A Randomized, Double-Blind, Placebo-Controlled, Pilot Trial of Individualized Homeopathic Medicines for Cutaneous Warts

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Abstract

Background Though frequently used in practice, research studies have shown inconclusive benefits of homeopathy in the treatment of warts. We aimed to assess the feasibility of a future definitive trial, with preliminary assessment of differences between effects of individualized homeopathic (IH) medicines and placebos in treatment of cutaneous warts.

Methods A double-blind, randomized, placebo-controlled trial ($n = 60$) was conducted at the dermatology outpatient department of D.N. De Homoeopathic Medical College and Hospital, West Bengal. Patients were randomized to receive either IH ($n = 30$) or identical-looking placebo ($n = 30$). Primary outcome measures were numbers and sizes of the warts; secondary outcome was the Dermatology Life Quality Index (DLQI) questionnaire measured at baseline, and every month up to 3 months. Group differences and effect sizes were calculated on the intention-to-treat sample.

Results Attrition rate was 11.6% (IH, 3; placebo, 4). Intra-group changes were significantly greater (all $p < 0.05$, Friedman tests) in IH than placebo. Inter-group differences were statistically non-significant (all $p > 0.05$, Mann-Whitney U tests) with

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- cutaneous warts
- dermatological life quality index
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- randomized controlled trial

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small effect sizes—both in the primary outcomes (number of warts after 3 months: IH median [inter-quartile range; IQR] 1 [1, 3] vs. placebo 1 [1, 2]; $p = 0.741$; size of warts after 3 months: IH 5.6 mm [2.6, 40.2] vs. placebo 6.3 [0.8, 16.7]; $p = 0.515$) and in the secondary outcomes (DLQI total after 3 months: IH 4.5 [2, 6.2] vs. placebo 4.5 [2.5, 8]; $p = 0.935$). *Thuja occidentalis* (28.3%), *Natrum muriaticum* (10%) and *Sulphur* (8.3%) were the most frequently prescribed medicines. No harms, homeopathic aggravations, or serious adverse events were reported.

Conclusion As regards efficacy, the preliminary study was inconclusive, with a statistically non-significant direction of effect favoring homeopathy. The trial succeeded in showing that an adequately powered definitive trial is both feasible and warranted.

Trial Registration CTRI/2019/10/021659; UTN: U1111–1241–7340

Introduction

Skin warts are benign tumors caused by infection of keratinocytes by human papilloma virus (HPV), visible as well-defined hyperkeratotic protrusions.[1,2] These may adopt a variety of patterns depending on the anatomical location or morphology, associated other skin diseases, on the causative agent, duration, immunologic status, family history, and treatment history.[3,4] Warts affect approximately 10% of the population worldwide.[5] Viral warts are a global burden, with an average "disability weight" of 0.029 (weighting factor that reflects severity of the disease on a scale from 0 [perfect health] to 1 [equivalent to death]).[6] Though rare in infancy and early childhood, overall prevalence is as high as 10 to 20% in school-going children, with a peak at 12 to 16 years.[7] The same scenario is found in the Indian population, where 46% of cases are in the age group 14 to 20 years.[8] India, being a mostly tropical country, has a climate that favors viral infections including warts. Some warts, especially plantar, are found to have a seasonal variation, increasing during the winter months.[9,10]

"Wait and watch" is the preferred form of treatment for warts, as the rate of spontaneous regression is high.[11,12] Besides, many other treatments are also available—home remedies (hot water,[13,14] garlic extract,[15,16] duct tape,[17] etc.), over-the-counter (OTC) therapies (salicylic acid[18,19]), and destructive treatment[20] (surgical[21,22] and chemical[23]). No single treatment is found to be fully effective.[24] Viral infection is not assumed to be the sole cause of warts in infected people.[25] This, in turn, supports the homeopathic philosophy that it is not just the virus/external cause that produces disease but that some internal malady lies behind the production of disease.[26] The removal of the end product of the disease by local means leaves the disease lingering in the system and it recurs either in the same manner or in another form. Viral warts are not the sole results of virus but remain merely as an external sign. The internal causes refer to natural disposition and individuality of the patient.[27] Warts appear in different forms, shapes, sensations, discharges, and at different sites according to the predominant "miasm" of the patient.[26] Though warts are the external manifestations, they represent the internal derangement and play an important role in distinguishing between different cases of disease and thus the appropriate remedy.[26]

There are studies[28–30] exploring the effects of various homeopathic medicines in warts. Successful treatment and complete remission of warts with homeopathic medicines have been documented in observational studies,[31,32] a case series,[33] and case reports.[34,35] In contrast to these findings, there are also several placebo-controlled, double-blind trials[36–40] that have reported non-significant results. One reason for the discrepancy might be that selection of trial medicines was from a pre-defined list, which does not fully comply with the homeopathic principle of individualization. Reviews concluded that there was no consistent evidence for the efficacy of homeopathy for warts, considering the heterogeneity in the design of the trials.[41,42] A double-blind trial with pre-defined remedies has also been initiated in 2019 by the Central Council for Research in Homoeopathy (CCRH).[43] With such scarcity of quality evidence, the treatment of warts remains a "gray area" in homeopathy.

