

# Moderately high-protein enteral formula improved retinol-binding protein in tube-fed patients: A multicentre open study

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## Abstract

**Background:** Long-term inadequate dietary consumption may increase the possibility of malnutrition, morbidity and mortality. Enteral nutrition (EN) is a beneficial support that could help to maintain nutritional status and gut function. **Aim:** Our aim was to evaluate the effect of moderately high-protein enteral formula containing fibre on nutritional status, and its safety. **Method:** A total of 23 tube-feeding-dependent adult patients were included in this multicentre, open-label study. The patients were fed with the study formula for 7–12 days or equal to the required nutritional support period, during which we performed physical examinations and assessed nutritional status. The primary endpoint was the statistical difference in nutritional status after the treatment, and the secondary outcome was the desirable safety profile. **Results:** A significant improvement in cumulative energy balance after intervention was observed ( $p = 0.008$ ). However, the differences in nutritional status, weight and BMI before and after the intervention do not reach statistical significance. Retinol-binding protein (RBP), a marker for nutritional status, increased from baseline levels. Few cases of diarrhoea and constipation had been reported during the study as a safety concern. **Conclusions:** This study investigated the efficacy and safety of an enteral feed formulation containing fibre. The patients were nourished with the studied formulation via tube feeding for a short period without serious adverse events. After the intervention, the significant increase in cumulative energy balance was observed. However, an extended period of the intervention may be required to attain the significance in other indicators for nutritional status.

## Keywords

High-protein formulas, enteral nutrition, retinol-binding protein, tube-feeding, open-label study

## Introduction

Long-term insufficient dietary intake, especially in critically ill patients, can cause malnutrition and morbidity leading to a higher rate of infections, longer duration of hospital stays, together with a problematic healing of wounds, and eventually, an increase in mortality (Ahmed and Haboubi, 2010; Chapman, 2006). To prevent and manage malnutrition, nutritional support should be timely instigated.

Enteral nutrition (EN) is the preferred route of nutrition support for hospitalised patients with intact gastrointestinal function who are incapable of eating or unable to meet nutritional requirements via the oral route (Kamarul et al., 2015; Tarleton et al., 2013). In addition, administration of nutrition enterally could preserve gut function through preventing mucosal atrophy, diminishing endotoxin translocation, and stabilising gut immunity (Alpers, 2002; Kamarul et al., 2015; Luyers et al., 2004; Sigalet et al., 2004). Fibre has been recommended as a supplement in

enteral nutrition in order to normalise bowel function, improve feeding tolerance and reduce diarrhoea (Alam et al., 1998; Kapadia et al., 1995; Nakao et al., 2002; Spapen et al., 2001). Numerous fibre-supplemented enteral formulas are currently obtainable (Elia et al., 2008). Naturally occurring fibres named fructo-oligosaccharides (FOS) are soluble fibres that can be fermented in the colon and generate short-chain fatty acids and exhibit a

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positive effect on bowel flora (Bouhnik et al., 1999; Wierdsma et al., 2009). Furthermore, the fibres also have a positive effect on blood glucose level, insulin sensitivity and cholesterol level (Kishimoto, 2009; Śliżewska et al., 2012).

Several enteral formulas have been available in market for people who are suffering from malnutrition including elderly adults. In fact, elderly adults require slightly reduced amount of fluid and energy, and slightly increased protein requirements 1.0–1.2 g/kg/day (Mueller and Zelig, 2012). The enteral products available on the market typically contain only 15–16% of protein, which is not sufficient for the patients. Therefore, the study formula was developed with a different composition, increasing protein in the formula to 18% or 1.0–1.2 g/kg/day, as recommended the American Society of Parenteral and Enteral Nutrition (ASPEN) guideline, which would be appropriate for elderly adults and critically ill patients (Mueller and Zelig, 2012). The soluble fibre contained in the formula was expected to control blood glucose by slowing down the release of carbohydrate, have a positive effect on insulin sensitivity and cholesterol level, and promote bowel regulation and a softer stool (Costa et al., 2012; Kishimoto, 2009; Nancy et al., 2003; Śliżewska et al., 2012).

In this study, we investigated the efficacy and safety of high-protein fibre-enriched enteral formula on nutritional status and safety of tube-fed patients.

