Original Article

Pancreatic enzyme replacement therapy (PERT) in children with persistent diarrhea: avoidance of elemental diet need, accessibility and costs

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Background and Objectives: Persistent diarrhea has been proven to cause pancreatic exocrine insufficiency, due to decreased stimulation to the pancreas caused by prolonged mucosal injury. Pancreatic enzyme replacement therapy (PERT) given in conjunction to regular treatment is thought to be beneficial in replacing this pancreatic enzyme deficiency, avoiding the need of elemental diet. This study aims to evaluate the benefit of PERT in children with persistent diarrhea. **Methods and Study Design:** This is a randomized, two double-blind parallel group, placebo-controlled clinical trial to evaluate the effects of pancreatic enzyme supplementation in persistent diarrhea. Children age 6-60 months were recruited from pediatric inpatient and outpatient units of five hospitals in Jakarta. Subjects was randomly assigned to either pancreatic enzyme 8371 USP unit of lipase or placebo, 3 times daily for 1 month, as an adjunctive therapy to standard treatment. Subjects were then reevaluated at 2 weeks and 4 weeks interval after administration of enzyme or placebo. Variables observed were length of diarrhea after the start of intervention, change in serum prealbumin, and change in FE-1 between week 0 and week 4. **Results:** Pancreatic enzyme supplementation shortens the length of diarrhea by 7 days in the intervention group compared to placebo (p=0.019). Serum prealbumin and FE-1 shows trend that favors the intervention group, although not statistically significant (p>0.05). **Conclusion:** PERT is clinically effective in reducing the length of diarrhea, thus minimizing the need, accessibility and costs of an elemental diet.

Key Words: persistent diarrhea, pancreatic exocrine insufficiency, pancreatic enzyme supplementation, children, length of diarrhea

INTRODUCTION

Persistent diarrhea is a type of diarrhea caused by infection which lasts for 14 days or longer. It is a serious health problem, and although the prevalence is only 5-20% of all diarrhea incidence, it is the cause of 36-45% of deaths due to diarrhea.[1-3] Persistent diarrhea has been proven to cause pancreatic exocrine insufficiency, due to decreased stimulation to the pancreas caused by prolonged mucosal injury, as proved by a study by Widodo et al.[4,5] Decreased pancreatic enzyme production from the acinar cells as the main component of pancreatic exocrine gland can cause serious consequences through ineffective absorption of nutrients, showing as persistent diarrhea, malnutrition and growth and development problems.[6-8] In persistent diarrhea which persists for 14 days or more, elemental diet is often given to assist with nutrients absorption, while waiting for the healing of the intestine.[9] However, this therapy is relatively more costly, not readily available in area with limited resources, and its administration requires more skill and knowledge while the

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expert is limited. Administration of PERT is expected to solve this problem much earlier at the stage of food digestion by supplying the enzymes required to digest the food to be easily absorbed by the gut, therefore minimizes the need of elemental diet therapy. The aim of this study is to evaluate the benefit of PERT in children with persistent diarrhea.

PARTICIPANTS AND METHODS

This is a randomized, double-blind, placebo-controlled clinical trial to evaluate the effectiveness of pancreatic enzyme supplementation in children with persistent diarrhea in conjunction with regular treatment given by the attending physician. This study was conducted in pediatric inpatient and outpatient units of Harapan Kita Women and Children Hospital, Cipto Mangunkusumo Hospital, Budhi Asih Hospital, Persahabatan Hospital, and Fatmawati Hospital from January 2015 to July 2016. Children 6-60 months of age with persistent diarrhea were recruited consecutively and randomized into placebo and treatment groups. Patients with pancreas exocrine function problem known since birth, has inflammatory bowel disease (IBD) or other types of chronic diarrhea which has been proved or consume antacids, antidiarrheals, antiparasitics, antibiotics, or laxative agents within 2 days prior to sample collection were excluded.

