Original Article

Pectin-containing compared with standard polymeric formula in enteral nutrition: A randomized controlled parallel study in Thailand

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Background and Objectives: To evaluate the effects of a Ready to Hang (RTH), pectin-containing enteral nutrition on gastrointestinal symptoms and nutrition status. **Methods and Study Design:** An open-label, randomized, prospective controlled study. Thirty hospitalized patients with tube feeding for 9 days or more. Intervention: A pectin-containing enteral formula (Hine E-Gel®) or a standard polymeric formula (Ensure®) was administered for 1 week. Administration methods: Administered via a nasogastric tube 4 times per day (every 6 hours), 30 minutes per administration. **Results:** There was no significant difference in the frequency of diarrhea or the nutritional indicators. An additional survey was conducted of 50 nurses who were involved in the administration of the study products. Most respondents replied that the RTH, pectin-containing formula was easier to use and that the duties related to its administration were decreased. **Conclusions:** The pectin-containing formula was not detectably superior to the standard polymeric formula in terms of gastrointestinal symptoms. The use of RTH may simplify medical care and enable efficient management.

Key Words: tube feeding, diarrhea, ready to hang (RTH), enteral nutrition, pectin-containing formula

INTRODUCTION

An oral diet is fundamental to nutritional management, but if spontaneous oral intake is not adequate in patients with malnutrition or those at risk of malnutrition, enteral tube feeding is indicated.[1] Although enteral nutrition is considered a physiologic route of nutrition support, it may result in complications, including diarrhea, vomiting, abdominal distention or other undesirable gastrointestinal symptoms. The use of enteral nutrition products with appropriate osmolality or peptide-based formulations as well as decreasing the rate of administration are conventional methods employed to alleviate these symptoms.[2] In recent years, products with increased viscosity, known as semisolid nutrition, have been developed. These products are designed to be physiologically similar to general or regular food and may help decrease these adverse gastrointestinal symptoms.[3-5] However, their major limitation is the need for large diameter feeding tubes for administration.

Pectin is a dietary fiber with special properties. When added to a liquid enteral formulation, the admixture becomes more viscous (semisolid) when exposed to acid in the stomach. The mechanism for the change in viscosity of the product is that when the calcium phosphate contained in the product is exposed to a low pH, such as the acidic environment in the stomach, the calcium in the calcium phosphate becomes free ions. These free calcium ions then react with pectin, which results in an increased viscosity.[6]

In a multicenter randomized controlled trial (RCT), the use of a viscosity-regulating pectin solution resulted in an improvement in stool form when compared to a standard liquid enteral nutrition product.[7] Another multicenter RCT conducted by the Japanese Society for Clinical Nutrition and Metabolism (JSPEN) demonstrated the efficacy of a pectin-based enteral nutrition product for reducing composite enteral nutrition-related events such as diarrhea when compared to a standard liquid formulation and that nutrition management could be conducted more completely when using a pectin-based enteral nutrition product.[8] Gastroesophageal reflux was significantly decreased by the use of semisolid formulations in an imag-

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ing study using a radiolabeled technique.[5] However, these studies were conducted in Japan using a novel product developed in Japan. This product and its potential benefits have not been evaluated outside of Japan. In this study, we evaluated the effects of a pectin-containing formula on gastrointestinal symptoms and nutrition status in hospitalized patients.

Objectives

To compare the effects of a pectin-containing formula with a nonpectin containing formula (standard polymeric formula) administered via tube feeding on gastrointestinal symptoms. The primary endpoint was the incidence of diarrhea. Secondary endpoints were the nutrition parameters (transthyretin (TTR) and body weight) and subjective global assessment (SGA).

Additionally, a survey was conducted with nurses participating in administration of the study products to explore the preferences of healthcare professionals regarding a ready-to-hang versus a powdered type formula.

METHODS

Ethical issues

The present study was performed according to the ethical recommendations of the Declaration of Helsinki and International Conference on Harmonization in Good Clinical Practice (ICH-GCP). The study protocol, informed consent, and other necessary documents were reviewed and approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University prior to initiation of the study at that site (IRB 210/60). All enrolled patients provided written informed consent prior to starting any study activities. The study was registered in the Thai Clinical Trials Registry (TCTR) with registration number: TCTR20200430002.

