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Original Research

Challenges of Administering Pancrelipase in Pancreatitis Patients

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Key words: diets, metabolism, Preventative Nutrition and Chronic Disease, supplements and functional foods, nutriceuticals

Objective: This study evaluated nutrition status to determine the impact of a novel approach using elemental nutrition compared to pancrelipase administration in patients with pancreatitis.

Methods: This retrospective study included adult patients with pancreatitis who were nil per os (NPO) and received elemental nutrition from August 2008 to 2010 ($n = 24$) or pancrelipase enzyme supplementation (PES) plus nonelemental enteral nutrition from August 2011 to 2013 ($n = 41$) at a large academic medical center. The primary outcome is the percentage of diarrhea-free days. Secondary outcomes include time-to-goal enteral nutrition from the enteral nutrition initiation and pre-albumin and albumin changes pre- and postenteral nutrition.

Results: There were no statistically significant differences between the 2 groups in percentage of diarrhea-free days (46.80% $\pm$ 29.03% vs 53.45% $\pm$ 36.76%, $p = 0.45$). Additionally, there were no differences in secondary outcomes of time-to-goal enteral nutrition and pre-albumin and albumin changes pre- and postenteral nutrition.

Conclusion: Utilizing elemental nutrition compared to PES plus nonelemental enteral nutrition in patients with pancreatitis was not associated with a significant reduction in percentage of diarrhea-free days, time-to-goal enteral nutrition, and nutrition status. A multicenter, prospective, randomized, controlled trial is warranted to further evaluate the efficacy of elemental nutrition in patients with pancreatitis.

INTRODUCTION

Nutrition support is a critical part of the medical management of patients with pancreatitis who are in a hypercatabolic state with a negative nitrogen balance [1]. Utilizing enteral nutrition alone in patients with pancreatitis with decreased production of pancreatic enzymes may lead to malabsorption and ultimately malnutrition [2]. Pancreatic enzyme capsules contain various amounts of lipase, protease, and amylase that are essential for the breakdown of carbohydrates, proteins, and fat and can be used in addition to enteral nutrition [1]. Enteral access devices can be used to administer the pancrelipase enzyme supplementation (PES) for patients who are unable to swallow; however, administration challenges exist. PES has a unique enteric-coated formulation that may lead to enteral access device obstruction and inconsistent enzyme activity [3].

Enteral nutrition is preferred over parenteral nutrition in this patient population due to increased infection risk and longer hospital stays [2]. Patients receiving enteral nutrition may benefit from PES to reduce oily stools and to maintain adequate nutrient absorption [3].

Previous studies have attempted to answer the question on the best practice for administering PES via an enteral access device. Ferrie and colleagues utilized a method involving crushing and suspending of PES in sodium bicarbonate with a 10,000 international units of lipase to 800 mg of sodium bicarbonate ratio [3]. The authors concluded that patients can continue to receive PES with enteral nutrition because the PES–sodium bicarbonate formulation minimized enteral access device obstruction and maintained optimal enzyme activity. Similarly, a case series also described the administration of PES with water, apple juice, applesauce, or sodium bicarbonate via an enteral access device [4]. The authors concluded that all techniques except the dilution of PES in sodium bicarbonate solution resulted in enteral access device obstruction or continued gastrointestinal complaints including abdominal pain and loose stool output. Potential factors that may have caused the obstruction include pH differences between PES and stomach

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and/or duodenum, narrow enteral access device lumens, and microsphere inconsistency once adulterated.

Per the European Society for Clinical Nutrition and Metabolism guidelines, patients with pancreatitis will need pancrelipase administration in addition to enteral nutrition [1]. The PES manufacturer product labeling lacks specific instructions for enteral access device administration and also discourages adulterating enteric-coated products [5]. Therefore, institutions have developed PES protocols or added elemental nutrition to their formulary to circumvent PES use for patients with pancreatitis who are nil per os (NPO) [4,5]. The primary objective of this study was to determine the percentage of diarrhea-free days in patients with pancreatitis who are NPO on elemental nutrition or PES plus nonelemental enteral nutrition. Diarrhea-free days were selected as an endpoint because diarrhea is a common side effect of malabsorption, high fat intake, decreased gastrointestinal bicarbonate secretion, and/or increased production of nitric oxide and cytokine production, leading to organ failure and pancreatic infection [2]. The secondary outcomes were time-to-goal enteral nutrition and to compare pre-albumin and albumin changes pre- and postenteral nutrition.

