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A randomized controlled trial of homeopathy in rheumatoid arthritis

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Abstract

Objective. To test the hypothesis that homeopathy is effective in reducing the symptoms of joint inflammation in rheumatoid arthritis (RA).

Method. This was a 6-month randomized, cross-over, double-blind, placebo-controlled, single-centre study set in a teaching hospital rheumatology out-patient clinic. The participants of the study were 112 patients who had definite or classical RA, were seropositive for rheumatoid factor and were receiving either stable doses of single non-steroidal anti-inflammatory drugs (NSAIDs) for $\geqslant 3$ months or single disease-modifying anti-rheumatic drugs (DMARDs) with or without NSAIDs for $\geqslant 6$ months. Patients who were severely disabled, had taken systemic steroids in the previous 6 months or had withdrawn from DMARD therapy in the previous 12 months were excluded. Two series of medicines were used. One comprised 42 homeopathic medicines used for treating RA in 6cH (10^{-12}) and/or 30cH (10^{-30}) dilutions (a total of 59 preparations) manufactured to French National Pharmacopoeia standards, the other comprised identical matching placebos. The main outcome measures were visual analogue scale pain scores, Ritchie articular index, duration of morning stiffness and erythrocyte sedimentation rate (ESR).

Results. Fifty-eight patients completed the trial. Over 6 months there were significant decreases ($P < 0.01$ by Wilcoxon rank sum tests) in their mean pain scores (fell 18%), articular indices (fell 24%) and ESRs (fell 11%). Fifty-four patients withdrew before completing the trial. Thirty-one changed conventional medication, 10 had serious intercurrent illness or surgery, 12 failed to attend and three withdrew consent. Placebo and active homeopathy had different effects on pain scores; mean pain scores were significantly lower after 3 months' placebo therapy than 3 months' active therapy ($P = 0.032$ by Wilcoxon rank sum test). Articular index, ESR and morning stiffness were similar with active and placebo homeopathy.

Conclusions. We found no evidence that active homeopathy improves the symptoms of RA, over 3 months, in patients attending a routine clinic who are stabilized on NSAIDs or DMARDs.

KEY WORDS: Homeopathy, Rheumatoid arthritis, NSAIDs, DMARDs.

Patients with rheumatoid arthritis (RA) often take alternative treatments [1], including homeopathy [2]. One trial by Gibson *et al*. [3] published in a mainstream journal provides evidence that homeopathy is effective in RA. A meta-analysis of randomized controlled trials (RCTs) of homeopathy [4], which reached a favourable conclusion on its efficacy, identified three other RCTs. Two positive trials [5, 6] were not in mainstream journals, but a negative report was [7]. Another, independent meta-analysis has also concluded that there is evidence that homeopathic treatments are more effective than placebo therapy [8]. Here we report the results of an RCT of homeopathy in RA. This tested the hypothesis that homeopathy is effective in reducing the symptoms of joint inflammation in RA.

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Methods

Between 1986 and 1994 we recruited patients from a single routine rheumatology clinic who had definite or classical RA (American Rheumatism Association criteria), were seropositive for rheumatoid factor and were receiving either stable doses of single non-steroidal anti-inflammatory drugs (NSAIDs) for $\geqslant 3$ months or single disease-modifying anti-rheumatic drugs (DMARDs) with or without NSAIDs for $\geqslant 6$ months. Patients who were severely disabled (functional class IV), had taken systemic steroids in the previous 6 months or had withdrawn from DMARD therapy in the previous 12 months were excluded.

Two series of medicines (designated A and B) were manufactured by Laboratoires Boiron (Lyon, France). One comprised 42 homeopathic medicines in 6cH (10^{-12}) and/or 30cH (10^{-30}) dilutions (a total of

59 preparations) manufactured to French National Pharmacopoeia standards. The other comprised identical pillules to which only unmedicated pharmaceutical ethanol was added. The A and B series were packed and labelled identically. The manufacturer retained the master code identifying active and placebo series.