## Materials and methods

### Study participants

A total of 23 patients (17 men and 6 women) were recruited from the in-patient services of Ramathibodi Hospital (Mahidol University, Bangkok, Thailand) and Srinagarind Hospital (Khon Kaen University, Khon Kaen, Thailand). They were aged 18 years or older and willing to receive tube-feeding for at least 5 days. They were evaluated to have a sequential organ failure assessment score (SOFA score)  $\leq 6$ , and had good consciousness. Exclusion criteria were patients being diagnosed with gastrointestinal obstruction or gastrointestinal dysmotility, diarrhoea (at least three episodes of loose stools per day), aspiration or requiring ventilation, sepsis (body temperature  $> 38.3^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$ , heart rate  $> 90$  beats/min, white blood cells  $> 12,000/\mu\text{L}$  or  $< 4000/\mu\text{L}$ , or systolic blood pressure (SBP)  $< 90$  mmHg); patients who had aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels at least three times the upper limit of normal or history of liver failure or serum creatinine  $\geq 2$  mg/dL; and patients who were pregnant or lactating, or patients who were allergic to whey, casein or any other components of the study formula. All enrolled patients received comprehensive information about the study and provided written informed consent before any study-related procedures were initiated.

### Feeding formula

The content and nutrient composition of the complete nutrition formula are described in Table 1. This study formulation

**Table 1.** The composition of enteral formula used in this study.

Nutritional information	
(Kcal/mL)	1
Macronutrients	% kcal distribution
Protein	18
Carbohydrate	47
Fat	35
Source	
Protein	
Whey protein	20%
Sodium caseinate	80%
Carbohydrate	
Dextrin	81.87%
Isomaltulose	13.18%
Fat	
Canola oil	15.40%
High oleic safflower oil	12.82%
Rice bran oil	30.75%
MCT oil	41.03%
Fibre	
Fructo-oligosaccharide	4.95%

was freshly prepared by mixing the dry powder of the formula with distilled water according to the standard method. The caloric density of the studied formula was 1 kcal/mL.

### Study procedure

All patients recruited into the study were checked by physical examination and nutritional status was assessed (include body composition by bioelectrical impedance analysis (BIA) method using Inbody S10 Body Water Analyzer (Inbody, CA, USA) and Nutrition Alert Form (NAF) (Komindr et al., 2013). Blood and urine samples were collected for haematology, glucose, lipids, electrolytes, prealbumin, albumin, liver function, renal function, thyroid hormone function, urinalysis, urine urea nitrogen and urine pregnancy test (for reproductive female participants) were measured by the central laboratory of the hospital using automated analysers. Retinol-binding protein (RBP) was assessed by Quatikine ELISA human RBP4 Immunoassay (R&D system, Minnesota, USA). The patients were fed with the study formula (fibre-enriched enteral formulation) for 7–12 days or equivalent to the desirable nutritional support period. The administration period was separated into two phases. The initial phase was between day 0 to 5: the patient's intake was titrated until total energy intake had met the patient's energy requirement of 30–35 kcal/kg/day and the patient's protein requirement of 1.3–1.6 g/kg/day according to the stress levels (Wooley and Freankenfield, 2012) and maintenance phase. The target volume of study formula was maintained until 5 days or the last day of administration period. The nutritional status (body weight, RBP, prealbumin, albumin, nitrogen balance, body composition and NAF) was measured at the end of initial phase, and the end of maintenance phase or the last day of the administration period. Moreover, haematology, glucose (fasting plasma glucose (FPG), dextrostix

(DTX)), liver function, renal function, electrolytes and tolerance parameters such as constipation, diarrhoea, abdominal pain, nausea, vomiting, aspiration, abdominal distention and allergy were also monitored.

### Efficacy assessment

The primary outcome was nutritional status (body weight, RBP, prealbumin, albumin, nitrogen balance, body composition and NAF). The secondary outcomes were indicators of tolerance (constipation, diarrhoea, abdominal pain, nausea, vomiting, aspiration, abdominal distention and allergy) and other laboratory results (blood urea nitrogen (BUN), serum creatinine (SCr), AST, ALT, ALP, FPG and urinalysis (UA)).

