

A Comparative Study of Diane-35 plus Spironolactone and Diane -35 Plus Finasteride in Cases of Hirsutism and Acne

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To compare the efficacy and safety of Diane 35 plus spironolactone and Diane 35 plus finasteride in the treatment of hirsutism and acne. **Materials and Methods:** A prospective randomized clinical trial was conducted on 120 Indian women with hirsutism. Group I patients were treated with Diane 35 plus spironolactone 100 mg daily and group II patients with Diane 35 plus finasteride 5 mg daily for 12 months. Hirsutism and acne score were graded every 3 months, for 18 months. The basal gonadotropins levels and androgens level were measured before the study. Statistical analysis was done by Student's t-test and repeated measure analysis followed by post hoc comparison. **Results:** Reduction in hirsutism and acne scores assessed every 3 months was significant ($p < 0.001$) and similar between the two groups, indicating that if treatment was prolonged for over 12 months, reduction scores would have been better. A significant decrease in the hirsutism score of $55.3\% \pm 17.2$ and $59.4\% \pm 17.5$ was observed after 12 months in groups I and II respectively. Total reduction in hirsutism & acne scores of both groups was similar ($P > 0.05$). **Conclusion:** Diane 35 plus spironolactone and Diane 35 plus finasteride are equally effective and safe in the treatment of hirsutism and acne. For better outcomes, it is recommended that the treatment period be over 12 months.

Key Words: Hirsutism, Treatment, Diane 35,

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Introduction

Hirsutism, defined as the excess of terminal hair in the male distribution pattern in women, is due to increases in circulating androgen concentration or an increase in the sensitivity of the pilosebaceous unit to normal androgen concentration or a combination of these factors.¹ It is an important clinical and psychological problem affecting 5% to 10% of women, depending on their ethnicity.²

Of the many treatment options including mechanical and pharmacological ones available for the management of hirsutism, the most reliable therapeutic tool in hirsute women is use of antiandrogen drugs, usually in association with combined oral contraception pills.³

Diane-35, used in the treatment of hirsutism since many years, consists of a combination of ethinyl estradiol (35µg) and Cyproterone acetate (2 mg). Ethinyl estradiol increases levels of sex hormone binding globulin (SHBG) which binds to free testosterone, thus reducing the levels of circulating testosterone. Cyproterone acetate is the powerful progesterone that also acts as an antiandrogen at target sites and has an antigonadotrophic

action.⁴ Minimal gastrointestinal distress and headache are noticed in patients on Diane therapy.

Spironolactone is an antiandrogen which competes with dihydrotestosterone (DHT) for androgen receptors in the skin. It also increases the metabolic clearance of testosterone and inhibits androgen production.⁵ Hyperkalemia may occur in patient on Spironolactone treatment. Another antiandrogen, finasteride, is a very potent competitive inhibitor of the type 2 isoenzyme of 5 alpha reductase and this enzyme is responsible for the conversion of testosterone to the active metabolite Dihydrotestosterone (DHT).⁶ Reduction in DHT concentration helps in reduction of hirsutism score. Altered liver function may be observed in patients on prolonged treatment with finasteride.

To date there is no definite solution or permanent medical cure for hirsutism and acne. Diane-35 per se is the old golden standard for treatment of these conditions. However many investigators believe that, in combination, antiandrogen and Diane 35, have a synergistic effect and hence better outcomes.⁷ Various studies have been conducted to observe the synergistic effects but none have compared the effects of Diane-35 plus spironolactone and Diane-35 plus Finasteride, and no definite data is documented regarding the treatment duration of antiandrogens in cases of hirsutism. The 2009 Cochrane review reports that there is no evidence of effectiveness of antiandrogen for treatment of acne vulgaris.⁸ The present prospective randomized clinical trial was conducted to compare the effects of Diane-35 plus spironolactone and Diane-35 plus finasteride in cases of hirsutism with modified Ferriman-Gallway scores of 8 and more. The effects of the above were also compared on acne in cases of hirsutism with acne.

