

Retrospective Study

Peptide-based enteral formula improves tolerance and clinical outcomes in abdominal surgery patients relative to a whole protein enteral formula

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Informed consent statement: A retrospective study was deployed to investigate the effects of a dipeptide- and tripeptide-based enteral formula. Patients were screened from the ICU database, therefore we did not seek informed consent. Acquisition of patient data and its subsequent use were approved by the ethics committee of the Tainan Sin-Lau Hospital (Grant No. SLH919-02). Patient information was anonymized and de-identified prior to analysis.

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Abstract

AIM

To compare a dipeptide- and tripeptide-based enteral formula with a standard enteral formula for tolerance and nutritional outcomes in abdominal surgery patients.

METHODS

A retrospective study was performed to assess the differences between a whole-protein formula (WPF) and a dipeptide- and tripeptide-based formula (PEF) in clinical outcomes. Seventy-two adult intensive care unit (ICU) patients with serum albumin concentrations less

than 3.0 g/dL were enrolled in this study. Patients were divided into two groups (WPF group = 40 patients, PEF group = 32 patients). The study patients were fed for at least 7 d, with ≥ 1000 mL of enteral formula infused on at least 3 of the days.

RESULTS

The mean serum albumin level on postoperative day (POD) 10, prealbumin levels on POD-5 and POD-10, and total lymphocyte count on POD-5 were significantly higher in the PEF group compared to those in the WPF group ($P < 0.05$). The average maximum gastric residual volume of the PEF patients during their ICU stays was significantly lower than that for WPF patients.

CONCLUSION

Dipeptide- and tripeptide-based enteral formulas are more efficacious and better tolerated than whole-protein formulas.

Key words: Dipeptides and tripeptides; Enteral nutrition; Abdominal surgery; Gastric residual volume; Absorption

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Core tip: Few trials thus far have investigated the benefits of dipeptide- and tripeptide-based enteral formulas for abdominal surgery patients. The results of the present study suggest that dipeptide- and tripeptide-based enteral formulas are more efficacious and better tolerated than whole-protein formulas and could shorten the intensive care unit stays of malnourished abdominal surgery patients.

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INTRODUCTION

Malnutrition is a common finding in critically ill patients. Enteral nutrition is a preferred means of support for stimulating gut hormones, modulating immunity, and maintaining the barrier function of the intestinal mucosa. However, malabsorption, poor emptying, and hypoalbuminemia often occur in patients given enteral nutrition.

Proteins are hydrolyzed to small peptides in the intestines, which are then efficiently absorbed through a variety of specific transport mechanisms, as has been previously described^[1]. Some investigators have reported that peptide-based enteral diets are associated with better protein responses and less diarrhea compared to

intact-protein diets^[2,3]. On the other hand, others have reported that peptide-based formulas seem to offer no benefits over intact-protein diets in acutely injured, hypoalbuminemic patients^[4]. However, while previous studies have described the small peptide formulas, no particular dipeptide- or tripeptide-based formulas have been investigated.

Studies have demonstrated that dipeptides and tripeptides are the major products of proteins that are absorbed. Proteins are hydrolyzed in the intestines to small peptides, which are then efficiently absorbed through specific transport mechanisms. The major mechanism for absorption of the dipeptides and tripeptides of protein digestion products across the brush border is absorption through proton-coupled oligopeptide transporters (POTs)^[5-11]. Dietary proteins are converted into large peptides by gastric and pancreatic proteases in the gastrointestinal lumen and then undergo further hydrolysis into small peptides (80%) and free amino acids (20%) by various peptidases in the brush border membrane of the intestinal epithelium^[12]. Previously, Yoshihara *et al.*^[13] studied the absorption of a 100% free amino acids formula, a 60% dipeptides and tripeptides with 40% free amino acids mixture, a 100% dipeptides and tripeptides mixture, and a lactalbumin mixture. Absorption was evaluated by calculating the area under the curve of amino acid concentration in portal vein plasma of rats for 120 min after administration of each nitrogen source^[13]. The results indicated that the absorption was maximal upon administration of the nitrogen source when the 60% dipeptides and tripeptides with 40% free amino acids mixture was used.

