Original Article

The efficacy of oral isotretinoin versus cyproterone compound in female patients with acne and the triad of cutaneous hyperandrogenism: A randomized clinical trial

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Abstract

Background: SAHA (Seborrhea, Acne, Hirsutism and Androgenetic Alopecia) syndrome is a dermatologic disorder, with variant response to treatment. Triad of cutaneous hyperandrogenism included nodulocystic or severe acne, female pattern hair loss and hirsutism.

Aim: The aim of this study is to compare the effectiveness of isotretinoin and cyproterone compound in the treatment of nodulocystic acne, in patients with SAHA syndrome or triad of cutaneous hyperandrogenism.

Materials and Methods: 30 female patients with SAHA syndrome were divided randomly into two groups. Group A was treated with cyproterone compound from day 5 of menstrual cycle onwards for 3 weeks and a week without it and group B received isotretinoin, with a dose of 0.75 mg/kg per day from the beginning of menses onwards for 4 months. The results were evaluated by a blind dermatologist using Acne Severity Index (ASI) score at baseline and monthly for 4 months.

Results: Despite a continuous reduction in ASI score in both the groups, according to both physician ($P = 0.63$) and patient ($P = 0.25$) assessment, cyproterone compound was not statistically more effective than conventional treatment of nodulocystic acne at the end of the study. Side-effects were reported in patients in both groups, generally being mild and tolerable except in two subjects.

Conclusion: This study indicates that cyproterone compound is not superior to isotretinoin in the treatment of nodulocystic acne in patient with SAHA syndrome or triad of cutaneous hyperandrogenism. Indeed, other studies are needed to evaluate the effect of cyproterone compound (regardless of androgen level) and isotretinoin in subjects with only nodulocystic acne.

Key Words: Acne, cyproterone compound, hyperandrogenism, isotretinoin, SAHA

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Received: 10.01.2014, **Accepted:** 20.02.2014

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.148236

INTRODUCTION

Acne as a common dermatologic disorder occurs worldwide. The conventional treatments, such as

How to cite this article: Faghihi G, Jamshidi K, Tajmirriahi N, Abtahi-Naeini B, Nilforoshzadeh M, Radan M, *et al.* The efficacy of oral isotretinoin versus cyproterone compound in female patients with acne and the triad of cutaneous hyperandrogenism: A randomized clinical trial. Adv Biomed Res 2014;3:262.

topical and systemic antibiotics and retinoids, remain the benchmark for the new proposed modalities to be compared with them. Among the common agents, isotretinoin is widely used. However, cyproterone compound plays its role by an antiandrogenic effect in patients with SAHA syndrome.

Clinical manifestations of androgen excess including seborrhea, androgenetic alopecia, hirsutism and acne are very common distressing symptoms in women of reproductive age. SAHA (Seborrhea, Acne, Hirsutism and Androgenetic Alopecia) syndrome is coined for this complex dermatological androgenization syndrome (Seborrhea, Acne, Hirsutism and possibly also, Androgenetic Alopecia).[1-3] The development of sudden-onset acne, acne associated with hirsutism or irregular menses, treatment-resistant acne, acne onset as adult, premenstrual acne flare-ups and inflammatory acne on mandibular line and neck may be associated with hyperandrogenism from several different causes.[4] The two most causes of which are polycystic ovarian syndrome (PCOS) and congenital adrenal hyperplasia.[5-7] The combination of cyproterone acetate (2 mg) and ethinyl estradiol (35 μg) is of proven efficacy in management of symptoms of androgenic alopecia and hirsutism in females. Cyproterone acetate inhibits gonadotropin-releasing hormone (GnRH) and blocks androgen receptors. Due to menstrual alteration and the threat of male fetus feminization, adding of ethinyl estradiol in the compound form is recommended.[8] After the advent of isotretinoin in the early 1970s, a revolution occurred in the treatment of nodulocystic acne and acne unresponsive to oral antibiotics.[9,10] The aim of this study is to compare the effectiveness of isotretinoin and cyproterone compound in patients with SAHA syndrome or triad of cutaneous hyperandrogenism.

