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COMPARISON OF EFFICACY OF SPIRONOLACTONE PLUS ORAL CONTRACEPTIVES WITH METFORMIN IN PATIENTS OF PCOS WITH HIRSUTISM

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ABSTRACT

Objective: To compare the efficacy of spironolactone plus oral contraceptives with metformin in treatment of hirsutism among patients with polycystic ovarian syndrome (PCOS).

Study Design: Randomized controlled trial.

Place and Duration of Study: Dermatology department, Military Hospital Rawalpindi, from Jan 2016 to Jul 2016.

Material and Methods: A total of 84 women with PCOS and hirsutism with ages ranging between 16 and 50 years were included in the study. Patients with hirsutism due to etiologies other than PCOS like idiopathic hirsutism, Cushing syndrome or late-onset congenital adrenal hyperplasia were excluded. Random allocation of treatment was done, those reporting on even dates were enrolled in group A and those reporting on odd dates were placed in group B. Group A received oral tablet spironolactone 50mg twice a day along with combined oral contraceptive pills (cOCPs) containing levonorgestrel 0.15mg / ethinyl estradiol 0.03mg daily as combination therapy for 6 months, while group B received oral metformin 500mg twice daily for 6 months. Hirsutism scores were determined according to the modified Ferriman-Gallwey (mFG) scoring system (attached as annexure A) and 50% reduction from the baseline was considered effective therapeutic response.

Results: The mean age of patients in group A was 32.83 ± 8.28 years and in group B was 32.57 ± 8.21 years. The mean duration of disease in group A was 18.84 ± 7.26 months and in group B was 18.04 ± 7.11 months. Efficacy in group A was observed in 29 (69.05%) patients while in group B it was observed in 17 (40.48%) patients.

Conclusion: The efficacy of spironolactone plus cOCPs combination therapy is better than metformin alone in the treatment of hirsutism among patients of PCOS.

Keywords: Hirsutism, Oral contraceptives, Polycystic ovarian syndrome, Spironolactone.

INTRODUCTION

Hirsutism, defined by the presence of excessive terminal (coarse) hair in androgen-sensitive areas of the female body, affects almost 5-10% of women[1] during reproductive age in most populations, with the important exception of Far-East Asian women who present with hirsutism less frequently[2]. It is a cause of psychosocial distress to the patients[3].

The most common cause of hirsutism is Polycystic ovary syndrome (PCOS)[1]. Other less common causes include endocrinopathies and neoplasms, such as congenital adrenal hyperplasia, thyroid dysfunction, cushing syndrome, and androgen-secreting tumors and drugs[4].

The modified Ferriman–Gallwey score (mFG) is now considered the gold standard for the evaluation of hirsutism[5]. Clinical features including hirsutism, acne, obesity, subfertility and androgenic alopecia, are common in PCOS[6]. In our population as well the commonest cause of hirsutism was found to be PCOS according to a local study[7].

Many different treatment modalities are available for the management of hirsutism in PCOS including non-pharmacological and pharmacological therapies like eflornithine OCPs, metformin, cyproterone acetate, and spironolactone. Oral contraceptives are the best first-line treatment for mild to moderate hirsutism and can be used in combination with antiandrogens or other therapies[8].

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Different studies have shown variable effectiveness of these agents individually. A study done in Baghdad showed combination of spironolactone and cOCPs (containing levonorgestrel 0.15 mg/ ethinyl estradiol 0.03mg) to have a response rate of 60%[8] but this study utilized the hair shaft diameter as their response parameter. A beneficial response of 2.3%[1] improvement in mFG score was seen in patients using metformin while another study has shown a response as good as 33%[9].

This study was designed to compare the therapeutic efficacy of spironolactone plus cOCPs with metformin as no such local or international study was available comparing these two groups of drugs. By making a comparison, we would be able to offer better treatment option which would facilitate more effective medical care for patients with hirsutism.

Table-I: Age distribution for both groups (n=84).