This double-blind, placebo-controlled, pilot trial aimed to assess differences between individualized homeopathic (IH) medicines and placebos in the treatment of cutaneous warts. Most importantly, it aimed to explore feasibility of a future larger-scale trial, related to the issues of recruitment, randomization, treatment, assessment of outcome measures, follow-up, and the time needed to collect and analyze data.

Methods

Trial Design

A double blind, randomized, placebo-controlled, two parallel arms, pilot clinical trial was conducted at the Out-Patient Department-3 (OPD-3) of D.N. De Homoeopathic Medical College and Hospital, West Bengal. 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/2019/10/021659], prior to enrolment of the patients. It also had a secondary identifier (Universal Trial Number) of U1111–1241–7340. The trial protocol and full project report were submitted under a Short-Term

Studentship in Homeopathy 2019 to CCRH, identification number 190292 (https://ccrhscholarship.in/results/result-stsh-2019).

Participants

Inclusion criteria included adults aged between 18 and 65 years, of either sex, literate, consenting to participate, and suffering from cutaneous warts (non-genital; 2020 ICD-10-CM diagnosis code B07.9) for variable periods of time and not taking any other treatment for those warts for at least 1 month. Patients already undergoing treatment for warts were recruited only after having completely stopped that therapy and with a subsequent wash-out phase of 1 month or more. Exclusion criteria consisted of patients with ano-genital and genital warts, individuals diagnosed with unstable psychiatric illnesses or any disease affecting quality of life (QoL), immuno-compromised state, pregnant women and lactating mothers, substance abuse and/or dependence, or undergoing homeopathic treatment for any chronic disease within the last 6 months.

Intervention

Patients were randomized into two parallel arms:

1. Verum: Indicated homeopathic medicines in centesimal potencies, as decided appropriate to the case or condition, were administered. In centesimal scale, each dose consisted of six to eight globules (no. 10) of cane sugar, medicated with a single drop of 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 cases. Duration of therapy was 3 months. Final selection of the single individualized medicine and dosage was in accordance with the standard homeopathic guidelines and agreement among three homeopaths. The prescriptions on follow-up visits were generated as per relevant homeopathic principles and were recorded in follow-up sheets. One of the prescribers possessed a Master's degree in homeopathy, with more than 15 years of experience of teaching and practicing classical homeopathy; the other two prescribers were a postgraduate trainee and an intern at D.N. De Homoeopathic Medical College and Hospital, West Bengal. All the homeopaths were affiliated with state councils.
2. Comparator: Placebos, visually indistinguishable from verum, were administered over a period of 3 months. Each dose of placebo consisted of six to eight globules (no. 20) of cane sugar, moistened with rectified spirit, to be taken orally on a clean tongue and with empty stomach; dosage and repetition depending upon the individual requirement of the cases. Participants in the control arm were assessed by the three homeopaths in the same way as was done in the experimental arm. "Placebo prescription" was similar to that for patients receiving an actual medicine and was dispensed by the blinded pharmacist from identical-looking coded vials as per the random number chart. Thus "placebo prescription" seemed similar to verum and was blinded to the patients, prescribing doctors and outcome assessors. Irrespective of codes, provision was kept to prescribe different "acute medicines" (rescue remedies) based on "acute totality" to counter any adverse or serious adverse events as per homeopathic principles.

The homoeopathic medicines and placebos were both provided by Hahnemann Publishing Company Private Limited (HAPCO; 165, Bipin Bihari Ganguly Street, Baithakkhana, Bowbazar, Kolkata 700012, West Bengal, India)—a good manufacturing practice (GMP)-certified pharmaceutical company. Both medicines and placebos were re-packed in identical glass bottles and labeled with code, name of medicine, potency, and were dispensed according to the randomization list.

General Management

To prevent spread of the virus, patients were asked to maintain basic personal hygiene measures, with thorough hand washing after touching any wart, avoiding brushing, combing, shaving, or picking the areas where warts were present.

Outcomes

1. *Primary:* The number of the warts was counted, and the size of each wart was measured by a millimeter (mm) scale on its longest diameter. Each patient was followed up every month for 3 months.
2. *Secondary:* Dermatological Life Quality Index (DLQI)[44] is a valid generic questionnaire comprising 10 items provided with a Likert-type scale (3, very much; 2, a lot; 1, a little; and 0, not at all or not relevant) for assessing dermatological conditions in adults. Total score is calculated by summing up the scores for each of the 10 questions. Maximum score is 30; higher scores represent worse QoL. The questions are also classified into six domains: symptoms and feelings (items 1 and 2); daily activities (items 3 and 4); leisure (items 5 and 6), and personal relationships (items 8 and 9); work and school (item 7); and treatment (item 10). Question number 7 is rated as either "3" (prevented work or studying) or "0" (no, or not relevant). English and Bengali versions of the DLQI questionnaire are shown in ►**Supplementary Files 1** and **2**, available online only.

