Double-Blind, Randomized, Placebo-Controlled Trial of Individualized Homeopathic Medicines in Atopic Dermatitis in Adults: A Replication Trial with 6 Months' Follow-up

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Abstract

Background Atopic dermatitis (AD) is a chronic relapsing and remitting inflammatory skin disease that can have a significant impact on quality of life. During the last four decades, a rising trend in AD has been observed in India. Homeopathic medicines are claimed to be beneficial in AD; however, convincing research evidence has been lacking. We compared the efficacy of individualized homeopathic medicines (IHMs) against placebos in the treatment of AD.

Methods In this double-blind, randomized, placebo-controlled trial of 6 months' duration ($n = 60$), adult patients were randomized to receive either IHMs ($n = 30$) or identical-looking placebos ($n = 30$). All participants received concomitant conventional care, which included the application of olive oil and maintaining local hygiene. The primary outcome measure was disease severity using the Patient-Oriented Scoring of Atopic Dermatitis (PO-SCORAD) scale; secondary outcomes were the Atopic Dermatitis Burden Scale for Adults (ADBSA) and Dermatological Life Quality Index (DLQI) – all were measured at baseline and every month, up to 6 months. Group differences were calculated on the intention-to-treat sample.

Keywords
- atopic dermatitis
- homeopathy
- placebo
- quality of life
- randomized controlled trial

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Results After 6 months of intervention, inter-group differences became statistically significant on PO-SCORAD, the primary outcome (−18.1; 95% confidence interval, −24.0 to −12.2), favoring IHMs against placebos ($F_{1,\ 52} = 14.735$; $p < 0.001$; two-way repeated measures analysis of variance). Inter-group differences for the secondary outcomes favored homeopathy, but were overall statistically non-significant (ADBSA: $F_{1,\ 52} = 0.019$; $p = 0.891$; DLQI: $F_{1,\ 52} = 0.692$; $p = 0.409$).

Conclusion IHMs performed significantly better than placebos in reducing the severity of AD in adults, though the medicines had no overall significant impact on AD burden or DLQI.

Introduction

Atopic dermatitis (AD) is a chronic/relapsing pruritic inflammatory skin disease with a predilection for the skin flexures, and usually develops during early childhood.[1] It is associated with high serum immunoglobulin E, and a personal or family history of AD, hay fever, and/or bronchial asthma.[1,2] The prevalence of AD is higher among children than adults worldwide.[3] A rising trend in AD has been observed in India in the last four decades.[4] A study from the eastern Indian state of Bihar reported an incidence of 0.38% of the total number of outpatient children; however, true point prevalence data in the community are still scarce.[5] Conventional therapy includes topical corticosteroids and calcineurin inhibitors, emollients, oral antihistamines, and immune suppressants, with varying effectiveness and potential adverse effects.[6,7]

The prevalence of all the atopic disorders, including AD, asthma and allergic rhinitis, was substantially higher in an open population compared with general practice.[7] AD remains one of the most frequently reported dermatological disorders in homeopathy outpatients,[8] especially in classical homeopathic medical practices in Germany and Switzerland,[9] and also in India,[10] but conclusive evidence claiming its efficacy or effectiveness is lacking.[11] Studies have been heterogeneous in design and contradictory in their conclusions.[12–19] Single-arm studies have yielded positive results favoring homeopathy, but with obvious methodological shortcomings.[15–18] One comparative cohort study comparing homeopathy with conventional treatment also yielded promising results.[13] However, randomized controlled trials (RCTs) of homeopathy in AD have remained inconsistent in findings.[12,14,19] Thus, the overall evidence fails to demonstrate any conclusive treatment effect of homeopathy in AD.

There are ample instances of successfully treated cases of AD in the homeopathy literature. Logan recommended AD to be classified under "one-sided diseases", as had been advocated by Hahnemann, and suggested treating it with much caution.[20] Morrison[21] and Boedler[22] suggested several homeopathic and Bach flower remedies in the treatment of AD in children. Allen[23] and Roberts[24] suggested the presence of psora, pseudo-psora and sycotic miasms behind the development of AD. Hempel[25] and Lilienthal[26] suggested a list of different homeopathic medicines to treat different variants of AD. Coulter mentioned a series of 86 cases of AD treated successfully with different homeopathic medicines.[27]

The present RCT was a replication of the trial reported by Dey et al,[19] but with an extended end-point of 6 months (instead of 3 months), intended to evaluate the efficacy of individualized homeopathic medicines (IHMs) against identical-looking placebos in the treatment of AD.

Methods

Study Design

A double-blind, randomized (1:1), placebo-controlled, two-parallel-arms trial was conducted in the outpatient departments of Mahesh Bhattacharyya Homoeopathic Medical College and Hospital, West Bengal, India.

