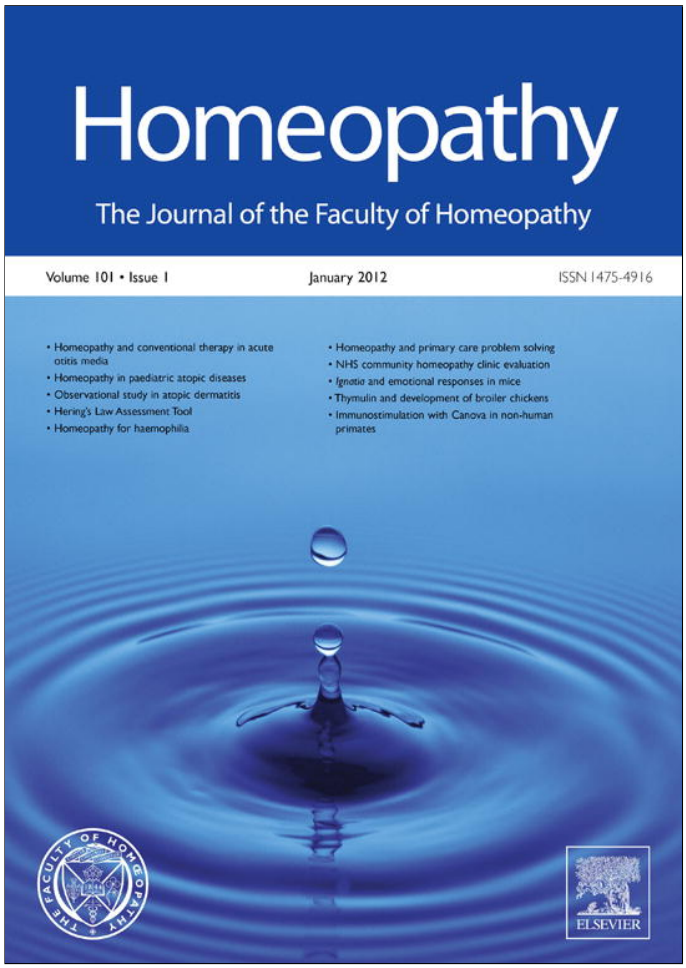

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ORIGINAL PAPER

Homeopathic medicines substantially reduce the need for clotting factor concentrates in haemophilia patients: results of a blinded placebo controlled cross over trial

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Background: **Modern management of haemophilia patients is expensive: 90% of expenditure is on clotting factor concentrates. Any intervention which reduces the need for clotting factor concentrates in these patients without compromising the quality of life is of interest.**
Aims and objectives: **To investigate the effectiveness of individualised homeopathic medicines in reducing the requirement of factor concentrates in haemophilia patients.**
Materials and methods: **In a single blind placebo controlled cross over trial 28 consecutive persons with haemophilia (PWH) with severe (24) or moderately severe (4) disease received standard management with placebo homeopathy for 1 year and active homeopathic treatment in the subsequent year with the same conventional management. There was no wash out period. They received standard managements for any acute emergency during the study period. Development of inhibitor during the study period was a withdrawal criterion. Sample size for the trial was calculated as 24 PWH.**
Transfusion requirements, bleeding scores, pain scores were evaluated blind by independent experts. Homeopathic medicines were selected by experienced homeopathic physicians depending on clinical condition of the patient. Chi-squared and paired *t* tests were used in statistical analysis.
Results: **28 patients were recruited. Homeopathic medicines improved frequency of bleeding, extent of bleeding, blood products consumed and pain scores ($P < 0.0001$). There was also significant improvement in well being. Plasma levels of clotting factors did not change. No patients developed inhibitors during the study there were no drop-outs.**
Conclusion: **Individualised homeopathic medicines may have an important supportive role in the management of PWH, where blood products and factor concentrates are not easily available. Larger, perhaps multicentric trials are warranted.** *Homeopathy* (2012) **101**, 38–43.

