Original Research Article

A randomized placebo controlled trial of metformin alone and metformin plus fixed dose combination of cyproterone acetate and ethinyl estradiol in hirsute women with polycystic ovarian syndrome

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ABSTRACT

Background: Polycystic ovarian syndrome is a common endocrine disorder seen in reproductive age group. Hirsutism, oligomennorhea and infertility being the most common chief complaint. Oral contraceptives have shown their efficacy in hirsute females. Metformin, an insulin sensitizer, have also shown some beneficial effects in improving metabolic abnormalities. Aim of this study is to compare the efficacy of metformin alone and metformin with fixed dose combination of cyproterone acetate and ethinyl estradiol in hirsute women with PCOS.

Methods: 60 females of PCOS with chief complaint of hirsutism were enrolled. Patients were randomized to either metformin and Diane -35 (35 microgram ethinyl estradiol plus 2mg cyproterone acetate) or metformin and placebo for 9 months. Ferriman Gallwey score and body mass index was calculated at baseline, 3months, 6months and 9 months. FSH/LH/Prolactin/Testosterone/Fasting glucose and Fasting insulin levels were measured at the baseline and at the end of treatment.

Results: Majority of females enrolled in the study were in third decade of life. Metformin and Diane- 35 showed higher reduction in Ferriman Gallwey score but Body mass index was reduced in both the groups. There was no significant difference seen between the groups with respect to biochemical profile.

Conclusions: This data show that a combination of metformin and contraceptive pill may be more effective in treating hirsutism than metformin alone. Beneficial effects of therapy were seen in relation to BMI as well. Hence, combination therapy is better therapeutic option for treating hirsutism in PCOS.

Keywords: Ferriman Gallwey score, Hirsutism, Metformin, PCOS

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex reproductive and endocrine disorder, characterized by menstrual irregularity, hyperandrogenism, polycystic ovaries, metabolic and psychological disorders and affects up to one fifth of women of reproductive age group.[1] The key pathogenic mechanism involved in PCOS is the excessive androgen biosynthesis and secretion by ovarian theca cells. Many patients of PCOS presenting with weight excess and showing hyperandrogenic features also have insulin resistance. This insulin resistance and its compensatory hyperinsulinism increases ovarian and adrenal androgen secretion, which favours visceral fat deposition.[2] This worsens the insulin resistance and hyperinsulinism. Indians are known to have high prevalence of insulin resistance, so the prevalence of PCOS may be high in this population.[3] Hirsutism, the hallmark feature of patients of PCOS, refers to the presence of excessive terminal (coarse) hair in androgen-sensitive areas of the female body (upper lip, chin, chest, back, abdomen, arms, and thighs). This excess hair growth is caused by an increased level of male hormones that are androgens. The modified Ferriman Gallwey (FG) score is

used to determine the severity of hirsutism by assessing the extent of hair growth in nine key anatomical sites.[4]

Metformin has been used primarily in the treatment of type 2 diabetic patients and has also shown to improve metabolic abnormalities in patients with PCOS.[5] Furthermore, metformin administration has been associated with decreased androgen levels, regularisation of menstrual flow and improve ovulatory function.[6,7] Oral contraceptive pills are commonly used in the treatment of menstrual disturbances and hyperandrogenism in women with PCOS. Cyproterone Acetate (CA) has strong progestogenic and antiandrogen properties. It produces a decrease in circulating testosterone and androstenedione levels through a reduction in circulating LH and has been used as an effective treatment for hirsutism. CPA is available in combination with ethinyl estradiol (EE) (2mg CPA and 35μg EE/tablet).[8] This study aims to compare treatment outcomes with metformin alone and metformin with ethinyl estradiol-cyproterone acetate in PCOS patients.

METHODS

Trial design

An interventional, prospective, randomized and open label design.

Participants

Patients in the age group of 15-45 years whose primary complaint was hirsutism (FG score >8) were included in the study. The diagnosis of PCOS was made according to the Rotterdam's criteria which includes at least two of the three following features: oligomenorrhea/amenorrhea, polycystic ovaries on ultrasound, or an elevated free androgen.[9]

Patients with prior history of systemic diseases like diabetes mellitus and hypertension, patients taking medication which will effect gonadal and adrenal function, patients with history of use of oral contraceptives or metformin for three months or more, patients who were pregnant or with idiopathic hirsutism, with excess androgen secretion by ovary (tumour), with excess androgen secretion by adrenal gland (congenital adrenal hyperplasia, Cushing syndrome) or taking medications known to cause hirsutism (steroids, danazol, metclorpromide, methyldopa) were excluded from the study. All patients were those treatment for PCOS from the outpatient department of Department of Dermatology, Venerology and Leprosy at Government Medical College, Amritsar from January 2016 till January 2017.

