ORIGINAL RESEARCH

Comparative Efficacy of Cyproterone/EE vs Desogestrel/EE on Acne in PCOD: A Hospital based Study on 40 Patients

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ABSTRACT

Introduction: To compare the efficacy of combined oral contraceptive containing desogestrel/ethinyl estradiol(EE) (femilon) and an anti-androgenic preparation containing cyproterone acetate/EE (krimson-35) in women with acne and PCOD (polycystic ovarian disease).

Material and methods: In an hospital based, randomized study, 20 women having PCOD with acne of various grades using femilon and 20 using Krimson-35 were followed for 6 treatment cycles. The measured variables were: objective severity of acne, plasma SHBG(Sex hormone binding globulin) levels, free and total testosterone, ultrasound study of ovarian cysts.

Results: Effects on acne: In group A, with femilon the decrease in mean semi quantitative acne score reached statistical significance after 3 months($p<0.05$) and completely after 6 months($p<0.01$) while in group B with krimson-35, this decrease reached statistical significance completely only after 6 cycles($p<0.01$).On biochemical variables: After 3 and 6 treatment cycles, in both preparations included a significant increase in SHBG levels($p<0.01$). Although there was a decrease in plasma levels of both free and total testosterone with both preparations but this is significant with krimson-35 after 6 cycles ($p<0.05$) On PCOD: decrease in cyst count is achieved with krimson($p<0.05$) after 6 cycles, while it is insignificant with femilon ($p>0.05$).

Conclusion: Both femilon and krimson-35 are effective. The contraceptive dose of cyproterone in krimson(2mg) is better useful for menstrual irregularity, as it breaks down the vicious cycle of androgens in ovaries at much lower doses. So, higher doses (50 mg per day) are necessary for first 10 days of cycle for early and effective action on acne.

Keywords: Acne, PCOD(polycystic ovarian disease), serum hormone binding globulin(SHBG), testosterone, cyproterone, desogesterol.

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INTRODUCTION

Although etiology of acne vulgaris is multifactorial, it is well accepted that androgenic hormones play an important role in its pathogenesis.[1] Androgen overproduction or hyperresponse of these sebaceous glands to normal androgen levels can lead to increased sebum production and acne.[1-3] As such, modulation of androgen levels represents a valid treatment option for acne in women. Evaluating effective therapies for acne is important, considering the potential adverse psychosocial consequences of this skin disease.

Combined oral contraceptives are a highly effective treatment option for acne in women, particularly in those with symptoms of androgenism.[4-7]

Combined oral contraceptives

They have both estrogen(ethinyl estradiol) and progesterone components.[10-12] Estrogen dose is used in low doses (20-50 μg)in combined pills nowadays. (20/50 μg)

Estrogen in combined pills acts by 4 mechanisms mainly:

- Decrease gonadal androgen production by decreasing secretion of the gonadotropins (LH and FSH) which blocks ovulation and blocks LH-induced ovarian androgen production
- Blocking the AR(androgen receptor)
- Increasing the synthesis of SHBG(sex hormone binding globulin) from the liver, decreasing the se-

rum levels of free available testosterone
- Some progestins also inhibits 5 α-R and inhibits conversion of weaker androgens to the potent ones.

Progestins

These are 19Nortestosterone derivatives and may cross react with the AR causing aggravation of acne, hirsutism, or androgenetic alopecia

Unlike endogenous progesterone, synthetic progestins have androgenic activity. Third generation progestins (norgestimate, desogestrel, and gestodene) are more selective for the progesterone receptor than for the AR and thus are least androgenic whereas norgestrel and levonorgestrel have more androgenic potential.[13] Thus COCs containing these progestins with EE would be preferred i.e., Novelon(Infar (India) DG-0.15 mg; EE-0.03 mg)

Femilon (Infar (India) DG-0.15 mg; EE-0.03 mg)

Cyproterone acetate

It is a progestin with anti androgenic action. It is used both singly and as combined pill in combination with ethinyl estradiol (*Krimson-35 Sun Pharmaceuticals CPA 2 mg; EE 0.035 mg, India).*As it acts at the level of cutaneous androgen receptor level also apart from decreasing androgen levels,it has well established role in conditions with cutaneous hyperandrogenism like acne,hirsutism and androgenetic alopecia or in syndromes of hyperandrogenism which have a combination of these symptoms like in PCOD.[14-15] For better efficacy high dose of cyproterone(50mg or 100 mg) is added to first 10 days of menstrual cycle in recalcitrant acne as it acts well on cutaneous androgens well at this dose.[17]

MATERIALS AND METHODS

This study has an approval of ethics committee of RMC,Kakinada. The study is conducted in a duration of 2 years. 40 female patients of age group 15 to 40 years-diagnosed to have PCOD coming to government general hospital,kakinada with acne vulgaris are involved in study.

Exclusion criteria

Pregnant and lactating women,women with connective tissue disorders & vasculitis, patients with other co-morbidities like hypertension,clottingdisorders,stroke,migraine,cardiac disease& thyroid abnormalities. Informed consent is taken from every patient. A detailed history and examination is carried out, recorded in each and every patient in a well designed proforma.Acne grading is done in all patients according to global acne grading system.

The global acne grading system

Location	Factor
Forehead	2
Left cheek	2
Chin	1
Right cheek	2
Nose	1
Chest and upper back	3

Calculation: Each type of lesion is given a value depending on severity: no lesions=0, comedones=1, papules=2, pustules=3 and nodules=4. The score for each area (local score) is calculated using the formula: Local score=Factor×grade (0-4). The global score is the sum of local scores and acne severity was graded using the global score. A score of 1-18 is considered mild, 19-30, moderate; 31-38, severe; and>39, very severe Routine blood investigations are conducted in every patient. Hormonal profile is done in all patients 1 month before starting therapy,3 months and 6 months after completion of therapy to evaluate response to therapy.After clinical examination and investigation,patients include in the study are divided in to 2 groups,Group A & B.