MATERIALS AND METHODS

This prospective randomized, double-blinded study was conducted at the department of dermatology, Al-Zahra Hospital in Isfahan, Iran, during April 2012-February 2014. The study was approved by the ethical committee of Isfahan University of Medical Sciences. The research project number was 291042 and it is adhered with the deceleration of Helsinki. We enrolled and assessed the subjects (from 15 to 45 years old) with inflammatory moderate to severe or very severe nodulocystic acne that really need antiandrogens or isotretinoin medico-legally as mild types are not justified to be treated with such therapeutic agents.

Patients with contraindications to receive cyproterone compound including smoking, migraine headaches with aura, and hypertension and contraindications to use isotretinoin including pregnancy, lactation and history of related hypersensitivity were excluded from the study. With regard to type I error (alpha) = 0.05, study power = 80%, and expected difference of 30% in response rate, sample size was calculated as 15 subjects in each group.

The diagnosis was established on the basis of clinical findings. In each group, 15 patients were enrolled. The patients were divided into two different treatment groups, using a table of random numbers to receive either oral isotretinoin or cyproterone compound pills. The patients in group A received cyproterone compound (35 μg ethinyl estradiol and 2 mg cyproterone acetate; Aburaihan pharmaceutical company) from day 5 of menstrual cycle onwards (for 3 weeks on, and a week off) and the patients in group B received isotretinoin (Iso-Tret® Hexal Company, Germany), at a dose of 0.75 mg/kg per day. The latter drug was administered from the beginning of menses onwards. All the recruited patients received azithromycin (250 mg daily for 2 weeks each month for 4 months) plus topical clindamycin 1% solution on routine basis. The duration of treatment was 4 months in both groups. The clinical response was evaluated by a dermatologist blinded to the clinical trial identifications before the initiation of the treatment and monthly for 4 months using Acne Severity Index score (ASI)[11]. According to this method, ASI is calculated as below:

2 × pustules + papules + 1/4 × comedones

In order to perform patient satisfaction surveys, the assessment of the treatment was conducted by patient-based satisfaction at the 16th week of treatment (Patient Global Assessment [PGA]). The improvement was scored from 0 (as no improvement) to 10 (as the best possible improvement).

For isotretinoin users, laboratory tests including serum levels of fasting lipids and liver function (LFT) were performed at the beginning and monthly throughout the course of treatment. The statistical analysis was done by SPSS by using chi-square, repeated measures ANOVA and independent *t*-test. The significance level was set at a *P* value of less than 0.05.

RESULTS

The demographic characteristics of our patients are shown in Table 1. At the end of the study two subjects (two from thirty) failed to complete the study. There were one subject with severe nausea and gastrointestinal upset in group A and one subject in group B with severe headaches. We recruited the

eligible patients and designed a flow-chart diagram through our study as shown in Figure 1. The remaining (28 from 30) completed the study. The mean age of patients was 25.2±8.1 years in group A and 26.6±6.3 years in group B. The mean ASI score before treatment was not statistically different between the two groups ($P = 0.73$). A steady decrease in the mean ASI score in both groups was detected. By means of repeated measure ANOVA test, the reduction in ASI values from the base to the end of the study in both group A ($P = 0.01$) and group B ($P = 0.015$) was confirmed. By Independent t test, at the end of first month, patients in group A were more likely experienced improvement ($P = 0.003$), but no statistically significant difference at the end of second month ($P = 0.41$), third month ($P = 0.503$) and forth month ($P = 0.62$) was noted [Table 2]. With regard to the scores from 0 to 10 by the PGA at the end of the study, patients reported scores greater than 5 were 12 (86%) and 10 (71%) subjects in group A and group B, respectively [Table 3]. In addition, nobody in both groups reported satisfaction less than 4 according to PGA score. However, by means of independent t test, patient's satisfaction survey was compatible with dermatologist evaluation. Side-effects reported in patients in group A were generally mild and tolerable, except one subject with severe nausea and gastrointestinal upset that gave up the study. Other side effects in group A include: Breakthrough and premature bleeding, mild breast tenderness and hardness, headache. In group B, only one subject with severe headache gave up the study and other side effects in this group were generally mild (e.g. cheilitis, xerosis).

