Individualized Homeopathic Medicines in Treatment of Hyperuricemia: Evaluation by Double-Blind, Randomized, Placebo-Controlled Trial

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Abstract

Introduction Hyperuricemia (HU) is a major health issue in India and across the globe. It increases the disease burden and hampers quality of life. This study was aimed at exploring the effects of individualized homeopathic medicines (IHMs) against placebo in the treatment of HU.

Methods This double-blind, randomized, placebo-controlled trial was conducted on 60 patients suffering from HU in the outpatient department of D. N. De Homoeopathic Medical College and Hospital, Kolkata. Each patient received either IHMs or identical-looking placebos, along with advice on dietary modifications irrespective of codes. Serum uric acid (SUA) level was the primary outcome measure; the HU quality of life questionnaire (HUQLQ) and the Measure Yourself Medical Outcome Profile version 2 (MYMOP-2) were the secondary outcomes; all measured at baseline, and every month, up to 3 months. Group differences were examined by two-way (split-half) repeated-measures analysis of variance after adjusting for baseline differences. Significance level was set at $p \leq 0.05$, two-tailed.

Results The intention-to-treat sample ($n = 58$) was analyzed. Between-group differences in SUA levels ($F_{1,\ 56} = 13.833$, $p < 0.001$), HUQLQ scores ($F_{1,\ 56} = 32.982$,

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- serum uric acid

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$p < 0.001$) and MYMOP-2 profile scores ($F_{1, 56} = 23.873$, $p < 0.001$) were statistically significant, favoring IHMs against placebos, with medium to large effect sizes. *Calcarea carbonica* and *Pulsatilla nigricans* were the most frequently prescribed medicines. No serious adverse events were reported from either of the groups.

Conclusion IHMs showed significantly better results than placebos in reducing SUA levels and improving quality of life in patients suffering from HU.

Trial registration CTRI/2019/10/021503; UTN: U1111–1241–1431.

Introduction

Hyperuricemia (HU) is a disorder in purine metabolism, either excess in production and/or failure in excretion, resulting in an increase in serum uric acid (SUA) (reference range for males: 2–7 mg/dL and for females: 2–6 mg/dL).[1] This excess SUA may form sharp crystals in blood and produce the manifestations of gout.[2] HU also shows a close association with cardiovascular and kidney diseases, diabetes mellitus and obesity.[3] In a review on population-based prevalence, HU was placed at 13th position among 21 disorders contributing to the Global Burden of Disease.[4] About 21% of the general population and 25% of hospitalized patients had asymptomatic HU worldwide.[5] As per the National Health and Nutrition Examination Survey (NHANES) data, approximately 20.2% men and 20.0% women were suffering from HU in 2015 to 2016 in the U.S. population.[6] Overall prevalence of HU in India was 25.8% and disease burden was higher when both type 2 diabetes and hypertension were present together. In West Bengal, the prevalence was 3.2%.[7,8] HU prevalence was also higher in different Asian countries such as Taiwan, Japan and China in comparison to the United States, Brazil and Italy.[9] Urate-lowering therapy, like allopurinol, probenecid and febuxostat, is the mainstay treatment despite having certain unavoidable toxicities and limitations.[10,11]

HU falls under Bouchard's old classification of arthritic diathesis (uric acid diathesis).[12] Musculoskeletal and rheumatic disorders are amongst the most frequently treated complaints treated by homeopathic medicines[13,14] and comprise a significant section of the published literature of clinical trials in homeopathy.[15] Until 2011, 43 relevant trials of homeopathy had been identified—26 peer-reviewed, the remainder not peer-reviewed. Among the peer-reviewed publications, seven were trials of individualized homeopathic medicines (IHMs) against placebo, 14 were of non-IHMs against placebo, two were IHMs against other than placebo (OTP) and three were non-IHMs against OTP.[15]

Although the homeopathy literature contains ample numbers of successfully treated cases of HU and gout, high quality research evidence—especially randomized controlled trials—remains scarce. A clinical case series of 10 patients suffering from acute gout showed improvement of all acute symptoms and reduction of SUA levels after homeopathic treatment.[16] In one non-randomized, open-label, single-arm study on 32 adults suffering from gout, a promising treatment effect of IHMs was observed in SUA levels, Gout Assessment Questionnaire (GAQ-2) scores and Measure Yourself Medical Outcome Profile-2 (MYMOP-2) scores.[17] Another open but randomized trial on 90 patients suffering from HU with three parallel arms (i.e., IHMs, *Urtica urens* mother tincture [UUMT] and IHMs plus UUMT), revealed that IHMs + UUMT worked slightly better than the others in improving SUA levels, GAQ-2 scores and MYMOP-2 scores.[18] One case report of HU with nephrolithiasis revealed reduction of SUA after treatment with IHMs.[19] However, no published efficacy trial of IHMs in HU could be identified, leading the authors to plan and conduct the trial reported here.

Methods

Study Design

This double-blind, randomized, placebo-controlled, two parallel arms trial was conducted at the outpatient department of D. N. De Homoeopathic Medical College and Hospital, Govt. of West Bengal, India. Based on the research, a full dissertation was submitted as the postgraduate thesis of the corresponding author to the West Bengal University of Health Sciences (WBUHS). The total study duration was 18 months: from mid-October 2019 to mid-April 2021.

Participants

The inclusion criteria were patients aged between 18 and 65 years, of either sex, suffering from HU (ICD-10-CM code E79.0; SUA level above 7 mg/dL in men and above 6 mg/dL for women, for at least the past 3 months), literate (able to read Bengali and/or English), and willing to provide their written informed consent. Patients already receiving treatment for HU were enrolled into the study after a washout period of 1 month, subject to fulfilment of the eligibility criteria. Exclusion criteria were cases of overt HU (SUA more than 10 mg/dL), secondary gout, severe or advanced gout requiring surgical procedures or orthopaedic corrections, unstable mental or psychiatric illness or other systemic disease affecting quality of life, currently receiving homeopathic treatment for any chronic condition(s), self-reported immune-compromised state, pregnant, puerperal and lactating women, and cases of substance abuse and/or dependence.