After obtaining informed consent from the parents, baseline data was collected through anamnesis and physical examinations at the beginning of the study (week 0) before the enzyme intervention, the second week after the start of intervention and the fourth week or at the end of intervention. Parents/guardians were educated regarding procedure for collection, storage, and transportation of faecal sample and collecting kits were supplied. Fecal sample were collected for stool analysis, steatocrit test, and fecal elastase-1 (FE-1) using ELISA method at weeks 0 and 4, serum sample were collected for serum prealbumin at weeks 0 and 4.

Subjects were randomized to pancreatic enzyme supplementation for 1 month with a lipase dose of 8371 USP unit 3 times daily or placebo with similar packaging. Both investigator and research subjects did not know the types of intervention administered. The randomization list was kept by the pharmacy. Outcome variables were duration of diarrhea, serum prealbumin, and FE-1.

Data collected were analyzed using SPSS version 11.5. Data were analyzed using independent t-test for normally distributed data and the Mann-Whitney test for data with abnormal distribution. Analysis was performed on the basis of intention-to-treat and per study performance allowing for drop-out. The study was granted ethical clearance from the Ethics Committee of the Faculty of Medicine Universitas Indonesia-Dr. Cipto Mangunkusumo Hospital.

RESULTS

Thirty-one children with persistent diarrhea were recruited in this study. After 4 weeks of follow up, 4 subjects (3 in placebo group, 1 in intervention group) dropped out of

