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Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials

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Background. **Previous studies have shown a positive treatment effect of individualized homeopathic treatment for acute childhood diarrhea, but sample sizes were small and results were just at or near the level of statistical significance. Because all three studies followed the same basic study design, the combined data from these three studies were analyzed to obtain greater statistical power.**

Methods. **Three double blind clinical trials of diarrhea in 242 children ages 6 months to 5 years were analyzed as 1 group. Children were randomized to receive either an individualized homeopathic medicine or placebo to be taken as a single 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. The duration of diarrhea was defined as the time until there were less than 3 unformed stools per day for 2 consecutive days. A metaanalysis of the effect-size difference of the three studies was also conducted.**

Results. **Combined analysis shows a duration of diarrhea of 3.3 days in the homeopathy group compared with 4.1 in the placebo group (P = 0.008). The metaanalysis shows a consistent effect-size difference of ~0.66 day (P = 0.008).**

Conclusions. **The results from these studies confirm that individualized homeopathic treatment decreases the duration of acute childhood diarrhea and suggest that larger sample sizes be used in future homeopathic research to ensure adequate statistical power. Homeopathy should be considered for use as an adjunct to oral rehydration for this illness.**

INTRODUCTION

Worldwide, homeopathy is one of the most popular of complementary and alternative therapies. Nearly 40% of physicians in England refer for homeopathic treatment and >60% of the French public use homeopathy.[1, 2] Although less than in Europe, the use of homeopathy in the United States has increased 5-fold since 1990, most of it in the over-the-counter self-treatment market.[3, 4] Based on the principle of similars, or "like cures like," homeopathy postulates that small doses of a substance that can cause symptoms in a healthy person can be used to cure similar symptoms of disease in someone who is ill.

In addition to being popular, homeopathy is one of the most controversial of the complementary and alternative therapies. This is largely because of the high dilutions of the medicines used, often beyond Avogadro's number (10^{-23} M).[2] A tenet in homeopathy is that drugs retain selective activity when they are diluted if they are applied according to specific homeopathic selection principles.[5] The use of these dilutions has led some to reject homeopathy altogether without examining the clinical evidence of its effects.[6] Homeopathic remedies are generic and therefore inexpensive, available in bottles of 100 tablets for as little as $6 to $8 in many health food stores in the US.

A recent metaanalysis of 89 homeopathic clinical trials found a combined odds ratio of 2.45 (95% confidence interval, 2.05, 2.93) in favor of homeopathy.[7] The authors concluded that the effects of homeopathy cannot be explained entirely by placebo but that the small number of studies precluded concluding that homeopathy is effective for any one condition. In most homeopathic clinical trials, the sample sizes have been small. In the metaanalysis mentioned above, 65% of studies had fewer than 100 subjects, 29% had 100 to 200 and only 6% had >200 participants.[7] This leads one to question whether there was adequate statistical power

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in some of these studies to rule out a type II error, which occurs when there are not enough subjects to test the hypothesis fully. Many conventional drug trials enroll 500 to 2000 subjects to generate enough power to detect a statistically significant result.[8] Some of the reported effects (both positive and negative) of homeopathy may be a result of the bias that results from such small trials.[9] Comparing the consistency of treatment effects from trial to trial and pooling results from identical trials to increase sample size are methods that could help in evaluating the generalizability of results from small trials. We applied these two techniques to our previous studies on homeopathic treatment of acute diarrhea to assess such effects.

In our previous three studies, we evaluated the use of individualized homeopathic treatment of childhood diarrhea in Nicaragua and Nepal.[10–12] The results of the two larger studies ($n = 81$, $n = 116$) were just at or near the level of statistical significance. Because all three studies followed the same basic study design, including similar entry criteria, treatment assignment, follow-up schedule, outcome measures and data analysis, we analyzed the combined data from these three studies to obtain greater statistical power. In addition we conducted a metaanalysis of effect-size difference using the three individual studies to look for consistency of effects.

Acute childhood diarrhea. Acute diarrhea is a leading cause of death in children in the developing world, with more than 3 million deaths per year worldwide.[13] Both acute and chronic diarrheas are important contributing factors in malnutrition among children of the developing world.[13, 14] In the US diarrheal disease is a common cause of morbidity and exerts a heavy burden on the health care system.[15]

The recommended treatment for diarrhea, oral rehydration therapy (ORT), reduces deaths from dehydration but in most cases does not decrease the duration of illness.[16, 17] This has led to underutilization of ORT and inappropriate use of antibiotics and other drug therapies, as well as to increased efforts to find adjunctive therapies to reduce stool output.[18–21] If a therapy were found that could be used along with ORT to decrease the number and frequency of stools in acute diarrhea, this might encourage greater use of health care services providing ORT, reducing the overall morbidity and mortality from this illness.

