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Efficacy of individualized homeopathy in bronchial asthma in adults: Double-blind, randomized, placebo-controlled, clinical trial in the context of usual care

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ABSTRACT

Background: Asthma remains a major public health problem despite recent advances in management. Sizeable minorities of asthma patients prefer complementary therapies, including homeopathy, for treatment. This trial examines whether usual care plus individualized homoeopathy (UC + IH) can produce significantly different treatment effects compared to usual care plus placebo (UC + P) in adults suffering from bronchial asthma.

Methods: In this double-blind, randomized, placebo-controlled, parallel arm, efficacy trial, 140 adults suffering from bronchial asthma were randomized to receive either UC + IH (verum: n = 70) or UC + P (control: n = 70). The trial was of 3.5 years duration. Spirometric measures, blood eosinophil percentage and serum immunoglobulin E were primary outcomes and symptom severity and different questionnaire scores were secondary outcomes; measured at baseline, and after 3 and 6 months.

Results: Eighteen patients dropped out (verum: 8, control: 10). Intention to treat sample (n = 140) was analyzed. The two trial arms were comparable at baseline. Group differences over 3 and 6 months showed significant differences in improvement in UC + IH compared to UC + P ($P < 0.01$) with moderate to large effect sizes (Cohen's d) for both primary and secondary outcome measures.

Conclusion: UC + IH produced significantly better effect than UC + P in this trial, indicating homeopathy seemed superior to placebo. Further evaluation involving a larger sample in a multi-centre design is necessary prior to making firm recommendations. [Trial registration: CTRI/2017/08/009192].

1. Introduction

Asthma is a chronic inflammatory disorder associated with variable airflow obstruction and bronchial hyper-responsiveness; presenting with recurrent episodes of wheeze, cough, shortness of breath, and chest tightness [1]. Asthma has been characterized by increased responsiveness of the trachea-bronchial tree to a multiplicity of stimuli [2], increased infiltration of various inflammatory cells especially eosinophils into the airway, epithelial damage, airway smooth-muscle hypertrophy [3], constriction, variable airway obstruction usually associated with inflammation in the conducting airways of the lungs [4] and mucous hypersecretion in the bronchiolar walls of the lung. Asthma is critically dependent on a series of cell adhesion molecule-mediated interactions between vascular endothelium and leukocytes, leading to symptoms, and elevation in total serum immunoglobulin E (IgE) [5]. Asthma is manifested physiologically by widespread narrowing of the air passages and clinically by paroxysms of dyspnoea, cough, wheezing and tightness, provoked by one or more triggers, such as physical exertion and airway irritants (cold, dry air, smoke, etc.) [6]. Approximately 5% of the world's population (about 300 million people worldwide) are currently estimate to suffer from asthma, with the prevalence increases by 50% every 10 years [7]. Worldwide, approximately 180,000 deaths

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annually are related to asthma, though the mortality rate has generally declined since the year 1980 [8]. Asthma's prevalence is increasing despite the recent advances in its management [9]. The associated human and economic burden is severe and the costs of treatment remain very high, and asthma is a major cause of impaired quality of life with impact on work and recreational as well as physical activities and emotions [10].

Current control of asthma includes achievement of symptom improvement in activity, and improvement in lung function [11]. Asthma related healthcare expenses in patients with exacerbations are double those of patients without exacerbations [12]. Asthma patients experience problems with the quality of usual care, including gaps in information provision [13]. Asthma patients' treatment expectations may differ from those of clinicians; patients often do not adhere to treatment regimes, use their own coping strategies to manage their condition and expect clinicians to acknowledge their personal disease experiences [14,15]. In response to these differing expectations, many patients may turn to complementary therapies for asthma management. Motivating factors for complementary therapy use included concerns about conventional care ("push factors") and attractive aspects of complementary therapies ("pull factors"). Qualitative studies of complementary therapy use indicate that patients use such therapies because of dissatisfaction with conventional medicine, perceived harmful effects of conventional treatments, the desire for a more holistic approach and greater philosophical congruence with complementary therapies. One study comparing patients using homeopathy and conventional asthma treatment found that homeopathy users expressed stronger preferences for doctors to treat them as a whole person [16]. Sizeable minorities of asthma patients seem to be turning to complementary therapies, though patients are often uncertain whether complementary therapies directly help their asthma [17]. Estimates of the prevalence of complementary therapy use for asthma vary widely, from 6% to 70% [18]. However, the clinical evidence is inconclusive regarding the effectiveness of complementary therapies for asthma, with systematic reviews noting the paucity of high quality randomized controlled trials (RCTs) in complementary therapies more generally, and in specific therapies such as homeopathy as well [19,20]. Overall, the results are insufficient to provide evidence-based recommendations for the use of complementary medicine in clinical practice [21–24].

Research evidence for of homeopathy in bronchial asthma is limited, with little research for all available forms of homeopathy – individualized (classical), complex, standardized (non-individualized), and isopathy (immunotherapy). Trials of individualized homeopathy comprised pragmatic RCTs and placebo-controlled RCTs, which generated conflicting results. One study reported poor asthma control without any additional medical or financial benefits in both groups – standard treatment ± individualized homeopathy [25]. One trial reported no statistically significant difference between two groups – individualized homeopathy vs. placebo in pediatric asthma [26]. Another trial reported that homeopathy was therapeutically superior to placebo [27]. A different trial also reported in favour of homeopathy while comparing individualized prescription of most relevant allergens in C30 and placebo [28]. In a review summarizing two Cochrane systematic reviews that assessed the safety and efficacy of homeopathy in individuals with chronic stable asthma, six placebo-controlled, randomized, and double-blind trials with a total of 556 people were included. The results were conflicting in terms of effects on lung function and there was not enough evidence to reliably assess the possible role of homeopathy in the treatment of asthma [29]. In a prospective multicenter observational study, the symptoms of allergy and asthma patients undergoing homeopathic treatment were shown to improve substantially and conventional medication dosage and expenses could be substantially reduced [30]. In a retrospective observational study in Italy, homeopathic treatment for respiratory diseases including asthma was associated with a significant reduction in the use and costs of conventional drugs [31]. But another recent study found that, compared with usual care, additional homeopathic treatment was associated with significantly higher costs [32].