Keywords: Homeopathy; Severe haemophilia; Supportive therapy; Developing country; Haemarthrosis; Pain relief; Behavioural changes

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Introduction

Haemophilia is a low frequency high cost disease, 90% of world's haemophilia population lives in developing countries where proper management with factor concentrates

is not widely available.[1] In many centres in India factor concentrates are used for haemophilia patients only when nothing else is working and complications due to bleed are life threatening. The situation in India is slowly changing for the better but there is still a long way to go before modern comprehensive care for haemophilia patients is available.[2] Until then wet blood components and nonfactor concentrate management including various physical therapies will play a major role in keeping our persons with haemophilia (PWH) fit and functional.[3,4]

India is home to many forms of alternative and complementary medicine including Ayurveda, Unani, Siddha and Homeopathy. AYUSH, a department of the Ministry of Health and Family Welfare encourages manpower development and funds research in these areas of medicine. All these forms of alternative and complementary medicine are recognised by the government of India, like mainstream medicine. Undergraduate and specialised MD postgraduate programmes are available for students in these branches of medicine.

We evaluated homeopathic treatment in 28 severe/moderately severe PWH. The main objective of the study was to see whether homeopathic medicines can reduce the usage of blood products and improve the quality of life of these patients in terms of pain and behaviour.

Materials and methods

Trial design

Blinded placebo controlled single arm cross over design. Each PWH was treated for one year with placebo homeopathy under the guidance of homeopathic physician along with standard medical management with factor concentrates, pain relief with paracetamol and Rest, Ice, Compression, Elevation (RICE) therapy for active joint bleeds. The treating homeopathic physicians were not blinded. In the second year the same patients received active homeopathic medicines along with standard management. Hence each patient was their own control, the cross over design improved the statistical power of the study as variability was reduced. Patients were assessed by physiotherapists and doctors trained in modern medicines blind to the nature of homeopathic intervention: active or placebo. The PWH were also blind. Each patient maintained a diary of his number and site of bleeds, pain score during each bleed, duration of bleeding and amount and nature of factor concentrates used.

Participants

Patients were diagnosed as haemophilia and the severity was classified with factor assays from National Institute of Immunohaematology at KEM Hospital, Mumbai. Patients with less than 0.01 iu/ml of factor level in the plasma were regarded as having severe disease, those with 0.01−0.05 iu/ml moderate disease. The patients were evaluated regularly for inhibitor development using APTT (Activated Partial Thromboplastin Test) based correction assays using 50:50 normal and patients plasma. More than 8 s prolongation of APTT in pre-mixed incubated plasma compared to separately incubated and mixed plasma was regarded as positive for inhibitors as per the norm of this laboratory.

Eligibility criteria

Patients with inhibitors and those who required less than 1000 Unit of factor concentrates or its equivalent in the previous year or who had active hepatitis as evidenced by liver function tests or positive hepatitis virus serology or HIV positive serology were excluded from the study. Haemophilia patients who had <3 bleeds/year were also excluded from the study.

Of 34 patients with haemophilia, 1 was excluded because of presence of inhibitors and another 5 were excluded because of abnormal liver function test or hepatitis B or hepatitis C virus positivity, 28 patients were finally selected for the study. Relevant informed consent from the patients and from their parents in their own mother tongue for this trial was taken and the study was sanctioned by the Institutional Review Board of MB Homeopathic Medical College, Nashik, Maharashtra, India on 27th September 2002. The study period was from January 2003 to October 2006.

Sample size

Sample size was determined on the basis of 80% power to detect a reduction of 20% or more of factor concentrate usage with 95% confidence interval. The number required was computed at 24. We recruited 28 PWH patients to allow for removal due to inhibitor development and default.

