Original Article

Efficacy of dioctahedral smectite in infants with acute diarrhea: a double blind randomized controlled trial

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Abstract

Background Acute diarrhea is a sudden diarrhea which lasts less than seven days on babies and children. The standard treatment by WHO in managing acute diarrhea is still not satisfactory for parents whose infants and children suffering from the disease. Dioctahedral smectite is expected to decrease the volume, frequency, and duration of diarrhea.

Objective To assess the clinical effects of dioctahedral smectite in infants with acute diarrhea.

Methods A double-blind, randomized clinical controlled trial was performed on six to 12 months-old infants who were hospitalized in Sanglah Hospital, Denpasar due to acute diarrhea. The subjects were divided into two groups. The treatment group was given standard management with adjuvant dioctahedral smectite while and control group was given standard management with placebo.

Results From 68 infants enrolled in this study, the mean duration of diarrhea was significantly shorter in treatment group compared to placebo group [39.03 hours (SD 2.03) vs 70.58 hours (SD 3.78), mean difference 31.6 (95% CI 22.90 to 40.19), P=0.001]. The RRR was 50%, and ARR was 29%. Kaplan-Meier survival analysis showed that duration of acute diarrhea was shorter in treatment group [36 hours (SD 1.7) versus 72 hours (SD 4.18), mean difference 36.0 (95% CI 21.81 to 50.19), log rank test, P<0.0001]. In multivariate Cox regression analysis, it was found that dioctahedral smectite influenced the duration of diarrhea in infants with acute diarrhea [OR 4.403 (95% CI 2.39 to 8.12), P<0.0001].

Conclusion Dioctahedral smectite can shorten the duration of acute diarrhea. **[Paediatr Indones. 2009;49:48-53]**.

Keywords: acute diarrhea, dioctahedral smectite, diarrhea duration

Diarrhea is still a children health problem in Indonesia where 60-80% who suffers from diarrhea are under five years old.[1] In 2003, the incidence of diarrhea in Bali was 4.5%. From list of consultation to primary health care, outpatient clinic and hospitalized patients, diarrhea is always on top three diseases in their monthly census.[2] In pediatric outpatient clinic, Sanglah Hospital, there were 1423 patients with diarrhea in 2004.[3]

In 1990, WHO published a rational medication in management of acute diarrhea for infants and children.[4] Oral rehydration effort and early solid food intake has a positive impact for recovery of diarrhea. However, parents whose children sufferred from the disease tend to expect for drugs to shorten the period of diarrhea. Therefore, nowadays, numerous researches have been done to study types of drugs which can be given along with oral rehydration effort.[5,6]

Hypersecretion is a problem in diarrhea. Dioctahedral smectite (DS) as an anti-secretoric has been studied in many countries and most of the results

had stated that DS are safe, effective and efficient. DS has a role in reducing cAMP level and reduce the leakage of fluid and electrolyte, binds with potential agents that can cause diarrhea, reduces membrane permeability, increases amount of mucous area, and decreases the recovery time of intestine injury in chronic diarrhea.[7] DS has more benefits in decreasing secretion, increasing absorption, and normalizing intestine peristaltic. Based on this mechanism, we were interested in researching cheap, affordable, effective, and safe medication which can be added to standard medication that might accelerate the recovery time of diarrhea.

Methods

A double blind randomized clinical trial was conducted on Gastroenterology Division, Child Health Department of Udayana University, from January to July 2007. Eligible patients were chosen using consecutive sampling. The study had been approved by the Ethical Clearance from the Ethics Committee of Medical School, Sanglah Hospital, Denpasar, and informed consent was obtained from parents.

The inclusion criteria were patients with mild to moderate dehydration due to acute diarrhea, aged 6-12 months old, and the duration of diarrhea before hospitalization was two days or less. Infants with complicated diarrhea, diarrhea with complication, and infants whose parents refused to participate in this study were excluded.