Therefore, the overall scenario remains inconclusive about the efficacy of homeopathy in in the treatment of bronchial asthma. This study aims to remedy this research gapby examining whether usual care plus individualized homoeopathy (UC + IH) can produce significantly different treatment effect beyond usual care plus placebo (UC + P) in adults suffering from bronchial asthma.

2. Methods

2.1. Trial design

This prospective, double-blind, randomized, placebo-controlled, parallel arm trial was conducted at the Homeopathy outpatient, Clinical Research Unit, District Medical College and Hospital, Darbhanga, Bihar in association with District Joint Hospital, Darbhanga, Govt. of Bihar. The study protocol (unpublished) was submitted as PhD synopsis of the corresponding author to the Homoeopathy University, Jaipur, Rajasthan, India [HU/2016/1301/A], was approved by the Institutional Ethics Committee and was registered subsequently in the Clinical Trials Registry – India [CTRI/2017/08/009192].

2.2. Participants

Inclusion criteria were diagnosed cases of persistent bronchial asthma – mild to moderate, typical regular asthmatic attacks and illness persisting for 1 year or longer, age 18–65 years, both sexes, and ability to read Hindi and written consent to participate. Exclusion criteria were unwillingness to participate or to comply with trial requirements, too unwell to take part, declined to provide informed consent, respiratory tract infection within last 3 weeks, other diseases causing pulmonary obstruction, other uncontrolled pulmonary or systemic diseases and/or pathologies, psychiatric illness, pregnancy or lactation, previous immunotherapy, ongoing use of homeopathic remedies for any chronic purpose, any change in concurrent medication in the two weeks before entry, and drug or substance abuse and/or dependence.

2.3. Intervention

2.3.1. Experimental arm (verum)

The patients randomized to this arm received usual care plus individualized homoeopathy (UC + IH; verum: n = 70). Usual care for bronchial asthma comprised β agonists, corticosteroids, antihistamines, montelukasts, etc. along with oral short-acting bronchodilators and breathing exercises. In homeopathic centesimal potencies (6C, 30C, 200C, 1000C, and 10,000C), each dose consisted of 4 cane sugar globules medicated with a single drop of the indicated medicine, preserved in 88% v/v ethanol. Repetition 24, 12 or 8 hourly or even oftener, depending upon the individual requirement of the case. Each dose was instructed to be taken orally on clean tongue in empty stomach. Duration of therapy was 6 months. Single individualized medicine was prescribed on each occasion taking into account presenting symptom totality, constitutional features, miasmatic expressions, and consensus

between two physicians. Dose was also individualized and was based on physicians' judgment of susceptibility and consensus of two homeopaths. Subsequent prescriptions were generated as per Kent's observations and Hering's law. Each of the two prescribers in the study possessed master degree in homeopathy with more than 30 years of experience of practicing classical homeopathy.

2.3.2. Control arm

Randomized patients to this arm received usual care as above plus placebo (UC + P; control: n = 70). Placebo was indistinguishable from verum by appearance, smell, and taste. Each placebo dose consisted of 4 cane sugar globules no. 30 moistened with a single drop of rectified spirit; instructed to be taken thrice a day orally on clean tongue in empty stomach. Duration of therapy was 6 months. Participants in the control arm were assessed similarly by the same two experienced homeopaths as was done in the experimental arm. 'Placebo prescription' was similar to that for patients receiving an actual medicine and could be identified only by the pharmacist as per the randomization chart.

Irrespective of codes, we planned to prescribe different 'acute medicines' (rescue remedies) on 'acute totality' [33] to encounter acute asthma attacks as per homeopathic principles.

2.4. Outcomes

2.4.1. Primary

Forced Expiratory Volume (L) in 1st second (FEV1; % predicted), Forced Vital Capacity (L) (FVC; % predicted), FEV1/FVC, Forced Expiratory Flow (L/s) ($FEF_{25-75\%}$; % predicted), and Peak Expiratory Flow (L/s) (PEF; % predicted) and blood eosinophil % and serum Immunoglobulin E (IgE; IU/ml) levels; assessment endpoint 6 months.

2.4.2. Secondary

No. of asthmatic attacks last week, days of suffering last week, average sleep interference and night awakening in hours/day last week, bronchodilator use last week, patient-assessed severity on 0–10 point numeric rating scale (NRS), patient rated global outcome 0–10 point NRS, Juniper's Asthma Control Questionnaire (ACQ), and Asthma Control Test (ACT) Questionnaire; assessment endpoint 6 months.

All the outcomes were measured at baseline, after 3 months, and after 6 months. Primary outcomes were laboratory parameters and the secondary ones were patients' self-rated. We also planned to record the frequency of occurrence of harms and (serious) adverse events between the groups.

2.5. Sample size

There has been no published placebo controlled trial of individualized homeopathy in bronchial asthma in adults in the context of usual care. This precluded formal calculation of standardized difference (effect size) and sample size. Mean predicted value (±sd) of FEV1 was reported to be 4.293 ± 0.51 l [34]. The minimal clinically important difference (MCID) in FEV1 has not been rigorously established for asthma, but it is likely that changes of 100–200 mL in FEV1 are clinically important [35]. We assumed 150 mL and 175 mL increase in FEV1 post treatment in the control (UC + P) and verum (UC + IH) groups respectively. Thus the effect size (Cohen's d) became 0.490. Now keeping $\alpha = 0.05$, power $(1-\beta) = 0.80$, and allocation ratio 1:1, to detect a significant difference in the mean FEV1 by comparing difference between two independent means (two groups) of FEV1 by two tailed unpaired *t* test, calculated sample size comes to 134. Keeping a provision for around 5% drop-outs, target sample size becomes 140 (i.e. UC + IH: 70; UC + P: 70).

