

An Open-Label Observational Trial to Evaluate the Possible Effects of Individualized Homoeopathic Medicines in Symptomatic Nasal Polyp

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ABSTRACT

Introduction

Nasal polyps presenting with chronic rhino-sinusitis (CRS) is a commonly encountered condition characterized by nasal obstruction, loss of sense of smell (anosmia), postnasal drip, headache, and sleep disorders. Possibly 60-65% of the populations suffering from CRS has predisposition to nasal polyps. Homoeopathic literature claims to offer successful treatment of nasal polyps; but scarcely subjected to systematic research.

Materials and Methods

A prospective, open, non-randomized, single arm, observational trial of pre-post comparison design was conducted on 44 patients suffering from symptomatic nasal polyps. Sino-nasal outcome test (SNOT-20) and European Quality of Life (EQ-5D-5L) questionnaires were taken as the primary and secondary outcome measures respectively; assessed at baseline and after 3 months. Individualized homoeopathic medicines were prescribed on 'totality of symptoms'. Intention to treat sample was subjected to statistical analysis. Data distribution was examined. Non-parametric Wilcoxon signed rank test and post hoc parametric paired *t* test were used accordingly. *P* values less than 0.05 were considered as statistically significant.

Results

Forty four patients were enrolled; 4 dropped out. Skiagrams revealed complete regressions of polyps in 23 (58%) cases. Statistically significant improvements were observed in both the subjective patient-rated outcomes – mean reduction of SNOT-20 scores by 19.9 [sd 15.5; 95% CI 15.5 to 24.2; *P* < 0.001], EQ-5D-5L questionnaire score by 0.9 [sd 2.6; 95% CI 0.1 to 1.7; *P* = 0.029]; and EQ-5D-5L VAS by 14.4 [sd 4.7; 95% CI 12.9 to 15.9; *P* < 0.001].

Conclusion

Homoeopathic medicines showed promising treatment effect in symptomatic nasal polyps. Randomized trials are warranted..

Keywords

Homeopathy; Nasal Polyp; Quality of Life

Nasal polyps (NP) presenting with the symptoms of chronic rhino-sinusitis (CRS) is one commonly prevalent disorders of the nose and para-nasal sinuses. These are non-cancerous growths within the nose or sinuses characterized by trouble breathing through the nose, loss of smell, decreased taste, post-nasal drip, and a runny nose. Possibly 60-65% of the population suffering from CRS have predisposition to nasal polyp.¹

Incidence of nasal polyp with the symptoms of CRS is seen to be on the rise in correlation to the increasing levels of environmental pollution and stress.² CRS is a common disorder, with up to 35 million people being

affected annually, and results in over 12 million office visits yearly.³ The physical symptoms of CRS are

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associated with functional and emotional impairment, which can lead to an overall poor quality of life (QOL).^{4,5} Likewise, obstructive sleep apnoea (OSA) is just as common. With up to 40 million Americans affected, it is increasing in prevalence and has been demonstrated in approximately 24% of men and 9% of women. Similar to CRS, it is associated with a poor QOL and functional and emotional impairment.^{6,7} CRS is a common health condition in industrial countries concerning 10-15% of the German population.⁸

In the US, it was the most frequently reported chronic disease in a representative cohort of 100,000 adults participating in the National Health Interview Survey 1988.⁹ Negative effects of CRS on QOL of the patients have frequently been underestimated. Nevertheless, many patients report higher impacts of CRS on QOL dimensions like bodily pain or social functioning compared with other diseases like angina pectoris, pulmonary emphysema or chronic bronchitis.¹⁰ Economic impact of CRS has rarely been investigated. In 2006, nearly 45,000 patients with CRS were operated in German hospitals.¹¹ In 1996, the healthcare expenditures for sinusitis in the US were 5.8 billion dollars.¹² Gliklich and Metson¹³ performed a break-even analysis and calculated a time period of 7 years until amortization of treatment costs can be achieved by reduced postoperative use of resources. Under these conditions, effective and successful treatment of NPs with CRS has an increasing medical and economic importance. In 1942, the revision surgery rate in 190 patients after trans-facial extra-nasal procedures was nearly 31%.¹⁴ Modern Functional Endo-nasal Sinus Surgeries (FESS) resulted in stable subjective success rates between 70% and 92%.^{15,16,17}