Informed consent was taken from all the patients enrolled after explaining study drugs, its benefits and side effects and further approval from Institutional Ethical Committee was obtained. (Figure 1).
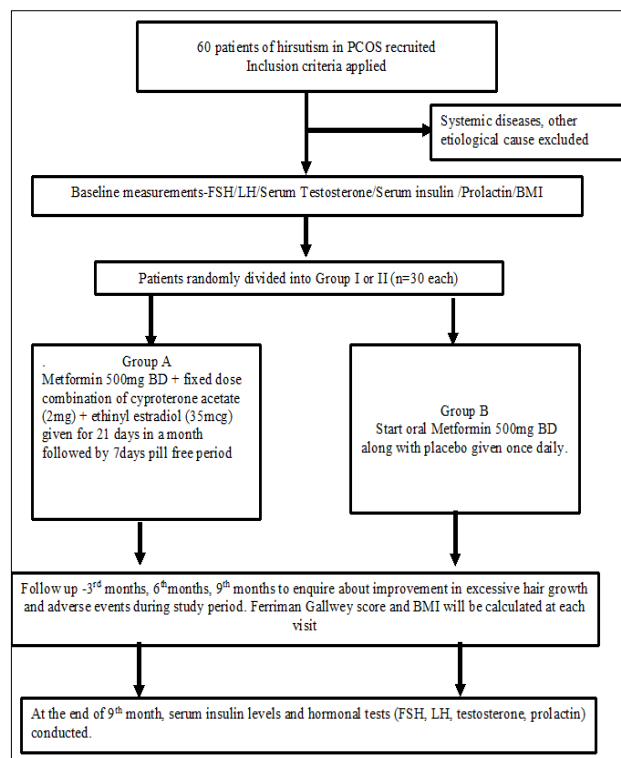

Figure 1: Consort diagram describing the flow participants in the study.

Interventions

Patients were randomized into two groups. Group A received Metformin 500 mg thrice a day for 9 months plus a fixed dose combination of ethinyl estradiol (35mcg) plus cyproterone acetate (2mg) for 21 days in a month followed by 7 day pill free period for a period of 9 months. From first day of menstrual cycle daily oral administration of fixed dose combination for 21 days was done and then pill was stopped for the next 7 days. Patient were asked to start the pill again on 8th day. Group B received Metformin in the doses of 500mg thrice a day along with placebo for 9 months. Metformin 500mg BD was started in the morning and evening after meals. After one week, dose was titrated to 500mg thrice a day. If gastrointestinal symptoms appeared, dose was again reduced to 500mg twice a day for one week and if tolerated well by the patient the same dose was made thrice a day.

Outcomes

At the time of enrolment, various biochemical parameters (FSH, LH, prolactin, testosterone, fasting sugar and fasting insulin) were recorded and these were repeated at the end of treatment. FG score and BMI was calculated at baseline and at the end of the treatment. Detailed flow chart of the study protocol is described in figure below. Ferriman Gallwey score is gold standard for evaluation of hirsutism.[10] Nine out of eleven body areas are taken into consideration (upper lip, chin, chest, arm, upper abdomen, lower abdomen, upper back, lower back and thighs).

Scoring ranges from 1 (minimal terminal hair present) to 4 (equivalent to a hairy man). If no terminal hair are observed in the body area being examined the score is zero (left blank). Clinically, terminal hair can be distinguished from vellus hair primarily by their length (i.e. 0.5 cm) and the fact that they are usually pigmented. Women with established diagnosis of hirsutism have FG scores of 8 or higher.

