The Professional Medical Journal
www.theprofesional.com

DOI: 10.29309/TPMJ/18.4295

ORIGINAL PROF-4295

PCOS;
COMPARISON BETWEEN PIOGLITAZONE AND METFORMIN FOR OVULATION IN PATIENTS

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Article received on:
07/09/2017
Accepted for publication:
30/12/2017
Received after proof reading:
05/04/2018

ABSTRACT... Objectives: The objective is to compare the efficacy of Pioglitazone and Metformin for ovulation in patients of polycystic ovarian syndrome. **Study Design:** Randomized control trial. **Setting:** Department of Obstetrics and Gynecology, Nishtar Hospital Multan. **Period:** January 2017 to June 2017. **Methodology:** Total number of 66 patients was recruited for this study. These patients were admitted through or outpatient department. Group A and Group B, 33 patients each. In Group-A patients received metformin while in Group B pioglitazone was administered. Sample size was calculated using the reference study by Chaudhry I et al (9) using sample size calculator for two proportions (power of study 80% and confidence interval 95% where prevalence (P1) was 52.17% and (P2) 75%). In group-A patients, Metformin with dose of 1500 mg per day in three divided doses were given for 6 months. In group B patients, Pioglitazone 15mg was administered for 6 months. At the end of 6 months, all the patients were evaluated for efficacy. **Results:** Total no. of 66 patients was included. The mean age and BMI of the patients was 29.35±4.01 years and 29.74±2.75 kg/m^2 respectively. The age distribution noted as 66.7% (n=44) patients between 18-30 years and 33.3% (n=22) between 31-37 years. BMI distribution observed as 45.5% (n=30) patients between 24-29 kg/m^2 and 54.5% (n=36) patients between 30-34 kg/m^2. These 100% (n=66) patients were divided into 2 groups equally, 33 in each, i.e. group A and group B. The mean age and BMI of the patients of group A was 29.42±4.32 years and 29.87±2.58 kg/m^2 respectively, while the mean age and BMI of the patients of group B was 29.27±3.75 years and 29.60±2.94 kg/m^2 respectively. Ovulation was noted as 42.4% (n=14) and 45.5% (=15) for groups A and B respectively. No association was found between efficacy and ovulation (p=0.849). Efficacy was notes as 69.7% (n=23) and 72.7% (n=24) for group A and group B respectively. No difference was found between efficacy and groups i.e. between pioglitazone and metformin for ovulation in patients of polycystic ovary syndrome (p=0.786). Similarly, no association was found between efficacy with age (p=0.442) and BMI (p=0.728), after applying the chi-square. **Conclusion:** This study concludes that Pioglitazone is as much effective as metformin for ovulation induction in women with PCOS.

Key words: Pioglitazone, Metformin, Polycystic Ovarian Syndrome.

Article Citation: Tariq A, Mir MA, Babar S, Akhtar R. PCOS; comparison between pioglitazone and metformin for ovulation in patients. Professional Med J 2018; 25(4):568-572. **DOI:**10.29309/TPMJ/18.4295

INTRODUCTION

An endocrine disorder leading to cyst formation in the ovaries among the women of reproductive age is known as polycystic ovary syndrome. Its prevalence among females of child bearing age is reported to be 6.8% to 18%.[1] Presenting symptoms of cases of polycystic ovary syndrome are hyperandrogenism, obesity and infertility.[2] An abnormal increase leads to increased androgen secretion leads to excessive estrogen precursors in granulosa cells along with early appearance of luteinizing hormone receptors, in presence of hyperinsulinemia. This results in synthesis of estrogen in these cells by ofaromatase enzyme.[3] These entire phenomenons in the end result in increased estrogen hormone secretion and through negative feedback mechanism on FSH and positive feedback on luteinizing hormone, thus resulting in interrupted folliculogenesis. Excessive secretion of androgens and resistance to insulin comprise the causes of chronic infertility by anovulation.[4] Treatment of an ovulation and chronic infertility in patients with polycystic ovary syndrome has multiple options including weight reduction, assisted reproductive therapy (ART), metformin, thiazolidinedione, letrozole and

clomiphene citrate.[5] Initial oligo-ovulatory and anovulatory cases of polycystic ovary syndrome can be improved by the use of metformin and it can also restore menstrual cycles. Metformin is used as a second-line therapy in some setups as it can improve ovulation and reduce the metabolic effects of polycystic ovary syndrome.[6] There are many studies which provide sufficient reports on effects of metformin on endometrial surface, which in turn makes the endometrium a suitable place for pregnancy to occur.