MATERIALS AND METHODS

Study Design and Patients

A retrospective chart review was conducted at a 939-bed tertiary academic medical center. Adult patients were eligible for inclusion if they had a diagnosis of pancreatitis and received PES (Zenpep or Creon) with enteral nutrition from August 2008 to August 2010 or elemental nutrition (Vital 1.2) from August 2011 to August 2013. Patients were excluded if survived less than 48 hours, received PES for enteral access device clearance, or concurrently received PES and elemental nutrition or parenteral nutrition. A practice change was implemented within the study institution due to the lack of standardization and challenges in administering PES among patients with pancreatitis. Some of the challenges in the study institution include crushing PES resulting in unbroken pancrelipase miscrospheres, soaking PES microspheres in various mediums (i.e., hot water, apple sauce) resulting in a thick sludge, or placing PES capsules within enteral nutrition resulting in the capsules suspended toward the top of the enteral nutrition formula.

Data Collection

The primary outcome was the percentage of diarrhea-free days. Diarrhea was defined as having documented continuous stool output over a 24-hour period. The percentage of diarrhea-free days was calculated by taking the number of days the patient had diarrhea divided by the number of days the patient was on goal enteral nutrition. Secondary outcomes included nutrition status, institution-based nutrition protocol adherence, and malabsorption status. To assess nutrition status, weekly pre-albumin and albumin were recorded. For nutrition protocol adherence, the variables assessed included enteral nutrition rate, goal rate defined by the registered dietitian, date of enteral nutrition initiation and goal rate, time-to-goal enteral nutrition, and duration of enteral nutrition. Adherence with the nutrition protocol was defined as documented evidence of the written order and the variables received per protocol was charted on the electronic medication administration record. To assess malabsorption, fecal fat tests were recorded. Patient demographics extracted from medical records included age, sex, height, and weight.

Data were collected from Epic 2009 software (Intersystems, Verona, WI) as the sole electronic medical record. Decision Support System and Business Objects were queried to identify all *International Classification of Diseases* (ICD-9) codes for patients with pancreatitis with enteral nutrition revenue codes (ICD-9 codes: 577.0–577.9, 579.4, 863.81–863.84, 863.91, 863.94, 211.6, 157.0–157.9, 251.9, 751.7; enteral nutrition revenue codes: 8311 and 8315) [6]. Decision Support System is an internal data reporting computer program and Business Objects is a pharmacy computerized database that queries the computerized order entry system.

Data collected that are confounders included other PES formulations added to formulary, concomitant *Clostridium difficile* infection (CDI), broad-spectrum antibiotic(s), prokinetic medication(s), sorbitol-containing medication(s), bowel regimen, and stress ulcer prophylaxis (SUP), which included stool softeners and laxatives.

This study was approved by the University of Florida Institutional Review Board prior to the retrospective evaluation with a waiver of the requirement for informed consent.

Statistical Analysis

Baseline characteristics, primary and secondary outcomes that were normally distributed continuous variables, were described using mean and standard deviation and were analyzed using Student's *t* test.

RESULTS

Patients and Baseline Characteristics

A total of 75 patients were assessed for eligibility in the PES plus nonelemental enteral nutrition group and 78 patients in the elemental nutrition group (Fig. 1). Patients were excluded due to missing data (30 in PES plus nonelemental enteral nutrition and 9 in elemental nutrition) such as lack of documentation of nutrition progress notes, nutrition rates, and

