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A PROSPECTIVE STUDY ON THE EFFECTIVENESS OF METFORMIN AND ETHINYL ESTRADIOL-CYPROTERONE ACETATE IN THE MANAGEMENT OF HYPERANDROGENISM IN POLYCYSTIC OVARY SYNDROME PATIENTS

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting 5-8% of women of reproductive age group characterized by associated problems such as infertility, diabetes mellitus, hypertension, dyslipidemia, endometrial cancer, depression and hyperandrogenism. The aim of the review is to evaluate the effectiveness of Metformin and Ethinyl Estradiol- Cyproterone Acetate (EE-CA) in the management of Hyperandrogenism in PCOS patients. As there are only few studies in Indian literature regarding the evaluation of effectiveness of the drugs in the management of hyperandrogenism associated with PCOS, the present review is undertaken. The review had shown that EE-CA is a more effective way of treating hyperandrogenism and menstrual dysfunction compared to Metformin which outperforms EE-CA in improving insulin resistance, reducing Body Mass Index and improving ovulation.

KEYWORDS: Hyperandrogenism, Insulin resistance, Metformin, Ethinyl Estradiol-Cyproterone Acetate.

INTRODUCTION

Polycystic Ovary Syndrome characterized by hyperandrogenism, hyperinsulinemia and menstrual dysfunction is the most common endocrine disorder among women. The exact cause of PCOS is not fully understood but excess insulin, excess androgen, genetics and low grade inflammation can be the factors. Insulin resistance appears to be the fundamental common pathway to disease amongst women with PCOS. Hence, women with PCOS produce higher levels of insulin. The impact of higher levels of insulin and Insulin like growth factor 1 on the ovary is the reason for the release of higher levels of testosterone.

Insulin resistance is recognized as a major risk factor for the development of type 2 diabetes mellitus. Elevated androgens such as Dehydroepiandrosterone sulphate (DHEAS) and testosterone are associated with insulin resistance, obesity and altered lipid metabolism. Therefore, elevated androgens may raise the risk for cardiovascular disorders. Women of all ages with PCOS are at an increased risk of endometrial cancer and increased emotional stress such as depression as compared with non-PCOS women.

The main aim of the review is to evaluate the effectiveness of Metformin and Ethinyl Estradiol-Cyproterone Acetate in the management of hyperandrogenism in PCOS patients. The objectives of the review include the comparison of Metformin and EE-CA in the management of hyperandrogenism in PCOS, to determine the impact of medication adherence in the management of the disease and to evaluate the ADR of Metformin and EE-CA. It was found that EE-CA showed greater effectiveness in the management of hyperandrogenism and its symptoms in PCOS when compared to Metformin. Medication adherence was evaluated by Morisky 8 item medication adherence scale and was found to be improved after follow up. Metformin was found to have lesser ADR's when compared to EE-CA.

There is well documented evidence in the literature by Leopolo Falsetti *et al* that suggest a significant decrease in the androgen level and hirsutism by treatment with the combination of Ethinyl Estradiol and Cyproterone Acetate. Also, improvement in frequency of menstruation, reduction in plasma insulin and increased insulin sensitivity upon treatment with Metformin was mentioned in previous literature by Paolo Moghetti *et al*. This review is done to compare the effectiveness of Metformin and EE-CA in the management of hyperandrogenism in PCOS patients.

MATERIALS AND METHODS

This is a prospective observational study conducted in 70 out patients diagnosed with Polycystic Ovary Syndrome in the Gynaecology department of Pushpagiri Medical College Hospital, Thiruvalla. The pharmacological agents included in the study were Metformin and Ethinyl Estradiol - Cyproterone Acetate. The study population was divided in to two groups. In each group, 30 patients were enrolled. One group included the patients who were taking Metformin 500 mg and the other group with Ethinyl Estradiol (0.035 mg) - Cyproterone Acetate (2 mg). The study was implemented by direct interview with patients. A written informed consent was obtained from the patient or care giver before the commencement of the study. The data was analyzed through patient prescription records and patient collection Performa. A patient documentation form was prepared on the parameters like age distribution, family history, marital status, co morbidities present, and medication adherence of patients before and after pharmacist intervention. Also parameters like Body Mass Index (BMI), Hirsutism score, Waist Hip Ratio (WHR), Testosterone, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Dehydrepiandrosterone Sulfate (DHEAS), Anti Mullerian Hormone (AMH) and Fasting insulin levels were recorded and evaluated for the effectiveness study of the drugs. The patients were followed up after 3 months of treatment and the parameters were re evaluated and recorded. The medication adherences of the patients were checked using Morisky 8 Item adherence scale (MMAS-8). Hirsutism score was calculated using Ferriman-Gallwey score (FG score) and the ADR of Metformin and Ethinyl Estradiol-Cyproterone Acetate was evaluated.

STATISTICAL METHODS

The data was analyzed using Microsoft Excel Worksheet and SPSS 17.0 Software. Results were analyzed using paired *t*-test to compare the baseline and discharge readings within each group. Independent *t*-test was applied to compare the significant difference between the groups. A *P* value of < 0.05 was considered significant.

