

Efficacy of Dioctahedral Smectite in Acute Watery Diarrhea in Indian Children: A Randomized Clinical Trial

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Summary

Objective: To determine the effects and safety of dioctahedral smectite (DS) on the duration of acute watery diarrhea in children. **Methods:** A Randomized, open labeled, clinical controlled trial in a tertiary care hospital outpatient department (OPD) and emergency department. Participants were one hundred and seventeen children without any chronic illness between 2 and 5 years presenting to OPD, having acute watery diarrhea for <48 h with mild to moderate dehydration, not on antibiotics and requiring oral rehydration therapy. Intervention done was DS with a dose of 1.5 g thrice daily. **Results:** Freshly dissolved DS in a dose of 1.5 g thrice daily for 5 days significantly shortened the duration of acute watery diarrhea in 20 children aged 25 years. There were no adverse effects on the use of DS. DS was acceptable to the children, and its administration was not accompanied with any side effects. **Conclusion:** DS reduces the duration of diarrhea in Indian children and prevents a prolonged course, and therefore, may consistently reduce the costs in treatment of acute watery diarrhea.

Key words: diarrhea, dioctahedral smectite, dehydration.

Introduction

Dioctahedral smectite (DS) is natural adsorbent clay. It is capable of adsorbing viruses, bacteria and other intestinal irritants *in vitro*. It is claimed to possess beneficial 'anti-diarrheal' properties. Since recent data suggest that safety of DS in children with

diarrhea and study about its use in Indian scenario is lacking, this study was undertaken.

Methods

The study was designed as a randomized, open labeled, clinical controlled trial and was conducted in a tertiary care hospital in India, from January to August 2009. Clearance was obtained from the institutional ethical committee. The study protocol was fully explained to the parents/guardian, and a written informed consent was obtained.

Objective

The study was conducted to determine the effects and safety of DS on duration of acute watery diarrhea in Indian children.

Sample size

The sample size was 117 patients.

Data collection

The baseline data collected included: name; age; address; telephone number; duration of illness;

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frequency of diarrhea and vomiting prior to admission; and presence of associated symptoms including abdominal pain, fever and abdominal distension. A history of previous antibiotic/antidiarrheal ingestion in the past 48 h was elicited. Evaluation was done for general hygiene, vitals and signs of dehydration. Questionnaires were used for evaluating the duration of diarrhea, frequency of defecation, consistency of feces, complication and adverse events. Patients were followed up daily telephonically by resident doctors and interns.

Enrollment

Children between 2 and 5 years having watery diarrhea for ≤ 48 h with features of mild to moderate dehydration were enrolled. Children with complicated diarrhea and those whose parents refused to participate in the study were excluded. Prior consent was obtained from parents before the administration of drugs. Children with malnutrition [as per Indian Academy of Pediatrics (IAP) classification], a co-existing systemic illness, blood in stool and those having received an antibiotic/antidiarrheal within the preceding 48 h of the disease were excluded. Children with vomiting were excluded from the study as an oral drug was being given.

Randomization

It was done as per the serial number. All even numbered patients were assigned to treatment group and odd numbered to control group. Treatment group was provided standard oral rehydration solution (ORS) plus DS therapy, whereas control group was given standard ORS therapy alone.

Definitions

Acute watery diarrhea was defined as defecation frequency for more than the usual habit accompanied by changes in feces consistency to watery, without blood or mucous, lasting for < 7 days.

Recovery time was the time needed to achieve normal stool consistency without any complication with usual frequency of defecation.

Diarrhea with complication was defined as diarrhea episode accompanied by direct effect of acute diarrhea such as severe dehydration, metabolic acidosis, seizures and paralytic ileus.

Complicated diarrhea was defined as acute diarrhea with severe malnutrition, severe dysentery, respiratory infection and anemia.

Dehydration status was assessed according to the World Health Organization (WHO) standard.

Malnutrition was assessed at below 80% of expected weight for age (as per IAP classification).

Patients, who followed up with another pediatrician for a different treatment 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 5, or had co-infection or adverse events affecting the duration of diarrhea.

All subjects were managed according to the standard therapy recommended by WHO for acute diarrhea with rehydration.

Data collection

Questionnaires were used for evaluating the duration of diarrhea, frequency of defecation, consistency of feces, complication and adverse events. Patients were followed up daily telephonically by resident doctors and interns. All study subjects were followed up until they recovered.

Data analysis

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented in mean \pm SD (Min-Max) and results on categorical measurements are presented in number (%). Level of significance is assessed at 5%. Student's *t*-test (two-tailed, independent) has been used to find the significance of study parameters on continuous scale between the two groups (inter-group analysis) on metric parameters, and Levene's test has been performed for equality of variances. Chi-square/Fisher's exact test has been used to find the significance of study parameters on categorical scale between two or more groups [1-4].

Results

During the study period, a total of 117 children aged 2-5 years were enrolled in the study. Four patients each were dropped out from the study group and control group. There were five treatment failures in control group and four in study group.

Drop out and treatment failure patients were included in the study and analyzed as per intention-to-treat analysis. The study flow chart is shown in Fig. 1.

