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Azadirachta indica in treatment of acne vulgaris–an open-label observational study

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ABSTRACT

Introduction: *Azadirachta Indica* (*Aza.*) has been used since decades in traditional medicine for the treatment of acne; even in Homoeopathy, it is recommended but its precise indications are still elusive. This study was undertaken to determine the usefulness of *Azadirachta indica* in the treatment of acne vulgaris and find its indications.

Materials and Methods: A prospective, non-randomized, open-label interventional study was conducted after approval from ethical committee. *Azadirachta indica* was prescribed in raising potencies from 6C up to 1M. The observational period was of 6 months. Outcome measures were Lesion counts, Global Acne Grading System (GAGS) score and Acne-specific Quality of Life questionnaire (Acne-QoL) score. Data was analyzed using paired *t*-test, Wilcoxon signed rank tests and Pearson's correlation tests.

Results: Out of 31 enrolled participants, 29 completed the 6-months follow-up. Two subjects did not report after 2–3 months but were included under Intention-To-Treat (ITT). Though there were overall statistically significant results in respect of Lesion counts, GAGS and Acne QoL score ($P < 0.001$) but no effect was seen in inflammatory lesions.

Conclusions: *Azadirachta indica* has a role in early and recovery phase of acne when inflammatory changes are least. Further study on a larger sample size is desirable.

Trial is registered at Clinical Trials.gov Identifier: NCT01321645.

Keywords: Acne vulgaris, Acne-QoL, Azadirachta Indica, Global Acne Grading System, Lesion counts

INTRODUCTION

Acne vulgaris is a common dermatological disease affecting adolescents and young adults.[1] More than 250 remedies are mentioned in the homoeopathic literature[2] for its treatment that includes lesser known medicines namely *Lappa arctium, Zingiber officinale* and *Azadirachta Indica* (*Aza.*). Two studies have already been published; this is third in the series. Statistically significant results were seen with *Lappa arctium*.[3] *Zingiber officinale.* was found beneficial in facial acne with statistically significant results.[4] *Azadirachta indica* was chosen for the third study as it is being used traditionally in India since centuries for various blood and skin disorders.[5] Commonly known as *Neem*, it is called as 'sarvaroganivarini' (that which keeps all diseases at bay) in Ayurveda's text 'Charaka Samhita' and is an active ingredient of most ayurvedic formulations for the treatment of skin disorders including acne.[6] It inhibits the growth of *Propionibacterium acnes (P. acnes)* and *staphylococcus epidermidis* and also has antioxidant properties.[5,6] An *in vitro* study demonstrated that *Azadirachta indica.* caused the

highest inhibition of *P. acnes* induced inflammatory mediators.[7]

In Homoeopathy, *Azadirachta indica* was introduced by Dr. P. C. Majumdar in 1890s, followed by homoeopathic pathogenetic trials by Dr. H. Chakrabarti[8] in 1895, Central Council for Research in Homoeopathy (CCRH) in 1988–1989[9] and Sharda Bioron Laboratory (SBL), India in 2004.[10] It is mentioned in therapeutic uses for the treatment of 'pimples' but no symptoms delineated.[10-12] This study was undertaken to explore its potential in treatment of acne vulgaris using validated scales for clinical assessment and to identify useful prescribing indications.

MATERIALS AND METHODS

Design overview

A prospective, non-randomized, open-label interventional study was conducted on human subjects from March 2011 to June 2012. The protocol was approved by the Ethical Committee of Sri Guru Nanak Dev Homoeopathic Medical College and Hospital (SGNDHMC and H), Ludhiana, India. The study was conducted in accordance with the Declaration of Helsinki on human experimentation and on good clinical practice. Subjects gave written informed consent before initiation of the study. In case of minor, guardian provided the written consent. The case of each subject was recorded on a predesigned case taking questionnaire. The trial is registered at Clinical Trials.gov Identifier: NCT01321645.

Setting

The study was conducted at Homoeopathic unit of Delhi Government Health Centre, Sector 12, Dwarka, New Delhi, India.

Inclusion and exclusion criteria

Subjects were Outpatient Department (O.P.D) patients aged between 12 to 25 years who had inflammatory and non-inflammatory acne lesions and had not taken any medication for acne in preceding 1 month. Subjects who had acne conglobata, any drug or alcohol addiction, suffering from any systemic disease or who had any chronic disease treated with medications in the preceding 1 month which might affect acne condition and treatment outcome were excluded. Females who were breast feeding, pregnant or intended to become pregnant were also excluded from the study.