2.6. Randomization

Computer generated random number lists were used to generate random sequence. The list was generated using restricted 14 different blocks of size 10 to maintain equal distribution between groups and 1:1 ratio (verum: 70, control: 70) easily. Randomization was strictly pharmacy controlled. Randomization codes '1' and '2' were allocated randomly and in strict confidentiality. The chart was available only to the pharmacist, not to the prescriber. The prescriptions were sent to the pharmacist who was responsible for dispensing in two forms with identical appearance – genuine homeopathic preparation prepared in the standard manner or placebo, indistinguishable in appearance to the patients according to the random number chart. Generation of random number chart and allocation concealment was done in strict confidentiality by third parties, who were not allowed to influence the study in any way.

2.7. Blinding

The participants and the investigators were blinded to the allocated codes. Codes were broken at the end of the trial after the data set was frozen.

2.8. Statistical methods

All the collected data in the standardized format were subjected to data extraction in a specially designed Excel spreadsheet and underwent statistical analysis – both descriptive and inferential. Intention-to-treat (ITT) sample was analyzed in the end. Missing values were calculated using last value carried forward (LVCF) method. Descriptive statistics were presented in terms of absolute values, percentages, means, and standard deviations, as appropriate. Parametric tests were used as inferential statistics accordingly. The groups were checked for comparability of socio-demographic characteristics and outcome measures at baseline using independent *t* test or chi-square test. Group differences after 3 and 6 months were tested by independent *t* test. *P* values were set at less than 0.01 two-tailed as statistically significant. SPSS® IBM® version 20 software was used for analysis of the data. Reporting adhered to the CONSORT guidelines for reporting trials [36] and reporting criteria for quality of homeopathic individualization in clinical trials [37].

3. Results

3.1. Participant flow

Total 308 patients suffering from bronchial asthma were screened preliminarily; 66 were screened out. The remaining 242 patients underwent detailed screening as per specified eligibility criteria; 102 were excluded for varying reasons. Total 140 patients were enrolled in the study and randomized to either verum (UC + IH) or control (UC + P) in 1:1 ratio. Total 122 patients completed the follow-up; 18 patients dropped out – 8 in the homoeopathy group, and 10 in the control. The intention to treat sample (n = 140) was analyzed in the end. (Fig. 1)

3.2. Recruitment

The trial started in January 2014 and was finished in June 2017.

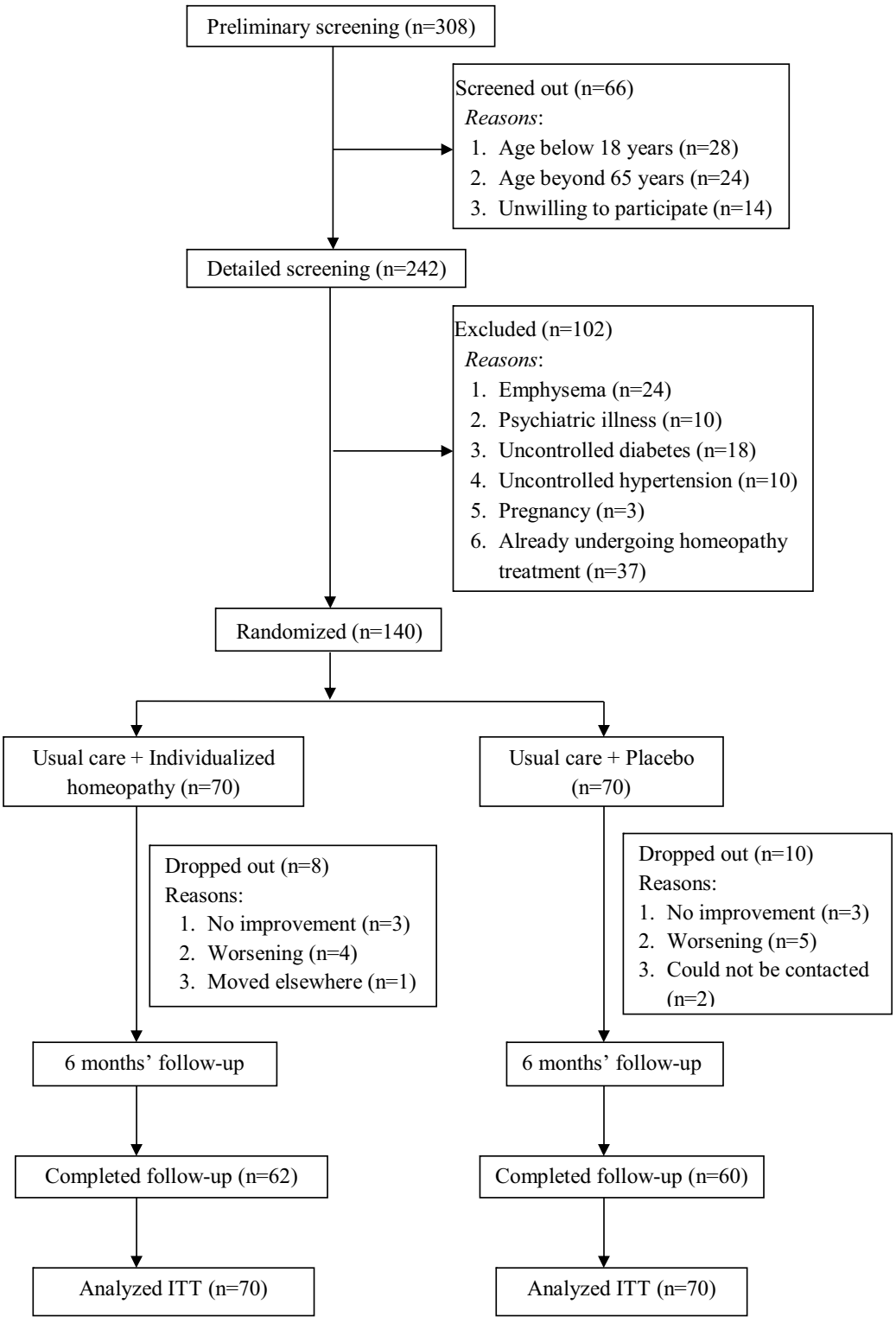

Fig. 1. Study flow diagram.