Mean age of children in treatment group was 37.24 ± 9.03 months vs. 35.95 ± 7.67 months in control group. There were 37 males and 21 females in treatment group vs. 35 males and 24 females in control group. Patients in the control group presented with a mean of 27.10 ± 10.79 h of diarrhea vs. 25.32 ± 10.63 h in control group.

At baseline, there was no statistically significant difference between case and control in all variables including age, sex and mean duration of diarrhea at presentation as seen in Table 1.

The mean time taken for resolution of diarrhea result was significantly shorter in the treatment group (64.34 ± 14.86 h) compared with controls (82.37 ± 21.43 h). A mean difference of 18.03 h between duration of diarrhea after initiation of

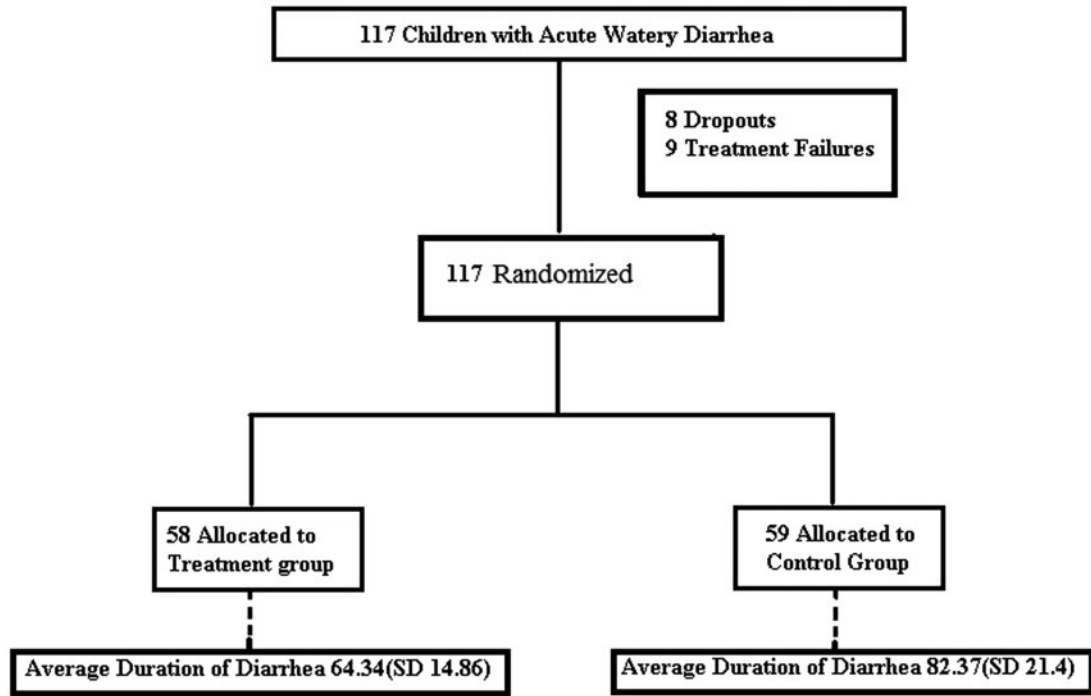


FIG. 1. Study flow chart.

TABLE 1
Group statistics of patients studied

Characteristics	Smectite given	Smectite not given	<i>p</i> -value
Gender			
Male (<i>n</i>)	37	35	0.619
Female (<i>n</i>)	21	24	
Total	58	59	
Age, mean ± SD (months)	37.24 ± 9.03	35.95 ± 7.67	0.406
Hours of diarrhea before Rx, mean ± SD	27.10 ± 10.79	25.32 ± 10.63	0.370

Samples are gender matched with $p=0.619$, age matched with $p=0.406$ and hours of diarrhea before Rx with $p=0.370$.

treatment in the two groups was observed. This difference was statistically significant ($p < 0.001$). Table 2 illustrates these results. DS was well tolerated by children with no side effects.

Discussion

DS is naturally adsorbing clay, which is chemically formed of fine sheets of aluminomagnesium silicate of phyllitic nature. Since it has a nonfibrous crystalline structure, it has better adsorbent properties compared with other clays used as antidiarrheal agents [5, 6]. As it is not absorbed from the gastrointestinal tract, it does not cause any systemic side effects and is classified by Food

and Drug Authority as a safe over-the-counter drug [7].

DS has also been shown to have anti-secretory properties by virtue of reducing cyclic adenosine monophosphate levels and reducing leakage of fluids and electrolytes [8]. It protects the intestinal mucosal barrier, adsorbs toxins, bacteria and viruses [9, 10]. It has mucoprotective effect and is shown to repair intestinal mucosal integrity [11].

Various studies have shown that *in vitro* it protects intestinal mucosa. In a classical study done by Mahraui *et al.* [12], it was shown to fully restore barrier properties of human intestinal cell monolayers after exposure to TNF- α in Ussing Chamber experimental model.