RESULTS

COMPARISON OF METFORMIN AND ETHINYL ESTRADIOL-CYPROTERONE ACETATE BASED ON BODY MASS INDEX

Table 1: Comparison of Metformin and EE-CA based on BMI.

PARAMETERS	BMI VALUE	
DURATION OF TREATMENT (MONTHS)	METFORMIN	EE-CA
0	31.04±2.26	26.91±1.79
3	26.53±1.52	25.05±1.82
MEAN DIFFERENCE	4.5125	1.861
P VALUE	*P* =0.001	

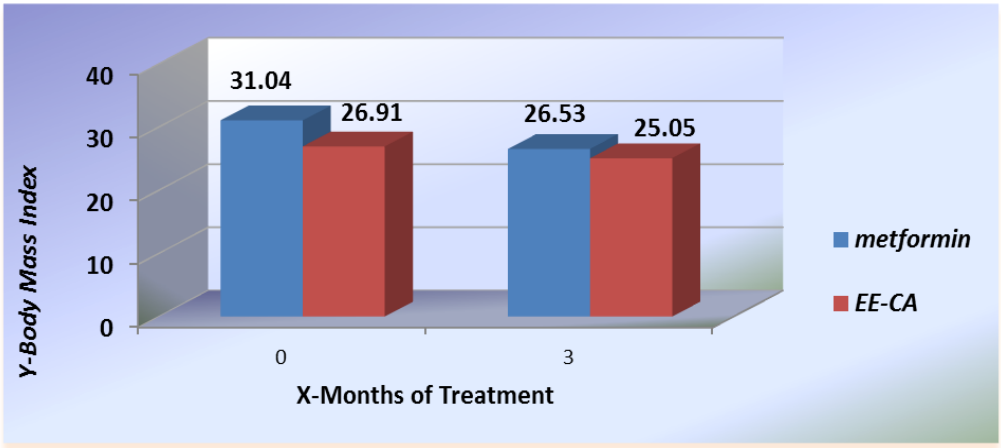

Figure 1: Comparison of Metformin and EE-CA based on BMI.

From the graph it can be found that, there is a significant difference between the before and after treatment values of Body Mass Index in Metformin group & EE-CA group and there is more mean difference in Metformin (4.5125) when compared to EE-CA (1.861). Therefore we can say that Metformin is more effective than EE-CA. *P* value of BMI is *P* = 0.001, i.e. *P*<0.05. Therefore, it is statistically significant.

COMPARISON OF METFORMIN AND EE-CA BASED ON FERRIMAN-GALLWEY SCORE

Table 2: Comparison of Metformin and EE-CA based on Ferriman-Gallwey score.

PARAMETERS	FERRIMAN-GALLWEY SCORE	
DURATION OF TREATMENT (MONTHS)	METFORMIN	EE-CA
0	8.66±1.413	10.17±1.413
3	6.86±1.43	5.06±1.43
MEAN DIFFERENCE	1.800	5.114
P VALUE	*P* =0.001	

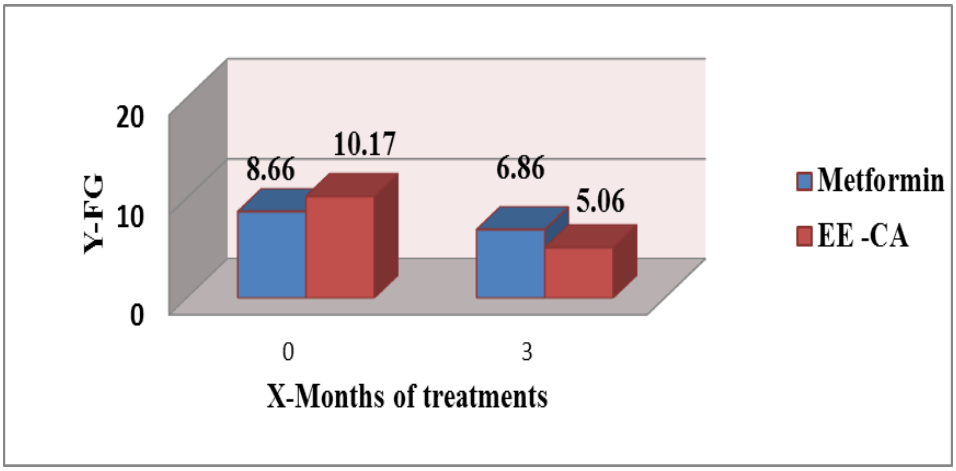

Figure 2: Comparison of Metformin and EE-CA based on Ferriman-Gallwey score.

From the graph, it is evident that there is a significant difference between the before and after treatment values of FG score in Metformin group & EE-CA group and there is more mean difference in EE-CA (5.114) when compared to Metformin (1.800). Therefore we can say that EE-CA is more effective than Metformin. *P* value of FG score is *P* = 0.001, i.e. *P*<0.05. Therefore, it is statistically significant.

