Original

Effectiveness of peptide based oral nutrition supplement to improve gastrointestinal intolerance among patients in Hospital Kuala Lumpur: The E-PEG Study

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ABSTRACT *Background and purpose.* Gastrointestinal intolerance (GI) remains a challenge in delivering optimum nutrition support for patients receiving enteral nutrition. Role of peptide-based products (PBP) has shown clinical benefits in improving intolerance. The objective of this study was to determine whether a novel peptide based oral nutrition supplement will help to reduce the gastrointestinal intolerance among hospitalized patients at Hospital Kuala Lumpur. *Methods.* This retrospective study used data of patients seen by Dietitians in 2022. Descriptive analysis was used to describe patient characteristics, prevalence of GI intolerance and reduction of GI intolerance after PBP usage. The changes of GI intolerance score between baseline and after were assessed using the Wilcoxon Signed Rank Test stratified by PBP group. A *p*-value of < 0.05 was set as the cut-off for statistical significance. *Results:* A total of 132 patients were recruited for this study; only 80 patients (60.6%), remained on PBP until end of study. Indications for PBP usage was mainly for GI Intolerance 58 (60.4%) and unspecified indication 21 (60%). Significant association was between calorie intake ($p=0.047$), % of PBP energy consumed from total requirement ($p= 0.044$), reduced frequency of diarrhoea ($p= 0.018$) and lower gastric residual volume ($p< 0.000$). There was significant association ($p<0.001$) between resolved GI Intolerance and usage of PBP till end of study. *Conclusion.* This study describes that PBP is significantly effective in helping patients achieve their energy requirements and reduction in frequency of GI intolerance. However, larger clinical studies are required to yield better in the future.

Keywords: Peptide based product, gastrointestinal intolerance, enteral nutrition, diarrhoea, gastric residual volume

INTRODUCTION

Gastrointestinal (GI) intolerance has always remained a challenge to patients, caregivers, and nutrition care providers causing a less than optimal nutrition therapy (1). There are many studies to date that supports the role of peptide-based products (PBP) in managing GI intolerance with studies producing significant reduction in symptoms of intolerance among patients (2). Additionally, it was shown that prevention and/or management of GI intolerance with the use of PBP can also be cost-effective as it has resulted in minimizing healthcare utilization and cost (3).

GI intolerance can happen in patients with conditions such as celiac disease, chronic diarrhea, cystic fibrosis, early enteral feeding, inflammatory bowel disease (e.g., Crohn's Disease and ulcerative colitis), malnutrition, pancreatic disorders (e.g., pancreatitis), pre/post-operative feeding, and short-bowel syndrome (e.g., surgical removal of a portion of the GI tract). Patients with impaired GI function have reduced ability to digest and absorb nutrients and need appropriate nutritional support (4-6).

Patients with GI intolerance are usually unable to tolerate oral nutritional supplements (ONS) containing whole protein or long chain triglycerides and require a product containing hydrolyzed protein and medium chain triglycerides. These products reduce the need for hydrolysis of protein by the brush border peptidases in the intestinal lumen and are more easily absorbed (7-9).

Peptide-based products contain protein that is hydrolyzed or pre-digested into peptides of different size and lengths. Peptide based formulas are commonly high in protein. These products are easier to digest as protein is hydrolyzed into small chain peptides. Hydrolyzed or peptide-based protein systems help improve absorption and tolerance compared to protein systems composed entirely of free amino acids or intact protein (8).

Oral nutritional supplements (ONS) have been shown to be clinically effective in the management of GI

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diseases. Specially formulated ONS for GI intolerance utilize ingredients that may be beneficial in patients with malabsorption or significant GI intolerance (9). Special formulas, including peptide-based protein products that are quickly and efficiently absorbed compared with intact protein, may help minimize the symptoms of GI intolerance (10). Additionally, products containing medium-chain triacylglycerol (MCTs) may provide a more easily absorbable lipid source compared with long chain triacylglycerol for patients with GI disorders, including fat malabsorption (11- 13).

Local data from Malaysia research showed that prevalence of GI intolerance was high gastric residual volume (GRV) (38%), diarrhea (8.4%), and vomiting (2.9%) among hospitalized patients (14-15). Meanwhile, the information on usage of peptide-based products among Malaysian hospitalized patients are scarce with this type of enteral nutrition. Based on this context, this study was conducted to determine whether this type of product will help to reduce the GI intolerance among hospitalized patients at Hospital Kuala Lumpur.