Research Ethics

The study protocol was approved by the Institutional Ethical Committee (IEC) (Ref. No. DHC/Eth-45/2018/643/19, dated September 17, 2019) and was registered prospectively in the Clinical Trials Registry—India (CTRI) (Trial registration no. CTRI/2019/10/021503; secondary identifier, UTN: U1111–

1241–1431). The protocol was in accordance with the latest revision of the Declaration of Helsinki on human experimentation.[20] Each participant expressed his or her informed consent to take part in the trial.

Intervention

- Verum—In the experimental arm, IHMs were administered in centesimal potencies. Each dose consisted of six to eight globules (no. 20) of cane sugar, medicated with the indicated medicine (preserved in 90% v/v ethanol), taken orally on a clean tongue and with empty stomach; dosage and repetition depending upon the individual requirement of the case. Patients were advised to refrain from handling the globules or from eating, drinking, smoking or from brushing teeth within 30 minutes of taking the globules, and were asked to suck the globules rather than simply swallowing them. The homeopathic medicines and sundry goods were purchased in bulk from Hahnemann Publishing Company (HAPCO), Kolkata. Both medicines and placebos were re-packed in identical glass bottles and labeled with code, name of medicine and its potency, and were dispensed according to a random number list. A single medicine was prescribed on each occasion, considering the presenting symptom totality, clinical history, constitutional features, and repertorization by appropriate repertories, using HOMPATH ZOMEO 3.0 software when required. Materia medica was consulted and consensus was arrived at among three homeopaths for the final selection of the medicine and dosage. Provision was made to change the medicines or potencies and adjust the dosage in subsequent visits, in compliance with homeopathic principles. Each of two of the homeopaths possessed a Master's degree in homeopathy, with more than 20 years of teaching experience and practicing classical homeopathy. The other prescriber was either one of two postgraduate trainees or a house staff member of the institution. All the homeopaths involved were affiliated with their respective state council.
- Comparator—This group received identical looking placebos for a period of 3 months. Each dose of placebos consisted of six to eight globules (no. 20), moistened with non-medicinal rectified spirit, and taken orally on a clean tongue and with empty stomach; dosage and repetition depended upon the requirement of individual cases. Dosage regimen was similar to that of verum.
- Concomitant care—Irrespective of the allocated codes, all the patients received dietary instructions, which included lacto-vegetarian and low-fructose diet, restriction or moderation of high purine content food (e.g., meat, poultry, sea food, yeast and yeast extracts, cauliflower, mushrooms, lentils, spinach, beans, peas), moderation of alcohol consumption, and plenty of fluids (2 L/d).[21] Compliance to the advice was assured by reminders to the participants in weekly phone calls and at every follow-up visit by the research assistants. Returned globules were counted to check consumed dosage and were recorded in the drug accountability log.

Outcomes

Primary:

- SUA levels were measured at baseline and every month up to 3 months.

Secondary:

- Hyperuricemia quality of life (HUQLQ) is a validated patients' self-administered questionnaire in the Bengali language, consisting of 19 items and framed within five components: concern; inconvenience in daily activities; professional restriction; mood and temperament; treatment hazards.[22] Items are derived from the GAQ-2 questionnaire. Each item is measured on a 5-point (0–4) Likert scale: the higher the score, the greater is the problem.
- MYMOP-2 is a patient-administered questionnaire.[23,24] It requires the patient to specify one or two symptoms which are concerning them the most and for which they are seeking treatment. It is problem-specific and reflects daily activity (physical, mental, social) as well as general wellbeing. Each of the four items is rated on a 7-point scale, where "0" means "as good as it could be" and 6 means "as bad as it could be". Hence a decrease in the MYMOP-2 score represents an improvement in health outcome. A mean of the four item scores is calculated and is referred to as the "MYMOP-2 profile score".

Sample Size

No formal sample size calculation was possible owing to the absence of relevant published data from any clinical trial of similar design. Also, the minimal clinically important difference of SUA levels was not pre-established. In an earlier study, mean SUA level was reduced from 7.4 ($\pm$ 1.2) to 5.9 ($\pm$ 1.2) after 3 months of intervention using IHMs.[18] We assumed 7 to 8% mean reduction in the mean SUA level in the placebo group after 3 months of intervention. Effect size (Cohen's *d*) was estimated as 0.792. With this assumed effect size and 1:1 allocation, to detect a statistically significant difference between two independent means of SUA levels using unpaired *t*-test, a study with 54 (27×2) patients would provide 80% power based on a two-sided significance level of 5%. Allowance for a 10% attrition rate inflated the target sample size further to 60 (30×2).

Randomization

A random number chart was generated using the StatTrek random number generator, by an independent third party, using the permuted block randomization method (six variable blocks of fixed size 10; $6 \times 10 = 60$) and maintaining a 1:1 ratio. Thus, an equal number of participants was randomized to the verum and the control groups.

Blinding

The double-blinding method was adopted by masking the patients and the treating physicians. The pharmacist, outcome assessors and data entry operators were also kept blinded throughout the trial. Identical looking vials were coded as either "1" or "2" and contained either medicines or alike placebos. Codes were assigned randomly and confidentially by an independent third party. Both medicines and placebos

were re-packed in identical glass bottles and labeled with code, name of medicine and potency, and were dispensed according to the random number list. The vials were destined for each patient by the random number chart. Codes were broken at the end of the trial after the dataset was frozen.

Allocation Concealment

Blinded postgraduate trainees were involved in screening, enrollment and assigning serial numbers to the participants. Subsequently, the blinded participants were interviewed by the blinded homeopaths for prescription. Thus, allocation concealment was achieved by having both the recruiters and the treating physicians unaware of the randomization sequence. The blinded pharmacist was provided in strict confidentiality with the coded random number chart for dispensing of either medicines or alike placebos to the participants sequentially.

