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# The use of homeopathic combination remedy for dengue fever symptoms: a pilot RCT in Honduras

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**A double-blind, placebo-controlled randomized trial of a homeopathic combination medication for dengue fever was carried out in municipal health clinics in Honduras. Sixty patients who met the case definition of dengue (fever plus two ancillary symptoms) were randomized to receive the homeopathic medication or placebo for 1 week, along with standard conventional analgesic treatment for dengue. The results showed no difference in outcomes between the two groups, including the number of days of fever and pain as well as analgesic use and complication rates. Only three subjects had laboratory confirmed dengue. An interesting sinusoidal curve in reported pain scores was seen in the verum group that might suggest a homeopathic aggravation or a proving. The small sample size makes conclusions difficult, but the results of this study do not suggest that this combination homeopathic remedy is effective for the symptoms that are characteristic of dengue fever.** *Homeopathy* (2007) **96, 22–26.**

**Keywords:** homeopathy; dengue fever; influenza; combination remedies

## Introduction

Dengue fever is caused by a mosquito-borne virus endemic to many tropical areas of the world, with millions of cases reported yearly. In the past 25 years, this disease has reemerged with an expanded geographical distribution, increased epidemic activity, and an increase in the number of cases of the more severe form, dengue hemorrhagic fever.[1] Prevention efforts for this illness have emphasized mosquito control and increased community surveillance and a vaccine is under development. Treatment is supportive, with paracetamol for fever and aching and fluid replacement in severe cases with hemorrhage and/or shock.[2]

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Homeopathy was used extensively for treatment of dengue outbreaks in the US in the 19th century[3] and it has been recommended as an effective treatment, based on anecdotal reports.[4] A computer search of the homeopathic literature found 43 references to dengue and included 20 homeopathic medicines,[5] the most frequently indicated of which can be found in Table 1. Homeopathy has been used successfully for the prevention and treatment of a number of infectious diseases, including influenza[6] and diarrhea.[7–9] There have been no previous studies, however, to evaluate the efficacy of homeopathy in the treatment of dengue fever.

A double-blind randomized placebo-controlled pilot study of a homeopathic combination remedy for dengue fever was carried out in Honduras to determine if there is sufficient evidence that homeopathy can (1) shorten the clinical course of the disease, and (2) reduce the severity of symptoms to justify a larger trial.

**Table 1** Common homeopathic medicines for dengue fever and their indications[10]

*Aconitum napellus (Monkshood)*
Physical and mental restlessness, fright; does not want to be touched
Sudden and great sinking of strength; acute, sudden, and violent onset with fever
The pains are intolerable; burning headache
Mucous membrane dry, nose stopped up

*Belladonna (Deadly Nightshade)*
Hot, red skin, flushed face, glaring eyes, throbbing carotids
Excited mental state, hyperesthesia of all senses, delirium
Restless sleep, convulsive movements
Dry mouth and throat
Pains that come and go suddenly

*Bryonia alba (Wild Hops)*
Patient wants to lie completely still and is worse from any movement
Stitching, tearing pains that are worse from motion, better from rest
Dryness of mucous membranes with increased thirst
Irritable, wants to be left alone
Bursting, splitting headache and stiffness in the small of the back
Liver area sore and swollen, sensitive to touch
Joints red, hot, swollen

*Eupatorium perfoliatum (Thoroughwort)*
Throbbing pain in the head and feeling of pressure like a cap on the head
Occipital pain on lying down, with a feeling of weight; soreness of eyeballs
Severe bone and muscle pains accompanying a fever
Yellow tongue with bitter taste in the mouth
Increased thirst and aching in bones of the extremities preceding chills
Nausea and vomiting of bile; aching in back, arms, and wrists

*Gelsemium (Yellow Jasmine)*
Dullness of the mind with lethargy and apathy regarding the illness
Dull, heavy headache and backache; heaviness of the eyelids—wants to keep eyes closed
Face hot and flushed; weakness and trembling of limbs
Chills going up and down the back; episodes of heat alternating with sweats
Thirstlessness

*Rhus toxicodendron (Poison ivy)*
Extreme restlessness with constant change of position
Pains are worse on first moving, improve as limbers up
Heaviness and headache in the back of the head
Great thirst with dry mouth and throat
Pain and stiffness in small of the back; pain and swelling of the joints
Intense urticaria with vesicular skin rash

## Research design and methods

### Enrolment of study subjects

Patients over age 12 with a case definition of dengue (fever > 37C with any two of the following symptoms: headache, retro-orbital pain, myalgia, arthralgia, or skin rash) were considered for enrollment from two health centers in the Metropolitan area of Honduras. Patients with symptoms for more than 72 h and those with a history of anemia, malaria, liver disease, or arthritis were excluded. All subjects were asked to sign an informed consent form approved by the Human Subjects Committee of the University of Washington and the Ethics Committee of the Faculty of Medicine of Honduras prior to enrollment. An oral assent form with thumbprint was used for those who could not read and a parent or guardian also was asked to sign for those subjects under age 18.

