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Original Article

COMPARING THE EFFECTIVENESS OF ORAL ISOTRETINOIN AND CYPROTERONE COMPOUND IN ACNE TREATMENT AMONG ADULT FEMALES WITH CUTANEOUS HYPERANDROGENISM: A PROSPECTIVE STUDY.

[1]Smita Rani Samal, [2]Sujeet Kumar Singh, [2]Itismita Sahu, [3]Swadesh Kumar Mohanty[*]
[1]Assistant Professor, Department of Dermatology, SCB Medical College and Hospital, Cuttack, India
[2]Senior Resident, Department of Dermatology, SCB Medical College and Hospital, Cuttack, India
[3]Senior Resident, Department of Pulmonary Medicine, Sleep and Critical Care, All India Institute of Medical Sciences, Bhubaneswar, India

ABSTRACT.

Background:
Acne is a complex illness caused by androgenic stimulation of the sebaceous glands. As a result, combined oral contraceptives (COCs) including anti-androgenic progestogens are good candidates for acne treatment. The purpose of this study is to compare the effectiveness of oral isotretinoin and cyproterone compound in the treatment of nodulocystic acne, in adult females with signs of cutaneous hyperandrogenism.

Materials and Methods:
Thirty female patients with SAHA syndrome were randomly assigned into two groups of fifteen each. Group A got cyproterone compound (35 µg ethinyl estradiol and 2mg cyproterone acetate) starting day 5 of the menstrual cycle. Group B got isotretinoin at a dose of 0.5mg/kg daily. All recruited patients got topical benzoyl peroxide 3.5% gel regularly. SPSS was used to do statistical analysis. P-values < 0.05 were considered significant.

Results:
Despite a consistent reduction in ASI score in both groups, according to both physician (P = 0.63) and patient (P = 0.25) assessment, the cyproterone compound was not statistically more successful than traditional treatment of nodulocystic acne at the end of the trial. Patients in both groups reported minor and acceptable side effects, except in two cases.

Conclusion:
This study found that cyproterone compound is not more effective than isotretinoin in the treatment of nodulocystic acne in patients with SAHA syndrome or cutaneous hyperandrogenism. Indeed, additional research is needed to assess the efficacy of cyproterone molecules (independent of testosterone level) and isotretinoin in people with just nodulocystic acne.

Recommendation:
Oral isotretinoin is recommended for treating nodulocystic acne in patients with cutaneous hyperandrogenism due to its comparable efficacy to cyproterone compound and established effectiveness in reducing acne lesions. Further research should compare these treatments regardless of androgen levels in nodulocystic acne patients.

Keywords: *Acne, Cyproterone compound, Hyperandrogenism, Isotretinoin*
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Corresponding author: *Swadesh Kumar Mohanty*
Email: *dr.swadeshmohanty@gmail.com*
Senior Resident, Department of Pulmonary Medicine, Sleep and Critical Care, All India Institute of Medical Sciences, Bhubaneswar, India.

INTRODUCTION

Seborrhea, androgenetic alopecia, hirsutism, and acne are often observed as symptoms of excess androgen in women of reproductive age, causing significant suffering. The term SAHA (Seborrhea, Acne, Hirsutism, and Androgenetic Alopecia) syndrome is used to describe this intricate dermatological condition characterized by excessive androgen activity, resulting in symptoms such as seborrhea, acne, hirsutism, and potentially androgenetic alopecia. The list [1,2,3] Hyperandrogenism from various causes may be linked to the development of sudden-onset acne, acne

associated with hirsutism or irregular menses, treatment-resistant acne, acne start in adulthood, premenstrual acne flare-ups, and inflammatory acne on the mandibular line and neck [4]. The two primary causes are polycystic ovarian syndrome (PCOS) and congenital adrenal hyperplasia [5,6,7]. The use of cyproterone acetate (2 mg) and ethinyl estradiol (35 µg) has been scientifically demonstrated to control symptoms of androgenic alopecia and hirsutism in females effectively. Cyproterone acetate suppresses the activity of gonadotropin-releasing hormone (GnRH) and hinders the functioning of androgen receptors. It is advisable to include ethinyl estradiol in compound form due to changes in menstruation and the potential risk of feminization in male fetuses [8]. The introduction of isotretinoin in the early 1970s brought about a significant change in the way nodulocystic acne and acne that doesn't respond to oral antibiotics are treated [9-11]. This study aims to assess the comparative efficacy of isotretinoin and cyproterone compounds in patients diagnosed with SAHA syndrome or the triad of cutaneous hyperandrogenism.

