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Short communication

Clinical trials of ayurvedic formulations in the treatment of acne vulgaris

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Abstract

Oral and externally used dermatological preparation for acne vulgaris employing herbal extracts have been developed and standardized, the herbal extracts used here were of the plants described in ayurvedic treatise like Bhavprakasha Nighantu and Charak Samhita. The efficacy of the treatment using the oral formulation with or without external preparation has been assessed through conduct of Phase II clinical trials in 53 patients for 4 weeks in a randomized, double-blind, placebo-controlled fashion and following Good Clinical Practices guidelines. The results were statistically analyzed and indicated that combination of use of internal and external preparation showed better efficacy as compared to the use of oral formulation alone.

Keywords: Acne vulgaris; Ayurvedic formulations; Clinical trials

1. Introduction

Acne vulgaris, a chronic inflammatory disorder in adolescents consists of the pilosebaceous follicles, characterized by comedones, papules, pustules, cysts, nodules and often scars, chiefly on face, neck etc. The microorganisms involved include Propionibacterium acnes and Staphylococcus epidermidis. The comedo, commonly known as the 'black-head', is the basic lesion in acne. It is produced by hyperkeratosis of the lining of the follicles, which retains keratin, sebum and some microorganisms.

The general therapy in the treatment of acne vulgaris includes oral and topical therapy employing comedolytics (Benzoyl peroxide, tretinoin, azeleic acid and isotretinoin) and antibiotics for both oral and topical use (Tetracycline, Erythromycin, etc.) (Clark, 1993). In addition to producing bacterial resistance (Leyden, 1983), these drugs have several side effects. These are described for Tetracycline (Coskey, 1975), Erythromycin (Coskey, 1975) Clindamycin (Milestone et al., 1981) and Isotretinoin (Lammer, 1985).

Five thousand years old Indian traditional system of medicine, Ayurveda describes acne vulgaris as 'Tarunya Pitika' (the eruptions or pimples occurring on the face during adolescence) and 'Mukhadusika' (one which spoils, vitiates or disfigures the face). Ayurvedic treatise like Bhavaprakasha and Charak Samhita enlists various herbs and formulations to treat acne (Tarunya Pitika) and claim them to be safe and efficacious. However, claims have not been supported with controlled clinical trials.

The work reported here includes controlled Phase II clinical trials conducted using oral Ayurvedic preparations with or without the use of Ayurvedic multicomponent dermatological formulations developed in this laboratory.

2. Materials, patients and methods

2.1. Materials

Soft extracts of *Aloe barbadensis*, Miller, *Azardirachta indica*, Juss, *Curcuma longa*, Linn,

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Hemidesmus indicus, Linn, *Terminalia chebula*, Retzr, *Terminalia arjuna*, Rob and *Withania somnifera*, Linn (one part of the extract approximately representing four parts of dried/fresh plant material) were procured from Saiba Industries, Mumbai. The extracts were mixed in different proportions.

Several formulations were prepared and evaluated for their in vitro antibacterial and anti-inflammatory activity (Nandedkar, 1999); one showing the highest efficacy was evaluated for its safety-involving test for comedogenicity and local irritation. The methodology and the results of this study are being published separately. The selected combination was incorporated separately in a cream base and a gel base. Tablets having the same composition were prepared after adding definite quantity of *Piper longum*, Linn extract to improve bioavailability. In addition, placebo tablets (omitting the active ingredients) were also prepared. They were identical in weight and appearance.

2.2. Clinical studies

Following Good Clinical Practices guidelines, a randomized, double-blind, placebo-controlled parallel group clinical trial was conducted in the Panchkarma department of Ashthang Ayurvedic College and hospital, Pune. Fifty-three patients ($n = 53$) including 35 males and 14 females in the age group of 14–28 years were enrolled. They had mild to moderately severe acne exhibiting a minimum of 10 inflammatory lesions i.e. papules and pustules and minimum of five non-inflammatory lesions i.e. blackheads.

The patients excluded in the studies were pregnant women, breast feeding mothers and those patients who had a previous history of hypersensitivity to Ayurvedic drugs, serious hepatic or renal insufficiences and those on treament with other antibiotics in the proceeding four weeks.

