Original Article

Risk factors associated with intolerance to enteral nutrition in moderately severe acute pancreatitis: A retrospective study of 568 patients

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Abstract

Background/Aims: To assess the frequency of and risk factors for intolerance to enteral nutrition through nasogastric (NG) or nasojejunal (NJ) tube feeding in patients with moderately severe acute pancreatitis.

Patients and Methods: Patients who underwent enteral nutrition via the nasojejunal tube or nasogastric tube, from January 2012 to December 2017, were enrolled. Demographic and etiological data, admission variables, enteral nutrition related variables, and radiological variables were evaluated using univariate and multivariate analysis.

Results: A total of 568 patients were included, with 235 (41.4%) receiving nasojejunal tube feeding and 333 (56.8%) receiving nasogastric tube feeding. Tube-feeding intolerance was observed in 184 patients (32.4%), occurring at a median of 3 days (range, 1-5 days) after the start of enteral nutrition. The variables independently associated with risk of intolerance to tube feeding were hypertriglyceridemia (odds ratio, 8.13;95% CI, 5.21-10.07; $P = 0.002$), the presence of systemic inflammatory response syndrome (odds ratio, 6.58;95% CI, 3.03-8.34; $P = 0.002$), acute gastrointestinal injury-III status (odds ratio, 5.51;95% CI, 2.30-7.33; $P = 0.02$), the time from admission to commencement of enteral nutrition (odds ratio, 7.21;95% CI, 2.16-9.77; $P = 0.001$), and pancreatic infection (odds ratio, 6.15;95% CI, 4.94-8.75; $P = 0.002$) Patients with tube-feeding intolerance required prolonged enteral nutrition ($P < 0.001$) and had longer hospitalizations ($P < 0.001$).

Conclusions: Tube-feeding intolerance accounts for a considerable proportion in patients with moderately severe acute pancreatitis. The presence of hypertriglyceridemia, systemic inflammatory response syndrome and acute gastrointestinal injury grade III or pancreatic infection and the time from admission to commencing enteral nutrition increase the risk for tube-feeding intolerance.

Keywords: Acute gastrointestinal injury, feeding, hypertriglyceridemia, infection, revised Atlanta criteria

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INTRODUCTION

Acute pancreatitis (AP) is a heterogeneous disease with a highly variable clinical course. Although most cases are mild and self-limiting, 10% to 20% of patients develop severe acute pancreatitis (SAP) with systemic inflammatory response syndrome (SIRS), multiple organ dysfunction, or

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pancreatic necrosis; in 47% of patients, these complications result in significant mortality.[1] Substantial evidence suggests that mortality in AP is related to organ failure, and persistence of organ failure beyond 48 hours is associated with a mortality of 34% to 55%, whereas resolution within 48 hours is associated with a mortality of 0% to 3%.[2,3]

Due to these variable outcomes, the revised Atlanta criteria (RAC) of 2012 define a distinct subcategory of AP called moderately severe acute pancreatitis (MSAP), which includes a mixed population of patients characterized by the presence of local complications and the absence of persistent organ failure.[4] Although the duration of hospital stay and the need for intervention in patients with MASP are similar to those with SAP, the requirement for intensive care-unit (ICU) admission, duration of ICU stay, and mortality are significantly less.[5]

The use of enteral nutrition (EN) is well established in the management of SAP, as it is associated with a considerable reduction in morbidity and mortality.[6,7] EN can be given through either a nasogastric (NG) or nasojejunal (NJ) tube. Recently, multiple studies have compared NG and NJ feeding, demonstrating their equivalence in terms of efficacy, safety, and patient tolerance. NG enteral feeding is safe and well tolerated in most patients with SAP.[8-11]

With the common practice of both NJ and NG feeding in the management of SAP, the number of patients with tube-feeding intolerance (TFI) has increased. The symptoms of TFI include recurrent pain, distension, nausea and vomiting that require discontinuation of EN. TFI may delay oral feeding, prolong the length of hospitalization, and increase the risk of developing complications related to total parenteral nutrition (TPN). Although recent studies have reported feeding intolerance in patients with SAP, few studies have focused on MSAP, and the risk factors that might be associated with TFI in patients with MSAP have not been analyzed. In the present research, we performed a retrospective study to assess the frequency of and risk factors associated with TFI in patients with MSAP undergoing EN through either an NG or NJ tube.

PATIENTS AND METHODS

We conducted an observational, descriptive, retrospective study based on the review of clinical documentation-and clinical-history databases at our institution. We reviewed the records of patients who were discharged from our department with MSAP and placed on EN via an NJ or NG tube between January 2012-December 2017. Institutional review board approval was granted for this investigation before obtaining medical records and radiographic review.