Group A are kept on OC pills containing 0.030 mg ethinylestradiol& 0.15 mg desogestrol*(Femilon Infar (India) DG0.15 mg; EE0.02 mg).*

Group B are kept on 0.035 mg ethinylestradiol with 2 mg cyproterone acetate(*Krimson-35 Sun Pharmaceuticals CPA 2 mg; EE0.035 mg).*

Follow up of patient is done with necessary investigations for 6 cycles for any side effects and response to therapy.

STATISTICAL ANALYSIS

The results of the study are compiled, tabulated, analysed using SPSS software. Descriptive statistics was used to generate results.

RESULTS

Analysis of demographic and clinical charecteristics revealed that they were comparable. [Table 1]

At baseline no statistically significant differences were observed between the two groups in acne scores or hormonal levels. Reference range of measured hormones are shown in table 2

Effects on acne

The acne scores with femilon and krimson-35 after 3

and 6 treatment cycles are analysed.

In group A, with femilon the decrease in mean acne score reached statistical significance after 3 months ($p<0.05$) and completely after 6 months ($p<0.01$) while in group B with krimson-35, this decrease reached statistical significance completely only after 6 cycles ($p<0.01$)

Effect on biochemical variable

After 3 and 6 treatment cycles, in both preparations included a significant increase in SHBG levels($p<0.01$). Although there was a decrease in plasma levels of both free and total testosterone with both preparations but this is significant with krimson-35 after 6 cycles ($p<0.05$) as shown in table 3 and table 4.

AGE(yrs)	
Range	15-30
Mean ±SD	19.01±3.4
BODY WEIGHT(kg)	
Range	45-80
Mean±SD	58±18.2
BMI(kg/m^2)	
Range	20.5-23.5
Mean± SD	22±2.3
PCOD(polycystic ovarian disease)	
Disease duration	6-8 months
Mean ±SD	6.6±2.8
ACNE	
Disease duration	3-18 months
Mean ±SD	6.5±3.6

Table-1: Demographic and clinical data

Effect on polycystic ovarian disease

Ultrasound examination of follicular count of ovary was at 0,3&6 treatment cycles. Statistically significant decrease in count is achieved with krimson-35($p<0.05$) after 6 treatment cycles. While there was no decrease in count with femilon ($p>0.05$) even after 6 cycles.

DISCUSSION

In this study, both femilon and krimson were effective in treatment of acne, without marked differences. since this estrogen dependent effect is not counteracted by intrinsic androgenecity of the progesterone component. The increase of serum hormone binding globulin increases the protein binding of plasma testosterone thereby reducing the free plasma testosterone concentration. It is thought that the plasma concentration of free and combined testosterone are correlated with the severity of acne. But we did not find any such correlation, instead there is a correlation between the hormone levels and menstrual irregularities. This might be due to that acne counts are also related to cutaneous androgen levels along with systemic androgen levels.

In a study by Bilhotta and Favilli on efficacy of OC Pills on acne,complete disappearance of symptoms is seen after 6 cycles and this is better than LNG(levonorgestrel).[18]

In another study comparing diane(oc pill with cyproterone) with LNG(levonorgestrel), diane was proved to be

Hormone	**Range**
Testosterone (ng/dl)	10-55
Free testosterone(pg/mL)	1.1-6.3
SHBG(nmol/L)	40-120

Table-2: Reference ranges of measured hormones

	A1	**A2**	**A3**
Testosterone(ng/dl)	10.06±0.96	8.78±0.07	6.48±1.08
Free testosterone(pg/ml)	2.5±0.4	2.12±0.55	2.0±0.37
SHBG(nmol/L)	91.8±12.6	155.0 ±11.2	160.0±14.6

Table-3: Hormone levels at initiation of therapy (A1),after 3 months (A2),after 6 months of therapy (A3) in group A(FEMILON) X±SD(N=20)

	B1	**B2**	**B3**
Testosterone(ng/dl)	10.01±1.02	6.29±0.71	5.16±1.18
Free testosterone(pg/ml)	3.63±0.5	2.06±0.4	1.79±0.37
SHBG(nmol/L)	92.6±7.2	170.5±14.6	173.5±11.2

Table-4: Hormone levels at initiation of therapy(A1),after 3 months(A2),after 6 months of therapy(A3) in group B(Krimson-35) X±SD(N=20)

more effective than LNG[19]

In a study conducted in France comparing the efficacy of oc pills containing desogestrel and cyproterone, both were proved to be of equal efficacy.[20]

In our study, both were proved to be equally effective, but effect on acne with krimson is seen after 6 cycle while it is more efficacious on menstural irregularities and other features of hyperandrogenism in PCOD.

Although it has been suggested that the anti acne efficacy of krimson can be attributed to the anti androgenic components of cyproterone acetate, the contraceptive dose of 2mg in krimson is too low to extend a clinically detectable effect. Instead, cyproterone acetate is more effective at higher doses in 50 mg per day given for first 10 days of cycle. The dose in krimson is useful for contraception and menstrual irregularities in acne. So anti acne effect of krimson is attributable to estrogenic component.

CONCLUSION

At the levels used for contraception, both krimson-35 and femilon were equally efficaceous on acne.This is better attributable to the estrogen component of oc pills through alteration in SHBG levels. This effect can be boosted by adding 50 mg of cyproterone acetate in the first 10 days of cycle. However long term efficacy on polycystic ovarian disease and other cutaneous features of hyperandrogenism are better with krimson than femilon as it breaks down the vicious cycle of polycystic ovarian disease by acting at the androgen receptor level.

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