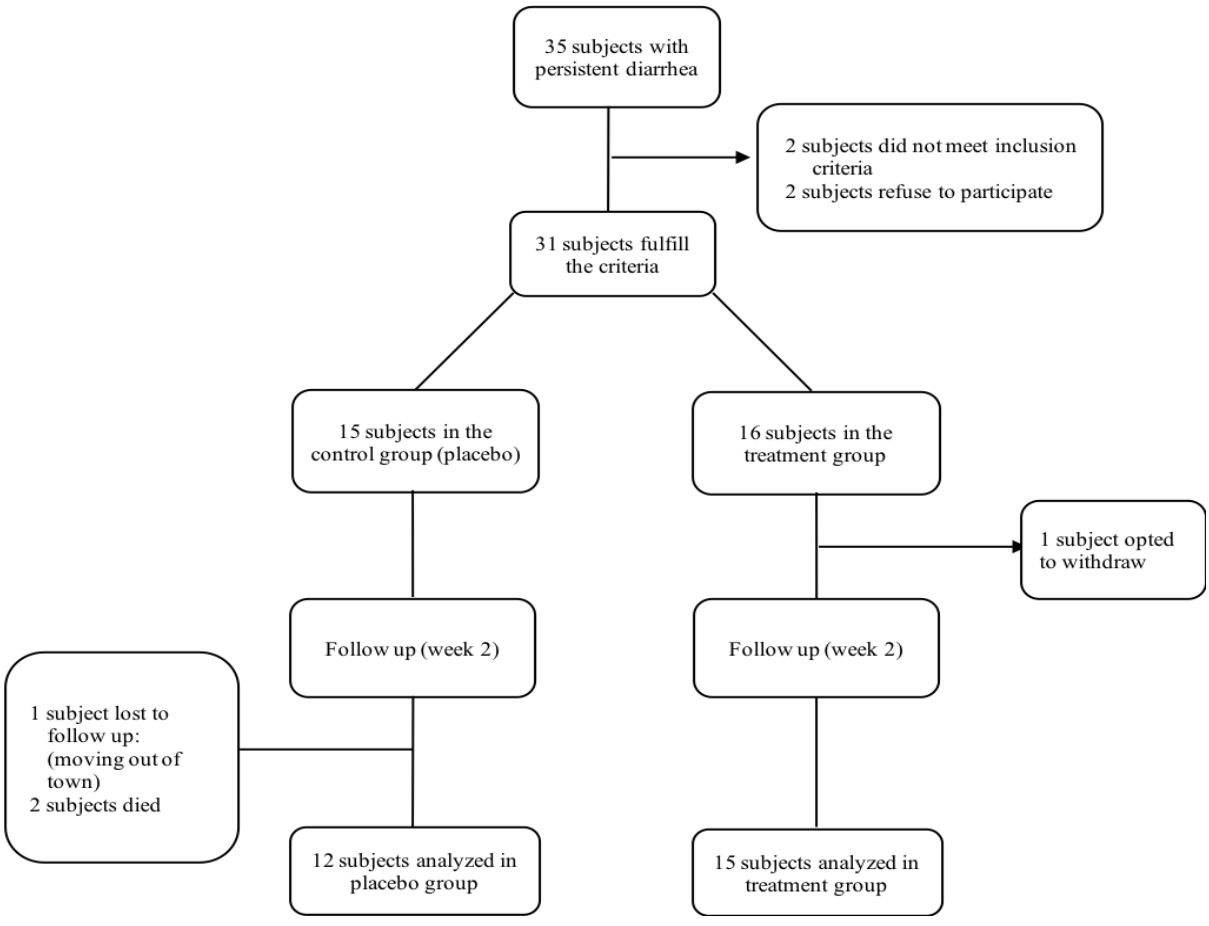

Figure 1. Subject recruitment for persistent diarrhea clinical trial.

Table 1. Baseline characteristics of persistent diarrhea subjects (n=27)

	Placebo (n=12)	Treatment (n=15)
Demographic		
Age (months)	23.1 (10.2)† (min. 11; max. 43)	23.2 (11.2)† (min. 9; max. 51)
Gender		
Male, n	7	11
Female, n	5	4
Exclusive breastfeeding, n	4	4
Socioeconomic status, n		
<Minimum regional salary	4	6
>Minimum regional salary	8	9
Birth weight (gram)	2974 (525)†	2841 (605)†
Anthropometric status		
Weight (kg)	10.3 (2.79)†	9.6 (7.3-17.9)‡
Height (cm)	80.8 (8.51)†	82 (74-104)‡
Head circumference (cm)	46.1 (3.82)†	45.2 (2.53)†
Arm circumference (cm)	15.1 (2.64)†	14.7 (1.46)†
Nutritional status, n		
Moderate-severe malnutrition	3	5
Normal	9	10
Energy intake (kcal)	887 (246)†	746 (257)†
Carbohydrate intake (gram)	123 (38.5)†	105 (39.1)†
Protein intake (gram)	28.4 (9.99)†	24.7 (11.9)†
Fat intake (gram)	30.1 (10.5)†	25 (9.16)†
Clinical symptoms		
Frequency of bowel movements (times)	5 (3-10)‡	6.27 (2.84)†
Loose consistency, n	12	14
Abnormal colour, n	2	4
Mucous, n	12	11
Acidic/foul smell, n	10	12
Abdominal pain, n	3	8
Bloating, n	1	1
Laboratory		
Fecal analysis		
Lactose malabsorption +, n	2	6
Fat malabsorption +, n	3	6
Carbohydrate maldigestion, n	2	4
Protein maldigestion, n	3	7
Leukocytes >5, n	4	2
Erythrocytes >3, n	2	3
Steatocrit (%)	0 (0-57)‡	5.3 (0-87)‡
Prealbumin (mg/dL)	13.4 (3.8)†	13.5 (5.89)†
Fecal elastase-1 (µg/g)	730 (10-1029)‡	696 (1-1503)†
Therapy other than intervention		
Probiotic therapy, n	8	8
Zinc therapy, n	10	9
Antibiotic therapy, n	9	11

†Mean (SD); ‡Median (min-max).
All data shown exhibited no differences between placebo and treatment groups at baseline (ns $p>0.05$).

the study, leaving 12 subjects in placebo group and 15 subjects in treatment group for analysis (Figure 1). The characteristics of persistent diarrhea subjects in placebo and treatment group were not different ($p>0.05$) according to medical history, food intake, anthropometric data, clinical condition, or laboratory results for any measured variable (Table 1).

