American Journal of Gastroenterology
© 2005 by Am. Coll. of Gastroenterology
Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2005.40587.x

A Randomized Study of Early Nasogastric *versus* Nasojejunal Feeding in Severe Acute Pancreatitis

F. C. Eatock, M.D., F.R.C.S., P. Chong, M.B., Ch.B., F.R.C.S., N. Menezes, M.B., Ch.B., F.R.C.S., L. Murray, B.Sc., C. J. McKay, M.D., F.R.C.S., C. R. Carter, M.D., F.R.C.S., and C. W. Imrie, M.B., Ch.B., B.Sc., F.R.C.S.
Lister Department of Surgery and Department of Nutrition and Dietetics, Glasgow Royal Infirmary, Alexandra Parade, Glasgow, Scotland

BACKGROUND: After 50 yr in which nasoenteric feeding was considered contraindicated in acute pancreatitis (AP), several clinical studies have shown that early nasojejunal (NJ) feeding can be achieved in most patients. A pilot study of early nasogastric (NG) feeding in patients with objectively graded severe AP proved that this approach was also feasible. A randomized study comparing NG *versus* NJ feeding has been performed.

METHODS: A total of 50 consecutive patients with objectively graded severe AP were randomized to receive either NG or NJ feeding via a fine bore feeding tube. The end points were markers of the acute phase response APACHE II scores and C-reactive protein (CRP) measurements, and pain patterns by visual analogue score (VAS) and analgesic requirements. Complications were monitored and comparisons made of both total hospital and intensive-care stays.

RESULTS: A total of 27 patients were randomized to NG feeding and 23 to NJ. One of those in the NJ group had a false diagnosis, thereby reducing the number to 22. Demographics were similar between the groups and no significant differences were found between the groups in APACHE II score, CRP measurement, VAS, or analgesic requirement. Clinical differences between the two groups were not significant. Overall mortality was 24.5% with five deaths in the NG group and seven in the NJ group.

CONCLUSIONS: The simpler, cheaper, and more easily used NG feeding is as good as NJ feeding in patients with objectively graded severe AP. This appears to be a useful and practical therapeutic approach to enteral feeding in the early management of patients with severe AP.

(Am J Gastroenterol 2005;100:432–439)

INTRODUCTION

Many believe that delivery of nutrients proximal to the duodeno-jejunal flexure will cause release of cholecystokinin (CCK), and an exacerbation of the inflammatory process in the pancreas, as a result of stimulation of exocrine pancreatic secretion (1). Various animal and human studies (2, 3) have shown an increase in exocrine pancreatic secretion in response to enteral feeding, with a greater response to intragastric feeding. However, none of these studies were carried out in acute pancreatitis (AP) where animal studies have shown that pancreatic exocrine secretion, in response to CCK stimulation, is suppressed (4). In addition, it is known that neural pathways affect pancreatic secretion and the presence of nutrients in the jejunum causes significant CCK release (5). The delivery of enteral feed distal to the ligament of Treitz does not prevent duodenal exposure to nutrients, as a degree of reflux is inevitable.

One study demonstrates that only 15% of tubes inserted for nasojejunal (NJ) feeding pass spontaneously through the pylorus; however, nasogastric (NG) feeding is safe in the critically ill, ventilated patient (6). Reliable placement of a NJ tube involves either siting at endoscopy or under radiographic screening, exposing the critically ill patient to the inherent risks of intrahospital transfer and delaying introduction of feeding (7). In addition, the risk of fiberoptic duodenoscopy is greater in a sick patient, and potentially poses logistical problems for the radiology and/or endoscopy services, as tubes require more frequent readjustment (8).

Several studies have now shown jejunal feeding to be cheaper than total parenteral nutrition (TPN), and associated with fewer septic complications and possible modulation of the acute phase response (9–15). Few studies have dealt with the potential problems associated with the insertion of NJ tubes and the delays in the introduction of feeding, which may be incurred because of the need to place these tubes under fluoroscopic or endoscopic guidance (7, 16, 17).

The results of our study of safety and feasibility of NG feeding in severe AP raised several questions (18). First, is NG feeding as safe and effective as NJ feeding? Secondly, would NG feeding result in exacerbation or reactivation of pancreatitis or a resurgence of pain? Thirdly, would NG feeding avoid some of the problems related to the insertion and use of NJ tubes, namely delay in insertion and introduction

of feeding and complications of the procedure undertaken to insert the tube? In an attempt to answer these questions we conducted a larger randomized study comparing NG and NJ feeding in a group of patients with severe AP.