TZDs are highly selective agonists of PPAR-γ when used as diabetes treatment. Thiazolidinedione, are insulin stimulators and this group contains a number of drugs like, pioglitazone, troglitazone and rosiglitazone. PPAR- γ may play a role in pathogenesis of polycystic ovary syndrome and through its different hypotypes, it seems to be involved as a major factor in fertility and metabolism. Polycystic ovary syndrome also involves insulin resistance which is observed in both obese as well as lean patients with polycystic ovary syndrome, and seems to be eminent part of polycystic ovary syndrome.[7] By decreasing insulin resistance in peripheral parts of the body, PPAR- γ agonists can indirectly decrease androgen genesis in ovaries. This provides both theoretical and practical evidence of effectiveness of treatment of polycystic ovary syndrome by TZDs. TZD therapy[8] has undergone many trails, clinical studies and investigations in animals, almost all the trails have shown high efficacy of this therapy. But still needs evidence based conclusions. Verification of safety and efficacy TZD therapy for PCOS treatment cannot be done on large-scale clinical trials. So its use has not been made public and still is not recommended by all the setups of PCOS treatment. Our study is a randomized control trail which was conducted to assess the efficacy and safety of PCOS treatment on clinical levels by comparing Metformin and Pioglitazone.

Rationale of this study is to compare efficacy of metformin and pioglitazone in treating anovulation and induction of ovulation in PCOS patients recruited from local population. Even though many studies have compared these two drugs but it was not sufficient enough to establish a proper evidence based support. So this study is going to aim in not only providing clinicians with an effective drug but also provide local stats about these drugs and their efficacy. In the end on the basis of evidence based results, we shall be able to recommend on practical basis in our setups by recommending more effective drug in PCOS patients and reduce infertility. Reference for our study was taken from a previous study conducted by Chaudhry I et al.[9]

MATERIALS AND METHODS

This randomized control trial was conducted in department of Obstetrics and Gynecology, Nishtar Hospital Multan from January 2017 to June 2017. Total number of 66 patients was recruited for this study. These patients were admitted through emergency or outpatient department. Authorization for the study protocol was obtained from the Hospital Ethics Committee and informed consent was taken from the patients. Exclusion criterion was set as follows; patients taking drugs like, estrogen, progesterone and anti-diabetic, pregnant women, nursing women, history of ISD and hyperthyroidism and patients with chronic disease like CLD, chronic liver failure. Patients were divided into two equal groups, Group A and Group B, 33 patients each. In Group A patients received metformin while in Group B pioglitazone was administered. Sample size was calculated using the reference study by Chaudhry I et al[9] using sample size calculator for two proportions (power of study 80% and confidence interval 95% where prevalence (P1) was 52.17% and (P2) 75%). Non-probability consecutive sampling technique was used.

Metformin was given as a 1500 mg dose per day in three doses for almost 6 months. Similarly in group B pioglitazone was also administered for 6 months. At the end of the treatment i.e. after 6 months patients were evaluated for efficacy. CBP, ESR, serum urea and creatinine, TSH, liver function tests, lipid profile, serum prolactin, serum testosterone, luteinizing hormone and FSH ratio and oral GTT with 75 gm glucose and insulin levels to investigate hyperinsulinemia. Other investigations involved USG abdomen and

pelvis to look for ovarian cysts, and other features of enlarged ovaries like ovaries enlarged 3-5 times the normal size and contained 7-10 micro cysts <5mm, thick and white, were evaluated by ovulation study. Six months period of treatment was advised with follow up every month. At every follow up visit, a questionnaire was given about compliance, side effects and individual assessment of the tolerability of metformin and pioglitazone. At the end of the treatment, i.e. at the end of 6 months again all the baseline investigations were performed to assess both clinical and biochemical findings.

Therapies for other diseases were allowed to carry on, only if they didn't interfere with the parameters under study in both groups demographic variables like age and BMI were calculated when treatment started and BMI was also calculated at each visit. The efficacy of drugs was labeled as good or poor based upon normalization of LH (5-25 IU\L), FSH (1.4-18.5 IU\L), prolactin (<20ng\ml) and reduction of BMI by 15-20%. Moreover ovulation was confirmed by USG abdomen by observing the formation of corpus leutium. Statistical analysis of the results was done using computer software SPSS version 23. Mean and standard deviation of demographic variables was calculated and association of these variables with outcome variable was checked using Chi square test (no association was found of efficacy with age p=0.442 and BMI p=0.728).