Participants

Inclusion criteria were newly diagnosed cases of AD (ICD-10-CM code L20.9) as per UK diagnostic criteria, with a minimum duration of 3 months' suffering, a Patient-Oriented Scoring of AD (PO-SCORAD) value >10, aged between 18 and 65 years, of either sex, literate with the ability to read and write local vernacular Bengali, and providing written informed consent. Patients already undergoing treatment for AD could be recruited on completely stopping the medicines and after a washout phase of 1 month and their fulfillment of eligibility criteria. Exclusion criteria for eligibility were patients who were too sick for consultation, diagnosed with unstable psychiatric or uncontrolled or life-threatening systemic illness affecting the quality of life or any organ failure, substance abuse and/or dependence, women who were pregnant, puerperal or lactating, and patients undergoing homeopathic treatment for any chronic disease within the previous 6 months.

Research ethics and trial registration

The research protocol was reviewed and approved by the institutional ethical committee of Mahesh Bhattacharyya Homoeopathic Medical College and Hospital (Ref. No. 1268/MBH/MCH/CH/PRIM/ADM/19; dated September 6, 2019) before initiation of the trial. It was registered prospectively in the Clinical Trials Registry – India [CTRI/2019/10/021712], with a secondary (UTN) identifier U1111–

1241–7121. The trial protocol's key details are included in the CTRI entry: http://ctri.nic.in/Clinicaltrials/showallp.php?mid1=37385&EncHid=&userName=CTRI/2019/10/021712. Written informed consent was obtained from each of the participants before their enrolment into the trial.

Intervention

- *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 with an empty stomach; dosage and repetition depend upon the individual requirement of the case. Patients were advised to refrain from directly handling the globules or from eating, drinking, smoking, or brushing their 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 (e.g., globules, rectified spirit, dispensing glass vials, corks) were obtained from Dr. Willmar Schwabe India (P) Ltd., New Delhi, India. Both the medicines and placebos were re-packed in identical glass bottles and labeled with code, name of medicine (without stating whether verum or placebo), and potency, and were dispensed according to a random number list. In compliance with homeopathic principles, a single medicine was prescribed on each occasion by a consensus among three homeopaths, and there was a provision to change the medicines or potencies and to adjust the dosage in subsequent visits. One of the homeopaths possessed a master's degree in homeopathy and had more than 20 years of teaching experience and in practicing classical homeopathy. The other two prescribers were postgraduate trainees of the institution. All the homeopaths involved were affiliated with their respective state councils. The duration of therapy was 6 months.
- *Comparator arm*: This group received identical-looking placebos for 6 months. Each dose of placebos consisted of six to eight globules (no. 20), moistened with non-medicinal rectified spirit. Each participant was instructed to take these orally on a clean tongue and with an empty stomach; dosage and repetition depended upon the requirement of the individual case. The dosage regimen was as per verum. The duration of the intervention was 6 months.
- *Concomitant care*: Along with the medicines, each of the enrolled participants (IHMs group and placebos group) received advice on applying olive oil to the affected parts twice a day.[28] They were also instructed to keep the area dry, avoiding the use of tight garments including synthetic clothes, and to maintain local hygiene.

Outcome Measures

- Primary: PO-SCORAD is the most widely used disease-severity scale in AD.[29] It uses the Rule of Nines to assess disease extent and evaluates five clinical characteristics to determine disease severity: (1) erythema; (2) edema/papulation; (3) oozing/crusts; (4) excoriation; and (5) lichenification. It also assesses subjective symptoms of pruritus and loss of sleep with visual analog scales. These three aspects – extent of the disease, disease severity, and subjective symptoms – combine to give a maximum possible score of 103. It is valid and reliable, and it has shown excellent agreement with global assessments of disease severity.[30,31]
- Secondary:

1. Dermatological Life Quality Index (DLQI) is a valid and one of the most frequently used quality-of-life instruments in dermatological conditions.[32,33] It is a 10-items questionnaire that enquires about skin symptoms, feelings of embarrassment, and how skin disease has affected day-to-day activities, work and social life. Each question on DLQI is scored from 0 to 3, with a maximum score of 30 and high scores representing worse quality of life. It also has high repeatability, internal consistency, and sensitivity to change.[34] The translated and prevalidated Bengali version of the DLQI questionnaire was used in the current study[35] (**Supplementary files 1** and **2**, available online only: English and Bengali versions of the DLQI questionnaire).
2. Atopic Dermatitis Burden Scale for Adults (ADBSA) is the first specific assessment tool for AD burden in adults.[36] The questionnaire comprises 19 questions and provides a six-point Likert scale – never (0), rarely (1), sometimes (2), often (3), very often (4), and constantly (5) – in answer to each question. A higher ADBSA score reflects a higher AD burden. In this trial, the translated and validated Bengali version of the ADBSA was used[37] (**Supplementary files 3** and **4**, available online only: English and Bengali versions of the ADBSA questionnaire).
3. All the outcomes were recorded monthly for 6 consecutive months. The primary end-point was PO-SCORAD value after 6 months of intervention. The secondary end-points were DLQI and ADBSA scores after 6 months of intervention.