Sample size

Prior to the start of the study, sample size of 26 subjects was estimated based on 50% change in lesion counts from baseline in order to achieve 5% level of significance and 90% statistical power. Considering a 20% drop-out rate, this translated to a target recruitment of 31 subjects.

Intervention

On first visit, *Azadirachta indica* was prescribed in 6C potency to be taken in form of four pills four times a day for 7 days. Medicine was not repeated till improvement lasted and the subject was given only placebo. If improvement stopped, *Azadirachta indica* was repeated in the same potency. If there was no further perceptible change, then higher potency of 30C was given three times a day for 7 days, followed by placebo. The potency was further increased to 200C and then 1M as a single dose. The repetition of dose and change of potency was done as per the clinical response of the subject and in accordance with homoeopathic principles. The subjects came for clinical evaluation every 2 weeks for monitoring the response to the medicine. The treatment was given for 6 months. The medicines were procured from SBL Industries Pvt. Ltd., Haridwar, India, a GMP compliant manufacturer. The subjects were not allowed to take any other medications during the study. Subjects who were taking any other medication for acne or had taken any medication for acne in preceding one month were excluded from the study. Since dietary restriction or consumption of specific foods do not affect acne,[13,14] no dietary restrictions or life style changes were advised.

Outcomes

The primary outcome was the percentage change in acne lesion counts and Global Acne Grading System (GAGS) score from baseline in 6 months. All types of acne lesions, i.e. closed and open comedones, papules, pustules and nodules on face, chest and back were counted and the total of each type of lesion was calculated on every visit. Counting was done manually without magnifying glass or skin stretching. Further intensity of acne was graded using validated GAGS.[15] This system divides the face, chest and back into six areas and assigns an area factor of 1, 2 or 3. Each type of lesion is given a value from 0–4. Area score is the product of the most severe lesion in that area multiplied by the area factor. The area scores were added to

give the total GAGS score. The lesion counting and GAGS score was calculated on each visit. The acne lesion counting and grading was done by the same homoeopathic physician (AM) to avoid multi-rater variance.[16]

The secondary outcome was change in Acne-specific Quality of Life questionnaire (Acne-QoL) score at the end of six months and to identify the prescribing indications of *Azadirachta indica*, if any. It is well documented that acne causes anxiety and can severely affect social and psychological functioning of an individual.[17] In this study, the validated Acne-QoL questionnaire[18-20] was used for psychological assessment. The questionnaire contains 19 items relating to self perception, social, emotional and acne symptoms as perceived by the participant on a seven point response scale with higher scores indicating a better Quality of Life. The subjects were asked to fill the questionnaire both at the start and at end of treatment.

Statistical analysis

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) 20.0 version. Subjects who had at least one follow-up were included in the study under Intention-To-Treat (ITT) analysis. Missing values were addressed using last observation carried forward (LOCF) technique. Data expressed as number (%), mean ± standard deviation (SD) and median (IQR). The statistical test of paired *t*-test was applied for analysis of Acne-QoL scores. The non-parametric test of Wilcoxon signed rank test was used for the analysis of total lesion count, inflammatory lesions, non-inflammatory lesions, individual lesions and GAGS score. The inflammatory lesions were papules, pustules and nodules combined together. The non-inflammatory lesions were the total of open and closed comedones. Response of each type of acne lesion in respect to different locations was also analyzed by Wilcoxon signed rank test. Pearson correlation test was used for testing the correlation of a particular symptom to clinical response. If the *P* value was less than 0.05, it was considered as significant result.

RESULTS

Thirty-one subjects were enrolled for the study. Two subjects did not report after 2–3 months of treatment but were considered under ITT and data analyzed [Figure 1].

Mean age of the subjects was 17.6 ± 3.2 years. There were 16 male and 15 female subjects ($n = 31$) [Table 1]. Duration of complaints was 1.9 + 1.2 years.

Subjects showed improvement in total, inflammatory and non-inflammatory lesions and in GAGS score ($P < 0.001$). On further analysis, significant decrease was seen in comedones, papules, pustules ($P < 0.001$) but not in nodules [Table 2].