Baseline demographic information was collected at the initial visit as well as past medical history, date of onset and severity of current symptoms, and the use of medications for current illness. Subjects then were given a complete physical examination and blood samples were obtained. A complete blood count, including platelets, and liver function tests were done at entry into the study to compare with later samples for complication rates. For diagnosis of dengue, specimens for MACELISA (IgM antibody capture enzyme linked immunosorbent assay), IgM, virologic culture, and HI (hemagglutination inhibition) testing on paired sera (the second sample was collected at 6 days) were drawn. Laboratory tests were carried out at the Hospital Escuela in Tegucigalpa, Honduras.

### Study medication and randomization

The homeopathic treatment used in the study was a combination medicine composed of six medicines with symptoms suggesting that they might be useful in the treatment of dengue fever: *Aconite, Belladonna, Bryonia, Eupatorium perfoliatum, Gelsemium, and Rhus toxicodendron* (Table 1). The medicines in the combination were all in the 12C potency, which means that the original tinctures were diluted 1:100 in a water/alcohol solution twelve times, for a resulting dilution of $10^{-24}$. The potentized medicines were then combined and used to impregnate lactose tablets. Placebo medication consisted of lactose tablets alone.

Patients were randomized to receive either the homeopathic combination or placebo, using coded bottles of study medication. A random numbers table was used by a pharmacist in the US to create a scheme for randomizing the bottles to the two study treatments in blocks of four and six. The coded bottles were then numbered in sequential order and treatment assignment for each patient was made by selecting the next bottle in sequence. There were no detectable differences in taste, odor, or color between the treatment medication and placebo, and they were packaged in identical tubes that were sealed at the laboratory and remained unopened until delivery to the patient. The tablets were furnished by the Boiron Laboratories, Newtown Square, Pennsylvania and the code was held by the pharmacist in the US who prepared them. All study personnel in Honduras were blinded as to treatment allocation.

Subjects were told to take two tablets four times each day, at 8 a.m., 12 noon, 4 p.m., and 8 p.m., for 1 week, or until symptoms resolved, whichever occurred first. Subjects were instructed not to eat or drink anything for 15 min before and after taking the study medicine, except water. An initial dose of two tablets was given to the subject in the clinic. An instruction sheet was given to each subject with simple illustrations of the study procedures. Subjects were allowed to take conventional analgesic medication (paracetamol) during the trial as needed for pain.

Subjects were given a simple card to record level of pain (using a smiley face VAS score on a 1–5 scale) and temperature twice daily, between 7–9 a.m. and 7–9 p.m. Two temp-o-dot oral strips were given to each subject daily to determine temperature along with instructions on how to use them.

### Patient follow-up

Follow up home visits were made daily for six consecutive days by community health workers to monitor the condition of the patients, record symptoms, evaluate compliance, and encourage further participation. Subjects were also questioned about their use of medications, as well as about any adverse effects attributed to the study medications. A new daily card and two additional temp-o-dot strips were given to the subject each day. In an attempt to check compliance, the medication bottles (for a pill count) were checked at the end of the study period. Blood samples were collected at 6 days follow-up to obtain paired serum samples and to evaluate possible complications. Patients who developed symptoms suggestive of dengue hemorrhagic fever (DHF) were to be hospitalized immediately and appropriate conventional treatment instituted.

## Results

Eighty-nine patients were screened for entry into the study during September, 2001. Of these, 60 fit the case definition of dengue fever and were enrolled in the study, 29 randomized to homeopathy and 31 to receive placebo. One patient from the homeopathy group was lost to follow-up, the remaining 59 completed the entire 7 days of the study.

Comparisons of patient characteristics using Student's *t*-tests for means and chi square with two by two tables for categorical data at entry into the study can be seen in Table 2. There was a statistically significant higher proportion of females in the verum and the same group reported more analgesic use prior to starting the study, this came close to statistically significance. No other significant differences found between the two groups.

Results of primary outcome variables can be seen in Table 3. There were no differences between the two groups in the mean number of days until the subject was free of pain, fever, or both pain and fever for at least two consecutive days. A chi-square analysis of these outcomes was also showed no significant differences (Table 4). There were no significant differences in the average scores for pain and fever at each consecutive 12 h period between groups (Fig. 1).