We considered *a priori* a recruitment rate of above 50% and retention rate of above 80% as satisfactory and as a specific indication for pursuing an adequately powered definitive trial in future.

Sample Size

There was no paper reporting relevant data for effect size (standardized mean difference) and sample size calculation. Accounting for an expected attrition rate of up to 10%, and to detect a statistically significant difference between two independent means of the number of warts (primary outcome measure) after 3 months of intervention through

unpaired *t*-test, a study with 2×70 patients would give 80% power based on a two-sided significance level of 5%. However, keeping in mind the stipulated timeframe of 6 months for the entire project (approval in October 2019, conclusion in March 2020, and final report submission by April 2020; available at: https://ccrhscholarship.in/), the exploratory nature of the pilot trial and feasibility issues, we aimed to achieve 60 patients (2×30), resulting in a compromised power of up to 60.4%, and warranting cautious extrapolation and interpretation of the findings.

Randomization

The randomization chart was generated using StatTrek random number generator (https://stattrek.com/statistics/random-number-generator.aspx) and patients were allocated to either the verum or the comparator group. The chart was prepared by an independent third party using restricted six blocks of size 10 ($6 \times 10 = 60$) to maintain 1:1 ratio. Thus, an equal number of patients was randomized to the verum and to the control group.

Blinding

A double-blinding method was adopted: the patients, the treating physicians, the outcome assessors, and the data-entry operator all remained blinded.

Allocation Concealment

It was maintained by identically coded containers having alike vials coded as "1" or "2" indicating either of medicine or placebo, assigned randomly and confidentially by a third party. The coded randomization chart was made available to the blinded pharmacist to provide medicines accordingly from the coded vials. Confidentiality was maintained strictly until the end of the trial. Randomization codes were broken at the end of the trial after the dataset was frozen.

Statistical Methods

Every included patient was entered for the final analyses—i.e., intention-to-treat (ITT) approach. Missing values were replaced by last observation carried forward. Non-parametric tests were used as inferential statistics. Dependent observations of continuous outcomes at baseline and at different points of time were compared using Friedman tests. Group differences were tested at baseline, every month, and up to 3 months by Mann-Whitney *U* tests. *p*-Values were set at less than 0.05, two-tailed, as statistically significant. A common effect size statistic, *r*, was calculated from the Mann-Whitney *U* test, as proposed by Cohen,[45] by dividing the *Z*-value by the square root of the total number of observations (N_{obs}): that is, $r = Z/\sqrt{(N_{obs})}$.[46] This effect size *r* varies from 0 to 1, where 0.10 to <0.30 is considered as small; 0.30 to <0.50 as medium; and ≥ 0.50 as large.[47] All analyses were performed in SPSS IBM v.20 for Windows.

Ethical Considerations

In this project, neither a new drug was experimented on nor any new treatment protocol adopted. Intervention was in strict adherence to IH principles. Prior to enrolment, each patient was provided with an information sheet in the local language, Bengali, detailing the objectives, methods, risks and benefits of participating, and confidentiality issues. Subsequent to that, written informed consent was obtained. Approval was obtained from the Institutional Ethics Committee (IEC) prior to initiation. The study was performed under the constant supervision of the IEC. We had prospective registration of the trial protocol in a trial registry (http://ctri.nic.in/Clinicaltrials/showallp.php?mid1 =37368&EncHid = &userName = CTRI/2019/10/021659), thus making it transparent in conduct and reporting. The protocol conformed to the Declaration of Helsinki for ethical conduct of clinical trials involving human participants.

Trial Reporting

Reporting of the trial was in compliance with the Consolidated Standards for Reporting Trials (CONSORT) extension statement for randomized pilot trials[48] and with the Reporting Data on Homeopathic Treatment (RedHot)[49] guidelines (►**Supplementary Files 3** and **4**, available online only: CONSORT and RedHot checklists).

Reporting of Adverse Events

The investigators had instructed the patients to report any harm, unexpected effect, serious adverse event, or undue aggravation—either directly in the OPD or over the telephone during the trial.

Results

Participant Flow

Eighty-nine patients with warts were screened as per specified inclusion and exclusion criteria; 60 met the eligibility criteria; 29 were excluded because of various reasons specified in the flow diagram (►**Fig. 1**). The patients were randomized to receive either of IH or identical-looking placebo. Following intervention for 3 months, seven patients (IH, 3; placebo, 4) dropped out from the study. The reasons were change of residence for two patients and dissatisfaction with treatment as reported by one; two did not specify any reason and two could not be contacted (►**Fig. 1**: Study flow diagram).

Recruitment

The enrolment period spanned 4 months, from October 2019 until January 2020 inclusive. Follow-up of the last enrolled patient was completed in March 2020. Total study duration was 6 months.