### Data analysis and statistical methods

The data were analysed by both the intention to treat (ITT), in which the data from all patients were included, and the per-protocol approach, in which only data from the patients who complied with the protocol were analysed. The results were expressed in continuous and categorical variables. The statistical significance of the differences in each parameter was examined using one-way analysis of variance (ANOVA) for comparisons of all parameters in each patient between baseline, on end of initial phase and end of maintenance phase (or the last day of study formula administration). A within-participant comparison of baseline and post-treatment (end of maintenance phase) values was analysed using paired *t*-test for continuous variables, and Chi-square test or the Fisher's exact probability test for categorical variables. All data were analysed using the STATA program for Windows (version 10 by StataCorp, TX, USA). All statistical tests were two-sided, and the differences were significant at  $p < 0.05$ .

## Results

### Patient disposition and baseline demographics

Overall, 23 patients admitted to the hospital with a principal diagnosis of neurological disorder, cancer and infection were screened and enrolled into this study. The distribution of patients by principal diagnosis group is displayed in Table 2. The patients had given voluntary, written informed consent, and 18 patients completed the study. Five participants discontinued participation due to the following reasons: One participant was on the study formula for less than 5 days, one participant was unwilling to continue the study due to inconvenience with the schedule, one participant suffered from a delirium complication (of his illness), one participant had diarrhoea and another participant had loose stools due to rapid rate of infusion (by gravity drip) at the beginning of the study. The baseline characteristics of participants were of normal distribution and are presented in Table 2.

**Table 2.** Measured baseline demographics of participants ( $n = 18$ ). Data are presented as frequency and mean  $\pm$  SD.

Characteristic	
Principal diagnosis	
Cancer	8 (44%)
Stroke	8 (44%)
Infection	2 (11%)
Sex	
Male	13 (72.2%)
Female	5 (27.8%)
Age (years)	63.67 $\pm$ 16.68
Height (cm)	162.35 $\pm$ 6.72
Weight (kg)	52.95 $\pm$ 13.31
Body mass index (BMI) kg/m <sup>2</sup>	19.97 $\pm$ 4.4
Body temperature (°C)	36.9 $\pm$ 0.49
Systolic (mmHg)	115.94 $\pm$ 12.22
Diastolic (mmHg)	69.33 $\pm$ 8.21
Pulse rate (beats/min)	83.56 $\pm$ 10.76
Respiratory rate (times/min)	20.12 $\pm$ 1.65
BUN (mg/dL)	16.03 $\pm$ 7.82
Creatinine (mg/dL)	0.75 $\pm$ 0.23
Fasting blood glucose (mg/dL)	117.78 $\pm$ 24.52
Sodium (mmol/L)	135.78 $\pm$ 3.39
Potassium (mmol/L)	4.23 $\pm$ 0.41
Chloride (mmol/L)	100 $\pm$ 4.17
Bicarbonate (mmol/L)	25.89 $\pm$ 2.89
Prealbumin (mg/mL)	20.35 $\pm$ 7.15
Albumin (g/dL)	24.93 $\pm$ 11.42
Retinol-binding protein ( $\mu$ g/mL)	29.24 $\pm$ 12.98

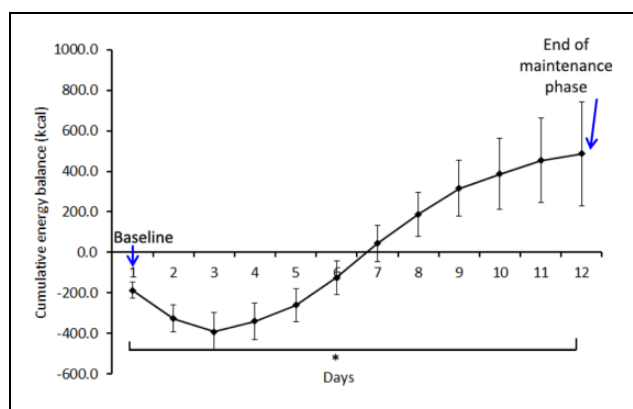
BUN: blood urea nitrogen.