METHODS

A total of 50 patients, admitted to Glasgow Royal Infirmary between October 1997 and July 2000, with both a clinical and biochemical presentation of AP (abdominal pain + serum amylase at least 3 times the upper limit of the reference range), and objective evidence of disease severity (Glasgow prognostic score of 3 or more (19), or an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 6 or more (20) or a C-reactive protein (CRP) level in excess of 150 mg/L (21, 22)) were entered into the study. The local research ethics committee approved the project and all patients gave written informed consent. Patients under 18 yr of age and pregnant females were excluded. Randomization was by computerized random number generation and the sequence was implemented using numbered containers. Due to the nature of the intervention, no blinding of participants or investigators was attempted.

Monitoring of the inflammatory response was performed in all patients by daily measurement of APACHE II score, CRP levels, visual analogue score (VAS) for pain, and total analgesic requirement. The analgesic requirement was equated to a daily total pethidine (meperidine, demerol) dose. Each of these four parameters was then observed on the day of commencement of feed and the following 4 days. Patients in both groups were followed throughout the period of hospitalization to detect any evidence of increase in the severity of pancreatitis as a result of the introduction of feeding.

NG tubes (size 8FG Flocare® polyurethane feeding tubes, Nutricia Ltd., Trowbridge, UK) (Fig. 1) were placed on the ward by either medical or nursing staff. The position was checked by aspiration and pH measurement. Where aspiration was unsuccessful, a chest radiograph was performed. The NJ tubes were passed at endoscopy with the first half of the patients in the study having the same Flocare® tubes clipped into the jejunal mucosa to hold position (Endoclip, Keymed, Southend-on-Sea, UK). The remainder had the more rigid 7FG nasobiliary catheter (Wilson Cook, Winston-Salem, NC, USA) utilized as this was much less prone to blockage, held its position better in the proximal jejunum on withdrawing the endoscope, and was generally more practical. Although not specifically designed for this purpose, these nasobiliary catheters have proven very effective. In two patients in the NJ group, passage of the tube into the jejunum did not prove possible and they received NG feeding. Analysis, however, was performed on an intention-to-treat basis.

Feeds were commenced at full strength and a rate of 30 ml/h increasing to 100 ml/h over 24–48 h. The caloric target was 2,000 kcal per day. This was chosen over an individually calculated target in an attempt to simplify administration. We used a low fat semielemental feed (Pepti 2000 LF, Nutricia ltd, Trowbridge, UK). This avoided the need for provision of pancreatic enzyme supplements. The feed contains 1 kcal/ml and 40 g protein/L (5.9 g/nitrogen per L). Carbohydrate provides 75% of energy in this feed, with protein and fat contributing 16% and 9%, respectively. Neither trace elements, vitamin supplements, nor, prokinetic agents were employed routinely and this was the same feed that we had used in the pilot study published in 2000 (18).

Figure 1. Flocare® nasogastric feeding tube.

The objective of the study was to assess any difference between NG and NJ routes, in tolerance, acute phase response, and pain. Primary outcome measures were CRP concentration, APACHE II scores, pain score, analgesic requirement, and the need for conversion from enteral to parenteral feeding. Secondary outcome measures were hospital and intensive care unit stay and mortality. A power calculation revealed that 854 patients would be required to show a 20% difference in mortality between the groups but 48 patients would be required to show a 20% difference in CRP concentrations. In a single institution, recruitment of 854 patients was not feasible and it was therefore decided to try to recruit 50 patients in the first instance.

One of the 50 patients was subsequently excluded on finding an entirely normal computerized tomography (CT) scan of pancreas after presentation with hyperamylasaemia. He had a background of chronic renal failure (explaining the elevation in serum amylase) and later in the admission miliary tuberculosis was found to be the major pathology. This reduced the original 23 NJ patients to 22.

Statistical analysis was performed using the Mann-Whitney U-test, Fisher's exact test, and the χ^2 test where appropriate with 95% confidence intervals (CI) quoted.