Materials and Methods

This prospective randomized clinical trial was conducted on 120 Indian women, of reproductive age (16-40 years), who presented

with hirsutism, at the outpatient gynecology endocrine clinic. They were recruited into the study following obtainment of informed consent. The study was approved by the Ethical Committee of the All India Institute of Medical Sciences, New Delhi, India. Patients with androgen secreting tumors of ovarian or adrenal origin, Cushing syndrome, thyroid dysfunctions, 21-hydroxylase deficiency, hyperprolactinemia, clitoromegaly or other evidence of virilism and intersex patients were excluded from the study, following detailed clinical and laboratory evaluation. Patients, who for at least 6 months prior to the study had been on medication known to affect pituitary-gonadal function were also excluded from the study. Patients with polycystic ovarian syndrome (PCOS) and idiopathic hirsutism are included in this study. PCOS was diagnosed by Rotterdam ESHRE/ASRM consensus workshop definition [9] Rotterdam definition consists of presence of anovulation or oligo-ovulation, clinical or biochemical evidence of hyperandrogenism and polycystic appearance of ovaries on ultrasonography.⁹ Two out of three criteria are necessary for the diagnosis. Idiopathic hirsutism was diagnosed when patient had a regular ovulatory menstrual cycles, normal androgen level and no other androgen producing tumor or other reason was found. The hirsutism score was graded according to modified Ferriman-Gallway scoring system¹⁰ by the same investigator who was unaware of treatment. The medicine prescribing physician and the investigator who scored hirsutism at each visit were different. Persons with hirsutism scores ≥ 8 , based on the modified Ferriman-Gallway scoring system, were recruited in the study. The choice of treatment for each patient was made using a computerized randomization number table.

Group I (n=60) patients were treated by Diane-35 (ethinyl estradiol 35µg and cyproterone acetate 2 mg) plus spironolactone (100mg). Diane-35 was given from day 5 to 25 of the menstrual cycle, plus spirono-

lactone (100mg) once daily and spironolactone (100mg) was given once daily, while group Group II (n=60) were given Diane 35 (from day 5 to 25 of the menstrual cycle) plus finasteride (5 mg) once daily. We preferred to use the Aldactone brand of spironolactone marketed by RPG and the Fincar brand of finasteride marketed by CIPLA to have uniformity of treatment. Total duration of the therapy was 12 months, and patients were followed up every 3 months until 6 months post therapy (18 months). At each visit, patient was asked for any side effects and hirsutism scoring was evaluated. Acne scoring was also done at each visit as per Indian system¹¹ for patients with acne. Patients were instructed to not undergo any cosmetic treatments, like shaving, waxing, electrolysis or/and laser throughout the treatment course.

A standard hormonal profile, including serum gonadotropins (LH, FSH, TSH, and Prolactin) and androgen (total testosterone (T), DHEAS) & 17OH-P was determined at initiation of the study to exclude other endocrine causes. Blood samples were drawn from the women after overnight fasting at 08.00 in the morning and in the early follicular phase of the menstrual cycle (if cycling regularly) or at a convenient day in those with amenorrhea. At the end 6, 12 and 18 months of the study Total T and DHEAS were again measured. Serum FSH, LH, TSH, and prolactin levels were measured by means of highly specific micro particle enzyme immunoassay (MEIA). Serum total T, DHEAS & 17OH-P levels were determined by RIA. Normal ranges of hormonal level and coefficient of variation (CV) of assays are given in Table 2. Fasting blood sugar and insulin was also measured. Trans-vaginal ultrasonography was performed in all patients except in unmarried patients, for whom trans-abdominal ultrasonography was performed to rule out ovarian or adrenal

tumors or any associated pathology and to diagnose polycystic ovaries. In suspected cases MRI was done to rule out ovarian or adrenal neoplasm and these patients were excluded from the study.

For statistical analysis, Students' t-test and repeated measure analysis followed by post hoc comparison was done, a p value <0.05 being considered statistically significant. Normality was checked for the variables. We applied log transformation to determine the possible significance between the two groups and skewed data was normalized.

