

Homeopathic Treatment of Acute Childhood Diarrhea: Results from a Clinical Trial in Nepal

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ABSTRACT

Objective: To investigate whether the finding in a previous study that homeopathic medicines decrease the duration of acute diarrhea in children could be replicated in a different study population.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: Private, charitable health clinic in Kathmandu, Nepal.

Subjects: A consecutive sample of 126 children, 6 months to 5 years of age, who presented during April through June, 1994, with more than three unformed stools in the previous 24 hours.

Intervention: Children received either an individualized homeopathic medicine or placebo, to be taken one dose after each unformed stool for 5 days. Parents recorded daily stools on diary cards, and health workers made home visits daily to monitor children.

Outcome measures: Predefined measures were based on the previous study: (1) duration of diarrhea, defined as the time until there were fewer than three unformed stools per day, for two consecutive days, and (2) Average number of stools per day for each group.

Results: Of the 126 children initially enrolled, 116 completed treatment. The mean number of stools per day over the entire 5-day treatment period was 3.2 for the treatment group and 4.5 for the placebo group ($P = 0.023$). A Kaplan-Meier survival analysis of the duration of diarrhea, which included data from all patient visits, showed an 18.4% greater probability that a child would be free of diarrhea by day 5 under homeopathic treatment ($P = 0.036$).

Conclusions: These results are consistent with the finding from the previous study that individualized homeopathic treatment decreases the duration of diarrhea and number of stools in children with acute childhood diarrhea.

INTRODUCTION

Acute diarrhea is the leading cause of death in children in the developing world, with an estimated 5 million deaths per year worldwide (Walsh and Warren, 1979). In Nepal, diar-

rhea is responsible for 40,000 deaths each year of children younger than 5 years of age, representing 46% of the annual infant and child mortality in this age group (Stapleton, 1989; Upadhyay and Pandit, 1990). In many parts of the developing world, children younger than age 5 average 5 to

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10 episodes of acute diarrhea per year, with an average of 6 days per episode (Anonymous, 1980; Schorling, 1988). In Nepal, one study found that 18% of all children younger than 5 years of age had diarrhea in the previous 2 weeks, and that the average number of episodes was 3.3 per child per year (WHO, 1991). Available evidence indicates that both acute and chronic diarrhea are important contributing factors in malnutrition among children of the developing world (Kumate and Isibas, 1986).

The recommended treatment for this illness, oral rehydration therapy (ORT), reduces deaths from dehydration but in most cases does not decrease the duration of illness (Feachem, 1988). Acceptance of ORT by mothers in developing countries has been slow, because in many cases it does not shorten the diarrheal episodes and in some cases it increases the total stool volume (Bentley, 1988; Molla et al., 1989; Hudelson, 1993; Sengupta et al., 1994). In Nepal, the use of ORT for acute diarrhea was estimated at 8% to 10% in a recent household survey (WHO, 1991).

The practice of homeopathic medicine uses naturally occurring plant, animal, and mineral substances to stimulate the defense mechanisms of the body, including the immune system. It is based on the similia principle, whereby a substance that can cause symptoms when given in large doses to a healthy person is used to treat those same symptoms in someone who is ill. Treatment is individualized; that is, two or more persons with the same clinical diagnosis may be given different homeopathic medicines depending on the specific signs and symptoms of illness in each person. Because there is no explanation for its possible action and the medicines are so highly dilute, many scientists doubt the effect of homeopathy could be other than placebo (Vandenbroucke, 1997).

Placebo-controlled trials have reported positive effects from homeopathic treatment of asthma, primary fibromyalgia, and influenza (Fisher et al., 1989; Ferley et al., 1989; Reilly et al., 1994), while negative results have been reported in studies of warts, dental pain, and recovery from hysterectomy (Lökken et al., 1995; Kainz et al., 1996; Hart et al., 1997). A 1991 systemic review of 107 controlled homeopathic trials showed an overall positive trend and called

for further well-performed clinical trials in this area (Kleijnen et al., 1991). A more recent meta-analysis of 89 placebo-controlled studies found a combined odds ratio of 2.45 (95% confidence interval 2.05–2.93) in favor of homeopathy, although the authors found that few studies had been replicated by different investigators (Linde et al., 1997).