Sample Size

Dey et al recommended a target sample size of 378 (2×189), using PO-SCORAD as the primary outcome measure.[19] However, achieving this sample size within the stipulated time frame and from a single site was deemed not feasible. A sample size of 60 (2×30) was targeted here, which reduced the power of the trial by 20%.

Randomization

A random sequence was generated by the permuted block randomization method, maintaining 1:1 allocation, by an independent third party in strict confidentiality using the StatTrek random number generator. This chart was made available to the blinded pharmacist in coded form for dispensing from the coded vials as per the prescriptions.

Blinding

The double-blinding method was adopted by masking the participants, trial recruiters, investigators, outcome assessors, pharmacists, and data entry operators throughout the trial. Blinding was maintained by identically coded vials coded as "1" or "2" and containing either medicine or placebo. Codes were assigned randomly and confidentially by another independent third party. Both medicines and placebos were re-packed in identical glass bottles and labeled with code, name of medicine (without stating whether verum or placebo) and potency and were dispensed according to the random number list. Codes were broken at the end of the trial after the dataset was frozen.

Allocation Concealment

This was achieved by making the trial recruiters unaware of the random number sequence and by the fact that the vials were destined for each patient solely by the pre-determined and confidential random number chart.

Statistical Methods

The intention-to-treat (ITT) approach was adopted; however, provision was kept for post-randomization exclusion of those participants who never received the intervention. Missing values were replaced by predicted values from linear regression models. Data distribution was examined by histograms, Q–Q plots, and Kolmogorov–Smirnov and Shapiro-Wilk tests; no significant departure from Normality was identified. The intra-group changes were examined using a one-way repeated measure analysis of variance (ANOVA). Inter-group differences were tested using two-way repeated measures ANOVA for the overall model and unpaired *t*-tests at different time points. The effect size is presented in terms of Cohen's *d* (small effect, 0.2; medium effect, 0.5; large effect, 0.8). A *p*-value less than 0.05 (two-tailed) was considered statistically significant. Statistical Package for Social Sciences (version 20.0; IBM Corp., IBM SPSS Statistics for Windows, Armonk, New York, United States) was used to analyze the data.

Reporting of Adverse Events

The investigators had instructed the participants to report any harm, unintended effects, serious adverse events, or unpleasant aggravations (homeopathic, medicinal, or disease symptoms), either directly in the outpatient departments or over the telephone, during the trial. Adverse events were assessed using the adverse drug reactions probability scale as proposed by Naranjo et al.[38]

Reporting Guidelines

Trial reporting adhered to the Consolidated Standards for Reporting Trials (CONSORT)[39] and the RedHot guidelines for reporting trials of homeopathy[40] (**Supplementary files 5** and **6**, available online only: CONSORT and RedHot checklists).

Results

Participant flow

The screening and retention rates were 58.3 and 86.7%, respectively. Out of the 103 patients screened, 43 were excluded due to various reasons; 60 were enrolled as per the eligibility criteria and were randomized subsequently. Eight patients dropped out (two in the verum group and six in the control group); 52 patients completed the trial (►**Fig. 1**).

Recruitment

The enrolment period spanned from December 2019 to January 2021 inclusive. Follow-up of the last enrolled patient was completed in June 2021. The total duration of the trial was 19 months.

Baseline data

The distribution of the confounder variables was similar between groups at baseline without any significant differences (►**Table 1**).

Numbers analyzed

Missing values were calculated for two participants, one in each group, using the ITT approach; the other six, one in the verum and five in the placebo group, were excluded post-randomization from the analysis because they never received the intervention at all. Thus, out of the 60 randomized, 54 participants (IHMs, 29; placebos, 25) entered the final analysis.