The diagnosis of AP required 2 of the following 3 features:[4] (1) abdominal pain consistent with acute pancreatitis (acute onset of persistent, severe, epigastric pain often radiating to the back); (2) serum lipase level or amylase level at least 3 times greater than the upper limit of normal; and (3) characteristic findings of acute pancreatitis on computed tomography (CT).

The moderately severe acute pancreatitis (MSAP) was defined according to the revised Atlanta criteria (RAC):[4] (1) the presence of transient organ failure; or (2) local complications including acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection, or walled-off necrosis; or (3) systemic complications exacerbating pre-existing comorbidities such as coronary artery disease or chronic lung disease, precipitated by the AP but without persistent organ failure. The modified Marshall scoring system[12] was used to diagnose organ failure, as described in the RAC. The presence of organ failure was assessed at admission and also at every 24 h thereafter during hospitalization. Transient organ failure was defined as lasting less than 48 h and involving the respiratory, cardiovascular, or renal systems, whereas persistent organ failure involved the same 3 organ systems but for a duration of more than 48 h.[13]

The following were exclusion criteria for the study: age less than 18 years, pregnancy, persistent organ failure at presentation that met the criteria of SAP according to the RAC, recurrent AP, and acute-on-chronic pancreatitis. The patients were also excluded if there was a delay of more than 1 week between the onset of pancreatitis and admission to the hospital, or if they were taking oral feeding at presentation.

The following data were collected on admission: (1) baseline variables including demographic information (age and sex), the etiology of MSAP, maximal C-reactive protein (CRP) level, the existence of SIRS, Ranson score, and acute physiology and chronic health examination-II (APACHE-II) score; (2) EN-related variables including time from admission to commencement of EN, duration of EN, route of tube feeding, and the presence of pancreatic infection; and (3) length of hospital stay and the CT severity index (CTSI) around 1 week after admission were also recorded. All the patients underwent at least 1 contrast enhanced CT (CECT) as this examination was routine for patients with AP in our institution. The severity of gastrointestinal function before EN was also assessed according to the acute gastrointestinal injury (AGI) system.[14] A diagnosis of AGI was defined as malfunctioning of the gastrointestinal tract due to acute illness and was divided into 4 grades: AGI

grade I (risk of developing gastrointestinal dysfunction or failure) and AGI grade II (gastrointestinal dysfunction), AGI grade III (gastrointestinal failure), and AGI grade IV (gastrointestinal failure with a severe impact on distant organ function).

All the patients received medical treatment including appropriate fluid support, pain control, organ supportive treatment and antibiotics in patients with proven infection; patients who were transferred to the ICU due to persistent organ failure were excluded from this study. We attempted to commence EN in all patients as soon as possible after admission. The patients were assigned to receive either NG or NJ feeding. Both routes of tube feeding were recommended to the patients, and the decision was mainly based on cost of tube placement, willingness of patients, and for cases with pyloric obstruction, NJ feeding was recommended as the preferred. NG tubes were placed in the ward by nursing staff at the bedside, and the position was confirmed by aspiration and pH measurement. NJ tubes were placed under endoscopic guidance, and the position was confirmed radiologically. A commercially available elemental enteral formula (Peptisorb; Nutricia Pharmaceutic Co., Ltd., Wuxi, China) was used at an initial rate of 25 mL/hr and gradually increased to the nutrient goal (20 kcal/kg/day) over 48 to 72 hr, as tolerated. The tube-feeding intolerance (TFI) is defined as when at least 20 kcal/kg BW/day via enteral route cannot be reached within 72 h of feeding attempt.[14] That is, if symptoms such as recurrent pain, distension, or nausea followed by vomiting occurred that led to discontinuation of EN, or was unable to reach the target (20 kcal/kg BW/day), then we considered these as TFI.

The patients were monitored daily for gastrointestinal symptoms (e.g., pain, nausea, vomiting, and diarrhea). If a patient was unable to tolerate the prescribed rate of EN feeding, the rate was reduced by half and gradually increased again as tolerated. When the enteral route was not usable, patients received TPN with the same feeding goal. Oral feeding was reintroduced based on the disappearance or alleviation of AP-related symptoms: the absence of subjective abdominal pain and no tenderness on physical examination.

