Original Article

Pectin-containing liquid enteral nutrition for critical care: a historical control and propensity score matched study

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Background and Objectives: Pectin-containing liquid enteral nutrition (PCLEN) contains pectin, which becomes solid in the stomach and therefore mitigates vomiting and diarrhea. Its efficacy for use in critical care medicine was evaluated. **Methods and Study Design:** We used liquid enteral nutrition (LEN) (traditional LEN (TLEN)) as the primary LEN at the emergency and critical care center. We adopted PCLEN as the primary LEN from 2014. During 2012–2016, 954 patients admitted to intensive care units and emergency wards were given PCLEN or TLEN. We conducted propensity score matching for 693 eligible patients for age, sex, and organ dysfunctions for six organs. **Results:** We included 199 PCLEN patients and 199 TLEN patients. Severity was higher in the PCLEN group. The enteral nutrition failure rate was significantly lower for PCLEN than for TLEN. The diarrhea incidence rates were 28.1% vs 38.2% (p=0.033), and the incidence rates of nosocomial pneumonia were 4.5% and 9.6% (p=0.048). For PCLEN, the enteral nutrition failure rates were not different for patients with gastric acid inhibitors and without them. **Conclusions:** PCLEN can be used effectively for critically ill patients irrespective of the use of gastric acid inhibitors. It can decrease the incidence of enteral nutrition failure and diarrhea.

Key Words: enteral nutrition, critical care, pectin, diarrhea, intensive care

INTRODUCTION

Liquid enteral nutrition (LEN) has been reported as important for critical care medicine. We recommend starting its administration as soon as possible in clinical practice.[1] Early enteral nutrition is physiologically advantageous for immunity and the gut tract system.[2] Nevertheless, various phenomena resist enteral feeding in critically ill patients: enteral nutrition failure often occurs.[3] Diarrhea and vomiting are the main reasons for enteral nutrition failure.[4] The recent widespread use of antibiotics reportedly exacerbates diarrhea events.[5] Severely ill patients often cannot be relieved with enteral nutrition.

Diarrhea and vomiting are common complications affecting chronic patients and those undergoing critical care. Therefore, approaches have been undertaken to make LEN solid and thereby decrease gastroesophageal reflux, vomiting, and diarrhea. Some LEN with a semi-solid consistency are sold. Although some studies have examined the efficacy of semi-solid LEN against gastroesophageal reflux,[6-8] no large clinical study has been reported. Especially, whether diarrhea can be decreased or not has not been studied.

Pectin is dietary fiber that changes to a solid by forming a bridged structure when exposed to calcium ion.[9-11] Pectin-containing liquid enteral nutrition (PCLEN), which can be given in a liquid condition, is expected to become solid in gastric acid pH. In Japan, PCLEN has been marketed as HINE E-GEL® from 2014. When given as a diet, the solidification can occur without risk of tube occlusion and can be expected to inhibit diarrhea and vomiting. The use of PCLEN is increasing in chronic enteral feeding patients in Japan. Nevertheless, no report has described a study examining the efficacy of PCLEN. Especially, no reported study has examined the use of PCLEN in critical care medicine. The efficacy of pectin alone reportedly decreases diarrhea in a small randomized study in critically ill patients. However, no significant difference was found between the pectin group and the fiber-free group.[12]

Because solidification of PCLEN occurs because of the gastric acid pH, it is necessary to examine for PCLEN whether gastric acid inhibitors weaken solidification or not. HINE E-GEL® is expected to be solid under acidic conditions with pH less than 5. Proton pump inhibitor

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(PPI) or H_2 blockers are often given in critical care medicine applications because of the risk of gastrointestinal bleeding.[1] Although gastric pH differs according to a patient's condition and the dose or frequency of the administered gastric acid inhibitor, gastric pH would temporarily be higher than 5 with gastric acid inhibitors.[13-15] Solidification of PCLEN might therefore be difficult. For that reason, it is necessary to examine the efficacy of PCLEN in patients who are given gastric acid inhibitors.

We used Mei Balance HP1.0®, which contains milk protein, as the primary LEN (traditional LEN (TLEN)) and adopted HINE E-GEL® from 2014 as the primary LEN for use in emergency and critical care centers. As described herein, we conducted a retrospective, historical control, and propensity score matched study to compare outcomes related to enteral nutrition between patients given TLEN and PCLEN for critical care treatment. We conducted subgroup analyses of patients with and without gastric acid inhibitors.