Outcomes and Estimation of Effect Size

- *PO-SCORAD*: Inter-group differences overall favored IHMs against placebos ($F_{1,\ 52} = 14.735$; $p < 0.001$; partial eta-square = 0.221; two-way repeated measures ANOVA). Mean inter-group differences increased gradually, starting from month 1 and became significant from month 3 onward (month 3: $p = 0.036$, month 4: $p < 0.001$, month 5: $p < 0.001$, month 6: $p < 0.001$). At 6 months, the inter-group difference was −18.1 (95% confidence interval [CI], −24.0 to −12.2); the associated effect size of 1.639 (►**Table 2**) can be rated as very large. Intra-group changes were significant in the IHMs group ($F_{6,\ 23} = 18.588$; $p < 0.001$), but not in the placebo group ($F_{6,\ 19} = 1.316$; $p = 0.298$). With a large effect size of 1.639, a further replication trial with 14 (7×2) patients would provide 80% power based on a two-sided significance level of 5%. Thus, our achieved sample size of 60 provided ample power to avoid a type II error.
- *ADBSA*: Inter-group differences overall, though favoring homeopathy, were statistically non-significant ($F_{1,\ 52} = 0.019$; $p = 0.891$; partial eta square = 0). Mean inter-group differences increased gradually over 6 months of intervention but they did not achieve significance at any time points (all $p > 0.05$). At 6 months, the inter-group difference was −4.4 (95% CI, −9.4 to 0.6). Intra-group changes were statistically significant in the IHMs group ($F_{6,\ 23} = 6.173$; $p = 0.001$), but not in the placebo group ($F_{6,\ 19} = 1.795$; $p = 0.154$) (►**Table 3**).
- *DLQI*: Inter-group differences overall, though they favored homeopathy, were statistically non-significant

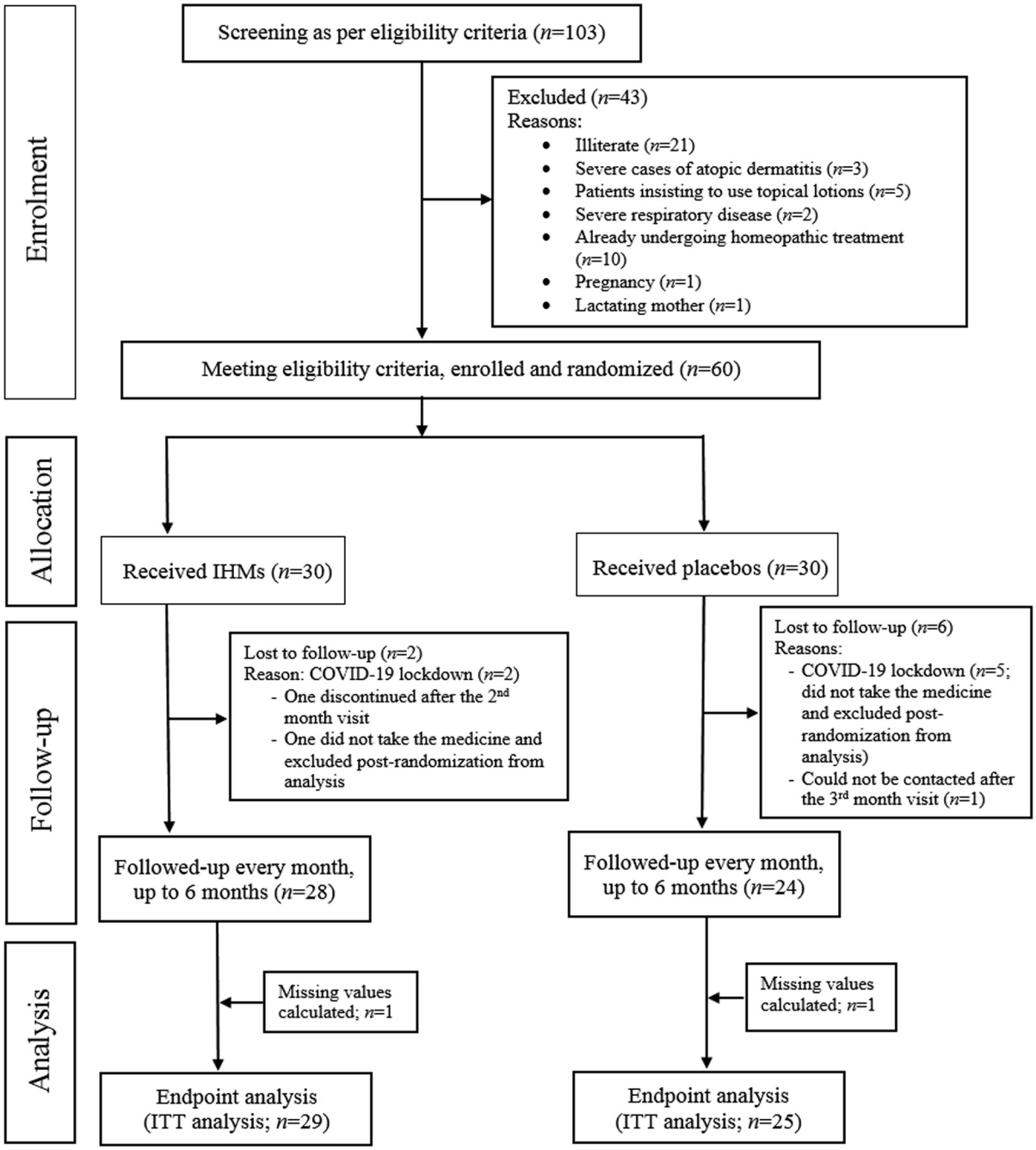

Fig. 1 CONSORT study flow diagram. COVID-19, coronavirus disease 2019; IHMs, individualized homeopathic medicines; ITT, intention-to-treat; PO-SCORAD, Patient-Oriented Scoring of Atopic Dermatitis.