Intervention

All PWH under the study were interviewed according to the homeopathic principle of case taking and the data were entered in a specific case record format.[5] Detailed interviews by homeopathic physicians were conducted during the initial presentation for the study and then once every three months. Consultations were scheduled once every 3 months unless earlier consultations became imperative due to active bleeding. After formative analysis and evaluation, the indicated homeopathic medicine was prescribed.[6] Patients had regular physiotherapy. In the event of joint bleed initially RICE technique was employed. If there was no relief within 6 h factor concentrates or equivalent FFP (Fresh Frozen Plasma) or cryoprecipitate was infused at 10 ml/kg body weight of FFP or 1 unit of cryoprecipitate/10 kg body weight. Most PWH could afford only a single dose of factor concentrate therapy. The patients maintained a diary noting the frequency of bleeding, amount of paracetamol taken, amount of factor concentrates and blood product infused and severity of pain. This management was continued for a year then the patients were switched to active homeopathic medicines.

Patients received individualised combinations of homeopathic medicines, given singly on separate occasions. The medicines were decided by three expert homeopathic physicians. The most frequently prescribed medicines were: *Arnica montana*, *Hamamelis*, *Phosphorus*, *Calcarea*

fluorica, *Magnesium phosphoricum*, *Ferrum metallicum*, *Ledum palustre*, *Causticum*, *Sulphur*, *Hypericum*. Generally patients were given one constitutional medicine and symptomatic medicines like *Arnica*, *Hamamelis*, *Ledum palustre*, *Hypericum*, *Magnesium phosphoricum* depending on severity site and nature of bleeding, pain or nature of the insult which produced the emergency.

All medicines were used in centesimal potencies of 30 and 200, on globules given orally every 1−2 hourly during acute bleeds (for symptomatic) and then once a day for few days after the bleeding stopped, except *Hamamelis* which was used in Mother Tincture (MT) 6−10 drops in 10 ml water 6 hourly till the bleeding stopped. Constitutional remedies such as *Sulphur*, *Hepar sulphuris calcareum*, *Calcarea carbonica*, *Calcarea fluorica*, *Causticum* and *Lachesis* were given once and not repeated as long as improvement lasted. Patients received no more 5 constitutional medicines during the study period. Patients were followed up every month when they were symptom free and as necessary during acute episodes.

All medicines were purchased from the same company with same batch and lot number (SBL, New Delhi, India). Placebos were dummy sugar globules or rectified sprit given in drop dosages without any active medicinal ingredient added. Homeopathy was used as supportive therapy, patients continued physiotherapy and other interventions as necessary.

Outcome

All the patients kept a diary noting the number of bleeds, treatment taken for pain relief, days of absence from school/working place, amount of factor concentrates/blood products taken. The results are evaluated as per Wong Baker Pain rating scale.[7] Behavioural changes before and after homeopathic treatment were scored by Vineland maladaptive behaviour scale.[8] This scale is evaluated on the basis of behaviour at home, school and society in terms of activity, cooperation and communication. Bruises in PWH are usually not treated hence they were not recorded. All evaluations were done by authors AN, RK, KG and SK. As no patients developed inhibitor during the study period and none defaulted, all 28 patients were included in the final analysis.

The statistical analysis was comparison between the same patients at the end of homeopathic placebo and at the end of active homeopathy (paired *t* test). All other management remaining the same and evaluation of different parameters was done by experts who had no knowledge of homeopathic therapy (AN, RK, KG and SK). Analysis was done in several areas i.e. improvement in pain score, frequency of joint and other bleeds and amount of factor concentrates or blood products used and days of absence from school/work due to bleeding and/or pain. For non-parametric tests Chi-squared test was used. $P < 0.05$ was considered statistically significant.

Results

Six patients excluded because either they had inhibitor or were seropositive for hepatitis or HIV. Twenty-eight patients aged 6−18 years were included. Demographic data are given in Table 1.

There were a total of 203 bleeding episodes/year in 28 patients in the placebo period. Of these, 14 bleeds were from mucous membranes: genitourinary, gums, epistaxis. There were no frank bleeds from skin. In the subsequent year on homeopathic medicines there were 21 bleeds of which one was epistaxis, 2 genitourinary and the remaining 18 joint bleeds.