METHODS

We used Mei Balance HP1.0®, TLEN, as primary LEN at the Emergency and Critical Care Center of Hitachi General Hospital. We adopted HINE E-GEL®, PCLEN, for use as the primary LEN from May 2014.

Mei Balance HP1.0® is LEN that contains milk protein 1.0 kcal/mL, osmotic pressure 420 mOsm/L and a protein, fat, carbohydrate balance of 20%, 22.5%, and 57.5%, respectively. It contains 1.2 g dietary fiber per 100 kcal. HINE E-GEL® is LEN that contains soy and collagen peptide protein 0.8 kcal/mL, osmotic pressure 360 mOsm/L and a protein, fat, and carbohydrate balance of 16%, 20%, and 64%, respectively. It contains 1.4 g dietary fiber per 100 kcal, which includes 0.9 g pectin.

The initiation of enteral nutrition was performed in both groups as explained below. Gastric residual volume GRV was evaluated routinely in our intensive care units. Enteral feeding was started via a nasogastric tube when there was no ileus condition and recent GRV was less than 500 mL after the second day from admission. We started LEN at the flow rate of 10 - 20 mL/h, increased by 10 - 20 mL/h to reach the necessary calorie goals at every 8 hours when the GRV was less than 500 mL. When patients presented refractory diarrhea, needed the restriction of water or protein, or the higher fat balance was appropriate for respiratory failure or severe diabetes or respiratory failure, the other specific LEN were chosen. Selection of the other LEN did not differ during the study period.

This study was approved by the Ethics Review Board of our hospital (2013-48).

Patient selection

An outline of patient selection is presented in Figure 1. Patients who were admitted to the Intensive Care Unit and the Emergency Ward at the Emergency and Critical Care Center of Hitachi General Hospital from October 2012 to August 2016 and to whom PCLEN or TLEN were given were included. Age <15 years old, patients who were given both PCLEN and TLEN in different periods, and patients who were given LEN except via nasogastric tube (for example via percutaneous endoscopic gastrostomy PEG or intestine duodenal tube) were excluded. Propensity score matching was conducted for patients of TLEN and PCLEN groups by age, sex, and the presence of organ dysfunction for six organs at admission: 1) cardiovascular dysfunction that required initiation of noradrenaline and/or dopamine on day 0; 2) respiratory dysfunction that required postsurgical continuous mechanical ventilation; 3) renal dysfunction that necessitated initiation of intermittent acute hemodialysis or continuous renal replacement therapy on day 0, except for maintenance hemodialysis patients; 4) hepatic dysfunction as a comorbidity at admission for recorded "liver failure," except for liver cirrhosis patients; 5) hematologic dysfunction that required platelet concentrate transfusion on day 0; and 6) neurological dysfunction of 100 on the Japan Coma Scale score, which is equivalent to scores of 6–9 on the Glasgow Coma Scale, or greater severity. Finally, the matched TLEN and PCLEN patients were analyzed. This organ dysfunction score matching was obtained from the Japanese Diagnosis Procedure Combination inpatient database.[16]

Outcome measurements

As the primary outcome, the enteral nutrition failure rate was analyzed. Enteral nutrition failure was defined as the discontinuation of enteral feeding or change to the other LEN by trouble related to enteral nutrition. 30-day survival, length of ICU stay and hospital stay, duration of enteral feeding, gastric residual volume GRV, incidence rate of vomiting, diarrhea, nosocomial pneumonia, the given LEN amounts, and calories per day on the seventh day were analyzed as secondary outcomes. GRV was analyzed at 2 hr and 24 hr after TLEN or PCLEN was started. Vomiting was recorded when observed during administration of TLEN or PCLEN. Diarrhea was defined as frequent stool more than three times per day and stool condition which met Bristol Stool Chart 5–7.[17] Nosocomial pneumonia was diagnosed by infiltration in chest X ray and 2 positive in 1) >38°C fever, 2) white blood cell counts <4000 or >11,000/μl, or 3) purulent sputum. Ventilator-associated pneumonia (VAP) was included. In subgroup analysis, the PCLEN group was divided to two groups with or without PPI or H_2 blocker. Their respective outcomes were compared with that of TLEN. PPI/H2 blocker was counted positively when intravenous PPI or H2 blocker was given at the time of PCLEN start.