Few clinical trials thus far have investigated the benefits of dipeptide- and tripeptide-based enteral formulas. In our hospital, however, critically ill patients in the intensive care unit (ICU) began receiving such a formula from July 2015. The aim of this study, then, was to compare this dipeptide- and tripeptide-based enteral formula with a standard enteral formula in terms of tolerance and nutritional outcomes in abdominal surgery patients.

MATERIALS AND METHODS

Patients

A retrospective study was deployed to investigate the effects of a dipeptide- and tripeptide-based enteral formula. Patients screened from the ICU database for abdominal surgery with serum albumin concentrations less than 3.0 g/dL were included in the study. The patients who received dipeptide- and tripeptide-based enteral formula from July 2015 to December 2015 were classified as the dipeptide- and tripeptide-based formula (PEF) group. Other patients who were fed a whole-protein formula were classified as the WPF group. These patients were generally included the study, although any patients with renal failure, hepatic

failure, or who required parenteral nutrition intervention were excluded. This study was approved by the ethics committee of Tainan Sin-Lau Hospital (Grant No. SLH 919-02). Patient information was anonymized and de-identified prior to analysis.

Enteral nutrition care

Patients in both groups received the same feeding protocol, when they were transferred to the ICU. Each patient received 18 kcal per kilogram of body weight on postoperative day (POD-) 1, 23 kcal on POD-3, and 28 kcal on POD-7. The patients were fed for at least 7 d, with ≥ 1000 mL of enteral formula infused on at least 3 of the days. The composition of the WPF (Osmolite HN, Abbott Laboratories) was 16.7% of protein, 54.3% of carbohydrate, and 29.0% of lipid. The composition of the PEF (Twinline, Otsuka Pharmaceutical Co, Ltd) was 16.0% of protein, 59.0% of carbohydrate, and 25.0% of lipid. The WPF contained only whole proteins (*e.g.*, calcium-potassium caseinate), whereas the protein source of the PEF (from enzymatically hydrolyzed milk protein) consisted of amino acids and peptides with molecular weights < 500 Da (approximately 78%), peptides with molecular weights between 500 and 1000 Da (approximately 15%), and peptides with molecular weights between 1000 and 3000 Da (approximately 7%).

On POD-1 with stable hemodynamic status, the full-strength diet was administered at 30 mL/h through a naso-gastric (NG) tube or *via* percutaneous endoscopic gastrostomy (PEG) feeding tubes, with the rate increasing as tolerated to a goal of 75-100mL/h. A gastric residual volume (GRV) of over 150 mL was the threshold for suspension of feeding^[14], which was followed by re-evaluation to reduce the feeding rate 2 h later. The GRV was calculated every 4 h by refractometry (Model N.O.W. 507-1; Nippon Optical Works, Tokyo, Japan) during each patient's stay in the ICU. A refractometer measures the "total soluble solids in solution" and a Brix value (BV) is assigned to the liquid. We examined the BV in order to measure the actual GRV^[15,16]. The GRV was recorded when volumes exceeded 150 mL. At such times, feeding of the patient was suspended for re-evaluation and reduction of the feeding rate 2 h later. No prokinetic drugs were used within 10 d in both groups.

Data collection

Demographic data obtained at the start of the study included gender, age, body mass index (BMI), APACHE II score, and major diagnoses. Additional data including the length of stay in the ICU, total enteral volume, GRV, and the prevalence of diarrhea were also collected for this study. The occurrence of diarrhea was defined as greater than three loose stools per day or greater than 300 mL/d. Serum albumin, prealbumin, C-reactive protein (CRP) and total lymphocyte count (TLC) were measured at baseline, day 5, and day 10.