($F_{1,\ 52} = 0.692$; $p = 0.409$; partial eta squared = 0.013). Mean inter-group differences increased gradually over 6 months of intervention and achieved statistical significance after 5 months ($p = 0.011$) and 6 months ($p = 0.008$). At 6 months, the inter-group difference was −3.6 (95% CI, −6.3 to −1.0); the associated effect size of 0.742 (►**Table 4**) can be rated as medium. Intra-group changes were statistically significant in the IHMs group ($F_{6,\ 23} = 9.744$; $p < 0.001$), but not in the placebo group ($F_{6,\ 19} = 1.383$; $p = 0.272$) (►**Table 4**).

Medicines used

A total of 28 different medicines, as verum or placebo, were prescribed in the trial and dispensed by the blinded pharmacist. Actual medicines were dispensed to the participants of the verum group, whereas identical-looking placebos were dispensed to the participants of the control group. The most frequently prescribed medicines were *Sulphur* ($n = 10$, 18.5%), *Pulsatilla nigricans* ($n = 4$, 7.4%), *Antimonium crudum* ($n = 3$, 5.6%), *Graphites* ($n = 3$, 5.6%), *Lachesis mutus* ($n = 3$, 5.6%) and *Natrum sulphuricum* ($n = 3$, 5.6%)

Table 1 Comparison of the socio-demographic characteristics between two groups at baseline ($N = 54$)

Features	IHMs group ($n = 29$)	Placebo group ($n = 25$)
Age (years)[a]	37.5 ± 13.2	40.7 ± 8.9
Body mass index[a]	22.5 ± 2.8	22.8 ± 2.7
Duration of suffering (years)[b]	2 (0.9, 5)	1 (0.6, 2.7)
Sex[c]		
• Male	14 (48.3)	12 (48)
• Female	15 (51.7)	13 (52)
Residence[c]		
• Rural	6 (20.7)	4 (16)
• Semi-urban	5 (17.2)	4 (16)
• Urban	18 (62.1)	17 (68)
Risk factors[c]		
• Family history of atopy	11 (37.9)	8 (32)
Treatment taken[c]		
• Conventional therapy	13 (44.8)	11 (44)
• Miscellaneous	3 (10.3)	2 (8)
Co-morbidities[c]		
• Allergic rhinitis	1 (3.4)	1 (4)
• Bronchial asthma	3 (10.3)	2 (8)
• Miscellaneous	4 (13.8)	8 (32)
Educational status[c]		
• 8^{th} Standard or less	6 (20.7)	6 (24)
• 9^{th} – 12^{th} Standard	9 (31)	13 (52)
• Higher than 12^{th} Standard	14 (48.3)	6 (24)
Employment status[c]		
• Service	7 (24.1)	5 (20)
• Business	4 (13.8)	4 (16)
• Dependent and others	18 (62.1)	16 (64)
Socioeconomic status[c]		
• Poor	7 (24.1)	5 (20)
• Middle	22 (75.9)	20 (80)

Abbreviation: IHMs, individualized homeopathic medicines.
[a]Continuous data presented as means ± standard deviations.
[b]Continuous data presented as medians (inter-quartile ranges).
[c]Categorical data presented as absolute values (percentages).

(►**Table 5**). However, this study does not help to identify effective homeopathic medicines for AD. In many instances, there was just one patient per medicine – too few to arrive at a conclusion about effectiveness. It is reflective of individualized selection as advocated in classical homeopathy (**Supplementary file 7**, available online only: Indications of the remedies).

Adverse events

During the trial, no serious adverse events were reported. Five cases of acute coryza were reported – four in the placebo group and one in the IHMs group. They were treated with *Rhus toxicodendron* 30c, six doses, thrice daily for 2 days ($n = 3$), *Belladonna* 30c, six doses, thrice daily for 2 days ($n = 1$), and *Bryonia alba* 200c, two doses, once daily for 2 days ($n = 1$). There was a case of minor injury in the IHMs group, which was treated successfully with *Arnica montana* 30c, six doses, thrice daily for 2 days. Two cases of acute diarrhea were reported in each group – these were treated with *Podophyllum peltatum* 30c, six doses, thrice daily for 2 days, and *Aloe socotrina* 30c, six doses, thrice daily for 2 days. The trial medicines were omitted during the administration of acute remedies and resumed afterward when the acute phase had settled down.