Statistical analysis

Propensity score matching was used to adjust for differences in age, sex, and severity of the condition at admission between TLEN and PCLEN. First, the propensity score was estimated. The log odds of the probability that a patient received PMX treatment was modeled for potential confounders: age, sex, and the six organ dysfunctions defined above. A one-to-one matched analysis using nearest-neighbor matching was performed based on the estimated propensity score of each patient. A match occurred when one patient in the PCLEN group had an estimated score within 0.25 SDs of another in the TLEN group.

Differences were assessed by application of Student t-tests, paired t-tests, chi-square tests, and one-way analysis

of variance between the TLEN and PCLEN group. Significant differences were then assessed using Tukey–Kramer and Steel–Dwass methods for multiple comparisons. The 30-day survival, length of ICU and hospital stay and duration of enteral nutrition were analyzed using log-rank tests. All statistical analyses were performed using statistical software (JMP 10; SAS Institute Inc.). Results are expressed as mean ± standard deviation values. *p*-values of <0.05 were inferred as significant.

RESULTS

During the study period, 954 patients were admitted to intensive care units or emergency wards and were given PCLEN or TLEN. From them, 261 patients were excluded according to exclusion criteria. Propensity score matching was performed for the remaining 693 patients for age, sex, and severity of condition at admission between TLEN and PCLEN. Finally, 199 PCLEN group patients and 199 TLEN group patients were included and analyzed. A patient selection outline is depicted in Figure 1.

Basic characteristics are presented in Table 1. Although renal failure was higher in PCLEN group patients, other basic diseases were not found to be significantly different. Invasive treatments such as mechanical ventilation or hemodialysis were not different between groups. Vital signs and laboratory findings on admission were not significantly different. Severity was higher in the PCLEN group than in the TLEN group: Acute Physiology and Chronic Health Evaluation (APACHE) II 15.3±6.8 vs 13.6±5.4 (p=0.0055) and sequential organ failure assessment (SOFA) 6.2±3.8 vs 5.1±3.3 (p=0.0029), respectively.

Outcomes for both groups are shown in Table 2. The enteral nutrition failure rate, at which enteral nutrition should be discontinued because of enteral feeding difficulty, was 10.6% for PCLEN and 17.6% for TLEN. PCLEN was associated with significantly better results (p=0.043). The enteral feeding durations were not different, as shown by the Kaplan–Meier curve (Figure 2A). The 30-day survival rates and length of ICU and hospital stay were not significantly different. The GRV at 24 hr was slightly lower for PCLEN: 7.9±24.3 mL for PCLEN vs 25.1±63.0 mL for TLEN (p=0.017). Although vomiting events were not different, diarrhea events were lower for PCLEN, 28.1% for PCLEN vs 38.2% for TLEN (p=0.033). The nosocomial pneumonia rate including VAP was also lower for PCLEN: 4.5% for PCLEN vs 9.6% for TLEN (p=0.048). Enteral nutrition amounts and enteral calories per day on the seventh day were not significantly different.

We conducted subgroup analysis of PCLEN in patients with and without PPI/H2 blocker (Table 3). In the PCLEN group, 122 patients were given PPI or H_2 blocker; 77 patients were not. The incidence of enteral nutrition failure was not different for PCLEN between groups of patients with and without PPI/H_2 blocker. Incidences for both groups were significantly lower than for TLEN. The groups' survival rates were not significantly different. GRV at 24 hr was slightly lower for PCLEN with/without PPI/H_2 blocker than for TLEN. Vomiting events and the nosocomial pneumonia rate were not different. Diarrhea was significantly lowest, 22.1% for PCLEN without PPI/H_2 blocker. Meanwhile, incidence of diarrhea was not different between with and without PPI/H_2 blocker for TLEN (Figure 2B). These results suggest that the diarrhea examined in this study was not associated as a side effect of PPI/H_2 blocker, but that it might be related to pectin solidification.