Results

Detailed analysis of the study revealed that 5 patients in group I and 3 patients in group II discontinued the treatment. Five patients in group I discontinued the treatment because of side effects, like mild hypertension in 1 (1.7%), depression in 1 (1.7%) and severe nausea & vomiting in 3 (5.5%). In group II, 3 patients discontinued the treatment because 1 (1.7%) patient had edema on the feet, while 2 (3.3%) had severe nausea & vomiting.

Mean age of the study group was 22.8 ± 5 years (range 16-40 years). Majority (72.5%) of the patients were unmarried. Hirsutism was found more in highly educated (graduates and above) women (70.9%) as compared to those with low levels of literacy; it was also more prevalent (74.2%) in higher socioeconomic strata (monthly family income over Rs. 20,000). Clinical characteristics of patients are shown in Table 1; all characteristics were similar in both the groups ($P > 0.05$), as were distribution of polycystic ovarian disease and idiopathic hirsutism ($p = 0.2$). Baseline median and range (min-max) of serum FSH, LH, TSH, Prolactin, total testosterone, DHEAS fasting blood sugar, fasting insulin and 17-OH progesterone levels are depicted in Table 2, values similar in both groups I and II ($P > 0.05$).

Table 1. Clinical variables before treatment

	Group I (spironolactone) n = 60	Group II (finasteride) n = 60
Age (yr)/range	24.1±5.5 (16-40)*	22.5±4.2 (16-40)
Body Mass Index (kg/m ²)	24.2±6.1	22.8±5.1
Modified Ferriman-Gallway score	11.4±2.8	11.1±2.4
Acne present (n)	20	25
Acne score (mean)	2.8±2	2.8±1.9
Polycystic ovarian Disease (n)	50	55
Idiopathic hirsutism (n)	10	5

Normality of all the variables is maintained as SD is less than ¼ in all the parameters except acne scores in which normality was achieved after log transformation. * Mean±SD

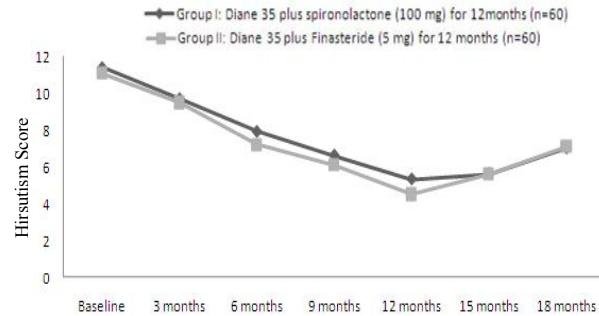
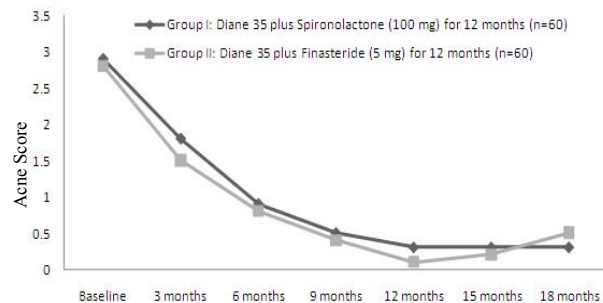
Table 2. Hormonal and biochemical profile before treatment

Variables	Normal Range	Group I (spironolactone) n = 60	Group II (finasteride) n = 60
Serum FSH (mIU/mL)	3.4-21.6	5.4±1.8*	5.6±1.9
Serum LH (mIU/mL)	2.4-6.6	7.9±5.7	9.1±6
TSH (µIU/mL)	0.4-4.9	2.4±1.6	2.9±1.8
Prolactin (ng/mL)	5.2-26.5	15.7±13.6	16.4±8.7
Total testosterone (ng/mL)	0.05-0.7	1.3±1.3	1.1±1
DHEAS (µg/dL)	80-390	212.4±117.6	219.5±126.3
17-OHP (ng/mL)	0.3-2.0	1.3±0.8	1.4±0.8
Fasting blood sugar (mg %)	70-100	84.6±10.2	85.5±8.1
Fasting insulin (IU/mL)	0.3-17	14.2±11.9	11.6±8.2

* Mean±SD

Mean hirsutism scores, before the treatment and at the 3 month intervals, and 18 months were similar between the groups (Fig 1); the change in hirsutism score at every 3 month interval was significant ($p<0.001$) and similar between the two groups. At the end of 12 months, hirsutism scores reduced from 11.4 ± 2.8 to 5.3 ± 2.6 ($55.3\% \pm 17.2$) in group I and from 11.1 ± 2.4 to 4.5 ± 2.1 ($59.4\% \pm 17.5$) in group II.