### Alteration of short-term nutritional status in response to enteral nutrition treatment

In this study, the patients were nourished with the study formula (fibre-enriched enteral formulation) for 7–12 days or equivalent to the desirable nutritional support period to evaluate the efficacy and safety of the enteral formulation. The results were analysed by the intention-to-treat and the per-protocol approaches. We found no significant difference between the results being analysed using the intention-to-treat and per-protocol approaches. Thus, only the results being analysed by per-protocol approach are presented. The nutritional status of the enrolled participants before and after the treatment was assessed using the NAF form. Overall, the cumulative energy balance had significantly improved after nourished with the study formula, as shown in Table 3. As a matter of fact, 14 patients displayed a significant increase in energy balance. Figure 1 shows the mean value of cumulative energy balance (kcal) on different days of the intervention. The finding clearly revealed that there was an improvement in cumulative energy balance after 5 days of the intervention until the end of study. On the other hand, no statistically significant change in the body composition analysis has been observed after the treatment (Table 3). Moreover, muscle-fat analysis indicated no significant change in total fat and muscle mass

**Table 3.** Per-protocol analysis: Assessment of the change in body composition. Continuous data are presented as mean  $\pm$  SD.

	Baseline (BS)	End of initial phase (IR)	End of maintenance phase (MR)	p-value		
				BS vs. IR	BS vs. MR	IR vs. MR
<b>Body composition analysis</b>						
Intracellular water (L)	16.48 $\pm$ 5.15	16.6 $\pm$ 5.5	16.59 $\pm$ 4.96	0.794	0.715	0.988
Extracellular water (L)	13.96 $\pm$ 7.86	14.18 $\pm$ 7.9	13.99 $\pm$ 8.08	0.384	0.926	0.447
Protein mass (kg)	7 $\pm$ 2.49	7.05 $\pm$ 2.61	7.03 $\pm$ 2.41	0.793	0.793	0.924
Mineral mass (kg)	2.52 $\pm$ 0.83	2.61 $\pm$ 0.86	2.55 $\pm$ 0.87	0.364	0.696	0.367
Body fat mass (kg)	12.97 $\pm$ 11.43	12.65 $\pm$ 10.83	12.96 $\pm$ 10.69	0.736	0.995	0.606

**Figure 1.** Mean values of cumulative energy balance (kcal) on different days of the intervention. The data are presented as mean  $\pm$  standard error.

\*Statistically significant reference:  $p=0.01$ .

after the intervention (Table 3). The results from NAF indicate that the differences in nutritional status, as well as weight and BMI before and after the intervention did not reach statistical significance, as presented in Table 4. The nitrogen balance tended to increase after receiving the study diet but it did not reach significance (Figure 2). A total of 66.7% of the participants were shown to have a positively increased nitrogen balance value as listed in Figure 2. Acute change of nutrition biochemical parameters revealed the RBP level to be significantly improved (Figure 3 and Table 5). However, longer half-life protein such as albumin and prealbumin remained stable. As considered individually, 27.8% and 23.5% of the participants exhibited an increase or no change in RBP and prealbumin level, respectively, at the end of initial phase. These numbers, however, increased to 66.7% and 61.1%, respectively, after the maintenance period.

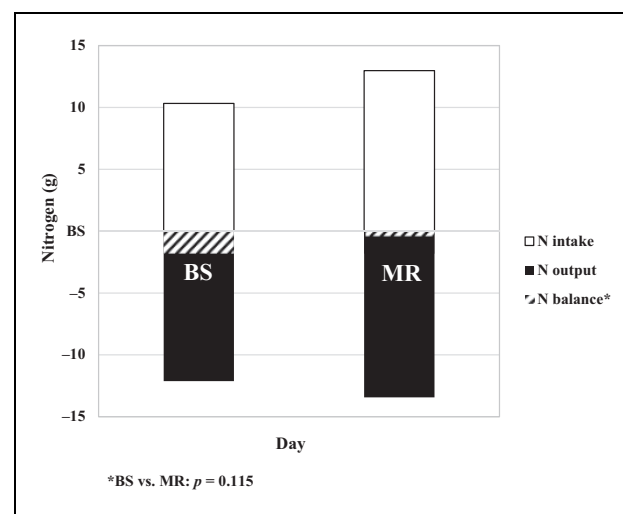
### Safety parameters

The safety of the study formula was also assessed and the adverse events relating to the study formula were recorded. No serious adverse effect of the study formula has been reported. However, one case of constipation had been reported during the study, the data are shown in the Table 6.

**Table 4.** Data analysis from the nutrition alert form (NAF) by per-protocol approach. Continuous data are presented as mean  $\pm$  SD, and number of patients are presented as frequency (%).