Subjects

In this study, 30 inpatients aged over 18 years, undergoing tube feeding with a 12–16 Fr nasogastric tube or percutaneous endoscopic gastrostomy (PEG) feeding and expected to be on tube feeding for at least 9 days were enrolled at the clinical site (King Chulalongkorn Memorial Hospital, Bangkok, Thailand) between March 2018 and April 2019. The main exclusion criteria were a history of a gastroduodenal ulcer, gastrectomy or other upper gastrointestinal disorders that may confound the results, unstable hepatic, renal or cardiac disorders or conditions that may raise safety concerns, or active cancer treatment with either chemotherapy or radiation, which may lead to diarrhea. Patients who had a history of food allergies or known allergies to the products used in the study were also excluded.

Study design

This study was a prospective randomized open-label and parallel-group study. There were two groups, a control group (standard polymeric formula) and a pectin group (pectin-containing formula). The patients were randomly assigned to either of the two groups according to a randomization table, which was prepared using Microsoft Excel. The number of patients in each group was the same (15 patients in each group).

Study products

The pectin-containing formula (Hine E-Gel®) is an oligomeric liquid enteral nutrition product with a protein: fat: carbohydrate ratio of 16:20:64. The product is packaged in a ready-to-hang container (RTH). It has been marketed in Japan since February 2014. In Thailand, it has not been approved for marketing, but approval for its import and use in this study was obtained from the Food and Drug Administration, Thailand (Thai FDA).

A standard polymeric formula (Ensure®) was selected as the comparator because it is a complete, balanced formula that is commonly used in Thailand. It is a powdered type of polymeric enteral nutrition with a protein: fat: carbohydrate ratio of 16:29:55 and must be prepared by dissolving it in water. In this study, the product was prepared to obtain a concentration of 0.8 kcal/mL to match the concentration of the test diet. Table 1 shows the nutritional composition of each product.

Administration methods

All participating patients were already undergoing tube feeding at the time of enrollment. After enrollment, the target energy per day was calculated for each patient and the test diet was prepared individually. Dosages were calculated based on the patient's body weight and clinical conditions using a simplistic weight-based equation (25–35 kcal/day/kg body weight).[9]

The pectin-containing formula and the standard polymeric formula were shipped to the clinical site as market packages. Both products were kept at the clinical site under controlled conditions as indicated on the product la-

Table 1. Composition of the enteral nutrition products per 1000 kcal

	Pectin-containing formula (Hine E-Gel®)	Standard polymeric formula (Ensure®)
Water (g)	1100	1100
Protein (g)	40	37
Fat (g)	22	32
Carbohydrate (g)	167.6	133.0
Sugar (g)	153.8	-
Dietary Fiber (g)	13.8 (Pectin 9 g and others)	10 (FOS 10 g)
Osmolarity (mOsm/L)	360	312

FOS: fructooligosaccharide.
-: Data are not available on the product label.

bels (15–25°C for the pectin-containing formula and below 35°C for the standard polymeric formula). The pectin-containing formula in the RTH package can be directly connected to an enteral feeding set while the standard polymeric formula needs to be prepared to a specific concentration before transferring to an enteral feeding bag and connecting to the feeding set.

To acclimate the patient to the new enteral nutrition (pectin-containing formula or standard polymeric formula), only 50% of the calculated amount was administered on Day 1. This was increased to 75% on Day 2. The administration on Day 1 and Day 2 was considered as the transitional phase and diarrhea during this period would result in subject withdrawal. From Day 3 through Day 9, 100% of the target amount was administered.

The daily dosage was separated into 4 administrations, with the first dose at 6 AM, followed by administrations every 6 hours (6 AM, 12 PM, 6 PM and 12 AM). The infusion rate was 30±5 minutes per administration, according to the standard feeding protocol at the clinical site.

Study procedure

After the subjects gave informed consent, demographic data, weight and height, medical history including underlying diseases and medications used, were collected. A physical examination and vital sign measurements were also performed. Blood for hematology and blood chemistry along with TTR were collected for screening. Subjective global assessment (SGA) was performed by a dietitian in the screening phase and eligibility (inclusion/exclusion) had been confirmed by the clinical investigator before the patient received their first meal. Only subjects who met the criteria received the test diet.