3.3. Baseline data

The two groups were comparable as per baseline socio-demographic data, i.e. no significant differences existed between groups in terms of age, gender, body weight, height, body mass index, residence, smoking history, education, employment, socio-economic status, patient-assessed severity, duration of suffering, atopic co-morbidities, and ongoing standard medications (all $P > 0.05$). (Table 1)

3.4. Numbers analyzed

After 6 months, 8 patients in the verum group and 10 in the control arm dropped out; i.e. 122 were protocol-compliant.

Table 1
Socio-demographic characteristics.

Features	UC + IH (n = 70)	UC + P (n = 70)	*P* value
Age: mean (sd)[¥]	41.4 (14.2)	42.1 (14.1)	0.766
Age groups[§]	29 (41.4)	24 (34.3)	0.486
18–35 years	18 (25.7)	23 (32.9)	0.458
36–50 years	23 (32.9)	23 (32.9)	0.857
51–65 years			
Sex[§]	37 (52.9) : 33 (47.1)	36 (51.4) : 34 (48.6)	1.000
Male : Female			
Weight (kg): mean (sd)[¥]	61.3 (7.8)	58.8 (7.5)	0.056
Height (m): mean (sd)[¥]	1.6 (0.1)	1.6 (0.1)	0.419
Body mass index: mean (sd)[¥]	24.1 (4.0)	22.7 (4.2)	0.059
Residence[§]	44 (62.9) : 26 (37.1)	41 (58.6) : 29 (41.4)	0.729
Rural : Urban			
Smoking: Yes[§]	35 (50.0)	33 (47.7)	0.866
Education[§]	20 (28.6)	23 (32.9)	0.714
10^{th} std. or less	21 (30.0)	26 (37.1)	0.474
12^{th} std.	29 (41.4)	21 (30.0)	0.217
Graduate or above			
Employment[§]	11 (15.7)	18 (25.7)	0.211
Service	18 (25.7)	12 (17.1)	0.303
Business	22 (31.4)	17 (24.3)	0.451
Farming	19 (27.1)	23 (32.9)	0.580
Others			
Socio-economic status [§]	16 (22.9)	21 (30.0)	0.443
Low	21 (30.0)	27 (38.6)	0.373
Middle	33 (47.1)	22 (31.4)	0.083
High			
Patient assessed severity[§]	42 (60.0) : 28 (40.0)	40 (57.1) : 30 (42.9)	0.864
Mild : Moderate			
Duration of suffering[§]	33 (47.1)	22 (31.4)	0.084
1–5 yrs	25 (35.7)	29 (41.4)	0.602
6–10 yrs	12 (17.1)	19 (27.1)	0.222
More than 10 yrs			
Atopic co-morbidity[§]	30 (42.9)	21 (30.0)	0.114
None	18 (25.7)	30 (42.9)	0.050
Eczema	22 (31.4)	19 (27.1)	0.710
Allergic rhinitis			
Ongoing therapy[§]	25 (35.7)	19 (27.1)	0.363
β-agonist + corticosteroid	27 (38.6)	25 (35.7)	0.861
Above + anti-histamine	18 (25.7)	26 (37.1)	0.203
Above + montelukast			

[¥] Continuous data presented as mean (standard deviation) and were compared using independent sample *t* test.
[§] Categorical data presented as absolute numbers (percentages) and were compared using Pearson's chi-square test; $P < 0.01$ two-tailed considered as statistically significant.

Missing values were replaced by LVCF method and intention-to-treat sample (n = 140; verum: 70 and control 70) was analyzed in the end.

3.5. Outcomes and estimation

At baseline, all the primary and secondary outcome measures were comparable without any significant difference (all $P > 0.05$) between groups. (Table 2)

Group differences after 3 months: Except FEV1/FVC and patient assessed severity on NRS, rest of the outcome measures differed significantly favoring verum over control ($P < 0.001$) with moderate to large effect sizes (Cohen's d). (Table 3)

Group differences after 6 months: All the outcome measures differed significantly favoring verum over control ($P < 0.001$) with moderate to large effect sizes (Cohen's d). (Table 4)

3.6. Harms

Apart from occurrence of two diarrhea cases (verum: 1, control: 1) and three minor injuries (all in the control group), no harms, adverse or unintended effects were reported from either group during the trial. Temporary worsening of existing complaints followed by rapid improvement (probably 'homeopathic aggravation') was observed in 8 out of 70 cases in the verum arm.