The historical homeopathic literature contains a number of reports of the use of homeopathy in the treatment of diarrhea, including books providing guidance on medication use for this condition (Coulter, 1973; Bell, 1888). It is thought that improved host resistance from treatment with homeopathic medicine might reduce the severity and length of diarrheal episodes. In our previous study in Nicaragua, 81 children, age 6 months to 5 years, were randomly assigned to receive either an individualized homeopathic medicine or placebo, along with standard ORT. The group receiving homeopathy had an average duration of diarrhea of 3.0 days after receiving treatment, compared to 3.8 days in the placebo group ($P < 0.05$) (Jacobs et al., 1994). If a therapy were found that could be used along with ORT to reduce the number and frequency of stools in acute diarrhea, this might encourage greater use of ORT and reduce the overall morbidity and mortality from this illness. In an attempt to replicate this study, a similar investigation was undertaken in Nepal. This article reports our findings from this more recent study conducted in a different population with different homeopathic practitioners.

MATERIALS AND METHODS

The study was carried out in Jorpati, a suburb of Kathmandu, Nepal, in a private, charitable health clinic during the period of April 25 through June 25, 1994. A total of 126 children, age 6 months to 5 years, with a history of diarrhea (more than three unformed stools per day) for no more than 5 days were enrolled into the study. Children who had received any anti-diarrheal medication within the previous 48 hours were excluded from the study, because this was previously found to affect treatment outcome (unpublished data). Patients who had severe diarrhea requiring hospitalization or intravenous hydration were also excluded from

participation. Informed consent was obtained from the parent or guardian, using a statement that had been approved by the Human Subjects Committee of the University of Washington.

Each child underwent a physical examination, including determination of height and weight, and dehydration was assessed using standard World Health Organization (WHO) protocols (WHO, 1987). Type A dehydration is characterized by no symptoms of dehydration. Type B dehydration is diagnosed when two or more of the following signs and symptoms are present: greater than normal thirst, small amount of urine or dark urine, child sleepy or irritable, tears absent, sunken eyes, dry mouth and tongue, faster than normal respiration or pulse, sunken fontanelle, and poor skin turgor. Type C dehydration is defined by the presence of two or more of the following: unable to drink, no urine for 6 hours; child very sleepy, unconscious, floppy, or having seizures; no tears, eyes very dry and sunken; mouth and tongue very dry; very fast or deep respiration; pulse very fast, weak, or imperceptible; fontanelle very sunken; very poor skin turgor.

A diarrhea-index score was also assigned to each child as an indicator of severity of illness (Ericsson et al., 1987). This previously described index was modified for children to include the degree of dehydration. Vomiting was assessed as none, some, or frequent, with corresponding scores of 0, 1, and 2, respectively. Abdominal pain, as reported by the mother, was scored as none (0), some (1), and much (2). Temperature was scored as follows: less than 37.25°C (0), 37.25°–38.25°C (1), 38.35°–39.35°C (2), and greater than 39.35°C (3). The number of unformed stools in the previous 24 hours were scored as none (0), one (1), two to three (2), four to five (3), six to seven (4), eight to nine (5), and ten or more (6). Dehydration was included as type A (0), type B (1), and type C (2).

Stool specimens were collected and analyzed for parasites, viruses, and bacteria. All laboratory tests were carried out in cooperation with the Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand, by standard techniques as previously described (Hoge et al., 1995).

An in-depth homeopathic interview was carried out by the homeopathic practitioner, in-

cluding questions about the nature of the stools, abdominal pain and/or vomiting, the mood and temperament of the child, degree of thirst and appetite, presence of a fever, abdominal bloating, sleep disturbance, amount of perspiration, and other characteristic signs and symptoms. This information was used along with the computer program RADAR with Vithoukas Expert System (Archimed, Inc., Namur, Belgium) to choose an individualized homeopathic medicine to match the symptoms of each child. Because patients were drawn from a mixed Nepali and Tibetan refugee population, interpreters with knowledge of Nepali, Tibetan, and English were used for the patient interviews. The homeopathic prescribing was done by a different set of practitioners (S.M., E.C., and M.M.) than those prescribing in the previous Nicaragua study. The symptom pattern indications for the most commonly used medicines are shown in Table 1.