DISCUSSION

This study analyzed the efficacy of PCLEN use in critical care medicine. The enteral nutrition success rate was significantly higher for PCLEN than for TLEN. Although vomiting events were not different, diarrhea, and nosocomial pneumonia events were significantly lower for PCLEN. The enteral nutrition success rates obtained with and without gastric acid inhibitors were not different. The

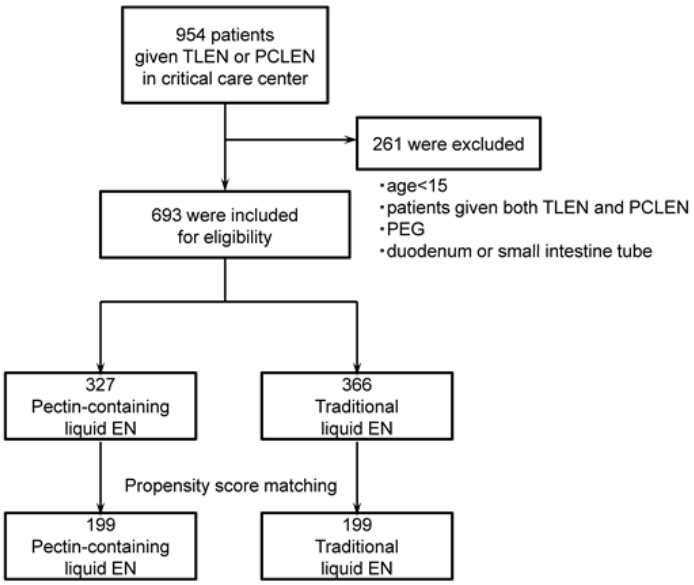

Figure 1. Outline of patient selection. PCLEN: pectin-containing liquid enteral nutrition; TLEN: traditional liquid enteral nutrition; PEG: percutaneous endoscopic gastrostomy.

Table 1. Basic characteristics†

Regimen	Pectin-containing liquid EN (n=199)	Traditional liquid EN (n=199)	*p* value
Sex (male)	130 (65.3%)	124 (62.3%)	0.53
Age (years)	73.9±16.4	73.9±14.0	0.97
APACHE2	15.3±6.8	13.6±5.4	0.0055*
SOFA	6.2±3.8	5.1±3.3	0.0029*
Other treatments during hospitalization			
Mechanical ventilation	78 (39.3%)	78 (39.3%)	1
Platelet transfusion	3 (1.5%)	5 (2.5%)	0.47
Dialysis	40 (20.1%)	35 (17.6%)	0.54
Acute surgery	41 (20.7%)	51 (25.8%)	0.23
Basic disease			
Infection	66 (33.2%)	58 (29.2%)	0.39
Heart failure	13 (6.5%)	8 (4.0%)	0.26
Renal failure	6 (3.0%)	1 (0.5%)	0.045*
Stroke	59 (29.7%)	69 (34.7%)	0.28
Convulsion	10 (5.0%)	6 (3.0%)	0.30
Trauma	17 (8.5%)	14 (7.0%)	0.57
Autoimmune disease	4 (2.0%)	7 (3.5%)	0.36
Endocrine disorder	10 (5.0%)	6 (3.0%)	0.30
Vital sign on admission			
Body temperature (°C)	36.8±1.2	36.7±1.2	0.38
Heart rate (/min)	94.5±22.8	91.5±24.4	0.22
Mean arterial pressure (mmHg)	100.1±27.2	97.0±24.0	0.24
Respiratory rate (/min)	22.2±12.6	20.5±8.7	0.18
Laboratory findings on admission			
P/F ratio	289.0±172.7	275.9±132.5	0.72
White blood cell counts (/μl)	11836.9±9571.3	10563.7±6535.5	0.12
Hematocrit (%)	37.1±9.2	37.1±7.8	0.94
Platelet (x10^4/μL)	19.4±8.3	20.0±9.1	0.49
Bilirubin (mg/dL)	1.0±0.8	1.1±1.7	0.61
Potassium (mEq/L)	4.17±0.8	4.1±0.7	0.36

APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; PMX-DHP: direct hemoperfusion with polymyxin B immobilized fiber.
†Severity and renal failure were higher in the PCLEN group than in the TLEN group. Other basic diseases were not found to be significantly different.
**p*-values of <0.05 were inferred as significant