3.7. Medicines used

Total 15 different individualized medicines on constitutional basis were prescribed for the two groups without any significant inter-group difference (all $P > 0.01$) in frequency of prescriptions; i.e. *Arsenicum album*,*Tuberculinum bovinum*, *Natrum sulphuricum*, *Medorrhinum*, *Sulphur*, *Pulsatilla nigricans*, *Calcarea carbonica*, *Phosphorus*, *Kali bichromicum*, *Lycopodium clavatum*, *Lachesis muta*, *Kali carbonicum*, *Natrum muriaticum*, *Psorinum*, and *Syphilinum*. (Table 5)

On 'acute totality', 11 different 'acute medicines' (rescue remedies) were prescribed to encounter acute asthma attacks on 41 and 45 occasions respectively for the verum and control groups in varied frequencies, but with no significant inter-group differences (all $P > 0.01$); i.e. *Ipecacuanha*, *Antimonium tartaricum*, *Nux vomica*, *Sambucus nigra*, *Allium cepa*, *Aralea racemosa*, *Carbo vegetabilis*, *Euphrasia officinalis*, *Grindelia robusta*, *Hepar sulphuricum*, and *Histamine hydrochloride*. (Table 6)

4. Discussion

Our study found that UC + IH produced significant treatment benefit in comparison to UC + P in terms of spirometric measurements, blood eosinophil % and serum IgE, symptom severity, and questionnaire scores in adults suffering from bronchial asthma.

Table 2
Baseline outcomes (N = 140).

Features	UC + IH (n = 70)	UC + P (n = 70)	Mean difference (95% CI)	*P* value*
Spirometry:	60.4 ± 2.3	60.6 ± 3.1	−0.200 (−1.123, 0.723)	0.669
FEV_1 (L; % predicted)	69.8 ± 3.6	70.5 ± 3.7	−0.729 (−1.953, 0.496)	0.241
FVC (L; % predicted)	0.9 ± 0.1	0.9 ± 0.1	0.006 (−0.014, 0.026)	0.547
FEV_1/FVC	40.2 ± 2.7	40.9 ± 3.9	−0.714 (−1.827, 0.398)	0.206
$FEF_{25-75\%}$ (L/s; % predicted)	20.1 ± 2.1	19.6 ± 2.1	0.543 (−0.148, 1.233)	0.122
PEF (L/s; % predicted)				
Blood:	7.9 ± 1.0	8.2 ± 1.5	−0.229 (−0.648, 0.191)	0.284
Eosinophil %	919.5 ± 104.7	960.4 ± 163.1	−40.957 (−86.761, 4.847)	0.080
IgE (IU/ml)				
Symptom severity:	4.1 ± 0.9	4.0 ± 0.8	0.114 (−0.169, 0.398)	0.427
No. of attacks last wk	5.1 ± 0.9	4.9 ± 0.8	0.229 (−0.059, 0.516)	0.118
Days of symptoms last wk	3.8 ± 1.1	3.5 ± 1.1	0.229 (−0.151, 0.608)	0.236
Avg. sleep interference last wk (hrs/day)	40.1 ± 4.4	39.9 ± 4.4	0.114 (−1.349, 1.577)	0.877
Frequency of bronchodilator use last wk	7.9 ± 1.2	7.6 ± 1.6	0.329 (−0.145, 0.802)	0.172
Severity on NRS (0–10)	7.0 ± 1.4	7.4 ± 1.2	−0.429 (−0.864, 0.007)	0.054
Global wellbeing NRS (0–10)				
Questionnaire scores:	3.3 ± 0.2	3.3 ± 0.2	0.004 (−0.067, 0.075)	0.908
ACQ	11.1 ± 1.6	11.1 ± 1.5	−0.086 (−0.597, 0.425)	0.741
ACT				

All values expressed as mean ± standard deviation unless otherwise stated; FEV_1: Forced Expiratory Volume in 1st second; FVC: Forced Vital Capacity; FEF25-75%: Forced Expiratory Flow between 25 and 75% of FVC; PEF: Peak Expiratory Flow; ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test.
* Independent sample *t* test; *P* values less than 0.01 two-tailed considered as statistically significant.

Table 3
Group differences after 3 months.

Outcome measures	UC + IH (n = 70)	UC + P (n = 70)	Mean difference [95% CI]	*P* value	Cohen's d
Spirometry:	64.5 ± 4.9	59.3 ± 2.8	5.2 [3.9, 6.6]	<0.001*	1.303
FEV_1 (L; % predicted)	74.9 ± 3.8	70.3 ± 3.3	4.6 [3.4, 5.8]	<0.001*	1.293
FVC (L; % predicted)	0.865 ± 0.1	0.845 ± 0.1	0.020 [−0.006, 0.046]	0.130	0.200
FEV_1/FVC	44.1 ± 3.1	41.8 ± 3.9	2.3 [1.1, 3.5]	<0.001*	0.653
$FEF_{25-75\%}$ (L/s; % predicted)	21.5 ± 2.6	19.7 ± 2.3	1.8 [1.0, 2.7]	<0.001*	0.733
PEF (L/s; % predicted)					
Blood:	5.8 ± 1.5	7.7 ± 1.7	−1.9 [−2.4, −1.4]	<0.001*	1.185
Eosinophil %	782.5 ± 123.6	915.8 ± 154.6	−133.3 [−180.0, −86.4]	<0.001*	0.952
IgE (IU/ml)					
Symptom severity:	3.0 ± 0.8	3.8 ± 0.8	−0.8 [−1.1, −0.5]	<0.001*	1.000
No. of attacks last week	3.8 ± 0.9	4.7 ± 1.2	−0.9 [−1.2, −0.5]	<0.001*	0.849
Days of symptoms last week	2.6 ± 0.6	3.7 ± 1.1	−1.1 [−1.4, −0.8]	<0.001*	1.242
Avg. sleep interference last week (hrs/day)	34.4 ± 4.7	39.4 ± 6.6	−5.0 [−6.9, −3.1]	<0.001*	0.873
Frequency of bronchodilator use last week	6.6 ± 1.0	6.8 ± 1.8	−0.2 [−0.7, 0.3]	0.424	0.137
Severity on NRS (0–10)	5.4 ± 1.3	6.8 ± 1.5	−1.4 [−1.9, −0.9]	<0.001*	0.997
Global wellbeing NRS (0–10)					
Questionnaire scores:	2.9 ± 0.2	3.0 ± 0.3	−0.1 [−0.3,−0.1]	<0.001*	0.392
ACQ	14.3 ± 1.9	11.5 ± 1.1	2.8 [2.3, 3.4]	<0.001*	1.804
ACT					

* $P < 0.01$ considered as statistically significant.