Stool evaluations were performed according to the Bristol Stool Scale after receiving the 1st meal until the end of follow-up on Day 10 by study nurses while diarrhea was assessed by the clinical investigator every day. Diarrhea was defined as the passage of 3 or more of grade 6 or 7 stools per day, according to the WHO definition of diarrhea.[10] If diarrhea occurred on Days 1–2, patients were withdrawn from the study for safety reasons. During Day 3 to Day 9, if a patient experienced diarrhea, the administration rate of the test diet was extended from 30±5 minutes to 2 hours for the remaining doses of the day, followed by close observation. The extended feeding rate was maintained on the following day. If no diarrhea occurred, the next dose was administered at the usual rate of 30±5 minutes. However, if diarrhea persisted, the patient was terminated from the study and their condition was followed until improvement.

Bodyweight, SGA and TTR were assessed on Day 3 as baseline values and on Day 10. The study procedure scheme is summarized in Figure 1.

Study endpoints

The primary endpoint was diarrhea (watery stool defined by the Bristol Stool Scale 6 or 7, more than 2 times per day).[11] The secondary endpoints were nutritional parameters, including TTR, body weight, body mass index (BMI) and SGA.

Sample size

Since this was an exploratory study, there was no statistical method involved in the sample size calculation. In addition, since the pectin-containing formula was not on the market in Thailand during the study period, there were no preliminary data or study available in the Thai population to show the potency of its inhibitory effects on diarrhea. Thus, the target sample size of 30 was determined to be the number of patients who could be enrolled at the study site during the study period.

Usage satisfaction survey

A questionnaire regarding the experience of using the investigational products was completed after the study completion by 50 nurses who were involved in the administration of the study products.

Statistical analysis

Patients who received 70–120% of the target dose were included in the primary (per-protocol) analysis. We determined whether there were differences in the primary endpoint index (patients who experienced diarrhea) between the pectin-based diet and control groups for 7 days (Day 3 through Day 9) using Fisher's exact test. The frequency of stool and stool condition evaluated by using the Bristol Stool Scale were summarized by the mean and standard deviation (SD) (mean ± SD). The frequency of stool with the Bristol Stool Scale 6-7 was also determined. Additionally, unpaired t-tests were conducted to determine the differences in the stool frequency and character between the 2 groups.

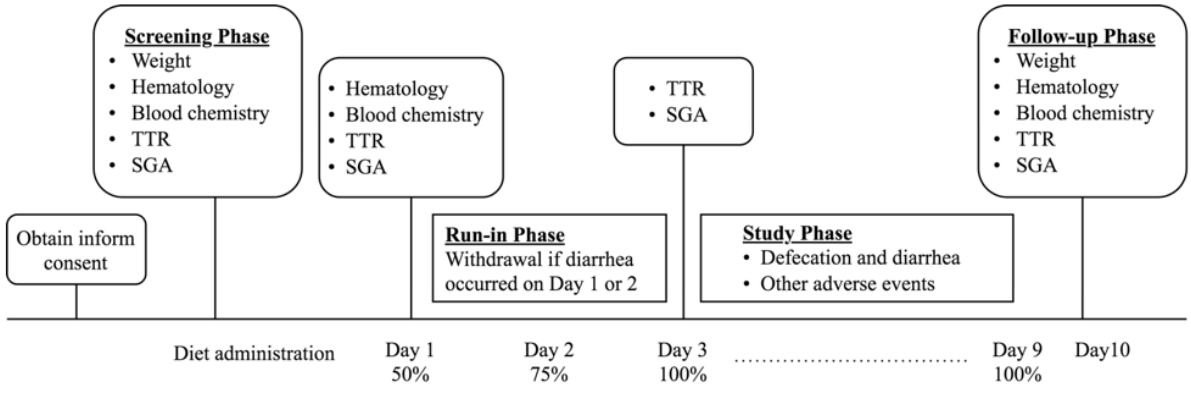

Figure 1. Study procedure scheme. TTR: transthyretin; SGA: subjective global assessment.