Table 2. Outcomes. For the enteral nutrition failure rate, PCLEN was associated with significantly better results†

Regimen	Pectin-containing liquid EN (n=199)	Traditional liquid EN (n=199)	*p* value
EN failure	21/199 (10.6%)	35/199 (17.6%)	0.043*
30 days survival	79.9%	78.9%	0.80
Length of ICU stay	9.3±4.2	10.5±5.1	0.14
Length of hospital stay	26.2±23.6	31.6±25.0	0.096
GRV 2h (mL)	10.0±31.4	13.3±28.1	0.52
GRV 24h (mL)	7.9±24.3	25.1±63.0	0.017*
Vomiting	6/199 (3.0%)	7/199 (3.5%)	0.78
Diarrhea	56/199 (28.1%)	76/199 (38.2%)	0.033*
Nosocomial pneumonia (including VAP)	9/199 (4.5%)	19/199 (9.6%)	0.048*
Total EN amounts per day on 7th day (mL)	1289.6±909.1	1107.8±979.0	0.071
Total EN calories per day on 7th day (kcal)	1031.7.0±727.3	1107.8±979.0	0.41

EN: enteral nutrition; GRV: gastric residual volume; VAP: ventilator associated pneumonia.
†The 30-day survival rates and length of ICU and hospital stay were not significantly different. The GRV at 24 hr was slightly lower in PCLEN. Although vomiting events were not different, diarrhea events were significantly lower in PCLEN. The nosocomial pneumonia rate including VAP was also lower in PCLEN.
**p*-values of <0.05 were inferred as significant

diarrhea event rate was lowest for PCLEN without a gas tric acid inhibitor, suggesting that gastric acid pH is important for diarrhea inhibition of PCLEN. Conceptual Diagram is showed in Figure 3.

Diarrhea is an important problem occurring during critical care.[18] The diarrhea incidence rate has been reported as 15–50% in critically ill patients, differing according to the definition of diarrhea.[19-21] Critical care physicians often struggle with its management. Various factors cause diarrhea in critically ill patients, one of which is enteral nutrition.[18] Although no cause-and-effect link has been clarified for any mechanism, long-term enteral nutrition, high-osmolality, low-fiber formula, bolus feeding, overly rapid increase to the target, and postpyloric enteral nutrition have been regarded as exacerbating the risk of diarrhea.[22,23] Diarrhea can be a reason for the discontinuation