Baseline Data

Ten socio-demographic and clinical features were studied at baseline to test for any statistically significant differences between the two groups, by using Chi-square tests and *t*-tests respectively for categorical variables (sex; residence; occupation; socio-economic status; shape, surface, color, and site of warts) and continuous variables (age; body mass index). The majority of warts were distributed on the face ($n = 23$; 38.3%) and extremities ($n = 17$; 31.6%), either rough

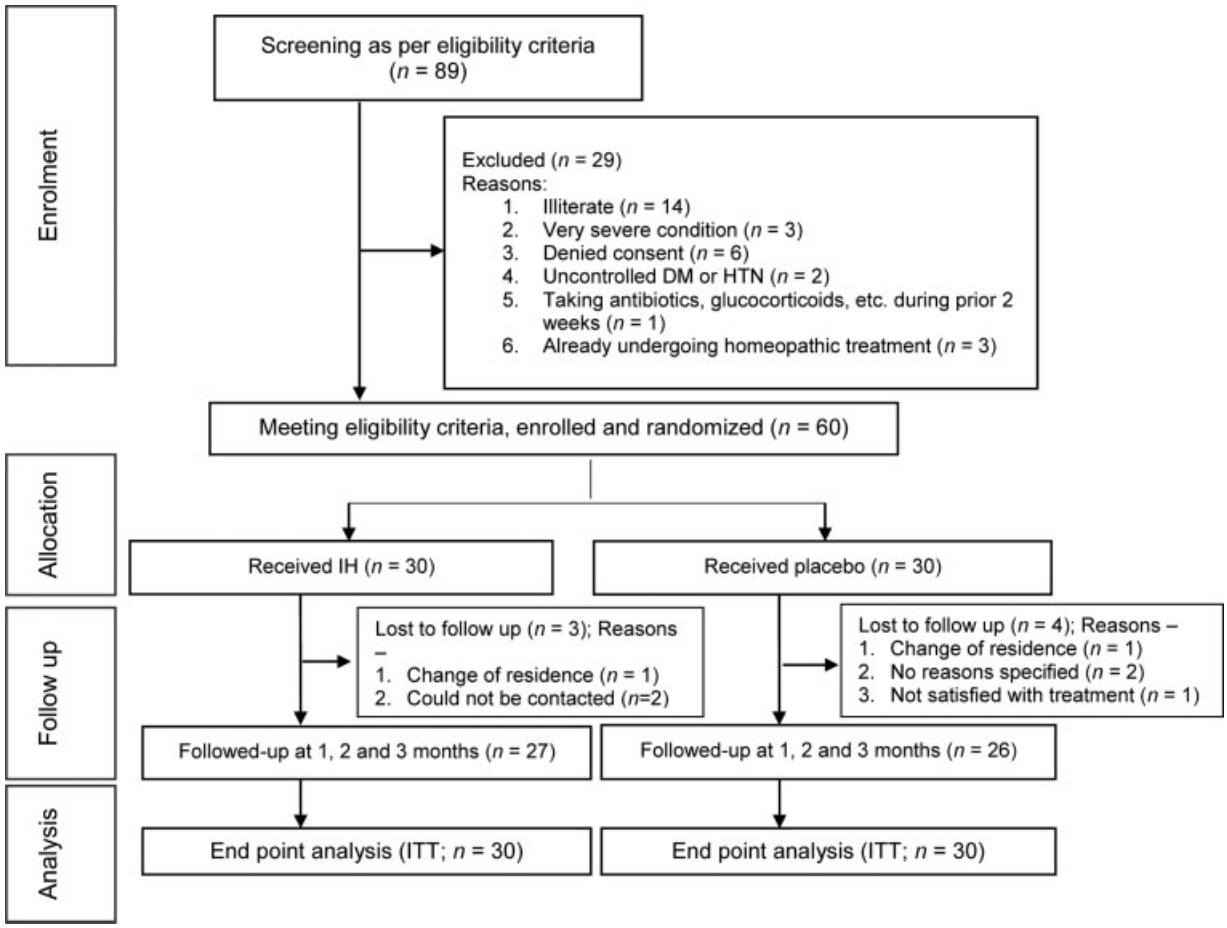

Fig. 1 Study flow diagram. ITT, intention to treat.

($n = 26$; 43.3%) or smooth ($n = 27$; 45%), mostly black in color ($n = 27$; 45%), and single in number ($n = 31$; 51.7%). There were no significant differences in distribution of any of these variables, thus ensuring comparability between the groups (►**Table 1**).

Numbers Analyzed

Out of the 30 enrolled in each group, outcomes data were complete for 27 and 26 patients in the IH and placebo groups respectively. ITT analysis included all the randomized patients ($n = 60$).

Feasibility Issues

Recruitment rate was found to be 67.4%. The major reasons for exclusion were illiteracy (48%) and declining to consent (20%). The retention rate of 88% in this trial was acceptable. There were no obstacles faced in relation to randomization, blinding, outcome assessment and follow-up of any patient.