The objective of this study was to evaluate the effectiveness of peptide-based product in treating patients having gastrointestinal intolerance (GI). The specific objective was to investigate whether the improvement and changes of GI intolerance were associated with usage of PBP.Methodology

MATERIALS AND METHODS

Study Type and Design

This retrospective cohort study used Malaysian Dietetic Care Notes (DCN) KKM/JDS/DC/OO4/2019 which is the standard documentation form used by dietitians in Malaysia for documenting their nutrition findings and medical records from the Medical Record Department. This study used a universal sampling method that refers to all eligible patients referred and seen by Dietitian that used PBP during 1-year data collection period (1st January 2022 until 31st December 2022). Malaysian DCN consists of complete documented nutrition care process of screening, assessing, planning nutrition intervention and monitoring for patients referred to dietitians. Variables of concern analyzed includes nutritional status, sociodemographic, blood and clinical investigations, GI intolerance (diarrhea; defined as loose stool of ≥4 times in a day, abdominal pain/cramping, gas/bloating, constipation and high gastric residual volume; which is defined as residual of more than 500 ml).

Dietary intake of patients on PBP or polymeric/ disease specific product were obtained from medical records charted by nurses. Height and weight were used in calculation for body mass index (BMI). A minimum of 5 days follow up of PBP usage by patients was required in order to get adequate data for analysis and results in improvements of GI intolerance as according to Dietitian Key Performance Index (KPI) criteria on tube feeding patients follow up. For patients who were transitioned from polymeric or standard products to PBP, the first day of starting PBP will be considered as Day 1 on product usage and will be followed up for at least once in 5 days.

Table 1. Energy and concentrations of protein, carbohydrate and lipid in oral nutritional supplement (/100g)

	Per 100g
Energy	468 kcal
N sources	
Hydrolyzed Whey Protein*	21g
Carbohydrate	
Maltodextrin	60g
Lipid	
Medium Chain Triglycerides Oil	9.6g
Omega 3	1.8g
Omega 6	0.9g
Evening Primrose Oil	3.7g

* The % of hydrolyzed whey protein used

- Large Peptide (7 amino acid residues) 8.61g/100g (41%)
- Medium Peptide (4 – 6 amino acid residues) 9.28g/100g (44.18%)
- Di and Tri Peptides (2 – 3 amino acid residues) 1.36g/100g (6.46%)
- Free Amino Acids 1.73g/100g (8.22%)

Study Tool

Oral nutritional supplement which was used in this study is a nutritionally complete, well tolerated and easily absorbed peptide based formula for patients experiencing GI intolerance or malabsorption. This product contains 100% hydrolyzed whey protein. The fat blend contains 60% medium chain triglycerides (MCT), an easily digested and well absorbed fat source. The % of MCTs is 60% out of the total fat content 9.60g/100g. Patients that were recruited in this study were those patients that were prescribed with PBP. Benefits of PBP was reported based on improvement or reduction of GI intolerance among patients after using PBP.

Study Population & Sampling Method

All adult patients seen by dietitians using peptide based products in Hospital Kuala Lumpur during the period of 1st January 2022 until 31st December 2022.

Inclusion Criteria

- All patients referred to dietitian by physicians
- Aged 18 years and received at least 75% of their requirement from PBP.
- Tube feeding patients.
- Minimum of at least 5 days on PBP

Exclusion Criteria

- Patients who transitioned back to polymeric or disease specific formula
- Death of patient.
- Medications that cause or induce GI intolerance
- Any malignant disease, psychiatric disorder or obstruction of GI tract
- Patients consuming a non-UNIMED / British Biological PBP or existing PBP product.
- Addition of probiotic/prebiotic or any fiber supplementation

Withdrawal Criteria

Not applicable

Sample Size

We used G*Power version 3.1.9.4 to determine the required sample size for detecting an improvement in GI intolerance with a medium effect size of 0.5, a significance level of 5%, and a power of 80%. As no information on effect size was available for this particular factor, we chose to use Cohen's guidelines for effect size interpretation to determine the target effect size. The sample size calculation showed that a total sample size of 34 participants is required to achieve the desired level of power

Study Visits and Procedures

The data of concern involved patients seen by Dietitian from 1st of January 2022 until 31st December 2022. These data were retrieved from copies of Dietetic Care Notes (DCN) which wasstored at Dietetic Clinical Store Office. These data of patients that were followed up by dietitians from the day of referral up to minimum of 5 days of follow up in Hospital Kuala Lumpur wards. The days of referral and follow ups were within the stipulated time of 1st January 2022 until 31st December 2022. Dietitians of Hospital Kuala Lumpur retrieved the data from the Dietetic Clinical Store Office and entered the variables of concern into SPSS for further analysis. These data collection period commenced from 1st August 2023 until 31st September 2023.