Materials and Methods

Trial setting and design: Samples were collected from amongst the patients attending the ENT out-patients. The study protocol was approved by the Institutional Ethical Committee (IEC). The trial protocol (unpublished) and full dissertation was submitted as the postgraduate thesis of the corresponding author to the West Bengal University of Health Sciences.

Inclusion criteria: All diagnosed cases of nasal polyp having symptoms of CRS, age 18 to 65 years, both sexes, patients willing to take part in the study and providing written consent. Patients availing any form of treatment for the same were enrolled after a wash-out phase of 1 month provided they had persistence of relevant signs and symptoms.

Exclusion criteria: Patients opting for surgical intervention, patients receiving active treatment from any other system of medicine, uncontrolled systemic or psychiatric illness, and patients denying consent.

Intervention: All medicines and vehicles in this project were procured from Homeopathy International – a GMP certified firm. All the patients were treated with individualized homeopathic medicines in 50 millesimal potencies as per need of the case. In 50 millesimal potencies, a single medicated cane sugar globule of poppy seed size (no. 10) was dissolved in 80 ml distilled water with addition of 2 drops of 90% v/v ethanol, 16 doses marked on the vial, each dose of 5 ml was instructed to be taken after 10 uniformly forceful downward strokes to the vial in 45 ml normal water in a clean cup, to stir well, to take 5 ml of this liquid orally, and to discard rest of the liquid from the cup.

Repetition was advised daily or every alternate day depending upon the individual requirements of the case and as decided appropriate by the treating homeopaths. Duration of therapy was 3 months. Single individualized medicine was prescribed on each occasion taking into account presenting symptoms totality, clinical history details, constitutional features, miasmatic expressions, repertorisation using the software RADAR[®] and consensus between two homeopaths. Dose was also individualized and was based on the homeopaths' judgment of susceptibility and consensus. Subsequent prescriptions were generated as per Kent's observations and Hering's law. Participants were assessed similarly by the two homeopaths in follow-up visits. One of the prescribers possessed a masters degree in homeopathy with more than 30 years of experience of practicing classical homeopathy and the corresponding author was a postgraduate trainee at NIH with 3 years of experience. All the homeopaths involved were affiliated with state councils.

Outcomes: Primary – translated Bengali version of the Sino-Nasal Outcome Test (SNOT) questionnaire; secondary – EQ-5D-5L questionnaire; available and pre-validated Bengali version [User license no. 24882]. The Sino-Nasal Outcome Test 20 (SNOT – 20) was one of the most widely used quality-of-life instruments for sino-nasal conditions¹⁸⁻²¹ and was intended for populations of people with rhino-sinusitis, rather than simply rhinitis. The SNOT-20 was a self-administered multiple choice 20 items test that is usually scored with a single summary score (0-5) without domains or subscales. The items were assigned to five subgroups (nasal symptoms, para-nasal symptoms, sleep-related symptoms, social impairment and emotional impairment). The score of the SNOT-20 was calculated by summation of all the symptoms scores. Therefore, scale values of the SNOT-20 ranged from 0 to 100. Additionally, patients could circle those 5 symptoms which have the highest impact on the impairment. This instrument assessed a broad range of health and health-related quality-of-life problem including physical problems, functional limitations and emotional consequence, but unlike many of the quality-of-life instruments designed to measure rhinitis symptoms, this rhino-sinusitis measure was not divided into subscales or domains related to these different areas. Another was the EQ-5D-5L questionnaire.