COMPARISON OF METFORMIN AND EE-CA BASED ON TESTOSTERONE LEVELS

Table 3: Comparison of Metformin and EE-CA based on Testosterone

PARAMETERS	TESTOSTERONE	
DURATION OF TREATMENT (MONTHS)	METFORMIN	EE-CA
0	3.49±0.9	5.162±0.6164
3	2.93±0.752	1.685±0.4205
MEAN DIFFERENCE	0.5571	3.477
P VALUE	*P* =0.001	

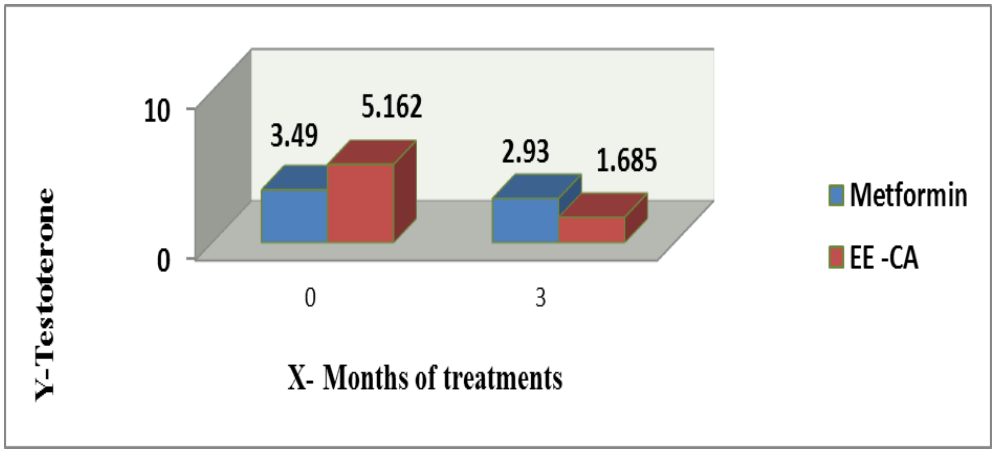

Figure 3: Comparison of Metformin and EE-CA based on Testosterone.

There is a significant difference between the before and after treatment values of Testosterone in Metformin group & EE-CA group and there is more mean difference in EE-CA (3.477) when compared to Metformin (0.5571). Therefore we can say that EE-CA is more effective than Metformin. P value of Testosterone is P = 0.001, i.e. P<0.05. Therefore, it is statistically significant.

COMPARISON OF METFORMIN AND EE-CA BASED ON LUTEINIZING HORMONE

Table 4: Comparison of Metformin and E-CA based on Luteinizing Hormone.

PARAMETERS	LUTEINIZING HORMONE	
DURATION OF TREATMENT (MONTHS)	METFORMIN	EE-CA
0	7.75±0.2862	8.86±0.576
3	6.53±0.5224	5.23±0.7677
MEAN DIFFERENCE	1.222	3.625
P VALUE	*P* =0.001	

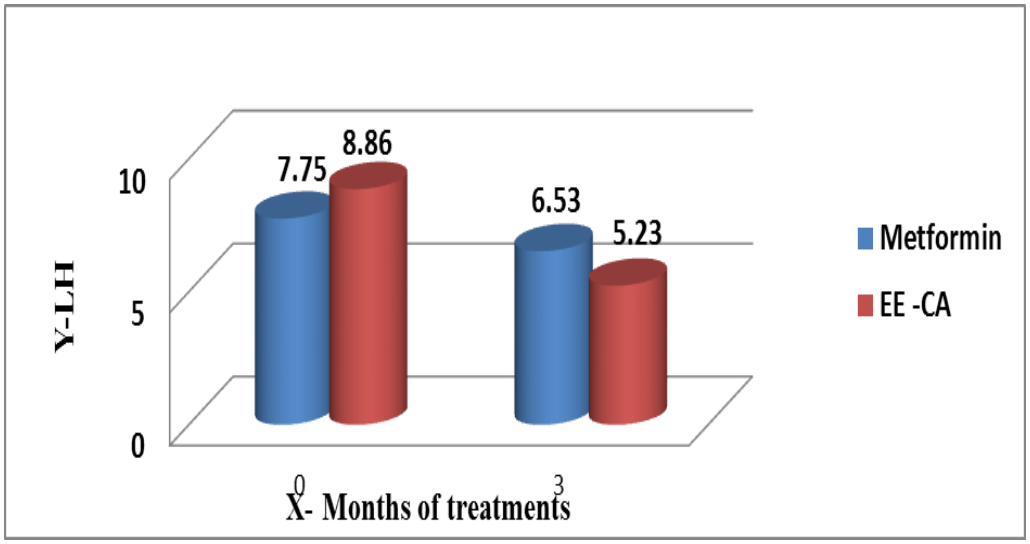

Figure 4: Comparison of Metformin and EE-CA based on LH.

There is a significant difference between the before and after treatment values of LH in Metformin group & EE-CA group and there is more mean difference in EE-CA (3.625) when compared to Metformin (1.222). Therefore we can say that EE-CA is more effective than Metformin. P value of LH is P = 0.001, i.e. P<0.05. Therefore, it is statistically significant.

COMPARISON OF METFORMIN AND EE-CA BASED ON FOLLICLE STIMULATING HORMONE

Table 5: Comparison of Metformin and EE-CA based on FSH.