Statistical Methods

The intention-to-treat (ITT) approach was followed[25]: i.e., every included patient who had baseline measurements and at least 1 month follow-up was entered into the final analysis. Missing values were replaced by predicted values from a linear regression model. Data distribution was examined by histograms, Q–Q plots, and Kolmogorov–Smirnov and Shapiro–Wilk tests; no significant departure from Normality was identified. For examining baseline comparability of the confounders, unpaired *t*-tests, the Mann-Whitney U test and Chi-square tests were applied. The baseline differences in SUA levels, MYMOP-2 activity and profile scores were adjusted using analysis of covariance (ANCOVA) models. Group differences were examined by two-way repeated measures analysis of variance (ANOVA) models overall and by unpaired *t*-tests at different time points. Effect size was presented in terms of Cohen's *d* (small effect, 0.2; medium effect, 0.5; large effect, 0.8). Intra-group changes with time were measured using one-way repeated measures ANOVA. A *p*-value $\leq$0.05 (two-tailed) was considered as statistically significant. SPSS-IBM version 20 was used for data analysis.

Reporting of Adverse Events

Patients were instructed to report any harm, serious adverse event, unintended effect or undue aggravations.

Trial Reporting

The trial report has been compiled in compliance with the Consolidated Standards for Reporting Trials (CONSORT)[26] and Reporting Data on Homeopathic Treatment (RedHot)[27] guidelines (**Supplementary files 1** and **2**, available online only).

Results

Participant Flow

A total of 94 patients were screened as per the pre-specified inclusion and exclusion criteria; 34 were excluded on account of various reasons and 60 eligible patients were enrolled. Baseline socio-demographic and outcome data were obtained, and the patients were randomized to receive either IHMs or identical-looking placebos. The outcome data were recorded every month up to 3 months. Attrition rate of the study was 10% (two from verum and four from placebo); 58 patients (verum, 28; placebos, 30) were subjected to ITT analysis (►**Fig. 1**).

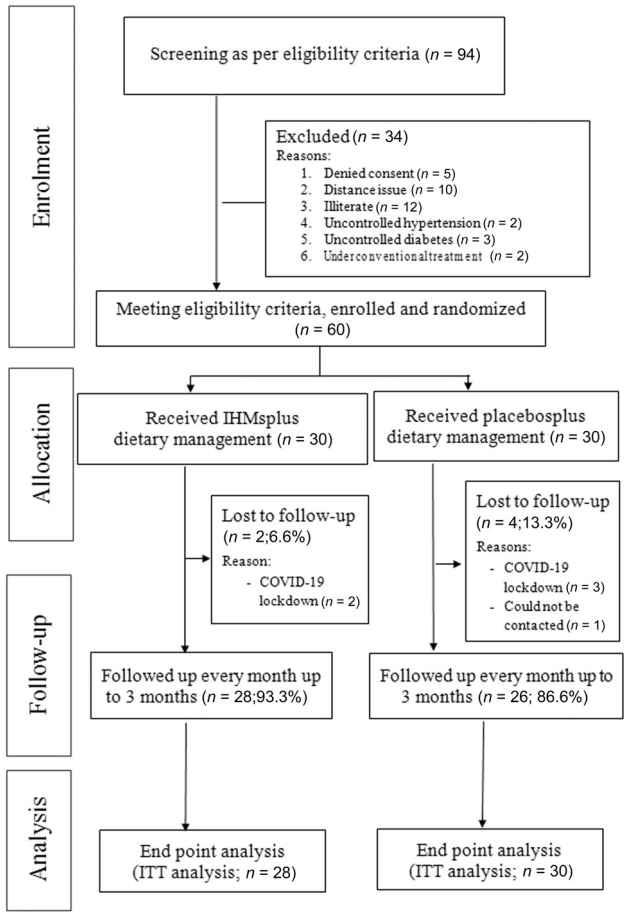

Fig. 1 CONSORT flow diagram. CONSORT, Consolidated Statement for Reporting Trials; IHMs, individualized homeopathic medicines; ITT, intention to treat.

Recruitment

From October 2019 until January 2021, a total of 60 participants were enrolled into the trial. Follow-up of the last enrolled patient was completed by mid-April 2021.

Baseline Data

No significant group differences were found in the distribution of socio-demographic variables between groups (all $p > 0.05$) (►**Table 1**). Significantly different distribution at baseline was observed in the SUA levels ($p = 0.051$), MYMOP-2 activity sub-scale score ($p = 0.002$) and profile score ($p = 0.025$), which were adjusted subsequently using ANCOVA models (►**Tables 2**, **4**).

Numbers Analyzed

Outcomes were complete from 28/30 and from 26/30 patients in the IHMs and placebo groups respectively; the remainder dropped out of the trial. The data from 58 patients (IHMs, 28; placebos, 30) entered into the final analyses.

Table 1 Comparison of the socio-demographic characteristics between two groups at baseline ($N = 58$)