Similar changes was observed in the acne score as well (Fig 2); acne was present in 20 women (33.3%) of group I and 25 women (41.7%) of group II; mean reductions in acne scores were similar ($p>0.05$) in both groups throughout the treatment period. Change in the acne score, at each interval, was significant ($p<0.001$) and similar between the two groups. Changes in mean reduction in total testosterone and DHEAS levels were similar ($p>0.05$) in both the groups, as shown in Fig 3, 4.

**Fig 1: Hirsutism scores in two groups.****Fig 2: Acne scores in two groups.**

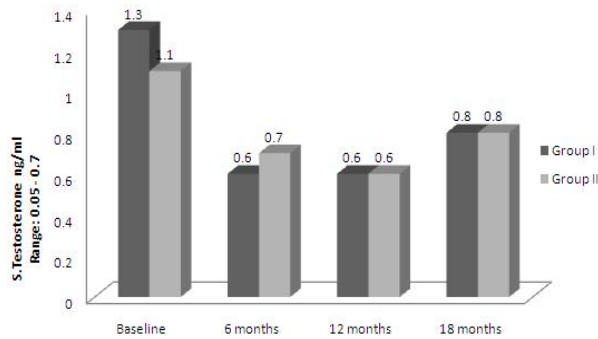


Fig 3: Comparison of testosterone levels in the two groups

Group I: Diane 35 plus spironolactone (100 mg)

Group II: Diane 35 plus finasteride (5 mg)

Discussion

In the present study we compared the treatment of hirsutism and acne using Diane-35 plus spironolactone and Diane-35 plus finasteride, in terms of efficacy & safety. We preferred to add Diane-35 to both the combinations for regular menstrual cycle, to prevent the subjects from getting pregnant and having synergistic effect on androgen levels. Though there are studies which have compared the effects of a combination versus Diane-35 per se, no data is available on the comparison of these two combinations. If we combine antiandrogen with medications of different actions, we can have a synergistic effect and hence better control over hirsutism. Diane-35 has antigonadotrophic effect; antiandrogen affects the targeted site and increases SHBG, thus reducing free testosterone level. On the other hand Spironolactone competes with dihydrotestosterone (DHT) for androgen receptors in the skin. It also increases the metabolic clearance of testosterone and inhibits androgen production.⁵ The other antiandrogen, finasteride acts peripherally and blocks DHT production.⁶

In the present study, the Diane 35+ spironolactone combination reduced hirsutism scores from 11.4 ± 2.8 to 7.9 ± 2.8 , i.e. total reduction of $32\% \pm 16.6$, by 6 months, a finding comparable to the study by Karakurt

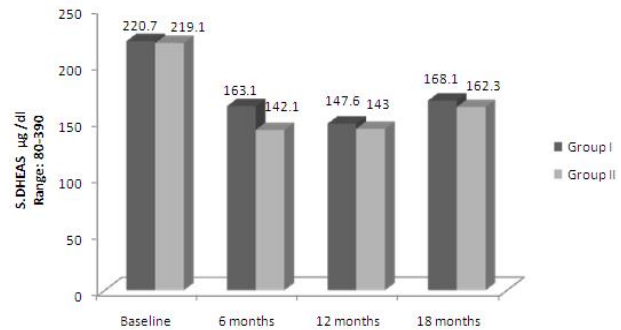


Fig 4: Comparison of DHEAS levels in the two groups.