MATERIALS AND METHODS.

Study design

A prospective randomized, double-blinded study.

Study site

Department of Dermatology, SCB Medical College and Hospital, Cuttack

Study duration

December 2014 – December 2015.

Study setting

The present research was conducted at the Department of Dermatology, SCB Medical College and Hospital, Cuttack, from December 2014 to December 2015. The study received approval from the ethical committee of SCB Medical College. We recruited and evaluated individuals (aged 15 to 45) who had moderately to severe or very severe nodulocystic acne and required antiandrogens or isotretinoin as a medical necessity, as milder forms of acne do not warrant treatment with these specific medications.

Inclusion criteria

Females with hyperandrogenism who visited the outpatient department of age between 15 and 45 are included in this randomized trial.

Exclusion criteria

Participants with contraindications to isotretinoin, such as pregnancy, nursing, or past experiences of associated hypersensitivity, were not allowed to participate in the research. Contraindications to receiving cyproterone compound included smoking, migraine headaches with aura, hypertension, and migraines.

Sample size

To calculate the sample size for this study, the following formula was used for estimating a proportion of a population:

$$n = \frac{Z^2 \times p \times (1-p)}{E^2}$$

Where:
- n = sample size
- Z = Z-score corresponding to the desired level of confidence
- p = estimated proportion in the population
- E = margin of error

Bias

There was a chance that bias would arise when the study first started, but it was avoided by giving all participants identical information and hiding the group allocation from the nurses who collected the data.

Study method

A diagnosis was determined based on the clinical evaluations. Fifteen patients were included in each group. Individuals were allocated into two distinct therapy cohorts, via a table of randomized numbers, to get either oral isotretinoin or cyproterone compound tablets.
The individuals in group A were administered a cyproterone compound consisting of 35 µg of ethinyl estradiol and 2 mg cyproterone acetate from day 5 of their menstrual cycle onwards. This treatment was given for 3 weeks, followed by a week off. On the other hand, the patients in group B were given isotretinoin at a dosage of 0.75 mg/kg per day. The latter medication was given starting from the onset of menstruation. Every patient who was recruited got a daily dose of azithromycin (250 mg) for 2 weeks each month, for a total of 4 months. In addition, they were also given a routine application of topical clindamycin 1% solution. Each group underwent a 4-month therapy period. The clinical outcome was assessed by a dermatologist who was unaware of the clinical trial's identifications. This assessment was done before the start of the treatment and continued monthly for 4 months. The Acne Severity Index score (ASI) was used to measure the degree of acne.

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Statistical analyses

Surveys and questionnaires were undertaken to evaluate the treatment. The evaluation relied on patient-based satisfaction at the 16th week of treatment, using the Patient Global Assessment (PGA). The degree of improvement was assessed on a scale of 0 (indicating no improvement) to 10 (representing the highest level of improvement achievable). Isotretinoin users had laboratory testing, particularly measurements of fasting lipids and liver function (LFT), at the start of treatment and monthly thereafter. The statistical evaluation was conducted with SPSS, employing chi-square, repeated measures ANOVA, and an independent t-test. The statistically significant level was established using a threshold of a P value below 0.05.

Ethical considerations.

The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

RESULTS

Table 1: Presents the demographic features of patients who were divided into two therapy groups.

Group	Group A (cyproterone)	Group B (isotretinoin)
Number (Female)	15	15
Mean age (range)	25.0 (17-40)	26.5 (17-39)
Skin prototype		
2	1	1
3	9	10
4	5	4
Past treatment		
Negative	3	4
Positive	12	11

In this study, the demographic characteristics of patients were compared between two therapy groups: Group A, treated with cyproterone, and Group B, treated with isotretinoin. Each group consisted of 15 female patients. The mean age of patients in Group A was 25.0 years, with a range of 17 to 40 years, while the mean age in Group B was slightly higher at 26.5 years, with a range of 17 to 39 years. The distribution of skin prototypes among the patients revealed that Group A had 1 patient with prototype 2, 9 patients with prototype 3, and 5 patients with prototype 4. In comparison, Group B had a similar distribution with 1 patient with prototype 2, 10 patients with prototype 3, and 4 patients with prototype 4. Regarding past treatments, 3 patients in Group A had negative past treatment experiences, whereas 12 had positive past treatment experiences. Similarly, in Group B, 4 patients had negative past treatment experiences, and 11 had positive ones. This demographic analysis provides a comprehensive overview of the patient characteristics in each treatment group.