Statistical analysis

An initial descriptive analysis of the study variables expressed qualitative variables as absolute numbers and percentages, and quantitative variables as medians and ranges. The independent samples *t*-test was used for continuous variables and the Chi-square or Fisher's exact test was used for categorical or discrete variables. A univariate analysis was performed, and those variables with a P value <0.05 were considered to be statistically significant or clinically relevant; these variables were then included in a multivariate logistic regression to evaluate the intolerance-related variables. Multivariate analysis consisted of forward logistic regression according to the Wald statistic. Variables with a P value of <0.05 remained in the final logistic model. Adjusted odds ratios and their respective 95% confidence intervals (CI) were presented in the final model. All statistical calculations were performed using SPSS statistical software, version 17.0 (SPSS Inc, Chicago, IL).

RESULTS

Descriptive analysis

During the study period, a total of 1365 patients were discharged from our department with the diagnoses of MSAP between January 2012-December 2017; a total of 568 patients who met the criteria of MSAP and underwent EN via an NJ or NG tube were enrolled in this study.

Of these 568 patients, 235 patients (41.4%) were given NJ tube feeding, and 333 patients (56.8%) received NG tube feeding. TFI was observed in 184 patients (32.4%), and intolerance occurred a median of 3 days (range, 1-5 days) after the start of EN. Of these 184 patients, 112 (60.9%) had aggravated distension, 46 (25%) had reflux and vomiting, 62 (33.7%) had diarrhea, and 16 (8.7%) had recurrent abdominal pain. Most cases of intolerance could be resolved by slowing the rate of feeding, adding prokinetic drugs or antisecretory drugs; however, 43 patients who had aggravated distension only achieved relief with short-time termination of EN, and 5 cases with gastrointestinal paralysis developed to abdominal compartment syndrome after EN. The symptoms of these 5 patients were relieved after conversion to NJ tube with 2-3 days transition of parenteral nutrition.

Association of clinical variables with tube feeding intolerance

On univariate analysis, the factors associated with TFI were hypertriglyceridemia as an etiology ($P < 0.001$), the presence of SIRS ($P < 0.005$), gastrointestinal function ($P = 0.005$), time from admission to commencement of EN ($P = 0.028$), and pancreatic pancreatic infection ($P < 0.001$). These factors are shown in Tables 1 and 2. These variables were introduced into a multivariate logistic regression analysis. The variables independently associated with risk of intolerance to tube feeding were hypertriglyceridemia (odds ratio, 8.13;95% CI, 5.21-10.07; $P = .002$), the presence of SIRS (odds ratio, 6.58;95% CI, 3.03-8.34; $P = .002$), AGI-III status (odds ratio, 5.51;95% CI, 2.30-7.33;

Table 1: Demographic, etiology and baseline variables at admission

	Intolerance				*P*
	Total, *n*=568	no, *n*=384	yes, *n*=184	OR (95%CI)*	
Age, y	47.4 (21-78)	49 (20-74)	46 (24-78)	-	0.468
Sex (male%)	329 (57.9%)	245 (63.9%)	130 (70.7%)	-	0.178
Etiology				-	
Biliary (%)	210 (37%)	143 (37.2%)	67 (36.4%)	-	0.261
HTG (%)	188 (33.1%)	89 (23.2%)	99 (53.8%)	-	<0.001#
Alcoholic (%)	147 (25.9%)	94 (24.5%)	53 (28.9%)	-	0.258
Others (%)	23 (4%)	18 (4.7%)	5 (2.7%)	-	0.985
Maximal CRP (>150 mg/L)	506 (89.1%)	340 (88.5%)	166 (90.2%)	-	0.895
SIRS (%)	411 (72.4%)	253 (65.9%)	158 (85.9%)	-	<0.005#
GI function					0.005#
AGI-I	244 (43%)	216 (56.3%)	28 (15.2%)	(Reference)	
AGI-II	221 (38.9%)	145 (37.8%)	76 (43.5%)	1.4 (0.778-2.406)	
AGI-III	103 (18.1%)	23 (6%)	80 (43.5%)	4.857 (2.11-6.281)	
Ranson score	4 (3-5)	4 (3-5)	5 (3-6)		0.996
APACHE-II score	10 (6-12)	10 (6-12)	10 (8-12)		0.144

Qualitative variables are expressed in absolute numbers and as a percentage of the total; quantitative variables are expressed as median (min-max).*OR: Odds ratio; CI: Confidence interval.#Significant at a <0.05.HTG indicates hypertriglyceridemia; GI function indicates gastrointestinal function; AGI indicates acute gastrointestinal injury

Table 2: Comparison of patients with or without intolerance on EN-related variables, infection complications, CTSI and hospital stay