Acute diarrhea was defined as defecation frequency for more than three times per day or more than the usual habit accompanied by changes in feces consistency, with or without blood and or mucous, lasting for less than seven days.[4] Recovery time was the time needed until the frequency of defecation was equal to or less than three time per day with normal stool consistency without any complication.[1,4] Diarrhea with complication was defined as diarrhea episode accompanied by direct effect of acute diarrhea such as severe dehydration, metabolic acidosis, seizure, and ileus paralytic.[4,8] Complicated diarrhea was defined as acute diarrhea with severe malnutrition, severe dysentery, respiratory infection, and anemia.[4,8] Dehydration status was assessed

according to the WHO standard,[4] while nutritional status was determined based on Z score of weight for length.[9] Patients who did not take either oral DS or control in the first twelve hours and discharged by request, were considered as drop-out case. Patients who had treatment failure were defined as patients who failed to recover on the fifth day of treatment, or those who had experienced any complication before day five, or had co-infection or adverse events affecting the duration of diarrhea, or patients who passed away.

Questionnaires were used to record the baseline characteristics of clinical and duration of diarrhea in the hospital, frequency of defecation, consistency of feces, complication, and adverse events. Total study subjects were 68 infants, the estimation was based on $\alpha=0.05$, power 80%. They were randomized into two groups; the treatment group who had standard diarrhea therapy with DS, while the control group who received standard diarrhea therapy with placebo. The randomization process was done with 6-block randomization and the codes were kept in closed envelopes. The envelopes were kept at Beaufour Ipsen PT Combiphar and opened after the study was finished.

All subjects were managed according to the standard therapy recommended by WHO for acute diarrhea, with rehydration. All medicines prescribed before admission was discontinued.

All study subjects were followed-up until the subjects recovered. To asses the outcome, we performed evaluation and measurement of dehydration status, frequency of defecation, stool consistency, adverse events, and complications every 12 hours, while evaluation and measurement of body weight, compliance of taking DS and placebo, were done every 24 hours. In this study, drop out and treatment failure rates were accepted if the rate was bellow 20%. Subjects that considered as drop out cases or treatment failures were analyzed within the group and treated afterward. Study procedures are shown in **Figure 1**.

Data were analyzed using computer program. The mean difference of recovery time was examined using student's t test. Additional variables (complications or adverse events on study duration) were analyzed using x^2 test. The primary outcome result was the difference in duration of diarrhea between groups showed by

Kaplan-Meier curve. Differences in duration of diarrhea between two groups were tested using log-rank test. Risk of treatment failure between the two groups was compared with relative risk reduction (RRR) and absolute risk reduction (ARR). We made adjustment of external variables to duration of diarrhea between two groups using cox-regression analysis. P value of <0.05 with 95% confidence interval were considered as statistically significant.

Results

During the study period, there were 144 infants aged 6-12 months old admitted to Sanglah Hospital due to acute diarrhea. Seventy-six infants with acute diarrhea accompanied with other problems or co-infections (three infants had severe malnutrition, six infants had bronchopneumonia, four infants had anemia, 23 infants had acute rhinopharyngitis, 19 infants had acute tonsilo-pharyngitis, one infant had acute otitis media, seven infants had acute bronchiolitis, and eight infants refused to participate in the study). Hence, there were 68 infants who were eligible for this study.

Table 1. Baseline characteristics of infants with acute diarrhea in treatment and control groups.

| Characteristic	Treatment Group (n = 34)	Placebo Group (n = 34)
Age (month), means (SD)	9.9 (1.86)	9.5 (2.21)
Sex, boys	17	13 (38.24)
Ideal body weight (gram), mean (SD)	8780 (1150)	8700 (1350)
Nutritional status		
Good	32 (94.19)	33 (97.18)
Moderate malnutrition	2 (5.97)	1 (2.98)
Diet intake		
Beast feeding	3 (8.84)	4 (11.75)
Formula	2 (5.85)	1 (2.94)
BF + Formula	4 (11.76)	2 (5.86)
BF+Formula+milk porrigde	16 (47)	12 (35.27)
Formula + milk porridge	9 (26.45)	13 (38.28)
Pre-hospital diarrhea (hours), mean (SD)	32.4 (10.45)	39.9 (11.04)
Pre-hospital diarrhea frequency, mean (SD)	6.5 (1.16)	6.7 (1.52)
Antibiotic before admission	8 (23.54)	8 (23.54)
OBW (gram), mean (SD)	9110 (1110)	9070 (1350)