Improvement observed in symptom profiles of the patients in our study and the medicines used were quite similar to earlier retrospective studies [38,39]. Our approach to treatment of asthmatics was different from studies using 'homeopathic immunotherapy', i.e. potentized allergens (house dust mite) [40], and the findings were also quite different. This approach of prescribing the causative agent itself is also termed *isopathy* and conflicts with the *similia* principle of prescribing individualized homeopathic medicines observed in classical homeopathy. Our findings were also contradictory to the study reported by White et al. [26], which claimed no clinically relevant or statistically significant changes in the active quality of life score and no evidence that adjunctive homeopathic remedies were superior to placebo in improving the quality of life of children with mild to moderate asthma. There may be a number of reasons why the study results are different. For example, in the trial by White et al., there was no disclosure about the medicines prescribed in the study, so it is unclear whether the individual remedies prescribed were in fact indicated in asthma management. Homeopathic remedies may also act identically to placebo if not properly individualized (i.e. if the precise remedy not given to the patient). Also, instead of relying on subjective quality of life outcomes as primary outcome, we opted for objective spirometry readings and blood parameters to avoid subjective biases to the largest extent possible. In our study, both for the primary and secondary outcomes, inter-group differences over time were not only statistically different but also clinically important. Our prescribing strategies were quite similar to that as perceived by Launsø et al. [41]. The study by Thompson et al. [25] reported poor asthma control without any additional medical or financial benefits from individualized homeopathy; however, the study solely depended on subjective assessment on quality of life outcomes. Prescribed remedies in our study, chronic or acute, were similar to those prescribed by Shafei et al. [42] and Ghosh et al. [43].

Efforts were made to minimize potential bias or confounders in the study. The study design was 'gold standard' (i.e. RCT) to examine

Table 4
Group differences after 6 months.

Outcome measures	UC + IH (n = 70)	UC + P (n = 70)	Mean difference [95% CI]	*P* value	Cohen's d
Spirometry:	67.7 ± 4.6	57.7 ± 2.7	10.0 [8.7, 11.3]	<0.001*	2.651
FEV_1 (L; % predicted)	77.9 ± 4.2	70.2 ± 3.4	7.7 [6.5, 9.1]	<0.001*	2.015
FVC (L; % predicted)	0.871 ± 0.1	0.825 ± 0.1	0.046 [0.024, 0.067]	<0.001*	0.460
FEV_1/FVC	46.1 ± 3.4	40.7 ± 3.9	5.4 [4.2, 6.6]	<0.001*	1.476
$FEF_{25-75\%}$ (L/s; % predicted)	22.4 ± 2.6	19.5 ± 2.3	2.9 [2.0, 3.7]	<0.001*	1.181
PEF (L/s; % predicted)					
Blood:	3.8 ± 1.6	7.7 ± 1.6	−3.9 [−4.4, −3.4]	<0.001*	2.438
Eosinophil %	535.5 ± 146.2	928.7 ± 166.1	−393.2 [−445.5, −340.9]	<0.001*	2.513
IgE (IU/ml)					
Symptom severity:	2.0 ± 1.0	3.5 ± 1.1	−1.5 [−1.8, −1.1]	<0.001*	1.427
No. of attacks last week	2.4 ± 0.9	4.6 ± 1.2	−2.2 [−2.5, −1.8]	<0.001*	2.074
Days of symptoms last week	1.2 ± 1.0	3.0 ± 0.9	−1.8 [−2.1, −1.4]	<0.001*	1.892
Avg. sleep interference last week (hrs/day)	25.4 ± 4.4	39.2 ± 5.9	−13.8 [−15.5, −12.0]	<0.001*	2.652
Frequency of bronchodilator use last week	3.6 ± 1.7	6.7 ± 1.7	−3.1 [−3.7, −2.5]	<0.001*	1.823
Severity on NRS (0–10)	3.2 ± 1.4	7.0 ± 1.4	−3.8 [−4.2, −3.3]	<0.001*	2.714
Global wellbeing NRS (0–10)					
Questionnaire scores:	2.3 ± 0.3	3.0 ± 0.2	−0.7 [−0.8, −0.6]	<0.001*	2.746
ACQ	17.6 ± 2.8	11.6 ± 1.1	6.0 [5.3, 6.8]	<0.001*	2.821
ACT					

* $P < 0.01$ considered as statistically significant.

Table 5
Indicated medicines in the two groups.

Medicines	UC + IH (n = 70)	UC + P (n = 70)	*P* value
1. Arsenicum album	15	13	0.833[a]
2. Tuberculinum bovinum	12	13	1.000[a]
3. Natrum sulphuricum	10	11	1.000[a]
4. Medorrhinum	7	9	0.791[a]
5. Sulphur	6	8	0.778[a]
6. Pulsatilla nigricans	5	4	1.000[b]
7. Calcarea carbonica	3	4	1.000[b]
8. Phosphorus	3	2	1.000[b]
9. Kali bichromicum	2	1	1.000[b]
10. Lycopodium clavatum	2	1	1.000[b]
11. Lachesis	1	1	1.000[b]
12. Kali carbonicum	1	1	1.000[b]
13. Natrum muriaticum	1	1	1.000[b]
14. Psorinum	1	1	1.000[b]
15. Syphilinum	1	0	1.000[b]

[a] Chi-square test.
[b] Fisher exact-test; $P < 0.01$ considered as statistically significant.

Table 6
Acute medicines used in the two groups.