It was a standardized measure of health status developed by the Euro QoL Group²² in order to provide a simple, generic measure of health for clinical and economic appraisal. It was applicable to a wide range of health conditions and treatments; it provided a simple descriptive profile and a single index value for health status that could be used in the clinical and economic evaluation of healthcare as well as in population health surveys. EQ-5D was available in 139 languages including Bengali, was designed for self-completion by respondents and was ideally suited for use in postal surveys, in clinics, and in face-to-face interviews. It was cognitively undemanding, taking only a few minutes to complete. Instructions to respondents were included in the questionnaire.^{23,24}

Sample size: No relevant data was available on reduction of SNOT score by individualized homoeopathic treatment using an open observational study design over

3 months of intervention. Thus, assuming a medium effect size (d) of 0.5, alpha = 0.05 and power of 90%, to detect a significant difference between two dependent means (mean pre- and post- SNOT scores) by paired t test, we would have required a sample size of 44.

Statistical methods: Intention to treat sample was subjected to statistical analysis. Missing values were replaced by Last value Carried Forward (LVCF) method. Data distribution was examined by histograms, Q-Q plots, Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics was used to represent baseline data. Inferential statistics was used in terms of non-parametric Wilcoxon signed rank test and parametric post hoc paired t test to compare SNOT-20 and EQ-5D-5L scores those obtained at baseline and after 3 months. P values less than 0.05 were considered as statistically significant. No interim and subgroup analyses were planned. SPSS® IBM® version 20 software for Windows was used for analysis of data. Reporting adhered to the CONSORT²⁵ and RedHot²⁶ guidelines for reporting trials, Mathie's criteria for model validity of homoeopathic treatment^{27,28} (MVHT), and Saha's criteria for reporting quality of homoeopathic individualization in clinical trials.²⁹

Results

Participant flow: As per the pre-specified inclusion and exclusion criteria, 70 patients suffering from nasal polyposis were screened; 26 were excluded on account of various reasons; 44 met the eligibility criteria and were enrolled into the study. Following that, baseline socio-demographic and outcome data were obtained (n=40). After 3 months of intervention, outcome data was recorded again. During course of treatment, 4 dropped out; 40 completed the trial; 44 entered into the analysis. (Fig. 1)

Recruitment: Starting from May 2017 until November 2017, total 44 participants were enrolled in the study.

Baseline data: Twelve socio-demographic features were studied – age (as continuous variable), age groups (categorical variable), gender, residence, duration of suffering, treatment taken, body mass index (BMI; as continuous variable), BMI classes (categorical variable), marital status, education, employment status,