Feature	IHMs group ($n = 28$)	Placebo group ($n = 30$)	*p*
Age (years)[a]	44.2 ± 8.8	48.5 ± 10.2	0.095
Duration of suffering (months)[b]	12 (7, 14.2)	12 (6, 12)	0.245
Anthropometric measures[a]			
Body mass index	25.4 ± 1.7	25.7 ± 1.6	0.458
Waist height ratio	0.5 ± 0.02	0.5 ± 0.02	0.611
Blood pressure[a]			
Systolic	132.3 ± 7.9	133.3 ± 8.9	0.639
Diastolic	87.2 ± 3.8	85.8 ± 5.6	0.266
Sex[c]			
Male	7 (25)	14 (46.7)	0.086
Female	21 (75)	16 (53.3)	
Residence[c]			
Rural	1 (3.6)	2 (6.7)	0.853
Semi-urban	9 (32.1)	10 (33.3)	
Urban	18 (64.3)	18 (60)	
Family history of hyperuricemia[c]	13 (46.4)	9 (30)	0.197
Food habit[c]			
Vegetarian	2 (7.1)	3 (10)	0.698
Non-vegetarian	26 (92.9)	27 (90)	
Risk factors[c]			
Tobacco	4 (14.3)	7 (23.3)	0.959
Alcohol	7 (25)	10 (33.3)	
Red meat	26 (92.9)	26 (86.7)	
Sea food	21 (75)	22 (73.3)	
Soft drink	19 (67.9)	21 (70)	
No exercise	24 (85.7)	29 (96.7)	
Treatment taken[c]			
Allopathy	5 (17.9)	7 (23.3)	0.607
Co-morbidities[c]			
Diabetes mellitus	2 (7.1)	5 (16.7)	0.279
Dyspepsia	5 (17.9)	6 (20)	
Headache	4 (14.3)	1 (3.3)	
Hypertension	8 (28.6)	5 (16.7)	
Hypothyroidism	5 (17.9)	2 (6.7)	
Insomnia	1 (3.6)	3 (10)	
Miscellaneous	3 (10.7)	8 (26.7)	
Marital status[c]			
Married	27 (96.4)	25 (83.3)	0.102
Single and others	1 (3.6)	5 (16.7)	
Educational status[c]			
8th std. or less	11 (39.3)	12 (40)	0.813
9th–12th std.	13 (46.4)	12 (40)	
Higher than 12th std.	4 (14.3)	6 (20)	
Employment status[c]			
Service	6 (21.4)	4 (13.3)	0.683
Business	10 (35.7)	13 (43.3)	
Dependent and others	12 (42.9)	13 (43.3)	
Income status[c]			
Poor	5 (17.9)	6 (20)	0.975
Middle	17 (60.7)	18 (60)	
Affluent	6 (21.4)	6 (20)	

Abbreviation: IHMs, individualized homeopathic medicines.
[a]Continuous data presented as mean ± standard deviation and unpaired *t*-tests applied.
[b]Continuous data presented as median (interquartile range) and Mann-Whitney *U* tests applied.
[c]Categorical data presented as absolute values (percentages) and Chi-square test (Yates corrected) applied; $p \leq 0.05$ two-tailed was considered as statistically significant.

Outcomes and Estimation

- SUA levels: Intra-group changes after 3 months showed statistically significant improvement in both the groups: $p < 0.001$ and $p = 0.003$ in the IHMs and placebo groups respectively. Overall, inter-group difference was statistically significant ($F_{1, 56} = 13.833$, $p < 0.001$; two-way repeated measures ANOVA). Inter-group differences were all statistically significant, with medium to large effect sizes favoring IHMs compared with placebos at all different time points (month 1, $p = 0.035$, $d = 0.542$; month 2, $p = 0.012$, $d = 0.7$; month 3, $p < 0.001$, $d = 1.352$) (►**Table 2**)
- HUQLQ scores: Statistically significant intra-group changes were obtained after 3 months in total score and all sub-scale scores in both the verum and placebo groups (all $p < 0.05$, except mood and temperament sub-scale score and HUQLQ total score in the placebo group). Inter-group differences were statistically significant, with medium to large effect sizes in total score and all sub-scale scores (all $p < 0.05$) favoring IHMs against placebos after 3 months of intervention (►**Table 3**).
- MYMOP-2 scores: Intra-group changes after 3 months of treatment revealed statistically significant changes (all $p < 0.05$) in all the sub-scales scores of both the verum and the placebo groups. Inter-group differences were statistically significant (all $p < 0.05$), with small to large effect sizes in MYMOP-2 profile score and most of the sub-scale scores, favoring IHMs over placebos (►**Table 4**).

Table 2 Comparison of the serum uric acid level at different time points ($N = 58$; baseline differences adjusted by ANCOVA)

Serum uric acid level	Baseline: Mean ± SD	After 1 month: Mean ± SD	After 2 months: Mean ± SD	After 3 months: Mean ± SD	Wilks' lambda	$F_{3, 25}$ or $F_{3, 27}$	p [(c)]	Partial eta-square
IHMs group ($n = 28$)	6.9 ± 0.6	6.2 ± 1.1	5.8 ± 1.0	5.4 ± 1.1	0.240	26.346	<0.001***	0.760
Placebo group ($n = 30$)	7.2 ± 0.7	6.7 ± 0.7	6.5 ± 1.0	6.7 ± 0.8	0.597	6.063	0.003**	0.403
Mean group difference ± SE	-0.3 ± 0.2	-0.5 ± 0.2	-0.7 ± 0.3	−1.3 ± 0.2				
95% CI	−0.7, 0.002	−1.0, −0.04	−1.2, −0.1	−1.8, −0.8				
t_{56}	−1.992	−2.162	−2.587	−5.321				
p[a]	0.051	0.035*	0.012*	<0.001***				
Effect size (Cohen's d)	–	0.542	0.7	1.352				
Two-way repeated measures ANOVA								
$F_{1, 56}$				13.833				
p[b]				<0.001***				
Partial eta-square				0.198				

Abbreviations: CI, confidence interval; IHMs, individualized homeopathic medicines; SD, standard deviation; SE, standard error.
[a]Unpaired t-tests; t_{56}: t score at 56 degrees of freedom.
p[a] Inter-group differences detected by unpaired t-tests.
p[b] Inter-group differences detected by two-way repeated measures ANOVA models.
p[c] Intra-group changes detected by one-way repeated measures ANOVA.
*$p \leq 0.05$.
**$p < 0.01$.
***$p < 0.001$.

Medicines Used

A total of 26 different IHMs were prescribed in both the verum and placebo groups. Among those, *Calcarea carbonica* and *Pulsatilla nigricans* ($n = 5$ each, 8.6%), *Bryonia alba*, *Lycopodium clavatum* and *Medorrhinum* ($n = 4$, 6.9%) were the most frequently prescribed medicines (►**Table 5**).