Children were randomly assigned into treatment and control groups using coded bottles of medication that were prepared in the United States before the beginning of the study. These medications were prepared by a homeopathic pharmacist in accordance with the *Homeopathic Pharmacopoeia of the United States* (Homeopathic Pharmacopoeia Convention of the United States, 1988) by impregnating no. 38 pellets made of 85% sucrose and 15% lactose with a liquid homeopathic dilution in the 30C potency (the active substance was diluted 1:100 in a water/alcohol solution 30 times for a final concentration of 1×10^{-60}). Placebo was prepared in the same manner using 87% alcohol instead of the homeopathic dilution.

Nineteen different homeopathic medications were available for use. For each of the different homeopathic medications, there was a box containing numbered vials of verum and placebo. Placebo was identical to verum in taste, odor, appearance, and packaging. A random numbers table was used to determine the randomization for each bottle in sequence for each medication. A total of 402 bottles were available (210 verum, 192 placebo), 126 of which were used in the study. All study personnel in Nepal were blinded as to treatment allocation, as was the statistician.

An individualized homeopathic medication

TABLE 1. COMMON HOMEOPATHIC REMEDIES FOR ACUTE DIARRHEA AND THEIR INDICATIONS

<i>Arsenicum album</i> (arsenic trioxide)	
Mind:	Great anxiety and restlessness. Tossing about in bed. Fearful, doesn't want to be alone.
General:	Prostration. Worse after midnight. Burning heat with thirst for small amounts. Chilly, better being covered, cold sweats. Vomiting immediately after eating or drinking.
Stools:	Acrid, burning, excoriating. Diarrhea worse at night, after midnight. Putrid, bloody, odor of rotten eggs.
<i>Chamomilla</i> (German chamomile)	
Mind:	Capricious; irritable; quarrelsome, nothing pleases. Asks for something, then rejects it, striking out, sensitive to pain; moaning; frenzied. Better being carried.
General:	One cheek red, other pale; hot; worse from heat, better from cold drinks. Worse evening, until midnight.
Stools:	Green, slimy, offensive, like chopped grass. Diarrhea during teething. Smelling like rotten eggs; colic with diarrhea, better after stool.
<i>Calcarea carbonica</i> (calcium carbonate)	
Mind:	Slow, lethargic, fears the dark and being alone.
General:	Profuse perspiration on the head during sleep. Sour smell to perspiration. Strong desire for milk, eggs, and indigestibles (pica). Plump children who get sick frequently and have swollen glands.
Stools:	Sour odor to the stools. Diarrhea during teething. Watery with bits of undigested food.
<i>Podophyllum</i> (May-apple)	
Mind:	Diarrhea after mental excitement. Fidgety and restless.
General:	Gagging or empty retching. Violent cramps of the feet, calves, and thighs. Head sweats during sleep. Thirst for large quantities of cold water.
Stools:	Profuse, frequent, gushing, painless, watery. Bloody with green mucus, very offensive. Rectal prolapse. Exhaustion after stool. Diarrhea during teething, after fruit.
<i>Sulphur</i> (flowers of sulphur)	
Mind:	Irritable, indifferent, weeping.
General:	Cold sweat on face and feet. Blue circles under eyes, weakness. Thirsty for cold drinks, little appetite.
Stools:	Diarrhea worse at night, after milk; involuntary, sudden expulsion. Worse 5:00 a.m. Red ring around anus. Offensive, acrid stools. Painless; sour; thin; watery. Odor of rotten eggs.

Bold type indicates the most important symptoms for each medicine.

Sources: Bell, 1888; Boericke, 1971.

(or placebo) was prescribed with instructions to take one dose after every unformed stool until the diarrhea resolved, or for no longer than 5 days. In addition to this treatment, each child also received the standard WHO-recommended ORT for acute childhood diarrhea, according to WHO protocols (WHO, 1987). All parents were instructed to continue normal feeding. A simple card with diagrams and non-alphabetic symbols was given to the parents to record daily symptoms. Daily home visits by community health workers to record the progress of each child were carried out for 5 days after entry into the study. Children found to have parasites in the stool were treated with standard antiparasitic medication at the end of the 5-day treatment period.