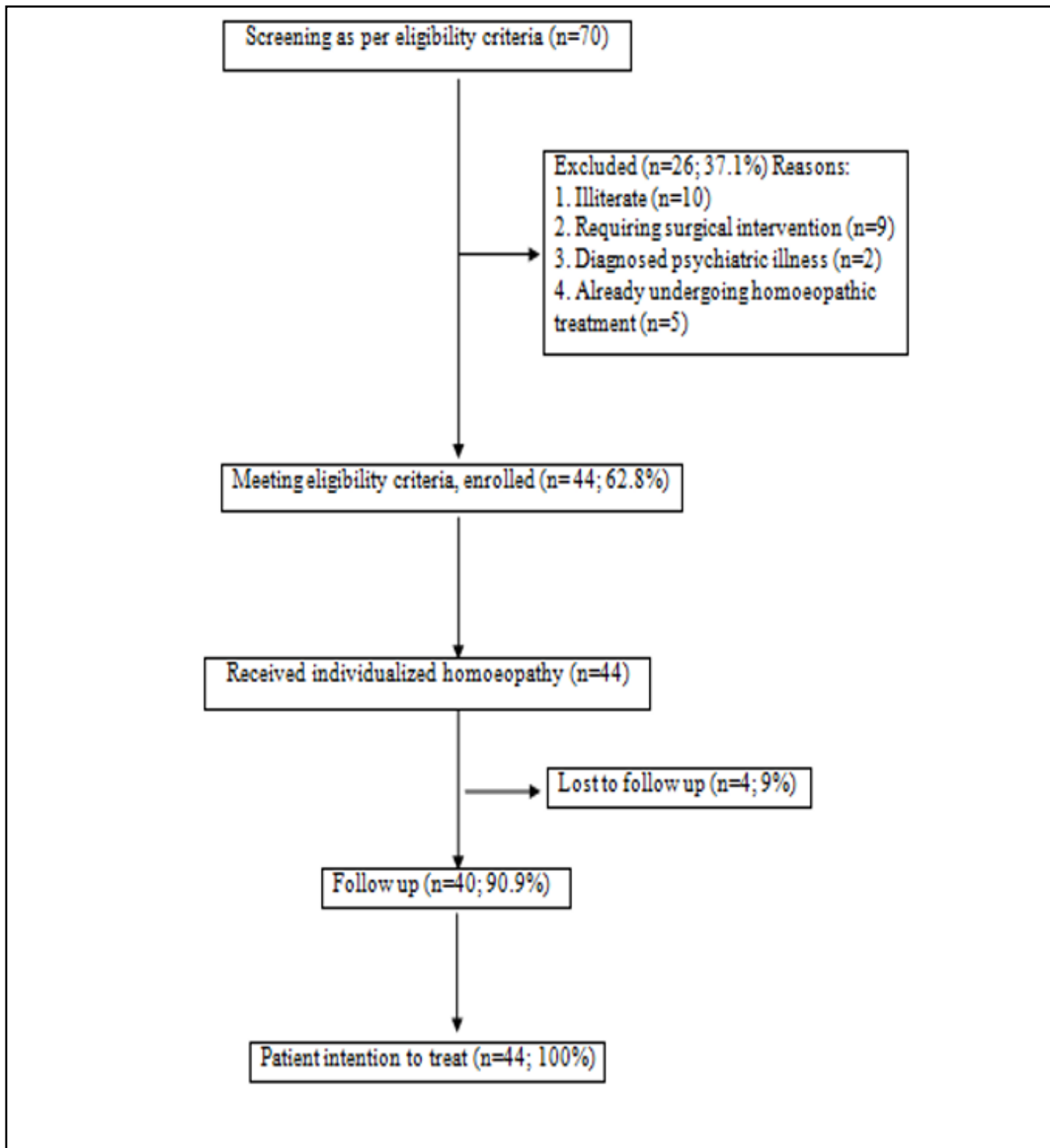


Fig. 1. Study flow diagram

and family income status (Table 1)

Data distribution: It was examined by histograms (Supplementary Data – Figures: 1-6), Q – Q plots (Supplementary Data – Figures: 7-12) and statistical tests – Kolmogorov Smirnov test and Shapiro Wilk test (Supplementary Data – Table 1). Data distribution seemed to follow a mixed pattern – at baseline normal but non-normal after 3 months. Thus, first non-parametric Wilcoxon signed rank test (Table II) was planned to perform; and if significance was detected, then post hoc parametric paired t test (Table III).

Numbers analyzed: All the enrolled patients (N=44) entered into the final analyses.

Changes in outcomes:

1. As per skiagrams of 40 protocol-compliant cases, there were complete regressions of nasal polyps in 23 (58%) cases, partial improvement in 11 (27%) cases and no changes in 6 (15%) cases.

2. After 3 months of treatment, there were statistically significant improvements in SNOT-20 scores, EQ-5D-5L questionnaire scores, and EQ-5D-5L VAS measures (all $P < 0.05$). (Tables II and III, Fig. 2)

Correlation statistics: The correlation scatter plots (Figure: 15 and 16) revealed weak to moderate positive linear relationships between changes in SNOT score and EQ-5D-5L scores.

Medicines used: The following medicines were prescribed – Tuberculinum [n=2; 5%], Thuja occidentalis [n=1; 2.5%], Sulphur [n=2; 5%], Sanguinaria canadensis [n=1; 2.5%] Pulsatilla nigricans [n=2; 5%], Psorinum [n=11; 27.5%], Nitric acid [n=2; 5%], Natrum muriaticum [n=1; 2.5%], Hepar sulphuricum [n=3; 7.5%], Dulcamara [n=10; 25%] Calcarea carbonica [n=5; 12.5%], Belladonna [n=1; 2.5%], Arnica montana [n=1; 2.5%]. (Table IV)

Adverse events: No harm, unintended effects, serious adverse events, and homeopathic aggravations were reported during the study period.