Adverse Events

No serious adverse events were reported throughout the study. Five and nine minor adverse events respectively occurred in the verum and placebo groups; however, all those seemed to be independent events rather than attributable to the interventions. In the verum group, adverse events such as headache, vomiting, coryza, fever and upper respiratory tract infection occurred. All were treated successfully by homeopathic medicines, except a case of fever where the patient took over-the-counter paracetamol 650 mg, two tablets, 6 hourly. In the placebo group, adverse events such as fever, diarrhea, headache, vomiting, neck pain, gastritis and vertigo were recorded. Two individuals with fever took over-the-counter paracetamol 650 mg. One case of neck pain and another case of gastritis took non-steroidal anti-inflammatory drugs. Other adverse events were successfully treated with short-acting homeopathic medicines as per indications (e.g., diarrhea with *Aloe socotrina* 30cH, headache with *Belladonna* 30cH, vomiting with *Arsenicum album* 30cH, vertigo with *Bryonia alba* 30cH, viral fever with *Rhus toxicodendron* 200cH, common cold with *Dulcamara* 30cH, and URTI with *Spongia tosta* 30cH), and once recovered they were returned to the previously allocated groups.

Discussion

This randomized, double-blind, placebo-controlled trial on 58 patients suffering from HU showed statistically significant improvement in both the primary and secondary outcomes, with medium to large effect sizes after 3 months of intervention, favoring IHMs against placebos.

Being a randomized controlled trial, the methodological strengths of the study were in-built in its design: minimized selection bias, balancing of the two groups with respect to confounders, and establishing the basis for inferential statistical tests by ensuring comparability between groups at baseline. The advantages conferred by blinding were minimized performance bias, ascertainment bias and detection bias. Further strengths included the choice of an objective measure (i.e., SUA) as the primary outcome and selection of a standardized and pre-validated disease-specific quality of life questionnaire (i.e., HUQLQ) and a generic patient-reported outcome measure (i.e., MYMOP-2) as the secondary outcomes. Adjustment of baseline differences in the outcome measures was accomplished prior to running inferential statistics.

The sample size may seem inadequate to draw any conclusive recommendations. However, with an effect size of 1.352 as detected after 3 months of intervention in the SUA levels, to detect a statistically significant difference between two independent means of SUA levels using unpaired t-test, a replication trial with 20 (10×2) patients would provide 80% power based on a two-sided significance level of 5%. Thus, our achieved sample size of 58, though it was based on

Table 3 Comparison of the hyperuricemia quality of life (HUQLQ) questionnaire scores at baseline and at different time points ($N = 58$; baseline differences adjusted by ANCOVA)

HUQLQ	Baseline: Mean ± SD	After 1 month: Mean ± SD	After 2 months: Mean ± SD	After 3 months: Mean ± SD	Wilks' lambda	$F_{3,\ 25}$ or $F_{3,\ 27}$	p^c	Partial eta-square
Concern score								
IHMs group ($n = 28$)	14.6 ± 1.2	12.5 ± 1.6	10.1 ± 1.6	7.4 ± 2.4	0.081	94.245	<0.001***	0.919
Placebo group ($n = 30$)	15.4 ± 2.5	14.2 ± 2.5	13.9 ± 2.7	14.2 ± 3.5	0.726	3.390	0.032*	0.274
Mean group difference ± SE	−0.8 ± 0.5	−1.7 ± 0.5	−3.8 ± 0.6	−6.8 ± 0.8				
95% CI	−1.8, 0.3	−2.8, -0.6	−5.0, −2.6	−8.4, −5.2				
t_{56}	−1.502	−3.115	−6.464	−8.550				
p^a	0.139	0.003**	<0.001***	<0.001***				
Effect size (Cohen's d)	–	0.810	1.712	2.266				
Two-way repeated measures ANOVA								
$F_{1,\ 56}$				41.401				
p^b				<0.001***				
Partial eta-square	-–			0.425				
Inconvenience in daily activities score								
IHMs group ($n = 28$)	21.8 ± 3.8	17.7 ± 4.4	14.7 ± 4.0	10.6 ± 4.8	0.179	38.207	<0.001***	0.821
Placebo group ($n = 30$)	23.5 ± 6.0	22.0 ± 5.8	20.8 ± 4.9	20.9 ± 5.7	0.625	5.398	0.005**	0.375
Mean group difference ± SE	−1.7 ± 1.3	−4.3 ± 1.3	−6.1 ± 1.2	−10.3 ± 1.4				
95% CI	−4.3, 1.04	−7.0, −1.6	−8.4, −3.7	−13.0, −7.5				
t_{56}	−1.229	−3.180	−5.165	−7.431				
p^a	0.224	0.002**	<0.001***	<0.001***				
Effect size (Cohen's d)	–	0.835	1.364	1.955				
Two-way repeated measures ANOVA								
$F_{1,\ 56}$				22.116				
p^b				<0.001***				
Partial eta-square				0.283				
Professional restriction score								
IHMs group ($n = 28$)	5.8 ± 0.9	5.1 ± 1.0	3.8 ± 0.9	2.7 ± 1.0	0.124	58.880	<0.001***	0.876
Placebo group ($n = 30$)	6.0 ± 1.4	5.6 ± 1.3	5.4 ± 1.1	5.5 ± 1.6	0.750	3.008	0.048*	0.250
Mean group difference ± SE	−0.2 ± 0.3	−0.5 ± 0.3	−1.6 ± 0.3	−2.8 ± 0.3				
95% CI	−0.8, 0.4	−1.1, 0.1	−2.2, -1.1	−3.4, −2.1				
t_{56}	−0.697	−1.715	−5.818	−7.898				
p^a	0.489	0.092	<0.001***	<0.001***				
Effect size (Cohen's d)	–	0.431	2.099	2.099				
Two-way repeated measures ANOVA								
$F_{1,\ 56}$				23.641				
p^b				<0.001***				
Partial eta-square				0.297				
Mood and temperament score								
IHMs group ($n = 28$)	5.7 ± 0.6	5.0 ± 1.1	3.8 ± 0.9	2.7 ± 1.0	0.110	67.557	<0.001***	0.890
Placebo group ($n = 30$)	5.9 ± 1.5	5.8 ± 1.4	5.8 ± 1.3	5.6 ± 1.5	0.914	0.848	0.480	0.086
Mean group difference ± SE	−0.2 ± 0.3	−0.8 ± 0.3	−2.0 ± 0.3	−2.9 ± 0.3				
95% CI	−0.8, 0.4	−1.5, −0.1	−2.5, −1.3	−3.5, −2.1				
t_{56}	−0.595	−2.418	−6.538	−8.203				
p^a	0.555	0.019*	<0.001***	<0.001***				
Effect size (Cohen's d)	–	0.635	1.789	2.275				