Tables 2, 3 and 4 show the comparison between various clinical and laboratory variables in both treatment and placebo group at baseline (week 0), week 2 and endpoint (week 4). Overall, we observe a trend of improvement of subjects' clinical conditions in nearly every variables studied. Table 2 shows the comparison of subjects clinical conditions between baseline and endpoint in both placebo and treatment group. The differences of anthropometric data such as weight, height, head circumference and arm circumference between the two groups are found to be statistically insignificant with $p>0.05$. The same result is observed in frequency of bowel movement variable.

Table 3 shows that the changes in clinical variables between placebo and treatment group are subtle, except for abdominal pain and length of diarrhea. In treatment group, 8 subjects no longer experienced abdominal pain after treatment, compared to 3 subjects in placebo group. The difference in length of diarrhea between placebo group and treatment group is around 7 days ($p=0.019$). Figure 2

Table 2. Effects of enzyme supplementation on placebo and treatment group based on anthropometric and clinical characteristics (n=27)

	Placebo (n=12)	Treatment (n=15)	*p* value
Weight (kg)			
Week 0	10.3 (2.79)†	9.6 (7.3–17.9)‡	0.323
Week 2	10.5 (2.98)†	9.6 (7.4–16.5)‡	0.256
Week 4	10.9 (3.17)†	10 (7.9–17)‡	0.139
Δ Week 0-2	-0.15 (0.53)†	-0.12 (0.6)†	0.894
Δ Week 2-4	-0.42 (0.6)†	-0.4 (-1.1–2)‡	0.648
Δ Week 0-4	-0.66 (-1.05–0.5)‡	-0.22 (0.69)†	0.139
Height (cm)			
Week 0	80.8 (8.51)†	82 (74–104)‡	0.792
Week 2	81.5 (8.39)†	82 (75–104)‡	0.755
Week 4	82 (8.54)†	82 (75–104)‡	0.755
Δ Week 0-2	-0.5 (-2–0)‡	0 (-2–0)‡	0.200
Δ Week 2-4	0 (-3–0)‡	0 (-2–0)‡	0.719
Δ Week 0-4	-0.75 (-5–0)‡	-1 (-2–0)‡	0.829
Head circumference (cm)			
Week 0	46.1 (3.82)†	45.2 (2.53)†	0.462
Week 2	46.2 (3.74)†	45.6 (2.44)†	0.595
Week 4	46.5 (3.6)†	45.7 (2.47)†	0.519
Δ Week 0-2	0 (-1–0)‡	0 (-1–0)‡	0.167
Δ Week 2-4	0 (-1–0.5)‡	0 (-1–0)‡	0.719
Δ Week 0-4	0 (-2–0)‡	-0.5 (-2–0)‡	0.486
Arm circumference (cm)			
Week 0	15.1 (2.64)†	14.7 (1.46)†	0.665
Week 2	16 (9–19)‡	14.9 (13–18)‡	0.200
Week 4	16 (9.5–19)‡	15 (13–20)‡	0.277
Δ Week 0-2	0 (-1–0)‡	0 (-1–0)‡	0.614
Δ Week 2-4	0 (-1–0)‡	0 (-2–1)‡	0.427
Δ Week 0-4	0 (-1–0)‡	-0.5 (0.78)†	0.399
Frequency of bowel movements (times)			
Week 0	5 (3–10)‡	6.3 (2.84)†	0.719
Week 2	3 (2–5)‡	2.47 (0.99)†	0.648
Week 4	1 (1–7)‡	2 (1–6)‡	0.581
Δ Week 0-2	3.17 (2.82)†	3.8 (3.34)†	0.605
Δ Week 2-4	1 (-4–2)‡	0.27 (1.67)†	0.427
Δ Week 0-4	3.75 (3.77)†	4.07 (2.79)†	0.804

†Mean (SD); ‡Median (min-max).