Discussion

This prospective, open, non-randomized, single arm, observational clinical study of pre-post comparison

Table I: Baseline features

Age Δ (yrs; mean \pm sd)	30.0 \pm 10.5
Age groups (yrs) §	
§ 18 – 25	20 (45.5)
§ 26 – 40	18 (40.9)
§ Above 40	6 (13.6)
Gender §	
§ Male : Female	30 (68.2) : 14 (31.8)
Residence §	
§ Rural : Urban	26 (59.1) : 18 (40.9)
Duration of suffering Δ (yrs; mean \pm sd)	3.5 \pm 2.3
Treatment taken §	
§ Allopathy	11 (25)
§ Homocopathy	11 (25)
§ None	22 (50)
BMI Δ (mean \pm sd)	23.5 \pm 3.9
BMI classes §	
§ Underweight to normal	26 (59.1)
§ Overweight	15 (34.1)
§ Obese	3 (6.8)
Marital status §	
§ Single : Married	19 (43.2) : 25 (56.8)
Educational status §	
§ 8th std or below	25 (56.8)
§ 9th to 12th std	4 (9.1)
§ Graduate or above	15 (34.1)
Employment status §	
§ Unemployed	14 (31.8)
§ Farmer	5 (11.4)
§ Business	19 (43.2)

Table I: Baseline features (contd.)

Family income status §	
§ Low	25 (56.8)
§ Medium to affluent	19 (43.2)

Δ Continuous data presented as mean ± standard deviations; § Categorical data presented as absolute values and percentages

design was conducted on 44 patients suffering from nasal polyps associated with CRS. SNOT-20 and EQ-5D-5L questionnaires were taken as the primary and secondary outcome measures respectively; assessed at baseline and after 3 months. Individualized homeopathic medicines were prescribed on 'totality of symptoms.' Complete regression of polyps was achieved in 23 (58%) cases. Statistically significant improvements were observed in both the outcomes over a period of 3 months. Thirteen individualized homeopathic medicines were prescribed. Out of those, Psorinum [n=11; 27.5%] was the most frequently prescribed medicine. Individualized

homeopathic medicines seemed to be promising treatment for symptomatic nasal polyps.

The methodological strengths of the study included the prospective patient enrolment and use of standardized and already validated outcome scales – SNOT-20 and EQ-5D-5L questionnaires. This study is representative of individualized homeopathy only. In a broader interpretation of the law of similar, medicines were selected on the basis of 'totality of symptoms.' Observational trials are important for establishing hypothesis and the sample size for significant result. Though the sample size of this study was small, still was adequately powered to detect changes in the specified outcome measure over 3 months. The sample size had to be kept small keeping in mind the feasibility issues and stipulated time frame of postgraduate thesis. All the collected data (hard form) was converted into an analyzable and reproducible master chart (soft copy) where all data was extracted systematically and underwent statistical analysis subsequently.

At the end of the study, forty protocol-compliant

Table II: Changes in outcomes over time: analysis by Wilcoxon signed rank test (N=44)

OUTCOMES	BASELINE	AFTER 3 MONTHS	Z SCORE	P VALUE
	MEDIAN (IQR)	MEDIAN (IQR)		
SNOT-20 score	33.5 (25.5 to 47.0)	16.5 (13.3 to 22.0)	-5.472	< 0.001
EQ-5D-5L:				
§ Questionnaire score	5.0 (3.0 to 6.0)	3.0 (2.0 to 5.8)	-2.844	0.004
§ VAS score	60.0 (50.0 to 70.0)	74.0 (62.0 to 81.8)	-5.528	< 0.001

Table III: Changes in outcomes over time: pair-wise analysis by post hoc paired t test (N=44)