Survival Functions
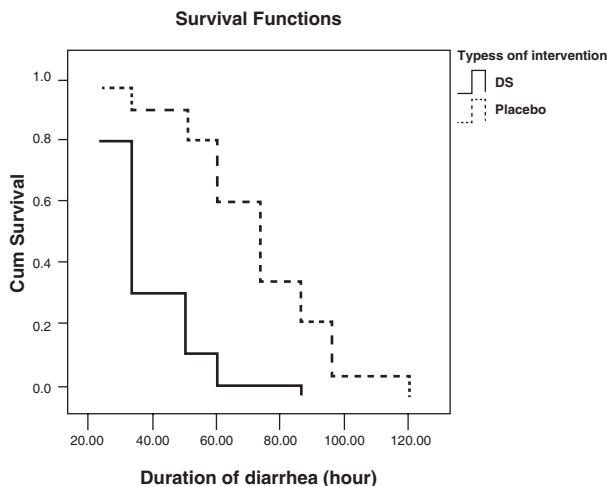
Figure 2. Kaplan – Meier survival curve of duration of diarrhea in the treatment group and control group on day 5 study.

Mean age of infants in treatment group was 9.9 (SD 1.86) months while in the control group was 9.5 (SD 2.21) months. Baseline characteristics of the two groups are shown in **Table 1**.

Reduction in frequency of defecation was significantly occur in the treatment group 39.0 hour (SD 11.62) versus 70.6 hours (SD 22.06), mean difference of 31.5 [(95% CI 22.90 to 40.19), P=0.001]. Recovery of stool consistency was significantly had shorter duration in the treatment group {40.3 hours (SD 12.30) versus 71.47 hours (SD 21.82), mean difference of 31.1 [(95% CI 22.42 to 39.78), P=0.001].

Mean duration of diarrhea as a primary result was significantly shorter in the treatment group compared to that in control group 39.0 hours (SD 2.03) versus 70.6 hours (SD 3.78), mean difference 31.5 [(95% CI 20.11 to 42.99), P=0.001]. Based on Kaplan-Meier analysis, duration of diarrhea was significantly shorter in treatment group compared to that in control group (log rank test, P< 0.0001). Primary outcome is showed on **Figure 2**.

There were two infants who failed in control group due to bronchopneumonia and acute otitis media on day-two and day-three hospitalization and one infant in treatment group was also considered as a drop-out case. The differences of treatment failure between two groups were expressed as RRR of 50% and ARR of 29%.

Table 2. Inter-variables connections that affected acute diarrhea duration in treatment group vs. control group.

Free Variable	B	SE	P	Exp (B)	95% CI for Exp (B)
Age	0.078	0.081	0.335	1.081	0.922 to 1.268
Diet intake	-0.082	0.129	0.523	0.921	0.715 to 1.186
Nutrition status	0.254	0.624	0.683	1.290	0.380 to 4.379
Pre-hospital diarrhea duration	-0.011	0.012	0.356	0.989	0.966 to 1.013
Antibiotics before admission	-0.049	0.181	0.787	0.952	0.667 to 1.359
DS	1.482	0.312	<0.0001	4.403	2.388 to 8.119

In this study, there were no significant difference in the body weight gain between treatment and control groups at the time of admission and discharged from hospital 0.30 (SD 0.13) versus 0.38 (SD 0.19); mean difference was 0.08 (95% CI 0.04 to 0.12), P=0.35.

From multivariate analysis (Cox regression), it was proven that only DS significantly affected the duration of diarrhea [OR 4.403 (95% CI 2.39 to 8.12), P<0.0001] (**Table 2**). In this study, we found no adverse events caused by DS.

Discussion

Several studies in many countries about DS as an adjunctive medication in management of diarrhea showed a significant result in shortening the duration of diarrhea and nursing time in the hospital. A meta-analysis study by Zue-Shenyen *et al* [10] from 21 RCT with 1067 infants reported that DS statistically significant to reduce the length of diarrhea.