PARAMETERS	FOLLICLE STIMULATING HORMONE	
DURATION OF TREATMENT (MONTHS)	METFORMIN	EE-CA
0	6.98±0.558	8.32±0.576
3	5.40±0.462	5.55±0.826
MEAN DIFFERENCE	1.571	2.77
P VALUE	*P* =0.001	

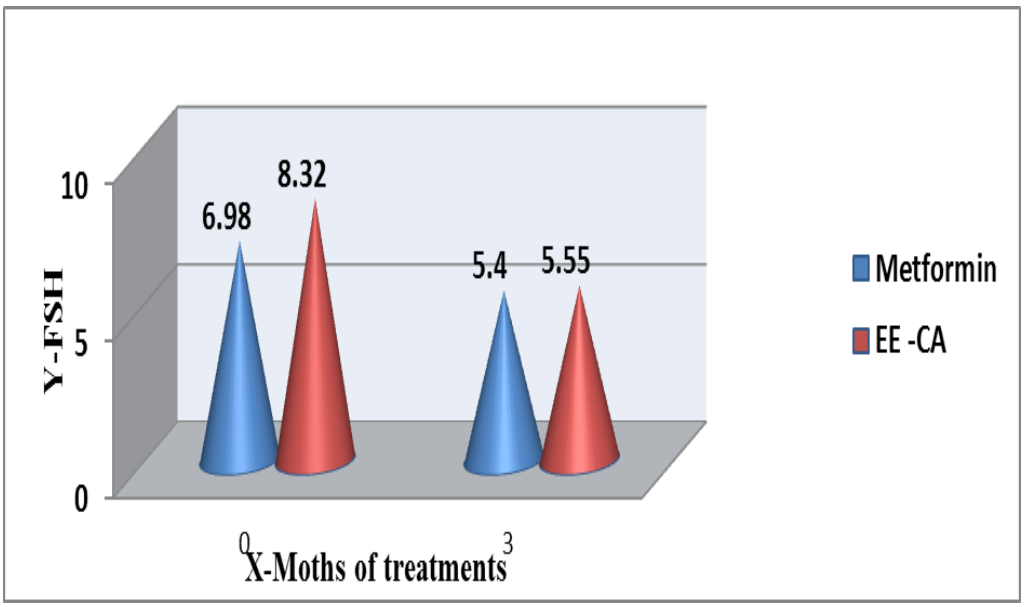

Figure 5: Comparison of Metformin and EE-CA based on FSH.

There is a significant difference between the before and after treatment values of FSH in Metformin group & EE-CA group and there is more mean difference in EE-CA (2.77) when compared to Metformin (1.571). Therefore we can say that EE-CA is more effective than Metformin. P value of FSH is P=0.001, i.e. P<0.05. Therefore, it is statistically significant.

COMPARISON OF METFORMIN AND EE-CA BASED ON FASTING INSULIN

Table 6: Comparison of Metformin and EE-CA based on Fasting Insulin

PARAMETERS	FASTING INSULIN	
DURATION OF TREATMENT (MONTHS)	METFORMIN	EE-CA
0	20.6±1.66	19.400±1.354
3	15.73±0.982	17.16±1.361
MEAN DIFFERENCE	4.871	2.237
P VALUE	*P* =0.001	

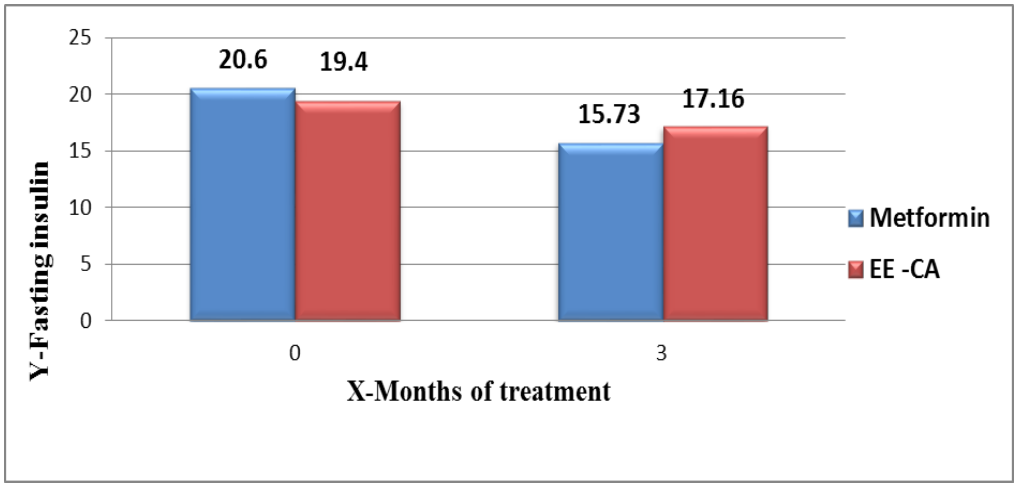

Figure 6: Comparison of Metformin and EE-CA based on Fasting Insulin.

There is a significant difference between the before and after treatment values of Fasting Insulin in Metformin group & EE-CA group and there is more mean difference in Metformin (4.871) when compared to EE-CA (2.237). Therefore we can say that Metformin is more effective than EE-CA. P value of Fasting Insulin is P=0.001, i.e. P<0.05. Therefore, it is statistically significant.

COMPARISON OF METFORMIN AND EE-CA BASED ON WAIST HIP RATIO

Table 7: Comparison of Metformin and EE-CA based on Waist Hip Ratio.