Group I: Diane 35 plus spironolactone (100 mg)

Group II: Diane 35 plus finasteride (5 mg)

F et al¹², in which the hirsutism score reduced from 9.9 ± 1.9 to 7.1 ± 2 (i.e. 28.3% reduction); at 9 months the score was reduced to 6.6 ± 2.6 (i.e. 43.7% ± 16 reduction). Inal MM et al found a reduction of 22.9% at 9 months¹³, a reduction lower than that of ours; this difference can be explained by the fact that his study investigated cases of idiopathic hirsutism whereas majority (87.7%) of our patients were from the PCOS group. In PCOS, there is hyperandrogenism and the Diane-35+spironolactone combination has better effect on androgen levels; hence total reduction in the hirsutism score is better than in idiopathic hirsutism. At 12 months the score reduced to 5.3 ± 2.6 , i.e. total reduction $55.3\% \pm 17.2$. Kelestimur et al compared Diane-35 alone and Diane-35+spironolactone and found the combination to be better, with reduction in hirsutism scores of $68.8\% \pm 19.6$ (mean % \pm SD) at 1 year.⁷ As compared to the present study, higher reductions in hirsutism score were reported by the Kelestimur et al study; this can be explained by differences of the initial hirsutism score, which was higher than that of our study (17.9 ± 5.3 vs. 11.4 ± 2.8). Higher hirsutism scores indicate higher androgen level or increased sensitivity of pilosebaceous units. Hence after antiandrogen treatment, there is more reduction than that of our study. Besides this effect, at every

3 month interval, there was significant decrease in hirsutism score (Fig 1). This is a very interesting finding, not documented before this. The decreasing trend in the hirsutism score, indicates that had we prolonged the treatment period for over 12 months, we could have better controlled hirsutism and probably have curtailed rebound recurrence.

Another combination Diane-35 plus finasteride reduced the hirsutism score from 11.1 ± 2.4 to 4.5 ± 2.1 (i.e. total reduction $59.4\% \pm 17.5$) at 1 year. Sahin Y et al compared treatments of Diane-35 and Diane-35 plus finasteride and found reduction in hirsutism score of $48.1\% \pm 14.3$ (mean % \pm SD) at 1 year¹⁴, results similar to those of our study. In this group, decrease in hirsutism score every 3 months was significant ($p < 0.001$), showing that treatment for more than 12 months is required for better results.

Comparison of reductions in the acne score followed the same trend observed for the hirsutism score. Both combinations proved equally effective. Fig 2 shows that 12 months treatment is inadequate and prolonged treatment is required to prevent recurrence. Shaw et al conclude that long term use of spironolactone for treatment of acne is safe and effective.¹⁵ There are no reports on the comparable effect of finasteride and Diane-35 in cases of acne with hirsutism.

Serum total testosterone levels decreased similarly in both the groups, a finding contradictory to that of Lobo et al, that the antiandrogen effect of spironolactone is primarily related to peripheral as compared to the hormonal effect¹⁶; the synergistic effect of Diane-35 and spironolactone might have caused this significant decrease in total

testosterone level. Beigi A et al¹⁷ in their study reported that finasteride increases levels of testosterone, whereas our findings are contrary to this, as the synergistic effect of Diane-35 might have neutralised the level of testosterone.¹⁸

Serum DHEAS level also decreased similarly ($p > 0.05$) in both groups, a finding that contradicts previous findings by Kelestimur et al and Beigi A et al^{7, 17} where there was no effect on DHEAS level. This can be explained by effect of cyproterone acetate on ACTH secretion or response.¹⁹ Ninety percent of DHEAS is contributed by the adrenals and ACTH is the hormone which regulates adrenal secretions.

A limitation of our study was that we did not assess the free androgen index (FAI). In the present study as we included both groups of PCOS and Idiopathic hirsutism, we were interested in clinical parameters rather than biochemical parameters, which is why Free Androgen Index was not measured.

Age and body mass index (BMI) had negative effects on treatment. Patients with hyperandrogenism responded better as compared to patients with normal androgen level.

To conclude, Diane-35 plus spironolactone and Diane-35 plus finasteride, are both equally effective and safe for the treatment of hirsutism and acne. Twelve month treatments seem inadequate, indicating prolongation of treatment to prevent recurrence.

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