Acne-QoL score at baseline was 71.03 ± 23.7 which became 88.48 ± 19.2 at the end of treatment. The improvement was statistically significant $P < 0.001$ [Table 3]. Out of the 31 subjects, 6 subjects showed 50–75% relief [Table 4]. The two subjects who became worse had stopped reporting despite reminders. The specific characteristics/symptoms of the 31 subjects was further analyzed [Table 5] to assess for correlation between clinical response and a particular character/symptom using Pearson correlation. Although none of the subjects showed

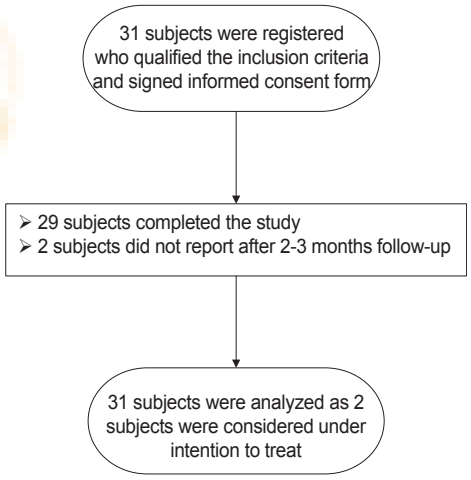

Figure 1: Flow chart of the study

Table 1: Baseline characteristics

	No.of cases (*n*=31)
Sex	
Male	16
Female	15
Location of acne lesions	
Face	14
	8
Face+back	6
Face + chest + back	11
Family history of acne	
Yes	12
No	19

Table 2: Comparison of types of acne lesions

	Median (IQR)		*Z* value	*P* value
	At entry	At end		
Total lesion count	128 (93, 218)	82 (55, 168)	4.802	<0.001*
Inflammatory lesion	20 (15, 31)	17 (13, 28)	4.462	<0.001*
Non-inflammatory lesion	106 (76, 188)	58 (41, 139)	4.802	<0.001*
Closed comedone	94 (69, 171)	56 (37, 124)	4.763	<0.001*
Open comedone	10 (6, 17)	4 (2, 8)	4.711	<0.001*
Papule	17 (12, 24)	14 (11, 23)	1.979	0.048*
Pustule	4 (3, 7)	3 (2, 5)	3.974	<0.001*
Nodule	0 (0, 0)	0 (0, 0)	1.633	0.102
GAGS	23 (20, 26)	20 (17, 24)	4.348	<0.001*

P value shows statistical significance at *P*<0.05*. GAGS: Global acne grading system

Table 3: Acne-specific quality of life-paired *t*-test

	Mean (SD)		95% CI	*P* value
	At entry	At end		
Acne-QOL	71.03 (23.7)	88.48 (19.2)	−23.4 to −11.5	<0.001*

P value shows statistical significance at *P* <0.05*. SD: Standard deviation; CI: Cumulative incidence; Acne-QOL: Acne-specific quality of life questionnaire

Table 4: Percentage of improvement in total lesion counts

Percentage improvement	No. of subjects
More than 75%	0
50-75%	6
25-50%	18
Less than 25%	5
No change	0
Worse	2

Table 5: Number of subjects with different character/symptom

Character	Total no. of subjects (*n*=31)
Thermal reaction	
Ambithermal	16
Chilly	3
Hot	12
Physical constitution	
Thin built/ectomorphic	26
Medium built/mesomorphic	5
Food desire	
No specific	4
Salty	10
Spicy	3
Fried food	1
Cold drinks	1
Warm food	2
Sweets	10
Mentals	
Authoritative	2
Anxiety	7
Dreams murder	1
Desire company	6
Fears	7
Sensitive	2
Reserved	6
Seasonal aggravation	
No specific	15
Summer	12
Winter	4
Premenstrual aggravation	
Yes	4
No	11
NA (males)	16
Associated symptoms	
Itching	11
Dandruff	1
Constipation	1
Profuse sweat	1
None	17

marked improvement, subjects who were mentally anxious showed more improvement in total lesion count. Subjects who preferred sweets responded better. Acne with itching responded well. Statistically significant response was seen in thin built subjects ($P = 0.007$).

Response of acne lesions at different locations was further analyzed [Table 6]. Maximum improvement was seen in lesions of face. Interestingly, the non-inflammatory lesions showed statistically significant response at all locations. Among inflammatory lesions, pustules on face and back responded but papules, nodules did not show improvement on any site.

DISCUSSION

Azadirachta indica lead to statistically significant response in total lesion counts, GAGS score and improvement in Acne-QoL score. Response in non-inflammatory lesions was better with 34.7% reduction in lesion counts as compared to inflammatory lesions which showed only 10.7% reduction. The overall improvement in lesion counts was 31.1% which is not very encouraging. It was ineffective in inflammatory acne.