Statistical Analysis Plan

All data was analyzed using Statistical Package for the Social Sciences (SPSS, IBM, Chicago, IL) version 28 Descriptive analysis was used to describe patient characteristics, prevalence of GI intolerance and reduction of GI intolerance after PBP usage. The changes of GI intolerance score between baseline and after were assessed using the Wilcoxon Signed Rank Test stratified by PBP group. Fisher exact test was applied to determine the association between resolved status of GI Intolerance and remained on PBP. A p-value of < 0.05 was set as the cutoff for statistical significance.

Risk and benefit to study participants

There is no risk and benefit to the participant as this is a retrospective study which does not involve direct contact with any patient.

Risk Benefit Assessment

This study can help to determine valuable insights into association between PBP and GI intolerance. Treatment using PBP should be considered to treat intolerance towards polymeric or disease specific products which might lead to significant improvement in relation to GI intolerance. Any significant reduction of findings will help in health care utilization related to nutrition therapy. As stated above, there is minimal risk from the investigated product and study procedures. Study findings shall potentially greatly improve treatment outcomes. The expected benefit outweighs the minimal risk to subjects and thus this study should be supported. If any injuries do occur as a direct result of participating in the study, treatment for such injuries shall be provided or paid for by the sponsor

Ethics of Study

Ethical approval was approved from the Medical Research and Ethics Committee, Ministry of Health Malaysia. This research was registered with National Medical Research Register (NMRR) Malaysia bearing the registration number of NMRR ID-23-02521-U1K. The study was performed in compliance with the principles of the Declaration of Helsinki, in accordance with the International Conference of Harmonization Guideline for Good Clinical Practice, and in accordance with applicable regulatory requirements.

Informed Consent/Assent Process

Waiver of consent was granted by MREC in view of retrospective study and no patient / participant contacts.

Privacy and Confidentiality

Subject's names were kept on a password-protected database and was linked only with a study identification number for this research. The identification number instead of patient identifiers was used on subject data sheets. All data will be entered into a computer that is password protected. On completion of study, data in the computer was copied to thumb drives and the data in the computer erased. Thumb drives and any hardcopy data was stored in a locked office of the investigators and maintained for a minimum of three years after the completion of the study. The thumb drives and data will be destroyed after that period of storage. The data will be keep as confidential and monitored by principle investigator. All data will be disposed/destroyed three (3) years upon publishing this study. Study data will not be shared with any third party.

RESULTS

Table 2. Description of sociodemographic characteristics (N= 132)

Variable	Remained on PBP until end of study		
	Yes, n (%)	No, n (%)	Total
Gender			
Male	46 (63.9)	26 (36.1)	72
Female	34 (56.7)	26 (43.3)	60
Age	62.0 (22.5)	67.0 (18.5)	132
Ethnicity			
Malay	50 (66.7)	25 (33.3)	75
Chinese	16 (50.0)	16 (50.0)	32
Indian	13 (59.1)	9 (40.9)	22
Others	1 (33.3)	2 (66.7)	3
BMI Classification			
Underweight	0 (0)	1 (100)	1
Normal	21 (75.0)	7 (25.0)	28
Overweight	5 (45.5)	6 (54.5)	11
Obese	2 (40.0)	3 (60.0)	5
Diabetes Mellitus			
No	56 (64.4)	31 (35.6)	87
Yes	24 (53.3)	21 (46.7)	45
Hypertension			
No	52 (64.2)	29 (35.8)	81
Yes	28 (54.9)	23 (45.1)	51
Dyslipidaemia			
No	73 (62.4)	44 (37.6)	117
Yes	7 (46.7)	8 (53.3)	15
Heart Disease			
No	70 (60.3)	46 (39.7)	116
Yes	10 (62.5)	6 (37.5)	16
Indication of PBP Usage			
Intolerance	58 (60.4)	38 (39.6)	96
Unspecified	21 (60.0)	14 (40.0)	35
Pancreatic Insufficiency	1 (100)	0 (0)	1
Duration on PBP	7.0 (5.0)	1 (0)	8
Reason for drop out			
Lost follow-up	0 (0)	48 (100)	48
Change product	0 (0)	2 (100)	2
Death	0 (0)	1 (100)	1
Discharged	0 (0)	1 (100)	1
Status of GI tolerance on PBP			
Resolved	40 (100)	0 (0)	40
Not resolved	5 (83.3)	1 (16.7)	6
Improved	18 (100)	0 (0)	18
Incomplete	0 (0)	35 (100)	35
Not Available	17 (51.5)	16 (48.5)	33