The duration of diarrhea was predefined as the time until there were two consecutive days with fewer than three unformed stools, the same primary outcome measure as in our previous study. All analysis was done before the

randomization code was broken. Differences in descriptive characteristics at the initial visit were compared by the two-sample, two-tailed *t* test for continuous data, and the chi-square test for categorical data. Because some cases were lost to follow-up, an intention-to-treat analysis for all available data on duration of diarrhea was carried out using the Kaplan-Meier survival analysis curve with the log-rank statistic. A linear regression model was used to adjust for disparities in patient characteristics at the initial visit. An independent statistician who was not one of the study investigators was consulted to carry out the linear regression and Kaplan-Meier survival analysis.

Random samples from both the placebo and verum groups were selected from bottles prepared for the trial and analyzed for contaminants by Fourier transform infrared spectroscopy by the Department of Environmental and Toxicological Pathology at the Armed Forces Institute of Pathology, Washington, D.C.

TABLE 2. COMPARISON OF DESCRIPTIVE CHARACTERISTICS OF CHILDREN WITH DIARRHEA AT INITIAL VISIT

Characteristic	Treatment group (n = 69)	Control group (n = 57)	Probability value
Age (mo)	20.6 (12.4)	16.6 (11.7)	0.07
Height (cm)	76.3 (9.1)	72.9 (8.4)	0.03
Weight (kg)	9.6 (2.5)	8.7 (2.7)	0.05
Weight-for-height percentile	33.8 (27.5)	28.3 (21.5)	0.21
Unformed stools past 24 hr	8.1 (4.0)	8.9 (5.0)	0.27
No. days of diarrhea	2.77 (1.2)	2.75 (1.1)	0.92
Diarrhea-index score	6.5 (1.6)	6.9 (1.9)	0.11

Values are means with standard deviation in parentheses.

RESULTS

Of the 126 children initially enrolled in the Nepal study, 116 (64 in the treatment group and 52 in the placebo group) completed treatment and 5-day follow-up. Ten children (five in each group) had incomplete follow-up. One was not located due to incorrect address (placebo group); seven children (4 in the placebo group, 3 in the treatment group) were removed from the study before the 5-day follow-up was completed by their parents, who elected other treatment; and two children (both in the treatment group) moved out of the area during the follow-up period.

Comparison of descriptive characteristics at the initial visit showed no significant differences between groups in the areas of weight-for-height percentile, diarrhea-index score, number of stools in the previous 24 hours, or number of previous days of diarrhea (Table 2). The randomization did result in an unintended disparity in age, as well as height and weight, between the two groups that was at or near statistical significance, with the placebo group be-

ing younger and smaller. In both groups there was a predominance of male children (65.7% in the treatment group, 69.6% in the group receiving placebo). Stool analysis completed on 123 of the 126 children showed no significant difference in specific pathogens between the two groups (Table 3).

Because some subjects did not complete follow-up, an intention-to-treat analysis (Kaplan-Meier plot) was used to compare the primary outcome measure, duration of diarrhea, at various points in time (Fig. 1). Because this model is able to handle censored data, information from patients who were lost to follow-up could be included. The log-rank test showed a statistically significant difference in the curves of the Kaplan-Meier plot between the two study arms in favor of the group receiving verum ($X^2 = 4.4$, $df = 1$, $p = 0.036$). At day 5, the probability of having diarrhea was 42.1% in the homeopathy group and 60.5% in the group receiving placebo.

A two-tailed, two-sample *t* test of the average number of stools per day for all cases indicated a statistically significant difference be-

TABLE 3. COMPARISON OF STOOL PATHOGENS AT INITIAL VISIT^a

Pathogen	Treatment group (n = 69) %	Control group (n = 54) %	Probability value
Enterotoxigenic <i>Escherichia coli</i>	32	31	0.96
<i>Campylobacter</i>	7	11	0.45
<i>Salmonella/Shigella</i>	3	4	0.80
Rotavirus	0	4	0.20
Parasites			
<i>Cyclospora</i>	6	4	0.46
<i>Giardia lamblia</i>	13	13	1.0
<i>Cryptosporidium</i>	4	4	1.0
Any of the above	54	61	0.40

^aValues represent percentage of subjects infected.