Table 2: Parameters of comparison of cyproterone and isotretinoin.

Group	A		B		P-value
	Mean ± SD	95% CI	Mean ± SD	95% CI	
Time	54.3 ± 0.4	53.5 - 55.0	54.5 ± 0.3	53.6 - 55.25	0.72
1st month	38.5 ± 0.3	37.5 - 39.3	49.5 ± 0.2	48.7 - 50.3	0.003
2nd month	32.1 ± 0.3	31.3 - 33.0	31.9 ± 0.2	31.1 - 32.7	0.40
3rd month	24.12 ± 0.2	23.39 - 25.0	23.16 ± 0.2	22.4 - 24.0	0.50
4th month	14.19 ± 0.25	13.3 - 14.9	14.15 ± 0.2	13.4 - 14.9	0.62
ASI score change	38.2 ± 0.20		39.1 ± 0.1		0.25

The study compared the parameters of cyproterone and isotretinoin over several time points. At baseline, the mean score for Group A was 54.3 ± 0.4 with a 95% confidence interval (CI) of 53.5 - 55.0, while Group B had a mean score of 54.5 ± 0.3 and a 95% CI of 53.6 - 55.25, resulting in a p-value of 0.72. At the 1st month, Group A's mean score was

38.5 ± 0.3 (95% CI: 37.5 - 39.3) compared to Group B's 49.5 ± 0.2 (95% CI: 48.7 - 50.3), with a significant p-value of 0.003. By the 2nd month, the mean scores were 32.1 ± 0.3 (95% CI: 31.3 - 33.0) for Group A and 31.9 ± 0.2 (95% CI: 31.1 - 32.7) for Group B, yielding a p-value of 0.40. In the 3rd month, Group A had a mean score of 24.12 ± 0.2 (95% CI: 23.39 - 25.0) and Group B had 23.16 ± 0.2 (95% CI: 22.4 - 24.0), with a p-value of 0.50. By the 4th month, the mean scores were 14.19 ± 0.25 (95% CI: 13.3 - 14.9) for Group A and 14.15 ± 0.2 (95% CI: 13.4 - 14.9) for Group B, resulting in a p-value of 0.62. The ASI score change was 38.2 ± 0.20 for Group A and 39.1 ± 0.1 for Group B, with a p-value of 0.25.

Table 3: Difference of distribution pattern of PGA among groups.

	Group A (n= 15)	Group B (n= 15)	P-value
Week 4	4 (27%)	3 (20%)	34
Week 8	8 (53%)	6 (40%)	23
Week 12	11 (73%)	9 (60%)	22
Week 16	13 (86.6%)	11 (73.3%)	19

The distribution pattern of PGA among groups A and B was analyzed over 16 weeks. At week 4, 27% (4 out of 15) of Group A and 20% (3 out of 15) of Group B showed improvement, with a p-value of 0.34. By week 8, the proportions increased to 53% (8 out of 15) for Group A and 40% (6 out of 15) for Group B, with a p-value of 0.23. At week 12, 73% (11 out of 15) of Group A and 60% (9 out of 15) of Group B showed improvement, resulting in a p-value of 0.22. Finally, at week 16, 86.6% (13 out of 15) of Group A and 73.3% (11 out of 15) of Group B showed improvement, with a p-value of 0.19.