MATERIALS AND METHODS

Study design and participants. The studies were conducted in Leon, Nicaragua in 1990 (pilot) and 1991 and in Jorpati, a suburb of Kathmandu, Nepal in 1994. A total of 247 children, ages 6 months to 5 years, with a history of diarrhea (3 or more unformed stools per day) for no more than 7 days (5 days in Nepal) were enrolled into the 3 studies. Children who had received antidiarrheal medication within the previous 24 to 48 h were excluded from the studies. Patients who had severe diarrhea requiring hospitalization or intravenous hydration also were excluded from participation. Informed consent was obtained from the parent or guardian, using a disclosure statement that had been approved by the University of Washington Human Subjects Review Committee. The study also was approved by local authorities in Nicaragua and Nepal.

Because a more detailed explanation of the study design was included in our previous publications,[10–12] only an abbreviated version will be presented here. Each child underwent a physical examination, including determination of height and weight, and dehydration status was assessed using standard WHO protocols. A previously described diarrhea index score was also assigned to each child as an indicator of severity of illness.[22] Stool specimens were collected and analyzed for parasites, viruses and bacteria.[11, 23] A computer-assisted homeopathic interview was conducted by an experienced homeopathic practitioner, using the RADAR program (with a Vithoulkas Expert System; Archimed, Inc., Namur, Belgium) to help determine an individualized homeopathic medicine for each child. Although the principal investigator was the same for all three studies the homeopathic prescribing was done by a different set of practitioners at each of the three study sites.

Randomization and treatment. Children were randomized into treatment and control groups as previously described, using coded bottles of medication that were prepared in the US before the beginning of each study by a homeopathic pharmacist. For each of the commonly used homeopathic medications for diarrhea that were available to study practitioners, there was a box containing numbered bottles of medicines. A random numbers table was used to determine the randomization sequence for each medication. When a medication was prescribed, the next bottle in sequence from the box containing that medicine was used.

Homeopathic medication in the 30C potency (or placebo) was dispensed with instructions to take one dose after every unformed stool until the diarrhea resolved, or for no more than 5 days. (In the 1990 Nicaragua pilot study, the medicine was given three times daily for 3 days.) These medications were prepared in the US in accordance with the Homeopathic pharmacopoeia of the United States,[24] by a homeopathic pharmacist by impregnating No. 38 pellets made of 85% sucrose and 15% lactose with a liquid homeopathic dilution in the 30C potency. The stock preparation for each remedy was diluted 1/100 in a water-alcohol solution 30 times for a final concentration of 10^{-60}. Placebo was prepared in the same manner with 87% alcohol instead of the homeopathic dilution. All study personnel (except the homeopathic pharmacist who held the randomization code and who was not present at or in communication with study

sites) were blinded as to treatment allocation until after the initial data analysis in each study.

In addition to this treatment, each child also received oral rehydration solution, according to standardized WHO protocols.[25] All parents were instructed to continue the child's normal diet and breast-feeding when applicable. A simple card with diagrams and nonalphabetic 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 made for 5 days after entry into the study (6 days in 1990 Nicaragua). Children who did not improve or who became worse were referred back to the clinic for further treatment. Children who had parasites in the stool were treated with appropriate antiparasitic drugs at the end of the treatment period.

Outcome measures and data analysis. The primary outcome measure, which was uniform in all three studies, was the duration of diarrhea, defined as the number of days until there were 2 consecutive days with less than three unformed stools per day. This outcome was used for the combined analysis, as was the mean number of stools per day, the other outcome that was identical in all three studies. This was calculated in two steps: (1) for each patient the average number of stools per day was first determined; and (2) the individual patient values were then averaged to form an overall average for each of the two treatment groups.

Differences in descriptive characteristics at the initial visit were compared using the 2 sample, 2 tailed *t* test for continuous data, as were the primary outcomes. Because some cases did not have full 5-day follow-up, an analysis for the duration of diarrhea for the 242 children for whom at least 1 day of follow-up information was available was performed with the use of the Kaplan-Meier survival analysis curve with the log rank statistic. Because the randomization inadvertently caused statistical or near statistically significant differences in weight, age, length and weight/height percentile, a Cox regression model was used to take into account these differences, as well as other covariate effects.