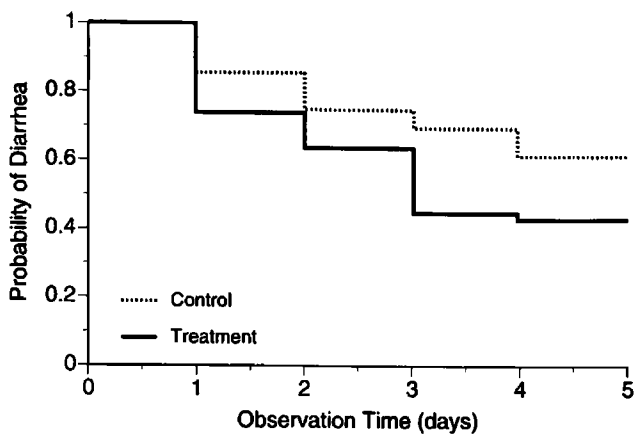


FIG. 1. Kaplan-Meier plot for duration of diarrhea, all cases, homeopathic treatment versus control (log-rank test: $X^2 = 4.4$, $df = 1$, $P = 0.036$).

tween treatment and control groups. The mean number of stools per day over the entire 5-day treatment period was 3.2 for the treatment group and 4.5 for the placebo group ($t = 2.30$, $df = 123$, $P = 0.023$). This variable was calculated first for each patient individually, using the average number of stools per day over those days for which data existed. The individual patient values were then combined to form an overall average for each of the two groups. Because the randomization between the two groups resulted in a disparity in age, height, and weight, with the placebo group being younger and smaller, a regression analysis of the average number of stools per day was done to adjust for these factors. A linear model containing the variables age, sex, weight-for-height percentile, previous days of diarrhea, diarrhea-index score, number of stools in the past 24 hours, and treatment group was used. (Because age, length, and weight were found to be

highly correlated, only the variable age was used in the model.) The results of this analysis show a statistically significant effect resulting from two variables: the treatment group verum ($p = .002$) and the number of stools in the 24 hours before entry into the study ($P < 0.001$) (Table 4).

An analysis of the most common remedies used in the Nepal study showed that Podophyllum, Sulphur, and Arsenicum album were used in 77% of cases. In contrast, in the Nicaragua study Podophyllum, Chamomilla, and Arsenicum album were used most frequently (59% of cases). The most frequently used five remedies in both studies—Podophyllum, Arsenicum album, Sulphur, Chamomilla, and Calcarea carbonica—covered 85% of cases in Nepal and 73% of Nicaraguan cases.

Infrared spectroscopic analysis of bottles chosen randomly from both the placebo and treatment groups showed no evidence of contamination of samples by inorganic or organic substances.

DISCUSSION

When evaluating a therapy such as homeopathy, where the mechanism of action is unknown, the possibility that positive results may have occurred by chance should be given serious consideration. As suggested in a recent review of the literature, results that have been replicated under different conditions and by different research teams should be given a higher priority for acceptance than those reported in only one trial (Linde et al., 1997). Our previous study in Nicaragua suggested a pos-

TABLE 4. LINEAR REGRESSION MODEL (MEAN NUMBER OF STOOLS PER DAY)

Variable	Value	SEM	t Value	P Value
Age	-0.03	0.018	-1.87	0.065
Sex	-0.22	0.227	-0.96	0.342
Group	-1.41	0.452	-3.12	0.002
Weight-for-height percentile	0.01	0.009	0.65	0.518
No. days diarrhea	0.09	0.186	0.47	0.636
Diarrhea-index score	-0.27	0.172	-1.56	0.120
No. stools in previous 24 h	0.49	0.067	7.29	0.000
Group \times stools, previous 24 hr	0.22	0.048	4.62	0.000

itive treatment association when comparing homeopathic medicines with placebo in the treatment of childhood diarrhea. With the results of this new study, we believe that those findings have been confirmed and indicate that a positive association does exist outside the realm of chance.