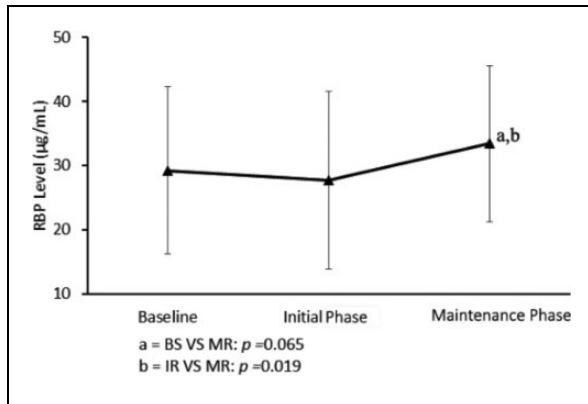
Characteristic	Baseline	End of maintenance phase	p-value
Weight (kg)	52.87 $\pm$ 13.43	53.09 $\pm$ 13.25	0.347
BMI (kg/m <sup>2</sup> )	19.93 $\pm$ 4.44	20.03 $\pm$ 4.39	0.273
<b>Total Score</b>	11.78 $\pm$ 3.02	12.28 $\pm$ 3.66	0.298
Normal-mild malnutrition (0–5)	0 (0%)	0 (0%)	
Moderate malnutrition (6–10)	7 (38.9%)	6 (33.3%)	0.564
Severe malnutrition ( $\geq 11$ )	11 (61.1%)	12 (66.7%)	0.564

BMI: body mass index.

**Figure 2.** Nitrogen balance during the study. Nitrogen balance during the study tended to increase after receiving the study diet. N: nitrogen; BS: baseline; MR: maintenance phase.

### Discussion

EN is the preferred method of nutritional support for patients who cannot achieve sufficient oral intake and who have at least a partially functioning gastrointestinal tract



**Figure 3.** Change in visceral protein markers (RBP level) at different stages of the intervention.

BS: baseline; IR: initial phase; MR: maintenance phase.

(Altomare et al., 2015). To improve the nutritional status of patients, the study formula was administered to patients, and the efficacy and safety of the study formula were evaluated. The study formula comprises whey protein and casein to replenish protein and meet the desirable requirement. Carbohydrate and lipid contained in the formula could help recover the energy balance. In addition, the soluble fibre, FOS, could improve diarrhoea, which is a very common adverse effect of enteral formulation (Elia et al., 2008). Generally, the typical response to a decrease in nutrient consumption is a reduction in plasma protein synthesis. In order to evaluate the nutritional status, the protein marker commonly used is albumin. However, the problem with albumin is that the long half-life of 20 days makes it a relatively insensitive measurement (Campbell, 1997). Thus, it may be not appropriate to use for evaluation of nutritional status in this study because the study duration was short. Thus, RBP, a short half-life marker, was selected as the nutritional status marker in this study (Lopez-Hellin et al., 2002). Nevertheless, BIA and NAF were also used along with the marker to evaluate the nutritional status, as well as the efficacy of the study formula.

According to analyses using the per-protocol approach to assess the efficacy of the study formula, there was a significant improvement in cumulative energy balance after the end of the study. This may be because the nutrition contained in the study formulation could efficiently

compensate the deficient energy during illness. However, the results show no significant changes in body composition. The nitrogen balance improved after the intervention. Subgroup analysis revealed that most (83.3%) of the participants whose principal diagnosis was stroke, infection, or cancer, but were not receiving chemotherapy, had shown an increase in nitrogen balance value after the maintenance period. This indicates that the study formula could maintain nutritional status. Patients who had a negative nitrogen balance could be explained by the effect of tumor necrosis during anticancer treatment (Gudny and Thorsdottir, 2008). A slight increase in mean weight of all participants with unchanged protein and fat mass at the end of maintenance phase indicated that the study formula could maintain and may improve the nutritional status of the feeding patients. Although few patients lost weight during the intervention, there were no significant changes in the muscle mass and body fat mass observed. Weight loss observed during the intervention is likely due to a decrease in total body water or hydration state. NAF, a nutrition screening form which consisted of clinical data and laboratory investigations, is validated for screening of malnutrition in Thai hospitalised patients (Komindr et al., 2013). However, it may be not sensitive enough for detecting short-term alteration in nutritional status, since some items may need a few weeks for determining the change. It is difficult to declare statistically significant changes in certain clinical indicators in our study due to too-short duration of taking the study formula. Moreover, indicators for nutritional status can be affected by non-nutrition parameters, such as the primary illness or volume status. Longer period of feeding may be required to obtain the desirable nutritional status. Although serum albumin is the most commonly used marker of nutritional status and has been a good indicator for malnutrition and mortality (Ingenbleek et al., 1975), its moderately long half-life makes it respond with low sensitivity and not suitable to be used for detection of early depletion of protein in the body (Ingenbleek et al., 1975). Prealbumin seems to be a better indicator than albumin, however, its half-life is longer than RBP. RBP, an index of vitamin A status, has a very short half-life of 10–12 hours and could be an accurate indicator of protein metabolism and rapidly responsive to dietary protein intake (Helms et al., 1986; Ikekpeazu, 2010). Our results show that there