No patients' deficient plasma clotting factor levels increased during active homeopathic treatment.

The demographic details, pain scores and behavioural scores before and after therapy are presented in Table 1. The pain score and behavioural scores improved significantly on homeopathic therapy ($P < 0.001$). Reduction of pain scores on homeopathic medicines also leads to reduction of analgesic usage. The reduction in frequency of bleeds during active homeopathic therapy was from 7.25 (sd 7.15) per patient per year to 0.75 (sd 1.08) $P < 0.0001$. Similarly factor usage ($P < 0.0001$), days of absence from school or work ($P < 0.0001$) was highly significantly improved on homeopathy compared to placebo (Table 2).

19 of 28 patients showed an improvement of over +4 on the Vineland behaviour scale (Table 1) ($P < 0.001$, Chi-squared test). Wong Baker Pain Scale scores also showed significant improvement (Paired *t* test $P < 0.0001$).

None of these patients developed inhibitors during the study, inhibitor frequency at this centre is 16% over 10 year period, thus we might have expected 4 patients in this cohort to develop inhibitor.

Arnica, *Ledum palustre*, *Magnesium phosphorica* and *Hypericum* were most useful for pain while *Arnica*, *Hamamelis*, *Millefolium*, were useful in acute bleeding. *Calcarea fluorica* was found to be of greatest help with haemophilic synovitis. *Millefolium* was effective for epistaxis. Most patients had haemophilic arthritis of one or more joints, constitutional remedies like *Causticum*, *Calcarea carbonica* and *Hepar sulphuris* and *Lachesis* were found useful (16/28 patients).

Illustrative cases

Case 1

6 year old boy (factor VIII < 0.01 iu/ml) had recurrent bleeding in the left knee joint. He was receiving cryoprecipitate as factor VIII replacement along with paracetamol 500 mg thrice daily for pain. During each bleeding episodes he received RICE therapy also. His acute bleeding responded well to *Arnica* 30c, 6 globules 4 hourly with *Hamamelis* MT 6 drops twice daily. Considering his knee joint involvement and exquisite sensitivity to pain he was prescribed *Causticum* 30c as constitutional. His bleeding episodes became fewer after two doses of *Causticum* separated by 3 months. Presently he bleeds occasionally.

Case 2

14 year old boy (factor VIII < 0.01 iu/ml) had urinary tract bleeds almost once every month. Ultrasound imaging

Table 1 Patient demographics and response to therapy for pain and maladaptive behaviour

Case no. (age in years)	*Case no.*	*Type of haemophilia*	*Wong Baker Pain Scale**		*Vineland maladaptive behaviour scale†*	
			Before treatment	*After treatment*	*Before treatment*	*After treatment*
1 (17)	H-1	Severe haemophilia A	10	2	6	12
2 (11)	H-2	Severe haemophilia A	8	6	8	14
3 (6)	H-3	Severe haemophilia A	10	6	10	16
4 (9)	H-5	Severe haemophilia A	8	2	6	14
5 (14)	H-6	Severe haemophilia A	8	2	8	16
6 (12)	H-7	Moderate haemophilia A	8	4	10	16
7 (12)	H-8	Severe haemophilia A	10	2	10	8
8 (18)	H-9	Severe haemophilia B	8	6	12	16
9 (11)	H-10	Severe haemophilia A	6	6	10	16
10 (7)	H-11	Moderate haemophilia A	8	2	14	24
11 (8)	H-13	Severe haemophilia A	8	2	14	24
12 (9)	H-14	Severe haemophilia A	10	4	4	10
13 (12)	H-15	Severe haemophilia A	8	4	8	16
14 (13)	H-16	Severe haemophilia A	10	6	12	20
15 (15)	H-18	Severe haemophilia A	8	4	6	14
16 (15)	H-19	Moderate haemophilia A	8	2	10	16
17 (18)	H-21	Moderate haemophilia A	6	2	12	16
18 (9)	H-23	Severe haemophilia A	6	2	10	18
19 (8)	H-24	Severe haemophilia A	8	2	6	12
20 (7)	H-25	Severe haemophilia B	8	2	12	20
21 (12)	H-27	Moderate haemophilia A	6	2	10	12
22 (12)	H-28	Severe haemophilia A	10	4	10	16
23 (18)	H-29	Severe haemophilia A	10	6	12	16
24 (12)	H-30	Moderate haemophilia A	10	4	10	14
25 (6)	H-31	Severe haemophilia A	8	4	12	16
26 (8)	H-32	Severe haemophilia A	6	2	4	12
27 (10)	H-33	Severe haemophilia A	6	0	10	14
28 (11)	H-34	Severe haemophilia A	6	4	10	14