The patients were examined for the following before being included in the trial: (1) height, (2) body weight; (3) blood pressure; (4) body status (Prakruti).

Each patients history was recorded for their: (1) gastrointestinal motility (Koshtha); (2) eating habits (veg/non-veg); (3) previous history of illness (Purva vyadhi vrutta); (4) seasonal occurrence of acne syndrome; and (5) effect of previous therapy and other relevant details.

Written informed consent was obtained from the patients after explaining to them the purpose of conducting the trial. They were randomized into four groups with 23, 23, 5 and 2 patients in Groups I, II, III and IV, respectively. They were suitably coded. Out of the total number of patients, 2, 3, 1 and 1 (total seven) patients dropped out of the trial from the respective groups.

Group I received oral tablets containing active ingredients along with the topical aqueous gel formulation containing active ingredients.

Group II received oral tablets containing active ingredients along with the topical cream formulation containing active ingredients.

Group III received oral tablets containing active ingredients with placebo topical preparation.

Group IV received placebo tablets with placebo topical preparation.

2.3. Dosage and care regimen

After completing the clinical examination, each patient in group I, II and III was given a packet with 28 tablets containing active ingredients and in group IV the placebo tablets. Sufficient amount of topical preparation to last at least for a week was given in a collapsible tube to each patient in-group II and I. They were explained in their local language to take two tablets twice daily and to apply the topical preparation twice daily on affected area. Total duration of study was 4 weeks.

The patients were directed not to take any other medication and not to use any antimicrobial agent containing soap or any cosmetics during the trial without investigator's permission. They were asked to report to the clinic every 7th day for a period of 4 weeks.

2.4. Clinical evaluation

A single physician recorded all the clinical observations using global assessment scale (Burke and Cunliffe, 1984), suitably modified in view of small number of patients for evaluation. In this, patient's overall change in facial acne compared with his or her appearance at the beginning of the study was made on a four-point scale ranging from 'excellent' to 'poor' response. This scale was being used in the trial center for quite some time and therefore had been validated.

1. Good to excellent, substantial improvement in pimples or acne blemishes.
2. Slight to fair improvement of pimples or acne blemishes.
3. Variable (sometimes good, sometimes poor) response.
4. No change or worse.

Recording by a single physician was intended to achieve uniformity in grading. The investigator also recorded adverse drug reactions if any, such as, symptoms of gastrointestinal upset, nausea and skin allergy occurring during the course of trial.

Patient compliance was assessed by counting the unused tablets and weight of the tube rendered by patients on the 7th day.

3. Results

Demographic distribution of the patients included in the study is shown in Table 1. The clinical changes (after decoding) at the end of the treatment are depicted in Table 2. In all, 46 patients completed the study and there were seven dropouts. None of the patients were non-compliant with respect to drug administration and application.

Statistical analysis: Clinical changes (data derived in rating scale not enclosed) were analyzed using one sided '*t*'-test viz. Monotone test (Lehman, 1952). The test compared the attribute i.e. decrease in pimples or acne blemishes for the two product combinations (Tablet + Cream versus Tablet + Gel) in two independent groups. Responses indicating 'no change or worse' (D in scale) and 'variable response' (C in scale) were not considered in the analysis. Also, a non-parametric test, i.e. Wilcoxon Rank Sum Test (Bolton, 1997), was performed under the assumption that the observations are independent. The P value $0.020 < 0.022$ (95% confidence intervals) signified that the treatment with combination of tablet + cream was more efficacious than with the combination of tablet + gel.

Levene's test for the equality of variance showed the F-value to be $0.064 < 0.802$ indicating that the variability between two groups was not significant. Assuming that the combination consisting of tablet and cream is superior to the combination of tablet + gel, the analysis showed that the value calculated was 2.14 and at 5% level of significance, the P value was 0.020 which is less than 0.05 indicating that treatment with combination of tablet and cream was more efficacious than with a combination of tablets and gel.