RESULTS

Of the 49 patients, 27 were allocated to NG feeding and 22 to NJ. The demographics of the group including etiology are

Table 1. Etiology of AP in 49 Patients

	NG Group	NJ Group
Gallstones	16	16
Alcohol	6	6
Hereditary	1	–
Hyperparathyroidism	1	–
Idiopathic	3	–
Total	27	22

shown in Tables 1 and 2. The most common etiology was gallstones with 65.3% of patients (16 in each group) having this etiology. Alcohol abuse accounted for another 24.5% of patients, while an idiopathic label was attributed to 6.1% of patients, hereditary AP and hyperparathyroidism accounting for the remaining two patients.

The median age, sex distribution, and etiology was similar between the two groups with the median age being 63 and 58 yr respectively with a slight male preponderance (Mann-Whitney, CI = −16.0–30.0, Fisher exact, CI = −0.31–0.25, and χ^2 test = 3.56, p = 0.47, respectively). No significant difference was identified in the time to commencement of feed, (Mann-Whitney U-test, CI = −2.0–0.0), but clinically some difficulties were experienced in rapidly placing NJ tubes. Likewise, there was no difference in the time to full rate of feeding at 100 ml/h, with this taking place at median 36 h from the start of enteral feeding (Table 2) in each group (Mann-Whitney U-test CI = −9.0–12.0).

The total hospital stay was similar at 16 and 15 days, respectively, while a similar proportion of patients in each group were admitted to the intensive care unit (Mann-Whitney U-test CI = −12.0–5.0 and Fisher exact test CI = −0.42–0.18, respectively). This amounted to 26% of the NG group and 36% of the NJ group. (7 and 8 patients, respectively). All of these 15 patients required assisted ventilatory therapy for respiratory failure (Table 3).

There were no complications associated with tube insertion in the NG group. In the NJ group, one patient suffered a cardiorespiratory arrest on being laid flat to have upper gastrointestinal endoscopy performed to allow insertion of the feeding tube. Resuscitation was successful and the tube was passed without further event. The patient went on to make a full recovery. It is notable, however, that this patient did not require ERCP and the procedure was carried out for the sole purpose of insertion of the feeding tube.

Table 2. Demographics and Onset to Feeding

	NG Feed	NJ Feed
Median Age (interquartile range [IQR])	63 (47–74)	58 (48–64)
Sex (M:F)	14:13	12:10
Feeding start—hours from onset of pain (IQR)	72 (24–72)	72 (24–72)
Interval to full rate—hours after feeding commenced (IQR)	36 (24–36)	36 (24–36)

Table 3. Total Hospital Stay and Duration of RICU

	NG Feed	NJ Feed
Total hospital stay (days)	16 (10–22)	15 (10–42)
Days in RICU	7	8

RICU = Respiratory intensive care.

The feeds were generally well tolerated with only one patient being converted to intravenous feeding from the NJ group. A total of 36 patients (73.5%) tolerated a rate of administration of at least 75% of the target within 48 h of commencing feeding and these were evenly distributed between the two groups (19 (70.4%) in the NG group and 17 (77.2%) in the NJ group) (Fisher exact CI = −0.40–0.22). By 60 h after commencement of feeding, 83.7% of patients were tolerating administration of at least 75% of target calories. A total of 77% of target calories was delivered beyond 60 h, and with 77.8% delivered in the NG group and 76.1% in the NJ group, there was no difference between the groups (Mann-Whitney CI 0.0–0.0). Abdominal bloating was a problem in one patient in the NJ group while troublesome diarrhea occurred in three patients in the NG group and one in the NJ group. In these four patients, the rate of feeding was temporarily reduced and two of the patients in the NG group received loperamide as well. These tended to be transient problems lasting a maximum of 72 h and all had feeding successfully continued. One of the NG group repeatedly removed the feeding tube. This was an exceptionally ill 74-yr-old patient with an APACHE II score of 18 and Glasgow score of 6. He died on his sixth day in hospital from multiple organ system failure (Table 4). Total reposition of the feeding tube was necessary in one patient in the NJ group necessitating reendoscopy. One patient in the NJ group required intravenous feeding due to duodenal obstruction. The risk of iatrogenic infection associated with TPN was therefore minimized. The limitations and complications of enteral feeding did not preclude feeding by either the NG or NJ route.