- PBP = Peptide Based Product

A total of 132 patients were recruited for this study; only 80 patients (60.6%) remained on PBP until end of study. Among these 80 patients, 46 (39%) were male while 34 (56.7%) were female. Reasons for dropouts were mainly due to loss of follow ups (36.3%), change of products (1.5%), death (0.8%), and discharge (0.8%). Indications for PBP usage was mainly for gastrointestinal intolerance 58 (60.4%) and unspecified indication 21 (60%).

Table 3: Description of association between resolved status of GI Intolerance and remained on PBP till end

		Remained on PBP until end of study				Chi-square	p-value
		YES		NO			
		n	%	n	%		
Status of tolerance on PBP	Resolved	40	50.0	0	0	93.99	<0.001
	Not resolved	5	6.3	1	1.9		
	Improved	18	22.5	0	0		
	Incomplete	0	0	35	67.3		
	N/A	17	21.3	16	30.8		
Total		80	100	52	100		

N/A= Not Available

In terms of status of GI intolerance in patients who were on PBP, resolved GI intolerance cases such as diarrhoea and high aspiration were 40 (50%), while improved status was 18 (22.5%). Only 5 (6.25%) patients on PBP GI intolerance remained unresolved throughout the study period (Table 2). Results from Table 2 also showed that there was significant association ($p<0.001$) between resolved GI Intolerance and usage of PBP till end of study.

Results from Table 3 showed significant associations were noted between PBP consumption with calorie intake ($p=0.047$), % of PBP energy consumed from total requirement ($p=0.044$), reduced frequency of diarrhoea ($p=0.018$) and lower gastric residual volume ($p< 0.001$).

Table 4. Description of median difference of parameter stratified for those remained on PBP until end of study.

Variable	Remained on PBP until end of study					
	Yes			No		
	Before	After	p-value	Before	After	p-value
Haemoglobin	9.25 (2.33)	9.45 (2.25)	0.419	8.80 (1.65)	8.80 (1.45)	0.3173
Total Protein	61.50 (12.25)	61.50 (11.75)	0.294	60.00 (8.50)	60.00 (8.50)	0.3173
Albumin	18.00 (7.75)	16.50 (6.75)	0.579	19.00 (6.00)	19.00 (6.00)	>0.999
Urea	8.60 (16.88)	8.60 (10.28)	0.038	6.90 (30.20)	6.90 (28.30)	0.3173
Creatinine	68.00 (41.50)	59.50 (84.25)	0.089	82.00 (54.00)	82.00 (54.00)	0.3173
Sodium	139.50 (7.75)	141.50 (9.25)	0.651	138.00 (13.00)	138.00 (13.00)	>0.999
Potassium	3.55 (1.03)	3.20 (0.45)	0.862	3.80 (0.55)	3.80 (0.55)	0.3173
Calcium	2.12 (0.25)	2.20 (0.29)	0.280	2.40 (0.75)	2.40 (0.75)	0.3173
Magnesium	0.88 (0.14)	0.90 (0.12)	0.046	0.83 (0.17)	0.83 (0.17)	>0.999
Phosphate	0.81 (0.65)	0.66 (0.64)	0.850	0.77 (0.81)	0.77 (0.81)	0.3173
Fasting Blood Serum	7.60 (2.83)	7.50 (3.15)	0.444	7.20 (6.10)	7.20 (6.10)	>0.999
Calorie Intake	1494.00 (646.50)	1551.00 (288.00)	0.047	1464.00 (879.00)	1464.00 (879.00)	0.3173
Protein Intake	70.80 (32.75)	71.00 (23.35)	0.123	60.50 (59.85)	60.50 (59.85)	>0.999
% PBP Consumed from total requirement	91.00 (39.00)	93.00 (18.00)	0.044	94.00 (51.00)	94.00 (51.00)	>0.999
Frequency of diarrhoea	3.00 (2.00)	2.00 (1.50)	0.018	3.00 (2.00)	3.00 (2.00)	>0.999
Gastric Residual Volume	160.00 (111.50)	90.00 (123.50)	<0.001	110.00 (113.50)	110.00 (113.50)	>0.999