Outcomes and Estimation

1. *Number and size of warts:* Intra-group changes in the number of warts after 3 months were significantly greater ($p < 0.01$, Friedman tests) in the IH group than in the placebo group ($p = 0.666$). However, the inter-group differences were statistically non-significant (all $p > 0.05$; Mann-Whitney *U* tests), with small effect sizes (IH median [inter-quartile range; IQR] 1 [1, 3] vs. placebo 1 [1, 2]; Mann-Whitney $U = 429$, Wilcoxon $W = 894$, $Z = [-0.330]$, $p = 0.741$, $r = 0.08$). Intra-group changes in the size of warts after 3 months were again significantly greater ($p < 0.001$, Friedman tests) in the IH group than placebo group ($p = 0.014$), but the inter-group differences were statistically non-significant ($p > 0.05$, Mann-Whitney *U* tests), with small effect sizes (IH median [IQR] 5.6 [2.6, 40.2] vs. placebo 6.3 [0.8, 16.7]; Mann-Whitney $U = 406$, Wilcoxon $W = 871$, $Z = [-0.652]$, $p = 0.515$, $r = 0.169$) (►**Table 2**).
2. *DLQI score:* Except for the domains of leisure and personal relations, intra-group changes with time showed significant improvement in each domain, and in total DLQI, in both the verum and placebo groups. The inter-group differences in all the domains (symptoms and feelings, $p = 0.903$; daily activity, $p = 0.760$; leisure, $p = 0.795$; work and school, $p = 0.643$; personal relations, $p = 1.000$; treatment, $p = 0.587$), and in total DLQI score ($p = 0.935$), were statistically non-significant (►**Table 3**).

Medicines Used

The most frequently prescribed medicines were *Thuja occidentalis* (28.3%), *Natrum muraticum* (10%), *Sulphur* (8.3%), *Dulcamara* and *Nitricum acidum* (6.7% each), *Antimonium*

Table 1 Comparison of socio-demographic characteristics between two groups at baseline ($N = 60$)

Features	Verum group ($n = 30$)	Placebo group ($n = 30$)	χ^2 value or t_{58} score	p-Value
Age (years)[a]	40.4 ± 16.1	40.5 ± 13.6	0.035	0.972
Body mass index[a]	24.0 ± 4.6	23.2 ± 5.3	−0.582	0.563
Sex[b]				
• Male	17 (56.7)	10 (33.3)	2.424	0.119
• Female	13 (43.3)	20 (66.7)		
Residence[b]				
• Rural	5 (16.7)	6 (20)	0.022	0.989
• Semiurban	1 (3.3)	2 (6.7)		
• Urban	24 (80)	22 (73.3)		
Occupation[b]				
• Service	1 (3.3)	3 (10)	2.737	0.434
• Business	9 (30)	3 (10)		
• Farming	3 (10)	3 (10)		
• Dependent	17 (56.7)	21 (70)		
Socio-economic status[b]				
• Poor or low	5 (16.7)	7 (23.3)	0.104	0.747
• Middle and upper	25 (83.3)	23 (76.7)		
Shape of warts[b]				
• Round or oval	21 (70)	21 (70)	0.274	0.965
• Irregular	2 (6.7)	2 (6.7)		
• Filiform	2 (6.7)	1 (3.3)		
• Others	5 (16.7)	6 (20)		
Surface of warts[b]				
• Rough	16 (53.3)	10 (33.3)	1.433	0.488
• Smooth	11 (36.7)	15 (50)		
• Others	3 (10)	5 (16.7)		
Color of warts[b]				
• Black	13 (43.3)	14 (46.7)	0.472	0.976
• Brown	9 (30)	9 (30)		
• Gray	3 (10)	3 (10)		
• Skin colored	3 (10)	2 (6.7)		
• Others	2 (6.7)	2 (6.7)		
Site of warts[b]				
• Neck	6 (20)	3 (10)	7.028	0.218
• Chest, abdomen, back	2 (6.7)	1 (3.3)		
• Arms, hands, and fingers	10 (33.3)	7 (23.3)		
• Face	6 (20)	17 (56.7)		
• Scalp	5 (16.7)	1 (3.3)		
• Thighs, legs, foot	1 (3.3)	1 (3.3)		

[a]Continuous data presented as means ± standard deviations and unpaired *t*-test applied; t_{58}: *t* score at 58 degrees of freedom.
[b]Categorical data presented as absolute values (percentages) and chi-square test with Yates' correction applied; *p*-Value less than 0.05 two-tailed was considered as statistically significant.

crudum and *Causticum* (5% each), *Mercurius solubilis* and *Calcarea carbonicum* (3.3% each)—►**Supplementary Files 5**, available online only. As per the protocol, medicines were prescribed in centesimal potencies only. There were no significant inter-group differences in the frequency of prescription of the indicated remedies (all $p > 0.05$) (►**Table 4**).

Adverse Events

No harms, homeopathic aggravations or serious adverse events were reported by any of the patients in the study period of 3 months.