Table 2 Comparison of the PO-SCORAD values between groups at different time points ($N = 54$)

Time points	IHMs group ($n = 29$)	Placebo group ($n = 25$)	Mean difference ± SE	95% CI	$p^{(a)}$	Effect size: Cohen's d
Baseline	40.8 ± 12.6	36.7 ± 11.8	4.1 ± 3.3	−2.6, 10.8	0.224	–
Month 1	31.4 ± 12.5	34.5 ± 10.8	−3.1 ± 3.2	−9.5, 3.3	0.341	0.265
Month 2	26.2 ± 11.4	32.8 ± 10.8	−6.5 ± 3.0	−12.7, −0.4	0.036*	0.594
Month 3	21.6 ± 11.0	34.1 ± 10.5	−12.5 ± 2.9	−18.5, −6.6	<0.001	1.162
Month 4	17.7 ± 9.3	33.7 ± 12.8	−16.0 ± 3.0	−22.0, −9.9	<0.001	1.430
Month 5	16.0 ± 7.6	33.0 ± 13.6	−17.0 ± 2.9	−22.9, −11.1	<0.001	1.543
Month 6	14.7 ± 7.5	32.8 ± 13.7	−18.1 ± 2.9	−24.0, −12.2	<0.001	1.639
Intra-group changes:	Wilks' $\lambda = 0.171$ $F_{6, 23} = 18.588$ $p^{(b)} < 0.001$ Partial $\eta^2 = 0.829$	Wilks' $\lambda = 0.706$ $F_{6, 19} = 1.316$ $p^{(b)} = 0.298$ Partial $\eta^2 = 0.294$				
Inter-group difference:	$F_{1, 52} = 14.735$; $p^{(c)} < 0.001$; Partial $\eta^2 = 0.221$					

Abbreviations: CI, confidence interval; IHMs, Individualized homeopathic medicines; SD, standard deviation; SE, standard error.
$p^{(a)}$ inter-group differences detected by unpaired *t*-tests at different time points.
$p^{(b)}$ intra-group changes detected by one-way repeated-measures ANOVA.
$p^{(c)}$ inter-group differences detected by two-way repeated-measures ANOVA models.
* $0.01 < p < 0.05$.

Table 3 Comparison of the ADBSA scores between groups at different time points ($N = 54$)

Time points	IHMs group ($n = 29$)	Placebo group ($n = 25$)	Mean difference ± SE	95% CI	$p^{(a)}$	Effect size: Cohen's d
Baseline	28.2 ± 15.8	23.2 ± 13.2	5.0 ± 4.0	−3.1, 13.0	0.220	–
Month 1	24.0 ± 11.5	21.1 ± 10.0	2.9 ± 2.9	−3.0, 8.8	0.334	0.269
Month 2	22.1 ± 9.9	20.4 ± 9.1	1.7 ± 2.6	−3.5, 6.9	0.521	0.179
Month 3	20.2 ± 9.7	21.4 ± 9.8	−1.2 ± 2.7	−6.5, 4.1	0.652	0.123
Month 4	18.0 ± 8.6	21.6 ± 11.9	−3.6 ± 2.8	−9.2, 2.0	0.204	0.347
Month 5	17.5 ± 8.7	20.4 ± 9.9	−2.9 ± 2.5	−8.0, 2.2	0.262	0.311
Month 6	15.8 ± 8.7	20.2 ± 9.6	−4.4 ± 2.5	−9.4, 0.6	0.084	0.480
Intra-group changes:	Wilks' $\lambda = 0.383$ $F_{6, 23} = 6.173$ $p^{(b)} = 0.001$ Partial $\eta^2 = 0.617$	Wilks' $\lambda = 0.638$ $F_{6, 19} = 1.795$ $p^{(b)} = 0.154$ Partial $\eta^2 = 0.362$				
Inter-group difference:	$F_{1, 52} = 0.019$; $p^{(c)} = 0.891$; Partial $\eta^2 = 0$					

Abbreviations: CI, confidence interval; IHMs, individualized homeopathic medicines; SD, standard deviation; SE, standard error.
$p^{(a)}$ inter-group differences detected by unpaired *t*-tests at different time points.
$p^{(b)}$ intra-group changes detected by one-way repeated-measures ANOVA.
$p^{(c)}$ inter-group differences detected by two-way repeated-measures ANOVA models.