To examine the consistency of effects from trial to trial and the impact of sample size on statistical significance we conducted a metaanalysis of effect size differences between homeopathic and placebo groups for all trials. We graphed these differences with 95% confidence intervals for each trial and the combined group. Calculations were done with STATA for Windows (SPSS, Inc., Chicago, IL).

To test for possible contaminants random samples from both the placebo and verum groups were selected from bottles prepared for each of the three trials and analyzed by Fourier transform infrared spectroscopy by the Department of Environmental and Toxicological Pathology at the Armed Forces Institute of Pathology, Washington, DC.

RESULTS

Descriptive characteristics. Of the 247 children initially randomized in the three studies, 242 had 1 day or more of follow-up, and 230 (93%) completed the full 5-day follow-up period. Of the 17 children who did not complete full follow-up, 9 were in the treatment group and 8 were in the placebo group. Subjects in the 3 studies were remarkably uniform in average age, length, weight, number of unformed stools in the 24 h before entering the study and prior days of diarrhea. The nutritional status of the children, as evidenced by the weight for height percentile, was better in the Nicaragua 1991 group than that of the others, and there was a preponderance of male children in the Nepal and 1990 Nicaragua cohorts compared with the 1991 Nicaragua study. The proportion of stool pathogens also varied among the 3 studies, with a larger percentage of children with rotavirus found in the 1990 Nicaragua study, more parasites in the Nepal cohort and an equal amount of bacteria (*Escherichia coli*) in Nicaragua in 1991 and Nepal. No children worsened to the extent that they were referred for additional care.

A comparison of descriptive characteristics at entry into the study was made of the 247 children who were initially recruited into the study (129 in the treatment group, 118 receiving placebo) (Table 1). There were no significant differences between groups in the length, number of stools in the previous 24 h or previous days of diarrhea. The randomization did result in a disparity in age, weight and weight for height percentile between the two groups, which was statistically significant, with the placebo group being slightly younger and smaller. No differences in the reported use of ORT were found between the groups.

Combined results. The outcomes for the combined studies are summarized in Table 2. Results for the primary outcome measure for the 230 patients for whom there were complete follow-up data showed a 18.5% reduction in the duration of diarrhea from 3.8 days in the placebo group to 3.1 days in the group receiving homeopathy ($P = 0.008$). Patients who finished the study and were not yet diarrhea-free were

TABLE 1. Comparison of descriptive characteristics at initial visit, with all subjects initially randomized: combined data from three studies of homeopathy for childhood diarrhea

Variable	Treatment ($n = 129$)	Control ($n = 118$)	*P*
Male gender (%)	60	56	0.50
Age (mo)	20.1 ± 12.1*	17.0 ± 10.8	0.04
Length (cm)	76.6 ± 8.7	73.6 ± 13.0	0.06
Weight (kg)	9.7 ± 2.2	9.1 ± 2.5	0.03
Weight for ht percentile	38.7 ± 27	31.7 ± 26	0.04
Unformed stools past 24 h	7.9 ± 3.9	8.0 ± 4.5	0.80
Prior days of diarrhea	2.8 ± 1.6	2.8 ± 1.5	0.92
Diarrhea index score	5.9 ± 1.7	6.0 ± 2.2	0.73

* Mean ± SD.

TABLE 2. Results in three studies of homeopathy for childhood diarrhea and combined results, with all children completing 5-day follow-up

Variable	Treatment	Control	*P*
Nicaragua, 1990	(*n* = 16)	(*n* = 17)	
Duration of diarrhea	2.4 ± 1.7*	3.0 ± 1.6	0.28
No. of stools/day	2.8 ± 1.8	3.5 ± 1.4	0.57
Nicaragua, 1991	(*n* = 40)	(*n* = 41)	
Duration of diarrhea	3.0 ± 1.9	3.8 ± 1.7	0.048
No. of stools/day	2.2 ± 1.7	2.9 ± 2.0	0.07
Nepal	(*n* = 64)	(*n* = 52)	
Duration of diarrhea	3.5 ± 2.0	4.2 ± 1.9	0.06
No. of stools/day	3.0 ± 2.2	3.7 ± 2.0	0.03
Combined	(*n* = 120)	(*n* = 110)	
Duration of diarrhea	3.1 ± 2.0	3.8 ± 1.9	0.008
No. of stools/day	2.7 ± 2.0	3.4 ± 2.0	0.004

* Mean ± SD.

assigned a duration of diarrhea equal to the last day of their follow-up. The mean number of stools per day for each patient during the entire 5-day treatment period was 2.7 for the treatment group and 3.4 for the placebo group ($P = 0.004$).