Table 1 Comparison of demographic and clinical characteristics between the whole-protein formula group and the dipeptide- and tripeptide-based formula group

| | WPF group | PEF group | P-value |
|--|-----------------|-----------------|---------|
| <i>n</i> | 40 | 32 | |
| Gender (Male/Female) | 23/17 | 19/13 | 0.873 |
| Feeding route (PEG ¹ /NG ²) | 2/38 | 3-29 | 0.468 |
| Major diagnoses | | | |
| Esophageal cancer | 4 | 5 | 0.473 |
| Colon cancer | 22 | 16 | 0.673 |
| Gastric cancer (subtotal gastrectomy) | 2 | 3 | 0.468 |
| Bile duct cancer | 4 | 2 | 0.567 |
| Ischemic bowel | 8 | 6 | 0.894 |
| Age | 67.5 \pm 10.5 | 64.7 \pm 10.1 | 0.263 |
| APACHE II score | 11.6 \pm 2.3 | 12.4 \pm 2.6 | 0.201 |
| Ventilator dependence, <i>n</i> (%) | 15 (37.5) | 13 (40.6) | 0.787 |
| Body mass index | 22.3 \pm 2.1 | 21.9 \pm 2.2 | 0.398 |

¹Percutaneous endoscopic gastrostomy; ²Naso-gastric tube. Values are presented as number of patients or mean \pm SD. WPF: Whole-protein formula; PEF: Dipeptide- and tripeptide-based enteral formula.

Statistical analysis

Data were analyzed using SPSS version 12.0 (SPSS, Inc). The differences between the two groups were analyzed by Student's *t*-test. Data are presented as mean \pm SD. χ^2 analysis was used for comparisons of the proportions of subjects in the two groups. A *P*-value < 0.05 was considered significant.

RESULTS

Study population

A total of 86 abdominal surgery patients with serum albumin concentrations less than 3.0 g/dL were identified who were admitted to the ICU during the study period. Seven of these 86 patients developed renal failure, one patient developed hepatic failure, and 6 patients required parenteral support; these 14 patients (WPF group = 6 patients, PEF group = 8 patients) were excluded from the study. The remaining 72 patients were divided into two groups (WPF group = 40 patients, PEF group = 32 patients), and the patient characteristics of the two groups are provided in Table 1. Colon cancer was the most common major diagnosis in both groups. Most colonic surgery patients can resume oral intake on POD-1. Some colon cancer patients were elderly, confused and had comorbid diseases such as diabetes, heart disease, and chronic obstructive pulmonary disease; thus they could not resume oral intake on POD-1. Therefore, we used an NG tube for intervention. There were no significant differences between the two groups in terms of age, APACHE II score, ventilator dependence, and BMI (Table 1).

Serum albumin, prealbumin, TLC and CRP

The patients were fed for at least 7 d, with ≥ 1000 mL of enteral formula infused on at least 3 of the days. On

Table 2 Differences in nutritional status between the whole-protein formula group and the dipeptide- and tripeptide-based formula group

| | WPF group | PEF group | P-value |
|--|-------------|-------------|---------|
| Albumin (g/dL) | | | |
| POD ¹ -1 | 2.59 ± 0.21 | 2.57 ± 0.19 | 0.652 |
| POD-5 | 2.60 ± 0.26 | 2.68 ± 0.28 | 0.198 |
| POD-10 | 2.70 ± 0.30 | 2.89 ± 0.27 | 0.010 |
| Prealbumin (mg/dL) | | | |
| POD-1 | 11.1 ± 1.4 | 10.6 ± 1.3 | 0.201 |
| POD-5 | 11.6 ± 1.2 | 12.8 ± 2.1 | 0.006 |
| POD-10 | 12.9 ± 1.7 | 15.1 ± 1.5 | < 0.001 |
| TLC ² (cell/mm ³) | | | |
| POD-1 | 1069 ± 135 | 1077 ± 148 | 0.801 |
| POD-5 | 1082 ± 149 | 1192 ± 168 | 0.012 |
| POD-10 | 1231 ± 162 | 1311 ± 182 | 0.052 |
| CRP ³ (mg/L) | | | |
| POD-1 | 43.7 ± 7.8 | 43.0 ± 9.4 | 0.742 |
| POD-5 | 32.7 ± 4.9 | 33.4 ± 5.2 | 0.824 |
| POD-10 | 19.7 ± 5.0 | 18.5 ± 5.4 | 0.416 |

¹Postoperative day; ²Total lymphocyte count; ³C-reactive protein. Values are presented as mean ± SD. WPF: Whole-protein formula.