Discussion

In this double-blind RCT conducted on 60 patients with AD, the primary outcome PO-SCORAD showed statistically significant results with very large effect sizes favoring IHMs against placebos. This large effect size was quite comparable with that observed with systemic immunomodulatory treatment.[41] The secondary subjective (patient-reported) outcomes – ADBSA and DLQI – overall were non-significant, though DLQI revealed significant effects of IHMs at 5 and 6 months, with a medium effect size at the latter time point. ADBSA might require more time to reflect detectable changes. Intra-group changes were significant in the IHMs group, but not in the placebo group. Objective end-points are

Table 4 Comparison of the DLQI scores between groups at different time points ($N = 54$)

Time points	IHMs group ($n = 29$)	Placebo group ($n = 25$)	Mean difference ± SE	95% CI	p [(a)]	Effect size: Cohen's d
Baseline	15.0 ± 5.5	12.8 ± 4.3	2.2 ± 1.4	−0.5, 5.0	0.106	–
Month 1	13.6 ± 4.2	12.6 ± 4.3	1.1 ± 1.2	−1.3, 3.4	0.366	0.235
Month 2	12.6 ± 4.4	11.8 ± 3.7	0.7 ± 1.1	−1.5, 3.0	0.507	0.197
Month 3	11.3 ± 5.3	12.5 ± 3.0	−1.2 ± 1.2	−3.6, 1.2	0.326	0.279
Month 4	9.9 ± 5.5	12.2 ± 4.7	−2.3 ± 1.4	−5.1, 0.5	0.111	0.449
Month 5	8.4 ± 4.3	11.6 ± 4.6	−3.2 ± 1.2	−5.6, −0.8	0.011*	0.719
Month 6	7.7 ± 4.9	11.3 ± 4.8	−3.6 ± 1.3	−6.3, −1.0	0.008**	0.742
Intra-group changes:	Wilks' $\lambda = 0.282$ $F_{6,23} = 9.744$ p [(b)] < 0.001 Partial $\eta^2 = 0.718$	Wilks' $\lambda = 0.696$ $F_{6,19} = 1.383$ p [(b)] $= 0.272$ Partial $\eta^2 = 0.304$				
Inter-group difference:	$F_{1, 52} = 0.692$; p [(c)] $= 0.409$; Partial $\eta^2 = 0.013$					

Abbreviations: CI, confidence interval; IHMs, individualized homeopathic medicines; SD, standard deviation; SE, standard error; H, eta; Λ, lambda.
p [(a)] inter-group differences detected by unpaired t-tests at different time points.
p [(b)] intra-group changes detected by one-way repeated-measures ANOVA.
p [(c)] inter-group differences detected by two-way repeated-measures ANOVA models.
* $0.01 < P < 0.05$.
** $0.001 < P < 0.01$.

usually easier to measure, collect, analyze and interpret. In contrast, subjective end-points are harder to assess and yet they may be clinically more meaningful in homeopathy. Despite the challenges of using subjective measurements in clinical trials, they remain an important component in many areas of medicine, especially for assessing quality of life in chronic diseases such as AD.

The chief strengths of the trial are in its study design. The fundamental principle of evidence-based medicine is that the most reliable evidence originates from trials with the lowest risk of bias, having adequate statistical power, randomization, blinding, and pre-specified outcome measures. There are several recognized risks of bias, such as selection bias, performance bias, detection bias, and attrition bias. Some of these can be controlled efficiently through rigorous measures such as randomization and blinding, key attributes of the current study. Further strengths of our trial include the use of pre-validated outcome measures, repeatedly measured data, and an ITT approach that enabled a robust analysis of the trial results. The choice of IHMs adhered to the principles of "classical" homeopathy and involved the input of experienced and well-qualified homeopaths.

The optimum timing of end-point is difficult to determine for a clinical trial in a chronic, relapsing condition such as AD. IHMs may have helped the disease go into remission. An even longer duration of follow-up might address this issue; however, being a placebo-controlled trial, increasing the follow-up duration, to (say) 1 year would potentially bring ethical concerns of treating some participants with placebos for that length of time. Many previous studies have shown that AD is associated with high absolute eosinophil count and elevated total serum immunoglobulin E levels.[42,43] These outcomes could not be measured in our current study because of infrastructural constraints, resulting in an important limitation of this trial.

In comparison with the previous RCTs by Siebenwirth et al[12] and Dey et al,[19] our trial had several advantages. Our achieved sample size of 54 was larger and our attrition rate of 15% was lower compared with the data reported by Siebenwirth. And our trial used multiple outcome measures instead of a single outcome. Thus, our study was methodologically stronger and more robust than its predecessors. In comparing our work with the preliminary trial by Dey et al,[19] both studies used the same outcome measures and the same sample size of 60, while ours extended the follow-up duration from 12 to 24 weeks as had been recommended by Dey, though it was shorter than the 32 weeks employed by Siebenwirth.