The differences in the nutritional parameters (secondary endpoints) between the follow-up day and baseline along with the screening were tested by paired t-tests and an analysis of variance was used for the determination of any difference among each day and each group. Improvement in nutrition status (SGA grade) at baseline and follow-up in each group was compared by the Wilcoxon signed rank test while the improvement of the SGA grades (defined as the improvement of SGA by at least 1 grade) between each group were analyzed by Fisher's exact test. All statistical analyses were performed in RStudio, version 1.2.5033.

RESULTS

Thirty-nine patients were screened for eligibility. Thirty patients (76.9%) who met all of the inclusion criteria and none of the exclusion criteria gave written informed consent and participated in this clinical study. Among the 30 enrolled patients, 15 patients were assigned to receive the pectin-containing formula while the other 15 patients received the standard polymeric formula. Four patients experienced diarrhea during Day 1 or Day 2 (2 from the pectin-containing group and 2 from the standard polymeric group) and were excluded from the study. One patient in the pectin-containing formula group withdrew consent to continue the study and 1 patient in the standard polymeric formula group had abdominal distension and did not continue past Day 3. Twenty-four patients (12 each for the pectin-containing formula or the standard polymeric formula group) continued in the study phase and received 100% of the targeted daily amount.

During the study phase (Day 3 to Day 9), 2 patients in the pectin-containing formula group were withdrawn due to nontreatment related serious adverse events and consent withdrawal. In total, 10 patients in the pectin-containing formula group received at least 70% of the target dose and were included in the primary analysis.

In the standard polymeric formula group, 9 of 12 patients received at least 70% of the target dose, while the other 3 patients failed to meet the target dose because of nontreatment related serious adverse events (1 patient) or consent withdrawal (2 patients). However, only 7 of 12 patients were included in the defecation and diarrhea analysis since 1 patient underwent a colostomy after randomization while the other had a protocol deviation. One patient who attained the target nutrition dose died due to his medical conditions in the early morning of Day 10 so the follow-up tests on Day 10 were not assessed. Despite this, the patient was included in the diarrhea and defecation analysis, and the analysis for the other outcomes could not be performed. The processes of enrollment, randomization, intervention and inclusion in the primary analysis are summarized in Figure 2.

Demographic and baseline data are summarized in Table 2. There were no significant differences between the two groups with regard to any of the baseline characteris-