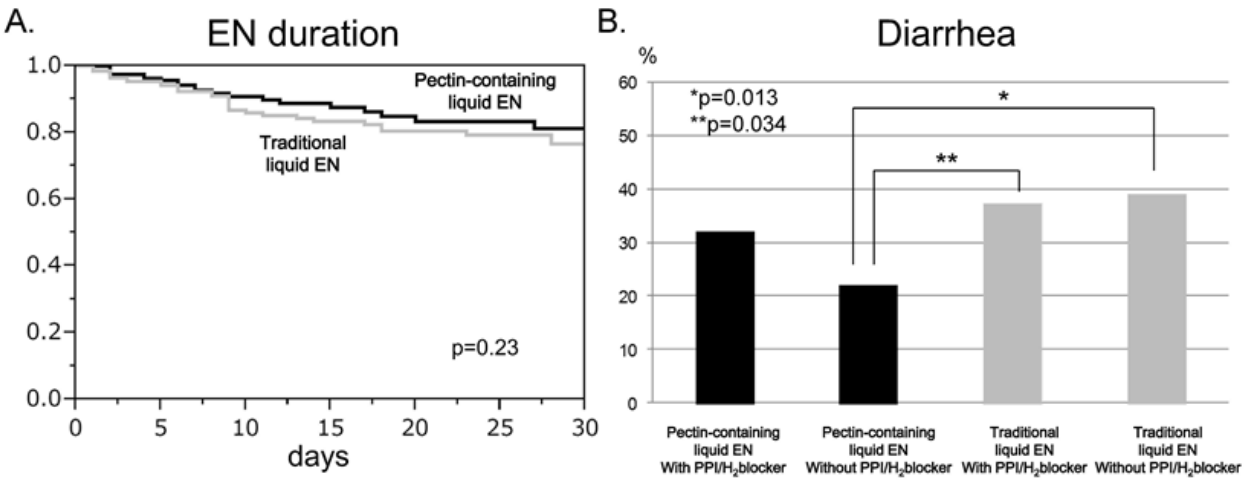

Figure 2. EN duration and Diarrhea incidence with and without PPI/H_2blocker. A: EN duration for PCLEN (black line) and that for TLEN (gray line) are shown with Kaplan–Meier curves. Durations in the groups were not significantly different. B: Diarrhea incidence rates for PCLEN (black box) or TLEN (gray box) with and without PPI/H_2blocker. The diarrhea rate for PCLEN without PPI/H_2blocker was significantly lower than for TLEN. That for PCLEN with PPI/H_2blocker was not significantly lower than for TLEN. No significant difference was found between those for TLEN with and without PPI/H_2blocker. EN: enteral nutrition; PCLEN: pectin-containing liquid enteral nutrition; TLEN: traditional liquid enteral nutrition; PPI: proton pump inhibitor; PPI: proton pump inhibitor.
**p*-values of <0.05 were inferred as significant

Table 3. Subgroup analysis with or without PPI/H_2-blocker[†]

Regimen	Pectin-containing liquid EN with PPI/H_2-blocker (n=122)	Pectin-containing liquid EN without PPI/H_2 blocker (n=77)	Traditional liquid EN (n=199)	*p* value
EN failure	13/122 (10.7%)	8/77 (10.4%)	35/199 (17.6%)	0.13
30 days survival	80.3%	79.2%	78.9%	0.95
GRV 2h (mL)	12.4±36.4	3.7±8.7	13.3±28.1	0.35
GRV 24h (mL)	9.6±28.0	3.4±8.3	25.1±63.0	0.046*
Vomiting	4/122 (3.3%)	2/77 (2.6%)	7/199 (3.5%)	0.93
Diarrhea	39/122 (32.0%)	17/77 (22.1%)	76/199 (38.2%)	0.032*
Nosocomial pneumonia (including VAP)	5/122 (4.1%)	4/77 (5.2%)	19/199 (9.6%)	0.13

EN: enteral nutrition; PPI: proton pump inhibitor; GRV: gastric residual volume; VAP: ventilator associated pneumonia.
[†]The incidence of enteral nutrition failure was not different for PCLEN between groups of patients with and without PPI/H2 blocker. Incidences for both groups were significantly lower than for TLEN. The groups' survival rates were not significantly different. GRV at 24 hr was slightly lower for PCLEN with/without PPI/H2 blocker than for TLEN. Vomiting events and the nosocomial pneumonia rate were not different. Diarrhea was significantly lowest in PCLEN without PPI/H2 blocker.
**p*-values of <0.05 were inferred as significant

of enteral feeding in critical care. Physicians should often consider strategies to choose a variety of LEN that supports control or prevention of diarrhea. Results of the present study are important: PCLEN can decrease diarrhea and enteral nutrition failure, suggesting that PCLEN can be beneficial for critical care medicine.

A number of studies have been conducted to examine whether solidification of LEN can inhibit difficulties related to enteral feeding, such as vomiting and diarrhea. Semi-solid LEN, which is already a semi-solid configuration before administration, reportedly inhibits gastroesophageal reflux.[7] One report described that gastroesophageal reflux was decreased in clinical PEG patients.[6] Another study of clinical PEG patients showed that nosocomial pneumonia was decreased.[8] However, one report described that gastroesophageal reflux was not changed by semi-solid LEN.[24] Therefore, the efficacy of semi-solid LEN has remained controversial. Moreover, although solidification of LEN theoretically inhibits diarrhea, no study has examined semi-solid LEN for diarrhea. One case report described the possibility of semi-solid LEN to inhibit diarrhea.[25]

Pectin, which is contained in PCLEN used for the present study, is expected to be transformed to a solid by gastric acid pH in the stomach and to present the benefit of solidification. Because its solidification is stronger than that of semi-solid LEN, it can prevent LEN from inflowing rapidly into the duodenum and intestine.[9-11] It is expected to inhibit diarrhea. Diarrhea was least frequent with PCLEN in this study when no gastric acid inhibitor was used, allowing pectin to contribute to diarrhea inhibition. PCLEN is liquid in the gastric tube, presenting little risk of tube occlusion.