Death occurred in 12 patients (24.5%) usually as a result of multiorgan failure (Table 4). Only 2 of 12 patients died

Table 4. Deaths from Severe AP—Etiology, Glasgow Scores, and Hospital Stay

Patient	Feed Route	Age	Etiology	Glasgow Score	Days in Hospital
1	NG	40	Alcohol	6	24
2	NG	62	Gallstones	4	50
3	NG	74	Gallstones	6	6
4	NG	77	Gallstones	5	14
5	NG	86	Gallstones	5	19
6	NJ	38	Gallstones	2	44
7	NJ	48	Alcohol	5	16
8	NJ	56	Alcohol	6	37
9	NJ	56	Gallstones	5	56
10	NJ	58	Gallstones	3	15
11	NJ	60	Gallstones	5	58
12	NJ	80	Gallstones	5	3

Table 5. Breakdown by Feeding Technique in Fatal AP

	Age (Years)	Glasgow Score	Hospital Stay (Days)
NG (5)	74 (68)	5	19 (23)
NJ (7)	56 (57)	5	37 (33)

Age and hospital stay values are median (mean).

in the first week of illness (16.7%). Both were elderly (74 and 80 yr) dying at day 6 and day 3, respectively. Four of the deaths occurred beyond 6 wk from presentation from multiple organ systems failure resulting from infected pancreatic necrosis (IPN). Three deaths occurred at approximately 2 wk from presentation as a result of uncontrollable multiple organ failure. The median age of those who died was very similar to that of the overall group, being 59 yr (Mann-Whitney CI = −13.0–10.0). The etiology of the pancreatitis was gallstones in 9 of 12 patients with a fatal outcome (Table 4). The proportion of gallstone patients in the fatal outcome group was therefore similar to the overall group (75% *vs* 63.5%) (Fisher's exact test CI = −0.18–0.38). With five deaths in the NG group (18.5%) and seven in the NJ group (31.8%), mortality was not significantly different (Fisher's exact test CI = −0.50–0.14).

The median and mean age of those who died in the NJ group was lower than those in the NG group but median and mean Glasgow scores were 5 in each group (Table 5). With such small numbers, these differences are not statistically significant (Mann-Whitney U-test CI = −16.0–30.0).

Early diagnostic endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) was carried out in 12 patients within the first 3 days of admission while a further 4 patients had a later ERCP and sphincterotomy performed to clear the bile ducts. Of the 16 patients subject to ES, 7 were in the NG group, and 9 NJ. Another three patients had early ERCP without sphincterotomy (Table 6). In one additional patient, the papilla could not be accessed due to duodenal compression, from unusually prominent swelling in the head of pancreas resulting from severe inflammation. No clinical deterioration was recorded from ES procedures.

Table 6. Endoscopic Retrograde Cholodocho Pancreatography (ERCP) and Sphincterotomy (ES)

	Attempted	Successful
ERCP	20	19
Diagnostic alone	4	3
Endoscopic sphincterotomy <72 hrs	12	12
Endoscopic sphincterotomy >72 hrs	4	4

Of the 16 successful ES procedures 7 NG: 9 NJ.

The comparison studies of APACHE II scores (Fig. 2) are virtually identical for the two groups of patients with the higher initial levels gradually decreasing during the first week of illness. The mean CRP scores follow a pattern, with high levels at 24–96 h. There was no statistical difference on any day (Mann-Whitney U-test CI APACHE II day 1 = −5.0–3.0, day 2 = −4.0–3.0, day 3 = −4.0–3.0, day 4 = −4.0–3.0, day 5 = −3.0–3.0; CI CRP day 1 = −71–65, day 2 = −82–60, day 3 = −95–29, day 4 = −39–79, day 5 = −90–67) (Fig. 3). Likewise there is a similar pattern of pain measured by VAS score and analgesic requirement (Figs. 4 and 5).