No differences in use of analgesics nor in the pill counts between the two groups were found (not shown). No subjects developed complications suggestive of DHF. Two patients were admitted to the hospital, one from each treatment group, one with acute glomerulonephritis and the other with acute fulminating malaria. Results of laboratory tests confirmed dengue fever in only three subjects, all in the placebo group. These patients had positive viral cultures, confirmed by positive IgM serology. Three patients had laboratory confirmed malaria, two in the

**Table 2** Patient characteristics at entry to study

| | *Homeopathy* ($n = 29$) | *Placebo* ($n = 31$) | *p-value* |
|---|---|---|---|
| Hours since onset of symptoms | 41 | 37 | 0.50 |
| Pain rating score | 3.9 | 3.9 | 0.92 |
| Temperature (Celsius) | 37.6 | 38.0 | 0.10 |
| Analgesic usage rate | 85.7% | 64.5% | 0.06 |
| Previous dengue episode | 28.6% | 22.6% | 0.60 |
| Married | 39.3% | 61.3% | 0.09 |
| Sex female | 82.1% | 54.8% | 0.02 |
| Age (mean) | 30.6 | 27.5 | 0.24 |
| Primary education only | 70.4% | 70.0% | 0.92 |

**Table 3** Comparison of mean duration of symptoms (with standard deviation), homeopathic combination remedy versus placebo

| | *Homeopathy* ($n = 28$) | *Placebo* ($n = 30$) | *p-value* |
|---|---|---|---|
| Days until no fever | 2.57 (1.9) | 2.26 (1.6) | 0.49 |
| Days until no pain | 3.46 (1.8) | 3.29 (1.8) | 0.69 |
| Days until no pain or fever | 3.71 (1.9) | 3.58 (1.7) | 0.77 |

**Table 4** Number of patients with corresponding duration of symptoms

| Duration: Hours | 24 | 48 | 72 | 96 | 120 | 144 | >144 |
|---|---|---|---|---|---|---|---|
| Days | 1 | 2 | 3 | 4 | 5 | 6 | >6 |
| *Until no pain* | | | | | | | |
| Homeopathy | 4 | 6 | 7 | 2 | 4 | 3 | 2 |
| Placebo | 4 | 10 | 5 | 3 | 4 | 4 | 1 |
| Chi-square 1.86, *p*-value 0.93 | | | | | | | |
| *Until no fever* | | | | | | | |
| Homeopathy | 11 | 7 | 3 | 2 | 1 | 3 | 1 |
| Placebo | 15 | 5 | 5 | 2 | 2 | 2 | 0 |
| Chi-square 2.84, *p*-value 0.83 | | | | | | | |
| *Until no pain or fever* | | | | | | | |
| Homeopathy | 3 | 7 | 5 | 2 | 4 | 5 | 2 |
| Placebo | 2 | 9 | 6 | 4 | 4 | 5 | 1 |
| Chi-square 1.39, *p*-value 0.96 | | | | | | | |

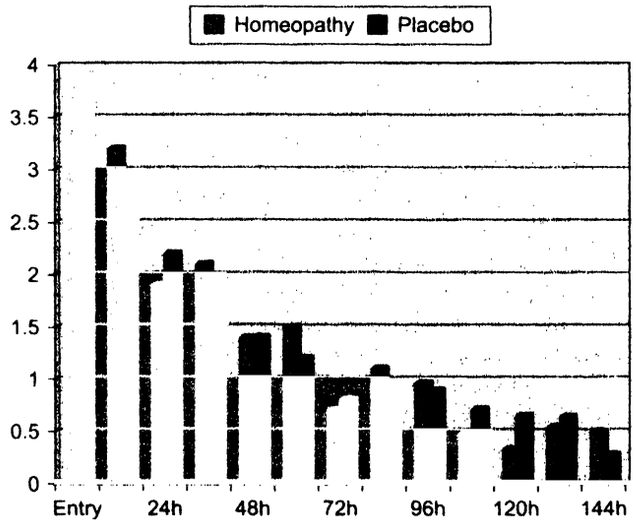


**Fig. 1** Comparison of mean pain rating scores over time (non-significant at any point).

group receiving homeopathy and one in the placebo group.