Sampling and randomization

Using the prevalence of PCOS as 50%, effect size 5 (on FG score), power of 80% and level of significance at less than 0.05 the sample size was calculated as 60. These patients were randomized to Group A or Group B by using block randomization method. Previous studies have shown obesity as a confounding factor for the metformin treatment. It was more effective in females with higher BMI. Therefore, patients were divided into three blocks. Each block represents a different body mass index, ranging from 20-25kg/m^2 (block 1), 25-30kg/m^2 (block 2), 30-35kg/m^2 (block 3) as normal, overweight and obese respectively. Each block received 20 patients each. Out of each block, 10 patients were selected according to random number tables (n=30) and given the drugs of Group A and rest received the drugs of Group B.

Blinding

Only patient as blinded to the treatment.

Statistical methods

Using SPSS version 23 quantitative data were described as mean and standard deviation and qualitative data as frequency distribution. Comparison of baseline demographic data was done with the help of chi square test and student's T test. To compare the means of various biochemical parameters between the two treatment groups unpaired t test was used. Similarly, to compare FG score and BMI between the two groups at different time points unpaired T test was used. Significance level was expressed as p value of < 0.05 for each analyses.

RESULTS

Present study enrolled 60 patients of PCOS with chief complaint of hirsutism. They were randomly divided to two groups (Group A and Group B). At baseline, socio demographic profile of the patients was recorded (Table 1).

Majority of patients were in third decade of life in both the groups. Mean age of patients in group A was 25.63±6.43 and group B was 25.07±4.61. In both the groups, maximum number of females were unmarried, literate, unemployed with rural background. Positive family history was present in both the groups. Majority patients were obese with BMI ranging above 30. Biochemical profile (FSH, LH, Prolactin, Testosterone, fasting blood sugar, fasting insulin) was also recorded at baseline and at the end of 9months (Table 2).

Table 1: Socio-demographic profile of the patients included in the study.

Variables		Group A	Group B	p value
Age (in years)	Less than 20	10 (30.3%)	5 (18.5%)	0.52
	20-30	17 (51.5%)	18 (66.6%)	
	30-40	5 (15.5%)	4 (14.8%)	
	More than 50	1 (0.03%)	0	
Marital status	Married	16 (46.9%)	12 (42.9%)	0.79
	unmarried	17 (53.1%)	15 (57.1%)	
Body mass index (kg/m^2)	Less than 25	8 (26.6%)	7 (25.92%)	0.64
	25-30	10 (33.33%)	7 (25.92%)	
	More than 30	12 (40%)	13 (48.1%)	
Occupation	Working	14 (42.4%)	6 (22.2%)	0.09
	Not working	19 (57.5%)	21 (77%)	
Education status	Illiterate	4 (12.1%)	7 (25.8%)	0.197
	Literate	29 (87.9%)	20 (74.2%)	
Type of residence	Urban	7 (21.2%)	12 (44.4%)	0.52
	Rural	26 (78.7%)	15 (55.5%)	
Positive family history	Yes	32 (96.9%)	23 (85%)	1.00
	No	1 (0.03%)	4 (14.8%)	

Though, there was decrease in hormonal, glucose and insulin levels in both the groups but no significant difference was seen at the end of 9 months. This shows that both the treatments were effective in improving the hormonal profile. FG score and Body mass index were calculated at each visit (Table 3). There was significant reduction in the score at 6 months in patients who were taking metformin and diane-35. Similar results were reported at the end of 9 months. Reduction in weight was also seen in both the groups and this change was significantly seen at 6 months and 9 months. Though there was no significant difference between the groups, but both the treatments had positive effect on BMI.

Table 2: Comparison of biochemical investigations of patients in the two groups at baseline and at 9 months.

	At Baseline			At 9 months		
Variables	Group A	Group B	p value	Group A	Group B	p value
FSH* (mIU/ml)	12.49±6.93	19.51±4.38	<0.05	9.56±6.12	9.25±3.68	0.81
LH* (mIU/ml)	18.39±6.5	19.44±8.61	0.59	14.92±8.2	17.9±7.98	0.92
Prolactin (ng/dl)	36.65±2.56	30.95±9.91	0.06	28.94±17.22	30.17±9.48	0.74
Testosterone (ng/dl)	119.2±48.51	102.31±31.4	0.6	89.04±46.26	94.4±26.3	0.6
Fasting blood sugar (mg/dl)	98.75±12.23	97.7±10.63	0.72	89.05±34.76	100.02±7.14	0.12
Fasting insulin (mIU/ml)	16.3±7.08	14.5±5.86	0.92	11.9±7.25	12±4.92	0.93

*FSH: Follicle stimulating hormone; LH: Luteinizing hormone
All values are mean±standard deviation

Table 3: Comparison of Ferriman Gallwey Score and Body Mass Index of patients in the two groups at baseline and at 9 months.