POD-1 with stable hemodynamic status, a full-strength enteral formula (1.0 kcal/mL) was administered through NG or PEG. The prealbumin levels and TLCs were similar between the two groups on POD-1. There was also no significant difference between the serum albumin levels on POD-1 and POD-5 for the two groups, but the level for the PEF group was significantly higher than that of the WPF group on POD-10 (2.89 ± 0.27 vs 2.70 ± 0.30, $P = 0.01$; Table 2). Prealbumin levels on POD-5 and POD-10 were significantly higher in the PEF group than in the WPF group ($P < 0.01$). The TLC of the PEF group was higher than that of the WPF group on POD-5, but there was no significant difference on POD-10. In critical patients protein parameters depend on inflammation. We checked the CRP levels, and there was no significant difference between the two groups.

Clinical outcomes

The prevalence of suspended feeding due to high gastric residuals and maximum caloric intake during ICU stay was similar between the two groups (Table 3). The average maximum GRV for the PEF group patients during their ICU stays was significantly lower than that for the WPF group (Table 3). There was no significant difference between the groups in terms of the caloric intake on POD-5, but the average intake for the PEF group on POD-10 was higher than that of the WPF group. There was no significant difference between the two groups in terms of the prevalence of diarrhea and pneumonia. The average length of stay in the ICU for the PEF group was 6.2 ± 0.8 d, which was significantly shorter than that for the WPF group (6.8 ± 1.5 d).

DISCUSSION

Providing enteral nutrition care for critically ill patients is challenging in general, but it is even more difficult to

Table 3 Clinical outcomes for the whole-protein formula group and the dipeptide- and tripeptide-based formula group

| | WPF group | PEF group | P-value |
|---|--------------|--------------|---------|
| Length of stay in the ICU ¹ (d) | 6.8 ± 1.5 | 6.2 ± 0.8 | 0.047 |
| Maximum caloric intake during ICU stay (kcal/kg) | 22.5 ± 1.9 | 23.2 ± 2.4 | 0.063 |
| Caloric intake (kcal/kg body weight/d) | | | |
| POD ² -5 | 20.7 ± 2.3 | 21.5 ± 1.7 | 0.116 |
| POD-10 | 23.5 ± 2.4 | 25.1 ± 2.9 | 0.010 |
| Maximum GRV ³ during ICU stay (mL) | 183.6 ± 88.0 | 138.0 ± 63.9 | 0.016 |
| Prevalence of suspended feeding due to high GRV (%) | 21.8 | 15.2 | 0.071 |
| Prevalence of diarrhea (%) | 19.9 | 13.2 | 0.056 |
| Prevalence of pneumonia (%) | 5 | 3.1 | 0.692 |

¹Intensive care unit; ²Postoperative day; ³Gastric residual volume. Values are presented as mean ± SD. WPF: Whole-protein formula.

provide such care for abdominal surgery patients. In this study, except the enteral formulas used, the care received by the two groups of patients was the same. Both groups of patients would be unable to achieve their caloric intake goals under normal circumstances. As noted above, there were no significant differences between the two groups in terms of their average caloric intakes and rates of diarrhea and pneumonia complications. The average maximum GRV recorded for each patient during ICU stay among the WPF group patients was higher than that among the PEF group patients, but there was no significant difference between the two groups in terms of the prevalence of suspended feeding due to high GRV ($P = 0.071$). It was easy and effective to calculate GRV values by refractometry. More specifically, BV measurements and the following equation were used: (GRV × pre-dilution BV) = (GRV + 30 mL water) × post-dilution BV. We accurately grasped the GRV values to avoid the risk of aspiration pneumonia and to assess the digestion conditions. The dipeptide- and tripeptide-based enteral formula seemed to have been efficiently absorbed and resulted in better prealbumin, albumin (POD-10), and TLC (POD-5) levels in the PEF group, in addition to shortening the ICU stay. Prealbumin is a rapid-turnover protein (half-life < 48 h), which is a more sensitive indicator to assess the nutritional status than albumin (half-life 21 d). When patients' nutrition is improved, the serum prealbumin will increase rapidly (POD-5 and 10).