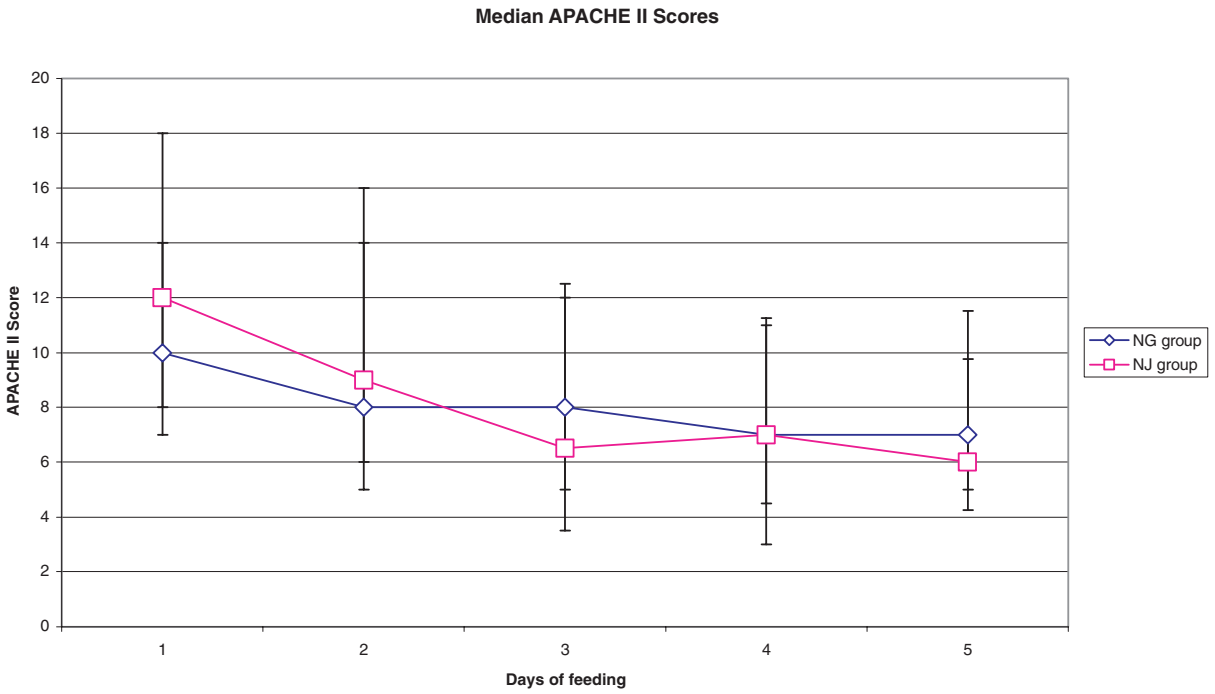

Figure 2. This graph depicts the daily median APACHE II scores commencing just prior to the introduction of feeding. The error bars show interquartile ranges.

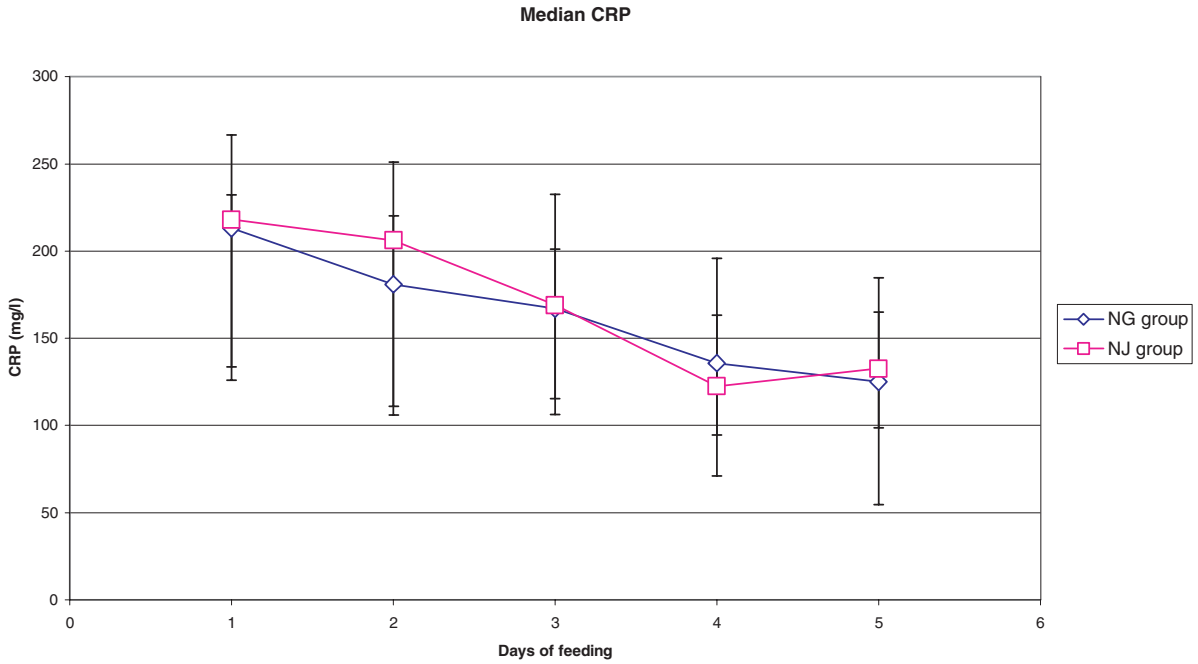

Figure 3. This graph shows the daily median C-reactive protein measurements. The first measurement was made prior to the introduction of feeding. The error bars show interquartile ranges.