Our study revealed that the defecation frequency was significantly decreased in the treatment group 39.0 hours (SD 11.62) versus the control group 70.6 hours (SD 20.82). Mostly on the second day of hospitalization, frequency of diarrhea had decreased to less than three times per day, cumulatively there were 29 infants (85.2%) versus six infants (17.6%). This study result was consistent with the finding from Vivatvakin study group.[11] Vivatvakin study showed that frequency of diarrhea reduced on day two of hospitalization in 28 infants (86%) from 32 infants in the treatment group versus 5 infants (16%) in control group. This study also revealed quicker time, i.e., 40.4 hours (SD 12.30) in feces consistency to become normal, soft, and formed in the treatment group compared to control group 71.5 hours (SD 21.82), the mean difference was 31.1. P= 0.001. On day two of hospitalization, the transformation of fecal consistency to normal was cumulatively significant in 31 infants (91%) within the treatment group compared to seven infants in control group (20%). Lexomboon *et al* [12] reported that transformation of fecal consistency to normal on day two of hospitalization were observed in 29 infants (85%) in the treatment group compared to 9 infants (26%) in control group. Based on two studies above, we conclude that recovery process of acute diarrhea in infants was faster in the treatment group if compared to the control group. In this study, we also had a result that duration of diarrhea in hospital was shorter in the treatment group, 39.0 hours (SD 2.03) versus 70.6 hours (SD 3.78), P=0.001.

This study result was also similar to Vivatvakin *et al* [11] in 62 infants aged between one to 24 months. The duration of diarrhea in the treatment group was 43.3 hours (SD 25.1) compared to 84.7 hours (SD 48.5) in control group. The results were statistically significant. In study by Madkour *et al* [13] with 90 infants aged between three to 24 months, the results were 54.1 hours (SD 2.35) in treatment group versus 72.9 hours (SD 1.98) in control group. Study by Narkeviciute *et al* [14] with 54 infants and children aged between six to 48 months revealed that the duration of diarrhea was 43.3 hours in the treatment group versus 61.8 hours in control group.

Recovery of acute diarrhea is determined by intestinal mucosa recovery. In acute diarrhea, patients treated with DS have a quicker small intestine mucosal recovery through mucous interaction, cells regeneration stimulation, and differentiation of mucosal intestine resulting in less fluid excretion, increased absorption, and intestinal peristaltic recovery. Dupont *et al* [15] reported recovery of small intestine structure depends on size of a damage. Severe damage would need four days to recover and the function of absorbing water, electrolyte, and nutrition will be improved in 1.3 days time.

There was no significant difference between both groups after intervention [0.3 (SD 0.13) versus 0.4 (SD 0.19)], although weight gain tended to be slightly higher in control group. This result was probably due to rehydration factor because DS did not show any influence in weight gain in short period of time. Similar study was done by Madkour *et al*[13] which found that there was no statistically significant difference in weight gain between control group (110.9 gram) and treatment group (94.9 gram). Vivatvakin *et al*[11] reported that there was a significant difference in increment of body weight, 112 grams body weight in the treatment group compared to 176 grams in the control group. Both studies were influenced by different period of monitoring. In Vivatvakin[11], the monitoring time was on the 10th day after treatment, whereas in our study, it was only performed when the patient was hospitalized.

In this study, RRR showed 50% decrease or ARR of 29% decrease in intervention group compare to control group. Based on covariate analysis (cox regression), DS only affected the duration of diarrhea episode. Other factors such as age, nutrition status, nutrition type, duration of diarrhea prior to admission, and antibiotic intervention were not statistically significant to influence the duration of diarrhea.

Adverse effects and complications were not encountered in our study. Meta-analysis study by Szajewska *et al*[16] showed that there was no adverse effects, which was caused by gut inability to absorb DS into the systemic circulation, found in nine randomized controlled trials with 1238 participants.

To strengthen its validity, the calculation on intention to treat analysis was also included in this study. We included the drop-out and failure-to-treatment subjects in our final analysis, with the worst assumption of subject's results as expected.

The weakness in our study was that there was no further investigation on the cause of diarrhea especially rotavirus, which had been known as the most common causeof diarrhea in children less than two years old. Due to the study limitation, its etiology remained unknown.

In conclusion, DS could be used as an alternative therapy on treating acute diarrhea in infants. However, the standard procedure of acute diarrhea recommended by WHO remained to be the main protocol. Based on its safety, DS is considered to be a treatment used in management of acute diarrhea in infants routinely in gastroenterology division of child health in Udayana University, Sanglah Hospital, Denpasar.

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