RESULTS

During the period of this study, a total number of 100% (n=66) patients were included. The mean age and BMI of the patients was 29.35±4.01 years and 29.74±2.75 kg/m^2 respectively. The age distribution noted as 66.7% (n=44) patients between 18-30 years and 33.3% (n=22) between 31-37 years. BMI distribution observed as 45.5% (n=30) patients between 24-29 kg/m^2 and 54.5% (n=36) patients between 30-34 kg\m^2.

These 100% (n=66) patients were divided into 2 groups equally, 33 in each, i.e. group A and group B. The mean age and BMI of the patients of group A was 29.42±4.32 years and 29.87±2.58 kg/m^2 respectively, while the mean age and BMI of the patients of group B was 29.27±3.75 years and 29.60±2.94 kg/m^2 respectively. Ovulation was noted as 42.4% (n=14) and 45.5% (=15) for groups A and B respectively. No association was found between efficacy and ovulation (p=0.849) (Table-I). Efficacy was notes as 69.7% (n=23) and 72.7% (n=24) for group A and group B respectively. No difference was found between efficacy and groups i.e. between pioglitazone and metformin for ovulation in patients of polycystic ovary syndrome (p=0.786). Similarly, no association was found between efficacy with age (p=0.442) and BMI (p=0.728), after applying the chi-square (Table-I).

Variable		Efficacy		Total	P-value
		Yes	No		
Groups	A	23	10	33	0.786*
	B	24	9	33	
Total		47	19	66	
*P-value is statistically insignificant with Pearson χ^2 = 0.074, d.f=1					
Stratified Age	18-30 Years	30	14	44	0.442*
	31-37 Years	17	5	22	
Total		47	19	66	
* P-value is statistically insignificant with Pearson χ^2 = 0.591, d.f=1					
BMI	24-29 kg/m^2	22	8	30	0.728*
	30-34 kg/m^2	25	11	36	
Total		47	19	66	
* P-value is statistically insignificant with Pearson χ^2 = 0.121, d.f=1					
Ovulation	Yes	21	8	29	0.849
	No	26	11	37	
Total		47	19	66	
* P-value is statistically insignificant with Pearson χ^2 = 0.036, d.f=1					

Table-I. Association of efficacy with groups, age and BMI (n = 66)

DISCUSSION

It has been stated earlier that many studies have been conducted about the efficacy of drugs in treating anovulation caused by PCOS, one of these studies showed a considerable benefit of metformin in inducing ovulation in cases of polycystic ovary syndrome.[10] In 44.2% of the patients of polycystic ovary syndrome ovulation was restored as a result of metformin administration. In the same study Sangeeta S has suggested that pioglitazone is a possible new treatment of polycystic ovary syndrome as it has beneficiary effect on ovulation, restores menstrual cyclicity, improves overall ovulation rates, achieves better clinical outcomes of hyperandrogenism and it can delay or stop type 2 diabetes onset and other chronic disorders.[11] A study about the efficacy of pioglitazone showed its benefit on hirsutism, insulin sensitivity and menstrual frequency.[12] Another study by Ota H et al[13] has documented 77.78% ovulation induction in cases of polycystic ovary syndrome when administered with pioglitazone.

Li XJ et al[14] conducted a meta-analysis about efficacy of TZDs and metformin and found that TZDs are more efficient as compared to metformin in reducing free testosterone levels and dehydroepiandrosterone sulphate levels with P value 0.002 when treated for 3 months. In another meta-analysis metformin was again found to be quite efficient in inducing ovulation.[15]

TZDs not only effect the induction of ovulation but also play role in improvement of insulin sensitivity and reduction of androgenaemia in polycystic ovary syndrome patients.[16] Brettenthaler et al stated that ovulation rate increased from 5.6% to 41.2% in cases of polycystic ovary syndrome when treated with pioglitazone.[17] When pioglitazone was used in combination with metformin, in treating non-responsive polycystic ovary syndrome patients, the combination proved to improve insulin sensitivity; it reduced androgen levels and also induced ovulation.[18] A meta-analysis indicated that pioglitazone ameliorated menstrual cycle and ovulation better than metformin and metformin ameliorated BMI and F-G scores better than pioglitazone in treating patients with PCOS. Pioglitazone might be a good choice for the patients with PCOS who were intolerant or invalid to metformin for the treatment.[19] In another study which was not directed to evaluate the ovulatory efficacy of these drugs showed that pioglitazone is as effective as metformin in improving insulin sensitivity and hyperandrogenism, despite an increase in body weight, body mass index, and the waist to hip ratio associated with pioglitazone.[20]

CONCLUSION

This study concludes that Pioglitazone is as much effective as metformin for ovulation induction in women with PCOS. Ovulation rate was found similar in both groups.

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