OUTCOMES	BASELINE;	AFTER 3 MONTHS;	CHANGE (0-3 MO);
	MEAN ± SD	MEAN ± SD	MEAN ± SD (95% CI)
SNOT-20 score	37.0 ± 16.3	18.5 ± 7.7	18.5 ± 14.2 (14.2 to 22.9) §
EQ-5D-5L:			
§ Questionnaire score	4.6 ± 2.5	3.6 ± 2.6	1.0 ± 2.4 (0.3 to 1.8) ψ
§ VAS score	58.0 ± 14.0	72.8 ± 12.5	14.8 ± 9.6 (11.9 to 17.7)*

§t43 = 8.660, P < 0.001 (significant); ψt43 = 2.831, P = 0.007 (significant); *t43 = 10.211, P < 0.001 (significant)

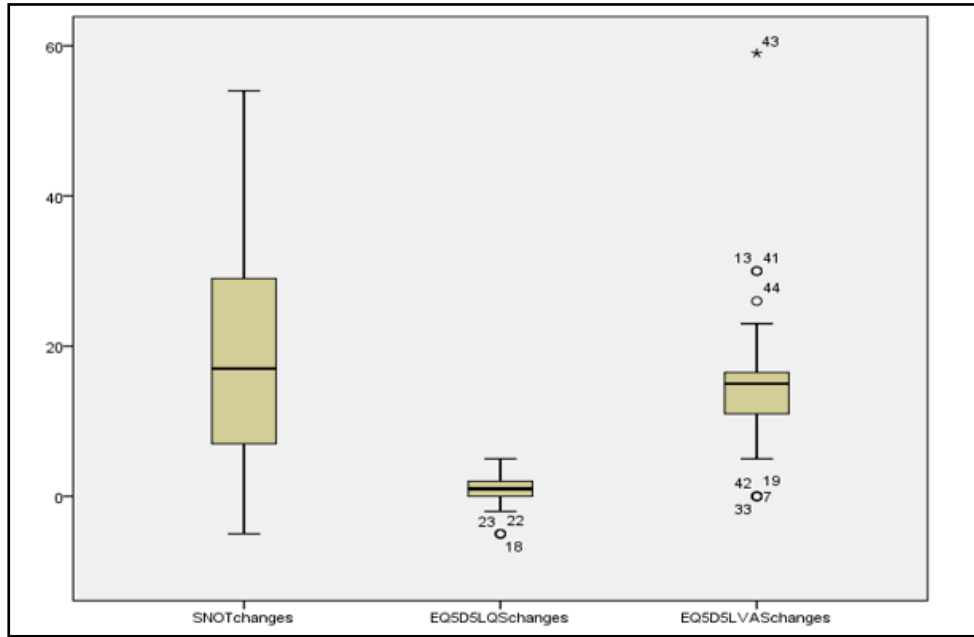


Fig. 2. Box and whisker plots showing changes in SNOT-20 scores, EQ-5D-5L questionnaire scores and EQ-5D-5L VAS scores over 3 months of treatment (N=44); SNOT-20 changes: Median 17.0, IQR 7.0 to 29.0; EQ-5D-5L questionnaire score changes: Median 1.0, IQR 0.0 to 2.0; EQ-5D-5L VAS score changes: Median 15.0, IQR 11.0 to 16.8

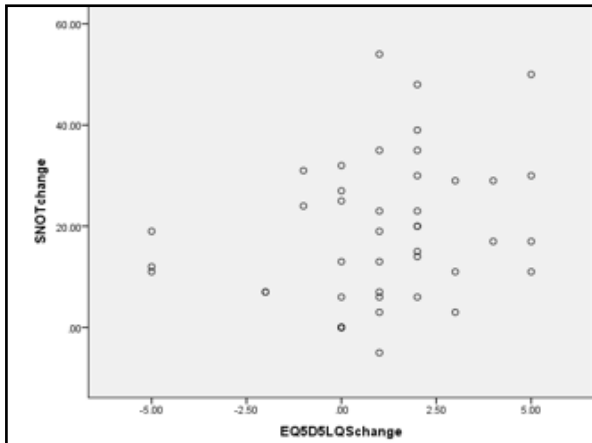


Fig. 3: Correlation scatter plot between changes in SNOT scores and EQ-5D-5L questionnaire score; Pearson's $r = 0.260$, $P = 0.088$