A list of all homeopathic medicines likely to be indicated in RA had been drawn up based on the list published by Gibson *et al*. [3], standard reference works [9, 10] and clinical experience. The medicines chosen comprised: Antimodum crudum (6cH), Apis mellifica (6cH, 30cH), Arnica montana (6cH, 30cH), Arsenicum album (6cH, 30cH), Aurum metallicum (30cH), Bellis perennis (6cH), Berberis vulgaris (6cH), Byronia alba (6cH, 30cH), Calcarea carbonica (6cH, 30cH), Calcarea fluronica (6cH, 30cH), Calcarea phosphorica (6cH), Caulophyllum thalictroides (6cH), Causticum (6cH, 30cH), Cimicifuga racemosa (6cH, 30cH), Dulcamara (6cH, 30cH), Ignatia amara (6cH), Kalmia latitolia (6cH, 30cH), Kalium bichromicum (6cH, 30cH), Kalium carbonicum (30cH), Kalium phosphoricum (6cH), Lachesis mutus (30cH), Ledum palustre (6cH, 30cH), Lycopodium clavatum (30cH), Magnesia phosphorica (6cH), Medorrhinum (30cH), Natrum muriaticum (30cH), Natrum sulphuricum (30cH), Nux vomica (6cH, 30cH), opium (30cH), Psorinum (30cH), Pulsatilla vulgaris (6cH, 30cH), Rhodendron chrysanthum (6cH), Rhus toxicodendron (6cH, 30cH), Ruta graveolens (6cH, 30cH), Sepia officinalis (30cH), Silicea (6cH, 30cH), Staphysagria (30cH), sulphur (6cH, 30cH), Thuja occidentalis (30cH), Tuberculinum bovinum (30cH), Viola odorata (6cH) and Zincum metallicum (6cH).

The St Bartholomew's and Homerton Ethical Committee granted ethical approval. Patients giving written informed consent were randomized to receive either 3 months of treatment A followed by 3 months of treatment B or *vice versa*. Randomization was stratified by NSAID and DMARD groups that could each have a maximum of 30 cases. Those patients who changed conventional therapy, had serious intercurrent illnesses or surgery, failed to attend two consecutive appointments or removed consent were withdrawn and replaced.

Patients were prescribed only one homeopathic medicine at any one time, but the treatment could be changed at any clinic attendance. Treatment was prescribed by one of us (PDF) according to the normal homeopathic clinical criteria. The dosage regimen was standardized. For medicines in the 6cH dilution, patients were instructed to suck one pilule twice daily. For medications in the 30cH dilution, patients were instructed to suck two pilules in the morning twice weekly. Patients were advised not to eat, drink, smoke or clean their teeth for at least 15 min before and after taking their medications, and to avoid all products containing menthol and camphor. These recommendations are in line with standard British homeopathic practice. The homeopathist was blind as to whether the patients were randomized to the A or B series of medicine. A blind observer (physiotherapist) then independently assessed 100 mm visual analogue scale pain scores. Ritchie articular index and duration of morning stiffness. Erythrocyte sedimentation rate (ESR) and haemoglobin were measured at 0, 3 and 6 months.

The data were evaluated independently using non-parametric statistical tests (in SPSS) by a rheumatologist (DS) before the randomization code was broken.

Results

A total of 360 homeopathic prescriptions (180 active and 180 placebo) were prescribed; 20 of the 42 available medicines and 30 of the 59 preparations were used. Seven medicines accounted for 80% of the prescriptions with Rhus toxicodendron prescribed in the 6cH dilution on 43 occasions and the 30cH dilution 21 times. The most prescribed single preparation was sulphur 30cH with 50 prescriptions. Twenty-three patients remained on the same homeopathic medicine throughout the 6 months of the trial; six were on Rhus toxicodendron and four on sulphur.

Fifty-eight patients (46 females, 12 males; mean age 54 yr, mean disease duration 10 yr) completed the trial. Over 6 months their mean pain scores fell 18% (51.7 to 42.6; $P < 0.01$ by Wilcoxon rank sum test), mean articular indices fell 24% (14.3 to 10.8; $P < 0.01$) and mean ESRs fell 11% (49.3 to 43.8; $P < 0.01$). Morning stiffness showed a non-significant 43% rise (75 to 107 min).

Fifty-four patients (41 females, 13 males; mean age 53 yr; mean disease duration 9 yr) withdrew before completing the trial. Thirty-one changed conventional medication (15 NSAIDs and 16 DMARDs), 10 had serious intercurrent illness or surgery, 12 failed to attend on two consecutive appointments and three withdrew consent. No patient withdrew due to an adverse reaction to homeopathic medicine. On average, patients were withdrawn after 2.4 months in the trial (range 1–5 months). The patients who were withdrawn had more severe initial disease. Their mean initial assessments comprised visual analogue scale pain score 57.1, articular index 18.5, ESR 59.1 and duration of morning stiffness 91.