Because some cases did not complete follow-up, an analysis based on a Kaplan-Meier plot was used to compare the duration of diarrhea in all 242 subjects for whom follow-up data was available (Fig. 1). The log rank test showed a statistically significant difference between the curves of the Kaplan-Meier plot between the two study arms in favor of the group receiving verum (chi square, 6.2; df = 1; $P = 0.013$). At Day 5 there is a probability of 38.1% of having diarrhea in the homeopathy group, compared with 51.4% in the placebo group. The Cox regression analysis, done to adjust for inequalities in randomization, found that in a model including age, sex, group, weight for height percentile, previous days of diarrhea and number of stools in the past 24 h, group assignment was statistically significant in influencing the outcome ($P = 0.025$).

Metaanalysis. Summary results of mean effect-size differences (between homeopathic and placebo groups) from all three studies and a metaanalysis of data from all three studies can be seen in Figure 2. Differences in duration of diarrhea between homeopathic and placebo

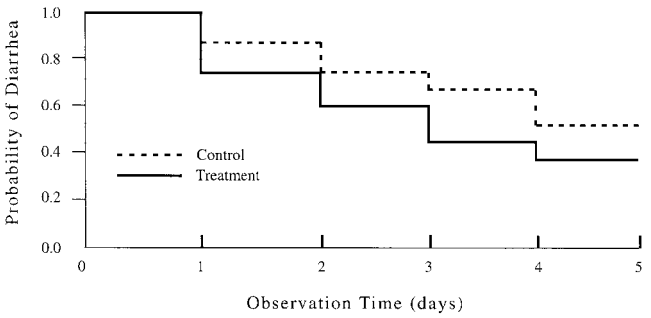

FIG. 1. Kaplan-Meier plot for the presence of diarrhea, all cases with any follow-up, homeopathic treatment *vs.* control, combined data. Log rank test chi square, 6.2; df = 1; and $P = 0.013$.

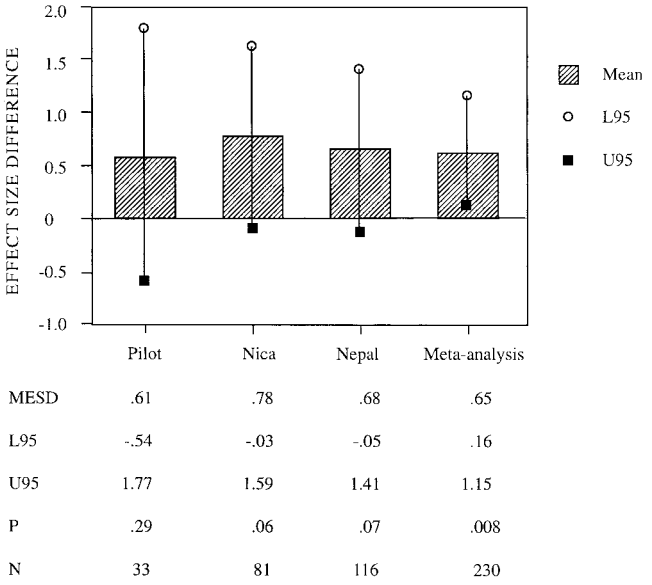

FIG. 2. Mean effect-size differences (*MESD*) for the duration of diarrhea from each of three childhood diarrhea studies and the metaanalysis. *Pilot,* Nicaragua, 1990; *Nica,* Nicaragua, 1991; *Nepal,* Nepal, 1994; *Meta-analysis,* all three studies; *L95,* lower 95% confidence interval; *U95,* upper 95% confidence interval.

groups were remarkably similar across all three studies (0.61, 0.78, 0.68 day) with the lower 95% confidence interval just at or below zero. The metaanalysis yields a effect-size difference similar (0.66 day) to that of the individual studies but with narrower confidence intervals of 0.16 and 1.15 ($P = 0.008$).

An analysis of homeopathic remedies used in the studies showed that the most common five remedies used in all studies, *Podophyllum, Arsenicum album*, Sulphur, *Chamomilla* and *Calcarea carbonica* were used in 85% of cases in Nepal and 78% of Nicaraguan cases. Infrared spectroscopic analysis of remedies chosen randomly from both the placebo and treatment batches from all three studies demonstrated the same spectra for all samples, which indicates uniform chemical components. Any contamination of samples by inorganic or organic substances would be expected to reveal differential spectra on spectroscopic analysis.