Age (years)	Group A (n=42)		Group B (n=42)		Total (n=84)	
	No. of patients	% age	No. of patients	% age	No. of patients	% age
18-30	19	45.24	21	50.0	40	47.62
31-50	23	54.76	21	50.0	44	52.38
Mean ± SD	32.83 ± 8.28		32.57 ± 8.21		32.70 ± 8.19	

Table-II: Percentage of patients according to duration of disease (n=84).

Duration of disease (months)	Group A (n=42)		Group B (n=42)		Total (n=84)	
	No. of patients	% age	No. of patients	% age	No. of patients	% age
>6-24 months	25	59.52	26	61.90	51	60.71
>24 months	17	40.48	16	38.10	33	39.29
Mean ± SD	18.84 ± 7.26		18.04 ± 7.11		18.95 ± 7.17	

Table-III: Hirsutism score.

	Group A (n=42)	Group B (n=42)	*p*-value
	Hirsutism score	Hirsutism score	
Baseline	27.98 ± 4.01	28.00 ± 3.38	0.9803
Post-treatment	15.67 ± 5.37	16.76 ± 4.34	0.3094

MATERIAL AND METHODS

This randomized controlled trial was carried out at dermatology outpatient department of Military Hospital Rawalpindi from January 2016 to July 2016. The sample size was calculated by World Health Organisation sample size calculator based on outcome variables with anticipated population proportion P1 of 60.0%[8] and anticipated population proportion P2 of 33.0%[9]. The sampling technique was non probability consecutive sampling. A total of 84 patients were enrolled in the study with 42 patients each in group A and B. Written informed consent from patients and permission from hospital ethical committee was duly sought. Patients with hirsutism due to etiologies other than PCOS like idiopathic hirsutism, Cushing syndrome or late-onset congenital adrenal hyperplasia, pregnant or nursing women and those with any concomitant illnesses or immunosuppression were excluded. Random allocation of treatment was done, those reporting on even dates were enrolled in group A and those reporting on odd dates were placed in group B. Group A received tab spironolactone 50mg twice a day plus cOCPs daily as combination therapy for 6 months, and group B received tab metformin 500mg twice daily for 6 months. Each patient underwent a complete medical and gynecological examination and laboratory evaluation with complete blood count, hepatic and renal function tests, Electrocardiography, urine for pregnancy test, serum cortisol levels, serum testosterone, prolactin levels and luteinizing hormone to follicle stimulating hormone ratio along with ultrasound pelvis for

polycystic ovaries. Hirsutism scores were determined according to the mFG scoring system (Annexure). These were calculated at baseline and at the end of therapy at 6 months. All patients were counseled to avoid pregnancy during the period of study. At least 50% or more reduction in the mFG score of each patient from the baseline score was considered effective therapeutic response. SPSS version-17.0 was used for statistical analysis of data. Mean and standard deviations were used to describe numeric variables like age, duration of disease and hirsutim score at baseline and at 6 months after treatment. Frequencies and percentages were used to describe categorical variables like duration of disease and efficacy. Chi square test was applied to compare the efficacy in two groups. Independent sample test was applied for the comparison of quantitative variables Effect modifiers like age and duration of disease were controlled by making stratified tables. Post stratification chi-square test was applied to see its effect on outcome. A *p*-value less than 0.05 was considered as significant.

RESULTS

The ages of patients enrolled in this study ranged from 18 - 50 years with mean age of 32.70 ± 8.19 years. The mean age of patients in group A was 32.83 ± 8.28 years and in group B was 32.57 ± 8.21 years. The mean duration of disease in group A was 18.84 ± 7.26 months and in group B was 18.04 ± 7.11 months (table-I).

The mean baseline hirsutism score in group A was 27.98 ± 4.01 and in group B was 28.00 ± 3.38. At the completion of 6 months treatment, it reduced to 15.67 ± 5.37 in group A and 16.76 ± 4.34 in group B (*p*-value=0.30; table-II).