Results represented for Median (IQR), $p<0.05$ was considered significant association

DISCUSSION

Our study demonstrated that more calories were tolerated with PBP compared to other ONS products. This may be due to the fact that this study product contains higher energy than other standard product. This study reported a significant association between PBP consumption with increased calorie intake ($p=0.047$). It correlates with previous study conducted which showed that patients using PBP consumed more calories compared to other standard products (22). According to the same study, tolerance of gradual increment of calorie and protein was better in patients who received PBP compared with standard product, allowing for higher percent of increase in calorie and protein provided between days 3 and 7 after tube feeding initiation (22).

However, no significant improvement in protein consumption was found in this study. Our study showed significant association of reduced diarrhoea ($p<0.014$) and reduced gastric residual volume ($p<0.001$) after transition of product from standard to peptide-based product.

These results were further supported by studies done by Wang et al, 2022 and Liu et al, 2016 (23, 4). Literature reviews support the evidence that peptide-based products, such as the study product is effective in patients having GI intolerance such as diarrhoea and high aspiration (6, 7, 24-26). Nearly 73% of patients on PBP showed improvement while using the product.

Possible cause of improved tolerance to PBP is mainly attributed to the physiological properties of PBP as a semi elemental formula. PBP contain larger quantity of MCT oil which does not influence the release of cholecystokinin; therefore, reducing secretion of pancreatic enzymes and gallbladder emptying. It also contains hydrolysed whey protein, which may lead to better protein absorption (24). PBP typically contains a significant amount of medium-chain triglycerides (MCTs) in comparison with standard products whose lipid component typically contain more long chain triglycerides (LCTs). These types of fat requires less lipolysis thus ensuring better absorption and less intolerance (27). Hydrolysed proteins and more easily digestible fats including medium-chain triglycerides tend to supply protein and fats to the best suitability of patients with impaired gastrointestinal function (27).

Limitations of our study was that it has a small sample size and it was a single centre study. A prospective intervention study with larger sample size would yield stronger clinical results. The main strength of our study was that the results were similar and consistent with other studies that indicates the effectiveness of PBP in improving GI intolerance among hospitalised patients (2, 10, 20).

To the best of our knowledge, this is also the first study that has been done in Malaysia involving peptide based product among GI intolerance hospitalised patients. Clinical implications of our findings is that transition to peptide based diet from a polymeric or disease specific formula among GI intolerant patients is a beneficial intervention towards achieving nutrition therapy goals by improving GI intolerance among patients with diarrhoea, abdominal pain/cramping, gas/bloating, constipation and high gastric residual volume.

CONCLUSION

This study describes that PBP is significantly effective in helping patients achieve their energy requirements and had a significant reduction in frequency of GI intolerance. Further study with large coverage may give a concrete or better results in future

CONFLIC OF INTEREST

Authors wish to declare there are no conflict of interest in this study.

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REFERENCES

1. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 38(1):48-79. 2019.
2. Mundi MS, Velapati S, Kuchkuntla AR, et al. Reduction in healthcare utilization with transition to peptide-based diets in intolerant home enteral nutrition patients. Nutr Clin Pract 35(3):487-494. 2020.
3. Ibrahim H, Mansour M, El Gendy Y. Peptide-based formula versus standard-based polymeric formula for critically ill children: is it superior for patients' tolerance. Arch Med Sci 16(3):592-596. 2020.
4. Liu MY, Tang HC, Hu SH, et al. Peptide-based enteral formula improves tolerance and clinical outcomes in abdominal surgery patients relative to a whole protein enteral formula. World J Gastrointest Surg 8:700e5. 2016.
5. Keller J, Layer P. The pathophysiology of malabsorption. Visz Gastrointest Med Surg 30:150e4. 2014.
6. Silk DBA, Fairclough P, Clark ML, et al. Use of a peptide rather than free amino acid nitrogen source in chemically defined ‘elemental’ diets. J Parenter Enteral Nutr 4:548e53. 1980.
7. Seres DS, Ippolito PR. Pilot study evaluating the efficacy, tolerance and safety of a peptide-based enteral formula versus a high protein enteral formula in multiple ICU settings (medical,