Again there is no statistically significant difference in either of these indicators of pain on any of the days studied (Mann-Whitney U-test CI VAS day 1 = −2.3–3, day 2 = −2.5–4.2, day 3 = −5.0–0.5, day 4 = 0.0–3.0, day 5 = −0.3–0.5; CI analgesia day 1 = −100–150, day 2 = −200–100, day 3 = −100–100, day 4 = −150–25, day 5 = 0–75). In addition, only two patients in the NG group showed an increase in pain score, both on day 4 of the study (*i.e.*, the third day of feeding). The first of these required no opiate analgesia on days 3, 4, or 5, while the second patient's analgesia requirement fell on the day in question compared to the day before. In comparison to the more accepted NJ feeding route, there was no increase in the early acute phase response or an exacerbation of pain pattern associated with NG feeding.

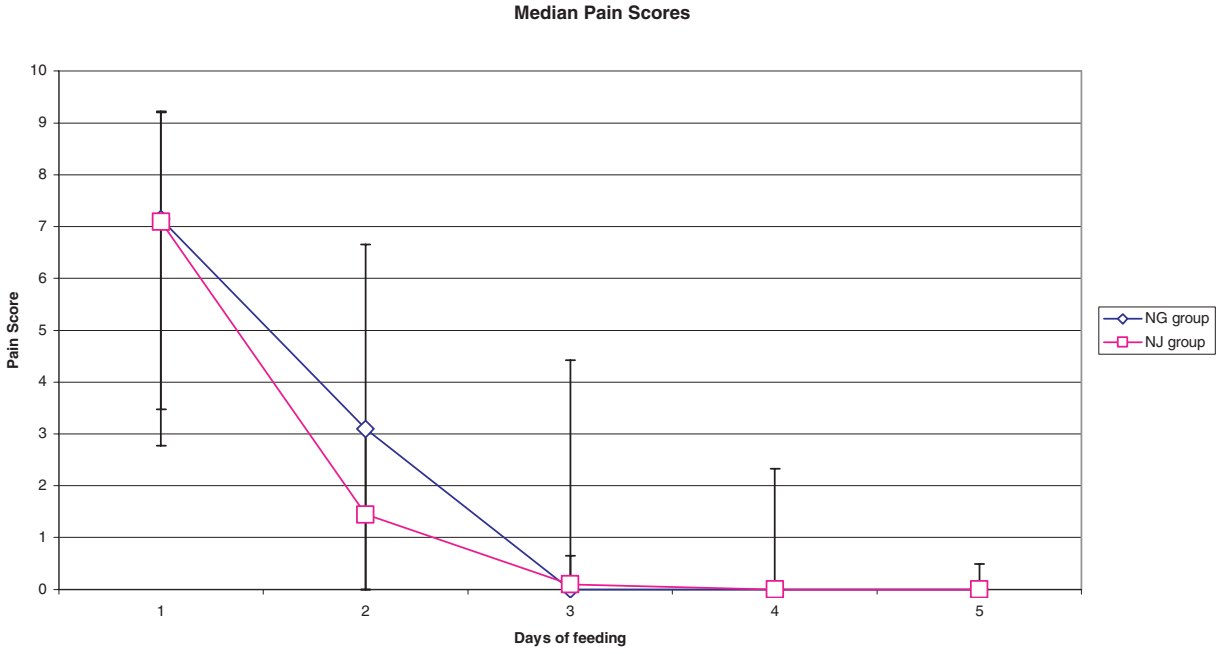

Figure 4. This graph shows the daily median pain score measured via a visual linear analogue scale. The first pain score measurement on each patient was taken prior to the introduction of feeding. The error bars show the interquartile range.