Table 3. Effects of enzyme supplementation on placebo and treatment group based on clinical characteristics (n=27)

Clinical symptoms	Placebo		Treatment	
	Baseline (n=12)	Endpoint (n=12)	Baseline (n=15)	Endpoint (n=15)
Duration of diarrhea (days)	10 (5-31)‡		3 (1-16)‡	
Loose consistency, n	12	6	14	6
Abnormal colour, n	3	0	4	0
Mucous +, n	12	4	11	3
Acidic/foul smell, n	10	0	12	3
Abdominal pain +, n	3	0	8	0
Malnutrition, n	3	3	5	3

†Mean (SD); ‡Median (min-max).

shows day-to-the reduction in length of diarrhea after PERT treatment. The length of diarrhea is shorter in the treatment group compared to placebo group. The relative risk (RR) value is 0.47 and the number needed to treat (NNT) is 2 children at the cut-off of 3 days for the duration of diarrhea.

Table 4 compares the characteristic of subjects based on the laboratory examination at baseline and endpoint in the placebo and treatment group. In placebo group, the median of steatocrit is increased from 0% to 2.15%, whereas in treatment group the median of steatocrit is decreased from 5.3% to 0%. Mean serum prealbumin increased by 0.60 mg/dL in treatment group and decreased by 0.47 mg/dL in placebo group. FE-1 in treatment group increased by 71.4 µg/g.

Table 5 shows the information regarding delta/differences between placebo and treatment group laboratory results. In placebo group, the mean of differences of prealbumin level between baseline and endpoint is -0.47 (2.92) mg/dL, while in treatment group the mean of differences is 0.59 (6.09) mg/dL. Overall, there is no significant difference observed between numerical varia-

Table 4. Effects of enzyme supplementation on placebo and treatment group based on laboratory examination results (n=27)

Laboratory	Placebo		Treatment	
	Baseline (n=12)	Endpoint (n=12)	Baseline (n=15)	Endpoint (n=15)
Fecal analysis				
Lactose malabsorption, n	2	0	6	1
Fat malabsorption, n	3	1	6	1
Carbohydrate maldigestion, n	2	4	4	7
Protein maldigestion, n	3	2	7	5
Leukocytes >5, n	4	2	2	1
Erythrocytes >3, n	2	0	3	0
Steatocrit (%)	0 (0-57)‡	2.15 (0-15)‡	5.3 (0-87)‡	0 (0-25)‡
Prealbumin (mg/dL)	13.42 (3.8)†	13 (3.88)†	13.5 (5.89)†	14.1 (4.45) †
Fecal elastase-1 (µg/g)	730 (10-1029)‡	698 (351.9)†	696 (1-1503)†	767 (540.9)†

†Mean (SD); ‡Median (min-max).

Table 5. Comparison of *baseline-endpoint* value on laboratory examination results (n=27)

	Δ (Endpoint-Baseline)		*p* value
	Placebo (n=12)	Treatment (n=15)	
pH	0.125 (0.74)†	0.33 (0.7)†	0.461
Prealbumin (mg/dL)	-0.47 (2.92)†	0.59 (6.09)†	0.559
Steatocrit (%)	0 (-45.7-12.5)‡	0 (-77-21.4)‡	0.905
Fecal elastase-1 (µg/g)	112 (371)†	73.3 (510)†	0.826

†Mean (SD); ‡Median (min-max).

bels shown in table 7 (p>0.05).

DISCUSSION

Persistent diarrhea has been proven to suffer from exocrine pancreatic insufficiency.[5] Thus administration of PERT alongside regular treatment is thought to contribute positively in this condition. PERT is expected to solve the problem earlier by replacing the pancreas enzyme function in digesting the food into molecules easily absorbed by the intestine.

A variation in the subject compliance towards the treatment given is observed in this study. Most of the subjects have a good compliance towards the treatment given. However, some of the subject experience difficulty in meeting the therapy administration instruction (enzyme or placebo). Nevertheless, most of the subjects still consume more than 50% of enzyme or placebo given.