	Intolerance			*P*
	Total, *n*=568	No, *n*=384	Yes, *n*=184	
Admission-EN (≥72 hr)	204 (35.9%)	125 (32.6%)	79 (42.9%)	0.028#
Feeding route (NJ)	318 (56%)	219 (57%)	99 (53.8%)	0.284
Pancreatic infection (%)	142 (25%)	60 (15.6%)	82 (44.6%)	<0.001#
CTSI	4 (3-6)	3 (3-5)	3 (3-6)	0.596
Duration of EN, d	5 (1-11)	5 (4-7)	8 (1-11)	<0.001#
Hospital stay, d	8 (6-20)	8 (6-11)	12 (8-20)	<0.001#

Qualitative variables are expressed in absolute numbers and as a percentage of the total; quantitative variables are expressed as median (min-max).#Significant at a <0.05.EN indicates enteral nutrition; CTSI indicate CT severity index

Table 3: Multivariate logistic regression analysis of risk factors for feeding intolerance

	Adjusted OR (95%CI)*	*P*
Time from admission to EN	7.21 (2.16-9.77)	0.001#
Pancreatic infection	6.15 (4.94-8.75)	0.002#
SIRS	6.58 (3.03-8.34)	0.002#
AGI-III	5.51 (2.30-7.33)	0.02#
HTG	8.13 (5.21-10.07)	0.002#

*OR: Odds ratio; CI: Confidence interval.#Significant at a <0.05

P =.02), the time from admission to commencement of EN (odds ratio, 7.21;95% CI, 2.16-9.77; *P* =.001), and pancreatic infection (odds ratio, 6.15; 95% CI, 4.94-8.75; *P* =.002). These variables are shown in Table 3. Patients with TFI required prolonged EN (*P* < 0.001) and had longer hospitalizations (*P* < 0.001), as shown in Table 2.

DISCUSSION

In the present study, we analyzed the risk factors for TFI in patients with MSAP. Although most patients tolerate NG or NJ feeding well, the occurrence of intolerance is not rare. We describe a series of symptoms related to intolerance and find a statistically significant relation between TFI and hypertriglyceridemia, SIRS, AGI-III status, time from admission to EN, and pancreatic infection. Moreover, we also confirm that TFI can increase the duration of EN and of the hospital stay.

Early EN has been widely applied to the management of SAP, and it has an important role in maintaining the mucosal integrity of the gastrointestinal tract and preventing bacterial translocation and infection of necrotic pancreatic tissue.[15,16] In a randomized controlled trial[17] comparing early and late feeding in patients with SAP, an onset of EN between 24 and 48 hours after admission significantly reduced the risk of organ failure and infectious complications. EN can be provided through either the NJ or NG route. The "pancreatic rest" paradigm has been challenged by several randomized controlled trials comparing NJ and NG tube feeding in SAP that revealed no difference between the routes in terms of tolerance of feeding, pancreatic complications and mortality.[18-21] One possible explanation for these findings may be that patients with AP have significantly lower rates of pancreatic enzyme secretion into the duodenum compared with healthy subjects. Another explanation might be that the severity of AP is inversely related to duodenal secretion of pancreatic enzymes, probably because the injured acinar cells are not able to fully respond to the physiological stimuli to secretion induced by feeding; this may be of some help in explaining why NG feeding does not appear to aggravate the severity of AP. In addition, NG feeding with a slow rate of continuous infusion may not be able

to stimulate the secretory cells of the pancreas. In our study, the route of EN was not associated with TFI. In consideration of the advantages of NG feeding such as less expensive, easy insertion and low risk even in serious cases, NG feeding is recommended as first-line choice for EN, and then switching on to NJ feeding if intolerance occurs. In previous studies, although full tolerance of NG feeding (no temporary reduction, stoppage, or withdrawal of feeding) was observed in over 80% of patients, there was some feeding intolerance reported. However, as the sample size was limited, no risk factors related to intolerance were analyzed.[9,18-21] In the present study, we detected the factors related to intolerance of EN with tube feeding and found an association between the risk of TFI and the duration from admission to the commencement of EN. This result demonstrates that delaying the onset of EN increases the possibility of TFI.