Apart from being prescribed on an individualized basis to treat AD, the same IHMs (e.g., *Rhus toxicodendron*) were also used as "rescue remedies" to treat acute ailments, such as acute coryza, that were probably unrelated to the trial. This additional homeopathic treatment might have acted as a confounder to the trial-specific medicines. Nonetheless, these were "short-acting" remedies selected on the "acute totality" of the cases, acting on a different (superficial) plane, and were unlikely to affect the actions of trial-specific medicines.[44,45] After an acute phase was over, the patient was re-evaluated by the treating physicians. Either the same trial medicine of the same code was repeated, or new medicines were prescribed by the physicians according to the symptomatology of the patient and as decided appropriate to the case or condition.

Further independent replications of the trial are recommended – perhaps at different extended end-points – to confirm or refute a positive impact of IHMs on AD in adults. Relevant blood allergy markers may be considered as secondary outcome measures in such future trials.

Table 5 Prescribed medicines in the two groups at baseline ($N = 54$)

Name of the medicines	Total; *n* (%)	IHMs group ($n = 29$); *n* (%)	Placebo group ($n = 25$); *n* (%)	*p*
1. *Antimonium crudum*	3 (5.6)	2 (6.9)	1 (4)	0.643
2. *Apis mellifica*	1 (1.9)	1 (3.4)	–	–
3. *Arsenicum album*	2 (3.7)	1 (3.4)	1 (4)	0.915
4. *Bacillinum*	1 (1.9)	1 (3.4)	–	–
5. *Bovista*	1 (1.9)	1 (3.4)	–	–
6. *Calcarea carbonica*	2 (3.7)	1 (3.4)	1 (4)	0.915
7. *Calcarea phosphorica*	2 (3.7)	1 (3.4)	1 (4)	0.915
8. *Causticum*	1 (1.9)	1 (3.4)	–	–
9. *Croton tigrium*	1 (1.9)	–	1 (4)	–
10. *Fagopyrum esculentum*	1 (1.9)	–	1 (4)	–
11. *Graphites*	3 (5.6)	–	3 (12)	–
12. *Hepar sulphuris*	1 (1.9)	1 (3.4)	–	–
13. *Lachesis mutus*	3 (5.6)	2 (6.9)	1 (4)	0.643
14. *Mezereum*	1 (1.9)	1 (3.4)	–	–
15. *Natrum muriaticum*	1 (1.9)	–	1 (4)	–
16. *Natrum sulphuricum*	3 (5.6)	2 (6.9)	1 (4)	0.643
17. *Nitricum acidum*	1 (1.9)	1 (3.4)	–	–
18. *Nux vomica*	2 (3.7)	1 (3.4)	1 (4)	0.915
19. *Petroleum*	2 (3.7)	1 (3.4)	1 (4)	0.915
20. *Phosphorus*	1 (1.9)	–	1 (4)	–
21. *Psorinum*	2 (3.7)	1 (3.4)	1 (4)	0.915
22. *Pulsatilla nigricans*	4 (7.4)	2 (6.9)	2 (8)	0.877
23. *Rhus toxicodendron*	1 (1.9)	1 (3.4)	–	–
24. *Sepia officinalis*	1 (1.9)	1 (3.4)	–	–
25. *Silicea terra*	1 (1.9)	–	1 (4)	–
26. *Sulphur*	10 (18.5)	6 (20.7)	4 (16)	0.658
27. *Thuja occidentalis*	1 (1.9)	–	1 (4)	–
28. *Veratrum album*	1 (1.9)	–	1 (4)	–

Abbreviation: IHMs, individualized homeopathic medicines.
Note: Chi-square or Fisher's exact tests applied, *p* less than 0.05 two-tailed considered as statistically significant.

Conclusion

IHMs reduced the severity of AD over a 6-month period in adults who participated in this randomized, double-blind, placebo-controlled trial. Whilst there were no significant overall effects of IHMs on secondary outcomes, an improvement in DLQI was noted after 5 months.

Highlights

- A double-blind, randomized, placebo-controlled trial of individualized homeopathic medicines was conducted over 6 months on 60 adults with atopic dermatitis.
- Homeopathic medicines produced significantly better effects than placebos in the treatment of atopic dermatitis after 6 months of intervention.

Data Availability

The data are available from the corresponding author upon reasonable request.

Authors' Contributions

S.M., S.G., A.D.D., B.B., C.P., N.G. and S.M. contributed to the literature search, study concept, conducting the trial, data collection, data evaluation and drafting the manuscript. S. D., N.K.S., 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.

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Supplementary Material

Supplementary file 1. DLQI English version.
Supplementary file 2. DLQI Bengali version.
Supplementary file 3. Atopic Dermatitis Burden Scale for Adults: English version.
Supplementary file 4. Atopic Dermatitis Burden Scale for Adults: Bengali version.
Supplementary file 5. CONSORT 2010 checklist of information to include when reporting a randomized trial.
Supplementary file 6. RedHot checklist of information to include when reporting randomized trials of homeopathy.
Supplementary file 7. Indications of the most frequently prescribed five medicines.

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Conflict of Interest
None declared.

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