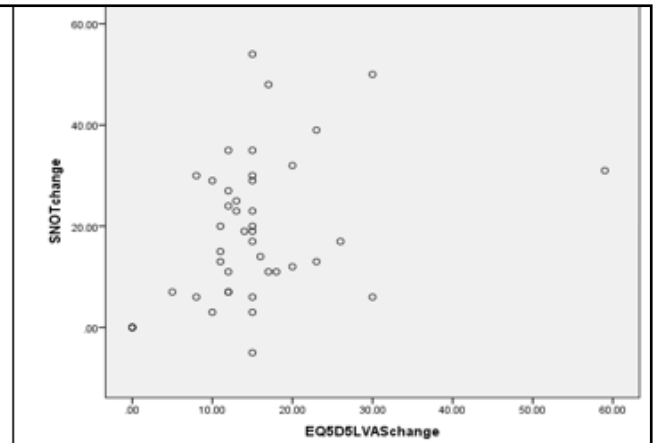


Fig. 4: Correlation scatter plot between changes in SNOT scores and EQ-5D-5L VAS measure; Pearson's $r = 0.385$, $P = 0.010^*$

Figs. 3 and 4. Correlation statistics between changes in outcomes

Table IV: Used medicines

PRESCRIBED MEDICINES	NO. OF PRESCRIPTIONS	PERCENTAGES (%)
Tuberculinum	2	5
Thuja occidentalis	1	2.5
Sulphur	2	5
Sangunaria canadensis	1	2.5
Pulsatilla nigricans	2	5
Psorinum	11	27.5
Nitric acid	2	5
Natrum muriaticum	1	2.5
Hepar sulphuris	3	7.5
Dulcamara	10	25
Calcarea carbonica	5	12.5
Belladonna	1	2.5
Arnica montana	1	2.5

patients entered into the final analysis. Descriptive statistics was used to represent baseline data. Inferential statistics was used in terms of paired t test. Statistically significant improvements were observed in both the outcomes – SNOT-20 scores and EQ-5D-5L questionnaire scores. Statistically significant improvements were observed in both the outcomes. There was no violation of routine homoeopathy practice and the outcome data was gathered at baseline and 3 months of treatment. All the medicines were prescribed in fifty millesimal potencies. Homoeopathic medicines provided promising aid in treatment of symptomatic nasal polyps.

Constraints in sample size and duration of follow-up were the major limitations of the study. This study did not support conclusions as to the efficacy or effectiveness of the homoeopathic medicines because no methodology for this purpose (control group, randomization, blinding, etc.) was built into its design. Another limitation was inherent in the observational design of the study, i.e. the trial was open; no blinding was used. Thus, patient selection bias, evaluation bias,

and data analysis bias might have affected the outcomes of the study. No causal inference could be attributed to the treatment and the treatment could not be regarded as the sole reason for the changes in the patients. Also, the other limitation was to use the subjective measures, namely SNOT-20 and EQ-5D-5L questionnaires, that might have incorporated some kind of bias.

Validity and reliability of the translated Bengali version of SNOT-20 questionnaire remain to be addressed formally in future studies. The data may also be helpful in the planning of further controlled research in homoeopathy. It would require specific objective measures for valid assessment and a longer observation period. Further independent replications and explorations by randomized trials with enhanced methodological rigor are warranted.

Conclusion

In this prospective, open, non-randomized, single arm, observational clinical study of pre-post comparison design conducted on 44 patients suffering

from symptomatic nasal polyps revealed complete regressions of polyps in 23 (58%) cases and statistically significant improvement in both SNOT-20 and EQ-5D-5L questionnaires after 3 months of individualized homoeopathic treatment. Further explorations by randomized trials are warranted.

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