DISCUSSION

The findings of our study indicate that there were no statistically significant disparities in the efficacy of isotretinoin and cyproterone compounds for treating acne in individuals with SAHA syndrome or triad of cutaneous hyperandrogenism. Isotretinoin functions by not only preventing the development of the basal sebaceous gland cells but also by restoring the normal process of follicular keratinization. The given sequence is [12, 13, 14, 15, 16]. The pathophysiology of acne is mostly driven by the hormonal influences on sebum secretion. The presence of androgen receptors in the cells of the basal layer of the sebaceous gland and the outer root sheath of the hair follicle has provided evidence for the involvement of hormones in the development of acne [12]. Although isotretinoin is commonly used as a traditional treatment for nodulocystic acne, the overall results are still inadequate and only partially successful. Approximately 40-60% of people require therapy following a single session of isotretinoin [4]. A study demonstrated the efficacy of a daily dose of 20 mg of isotretinoin in treating moderate acne, while also noting a minimal occurrence of serious adverse reactions. This study focused on the use of low-dose isotretinoin over a lengthy period for treating acne.[17] In a separate research carried out, a six-month course of alternate-day administration of isotretinoin at a dosage of 20 mg, in combination with topical application of clindamycin gel at a concentration of 1%, demonstrated efficacy in treating mild acne [18]. Certain medical professionals support the administration of high-dose isotretinoin (>1.3 mg/kg/day) as a treatment for severe nodulocystic acne. They also recommend conducting extensive, prospective, multicenter trials to further investigate this therapeutic method [19] According to research, all 250 typical acne patients (without clear symptoms of hyperandrogenism) showed complete clinical recovery after 16 weeks of treatment with isotretinoin. However, all of these patients (100%) experienced some negative effects [20] Treatment failures with isotretinoin in female patients often occur due to endocrinological dysfunctions. In addition to isotretinoin, hormonal therapies are regarded as the secondary therapy option for female patients with acne, irrespective of their blood testosterone levels [12]. Nevertheless, those who have identified endocrinologic problems and those who have severe acne are the most suitable candidates for hormone therapy. The given text represents a list of numbers: 21, 22, 23, and 24. Cyproterone acetate has a therapeutic effect by not only suppressing the release of follicle-stimulating hormone and luteinizing hormone but also by disrupting the binding of dihydrotestosterone to the androgen receptor, which may lead to menstrual abnormalities [8]. Although there was a decrease in the value of the ASI at the end of the first month for the patients in group A (P value = 0.03), statistical analysis did not find any significant difference between the two groups at the end (P value = 0.62).

Although hormone therapy is typically used as a second-line treatment for female patients with acne, in individuals with evident hyperandrogenism, the cyproterone molecule elicits a similar reaction to isotretinoin.

CONCLUSION

Our work demonstrates that the cyproterone compound and isotretinoin exert their effects through distinct mechanisms, converge at a certain point, and ultimately provide a comparable outcome. Oral isotretinoin is highly effective in treating acne lesions in people with cutaneous hyperandrogenism. Additionally, it is not required to prove androgen excess to benefit from antiandrogen medication for acne. In light of the minimal and inconsequential disparities observed in our study between the outcomes of the isotretinoin and cyproterone compound trials for treating individuals with acne and hyperandrogenism, it is recommended that future studies focus on comparing cyproterone compound, irrespective of androgen levels, against isotretinoin specifically in individuals with nodulocystic acne.

LIMITATIONS

The main constraint of our investigation lies in the area of case selection since the triad of hyperandrogenism needed to be clinically confirmed before participation in the study. Another factor was the high cost and limited availability of certain prescription brands, as well as the general public's and folklore's unclear perception of the side effects associated with oral therapy for severe acne. These factors imposed a significant obligation on us to thoroughly check the recruitment of participants for the experiment.

RECOMMENDATIONS

Based on the findings, oral isotretinoin is recommended for the treatment of nodulocystic acne in patients with cutaneous hyperandrogenism due to its comparable efficacy to the cyproterone compound, along with its well-established mechanism and effectiveness in reducing acne lesions. Further research should focus on comparing these treatments irrespective of androgen levels in patients with nodulocystic acne.

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LIST OF ABBREVIATIONS

COCs: Combined Oral Contraceptives
SAHA: Seborrhea, Acne, Hirsutism, Androgenetic Alopecia
ASI: Acne Severity Index
PGA: Patient Global Assessment
GnRH: Gonadotropin-Releasing hormone
PCOS: Polycystic Ovarian Syndrome
LFT: Liver Function Test

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CONFLICT OF INTEREST

The authors have no competing interests to declare.

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