An intention-to-treat survival analysis of all patients, including those lost to follow-up, gave significant results in our predefined primary outcome variable, with an 18.4% greater probability that a child would be free of diarrhea by day 5 under homeopathic treatment ($p = 0.036$). This procedure takes into account all patients with at least some follow-up. A significant difference also was found between the two groups in mean number of stools per day, even after adjustment for confounding that might have occurred because of differences between the groups in age, weight, and height at entry into the study.

The disproportional randomization, with 69 subjects in the treatment group and 57 in the placebo group, was unfortunate but can occasionally occur with certain randomization methods. Unlike the Nicaragua study, where randomization of bottles of study medication was done in blocks of four to ensure an equal number of subjects in each treatment group, the randomization of medicines in this study was done using a random numbers table individually for each bottle, without any blocking. This uneven randomization most likely led to the disparities in group characteristics at entry into the study, requiring adjustment in the linear regression analysis.

Because the principal investigators (J.J. and L.M.J) were the same in this and the previous study, one could argue that a truly independent replication has not occurred. However, the personnel who carried out the study and prescribed the homeopathic medicines in Nepal (S.M., E.C., and M.M.) were different from those who performed these functions in Nicaragua. This appears to demonstrate at least the ability of a different study team to obtain comparable results in a different region of the world. The large predominance of male over female children has been documented previously in Nepal's health clinics and is thought to be a reflection of the higher value placed on

male offspring in this culture (Upadhyay and Pandit, 1990).

Criticisms of our previous paper included questions about the clinical significance of such a modest decrease in duration of diarrhea. Although this research was carried out primarily as a model to determine whether there was a statistically significant difference between homeopathy and placebo, we believe that it also has clinical significance. When one considers that the average child in Nepal has three to four episodes of diarrhea per year, each lasting five to six days, an 18% decrease in duration per episode could significantly reduce overall days of morbidity and lessen the dehydration, malnutrition, and compromised host resistance that many such children experience. Certainly the mother of a child with diarrhea would prefer an earlier resolution, and transmission of infection to siblings and other playmates would be reduced accordingly. One also could expect that in the customary practice of homeopathy, where medicines can be changed in the course of an illness if they do not appear to be working, the results would be better than those in this experimental study, where the homeopathic prescribers were limited to only one remedy that was given for the entire duration of the study.

Because of the extremely high dilutions used in homeopathy, our previous study was subjected to an unusual degree of scrutiny by those who believe homeopathy to be nothing more than placebo. Some critics suggested that our previous results were caused by adulteration of the homeopathic preparations (Sampson and London, 1995). However, infrared spectroscopic analysis done by an independent laboratory on randomly chosen unopened samples from this study showed no evidence of contamination. Questions have also been raised about possible bias in the statistical analysis of data by study investigators. For this reason, we consulted an independent statistician to verify our results and carry out the more sophisticated tests necessary to fully analyze these data.

An inherent methodologic problem of this and any clinical trial of homeopathy is the use of more than one treatment medication. Because individualization is a key element of

homeopathic treatment, one of several different medicines was used for each patient to match the specific symptom patterns of diarrhea in that child. In this and our previous trial, we are testing the system of homeopathic therapeutics as a whole, not the individual medicines.

One or two studies cannot address the generalizability of these results. In this study, we used the model of acute childhood diarrhea to determine whether homeopathic medicines produced effects different from placebo, and whether those results could be replicated. Studies of efficacy using a theoretic model are different from those that would be done to determine effectiveness of a therapy in widespread practice. In the future, methods to simplify the prescribing of homeopathic medicines by local health workers should be explored. Because only a few homeopathic remedies were found to be indicated in a majority of patients, future studies using simple protocols to prescribe these common remedies, or a homeopathic preparation combining these remedies, should be considered.

These results are consistent with the findings from our 1991 Nicaragua study, that individualized homeopathic treatment decreases the duration and number of stools in children with acute childhood diarrhea. Further studies by independent investigators using this protocol should be carried out in other locations to verify these findings. In addition, practical methods of delivering this treatment should be developed for possible widespread use in areas where childhood diarrhea is a significant problem.

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