Medicines	UC + IH (n = 41)	UC + P (n = 45)	*P* value
1. Ipecacuanha	11	12	1.000[a]
2. Antim tartaricum	11	11	0.816[a]
3. Nux vomica	6	7	1.000[a]
4. Sambucus nigra	3	4	1.000[b]
5. Allium cepa	2	3	1.000[b]
6. Aralea racemosa	2	3	1.000[b]
7. Carbo vegetabilis	2	1	1.000[b]
8. Euphrasia officinalis	1	1	1.000[b]
9. Grindelia robusta	1	1	1.000[b]
10. Hepar sulphuricum	1	1	1.000[b]
11. Histamine hydrochloride	1	1	1.000[b]

[a] Chi-square test.
[b] Fisher exact-test; $P < 0.01$ considered as statistically significant.

the efficacy of any intervention; here UC + IH. We used a 'double-blind' design to minimize potential bias to the maximum possible extent. Instead of subjective parameters, we took objective outcomes of spirometry and blood parameters as primary outcome measure. Besides, we used two pre-validated questionnaires – ACQ and ACT. We planned usual care to continue uninterrupted because of ethical concerns. We kept provision for 5% drop-out; however, drop-out rate was 12.9% in the study. The study was conducted in a single centre, and may not be generalizable to patients in other settings. Additionally, as homeopathy prescriptions largely depend on the skill of the prescribers, the study outcomes may vary in different settings and with different prescribers. As such, the authors emphasize cautious interpretation of the study results. Still, results of our study warrants sincere consideration of individualized homeopathy as an adjunctive and complementary to standard care of bronchial asthma. Running cost-effectiveness analysis and conducting pragmatic trials comparing effectiveness of usual care and individualized homeopathy in bronchial asthma may also be warranted, to ascertain the impact of homeopathic treatment on system-wide issues and in real-life settings.

5. Conclusion

Our study found significant treatment benefit of adjunctive individualized homeopathy in bronchial asthma in adults in comparison to adjunctive placebo in terms of spirometric measurements, blood eosinophil percentage and serum IgE, symptom severity, and questionnaire scores in mutual context of usual care. These results suggest an integrative medicine approach incorporating homeopathy may facilitate further reducing symptoms and exacerbations of asthma in a more effective manner. We propose further research evaluating the cost-effectiveness and clinical effectiveness in a multi-center approach on a larger sample size to confirm the findings of our study.

Credit author statement

MQ: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Review & editing

SMS: Conceptualization; Data curation; Project administration; Supervision

CN: Conceptualization; Project administration; Supervision

MK: Conceptualization; Methodology; Formal analysis; Software; Validation; Visualization; Roles/Writing – original draft; Writing – review & editing

SS: Conceptualization; Methodology; Formal analysis; Software; Validation; Visualization; Roles/Writing – original draft; Writing – review & editing

Conflict of interest

We declare no conflict of interest. The trial was carried out as PhD thesis of the corresponding author.