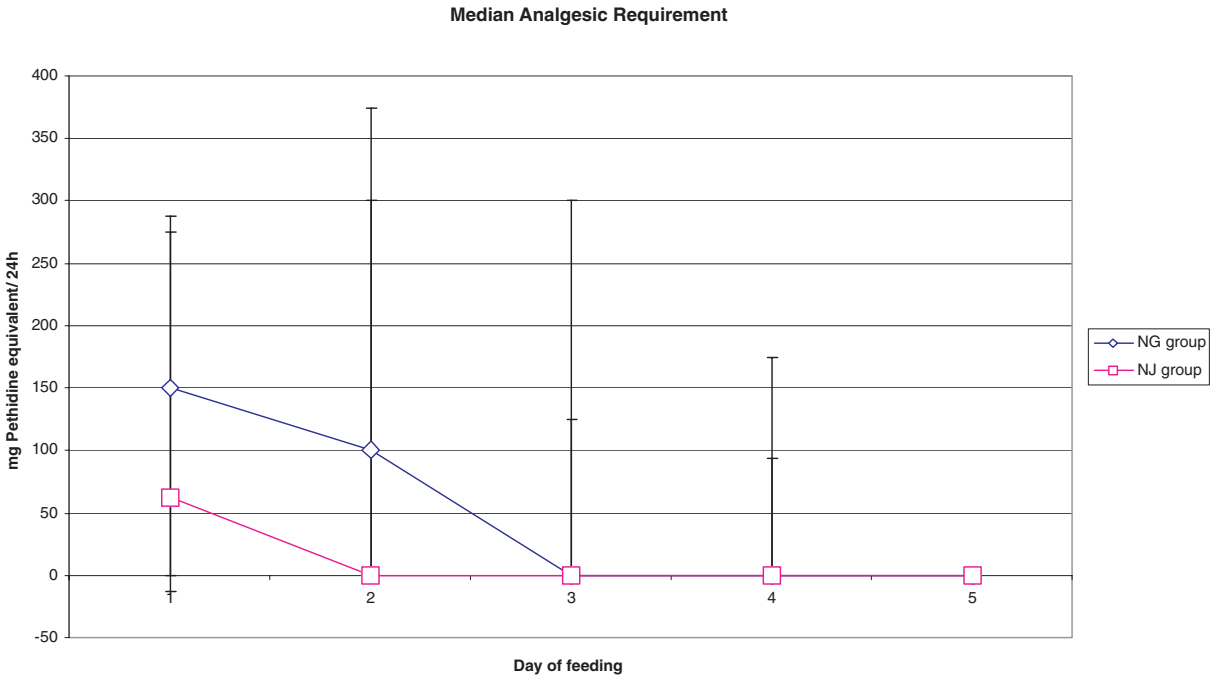

Figure 5. This graph shows the mean analgesic requirements in milligrams of pethidine per day over the first 5 days after feeding was commenced. The error bars show the standard errors of the means.

DISCUSSION

This study, the largest to date of enteral feeding in patients with objectively graded severe AP (Table 7), shows no evidence of exacerbation of disease associated with introduction of NG feeding compared with use of the NJ route and as such, not only supports the use of enteral feeding, but challenges the generally accepted view that it is essential to utilize a tube placed in the jejunum. This work therefore supports our pilot study in a similar cohort of 26 patients (18). The major advantage of NG feeding is its simplicity and clinical applicability, obviating the need for careful NJ tube placement with radiological or endoscopic assistance, usually necessitating intravenous sedation in these patients. The lack of any adverse effect on acute phase response, (measured by CRP and APACHE score) patient perception of pain, or analgesic requirement, associated with NG feeding is reassuring. From studies of enteral feeding in burn patients and from our own observations during this study and the earlier one, it seems that early onset of feeding, within 48 h of admission, helps to maintain gut function, allowing improved tolerance and fewer problems with ileus and gastric stasis compared with delaying introduction of feeding by 4 or 5 days (23, 24). This study, our previous one, and those of Kalferentzos *et al.*, Nakad *et al.*, and Windsor *et al.*, all suggest that in excess of 60% of daily nutritional requirements can be safely administered into the proximal gastrointestinal tract in patients with severe AP (11, 13, 14, 18). In addition, several studies have now shown improvement in outcome in patients receiving enteral nutrition (9, 12–14). Compared to TPN, enteral nutrition is reported to be cheaper and associated with fewer septic complications, a reduction in the acute phase response, shorter hospital stay, and more rapid return of gut function (9, 10, 12–14, 25). By contrast, the only study reporting a negative effect on the acute phase response, that of Powell *et al.* from Edinburgh, managed only a small volume feed, representing 21% of total nutritional requirement in the same time, the control group receiving no specific nutritional support (15). Whether enteral feeding in AP is better than no feeding, or simply more beneficial than TPN, requires resolution in future studies.