In this study some specific prescribing symptoms for acne could be elucidated. *Azadirachta indica* acted better in facial acne, comedonal acne and acne with itching. It acted better in thin built/ectomorphic

subjects who were anxious and preferred sweets. In the drug proving of *Azadirachta indica*, symptom 'anxiety'[8,9,11] and 'itching' are mentioned[9,21,22] and in this study also these symptoms were verified. However, the prescribing indications of *Azadirachta indica* are different from *Lappa arctium*[3] and *Zingiber officinale*.[4]

Table 6: Improvement indifferent types of lesions on different locations

Location	Median (IQR)		*Z* value	*P* value
	At entry	At end		
Face (*n*=31)				
Closed comedone	78 (60, 136)	41 (20, 84)	4.743	<0.001*
Open comedone	8 (5, 110)	4 (2, 5)	4.715	<0.001*
Papule	14 (9, 18)	14 (8, 19)	0.797	0.425
Pustule	4 (2, 5)	2 (1, 4)	3.760	<0.001*
Nodule	0 (0, 0)	0 (0, 0)	1.633	0.102
Chest (*n*=11)				
Closed comedone	0 (0, 13)	0 (0, 11)	3.211	0.001*
Open comedone	0 (0, 1)	0 (0, 0)	2.333	0.020*
Papule	0 (0, 2)	0 (0, 1)	1.000	0.317
Pustule	0 (0, 0)	0 (0, 0)	1.000	0.317
Nodule	0 (0, 0)	0 (0, 0)	0.000	1.000
Back (*n*=17)				
Closed comedone	15 (0, 26)	13 (0, 22)	2.561	0.010*
Open comedone	1 (0, 3)	0 (0, 2)	2.222	0.026*
Papule	2 (0, 4)	2 (0, 4)	1.732	0.083
Pustule	0 (0, 1)	0 (0, 0)	2.121	0.034*
Nodule	0 (0, 0)	0 (0, 0)	0.000	1.000

P value shows statistical significance at *P*<0.05*. IQR: Interquartile range

CONCLUSION

Azadirachta indica has shown positive results in comedonal acne and acne on face. The sample size being small, further trials with a larger sample may be conducted for verification of results. Though certain prescribing symptoms of this medicine in relation to acne have been elucidated but the likelihood ratio of these symptoms may be worked out in future studies for confirming their relevance.

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सामान्य पनसिका के उपचार में एज़ाडिराच्टा इंडिका – एक खुला नामपत्र, प्रेक्षणमूलक अध्ययन

सार

परिचय: एज़ाडिराच्टा इंडिका को मुहांसों के उपचार में पारंपरिक चिकित्सा पद्धति में दशकों से प्रयोग किया जा रहा है। होम्योपैथी में भी इसकी अनुशंसा की जाती है किंतु इसके सटीक संकेतन अभी भी सुनिश्चित नहीं हैं। इस अध्ययन का उपक्रम सामान्य पनसिका में एज़ाडिराच्टा की उपयोगिता का निर्धारण करने के लिए और उसके संकेतन ज्ञात करने के लिए किया गया था।

विधियां: नैतिकता समिति से अनुमोदन मिलने के पश्चात एक पुरोलक्षी, अयादृच्छिकृत, खुला नामपत्र, हस्तक्षेपी अध्ययन संचालित किया गया। एज़ाडिराच्टा को 6सी से 1एम तक वर्धमान शक्तियों में विहित किया गया। प्रेक्षणमूलक अवधि छः महीनों की थी। परिणाम के माप थे विक्षतियों की संख्या, समग्र पनसिका कोटि निर्धारण प्रणाली (ग्लोबल एक्ने ग्रेडिंग सिस्टम, जीएजीएस) एवं पनसिका–विशिष्ट जीवन गुणवत्ता प्रश्नोतरी (एक्ने–क्यूओएल) समंक। आँकड़ों का विश्लेषण युग्मित टी–परीक्षण, विलॉक्सन सचिह्न कोटि परीक्षणों एवं पियर्सन सहसंबंध परीक्षणों द्वारा किया गया।

परिणाम: 31 नामांकित प्रतिभागियों में से, 29 ने छः महीने का अनुवर्तन पूरा किया। दो प्रतिभागियों ने 2–3 महीनों के बाद सूचना नहीं दी किंतु उन्हें आईटीटी के अंतर्गत सम्मिलित किया गया। यद्यपि विक्षतियों की संख्या, जीएजीएस एवं एक्ने क्यूओएल के संबंध में समग्र सांख्यिकीय रूप से उल्लेखनीय परिणाम मिले (चमानढ0.001), किंतु शोथज विक्षतियों में कोई प्रभाव देखने को नहीं मिला।

निष्कर्ष: पनसिका की आरंभिक और पुनःप्राप्ति प्रावस्था, जब सूजन–संबंधी परिवर्तन न्यूनतम होते हैं, में एज़ाडिराच्टा की भूमिका है। आगे विशालतर नमूना आकार पर अध्ययन वांछनीय है।

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