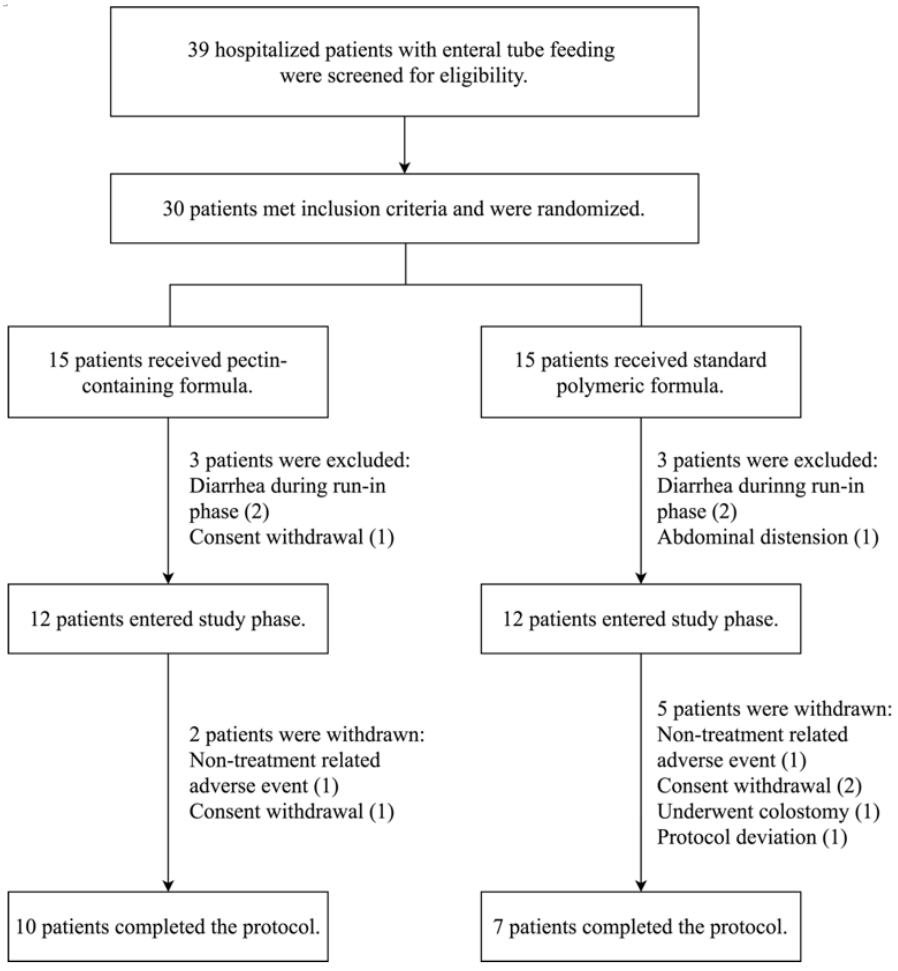

Figure 2. CONSORT flowchart of the distribution of participants throughout the study.

Table 2. Baseline characteristics of the patients

	All Mean±SD (Range)	Pectin-containing formula Mean±SD (Range)	Standard polymeric formula Mean±SD (Range)	*p*-value
N	17	10	7	
Gender†				
Male	14 (82.4%)	8 (80%)	6 (85.7%)	0.761
Female	3 (17.6%)	2 (20%)	1 (14.3%)	
Age (years)	71.9±15.3 (40-95)	70.3±14.7 (40-89)	74.1±16.9 (50-95)	0.636
Height (m)	1.6±0.1 (1.42-1.75)	1.62±0.09 (1.42-1.75)	1.62±0.07 (1.5-1.7)	0.866
Weight (kg)	46.8±10.9 (23.2-65)	46.1±7.7 (30.6-58.4)	47.8±15 (23.2-65)	0.789
BMI (kg/m^2)	17.7±3.5 (10.3-23.4)	17.6±2.5 (13.4-22.8)	17.9±4.8 (10.3-23.4)	0.895
TTR (μmol/L)	2.31±1.20 (0.65-4.69)	2.49±1.20 (0.65-4.69)	2.04±1.24 (0.82-4.55)	0.465
SGA score†				
A	2 (11.8%)	0 (0%)	2 (28.6%)	0.183
B	11 (64.7%)	7 (70%)	4 (57.1%)	
C	4 (23.5%)	3 (30%)	1 (14.3%)	
Primary diseases‡				
Diseases of the respiratory system	9	6	3	-
Certain infectious and parasitic diseases	4	2	2	-
Diseases of the nervous system	2	1	1	-
Diseases of the circulatory system	1	-	1	-
Mental and behavioral disorders	1	1	-	-
Diseases of the genitourinary system	1	-	1	-
Endocrine, nutritional and metabolic diseases	1	-	1	-
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	2	2	-	-

BMI: body mass index; TTR: transthyretin; SGA: subjective global assessment.
†Reported as number of subjects (%), *p*-value from Chi-square test.
‡Grouped by the ICD10, some patients reported more than 1 condition during their admission.

Table 3. Defecation related information

	All Mean±SD	Pectin-containing formula Mean±SD	Standard polymeric formula Mean±SD	*p*-value
N	17	10	7	-
Administration amount				
Total (kcal)	9520±1949.6	9470±1848.8	9591.4±2235.9	0.908
Percent of target amount (%)	95.6±9.2	94.6±9.1	96.9±9.8	0.633
Defecation				
Occurrence (time)	8.5±5	9.4±3.4	7.1±6.8	0.443
Frequency (time/day)	1.3±0.9	1.4±0.6	1.1±1.2	0.490
Bristol stool scale	5±0.9	4.7±0.7	5.4±1.1	0.158
Bristol stool scale 6-7				
Occurrence (time)	2.9±4.3	2.3±3.9	3.9±5	0.505
Frequency (time/day)	0.5±0.8	0.4±0.8	0.6±0.8	0.608
Diarrhea				
N experienced diarrhea	2	1	1	1.000

tics. Table 3 shows the details associated with defecation in all subjects included in the primary analysis.