A number of variables are compared between baseline and endpoint namely weight, height, head circumference, arm circumference, frequency of bowel movement, consistency of faeces, colour of faeces, the presence of mucous, the presence of abnormal smell, the presence of abdominal pain, nutritional status, the result of fecal analysis, steatocrit, serum prealbumin and FE-1. Overall, improvement of clinical conditions were observed in both groups, however it is statistically insignificant (p>0.05).

Duration of diarrhea is the most clinically significant variables in evaluating improvement of diarrhea. In this study, the treatment group was found to have a shorter duration of diarrhea (3 days) compared to placebo group (10 days) after the administration of enzyme. This difference of 7 days is very important clinically for a child with persistent diarrhea. With the cessation of diarrhea, the risk associated with mortality caused by diarrhea such as dehydration and electrolyte imbalance will also be reduced significantly therefore reducing mortality. Similarly, a shorter duration of diarrhea will have a positive impact on the other aspect such as the uncomfortable sensation caused by frequently visiting the restroom, perianal erythema causing pain and anxiety in children and babies, the absence of children from kindergarten or school, and the absence of parents from workplace. The relative risk value of 0.47 means that without PERT intervention, the risk of persistent diarrhea continuing more than 3 days will increase nearly two-fold. For every 2 children with persistent diarrhea treated with enzyme intervention, there will be 1 children who suffer less duration of diarrhea (<3 days).

An increasing steatocrit level is observed in placebo group and decreasing steatocrit level is observed in treatment group. This difference is not statistically significant (p>0.05), however clinically we can see that the level of steatocrit is increased in placebo group. In treatment group, the decreasing level of steatocrit shows an improvement in condition. This fact is supported by another data from this study that is FE-1. The increase in median of FE-1 is far greater in treatment group (200 µg/g) than placebo (20 µg/g). The study conducted by Girish et al[10] also stated that FE-1 is inversely correlated with steatocrit.

FE-1 test is actually a one-time examination.[11,12] However, one study[13] found quite a meaningful variation in FE-1 between one stool passage (mean coefficient variation 22%) and for day-to-day variation (mean coefficient variation 26%), suggesting that it might be beneficial to test FE-1 on more than one stool sample taken at different time for each patient. FE-1 can also be affected by conditions in sample collection such as food consumed, types of food, and children's food pattern. These things can cause a really wide range FE-1 results.