	Group A	Group B	p value
Ferriman Gallwey Score			
At baseline	21.15±4.29	21.11±3.51	0.96
At 3 months	20.33±3.96	20.75±4.55	0.70
At 6 months	19.22±3.84	21.02±2.97	<0.05
At 9 months	18.69±4.94	20.18±3.02	<0.05
Body Mass Index (kg/m^2)			
At baseline	27.6±3.77	27.3±3.11	0.74
At 3 months	27.8±3.86	27.7±3.31	0.88
At 6 months	26.72±3.61	26.01±3.06	0.72
At 9 months	25.62±3.54	25.72±2.86	0.64

All values are mean±standard deviation

DISCUSSION

Several data support the hypothesis that insulin resistance and the associated hyperinsulinemia play a pathogenetic role in PCOS.[11] These observations suggested that insulin sensitizing agents, such as metformin should be tested for the treatment of PCOS. These drugs improve insulin sensitivity by different mechanisms, thus determining a subsequent reduction in plasma insulin levels.[12] It has been hypothesized that a reduction in circulating insulin concentrations, leading to decreased free androgen concentrations, may ameliorate hirsutism. On the other hand, cyproterone acetate is an established treatment that acts as an antiandrogen at target sites and it seems to be effective in a large number of patients of hirsutism. In this study, 60 patients were randomly assigned to Group A (Metformin and fixed dose combination of cyproterone acetate and ethinyl estradiol) and Group B (Metformin and Placebo). Treatment in both the groups were found to be safe. There were no significant side effects reported apart from nausea, vomiting and abdominal pain. This can be attributed to metformin given in both the groups as it is known to cause gastrointestinal side effects.[13]

The baseline characteristics were similar in both the groups. Normal FSH and LH lies between the range 5-20mIU/ml and in PCOS usually FSH:LH ratio is 1:3. Our study reported FSH/LH levels within the normal range in both the groups with no LH surge. Though hyperprolactinemia and PCOS are independent disorders but raised estrogen levels can result in higher prolactin levels. In this study as well, we found raised prolactin levels in both the groups. Raised testosterone levels were seen in both the groups which was in accordance to the study done by Luque-Ramirez et al, where hyperandrogenism is the key feature of hirsutism.[14]

In order to look for the treatment effect on hirsutism, FG score was calculated at each follow up (3 months, 6 months, 9 months) for patients of both the groups. At baseline, it was seen that majority of patients were suffering from moderate hirsutism (>16). Similar results were reported by Sharma et al in which score of 38% females were ranging from 8-15.[15] There was no significant change in score in both the groups at 3 months, however the it showed significant reduction in both the groups at 6 months. The degree of reduction was more prominent in metformin and ethinyl estradiol-cyproterone acetate group as compared to metformin alone. It can be interpreted that, though there was no significant reduction in testosterone levels in metformin group but the subjective perception of hirsutism in the form of FG score improved. Similar results were reported by CG Kelly and D Gordon in double blind study where metformin had shown improvement in the score though there was no reduction in testosterone levels. Lauren Morin et al did a comparative study of metformin with ethinyl estradiol-cyproterone acetate where metformin had effect on hyperandrogenism, hyperinsulinemia whereas no effect was seen on insulin sensitivity in ethinyl estradiol-cyproterone acetate group.

Several studies have reported the reduction in weight as well as BMI in patients of PCOS on metformin. In this study as well, metformin was a component of both the groups, so BMI was significantly reduced in both the groups. This significant changes were not reported before 6 months. A study done by Harborne et al reported a modest reduction in weight in the group taking metformin

as compared to ethinyl estradiol-cyproterone acetate though majority of the patients were obese.[16]

CONCLUSION

This study found that metformin along with fixed dose combination of cyproterone acetate and ethinyl estradiol is better in decreasing Ferriman Gallwey score as compared to metformin alone. Mean reduction in body mass index was seen in both the groups but no significant reduction was seen in glucose levels. Biochemical parameters were similar in both the groups at the end of the treatment protocol. Future studies on larger populations are required to support the results of this study.

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