Discussion

A double-blind, pilot, RCT was performed on 60 patients suffering from cutaneous warts. The patients were treated with either IH or indistinguishable placebo. Intra-group changes were greater in IH than placebo, but inter-group differences were non-significant statistically. The results of our trial inform the feasibility of an adequately powered and more definitive trial in future.

The most common location of warts found in our trial was the face (38.3%), and the second most common site was the extremities (31.6%), especially the arms, a finding similar to that of Ghadgepatil et al[50] in Pune, India. In a prevalence study from Pondicherry, India,[8] single-site involvement for warts in adults was common. The finding of our study was similar—out of the total 60 patients, 31 complained of single warts and 29 of multiple warts. Villeda et al[51] compared *Thuja occidentalis* with placebo in children, and Labrecque et al[39] compared IH with placebo in adults. The effect sizes of all these studies were small and statistically non-significant. Whilst Manchanda et al[40] reported 63.3% improvement in the verum group, Schultz[38] found no clinically significant results with homeopathic treatment. One observational study on 100 patients spanning all age groups reported

Table 2 Comparison of the numbers and sizes of warts at baseline and every month up to 3 months

(*N* = 60; Verum group, 30; Placebo group, 30)						
Primary outcomes	**Baseline: Median (IQR)**	**After 1 month: Median (IQR)**	**After 2 months: Median (IQR)**	**After 3 months: Median (IQR)**	**χ^2 at df = 3**	***p*-Value[b]**
Number of warts						
• Verum group	1.5 (1, 3)	1.5 (1, 3)	1 (1, 3)	1 (1, 3)	12.000	0.007**
• Placebo group	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1.571	0.666
Mann-Whitney *U* test	382.5	400.0	412.0	429.0		
Wilcoxon W test	847.5	865.0	877.0	894.0		
Z-test	−1.099	−0.807	−0.605	−0.330		
p-Value[a]	0.272	0.420	0.545	0.741		
Eta-square (η^2)	–	0.009	0.005	0.002		
Effect size (*r*)	–	0.192	0.145	0.08		
Size of warts						
• Verum group	19.6 (6.5, 52.9)	9.4 (3.7, 47.9)	6.7 (3.1, 40.2)	5.6 (2.6, 40.2)	24.487	<0.001***
• Placebo group	12.6 (2.6, 21.9)	11.8 (2.6, 21.9)	6.7 (0.8, 20.0)	6.3 (0.8, 16.7)	10.660	0.014*
Mann-Whitney *U* test	348.0	401.5	383.0	406.0		
Wilcoxon W-test	813.0	866.5	848.0	871.0		
Z-test	−1.510	−0.718	−0.992	−0.652		
p-Value[a]	0.131	0.473	0.321	0.515		
Eta-square (η^2)	–	0.009	0.016	0.007		
Effect size (*r*)	–	0.186	0.258	0.169		

Abbreviation: IQR, inter-quartile range.
Note: $p < 0.05$ considered as statistically significant.
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.
p-Value[(a)] reflects inter-group differences detected by Mann Whitney U tests, whereas *p*-value[(b)] represents intra-group changes detected by Friedman test.

Table 3 Comparison of the DLQI measure at baseline and every month up to 3 months

(*N* = 60; Verum group, 30; Placebo group, 30)						
Outcome measures	**Baseline: Median (IQR)**	**After 1 month: Median (IQR)**	**After 2 months: Median (IQR)**	**After 3 months: Median (IQR)**	**χ^2 at df = 3**	***p*-Value[b]**
DLQI: Symptoms and feelings						
• Verum group	3 (2, 4)	2.5 (1, 3.2)	2 (1, 3)	2 (1, 3)	23.762	<0.001***
• Placebo group	2 (2, 3)	2 (2, 3)	2 (1, 3)	2 (1, 3)	15.361	0.002**
Mann-Whitney *U* test	367.5	383.0	427.5	442.0		
Wilcoxon W-test	832.5	848.0	892.5	907.0		
Z-test	−1.257	−1.028	−0.343	−0.122		
p-Value[a]	0.209	0.304	0.731	0.903		
Eta-square (η^2)	–	0.016	0.002	0		
Effect size (*r*)	–	0.258	0.086	0.031		
DLQI: Daily activity						
• Verum group	1 (1, 2.2)	1 (1, 2)	1 (0, 2)	1 (0, 2)	18.360	<0.001***
• Placebo group	1 (0, 2)	1 (0, 1.2)	1 (0, 2)	1 (0, 2)	10.763	0.013**
Mann-Whitney *U* test	392.0	338.5	421.0	430.5		
Wilcoxon W-test	857.0	803.5	886.0	895.5		
Z-test	−0.888	−1.727	−0.449	−0.306		
p-Value[a]	0.374	0.084	0.653	0.760		
Eta-square (η^2)	–	0.045	0.003	0.001		
Effect size (*r*)	–	0.436	0.111	0.074		
DLQI: Leisure						
• Verum group	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1.310	0.727
• Placebo group	1 (0, 1.2)	1 (0, 1.2)	1 (0, 2)	1 (0, 2)	7.062	0.070
Mann-Whitney *U* test	447.5	384.5	419.5	433.5		
Wilcoxon W-test	912.5	849.5	884.5	898.5		
Z-test	−0.039	−1.030	−0.482	−0.260		
p-Value[a]	0.969	0.303	0.630	0.795		
Eta-square (η^2)	–	0.016	0.003	0.001		
Effect size (*r*)	–	0.252	0.117	0.063		