Efficacy of treatment in group A (spironolactone plus cOCPs) was recorded in 29 (69.05%) patients while in group B (metformin) it was noted in 17 (40.48%) patients (*p*-value=0.009; figure).

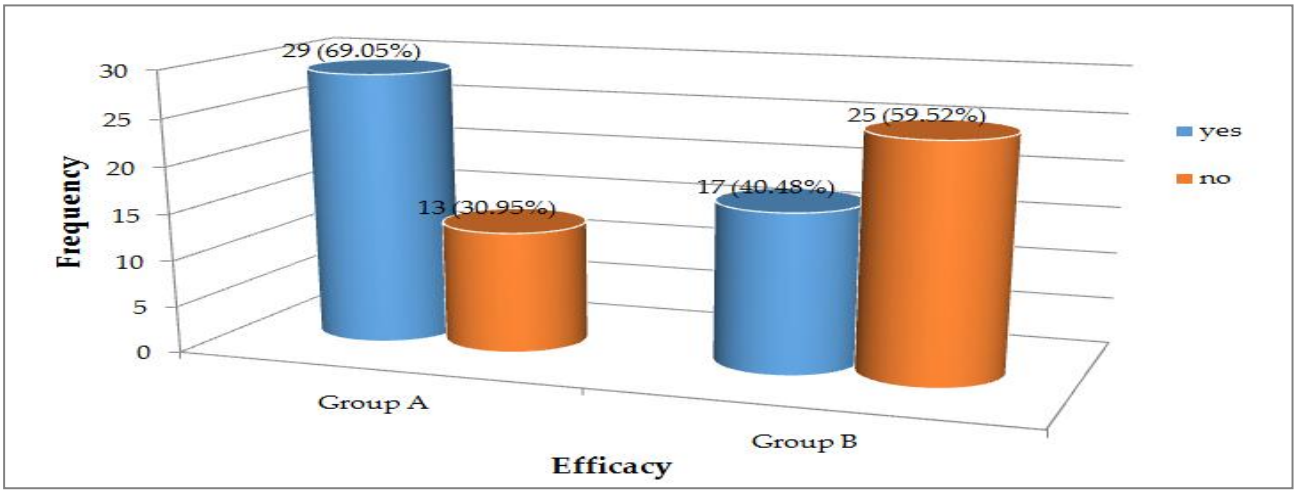

Figure: Comparison of efficacy in both groups.
p-value=0.009

DISCUSSION

PCOS is a common endocrine disorder and the leading cause of infertility in women of reproductive age[1]. Its prevalence among infertile women is 15%-20%[1]. The exact etiology of PCOS remains unclear; However, women with PCOS have abnormalities in the metabolism and control of androgen production[10]. PCOS is also associated with peripheral insulin resistance and hyperinsulinemia, and obesity amplifies the degree of both abnormalities[10].

Combination oral contraceptives, especially those with progestins like norgestimate, desogestrel, or drospirenone (because of their low androgenic effects), are among the most

commonly used medications for hirsutism in women with PCOS[11]. Spironolactone, an anti-androgenalso improves the metabolic parameters of PCO sand decreases serum total testosterone levels and insulin resistance parameters[10]. Combining spironolactone with oral contra-ceptives may be synergistic[12]. Spironolactone is FDA pregnancy category C and the risk of feminizing a male fetus, if pregnancy occurs, precludes its use as monotherapy in sexually active women with PCOS[13]. Insulin-sensitizing agents like metformin may also be used to treat hirsutism in women with PCOS1.

This study was conducted to compare the efficacy of combined use of spironolactone and oral contraceptives with metformin monotherapy in the treatment of hirsutism in patients of PCOS.

Administration of metformin in the present study improved the hirsutism score although not in proportion to the improvement observed with combination therapy using cOCPs and spironolactone. Metformin treatment targets not only the insulin resistance but also the ovulatory derangements of PCOS. It also improves hyper-androgenemia and hirsutism and reduces the serum lipid levels[14]. Although potential benefits of metformin appear promising, it still has not been approved by US FDA for use in PCOS[14].