PARAMETERS	WAIST HIP RATIO	
DURATION OF TREATMENT (MONTHS)	METFORMIN	EE-CA
0	0.831±0.038	0.7660±0.0271
3	0.770±0.032	0.7254±0.0217
MEAN DIFFERENCE	0.0608	0.0405
P VALUE	*P* =0.001	

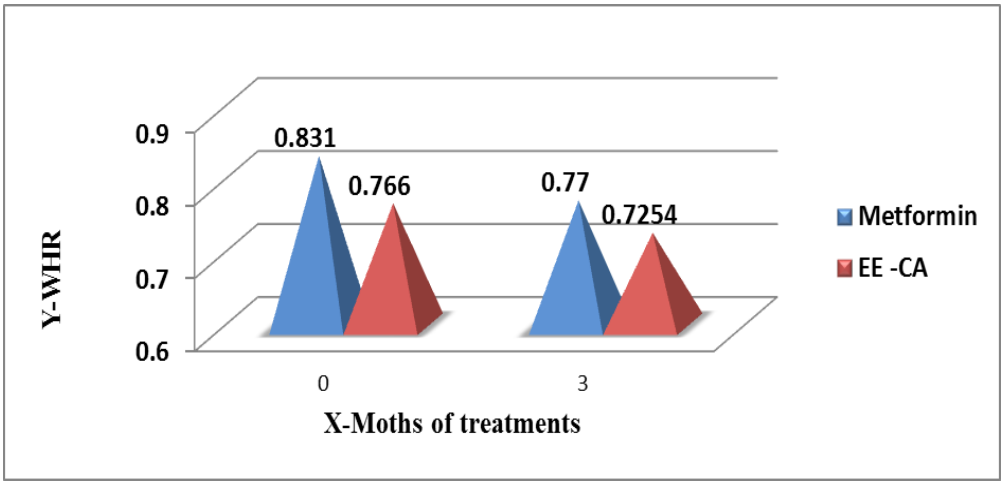

Figure 7: Comparison of Metformin and EE-CA based on WHR.

There is a significant difference between the before and after treatment values of WHR in Metformin group & EE-CA group and there is more mean difference in Metformin (0.0608) when compared to EE-CA (0.0405). Therefore we can say that Metformin is more effective than EE-CA. P value of WHR is P=0.001, i.e. P<0.05. Therefore, it is statistically significant.

COMPARISON OF METFORMIN AND EE-CA BASED ON DHEAS

Table 8: Comparison of Metformin and EE-CA based on DHEAS.

PARAMETERS	DHEAS	
DURATION OF TREATMENT (MONTHS)	METFORMIN	EE-CA
0	5.582±0.275	5.60±0.2417
3	5.30±0.244	3.097±0.865
MEAN DIFFERENCE	2.511	5.511
P VALUE	*P* =0.001	

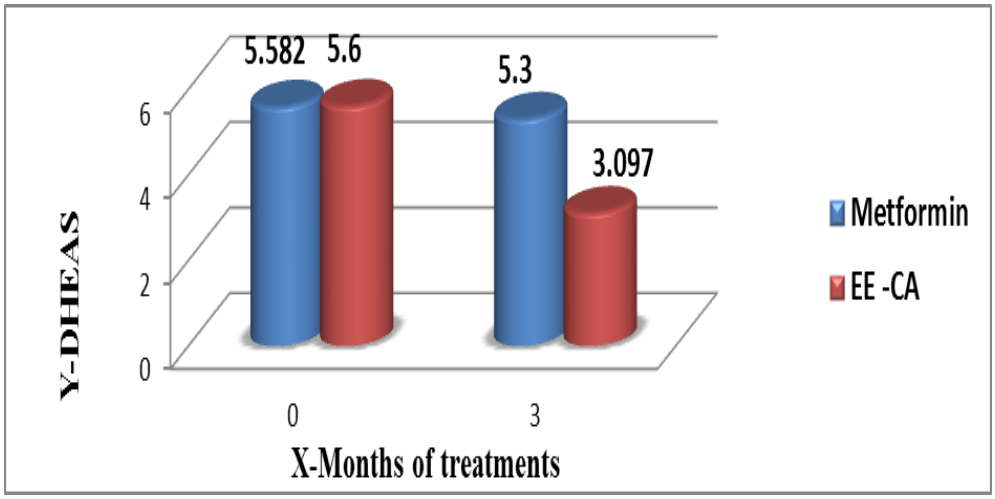

Figure 8: Comparison of Metformin and EE-CA based on DHEAS.

There is a significant difference between the before and after treatment values of DHEAS in Metformin group & EE-CA group and there is more mean difference in EE-CA (5.511) when compared to Metformin (2.511). Therefore we can say that EE-CA is more effective than Metformin. P value of DHEAS is P=0.001, i.e. P<0.05. Therefore, it is statistically significant.

COMPARISON OF METFORMIN AND EE-CA BASED ON ANTI MULLERIAN HORMONE

Table 9: Comparison of Metformin and EE-CA based on AMH.