DISCUSSION

When working in a field in which there is an unexplained mechanism of action, such as homeopathy, critics are likely to suggest that positive results occur by chance.[6] Although our previous studies indicated a decreased duration of diarrhea in children treated with homeopathic medicines, the results were just at or near the level of statistical significance. These combined data corroborate those findings and suggest further that an association exists that is not the result of a statistical artifact or systematic bias.

Negative studies must have sufficient power to avoid a type II error in which a true effect is missed. Type II error

is common but is frequently undetected in the medical literature; this results in claims of no effect even when important effects exist.[26] The power was low in the three individual studies reported here because of small sample sizes. This is reflected in effect sizes that are consistent across studies but of borderline statistical significance, which become clearly significant when data are combined. Because these studies were homogeneous (had similar designs, interventions and outcome measures), combining data may possibly provide a more accurate representation of the true effect of the treatment. The upper and lower 95% confidence intervals of the effect-size narrow with increasing numbers and become highly significant in the combined calculation (Fig. 2). The remarkable uniformity of both the effects and the standard deviations across these studies, which involved different practitioners in different sites of the world, suggests that there is a real and consistent effect from homeopathy for this condition.

Adequate statistical power in clinical trials is a problem recognized in both conventional and complementary and alternative medicine (CAM) research.[27–29] Other clearly effective therapies (such as H2 blockers used for the treatment of gastric and duodenal ulcers and with antihypertensive therapy) show similar patterns, in which multiple trials and large sample sizes may be needed to establish an effect.[30] This problem is exacerbated in CAM research because limited funding often prevents enrollment of optimal sample sizes.[29] Meta-analyses of specific clinical problems, such as the one presented here, could be useful in assessing the evidence of other CAM modalities as well.

Some critics have suggested that our previous results were a result of adulteration of the homeopathic preparations.[31] However, infrared spectroscopic analysis, done by an independent laboratory on randomly chosen unopened samples from each of the three studies, showed uniform chemical components without contamination. This would seem to rule out adulteration as a possible explanation for these results.

A difficulty in the evaluation of classical homeopathy by standard research methodology is that by its nature, individualized homeopathic treatment requires that each person be given a specific medicine, based on a unique pattern of signs and symptoms. In most clinical trials the same medicine is evaluated in all subjects. Our intention in these trials was not to test the individual homeopathic medicines, but rather the system of homeopathic treatment as a whole. Sample sizes for each of the individual medicines used in the study were not large enough for meaningful analysis on their own.

Another limitation is the questionable accuracy of reporting by the child's caretaker about the daily number of stools. We attempted to monitor this closely during the daily home visits and believe that any bias that may have existed would have occurred randomly in both groups, resulting in nondifferential misclassification which could diminish the overall treatment effect. Similarly we have no reason to believe that differences in reported ORT use or daily dietary intake occurred by group.

This study addresses one of the limitations of the homeopathic literature reported in the1997 metaanalysis[7] in that it provides further evidence that homeopathy is efficacious for a single clinical condition, acute childhood diarrhea. These results are consistent with our previous findings that individualized homeopathic treatment decreases the duration and number of stools in children with acute childhood diarrhea. Although ORT has been shown to reduce dehydration and mortality from diarrhea, homeopathy could be an inexpensive and important adjunct to further reduce morbidity. The 15 to 20% reduction in the duration of diarrhea we found in these studies would reduce overall days of dehydration, malnutrition and compromised host resistance, as well as ease the burden on the child's caretaker and perhaps prevent the use of unnecessary drugs. Used in combination with ORT, homeopathy should be considered for utilization on a widespread basis for childhood diarrhea.

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Intussusception-associated hospitalization among Venezuelan infants during 1998 through 2001: anticipating rotavirus vaccines

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Background. **The first licensed rotavirus vaccine was withdrawn from use in the United States because of a low risk of intussusception. Consequently tests of new rotavirus vaccines will require some baseline knowledge of the rates and treatment of intussusception in countries where these vaccines will be tested. Therefore the objective of this study was to assess hospitalization rates and describe the epidemiologic and clinical characteristics of intussusception in Carabobo, Venezuela.**

Methods. **This study reviewed hospital data and clinical records of pediatric patients with intussusception admitted to eight hospitals in Carabobo between January 1, 1998 and December 31, 2001.**

Results. **For the 4-year period the average annual hospitalization rate for intussusception among infants (<1 year old) in Carabobo was 35 per 100 000 infants per year (range, 22 to 44), and intussusception was more common among boys (58 per 100 000 infants per year) than girls (29 per**

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