* Wong Baker Pain Scale (0−10) Paired *t* test *P* value < 0.0001 ($t = 13.6850$, df = 27).
† Vineland scale Chi square $P < 0.001$.

showed no stones or other pathology. As hydration is one of the main therapy for urinary bleeds patient received 3−4 l of water to drink in addition to factor concentrates corrected to 40% levels. Replacement of factor concentrates stopped the bleeding in 48−72 h. On several occasions *Hamamelis* MT was given 4 hourly but bleeding did not stop without factor replacement. History of slow developmental milestones, lethargy, head sweats lead to prescription of *Calcarea carbonica* 30c as constitutional remedy rising to 1 M over six months. His urinary bleeding completely stopped on this medicine. He was very badly behaved at school, his behaviour also improved.

Case 3

18 year old boy with known severe factor IX deficiency (<0.01 iu/ml) had previous two episodes of cerebral bleed when he was treated with factor IX concentrates with 100% correction for 14 days along with antifibrinolytic drugs like Epsilon Amino Caproic Acid (EACA). Present admission was due to 3rd cerebral bleed. Unfortunately patient could not get factor IX concentrates and factor IX in FFP was not sufficient to treat such bleeding. Hence though patient was started on FFP infusion his condition deteriorated and neurosurgeons suggested surgery to remove the clot but in the absence of factor IX concentrates this was not possible. Patient became unconscious with Glasgow Coma Scale of 5. While he continued FFP and EACA his condition continued to deteriorate. He was given *Opium* 30c, 4 hourly and *Lachesis* 200c, 4 globules twice daily. The patient slowly recovered completely on this therapy. *Opium* was stopped as soon as patient became conscious but *Lachesis* was continued as an intermittent constitutional remedy. In the last three years the patient did not have any major or dangerous bleed though he continues to have small bleeds from nose and mouth which are controlled mostly with *Arnica* 30c and antifibrinolytic drugs.

Discussion

Modern management of severe and moderately severe haemophilia depends on adequate treatment with missing factor concentrates, pain relief and regular physiotherapy

Table 2 Changes in frequency of bleeds, factor concentrate requirements and absenteeism due to consequences of haemophilia before (placebo) and after homeopathic treatment

Patients (n = 28)	*Bleeds/year, mean (sd) [range]*	*Factor usage iu/year, mean (sd) [range]*	*Absenteeism in days/year, mean (sd) [range]*
Placebo	7.25 (7.14) [2−30]	3617 (3361) [1000−12,500]	50.4 (27.6) [8−111 days]
Homeopathy	0.75 (1.075) [0−5]**	632 (1077) [0−5000]**	4.75 (8.20) [0−40]

** P < 0.001.

and other modalities of treatment for various complications of this disease. Being a genetic disorder genetic counselling and in many countries carrier detection and prenatal diagnosis form an important components of the management strategy.[9,10] The prevalence of haemophilia is 1 in 10,000 births for factor VIII deficiency and 1 in 40,000 births for factor IX deficiency, and is constant in different parts of the world.[11]

Our trial showed better pain relief, less frequency of bleeds, less absenteeism and better quality of life in most patients when treated with homeopathy. It is true that we could not treat most of our patients with adequate dosage of factor concentrates as in wealthier countries and often we administered blood products, probably too little and too late. Yet the same was true in both arms. Moreover none of the 28 patients during study period developed any inhibitor when we would have expected 3 or 4 to do so.