PARAMETERS	AMH	
DURATION OF TREATMENT (MONTHS)	METFORMIN	EE-CA
0	11.74±0.634	11.99±0.5404
3	10.43±0.381	10.65±0.504
MEAN DIFFERENCE	1.342	1.342
P VALUE	*P* =0.001	

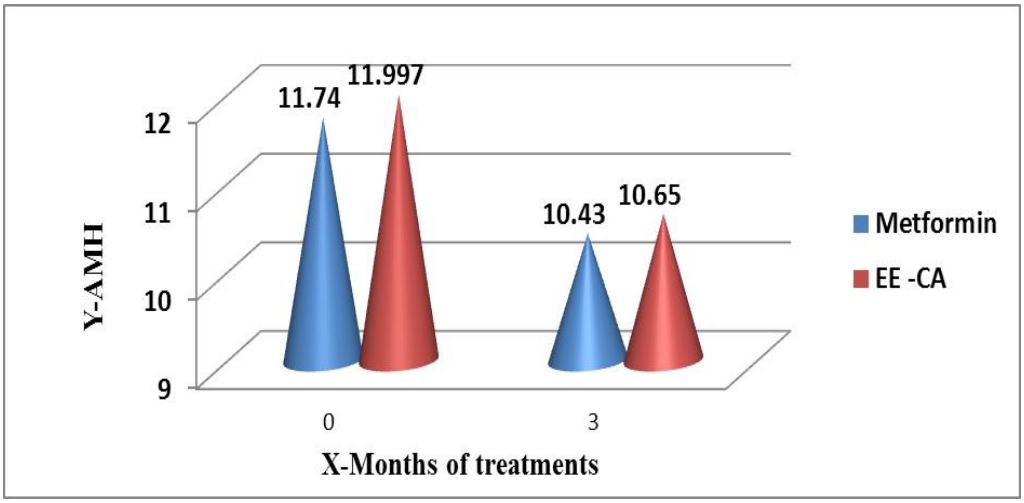

Figure 9: Comparison of Metformin and EE-CA based on AMH.

The mean difference in Anti Mullerian Hormone (1.342) when EE-CA compared to Metformin is same. P value of AMH is P=0.001, i.e. P<0.05. Therefore, it is statistically significant.

COMPARISON OF METFORMIN AND EE-CA BASED ON MORISKY 8 ITEM MEDICATION ADHERENCE SCALE (MMAS-8)

Table 10: Comparison of Metformin and EE-CA based on MMAS-8.

PARAMETERS	MMAS-8	
DURATION OF TREATMENT (MONTHS)	METFORMIN	EE-CA
0	6.20±0.531	6.00±0.0
3	7.51±0.507	7.31±0.471
MEAN DIFFERENCE	-1.314	-1.314
P VALUE	*P* =0.001	

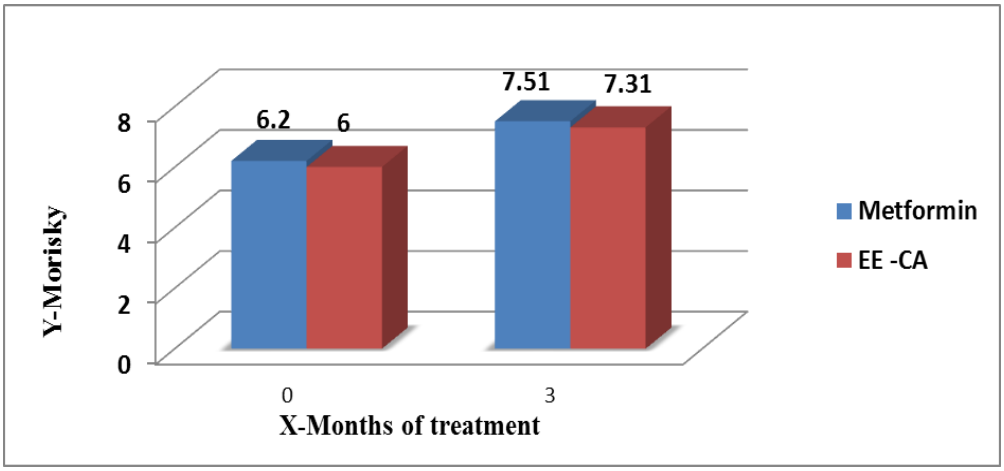

Figure 10: Comparison of Metformin and EE-CA based on MMAS-8.

The mean difference in Morisky 8 item medication adherence scale (-1.314) when EE-CA compared to Metformin is same. P value of MMAS-8 is P=0.001, i.e. P<0.05. Therefore, it is statistically significant.

MEDICATION ADHERENCE BEFORE AND AFTER PHARMACIST INTERVENTION

Table 11: Distribution of patients based on medication adherence before and after intervention.