4. Discussion

It was observed that the combined treatment of tablets and topical formulation showed better results than the tablets alone. In the combination therapy, Tablets + Cream showed better results than Tablets + Gel therapy. This can be explained on the basis of histopathology of the pustules, papules and comedones, all of which contain fatty sebaceous secretions and are keratinized (Knutson, 1974; Kigman, 1978). Oil in water creams has been reported to improve penetration as compared to the gels under these circumstances (Makee et al., 1945). Placebo did not show any effect. It has been also observed that the reduction in number of inflammatory lesions is more prominent than for non-inflammatory lesions.

In group I (i.e. Tablet + Gel), 31.58% of patients showed 'good to excellent' improvement in lesions, 63.16% showed 'slight to fair' improvement in lesions, 5.26% showed variable response.

In group II (i.e. Tablet + Cream) 57.89% showed 'good to excellent', 26.32% showed 'slight to fair' response, 15.79% showed variable response.

In group III (i.e. Tablets alone) not a single patient showed 'good to excellent response', 100% showed 'slight to fair' improvement in lesions.

In group IV (i.e. Placebo tablets alone) there was no improvement in the lesions.

The physician also recorded some interesting findings, which are elaborated below:

Table 1
Demographic characteristics of the patients completing the trial

Description	Group I ($n = 21$)	Group II ($n = 20$)	Group III ($n = 4$)	Group IV ($n = 1$)
Age (years)				
Mean	19.71	21.04	19.08	18.5
Range	13–30	15–29	15–24	18–19
Body weight (Kg)				
Mean	55.66	51.47	42.80	47.00
Range	36–88	44–68	37–47	43–51
Systolic and diastolic Blood pressure				
Mean	114.14/76.95	115.52/71.56	115/72	115/75
Diet				
Vegetarian	72%	74%	100%	100%
Non-vegetarian	28%	26%	0%	0%

Figures excluding seven drop outs.

Table 2
Summary of treatment effects on groups (expressed as % cured)

Clinical changes at the end of the treatment	Group I ($n=21$)	Group II ($n=20$)	Group III ($n=4$)	Group IV ($n=1$)
Clinically healed (A)[a]	31.58	57.89	0.00	0.00
Clinically improved (B)[b]	63.16	26.32	100.00	0.00
Variable results (C)[c]	5.26	15.79	0.00	0.00
No change or worse (D)[d]	0.00	0.00	0.00	100.00
Total	100	100	100	100

Figures excluding seven dropouts.
[a] Good to excellent, substantial decrease in pimples or acne blemishes (4).
[b] Slight to fair decrease in pimples or acne blemishes (3).
[c] Variable (sometimes good, sometimes poor) response (2).
[d] No change or worse (1).

In many patients, the summer season had a positive effect in the development of acne i.e. there was exacerbation. At the same time, an almost equal number of patients stated that they were not influenced by the seasons. In other seasons, in most of the cases, no such inter-relationship was observed.

Even though, most of the authors have found no influence of diet on appearance or aggravation of acne, in the present study, 40% of the patients reported exacerbation of acne due to sweet, oily, pungent or spicy diet. Most of the patient used internal or external home remedies or Over the Counter (OTC) products but did not achieve significant benefits from them. It was also reported that the products containing Benzoyl peroxide and Retinoic acid were found to give redness and pruritis and hence, led to discontinuation of treatment. Some of the acne patients reported that they had associated symptoms like acidity, indigestion, constipation and dandruff.

The drug therapies were well tolerated in all the groups during 4 weeks of treatment. Side effects observed included slight itching in two patients and increase in gastric motility in another two patients. Out of two, one showed mild increase and in the other, there was severe increase in gastric motility. In all four cases (except in the patient with severe increase in gastrointestinal motility) the adverse effect diminished in the course of treatment. The treatment was discontinued for 4 days in a patient with severe gastric motility. No other side effect was observed during the course of treatment.

5. Conclusion

From the treatment point of view, it appears: (1) that the use of combination of internal and external preparations showed better efficacy than use of internal preparation alone; (2) combination of tablets and cream showed better response than the combination of tablets and gel; (3) the control group that was given only placebo tablets did not show any significant improvement.

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