Table 1: Demographic characteristics of patients in two treatment groups

Group	Group A (cyproterone compound)	Group B (isotretinoin)
Number(female)	14	14
Mean age(range)	25.2 (17-40)	26.6 (17-39)
Skin phototype		
2	1	1
3	8	9
4	5	4
Previous treatment*		
Positive	12	11
Negative	2	3

*Past medical history of acne treatment at last six months prior of study initiation

Table 2: Acne parameters of comparison of cyproterone compound and isotretinoin

Group	A*		B**		*P* value
	Mean ± SE	95% CI	Mean ± SE	95% CI	
Time start	54.3±0.4	53.5-55.1	54.45±0.3	53.65-55.25	0.73
1st month	38.45±0.28	37.65-39.25	49.49±0.22	48.69-50.29	0.003
2nd month	32.1±0.28	31.3-32.9	31.87±0.2	31.07-32.67	0.41
3rd month	24.118± 0.2	23.318-24.918	23.157±0.18	22.357-23.957	0.503
4th month	14.118±0.25	13.318-14.918	14.157±0.2	13.357-14.957	0.62
ASI score change	38.2±0.22		39.1±0.1		0.25

*Group A = Cyperoterone compound **Group B = Isotretinoin

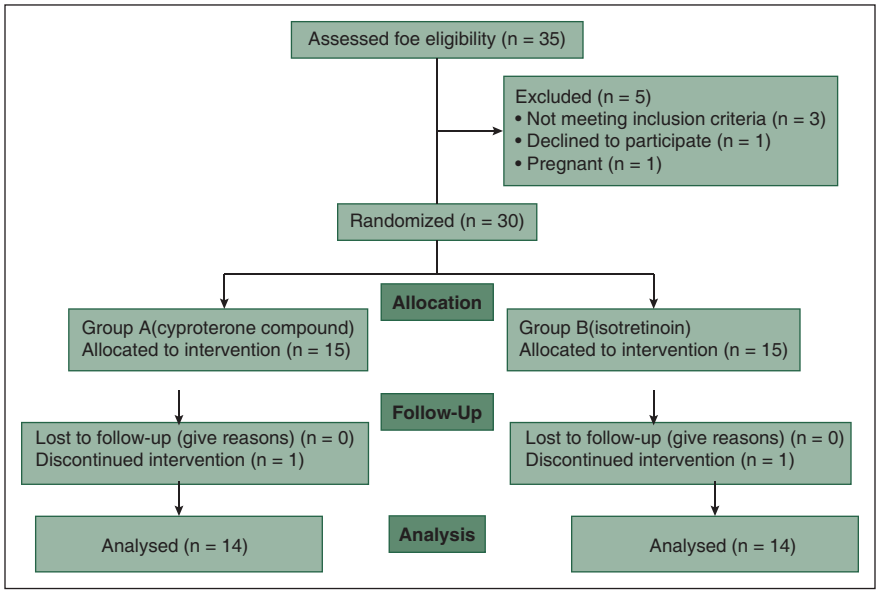

Figure 1: Consort chart of the study

Table 3: Comparison of distribution pattern of PGA between two treatment groups (Significant score level >5)

Group	A		B		*P* value
weak	*n* (%)	95% CI (%)	*n* (%)	95% CI (%)	
4	4 (28)	5-55	3 (21)	3-46	34
8	8 (57)	27-87	6 (43)	13-73	23
12	10 (71)	44-98	8 (57)	27-87	22
16	12 (86)	64-96	10 (71)	44-88	19