Patients with SAP are prone to gastric ileus caused by pancreatic inflammation.[22] Kumar[9] reported 2 patients with SAP and ileus who tolerated early NJ feeding in small volumes and at slow infusion rates; both experienced resolution of their ileus. However, in a study conducted by Eatock *et al*.,[8] 2 of 26 patients with SAP who had pre-existing gastric stasis were unable to tolerate NG feeding; 1 had success after changing to NJ feeding. Gunilla[20] reported that 13% of patients require interruption of NG feeding due to gastric retention. The gastrointestinal function is an important determinant in the outcome of critically ill patients. In 2012, the working group on abdominal problems of the European Society of Intensive Care Medicine (ESICM)[14] proposed a set of definitions and guidelines for a grading system of gastrointestinal dysfunction that is applicable to AGI treatment. Numerous studies have confirmed that the early commencement of EN helps maintain gut function, allows improved tolerance, and reduces problems with ileus and gastric stasis compared with delaying initiation.[18,23-25] We evaluated gastrointestinal function before the start of EN and found that AGI is common in patients with MSAP. In our multivariate analysis, severity of AGI status was associated with the intolerance of EN, therefore, it's important to assess the gastrointestinal function before the onset of EN, and for those with severe gastrointestinal injury, slow intake of EN can be more appropriate.

The systemic inflammatory response syndrome (SIRS) is increasingly recognized as an early indicator of severe pancreatitis.[4,26] When SIRS is persistent, there is an increased risk of developing organ failure.[27,28] In this study, the Ranson and APACHE-II scores were relatively low, and we found no association between TFI and the inflammatory indices (Ranson score and APACHE II) or with serum CRP. However, the presence of SIRS was confirmed to increase the risk of TFI, which might indicate that SIRS is a valuable predictor of severity in early-stage MSAP. CECT is a good imaging modality for identifying the severity of AP; however, the typical morphologic changes seen with local complications are usually not clear in the early stage of SAP or MSAP. Therefore, early CT examination is unable to be a predominant determinant of severity; CECT at 5 to 7 days after admission is considered more reliable in establishing the presence and extent of pancreatic necrosis.[29] All patients in our institution undergo CECT at 1 week after admission. Nevertheless, we found no relation between CTSI and TFI. Further studies are necessary with larger sample sizes to assess whether the location of collections is associated with TFI.

Infectious complications are the major contributors to the risk of death in patients with pancreatitis. Infected necrosis rarely occurs during the first week of illness, and convincing evidence suggests that there is no correlation between the risk of infection and the extent of necrosis or duration of symptoms.[30-34] Early EN has been proven to decrease the risk of pancreatic infection and to reduce bacterial translocation by maintaining the integrity of the intestinal mucosal barrier.[35-37] In this study, we report an infection rate of 25% in patients with MSAP. Most infected necrosis occurred after 1 week of admission, and multivariate analysis revealed that infectious complications could increase the risk of TFI in patients who might previously be tolerant of EN.

We found that patients with MSAP caused by hypertriglyceridemia are predisposed to TFI. Hypertriglyceridemia is a significant inciting factor of AP.[38] A previous systemic review reported the prevalence of hypertriglyceridemic AP as 9% of all AP, and hypertriglyceridemia causes more severe AP than other etiologies.[39] The most common definition of hypertriglyceridemic AP reported in the literature is AP with a serum triglyceride level of 1000 mg/dL.[40] Studies have found that patients with hypertriglyceridemia >500 mg/dL have higher 24-h APACHE-II scores, which are in turn associated with increased systemic complications, high mortality, prolonged hospital stays, and higher rates of ICU admission.[41,42] Our results show that hypertriglyceridemia increases the risk of TFI. This can be explained by the previously reported conclusion that hypertriglyceridemia is prone to inducing a more severe and complicated clinical course. Moreover, hypertriglyceridemia is usually accompanied by a disturbance in glucose- and lipid metabolism. Uncontrolled hypertriglyceridemia may

increase the risk of infection and gastrointestinal dysmotility that finally leads to intolerance of EN.

Our study has certain limitations. First, the placement of NG or NJ tube was not randomized, therefore, although no statistically significant difference in intolerance rate was observed between the 2 routes, further well-designed randomized-controlled studies with large sample size are needed to confirm this result. Second, selection bias cannot be excluded. Since we enrolled patients within a week of onset, any delay in admission might lead to a delay in commencing EN, which is considered clinically meaningful.

In conclusion, TFI in patients with MSAP accounts for a considerable proportion and is independently associated with hypertriglyceridemia, SIRS, AGI-III status, pancreatic infection, and increasing time from admission to commencing EN. Therefore, evaluation of disease severity and effective management at the early stage of illness is vital for patients with MSAP. Patients with hypertriglyceridemic AP require more intensive care than patients with AP of other etiologies.

Data availability statement

All the records of the patients that were used to support the findings of this study are traceable in the Neusoft hospital information system which is authorized to Shengjing hospital. Data are available from Feng Tian (tianfeng@sj-hospital.org) for researchers who meet the criteria for access to confidential data.

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Conflicts of interest

There are no conflicts of interest.

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