In recent critical care medical treatments, gastric acid inhibitors are often given to patients, possibly decreasing the solidification of PCLEN. However, PCLEN had a higher enteral nutrition success rate than TLEN in this study, irrespective of the presence of gastric acid inhibitors. These results were regarded as attributable to pectin solidification under gastric acid inhibitors and by other

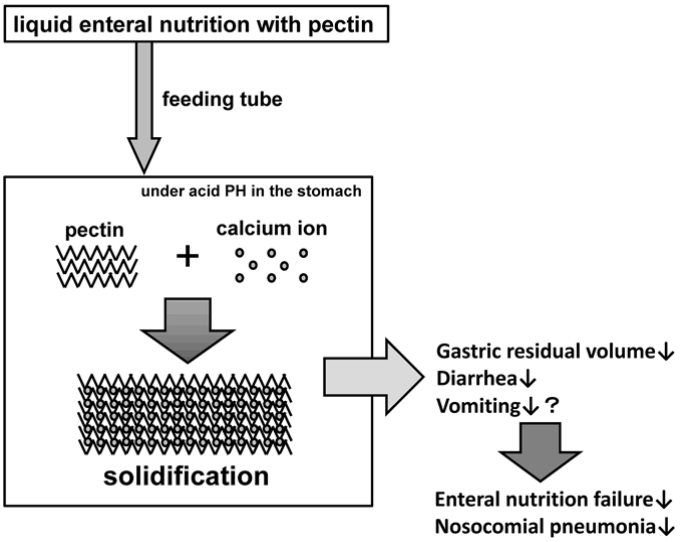

Figure 3. Conceptual diagram. Liquid enteral nutrition with pectin can be given safely through feeding tube. Pectin changes to a solid by forming a bridged structure with calcium ion under acid PH in the stomach. Effective solidification would be associated with decreased gastric residual volume, diarrhea and vomiting (?), and furthermore associated with decreased enteral nutrition failure and nosocomial pneumonia

characteristics of the PCLEN that was used, other than pectin. By the former reason, the degree to which gastric pH is shifted by gastric acid inhibitors depends strongly on the types and doses of PPI or H_2 blockers that were given. When a large dose of PPI is given, pH is increased considerably.[14,15] However, a typical dose of PPI/H_2 blockers often does not achieve pH >5; alternatively, no condition of pH >5 exists.[13] For the latter reason, differences contributing to results obtained between TLEN and PCLEN used for this study are the type of protein and slight difference of concentration, other than pectin: TLEN contained milk protein; PCLEN contained soy protein and collagen peptide. Although both milk and soy can cause diarrhea as one symptom of food allergy,[26] the prevalence and new-onset rates of these food allergies are low in adults. More than 90% of Asian and North American people reportedly have lactose intolerance, which differs among races.[27] Milk does not always cause diarrhea in people with lactose intolerance. However, a meal containing lactose can cause diarrhea under some conditions.[28] Soy protein or collagen peptide might be better than milk protein for critical care in such countries. In this study, PCLEN was 0.8 kcal/mL, 360 mOsm/L; TLEN was 1.0 kcal/mL, 420 mOsm/L. These differences of concentration and osmotic pressure might affect the results.

This study includes some limitations. Although propensity score matching and historical control were conducted, the study might include some biases because it was a retrospective study. One possible source of bias is the study period during which each LEN was given. As described above, some differences between PCLEN and TLEN existed other than pectin. It was difficult to analyze the effects of respective factors. Moreover, the definition of diarrhea is difficult, as discussed in recent reports.[18] Certification of diarrhea was difficult in this study because of its retrospective nature. In subgroup analysis, patients of the gastric acid inhibitors subgroup might have presented more severity than those without inhibitors. Their basic characteristics might have been different.

Conclusions

Compared to TLEN, PCLEN was associated with lower incidence of diarrhea and nosocomial pneumonia. PCLEN was also associated with the enteral nutrition success irrespective of the patient use of gastric acid inhibitors. Diarrhea was inhibited most for patients with PCLEN but without gastric acid inhibitors. For critical care, PCLEN can be used effectively for enteral nutrition via a nasogastric tube.

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AUTHOR DISCLOSURES

The authors state that they have no conflict of interest related to this paper or the study it describes.

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