Diarrhea occurred in 1 patient in the pectin-containing formula group and 1 patient in the standard polymeric formula group. There were no statistically significant differences between the 2 groups (p=1.000). However, the pectin-containing formula group had a favorable diarrhea occurrence rate when compared with the standard polymeric formula (10% and 14%, respectively). Regarding stool frequency and character, there were no statistically significant differences between the 2 groups in terms of the mean stool frequency (1.4±0.6 times per day and 1.1±1.2 times per day in the pectin-containing formula group and the standard polymeric formula group, respectively, p=0.490) and the mean Bristol Stool Scale score (4.7±0.7 and 5.4±1.1 in the pectin-containing formula group and the standard polymeric formula group, respectively, p=0.158).

For secondary outcome analyses, the patient who died before day 10 was excluded while the patient who underwent a colostomy was included in the analysis. Nutritional parameters, including body weight along with BMI,

Table 4. Changes in nutritional indicators

	Pectin-containing formula			Compared with baseline *p*-value	Standard polymeric formula†			Compare with baseline *p*-value	one-way ANOVA *p*-value
	Screening Mean±SD	Day 3 Mean±SD	Day 10 Mean±SD		Screening Mean±SD	Day 3 Mean±SD	Day 10 Mean±SD		
N	10	10	10	-	7	7	7	-	-
Weight (kg)	46.1±7.7	-	47.2±8.6	0.252	51.6±19.4	-	51.1±18.5	0.680	0.795
BMI (kg/m^2)	17.6±2.5	-	18±2.9	0.269	18.9±5.6	-	18.7±5.5	0.748	0.917
TTR‡ (µmol/L)	2.49±1.20	2.69±1.32	2.85±1.53	0.322	2.29±1.12	2.38±1.11	3.04±2.04	0.130	0.903
SGA Score									
A	0 (0%)	1 (10%)	0 (0%)	1.000	2 (28.6%)	1 (14.3%)	2 (28.6%)	0.7001	1.000
B	7 (70%)	7 (70%)	9 (90%)		4 (57.1%)	5 (71.4%)	4 (57.1%)		
C	3 (30%)	2 (20%)	1 (10%)		1 (14.3%)	1 (14.3%)	1 (14.3%)		

BMI: body mass index; TTR: transthyretin; SGA: subjective global assessment.
†Including patients who underwent colostomy but excluding patients who died before following up their nutritional status.

TTR and SGA, are summarized in Table 4. Statistically significant differences between the 2 groups and at each collection time were not found; however, TTR tended to increase over time in both groups.

In an exploratory analysis by the modified intention-to-treat method (including all patients who entered Day 3 of the study, except the colostomy patient for whom defecation and diarrhea could not be determined), 2 of 12 patients in the pectin-containing formula group had diarrhea while 2 of 11 patients in the standard polymeric formula group had diarrhea. There was no statistically significant difference between the 2 groups, giving a p value of 1.000.

DISCUSSION

In this study, the efficacy and safety of a pectin-containing formula were investigated. In a previous study using a pectin-containing formula for nutrition support after esophagectomy, it was reported that the incidence of diarrhea was lower in the patients using the pectin-containing formula compared to patients using polymeric enteral nutrition.[12] In our study, diarrhea occurred in 10% of patients in the pectin-containing formula group (1 out of 10 patients) and 14% of patients in the standard polymeric formula group (1 out of 7). Although the pectin-containing formula group showed a preferable result in the proportion of diarrhea patients, in concordance with the previous study, there was no statistical significance (p=0.787). The non-significant difference may be caused by inadequate power in this pilot study. This leads to the suggestion to conduct larger, well-designed studies in the future.

The stool frequency in the pectin-containing formula group was slightly higher than that in the control group. Despite the increased frequency of bowel movements, the frequency of muddy and watery stools was slightly lower in the pectin-containing formula group, suggesting that normal stools were excreted as a result of using a pectin-containing formula. The pectin-containing formula used in this study contains pectin, which when mixed with calcium ions, results in an increased viscosity (thickening) of formula under acidic conditions. Jam is an example of the application of pectin's mechanism. Animal studies have shown that pectin facilitates defecation by rapidly passing it through the gastrointestinal tract.[13,14] The high frequency of bowel movements observed in the pectin-containing formula group may be attributable to pectin. In a study using a viscosity-regulating pectin solution, the incidence of diarrhea was unchanged, but stool form improved compared with a commonly used enteral nutrition liquid diet.[7]