surgical, cardiothoracic). Clin Nutr 36:706e9. 2017.
8. Roberts PR, Burney JD, Black KW, et al. Effect of chain length on absorption of biologically active peptides from the gastrointestinal tract. Digestion 60:332e7. 1999.
9. Zaloga GP. Intact proteins, peptides, and amino acid formulas. In: Zaloga GP, editor. Nutrition in critical care. St Louis: Mosby p. 59e80. 1994.
10. Seres DS, Ippolito PR. Pilot study evaluating the efficacy, tolerance and safety of a peptide-based enteral formula versus a high protein enteral formula in multiple ICU settings (medical, surgical, cardiothoracic). Clin Nutr 36:706–9. 2017.
11. Brinson RR, Hanumanthu SK, Pitts WM. A reappraisal of the peptide-based enteral formulas: clinical applications. Nutr Clin Pract 4:211–7. 1989.
12. Shah ND, Limketkai BN. The use of medium-chain triglycerides in gastrointestinal disorders. Pract Gastroenterol 20–8. 2017.
13. Shea JC, Bishop MD, Parker EM, et al. An enteral therapy containing medium-chain triglycerides and hydrolyzed peptides reduces postprandial pain associated with chronic pancreatitis. Pancreatology 3:36– 40. 2003.
14. Z.-Y. Lee et al. / Nutrition 53, p26–33. 2018.
15. Yip KF, Rai V, Wong KK. Evaluation of delivery of enteral nutrition in mechanically ventilated Malaysian ICU patients. BMC Anesthesiol 14:127. 2014.
16. Mueller, C.M. (Ed.) The ASPEN Nutrition Support Core Curriculum, 3rd ed.; American Society of Parenteral and Enteral Nutrition: Silver Spring, MD, USA, ISBN 978-188-962-231-6. 2017.
17. Compher C, Bingham AL, McCall M, et al. Guidelines for the provision of nutrition support therapy in the adult critically ill patient: The American Society for Parenteral and Enteral Nutrition. JPEN J. Parenter. Enteral Nutr 46, 12–14. 2022.
18. Cawood AL, Elia M, Stratton RJ. Systematic review and meta-analysis of the effects of high protein oral nutritional supplements. Ageing Res Rev 11(2): 278e96. 2012.
19. Keller J, Layer P. The pathophysiology of malabsorption. Visz Gastrointest Med Surg 30: 150e4. 2014.
20. Roberts PR, Burney JD, Black KW, et al. Effect of chain length on absorption of biologically active peptides from the gastrointestinal tract. Digestion 60: 332e7. 1999.
21. LaVallee C, Seelam P, Balakrishnan S, et al. Real-world evidence of treatment, tolerance, healthcare utilization, and costs among postacute care adult patients receiving enteral peptide-based diets in the United States. JPEN J Parenter Enteral Nutr 45(8): 1729-35. 2021.
22. Hamaoui E, Lefkowitz R, Olender L, et al. Enteral nutrition in the early postoperative period: a new semi-elemental formula versus total parenteral nutrition. JPEN J Parenter Enteral Nutr 14(5): 501-507. 1990.
23. Wang YQ, Li YH, Li YT, et al. Comparisons between short-peptide formula and intact-protein formula for early enteral nutrition initiation in patients with acute gastrointestinal injury: a single-center retrospective cohort study. Ann Transl Med 10(10): 573. 2022.
24. Reignier J, Mercier E, Le Gouge A, et al. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding. A randomized trial. J Am Med Assoc 309(3): 249e56. 2013.
25. Seres DS, Ippolito PR. Pilot study evaluating the efficacy, tolerance and safety of a peptide-based enteral formula versus a high protein enteral formula in multiple ICU settings (medical, surgical, cardiothoracic). Clin Nutr 36(3): 706-709. 2017.
26. Reintam Blaser A, Deane AM, Preiser JC, et al. Enteral feeding intolerance: updates in definitions and pathophysiology. Nutr Clin Pract. 36(1):40-49. 2021.
27. Green B, Sorensen K, Phillips M, et al. Complex enterally tube-fed community patients display stable tolerance, improved compliance and better achieve energy and protein targets with a high-energy, high-protein peptide-based enteral tube feed: Results from a multi-centre pilot study. Nutrients. 18;12(11): 3538. 2020.