DISCUSSION

Our results showed that there were no significant differences between using isotretinoin and cyproterone compounds in the treatment of acne in patients with SAHA syndrome or triad of cutaneous hyperandrogenism. In fact, isotretinoin acts not only by inhibiting the maturation of the basal sebaceous gland cells, but also by normalization of follicular keratinization.[12-16] Hormonal effects on sebum secretion are the key to the pathogenesis of acne. The conjectural role of hormones has been revealed in the pathogenesis of acne by the detection of androgen receptors in the cells of the basal layer of the sebaceous gland and the outer root sheath of the hair follicle.[12] Despite the fact that isotretinoin is widely used as a conventional therapy for nodulocystic acne, the overall outcome remains incomplete and partially effective. Approximately 40-60 of patients demand therapy after a single course of isotretinoin.[4] Amichai *et al*. showed that isotretinoin 20 mg/day was effective in the treatment of moderate acne, with a low incidence of severe side effects. This study emphasized on the long-term low-dose isotretinoin in the treatment of acne.[17] In another study conducted by Sardana *et al*., 6 months of treatment with alternate-day isotretinoin 20 mg plus topical 1% clindamycin gel was effective in the treatment of moderate acne.[18] Some clinicians advocate the use of high-dose isotretinoin (>1.3 mg/kg/day) for treatment of severe nodulocystic acne and encourage large, prospective, multicenter studies into this therapeutic approach.[19] In Muhammad Tahir's study, clinical improvement was 100% at the end of 16 weeks treatment with isotretinoinin 250 ordinary acne patients (without obvious hyperandrogenism signs) but all of the patients (100%) had suffered from some adverse effects.[20] Treatment failures with isotretinoin in female patients are frequently related to endocrinological dysfunctions. Apart from isotretinoin, hormonal interventions are considered as the second-line treatment for female patients with acne, regardless of serum levels of androgens.[12] However, women with identifiable endocrinologic conditions and those with severe acne are the best candidates for hormonal therapy.[21-24] In addition to inhibiting the secretion of follicle-stimulating hormone and luteinizing hormone, another interesting mechanism by which cyproteronacetate is therapeutic is interfering with the binding of dihydrotestosterone to the androgen receptor due to the possibility of menstrual changes.[8] Despite the earlier reduction in the value of the ASI at the end of first month in the subjects of group A (*P* value = 0.03), by statistical analysis no significance difference was found between two groups at the end (*P* value = 0.62).

Despite the fact that hormonal modality is formed the second-line treatment for female patients with acne, in subjects with obvious hyperandrogenism, cyproterone compound makes the same response as the isotretinoin.

In summary, this study shows that cyproterone compound and isotretinoin begin to act from two different ways, meet in the middle and by the end have a nearly similar effect. On one hand, the use of oral isotretinoin should ensure excellent efficacy for acne lesions in patients with triad of cutaneous hyperandrogenism, and on the other hand, it is not necessary to demonstrate androgen excess to achieve the benefit from antiandrogen therapy in acne.

With regard to insignificant and negligible differences between the results of isotretinoin and cyproterone compound trial in the treatment of subjects with acne and hyperandrogenism in our study, it is advisable in future studies to compare cyproterone compound regardless of androgen level verses isotretinoin in subjects with only nodulocystic acne.

Limitations

The greatest limitation of our study is in the field of case selection as the triad of hyperandrogenism should have been fulfilled clinically before entering into the study. The other one was the cost and also rarity of some brands of the drugs, and the vague public and folkloric view toward side effects of such oral therapy in cases of severe acne that made for us the great responsibility to verifying their recruitment for the trial.

ACKNOWLEDGEMENTS

We are very grateful to dear staff of Sadaf dermatology Center of Isfahan for their helpful assistance.

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Source of Support: Skin Diseases and Leishmaniasis Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. **Conflict of Interest:** None declared.