Prealbumin (transthyretin) is the earliest laboratory in-

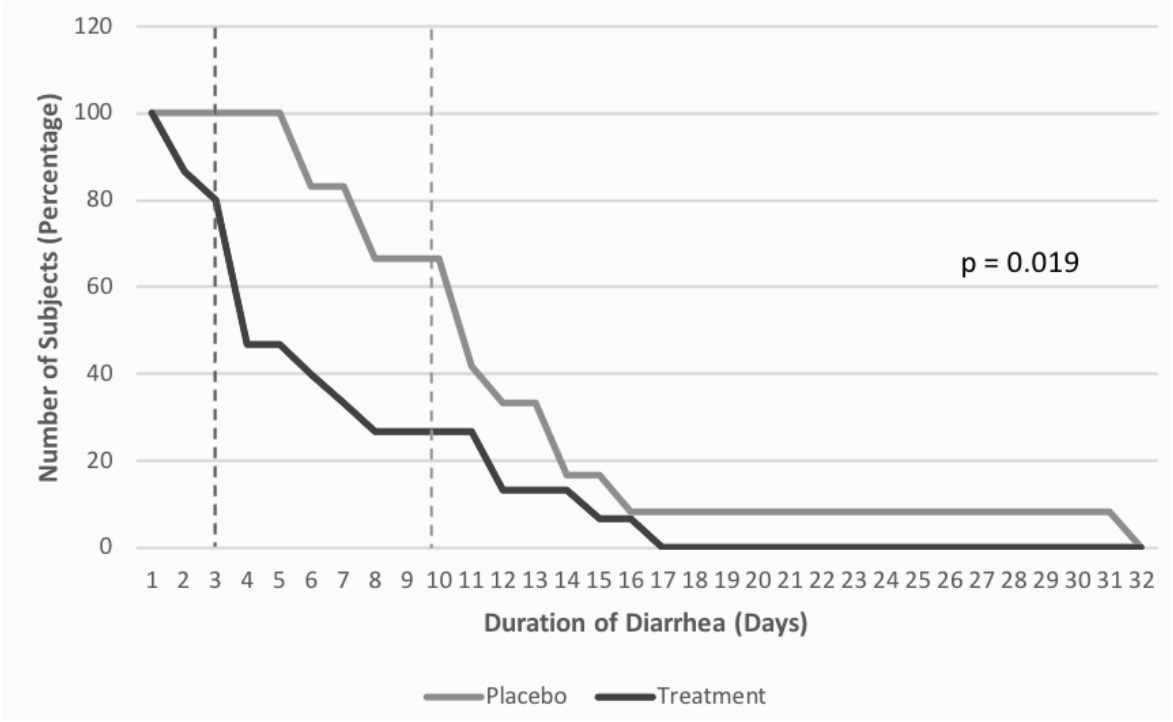

Figure 2. Comparison of duration of diarrhea between placebo and treatment group.

dicator available to evaluate the nutritional status because of its half life of 24–48 hours, causing prealbumin to be able to represent a shorter term nutritional intake. In placebo group, a decreasing prealbumin value was seen, whereas in treatment group, an increasing prealbumin value was seen. Prealbumin value itself can be an indicator of short term nutritional improvement therefore the increasing prealbumin value seen in treatment group compared to the decreasing prealbumin value seen in placebo group indicates a clinical improvement in subjects who receive pancreatic enzyme supplementation. The insignificant difference observed may be caused by administration of steroid in 3 subjects in placebo group. Steroid is known to increase prealbumin level and therefore causing mean level of prealbumin in placebo group to be greater than reality.

The increasing level of prealbumin observed in treatment group shows improvement of the intestinal villi which cause better nutritional absorption. The result observed in prealbumin variables has not been observed yet in FE-1 level, which possibly due to the fact that the turnover rate of pancreas acinar cells are about 4 months[14] with the number of acinar cells growing by 0.02–0.07% per day. The relatively slow pancreas acinar cells regeneration cause the pancreatic enzyme supplementation administered for 1 months to not being able to give enough time for injured pancreas cells to regenerate, and so a significant FE-1 difference has not yet been found. The pancreatic enzyme intervention in this study was given for 1 months considering the facts that prealbumin value will be significantly different in 2 weeks. However, considering the results of these research and also the turnover rate of pancreas cells, the intervention might be given for a longer period of time to observe a significant changes in FE-1 level. Previous study[15,16] has also stated that the dose of enzyme intervention in children can be further increased to a maximum dose of 10,000 IU/kg for each meal, which is equal to 10,000 USP unit/kg/meal.

In children with diarrhea, especially persistent diarrhea, parents are often afraid to give certain types of food such as meat. Children tend to be given soft, bland foods like porridge. The change of food pattern to low protein and low fat may become one of the factors affecting production of FE-1 and may also influence the result of steatocrit test. In fact, Aulia et al[17] proved that duration of diarrhea in protein-losing enteropathy was shorter with supplementation of high-protein diet.

During the study period, 3 subjects experience adverse event in form of upper respiratory tract infection and mild measles without complication. The number of measles at that time is indeed in an increasing trend. Three subjects experience serious adverse event respectively, one admission to hospital because of febrile seizure, one subject with cerebral palsy and global developmental delay who died at home because of aspiration pneumonia, and one patient with underlying malignancy who suffered from sepsis with multiorgan failure. All of the adverse event and serious adverse event have been analyzed dan was judged to be unrelated to the intervention given. All events have been reported to the ethics committee.

This study provides new information regarding the effect of PERT supplementation, which can greatly contribute to the treatment of children with persistent diarrhea in terms of providing earlier recovery and avoiding the unnecessary needs and costs of elemental diet.

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AUTHOR DISCLOSURES

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