In this study, the concentration of the standard polymeric formula in the control group was prepared at 0.8 kcal/mL in order to match the concentration of the pectin-containing formula. In Thailand, the standard polymeric formula is usually prepared and used at a concentration of 1 kcal/mL. Diluting the formula results in a lower osmolarity from 390 mOsml/L to 312 mOsml/L, which may have affected the results by decreasing the gastrointestinal symptoms observed in the control group. However, the osmolarity of both formulations used in this study were optimized as normal practice.[15]

In both groups, the nutritional management of the patients went well. Nutrition-related parameters could be maintained throughout the study. Transthyretin, a visceral protein synthesized by the liver, tended to increase over the course of nutritional treatment in both groups, implying that the administered nutrients were incorporated into visceral proteins effectively.

At our hospital, feeding is normally performed four times a day. The pectin-containing formula used in this study is packaged in an RTH container, resulting in a decreased amount of time required for medical staff regarding duties related to patient feeding. A survey was conducted of 50 nurses who were involved with the administration of the products in this study. The results are shown in Figure 3. Most of the respondents replied that the pectin-containing formula in the RTH was easier to use because it did not require dissolution or other measures necessary before administration and that the duties related to its administration were decreased.

This study has the limitation of inadequate sample size

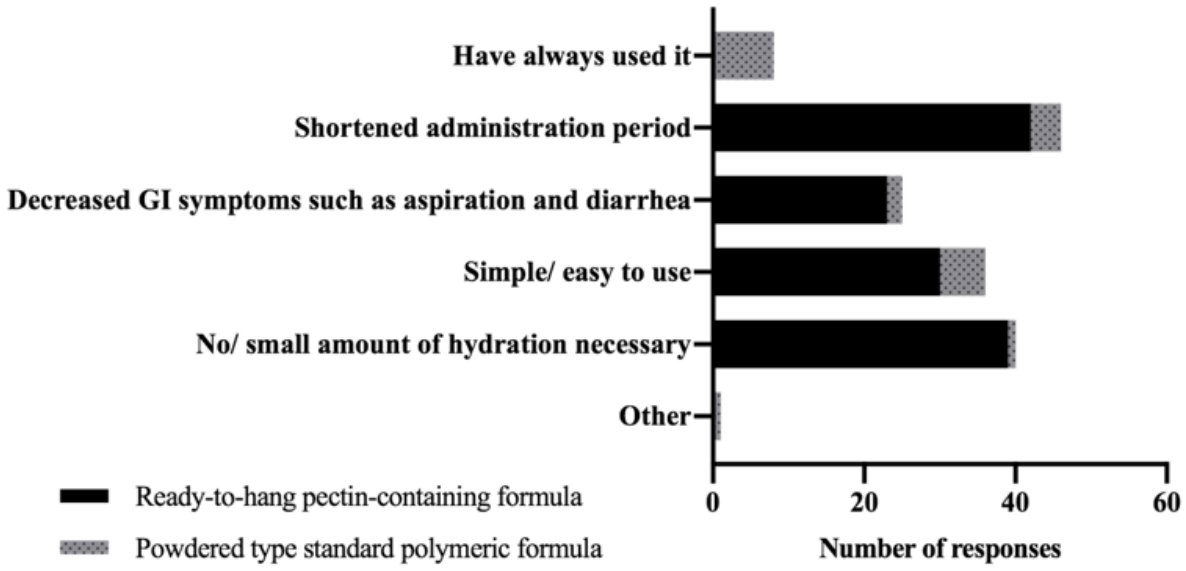

Figure 3. Survey results regarding the preference for the study products by the nurses involved in the study.

for extrapolation to enteral feeding practice in general. Patients studied were acutely ill with multiple comorbidities unlike general patients who might have less illness severity and feeding difficulties. Duration of observation was short with high dropout rate.

Conclusion

Pectin-containing liquid enteral nutrition was not detectably superior to the standard polymeric formula in this study in terms of gastrointestinal symptoms.

Safe and convenient nutritional management was made possible by using the pectin-containing formula. This ready-to-hang enteral nutrition product can be administered directly by connecting it to a feeding tube, resulting in safe, convenient, and hygienic nutritional management.

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AUTHOR DISCLOSURES

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