TABLE 2
Comparison of hours of diarrhea, hours of resolution after treatment and total diarrhea duration in two groups of patients

Time (h)	Smectite given	Smectite not given	p-value
Hours of diarrhea before treatment	27.10 ± 10.79	25.32 ± 10.63	0.370
Time taken for resolution after treatment (h)	64.34 ± 14.86	82.37 ± 21.43	<0.001**
Total diarrhea duration (h)	91.45 ± 17.53	107.53 ± 25.68	<0.001**

Data are expressed as mean ± SD.

Significant figures: *Moderately significant (p -value: $0.01 < p \leq 0.05$); **strongly significant (p -value: $p \leq 0.01$).

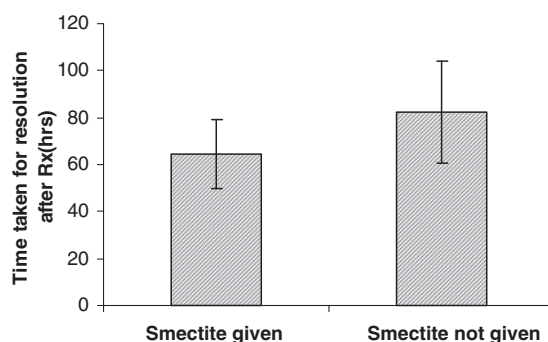


FIG. 2. The mean time taken for resolution of diarrhea in the two compared groups.

Considering this *in vitro* evidence and its safety profile, many studies have been conducted in various countries about its use in children with diarrhea. However, data are lacking from Indian perspective even though diarrhea is one of the largest killers of Indian children.

A meta-analysis by Yen and Lai [13] showed that DS significantly reduced the duration of diarrhea and nursing time.

Similar studies done by Narkeviciute *et al.* [14] with 54 patients showed significantly shorter duration of diarrhea in DS plus ORS group (42.3 ± 24.7 vs. 61.8 ± 33.9 , $p = 0.019$).

Vivatvakin *et al.* [15] conducted a prospective randomized controlled Trial of 62 patients (aged 1–24 months) with acute diarrhea randomized to DS plus ORS or ORS, which showed significantly shorter duration of diarrhea in the DS plus ORS group (43.3 ± 25.1 vs. 84.7 ± 48.5 , $p = 0.005$). This study showed reduction in the frequency of diarrhea on Day 2 of treatment in the smectite-given group and a shorter time required for stool consistency to become normal.

Guarino *et al.* [16] from Italy in a study of 804 patients (aged 3 months to 5 year) with acute diarrhea randomized to DS plus ORS or ORS showed significantly shorter duration of diarrhea in the DS plus ORS group (96 ± 21 vs. 119 ± 23 , $p < 0.001$). However, this study had incomparable baseline data.

Lexomboon *et al.* [8] from Thailand in a trial with 66 patients (aged 1–24 months) with acute diarrhea randomized to DS plus ORS or ORS showed that cure rate at 72 h was significantly higher in the DS plus ORS (71% vs. 34%, $p < 0.01$).

Our study also showed similar results in an Indian scenario with a reduction in time taken for resolution of diarrhea. The mean time taken for resolution of diarrhea result was significantly shorter in the treatment group (64.34 ± 14.86 h) as compared with controls (82.37 ± 21.43 h) as seen in Fig. 2.

The strength of our study was that our baseline data between the two groups was comparable in terms of nutritional status, age, sex, socioeconomic status and duration of diarrhea at presentation. Patients with vomiting, bloody diarrhea and antibiotic use were excluded from the study. Hence, these factors were not statistically significant to influence the duration of diarrhea.

The weakness of our study was that there was no further investigation on cause of diarrhea and patients with vomiting, antibiotic usage and blood in stools were excluded from the study. Hence, we could not ascertain if smectite is useful when given with antibiotics and in patients with bloody diarrhea.

It has shown to reduce the mean duration of diarrhea by ~18.03 hours in our study, hence we presume it would reduce morbidity and treatment costs of diarrhea (Figure 3).

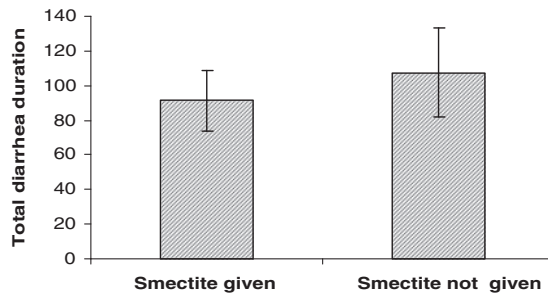


Fig. 3. The mean duration of diarrhea in the two groups.

Furthermore, studies are required to conclude whether smectite interferes with absorption of antibiotics and on hospitalized children to check stool frequency and stool output reduction.

Our results showed that smectite significantly shortened the duration of acute watery diarrhea in children. Smectite was well tolerated by children and there were no side effects associated with it.

Various studies done abroad have shown the usefulness and safety of smectite in diarrhea and our results also showed a mean reduction in duration of diarrhea in treatment group in Indian context. Hence, we conclude that DS can be used as an adjunct in the treatment of acute watery diarrhea in Indian children.

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