Four members of the POT superfamily have previously been identified, namely, PepT1 (SLC15A1), PepT2 (SLC15A2), PHT1 (SLC A4), and PHT2 (SLC A3). In humans, PepT1 expressed in the small intestine epithelium is involved in the absorption of nutritional peptides^[17,18]. Previously, the effects of PepT1 activity on a variety of pathological conditions have been studied. Ziegler *et al*^[19] found that patients with short-bowel syndrome may experience up-regulation of the expression of colonic PepT1 adapted to malabsorption of dipeptides and

tripeptides, independent of changes in the mucosal surface area. In other studies, intestinal villous atrophy due to prolonged fasting was investigated in fasting animals, and it was observed that PepT1 expression increased during metabolic fasting phases^[20,21]. Ojihara *et al.*^[22] showed that 4 d of starvation markedly increased the PepT1 in the jejunum, while a study by Ihara *et al.*^[23] demonstrated that starvation for 4 d and semistarvation for 10 d increased PepT1 mRNA and protein in the rat jejunum. That the cell population of PepT1 is increased in starvation may explain these results of earlier studies. In a study by Vazquez *et al.*^[24] this increase was expected to reduce the absorption of amino acids in human volunteers' jejunum after 14 d of hunger. In fact, while the absorption of amino acids was decreased, surprisingly, no significant change in the absorption of peptides was observed. In the present study of malnourished abdominal surgery patients, we conjectured that the patients' PepT1 levels would result in an increase in the absorption of dipeptides and tripeptides.

A randomized trial by Heimbürger *et al.* demonstrated that 10 d of feeding with a small-peptide diet produced slightly greater increases in serum rapid-synthesis proteins than did a whole-protein diet, especially between days 5 and 10^[25]. Our study found a similar result. The PEF group patients received the dipeptide- and tripeptide-based enteral feeding formula, and this formula was more efficacious and better tolerated than the whole-protein formula received by the patients in the other group. The present study suggests that 7 d of feeding of the dipeptide- and tripeptide-based enteral feeding formula may benefit a patient's nutritional status. Peptide formulas, however, are more expensive than whole-protein formulas, costing approximately five times more. More specifically, feeding a patient for 7 d with a peptide formula rather than whole-protein formula will cost roughly \$140 more. The mean cost of ICU is \$350 per day in Taiwan. However, peptide formulas seem to shorten the average ICU stay by about one day, and this should be factored into overall consideration of the cost and quality of care.

There were no significant differences in the prevalence of GRV, diarrhea, and pneumonia complications between the two groups, but the PEF group did exhibit a lower tendency for GRV and diarrhea than the WPF group. Two limitations of this study were its retrospective study design and low number of admitted patients. Well-designed clinical trials are needed to survey the efficacy, tolerance, and cost effectiveness of using dipeptide- and tripeptide-based enteral formulas for abdominal surgery patients.

In conclusion, the results of the present study suggest that dipeptide- and tripeptide-based enteral formulas are more efficacious and better tolerated than whole-protein formulas and could shorten the ICU stays of malnourished abdominal surgery patients.

intolerance often occurs in these patients. Few trials thus far have investigated the benefits of dipeptide- and tripeptide-based enteral formulas for abdominal surgery patients. The aim of this study, then, was to compare this dipeptide- and tripeptide-based enteral formula with a standard enteral formula in terms of tolerance and nutritional outcomes in abdominal surgery patients.

Research frontiers

The previous studies have described the small peptide formulas, but no particular dipeptide- or tripeptide-based formulas have been investigated.

Innovations and breakthroughs

The dipeptide- and tripeptide-based enteral formulas are more efficacious and better tolerated than whole-protein formulas, which shortened intensive care unit stay by about one day.

Applications

Early initiation of feeding with a dipeptide- and tripeptide-based enteral formulas for 7 d is a feasible approach in malnourished abdominal surgery patients.

Peer-review

This study is acceptable and very useful.

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COMMENTS

Background

Early enteral nutrition in critically ill patients is important, however, gut

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