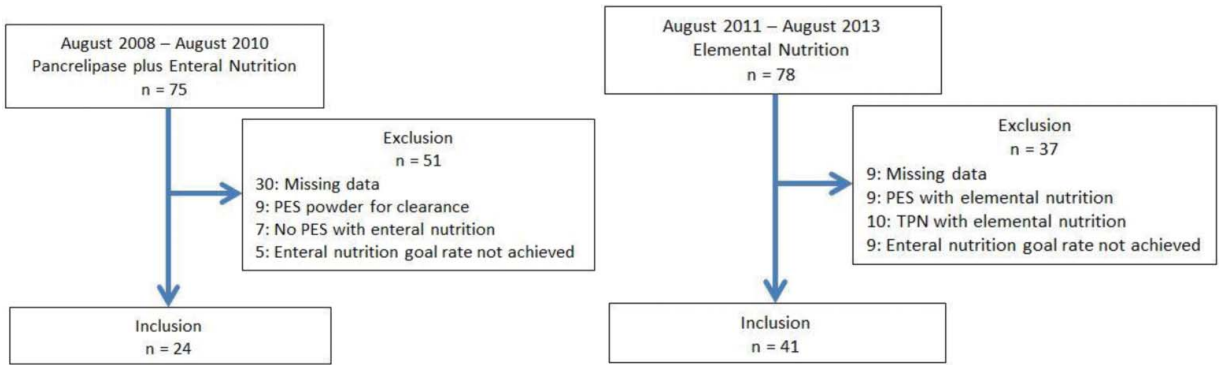

Fig. 1. Flow diagram of patient enrollment. TPN = total parenteral nutrition.

failure to achieve the goal nutrition infusion rate defined by the registered dietitian (5 in PES plus nonelemental enteral nutrition and 9 in the elemental nutrition group). Additionally, 16 patients were excluded from the PES plus nonelemental enteral nutrition group: 9 patients used PES powder for enteral access clearance and 7 patients received no PES administration at time of enteral nutrition. The standard administration times for PES are 1:30 AM, 9:30 AM, and 5:30 PM for patients with pancreatitis receiving continuous enteral nutrition. In the elemental nutrition group, 19 patients were excluded: 10 patients received parenteral nutrition with elemental nutrition and 9 patients received PES with elemental nutrition. A total of 65 patients with pancreatitis received ($n = 24$) PES plus nonelemental enteral nutrition and ($n = 41$) elemental nutrition were included in the analysis.

The baseline demographics (Table 1) of the patients in each group statistically significantly differed, with males as a majority of the elemental nutrition group (61.9%) compared to the PES plus nonelemental enteral nutrition (36%). Furthermore, the average actual weight was statistically different between the elemental nutrition group compared to the PES plus nonelemental enteral nutrition group (89 ± 27 vs 71 ± 21 kg, $p = 0.006$; Table 1). Although the PES plus nonelemental enteral nutrition group had higher baseline pre-albumin (8.27 ± 3.49 vs 6.77 ± 3.16 mg/dL, $p = 0.135$) and albumin (2.83 ± 0.73 vs 2.44 ± 0.71 g/dL, $p = 0.047$) compared to the elemental nutrition group; however, there were inconsistencies in the measurements beyond week 3 for pre-albumin and week 4 for albumin; therefore, data beyond those weeks were not collected or analyzed.

Endpoints

There was no difference between the 2 groups in the percentage of diarrhea-free days (Table 2). The percentage of diarrhea-free day in the PES plus nonelemental enteral nutrition group was 53.45% ± 36.76% compared to 46.80% ± 29.03% in the elemental nutrition group ($p = 0.45$).

Confounding variables were collected (Table 2). Six CDI were identified in the elemental nutrition group with none in the PES plus nonelemental enteral nutrition group. There were 29 incidences of broad-spectrum antibiotic(s) utilization in the elemental nutrition group compared to 17 incidences in the PES plus nonelemental enteral nutrition group (70.7% vs 70.6%). Moreover, 27 patients in elemental nutrition group (65.9%) compared to 15 patients in the PES plus nonelemental enteral nutrition group (62.5%) received sorbitol-containing medications. Four patients in each group received prokinetic medication(s) in the PES plus nonelemental enteral nutrition and the elemental nutrition groups, 16.7% and 9.8%, respectively. Furthermore, 10 patients received a bowel regimen in the PES plus nonelemental enteral nutrition group and 11 in the elemental nutrition group. Eleven patients (45.8%) in the

Table 1. Baseline Demographics of Study Patients

	PES Plus EN ($n = 24$)	Elemental Nutrition ($n = 41$)	p Value
Age[a] (years)	59 ± 14	56 ± 17	0.431
Male[b]	9 (36%)	26 (61.9%)	0.043
Actual weight[a] (kg)	71 ± 21.43	89 ± 25.90	0.006
Baseline pre-albumin[a] (mg/dL)	8.27 ± 3.49	6.77 ± 3.16	0.135
Baseline albumin[a] (g/dL)	2.83 ± 0.73	2.44 ± 0.71	0.047

PES = pancrelipase enzyme supplementation, EN = enteral nutrition.
[a]Mean ± standard deviation.
[b]Total number (%).

