwall has coordinated the study activities, evaluated the data and written the manuscript. Roland G Andersson, Bobby BÅ Tingstedt and Per E Bergenzaun have contributed to the screening of the patients. Roland G Andersson has been the supervisor of the project.

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Table 1. Patient characteristics

	Fasting (n = 30)	Oral feeding (n = 30)	P
Age, years	52 (38 - 60)	56 (48 - 72)	0.22
Sex, male:female	14:16	13:17	1.00
Etiology biliary	14	18	0.44
alcohol	5	3	0.71
ERCP	2	2	1.00
other	1	2	1.00
idiopathic	8	5	0.53
APACHE II	5 (3 - 6)	6 (4 - 6)	0.45
Pain onset to inclusion, hours	26 (23 - 37)	31 (24 - 48)	0.25
Amylase at admission, IU/L	720 (360 - 1440)	840 (420 - 1740)	0.69

ERCP, endoscopic retrograde cholangio-pancreatography; APACHE II, acute physiological and chronic health evaluation. Values are median (IQR).

Table 2. Nutritional outcome

	Fasting (n = 30)	Oral feeding (n = 29)	P
Intravenous fluids, days	4 (3 - 6)	2 (1 - 3)	< 0.001
Fasting, days	3 (2 - 3)	0 (0 - 1)	< 0.001
Solid food, on day	5 (4 - 7)	3 (2 - 4)	< 0.001

Values are median (IQR).

Table 3. Gastrointestinal symptoms

Symptom	Fasting (n = 30)	%	Oral feeding (n = 29)	%	P
Nausea	16	53	9	31	0.12
Vomiting	5	17	4	14	1.00
Gripes	9	30	9	31	1.00
Diarrhea	0		0		
Total	30		22		0.51

Table 4. Overall complications

Symptom	Fasting (n = 30)	%	Oral feeding (n = 29)	%	P
Pleural effusion	2	6	1	3	1.00
Atelectasis	1	3	0		1.00
Fluid collection	1	3	2	7	0.61
Total	4		3		1.00

LEGENDS

Figure 1. The length of hospital stay was significantly shorter in the oral feeding group than in the fasting group.