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References

[1] N.G. Papadopoulos, H. Arakawa, K.-H. Carlsen, et al., International consensus on (icon) pediatric asthma, Allergy 67 (2012) 976–997.
[2] J.E.R. McFadden, et al., Asthma, in: A.S. Fauci, E. Braunwald, D.L. Kasper (Eds.), Harrison'S Principles of Internal Medicine, McGraw-Hill, New York, 2005, pp. 1508–1516.
[3] X. Xin, F. Zhian, W. Binyan, et al., A genome wide search for quantitative-trait loci underlying asthma, Am. J. Hum. Genet. 69 (2001) 1271–1277.
[4] H. Los, G.H. Koppelman, D.S. Postma, The importance of genetic influences in asthma, Eur. Respir. J. 14 (1999) 1210–1227.
[5] S.J. Lin, L.Y. Chang, D.C. Yan, et al., Decreased intercellular adhesion molecule-1 (CD54) and L-selectin (CD62L) expression on peripheral blood natural killer cells in asthmatic children with acute exacerbation, Allergy 58 (2003) 67–71.
[6] A.H. Liu, J.D. Spahn, D.Y.M. Leung, Nelson textbook of pediatrics, Childhood Asthma, Elsevier, New Delhi, 2004, pp. 760–774.
[7] Global Initiative for Asthma (GINA), Global Strategy for Asthma Management and Prevention Available at:, (2017) . Accessed on 2017 Dec 23 http://www.ginasthma.org.
[8] S.S. Braman, The global burden of asthma, Chest 130 (Suppl. 1) (2006) 4S–12S.
[9] M. Masoli, D. Fabian, S. Holt, R. Beasley, Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report, Allergy 59 (2004) 469–478.
[10] A.J. Frew, S.T. Holgate, Respiratory disease, in: P. Kumar, M. Clarke (Eds.), Clinical Medicine, 7th ed., Saunders Elsevier Limited, Spain, 2009.
[11] Bethesda (MD). National Heart, Lung, and Blood Institute (US); 2007. National Asthma Education and Prevention Program, 3rd Expert Panel on the Diagnosis and Management of Asthma. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. [Last accessed on 2017 Dec 23].
[12] J.I. Ivanova, R. Bergman, H.G. Birnbaum, et al., Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma, J. Allergy Clin. Immunol. 12 (2012) 1229–1235.
[13] J. Haughney, G. Barnes, M. Partridge, J. Cleland, The living and breathing study: a study of patients' views of asthma and its treatment, Primary Care Respir. J. 13 (2004) 28–35.
[14] M.E. Hyland, E. Stähl, Asthma treatment needs: a comparison of patients' and health care professionals' perceptions, Clin. Ther. 26 (2004) 2141–2152.
[15] J. Douglass, D. Goeman, R. Aroni, et al., Choosing to attend an asthma doctors: a qualitative study in adults attending emergency departments, Fam. Pract. 21 (2004) 166–172.
[16] J. Ratcliffe, R. Van Haselen, M. Buxton, et al., Assessing patients' preferences for characteristics associated with homeopathic and conventional treatment of asthma: a conjoint analysis study, Thorax 57 (2002) 503–508.
[17] A. Shaw, E.A. Thompson, D. Sharp, Complementary therapy use by patients and parents of children with asthma and the implications for NHS care: a qualitative study, BMC Health Serv. Res. 6 (2006) 76.
[18] M.R. Partridge, M. Dockrell, N.M. Smith, The use of complementary medicine by those with asthma, Respir. Med. 97 (2003) 436–438.
[19] R.W. McCarney, K. Linde, T.J. Lasserson, Homeopathy for chronic asthma, Cochrane Database Syst. Rev. (2004), doi:http://dx.doi.org/10.1002/14651858.CD000353.pub2 Art. No.: CD000353.
[20] N. Mokhtar, S.C. Chan, Use of complementary medicine amongst asthmatic patients in primary care, Med. J. Malaysia 61 (2006) 125–127.
[21] G. Passalacqua, Complementary/alternative medicines in allergic disease, Expert Rev. Clin. Immunol. 1 (2005) 113–121.
[22] G. Passalacqua, P.J. Bousquet, K.H. Carlsen, et al., ARIA update: I – systematic review of complementary and alternative medicine for rhinitis and asthma, J. Allergy Clin. Immunol. 117 (2006) 1054–1062.
[23] U. Altunç, M.H. Pittler, E. Ernst, Homeopathy for childhood and adolescence ailments: systematic review of randomized clinical trials, Mayo Clin. Proc. 82 (2007) 69–75.
[24] R. Shah, P.A. Greenberger, Chapter 29: Unproved and controversial methods and theories in allergy-immunology, Allergy Asthma Proc. 33 (2012) S100–2.
[25] E.A. Thompson, A. Shaw, J. Nichol, et al., The feasibility of a pragmatic randomised controlled trial to compare usual care with usual care plus individualised homeopathy in children requiring secondary care for asthma, Homeopathy 100 (2011) 122–130.
[26] A. White, P. Slade, C. Hunt, et al., Individualised homeopathy as an adjunct in the treatment of childhood asthma: a randomised placebo controlled trial, Thorax 58 (2003) 317–321.
[27] J.H. Campbell, M.A. Taylor, N. Beattie, et al., Is homeopathy a placebo response? A controlled trial of homeopathic immunotherapy (HIT) in atopic asthma, Am. Rev. Respir. Dis. 141 (1990) A24.
[28] D.T. Reilly, M.A. Taylor, N.G.M. Beattie, et al., Is evidence for homoeopathy reproducible? Lancet 344 (1994) 1601–1606.
[29] R.W. McCarney, K. Linde, T.J. Lasserson, Homeopathy for chronic asthma, Cochrane Database Syst. Rev. (1) (2004), doi:http://dx.doi.org/10.1002/14651858.CD000353.pub2 Art. No.: CD000353.
[30] C. Gründling, W. Schimetta, M. Frass, Real-life effect of classical homeopathy in the treatment of allergies: a multicenter prospective observational study, Wien. Klin. Wochenschr. 124 (2012) 11–17.
[31] E. Rossi, L. Crudely, C. Endrizzi, D. Garibaldi, Cost-benefit evaluation of homeopathic versus conventional therapy in respiratory diseases, Homeopathy 98 (2009) 2–10.
[32] J.K. Ostermann, T. Reinhold, C.M. Witt, Can additional homeopathic treatment save costs? A retrospective cost-analysis based on 44500 insured persons, PLoS One 10 (7) (2015) e0134657.
[33] H.A. Roberts, Principles and Art of Cure by Homoeopathy. Ch. VIII. Taking the Case. Reprint Ed. May 2006, Indian Books and Periodicals Publishers, New Delhi, 2006 p. 78.
[34] P.H. Quanjer, G.J. Tammeling, J.E. Cotes, et al., Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society, Eur. Respir. J. Suppl. 16 (1993) 5–40.
[35] R.S. Tepper, R.S. Wise, R. Covar, et al., Asthma outcomes: pulmonary physiology, J. Allergy Clin. Immunol. 129 (Suppl. 3) (2012) S65–87.
[36] K.F. Schulz, D.G. Altman, D. Moher, CONSORT group, CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials, BMJ 340 (2010) c332.
[37] S. Saha, M. Koley, S. Ganguly, et al., Developing the criteria for evaluating quality of individualization in homeopathic clinical trial reporting: a preliminary study, J. Integr. Med. 12 (2014) 13–19.
[38] A.P. Castellsagu, Evaluation of 26 cases of bronchial asthma with homoeopathic treatment, Br. Homoeopathic J. 81 (1992) 168–172.
[39] F.X. Eizayaga, J. Eizayaga, F.X. Eizayaga, Homoeopathic treatment of bronchial asthma, Br. Homoeopathic J. 85 (1996) 28–33.
[40] G. Lewith, A.D. Watkins, M.E. Hyland, et al., Use of ultramolecular potencies of allergen to treat asthmatic people allergic to house dust mite double blind randomized controlled clinical trial, Br. Med. J. 324 (2002) 520–523.
[41] L. Launsø, J. Rieper, General practitioners and classical homeopaths treatment models for asthma and allergy, Homeopathy 94 (2005) 17–25.
[42] H.F. Shafei, S.M. Abdeldayem, N.H. Mohamed, Individualized homeopathy in a group of Egyptian asthmatic children, Homeopathy 101 (2012) 224–230.
[43] S. Ghosh, S. Das, M. Mundle, et al., An open label pilot study testing the role of classical homeopathy in chronic allergic rhinitis, Int. J. Pharm. Sci. Res. 4 (2013) 1475–1484.