Table 2. Confounding Variables

	PES Plus EN (n = 24)	Elemental Nutrition (n = 41)
CDI, *n* (%)	0 (0)	6 (14.6)
Broad-spectrum antibiotic(s), *n* (%)	17 (70.8)	29 (70.7)
Sorbitol-containing medication(s), *n* (%)	15 (62.5)	27 (65.9)
Prokinetic medication(s), *n* (%)	4 (16.7)	4 (9.8)
Bowel regimen, *n* (%)	10 (41.7)	11 (26.8)
Stress ulcer prophylaxis, *n* (%)	11 (45.8)	38 (92.7)

PES = pancrelipase enzyme supplementation, EN = enteral nutrition, CDI = *Clostridium difficile* infection.

Table 3. Outcomes

	PES Plus EN ($n = 24$)	Elemental Nutrition ($n = 41$)	p Value
Primary			
% Diarrhea-free days[a]	53.45 ± 36.76	46.80 ± 29.03	0.45
Secondary			
Time-to-goal EN[a] (hours)	88.79 ± 80.70	59.73 ± 43.82	0.064
Mean baseline pre-albumin[a] (mg/dL)	8.27 ± 3.49	6.77 ± 3.16	0.135
Week 1[a]	9 ± 3.71	9.73 ± 5.44	0.682
Week 2[a]	14 ± 7.94	10.58 ± 5.25	
Week 3[a]	30 ± 0	13.23 ± 9.46	
Mean baseline albumin[a] (mg/dL)	2.83 ± 0.73	2.44 ± 0.71	0.047
Week 1[a]	2.6 ± 0.64	2.57 ± 0.51	0.886
Week 2[a]	2.73 + 0.51	2.58 ± 0.63	
Week 3[a]	2.9 ± 0	2.39 ± 0.47	
Week 4[a]	3.3 ± 0	2.62 + 0.90	
Nutrition protocol adherence	—	76%	
Abnormal quantitative fecal fat test	—	1[b]	

PES = pancrelipase enzyme supplementation, EN = enteral nutrition.

[a]Mean ± standard deviation/

[b]6 patients were tested.

PES plus nonelemental enteral nutrition group received SUP, which includes initiation of pantoprazole or famotidine, and 38 patients (92.7%) in the elemental nutrition group (interquartile range = 0 days and −1 days, respectively).

For secondary outcomes of time-to-goal enteral nutrition, pre-albumin, and albumin, there were no statistical differences between the 2 groups. A total of 76% of patients were adherent with the institution-based nutrition protocol (Table 3).

DISCUSSION

This retrospective chart review study aimed to compare the percentage of diarrhea-free days between PES plus nonelemental enteral nutrition and elemental nutrition alone in adult patients with pancreatitis. The study observed no significant difference in percentage of diarrhea-free days between the 2 groups. Additionally, there was not a significant reduction in time-to-goal enteral nutrition or improvement in nutrition status with elemental nutrition.

This is the first study evaluating nutrition status using elemental nutrition compared to PES plus nonelemental enteral nutrition in patients with pancreatitis with no oral access. The study institution is a referral center for patients with pancreatitis. Because PES administration via an enteral access device often results in challenges causing inadequate drug delivery, the study institution selected to add elemental nutrition to the formulary as an alternative for patients with pancreatitis. This transition in practice prompted an evaluation on nutrition status outcomes.

No studies are currently available evaluating malabsorption with the use of enteral nutrition supplemented with PES. This study used pre-albumin as a marker of nutrition status but can be unreliable. The study institution began to use C-reactive protein (CRP) as a nutrition assessment with the implementation of an institution-based nutrition protocol in 2011. The documentation of CRP was not consistent; therefore, this was not included in the study.

The 2009 American Society of Parenteral & Enteral Nutrition guidelines do not address the use of PES plus enteral nutrition. However, the 2006 European Society for Clinical Nutrition and Metabolism guidelines [7] recommend PES with normal diet because more than 80% of patients can be treated adequately, with 10%–15% of all patients requiring with the goal of influencing malabsorption and preventing undernutrition as exocrine pancreatic insufficiency is seen by streatorrhea [1]. However, the guidelines do not address PES plus enteral nutrition.