(*Continued*)

Table 3 (*Continued*)

HUQLQ	Baseline: Mean ± SD	After 1 month: Mean ± SD	After 2 months: Mean ± SD	After 3 months: Mean ± SD	Wilks' lambda	$F_{3,\ 25}$ or $F_{3,\ 27}$	p^c	Partial eta-square
Two-way repeated measures ANOVA								
$F_{1,\ 56}$				26.387				
p^b				$<0.001^{***}$				
Partial eta squared				0.320				
Treatment hazards score								
IHMs group ($n = 28$)	0.3 ± 0.5	2.2 ± 1.1	1.8 ± 0.9	1.7 ± 0.6	0.192	35.003	$<0.001^{***}$	0.808
Placebo group ($n = 30$)	0.3 ± 0.6	2.5 ± 1.3	2.5 ± 1.0	2.5 ± 0.9	0.147	52.371	$<0.001^{***}$	0.853
Mean group difference ± SE	0.09 ± 0.1	−−0.3 ± 0.3	−0.7 ± 0.2	−0.8 ± 0.2				
95% CI	−0.2, 0.4	−1.0, 0.3	−1.2, −0.2	−1.3, −0.4				
t_{56}	0.602	−1.119	−2.733	−4.087				
p^a	0.549	0.268	0.008^{**}	$<0.001^{***}$				
Effect size (Cohen's *d*)	–	0.249	0.736	1.046				
Two-way repeated measures ANOVA								
$F_{1,\ 56}$				5.689				
p^b				0.020^{*}				
Partial eta-square				0.092				
HUQLQ total score								
IHMs group ($n = 28$)	48.3 ± 5.6	42.4 ± 6.6	34.3 ± 6.5	25.2 ± 7.9	0.116	63.753	$<0.001^{***}$	0.884
Placebo group ($n = 30$)	51.1 ± 10.9	50.1 ± 10.1	48.4 ± 9.4	48.6 ± 11.9	0.874	1.301	0.294	0.126
Mean group difference ± SE	−2.8 ± 2.3	−7.7 ± 2.2	−14.1 ± 2.1	−23.4 ± 2.7				
95% CI	−7.3, 1.9	−12.2, −3.2	−18.4, −9.8	−28.8, −18.1				
t_{56}	−1.194	−3.432	−6.600	−8.775				
p^a	0.238	0.001^{**}	$<0.001^{***}$	$<0.001^{***}$				
Effect size (Cohen's *d*)	–	0.902	1.745	2.317				
Two-way repeated measures ANOVA								
$F_{1,\ 56}$				32.982				
p^b				$<0.001^{***}$				
Partial eta-square				0.371				

Abbreviations: CI, confidence interval; IHMs, individualized homeopathic medicines; SD, standard deviation; SE, standard error.
[a]Unpaired *t*-tests; t_{56}: *t* score at 56 degrees of freedom.
p^a Inter-group differences detected by unpaired *t*-tests.
p^b Inter-group differences detected by two-way repeated measures ANOVA models.
p^c Intra-group changes detected by one-way repeated measures ANOVA.
$^{*}p \leq 0.05$.
$^{**}p < 0.01$.
$^{***}p < 0.001$.

assumption, still provided ample power to avoid a type II error.

An intervention period of 3 months only may be considered as an important limitation of the study. However, further lengthening of the period would have attracted ethical concerns in a placebo-controlled trial. Difficulties were faced in achieving compliance with follow-up due to the COVID-19 pandemic situation and imposed lockdown: six patients dropped out. Some IHMs were used as "rescue remedies" to treat acute ailments that were probably unrelated to the trial. This additional homeopathic treatment might have acted as confounder to the trial-specific medicines; nevertheless, these were "short acting" remedies selected on the "acute totality" of the cases and were unlikely to affect the actions of trial-specific medicines.[28,29] After the acute phases were over, the patients were re-evaluated by the treating physicians. Either the same trial medicine of the same code was repeated, or new medicines were prescribed according to the symptomatology of the patient and as decided appropriate to the case or condition by the physicians.

There are ample references in the literature to the homeopathic treatment of HU and gout. Burnett advocated two distinct treatment approaches for pre-deposit and post-deposit symptoms.[30] Farrington suggested dividing the treatment of gout into management of the acute paroxysm and of the general symptoms.[31] Grauvogl advocated that direction of

Table 4 Comparison of the Measure Yourself Medical Outcome Profile 2 (MYMOP-2) scores at baseline and after 3 and 6 months ($N = 58$; baseline differences adjusted by ANCOVA)