Placebo and active homeopathy had different effects on pain scores (Fig. 1); mean pain scores were significantly lower after 3 months' placebo therapy than 3 months' active therapy ($P = 0.032$ by Wilcoxon rank sum test). This difference was similar whether patients were in NSAID or DMARD groups and if they initially received placebo or active therapy. In 15 cases (26%) there were large differences in pain scores (>20 mm) between treatments; 11 (19%) favoured placebo and four (7%) active homeopathy. Articular index, ESR and morning stiffness were similar with active and placebo homeopathy (Table 1).

Discussion

Our results suggest that active homeopathy does not improve the symptoms of RA patients attending a routine clinic who are stabilized on NSAIDs or

TABLE 1. The effect of homeopathic therapy on pain and disease activity (mean values and 95% confidence intervals)

Variable	Initial	3 months of homeopathy	3 months of placebo	Wilcoxon rank sum test
Pain	51.7 (45.1, 58.4)	46.2 (38.8, 53.6)	39.6 (32.6, 46.7)	$P = 0.032$
Articular index	14.3 (11.8, 16.8)	11.8 (9.4, 14.1)	11.4 (8.8, 14.0)	NS
ESR	49.3 (42.8, 55.9)	42.9 (37.4, 48.3)	46.1 (40.3, 52.0)	NS
Duration of morning stiffness	75 (49, 102)	78 (48, 109)	86 (51, 122)	NS

NS, not significant.

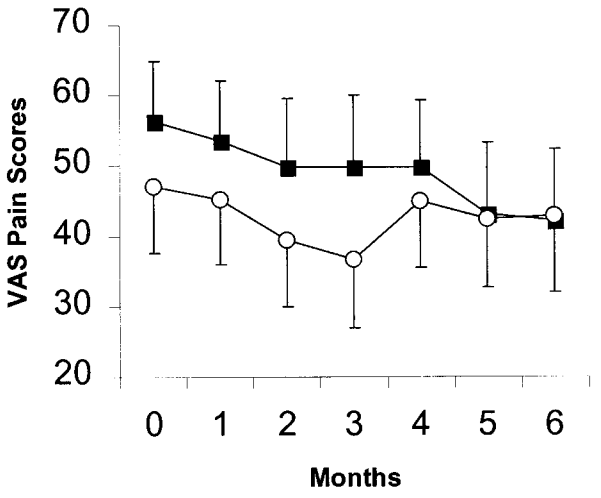

FIG. 1. Changes in visual analogue scale (VAS) pain scores in patients receiving placebo followed by active homeopathy and vice versa during 6 months' therapy (mean values and 95% confidence intervals).

DMARDs over a 3-month period. These findings contradict the positive results reported by Gibson *et al.* [3]. Although mean disease activity levels fell during the 6 months' study period, this almost certainly represents the reversion to the mean seen in any analysis of valid complaint completers. Such falls would not be seen if the results had been evaluated by an 'intention to treat analysis'.

Despite several years of intense debate we have not been able to identify the reason the placebo group showed a significant improvement in their pain scores. One approach is to discount the finding because it is small and can be eradicated by applying a Bonferroni correction for multiple statistical tests. An alternative explanation could be a worsening of symptoms in some patients given homeopathic treatment. This is well described in the initial phase of treatment of allergic rhinitis patients with homeopathic therapies [11, 12]. We have not identified any manner by which the homeopathist may have unconsciously but positively influenced the placebo response to one treatment series and have therefore excluded this as a mechanism.

There has been intense controversy surrounding the analysis of RCTs of homeopathy. This is shown in the extensive criticism of one meta-analysis [13], the major concerns raised in response [14] to an article about homeopathy by Vickers and Zollman [15] and in the statistical analysis of trials of homeopathy in other disorders [16]. They also highlight the difficulties in resolving whether blinding influences the results of RCTs in homeopathy, an issue previously dissected by Langman [17]. We have spent 15 yr planning, undertaking and reporting this study. During this period Ritchie articular index, valid complaint completer analyses and cross-over trials have all become unfashionable. While our methods are dated, their validity is unlikely to have changed. Over these years we have come to believe that conventional RCTs are unlikely to capture the possible benefits of homeopathy. We believe that a new investigational approach is needed which fulfils Vandenbroucke's [18] need for testing a credible hypothesis. Instead of trying to disentangle 'genuine' effects of homeopathy from the placebo response, we suggest that a more directly relevant research question is whether it is cost-effective to complement conventional therapy in patients requesting homeopathy. It seems more important to define if homeopathists can genuinely control patients' symptoms and less relevant to have concerns about whether this is due to a 'genuine' effect or to influencing the placebo response.

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