Only few studies have assessed the role of metformin in hirsutism in patients of PCOS. A

Annexure-A: Modified ferriman galeway score.

Sites	Grade 1	Grade 2	Grade 3	Grade 4
Upper Lip	Few hair at the outer margin	Small moustache at outer margin	Moustache extending halfway from the outer margin	Moustache extending to midline
Chin	Few scattered hair	Scattered hair with small concentrations	Complete cover, light	Complete cover, heavy
Chest	Circumareolar hair	Circumareolar hair with midline hair	Fusion of circumareolar hair with midline hair giving three quarter cover	Complete cover
Upper Back	Few scattered hair	More than a few scattered hair but still scattered	Complete cover, light	Complete cover, heavy
Lower Back	Sacral tuft of hair	Sacral tuft of hair with some lateral extension	Three quarter cover	Complete cover
Upper Abdomen	Few midline hair	Rather more but still midline	Half cover	Complete cover
Lower Abdomen	Few midline hair	Midline streak of hair	Midline band of hair	An inverted V shaped growth
Upper Arm and Thigh	Sparse hair growth affecting not more than a quarter of limb surface	More than a quarter coverage but still incomplete	Complete cover, light	Complete cover, heavy
Forearm and Legs	-	-	-	Complete cover, heavy

double blind randomized controlled trial in a small PCOS population favoured metformin 500mg thrice daily over placebo with mean FG scores of 17.7 ± 1.4, 15.8 ± 1.4 and 17.5 ± 1.2 respectively in the baseline, metformin and placebo group respectively (p=0.02)[15]. In a study done by Diri et al, comparative analysis of spironolactone and spironolactone plus metformin was done on hirsutism score with spironolactone alone showing 25.2% reduction while combination therapy resulted in 28.3% reduction[16]. However the dose of metformin used in this study was higher than our study (2000 mg/ day in that study versus 1000 mg/day in our study). Another prospective randomized trial showed marked improvement in FG score after 6 months of using cOCPs (containing 0.03mg ethinyl estradiol and 3mg drospirenone) from 17.3 ± 5.2 to 8.7 ± 2.5 (p<0.001)[17]. Comparison of cOCPs (having ethinyl estradiol 30 mcg/ desogestrel 150 mcg) plus spironolactone with cOCPs (containing ethinyl estradiol 35 mcg/ cyproterone acetate 2 mg) was done by Leelaphiwat et al and it showed improvement in mFG score from 4.27 ± 1.94 to 4.07 ± 1.91 in the combination group after 3 months of treatment[18]. In addition to the shorter duration of treatment, a 25mg/ day dose was used which was much lower than the dose used in our study (100mg/day of spironolactone).

The combination therapy used in our study (cOCPs and spironolactone) is more acceptable as it did not induce any significant menstrual irregularities seen with spironolactone alone to affect the patient compliance. However the effect may not have been as pronounced as it was in the study done by Maghrabyet al[19] due to the short duration of our study (6 months). Maghraby et al followed the patients on treatment for 24 months. Similarly we expect that the efficacy of metformin may have been improved if we had used it beyond 6 months, which is the half-life of the hair follicle[1].

In the present study we used the combination therapy with cOCPs and spirono-lactone to avoid pregnancy as well as enhance the antiandrogen effect of spironolactone and regularizing the menstrual cycle. These drugs have a synergistic effect on androgen level and hence provide better control of hirsutism.

Limitations of the current study include small sample size and shorter duration. Hence large randomized multicenter trials involving follow up for a longer duration are needed to further confirm the results of this study. The choice of the proper line of therapy should be tailored for every patient, according to her age, stage in life, presenting symptoms, various personal and familial risk indices as well as her choice.

CONCLUSION

This study concluded that efficacy of combined therapy with spironolactone and cOCPs is superior to metformin monotherapyin the treatment of hirsutism among patients of polycystic ovarian syndrome.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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