Table 7. Current Literature on Early Nasoenteric Feeding in Severe AP

Author (Reference)	Severe AP	Mild AP
Kalferentzos (14)	18	–
Nakad (11)	21	–
Windsor (13)	6	10
Powell (15)	13	–
Eatock (18)	26	–
Olah (12)	21	112
Abou Assi (9)	13	13
Gupta (25)	17	–
Present study	49	–
Total	167	135

All patients had NJ feeding except the 26 in (1) and 27 in the present study.

A total of 302 patients have been reported in studies of early enteral feeding in AP since 1997. One hundred and sixty-seven met the criteria for severe AP (Table 7). Thus far, our group are the only investigators to have assessed NG feeding. While it is feasible and easier to utilize than NJ feeding, neither of these routes has yet been conclusively

shown to be better than maximal supportive care without nutritional supplementation.

McClave was the first to compare parenteral and enteral feeding in AP patients, all of whom had mild disease (10). His 30-patient study found enteral feeding to be both safer and cheaper than TPN, and these observations have since been confirmed in severe AP (9, 12–14). This group reported clinical deterioration suggestive of sepsis in one patient on the sixth day of the study. There was an elevation of leukocyte count associated with fever, but no rise in serum amylase or lipase. Plain abdominal radiograph revealed the tip of the enteral feeding tube to be in the stomach and CT showed diffuse pancreatic edema. The feeding tube was repositioned and the patient recovered uneventfully. The timing of migration of the tube in this patient is unknown and may have occurred at any time between insertion and discovery, however, the authors attribute the deterioration to the gastric delivery of feed. We have found no evidence in our study to support such a causal relationship. There were also a number of patients in McClave's study who experienced pain on progression to oral diet. Pain settles in AP within a few days of onset, however, the recurrence of pain on reintroduction of diet is a well-recognized phenomenon (26). In this study, NG feeding did not result in an exacerbation of pain or pancreatic inflammation. The maximum rate of administration was less than 2 ml/min. It is possible that the recurrence of pain on reintroduction of diet is related to ingestion of larger volumes rather than further intrapancreatic release of enzymes.

Participation resulted in a delay in placement of NG tubes until randomization occurred. The median time to tube placement was not earlier than NJ intubation. For most of the study period one of the authors (FCE) was available to insert NJ tubes outwith fixed endoscopy sessions, thus speeding placement compared to that possible in normal clinical practice. Outside the setting of a clinical trial, it is very likely that NG placement will be speedier and NJ placement slower.

The steady reversal of clinical opinion since 1997 underlines that the complete avoidance of enteral nutrition was based more on tradition and extrapolated physiological theory than objective evidence. There remain a number of questions regarding the use of enteral feeding, including the exact timing and composition of feeds. However, the overall pattern of response is similar to clinical experiences in other areas, such as trauma, burns, elective abdominal surgery, and liver transplantation as well as in the management of the critically ill, where there has been a steady trend throughout the last decade to move almost totally from intravenous feeding to an enteral approach (23, 24, 27–29). Tolerance of enteral feeding in any of these conditions is certainly variable. Our study shows that the NG route can be well tolerated even in critically-ill patients and has the potential to circumvent many of the problems associated with NJ tube placement. It has long been believed that feeding the gut would exacerbate AP, however, we have found no evidence of this and the present study supports the view that the pancreas is nonresponsive to standard stimuli at such a time. NG feeding can now be considered a possible therapeutic option in the management of patients with severe AP.

ACKNOWLEDGMENTS

F.C. Eatock, C.R. Carter & C.W. Imrie took part in the development of the protocol. C.R. Carter generated the randomization sequence. Recruitment of patients was by F.C. Eatock, P. Chong, N. Menezes, and F.C. Eatock assigned all participants to their groups. Feed supervision was the primary responsibility of L. Murray. Clinical care was directed by C.J. McKay, C.R. Carter and C.W. Imrie. Data collection and analysis was by F.C. Eatock. Preparation of the report was done mainly by C.W. Imrie and F.C. Eatock, with all participants involved.

Reprint requests and correspondence: C.W. Imrie, Lister Department of Surgery, Glasgow Royal Infirmary, Alexandra Parade, Glasgow, G31 2ER, Scotland.

Received April 8, 2004; accepted September 14, 2004.

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