**Table 5.** Per-protocol analysis: Assessment of the change in nutritional markers (visceral protein markers). Continuous data is presented as mean  $\pm$  SD.

	Baseline	End of initial phase	End of maintenance phase	p-value		
				BS vs. IR	BS vs. MR	IR vs. MR
Prealbumin (mg/mL)	19.39 $\pm$ 7.96	18.14 $\pm$ 7.27	18.79 $\pm$ 8.20	NS	NS	NS
Albumin (g/dL)	2.91 $\pm$ 0.57	–	2.92 $\pm$ 0.64	–	0.956	–
Retinol-binding protein ( $\mu$ g/mL)	29.24 $\pm$ 12.98	27.69 $\pm$ 13.83	33.4 $\pm$ 12.12	NS	0.065	0.019*

NS = p-value > 0.2.

NS: not significant.

**Table 6.** Summary of adverse effects.

Adverse effect	Cases (n)
Aspiration	–
Abdominal distention	–
Abdominal pain	–
Vomiting	–
Constipation	1
Diarrhoea	–
Total	1

was a significant increase in serum RBP after the intervention compared with the initial phase of the study. Moreover, 66.7% of the participants were observed as having increased RBP after maintenance phase. The short half-life of RBP makes it appropriate for monitoring protein turnover in the body. Moreover, prealbumin has a tendency to increase during the intervention period and the number of participants who had an increased level of prealbumin and RBP was observed to significantly increase after the intervention. However, no significant differences in serum albumin and prealbumin level may be due to the short intervention period of this study. A longer period of enteral feeding with the study formula could lead to a significant increase in the nutritional status.

For monitoring of feed tolerance, the adverse reactions during the administration of the study formula was evaluated. There are some reports of diarrhoea and constipation during the feeding with the enteral formulation. Actually, impaired tolerance to EN is particularly frequent amongst critically ill patients. Diarrhoea is often reported as the most common complication related to enteral feeding in these patients (Payne-James et al., 1992; Halmos, 2013). Some research concludes that dietary fibre may prevent diarrhoea associated with enteral feeding. Moreover, fibre addition is recommended for treating constipation as well. The provision of fibre could also benefit patients receiving long-term enteral feeding (Nakao et al., 2002; Scheppach et al., 1990; Spapen et al., 2001; Vandewoude et al, 2005). The ASPEN guideline for critically ill patients suggests using mixed fibre-containing formula in patients with persistent diarrhoea, moreover, 10–20 g of a fermentable soluble fibre additive should be considered in all haemodynamically stable patients (McClave et al., 2016). In fact, the soluble fibre considered to prevent diarrhoea and constipation was included in the study formula and there were no reports of diarrhoea during the study. However, one case of constipation was observed. It must be noted that the case of constipation reported occurred in a patient who had this problem prior to participation in the study, nevertheless, the problem was not serious and the patient managed to follow the protocol until the end of the study. There were two participants who had diarrhoea and loose stools due to rapid infusion rate (by gravity drip) at the beginning of the study that led them to quitting the study.

The study's limitations are the short duration (less than 12 days) and the small number of patients that participated in the study.

## Conclusions

This multicentre, open-label study reported the efficacy and safety of the enteral formulation with fibre. The patients were nourished with the study formula via tube feeding for a short period. Most patients tolerated the study formula. The results revealed that the study formula significantly increased the cumulative energy balance and can maintain the nutritional status of the patients. Moreover, acute biochemical improvement may be demonstrated with the short half-life nutritional indicator RBP. However, a longer period of intervention may be needed.

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## Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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