(*Continued*)

Table 3 (*Continued*)

($N = 60$; Verum group, 30; Placebo group, 30)						
Outcome measures	**Baseline: Median (IQR)**	**After 1 month: Median (IQR)**	**After 2 months: Median (IQR)**	**After 3 months: Median (IQR)**	**χ^2 at df = 3**	***p*-Value[b]**
DLQI: Work and school						
• Verum group	0 (0, 3)	0 (0, 0)	0 (0, 0)	0 (0, 0)	17.690	0.001**
• Placebo group	0 (0, 3)	0 (0, 0.7)	0 (0, 0)	0 (0, 0)	13.846	0.003**
Mann-Whitney *U* test	450.0	420.0	420.0	435.0		
Wilcoxon W-test	915.0	885.0	885.0	900.0		
Z-test	0.000	−0.640	−0.853	−0.463		
p-Value[a]	1.000	0.522	0.393	0.643		
Eta-square (η^2)	–	0.003	0.003	0.001		
Effect size (*r*)	–	0.115	0.115	0.057		
DLQI: Personal relations						
• Verum group	1 (0, 1.2)	0 (0, 1)	0 (0, 1)	0 (0, 1)	7.800	0.050
• Placebo group	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	4.500	0.212
Mann-Whitney *U* test	331.5	440.5	433.0	450.0		
Wilcoxon W-test	796.5	905.5	898.0	915.0		
Z-test	−1.889	−0.156	−0.284	0.000		
p-Value[a]	0.059	0.876	0.777	1.000		
Eta-square (η^2)	–	0	0.001	0		
Effect size (*r*)	–	0.036	0.065	0		
DLQI: Treatment						
• Veum group	1 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	30.081	<0.001***
• Placebo group	1 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	15.000	0.002**
Mann-Whitney *U* test	393.0	435.0	415.0	420.0		
Wilcoxon W-test	858.0	900.0	880.0	885.0		
Z-test	−0.913	−0.263	−0.617	−0.543		
p-Value[a]	0.361	0.792	0.537	0.587		
Eta-square (η^2)	–	0.001	0.004	0.003		
Effect size (*r*)	–	0.057	0.134	0.115		
DLQI: Total score						
• Verum group	8.5 (5, 12)	6 (4, 9)	4.5 (2.7, 8)	4.5 (2, 6.2)	33.000	<0.001***
• Placebo group	7 (4.5, 9)	5.5 (3, 8)	5 (3, 8)	4.5 (2.5, 8)	35.082	<0.001***
Mann-Whitney *U* test	370.0	388.0	444.5	444.5		
Wilcoxon W-test	835.0	853.0	909.5	909.5		
Z-test	−1.187	−0.921	−0.082	−0.082		
p-Value[a]	0.235	0.357	0.935	0.935		
Eta-square (η^2)	–	0.014	0	0		
Effect size (*r*)	–	0.238	0.021	0.021		

Abbreviations: DLQI, dermatological life quality index; IQR, inter-quartile range; $p < 0.05$ considered as statistically significant.
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.
p-Value[(a)] reflects inter-group differences detected by Mann Whitney U tests, whereas *p*-value[(b)] represents intra-group changes detected by Friedman test.

promising effects of *Dulcamara* 1,000cH, *Natrum muriaticum* 1,000cH and *Thuja occidentalis* 1,000cH by shortening the duration of ailment.[31] A similar study in the same setting on 200 patients suffering from warts revealed encouraging results from the use of those same three medicines.[32]

There have been no studies exclusively in adults with warts, and none of the previous RCTs adhered fully to the principles of IH because they restricted the prescription choice within a specified number of medicines. Thus, our pilot study aimed at rectifying the perceived deficiency of existing trials by informing a future investigation. All the studies, except one, analyzed the results only on the basis of objective symptoms. One trial, which included subjective symptoms by using a questionnaire about satisfaction with the treatment, found that even if the size of the warts was not reducing significantly, the patients were satisfied with the mode of treatment, as the intervention was not only safer than destructive processes but it also gave psychological support to the participants.[38] In our study also, we considered both the objective measures (size and number of warts) and the subjective measure (DLQI scale) for the interpretation of the results. There were significant improvements in DLQI scores within both the groups, but without any statistically significant inter-group differences.