MEDICATION ADHERENCE	BEFORE INTERVENTION		AFTER INTERVENTION	
	FREQUENCY	PERCENTAGE	FREQUENCY	PERCENTAGE
HAVING MEDICATION ADHERENCE	30	42.857%	50	71.428%
NON-ADHERENCE	40	57.142%	20	28.571%

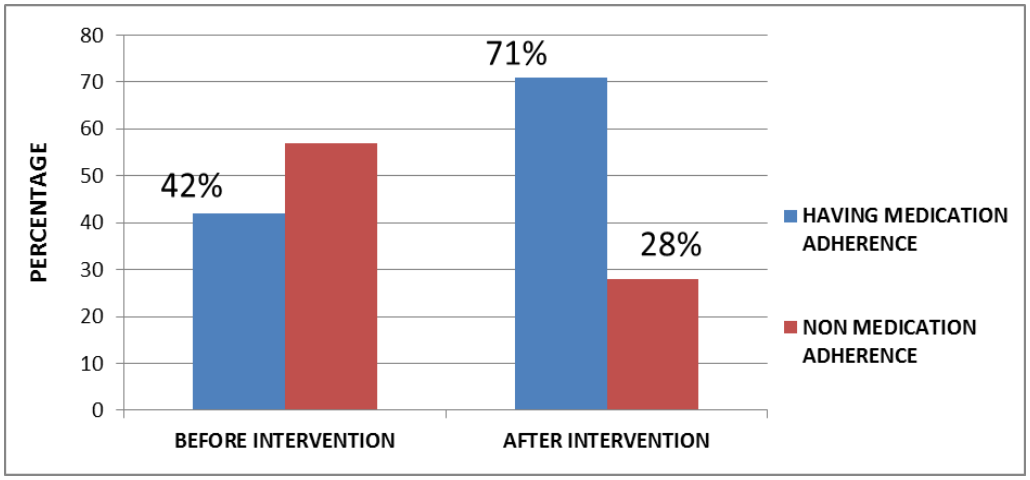

Figure 11: Distribution of patients based on medication adherence before and after intervention.

ADR EVALUATION OF METFORMIN

Table 12: ADR evaluation of Metformin.

ADR EVALUATION OF METFORMIN		
ADRs	**FREQUENCY**	**PERCENTAGE (%)**
DIARRHEA	15	42.85
ANOREXIA	5	14.28

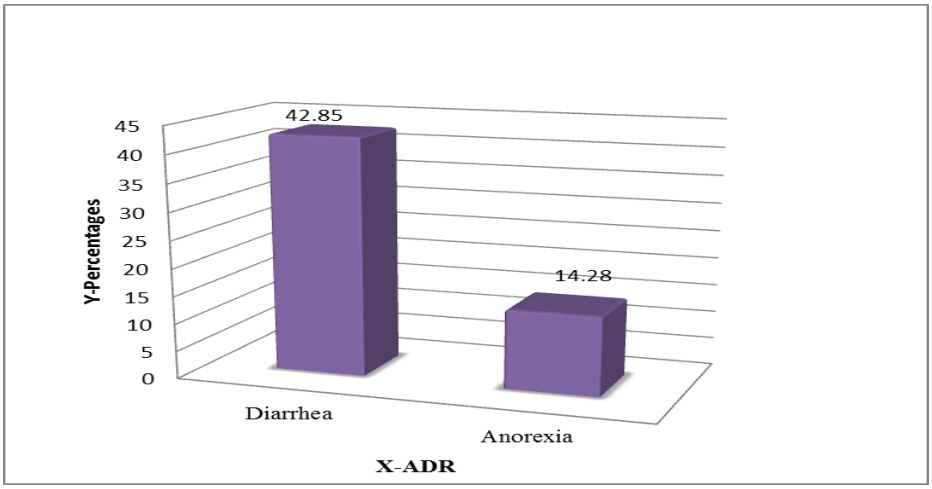

Figure 12: ADR evaluation of Metformin.

ADR EVALUATION OF EE-CA

Table 13: ADR evaluation of EE-CA.

ADRs	FREQUENCY	PERCENTAGE (%)
DIARRHEA	20	57.14
NAUSEA	10	28.57
WEIGHT GAIN	6	17.14
BREAST TENDERNESS	3	8.57
BREAKTHROUGH BLEEDING	7	20

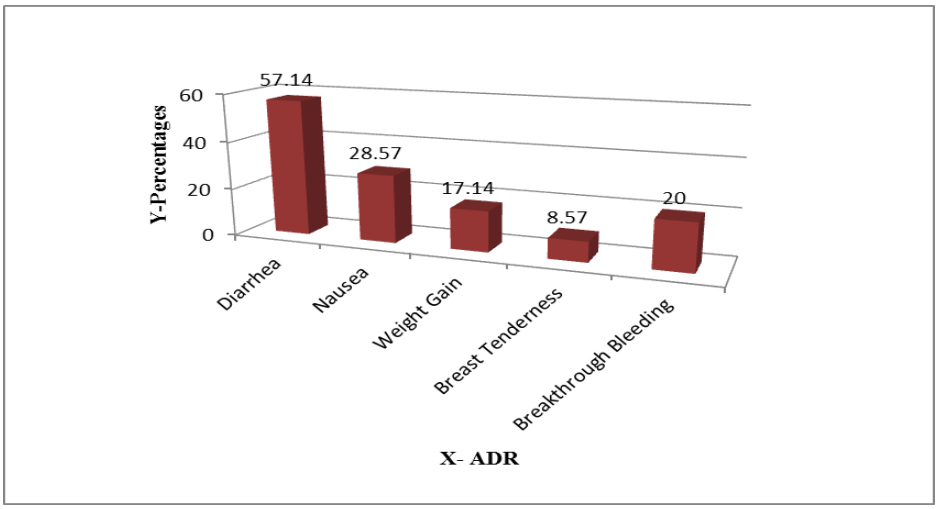

Figure 13: ADR evaluation of EE-CA.