PES use has been studied in patients with pancreatic enzyme insufficiency (PEI). One study reported fat absorption improvement from less than 40% to greater than 60% using enteric-coated PES [8]. Furthermore, recent studies that included randomized, blinded, placebo-controlled trials have demonstrated that with PES use in patients with documented PEI significantly improved the coefficient of fat absorption {[(fat intake − fat excretion)/fat intake] × 100} compared to placebo [6] In this current study, the authors could not draw any conclusions on fat malabsorption because only 6 patients of the 153 were tested. One patient in the study was tested and resulted in more than 7 g of fecal fat in 24 hours.

Although PES is beneficial in patients with PEI with oral access, no studies have assessed PES use via an enteral access device on malabsorption. One study addressed the challenge of administering PES via an enteral access device given the unique formulation with common problems such as enteral access obstruction and inconsistent enzyme activity [3]. In a study published in 2011, a novel technique was described for administration of pancreatic enzyme via enteral access devices

[3]. Ferrie and colleagues noted the importance of considering the size of the enteral access device, its position in the gut, and the type of feeding regimen prescribed. The study methods recommended that for every 10,000 international units of lipase, approximately 800 mg of sodium bicarbonate should be used. The solution is given via an enteral access device size greater than or equal to 10-French with adequate water flushes prior to or after administration along with a proton pump inhibitor [3,8]. Loss of enzyme activity with this novel method is to be expected, but timing and technique is essential to its success. Possible alternatives to PES discussed by the authors are elemental or semi-elemental formulas. The authors concluded that this novel method can optimize enzyme effectiveness while avoiding enteral access device obstruction to achieve the improved nutrition status and quality of life [3].

Another study performed in 2013 included 5 cases with administration of PES via an enteral access device in adult patients with cystic fibrosis [4]. In these cases, several methods of administration were attempted, including suspension of PES in sodium bicarbonate, applesauce, and/or apple juice, but none were found to be ideal. The authors noted that several factors were essential to success, such as placement of the enteral access device with the distal end in the stomach and use of larger-bore enteral access devices. Enteral access device obstruction was most likely due to inappropriate preparation and administration of PES. The authors concluded that further research is warranted to describe all clinical outcomes in these patients.

The results of the previous studies are not ideal and PES administration still remains a challenge. The current study's results are limited mainly by a retrospective study design. The subsequent patient population homogeneity of critically ill patients in the elemental nutrition group compared to heterogeneity of medical–surgical and critically ill patients in the PES plus nonelemental enteral nutrition group limit the interpretation of the results. There was a significant difference between study periods in gender and weight from observation, which did not allow for comparable groups due to the retrospective study design. The variety of enteral nutrition and pancrelipase formulation received was highly variable and this study was unable to decipher a trend. In addition, a major practice change was the implementation of an institution-based nutrition protocol that occurred during the addition of elemental nutrition to the formulary and documentation of a weekly CRP. This could have potentially affected the time-to-goal enteral nutrition and lack of CRP values for patients with pancreatitis. The nutrition protocol compliance of 76% and the inability to control for confounding variables on diarrhea also limit the assessment of our primary outcome. We were unable to assess nutrition protocol adherence in the PES plus nonelemental enteral nutrition group due to the lack of detail in documentation of nonelemental enteral nutrition rates; diarrhea definitions including number, volume, and consistency; and other gastrointestinal or abdominal symptoms. Receipt of bowel regimen, sorbitol-containing medications, and antimicrobials was collected to account for possible confounders for causes of diarrhea.

In summary, this study showed no differences in percentage of diarrhea-free days. There were also no significant differences in time-to-goal rate of enteral nutrition in either group. Our findings warrant a multicenter, prospective, randomized controlled study to evaluate the impact of this novel approach on nutrition status in patients with pancreatitis.

CONCLUSION

Utilizing elemental nutrition compared to PES plus nonelemental enteral nutrition in patients with pancreatitis was not associated with a significant reduction in percentage of diarrhea-free days, time-to-goal enteral nutrition, and nutrition status. A multicenter, prospective, randomized, controlled trial is warranted to further evaluate the efficacy of elemental nutrition in patients with pancreatitis.

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