Being an RCT with 1:1 randomization, every enrolled patient had an equal chance of being allocated to either of the groups, thereby minimizing the chances of selection bias. Warts not being an emergency condition, ethical concerns were relatively small. For the first time, the study was done exclusively in adults because warts in adults are more resistant to treatment and are less amenable to spontaneous regression in comparison to children.[11,12] Although the recruitment rate was not adequate and needs improvement, retention rate for this pilot trial was quite promising, thereby ensuring feasibility of a more definitive trial in future. Duration of the study was 3 months only; thus, there were

Table 4 Alphabetical list of medicines prescribed in the two groups at baseline

Name of the medicine	Total ($N = 60$); *n* (%)	Verum ($n = 30$); *n* (%)	Placebo ($n = 30$); *n* (%)	Chi-square	*p*-Value[a]
1. *Antimonium crudum*	3 (5)	–	3 (10)	–	–
2. *Arsenicum album*	1 (1.7)	–	1 (3.3)	–	–
3. *Calcarea carbonica*	2 (3.3)	2 (6.7)	–	–	–
4. *Calcarea phosphorica*	1 (1.7)	1 (3.3)	–	–	–
5. *Causticum*	3 (5)	2 (6.7)	1 (3.3)	0	1.000
6. *Dulcamara*	4 (6.7)	3 (10)	1 (3.3)	0.268	0.605
7. *Graphites*	1 (1.7)	–	1 (3.3)	–	–
8. *Lachesis mutus*	1 (1.7)	–	1 (3.3)	–	–
9. *Lycopodium clavatum*	1 (1.7)	–	1 (3.3)	–	–
10. *Medorrhinum*	1 (1.7)	1 (3.3)	–	–	–
11. *Mercurius solubilis*	2 (3.3)	2 (6.7)	–	–	–
12. *Mezereum*	1 (1.7)	1 (3.3)	–	–	–
13. *Natrum carbonicum*	1 (1.7)	1 (3.3)	–	–	–
14. *Natrum muriaticum*	6 (10)	1 (3.3)	5 (16.7)	1.667	0.197
15. *Natrum sulphuricum*	1 (1.7)	–	1 (3.3)	–	–
16. *Nitricum acidum*	4 (6.7)	3 (10)	1 (3.3)	0.268	0.605
17. *Nux vomica*	1 (1.7)	–	1 (3.3)	–	–
18. *Pulsatilla nigricans*	1 (1.7)	1 (3.3)	–	–	–
19. *Rhus toxicodendron*	1 (1.7)	–	1 (3.3)	–	–
20. *Ruta graveolens*	1 (1.7)	1 (3.3)	–	–	–
21. *Staphysagria*	1 (1.7)	1 (3.3)	–	–	–
22. *Sulphur*	5 (8.3)	3 (10)	2 (6.7)	0	1.000
23. *Thuja occidentalis*	17 (28.3)	7 (23.3)	10 (33.3)	0.328	0.567

[a]Pearson's Chi-square test with Yates' correction, $p < 0.05$ considered as statistically significant.

fewer chances that the lesions might develop complications or become malignant.

Owing to small sample size, our trial was underpowered, thus preventing the findings from being extrapolated[52]; nevertheless, the trial had not primarily aimed to enable such interpretation. Patients were enrolled only on the basis of clinical diagnosis; no histological examination, immunohistochemistry, or polymerase chain reaction (PCR) for HPV DNA could be used as confirmatory tools for diagnosis. Therefore, which particular type(s) of HPV responded best to treatment could not be explored in this trial.

Skin complaints, especially warts, seem an area where homeopathy can have favorable effects, especially in the context of non-invasive treatment options and with standard therapies having limited efficacy. Future studies with a suitably large sample size, along with PCR for HPV DNA analysis, can bring about more valid, interpretable, as well as more generalizable results.

Conclusion

As regards efficacy of treatment, the result of the pilot study was inconclusive, with a non-significant trend in favor of IH compared with placebo. Importantly, however, it paves the way for a future, adequately powered, definitive trial that could enable detection of a clinically meaningful difference.

Highlights

- A double-blind, randomized, placebo-controlled, two parallel arms, pilot trial was conducted at D.N. De Homoeopathic Medical College and Hospital, West Bengal, India, in 60 patients suffering from cutaneous warts.
- There was a statistically non-significant direction of effect favoring homeopathy.
- Adequately powered definitive trials are warranted.

Supplementary Files

Supplementary File 1. DLQI questionnaire (English version).
Supplementary File 2. DLQI questionnaire (Bengali version).
Supplementary File 3. CONSORT Checklist.
Supplementary File 4. RedHot Checklist.
Supplementary File 5. Most frequently prescribed medicines.

Authors' Contribution

S.D., S.H., S.S., M.M., A.R.S., E.A., P.G., N.S., M.K. and S.Saha contributed toward concept, design, literature search, data interpretation, and preparation of the article; S.D., S.H., A.R.S. and P.G. contributed to the clinical study and data acquisition. S.H. and A.R.S. contributed to data management and master-chart preparation; M.K. and S.Saha contributed to data interpretation and statistical analysis. All the authors reviewed and approved the final article.

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Conflict of Interest

None declared.

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