MYMOP-2	Baseline: Mean ± SD	After 1 month: Mean ± SD	After 2 months: Mean ± SD	After 3 months: Mean ± SD	Wilks' lambda	$F_{3,\ 25}$ or $F_{3,\ 27}$	p^c	Partial eta squared
Symptom 1 score								
IHMs group ($n = 28$)	3.9 ± 0.5	3.1 ± 0.4	2.7 ± 0.6	1.9 ± 0.6	0.067	116.836	<0.001***	0.933
Placebo group ($n = 30$)	3.7 ± 0.4	3.4 ± 0.5	3.4 ± 0.5	3.3 ± 0.5	0.551	7.346	0.001**	0.449
Mean group difference ± SE	0.2 ± 0.1	−0.3 ± 0.1	−0.7 ± 0.1	−1.4 ± 0.1				
95% CI	−0.04, 0.4	−0.5, −0.04	−1.0, −0.4	−1.7, −1.1				
t_{56}	1.624	−2.313	−4.642	−9.259				
p^a	0.110	0.024*	<0.001***	<0.001***				
Effect size (Cohen's d)	–	0.662	1.267	2.535				
Two-way repeated measures ANOVA								
$F_{1,\ 56}$				26.431				
p^b				<0.001***				
Partial eta-square				0.321				
Symptom 2 score								
IHMs group ($n = 28$)	3.4 ± 0.7	2.8 ± 0.6	2.1 ± 0.6	1.5 ± 0.6	0.127	57.073	<0.001***	0.873
Placebo group ($n = 30$)	3.3 ± 0.5	2.9 ± 0.4	2.9 ± 0.7	2.8 ± 0.7	0.520	8.302	<0.001***	0.480
Mean group difference ± SE	0.1 ± 0.1	−0.1 ± 0.1	−0.8 ± 0.2	−1.3 ± 0.2				
95% CI	−0.1, 0.5	−0.3, 0.2	−1.1, −0.4	−1.7, −0.1				
t_{56}	1.013	−0.555	−4.295	−7.670				
p^a	0.315	0.581	<0.001***	<0.001***				
Effect size (Cohen's d)	–	0.196	1.227	1.994				
Two-way repeated measures ANOVA								
$F_{1,\ 56}$				15.372				
p^b				<0.001***				
Partial eta-square				0.215				
Activity score								
IHMs group ($n = 28$)	3.7 ± 0.5	3.1 ± 0.4	2.5 ± 0.6	1.8 ± 0.6	0.106	70.374	<0.001***	0.894
Placebo group ($n = 30$)	3.3 ± 0.5	3.1 ± 0.4	3.0 ± 0.4	2.9 ± 0.4	0.690	4.035	0.017*	0.310
Mean group difference ± SE	0.4 ± 0.1	0.04 ± 0.1	−0.5 ± 0.1	−1.1 ± 0.1				
95% CI	0.2, 0.7	−0.2, 0.2	−0.7, −0.2	−1.4, −0.8				
t_{56}	3.250	0.394	−3.672	−7.869				
p^a	0.002**	0.695	0.001**	<0.001***				
Effect size (Cohen's d)	–	0	0.980	2.157				
Two-way repeated measures ANOVA								
$F_{1,\ 56}$				9.110				
p^b				0.004**				
Partial eta-square				0.140				
General wellbeing score								
IHMs group ($n = 28$)	3.7 ± 0.5	3.1 ± 0.4	2.4 ± 0.6	1.8 ± 0.6	0.098	76.741	<0.001***	0.902
Placebo group ($n = 30$)	3.5 ± 0.5	3.2 ± 0.4	3.1 ± 0.3	3.0 ± 0.5	0.656	4.727	0.009**	0.344
Mean group difference ± SE	0.2 ± 0.1	−0.1 ± 0.1	−0.7 ± 0.1	−1.2 ± 0.1				
95% CI	−0.03, 0.5	−0.2, 0.2	−1.0, −0.5	−1.5, −1.0				
t_{56}	1.810	−0.219	−5.839	−8.481				
p^a	0.076	0.828	<0.001***	<0.001***				
Effect size (Cohen's d)		0.25	1.476	2.173				
Two-way repeated measures ANOVA								

(*Continued*)

Table 4 (*Continued*)

MYMOP-2	Baseline: Mean ± SD	After 1 month: Mean ± SD	After 2 months: Mean ± SD	After 3 months: Mean ± SD	Wilks' lambda	$F_{3,\ 25}$ or $F_{3,\ 27}$	p^c	Partial eta squared
$F_{1,\ 56}$				20.451				
p^b				<0.001***				
Partial eta-square				0.268				
Profile score								
IHMs group ($n = 28$)	3.7 ± 0.4	3.1 ± 0.4	2.5 ± 0.5	1.7 ± 0.5	0.076	101.321	<0.001***	0.924
Placebo group ($n = 30$)	3.4 ± 0.4	3.1 ± 0.3	3.1 ± 0.3	3.0 ± 0.5	0.458	10.642	<0.001***	0.542
Mean group difference ± SE	0.3 ± 0.1	−0.08 ± 0.09	−0.6 ± 0.1	−1.3 ± 0.1				
95% CI	0.03, 0.5	−0.3, 0.1	−0.9, −0.4	−1.5, −1.01				
t_{56}	2.307	−0.940	−5.772	−9.721				
p^a	0.025*	0.351	<0.001***	<0.001***				
Effect size (Cohen's *d*)	–	0	1.455	2.6				
Two-way repeated measures ANOVA								
$F_{1,\ 56}$				23.873				
p^b				<0.001***				
Partial eta-square				0.299				

Abbreviations: CI, confidence interval; IHMs, individualized homeopathic medicines; SD, standard deviation; SE, standard error.
[a]Unpaired *t*-tests; t_{56}: *t* score at 56 degrees of freedom.
p^aInter-group differences detected by unpaired *t*-tests.
p^bInter-group differences detected by two-way repeated measures ANOVA models.
p^cIntra-group changes detected by one-way repeated measures ANOVA.
*$p \leq 0.05$.
**$p < 0.01$.
***$p < 0.001$.