DISCUSSION

The study was done to compare the effectiveness of Metformin and Ethinyl Estradiol - Cyproterone Acetate in the management of hyperandrogenism in PCOS patients. 70 PCOS patients were enrolled in the study based on inclusion and exclusion criteria. Here the effectiveness of the two drugs were analyzed by comparing parameters like Testosterone, LH, FSH, Fating Insulin, DHEAS, Anti Mullerian Hormone, Body Mass Index and Waist Hip Ratio. Hirsutism score was calculated using Ferriman-Gallwey score and the medication adherence was evaluated by Morisky 8 Item medication adherence scale. ADR of the drugs were also evaluated.

EVALUATION OF PARAMETERS

➢ TESTOSTERONE

There is a significant difference between the before and after treatment values of Testosterone in Metformin group & EE-CA group and there is more mean difference in EE-CA when compared to Metformin. Since P = 0.001, i.e. P<0.05, it is statistically significant.

➢ LH

There is a significant difference between the before and after treatment values of LH in Metformin group & EE-CA group and there is more mean difference in EE-CA when compared to Metformin. Since P = 0.001, i.e. P<0.05, it is statistically significant.

➢ FSH

There is a significant difference between the before and after treatment values of FSH in Metformin group & EE-CA group and there is more mean difference in EE-CA when compared to Metformin. Since P = 0.001, i.e. P<0.05, it is statistically significant.

➢ FASTING INSULIN

There is a significant difference between the before and after treatment values of Fasting Insulin in Metformin group & EE-CA group and there is more mean difference in Metformin when compared to EE-CA. Since P = 0.001, i.e. P<0.05, it is statistically significant.

➢ DHEAS

There is a significant difference between the before and after treatment values of DHEAS in Metformin group & EE-CA group and there is more mean difference in EE-CA when compared to Metformin. Since P = 0.001, i.e. P<0.05, it is statistically significant.

- **ANTI MULLERIAN HORMONE**

The mean difference in Anti Mullerian Hormone when EE-CA compared to Metformin is same. Since P = 0.001, i.e. P<0.05, it is statistically significant.

- **BODY MASS INDEX**

There is a significant difference between the before and after treatment values of BMI in Metformin group & EE-CA group and there is more mean difference in EE-CA when compared to Metformin. Since P = 0.001, i.e. P<0.05, it is statistically significant.

- **WAIST HIP RATIO**

There is a significant difference between the before and after treatment values of WHR in Metformin group & EE-CA group and there is more mean difference in Metformin when compared to EE-CA. Since P = 0.001, i.e. P<0.05, it is statistically significant.

- **MORISKY 8 ITEM MEDICATION ADHERENCE SCALE**

The mean difference in Morisky 8 item medication adherence when EE-CA compared to Metformin is same. Since P = 0.001, i.e. P<0.05, it is statistically significant.

- **FERRIMAN-GALLWEY SCORE**

There is a significant difference between the before and after treatment values of FG score in Metformin group & EE-CA group and there is more mean difference in EE-CA when compared to Metformin. Since P = 0.001, i.e. P<0.05, it is statistically significant.

- **MEDICATION ADHERENCE**

From 70 PCOS patients, before the pharmacist intervention 42.85% was having medication adherence and 57.14% was with non adherence when assessed with MMAS-8 medication adherence scale. After the intervention 71.42% was having medication adherence and 28.57% was with non adherence. P<0.05 shows that the pharmacist intervention was significant to improve medication adherence among the study subjects.

- **ADR EVALUATION**

Among 35 PCOS subjects who were treated with Metformin, 42.85% were affected with Diarrhea and 14.28% were affected with Anorexia. From the EE-CA group consisting of 35 subjects, 57.14% were affected by Diarrhea, 28.57% with Nausea, 17.14% with Weight gain, 8.57% with Breast tenderness and 20% were affected by breakthrough bleeding. Compared to EE-CA, Metformin was found to have fewer side effects.

CONCLUSION

PCOS is one of the most common endocrine disorders in women of reproductive age group. The parameters such as testosterone, LH, FSH, DHEAS were found to be lowered when treated with EE-CA than in case of Metformin. Also, Fasting Insulin, BMI, Waist Hip Ratio were reduced much more significantly in Metformin treatment when compared to EE-CA. It was observed that both EE-CA and Metformin are safe and effective in treatment of PCOS patients, both drugs showing overall beneficial effects on most of the clinical complaints characteristic of this common disorder. However, the data suggest that EE-CA is a more effective way of treating hyperandrogenism and menstrual dysfunction, considering that the improvement in hirsutism, the amelioration of hyperandrogenemia, and restoration of regular menstrual cycles occur more frequently with EE-CA than with Metformin. On the other hand, Metformin clearly outperforms EE-CA in improving insulin resistance, reducing body mass index and also improving ovulation and proved to be with lesser ADRs when compared to EE-CA. With proper medication adherence and by modifying the lifestyle, the PCOS could be controlled to an extent. From this review it could be concluded that EE-CA proved to be much more effective in controlling Hyperandrogenism as compared to Metformin.

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