Partly this may be explained by the substantial reduction in the requirement for blood products during the study period. This reduced the antigenic load and exposure days, which are important contributory factors for inhibitor development.

It was not possible to separate the action of constitutional remedies from acutely prescribed intercurrent medicines like *Arnica*, *Hamamelis*, *Millefolium* etc. in this small study which was not designed to dissect these two effects. It is possible that acute intercurrents stopped episodes of bleeding and constitutionals reduced the frequency and intensity of bleeding along with improved quality of life.

In a developing country one of the major problems is lack of availability of adequate amounts of factor concentrates mainly for financial reasons. This situation provided an opportunity to study the effects of alternative medicines like homeopathy in PWH without ethical problems. This kind of study would not have been possible in developed countries as adequate factor replacement therapy would effectively negate any advantage shown by homeopathic treatment.

There numerous arguments in the medical literature as to whether homeopathic medicines are mere placebos not.[12–15] Homeopaths feel that the way modern medicine looks at drug trial is not conducive in measuring positive homeopathic effects because different patients with same disease and disease complications may need different individualised rather than giving the same treatment for all patients with similar disease as in modern medicine.[14]

One of the arguments why the patients did better on homeopathy could be prior physiotherapy during the year of placebo treatment: when active homeopathic therapy was started patients already had a year of physiotherapy and this may have a bearing on the next year's well being while on homeopathic medicine and continued physiotherapy.

This trial used unanimous decision of three trained homeopathic physicians to select the drug(s) and its potencies and duration of treatment based on patients' condition, similium and the complications of haemophilia itself.

The present trial, although small shows the positive effect of homeopathic medicine in several important clinical consequences of haemophilic bleeding and a much larger randomised multicentric trial. If the results can be replicated homeopathy may be of use as an adjuvant therapy even in developed countries. One of the limitation of the present study is that it is a sequential study of placebo *versus* homeopathic treatment and it was not a parallel randomised comparison between two groups given management at the same time. In addition, in western countries inhibitor development is frequent (35–40%), we excluded patients with inhibitor and those with positive hepatitis or HIV serology in the current study. Hence this study is unable to answer the question as to whether homeopathy will be equally useful in patients with haemophilia who have developed inhibitor or are positive for transfusion transmitted infections (hepatitis/HIV).

Since this was a single centre study question about its generalisability arise particularly because homeopathic medicines were selected by a group of homeopaths trained in the same institution.

A multicentric double blind randomised study using homeopathic medicines is required. Such a study needs to consider that homeopathic treatment may alter the long term trajectory of patients illness. High quality clinical trials should be able to measure this changed trajectory of disease.[14]

In conclusion it appears that homeopathic treatment of severe and moderately severe haemophilia patients provides worthwhile relief in the form of reduced frequency and amount of bleeding, reduced requirement of costly factor concentrates and improved mental well being which translated into improved behaviour and reduced absenteeism.

Division of responsibilities and declaration of interests

Dr Tapas Kundu, Dr Afroz Shaikh and Dr Afzal Kutty are homeopathic physicians who prescribed the homeopathic medicines. Dr Sudhir Kulkarni, the surgeon and Dr Aparna Nalvade, the physiotherapist evaluated the patients blind without knowing when the patient was on placebo or on active homeopathic medicines. Dr Aparna Nalvade also gave physiotherapy to these patients. Dr Ranjan Kulkarni, pathologist was responsible for laboratory. Dr Kanjaksha Ghosh conceived the study in consultation with the above investigators, did the statistical analysis and wrote the final version of the paper, and evaluated patients. Factor assays, inhibitor screening were confirmed at National Institute of Immunohaematology, Mumbai.

There were no conflicts of interest. The sources of funding were the Haemophilia Society Nashik Chapter and NIIH Mumbai.

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