## Discussion

It is important to note that this study did not evaluate the efficacy of homeopathy in the treatment of dengue fever. This was a study of the use of a specific combination of homeopathic remedies in the treatment of patients with symptoms consistent with dengue fever. Although we used the case definition for dengue fever used by the Honduran Health Ministry, only three study subjects were confirmed to have dengue by laboratory analysis, which was carried out on all cases. This suggests that either many of the cases attributed to dengue in Honduras are not such and/or the laboratory techniques used in this study for confirmation of dengue were inadequate. Since very few clinically diagnosed cases of dengue in Honduras are subjected to laboratory testing, it is likely that the former is the case, especially since the results of both viral cultures and IgM serology were consistent in all cases.

Despite this misdiagnosis, from a homeopathic standpoint, these patients with pain and fever should theoretically respond to this combination of remedies, well known in the homeopathic literature for their use in flu-like syndromes. The fact that they did not is troubling, suggesting that further studies of this combination may not be indicated. However, there are several factors that could have contributed to this outcome.

The first to be considered is the small sample size. With only thirty subjects in each of two treatment groups, it is possible that the effect size difference is not large enough to be detected in this study. Most allopathic drug trials have thousands of subjects in each arm, which allows even a small difference in outcomes to be seen as statistically significant. It could be expected, however, to see some positive trend in one of the several outcomes we examined. Given the effort of mounting such a trial in a developing country such as Honduras, it would seem that a larger sample size would have been warranted to better evaluate our hypothesis.

Another mitigating factor could have been lack of sensitivity of outcome variables. While the smiley face VAS scale had been validated in previous studies of children, it is possible that it was not appropriate for use in adults. Since our subjects had a low literacy rate, however, we thought this was preferable to a standard adult outcome scale. While pain perception is subjective, differing among various people, one would expect this to be consistent in each individual subject over time. The use of the temp-o-dots to measure fever also could have been a problem, since many subjects lived in poor conditions and could not always keep them away from heat or sun. It is also possible that the medications were not stored, handled, or taken properly, although the pill count at the end of the study did not indicate a major problem in this regard.

The use of combination remedies is the mainstay of the over-the-counter homeopathic market and judging by their popularity, the consumer public finds them useful. It is possible, however, that there were problems with this particular product, which was manufactured specifically for this study. Perhaps these six medicines did not combine well, canceling out or antidoting each other in some way. For example, in the Relationship of

Remedies table compiled by R. Gibson Miller found in the back of Kent's Repertory, *Aconite, Belladonna,* and *Bryonia* are all listed as antidotes to *Rhus toxicodendron.*[12] Future studies could use combinations already manufactured and widely sold and/or pay stricter attention to possible antidoting interactions.

It is also possible that the repeated doses of the 12C potency caused a proving or aggravation in those taking verum, whereby the symptoms got worse temporarily after taking the doses each day. Of interest is the sinusoidal curve in the mean pain scores of those taking verum (Fig. 1) compared to placebo. Since medicines were taken uniformly at 8 a.m., 12 p.m., 4 p.m., and 8 p.m. and symptom scores were recorded in the morning (7–9 a.m.) and evening (7–9 p.m.), the higher scores at 36, 60, and 84 h would have coincided with the evening recording, after 3–4 doses of the medication had been taken. Conversely, the morning report would have reflected 12 h without medication. Considering this possibility, perhaps a lower potency combination, lesser dosages per day, or both, should be considered in future protocols.

Finally, one must address the now popular 'entanglement' theory.[13] This theory borrows from quantum physics and posits that the homeopathic interview along with the intention to heal from the homeopathic provider have a positive effect on the outcome of treatment. If this is correct, one would expect that a combination remedy given to all subjects without the involvement of the patient–physician relationship would fail. In our previous work, individualized homeopathy was found to be effective for childhood diarrhea in three separate studies[7–9] and a meta-analysis.[11] However, a more recent study of a combination medicine composed of the five most commonly prescribed remedies did not show a difference from placebo.[14]

It is clear that more research needs to be done to determine the usefulness of homeopathic combinations in public health settings. Epidemic diseases such as dengue fever, malaria, tuberculosis, and HIV-AIDS continue to plague humanity and there is much concern about the threat of an influenza pandemic. While conventional modern medicine makes valiant efforts to control these illnesses, resistance to antimicrobials, mutations of viruses, and variant strains such as those that occur in dengue continue to emerge. Whether or not homeopathy can contribute in this area remains to be seen, but historical records suggest that it might. While the individualized approach to homeopathic treatment is preferred by most, it is difficult to implement in resource limited settings where epidemic diseases are most common.

The results of this study do not suggest that this combination homeopathic remedy is effective for the symptoms that are characteristic of dengue fever. However, further well-designed studies of different combinations of remedies as well as individually-prescribed remedies should be carried out to explore the public health value of homeopathy in dengue and other epidemic diseases.

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