cure should always be from above downward, where that always indicated improvement.[32] Kent suggested, "If we are to arrest gouty formations, we must look for early mental symptoms, as the gouty concretions give a small clue to the remedy".[33] A very similar set of medicines as was found in our trial was also suggested by Hering in similar conditions.[34] Boenninghausen suggested *Arnica montana*, *Sabina* and *Causticum* for pain of gout attacks, *Sulphur* to prevent recurrences, and many other different remedies based on indications.[35] Dudgeon warned that selection of dose required great circumspection to treat chronic gout because the smallest dose often causes intolerable aggravation.[36] Different stalwarts have suggested that the secondary stage of the chronic miasm, sycosis, presents itself in a sub-acute gouty form of rheumatism.[37,38] Hahnemann suggested gouty attacks as symptoms of secondary psora.[39] As per miasmatic analysis of the enrolled cases in our trial, sycosis was the dominant miasm in a majority of the cases ($n = 26$, 44.8%), followed by psora ($n = 24$, 41.4%), syphilis and pseudo-psora ($n = 4$ each, 6.9%). Allen stated that even without the "accessary circumstances", sycosis alone had the power to produce gout or gouty diathesis. Timely treatment with proper IHMs, considering the predominating miasmatic state, can successfully prevent the propagation of miasm to a parent's offspring.[37]

A clinical case series of 10 patients suffering from acute gout revealed that all acute symptoms resolved, along with reductions in SUA levels, after homeopathic treatment, which is a similar finding to ours.[16] In a non-randomized, open-label, single-arm trial conducted on 32 adults suffering from gout, a positive treatment effect of IHMs was noted in alleviating the symptoms of gout and improving the quality of life.[17] Outcome measures used were SUA and MYMOP-2, the same as in our trial. In an open, randomized, three parallel arms pragmatic trial on 90 patients suffering from HU, IHMs plus UUMT worked better than IHMs or UUMT alone.[18] Again, the outcome measures used were SUA and MYMOP-2. An animal model study using *Ledum palustre* 30cH and 1000cH revealed hypouricemic effects;[40] *Ledum palustre* was prescribed for two patients in our trial.

Conclusion

In this randomized, double-blind, placebo-controlled trial on 58 patients suffering from HU, IHMs produced a significantly greater effect than placebo in reducing SUA levels and improving patients' quality of life.

Highlights

- A double-blind, randomized, placebo-controlled, two parallel arms trial was conducted at D. N. De Homoeopathic Medical College and Hospital, West Bengal, India on 60 patients suffering from hyperuricemia.
- Individualized homeopathic medicines showed significantly better results than placebos in the treatment of hyperuricemia.

Table 5 Prescribed medicines in the two groups at baseline ($N = 58$)

Name of medicine	Total; *n* (%)	IHMs group ($n = 28$); *n* (%)	Placebo group ($n = 30$); *n* (%)	*p*
1. *Acidum benzoicum*	1 (1.7)	1 (3.6)	0 (0)	–
2. *Bryonia alba*	4 (6.9)	2 (7.1)	2 (6.7)	0.943
3. *Calcarea carbonica*	5 (8.6)	3 (10.7)	2 (6.7)	0.583
4. *Calcarea fluorica*	2 (3.4)	2 (7.1)	0 (0)	–
5. *Calcarea phosphorica*	2 (3.4)	2 (7.1)	0 (0)	–
6. *Causticum*	1 (1.7)	1 (3.6)	0 (0)	–
7. *Chelidonium majus*	1 (1.7)	1 (3.6)	0 (0)	–
8. *Colchicum autumnale*	2 (3.4)	2 (7.1)	0 (0)	–
9. *Kali carbonicum*	2 (3.4)	1 (3.6)	1 (3.3)	0.960
10. *Lachesis mutus*	2 (3.4)	1 (3.6)	1 (3.3)	0.960
11. *Ledum palustre*	2 (3.4)	1 (3.6)	1 (3.3)	0.960
12. *Lycopodium clavatum*	4 (6.9)	2 (7.1)	2 (6.7)	0.943
13. *Medorrhinum*	4 (6.9)	1 (3.6)	3 (10)	0.334
14. *Mercurius solubilis*	2 (3.4)	0 (0)	2 (6.7)	–
15. *Natrum muriaticum*	3 (5.2)	0 (0)	3 (10)	–
16. *Natrum sulphuricum*	1 (1.7)	0 (0)	1 (3.3)	–
17. *Nux vomica*	2 (3.4)	1 (3.6)	1 (3.3)	0.960
18. *Phosphorus*	1 (1.7)	0 (0)	1 (3.3)	–
19. *Pulsatilla nigricans*	5 (8.6)	2 (7.1)	3 (10)	0.698
20. *Rhus toxicodendron*	2 (3.4)	0 (0)	2 (6.7)	–
21. *Ruta graviolens*	2 (3.4)	2 (7.1)	0 (0)	–
22. *Sepia succus*	1 (1.7)	0 (0)	1 (3.3)	–
23. *Sulphur*	2 (3.4)	1 (3.6)	1 (3.3)	0.960
24. *Thuja occidentalis*	2 (3.4)	0 (0)	2 (6.7)	–
25. *Tuberculinum bovinum*	1 (1.7)	1 (3.6)	0 (0)	–
26. *Urtica urens*	2 (3.4)	1 (3.6)	1 (3.3)	0.960

Abbreviations: IHMs, individualized homeopathic medicines.
Note: *p* less than 0.05 (two-tailed) considered as statistically significant.

Supplementary Material

Supplementary file 1. CONSORT 2010 checklist of information to include when reporting a randomised trial.
Supplementary file 2. RedHot checklist of information to include when reporting randomised trials of homeopathy.

Disclosure Statement

The trial was conducted as part of the postgraduate thesis of the corresponding author.

Authors' Contribution

P.G., S.G., S.K.M., S.D. and A.R.S. contributed to the literature search, study concept, conducting the trial, data collection, data evaluation and drafting the manuscript. S.S.A., N.K.S., P.B., M.K., and S.S. contributed to study design, data interpretation, statistical analysis, and drafting of the manuscript. All the authors reviewed and approved the final manuscript for submission.

Conflict of Interest

None declared.

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