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A Randomized Controlled Trial Comparing the Efficacy of Atorvastatin and Metformin in the Patients with Polycystic Ovary Syndrome

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Abstract:
INTRODUCTION: Polycystic ovary syndrome(PCOS) may be associated with overweight and obesity,hyperandrogenism, insulin resistance and impaired glucose tolerance, anovulation and infertility and abnormal lipid profile. Aim of our study is to compare the efficacy of metformin and atorvastatin in treatment of PCOS.
METHODS: A total of 108 patients suffering from polycystic ovary syndrome were recruited in this study according to Modified Rotterdam criteria. They were divided into equal three groups each comprising of 36 patients. They were given single blind (patient) treatment either with metformin (500mg twice daily) or atorvastatin (20mg once daily) or with both (metformin 500mg twice daily and atorvastatin 20mg once daily). The patients were followed up at the end of third month with appropriate investigations.
RESULTS: Reduction of BMI after three months treatment was statistically significant in each of three groups (metformin, atorvastatin and combined group).
*Total testosterone level (ng/dl) was decreased significantly only in metformin group (**p value 0.001**) but not in atorvastatin or in combined group. Insulin resistance (HOMA-IR) was decreased significantly in each of the three groups after treatment and it was comparable at baseline and after three months of treatment across the groups **(p value 0.2355 and 0.8176**). There were minor difference in improvement of lipid profile, improvement of hirsutism (FG score) and acne(acne score) among the groups.*
***Conclusion:** Treatment with atorvastatin and combination of drugs (metformin and atorvastatin) are as effective as metformin in reducing BMI, total testosterone level, fasting insulin level, FBS, PPBS, insulin resistance.*

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I. Introduction

Polycystic ovary syndrome(PCOS) is arguably one of the most common endocrine disorders in women of reproductive age, affecting 5% to 10% of women worldwide[----]. Overweight and obesity,hyperandrogenism, insulin resistance and impaired glucose tolerance, anovulation and infertility and abnormal lipid profile are the problems associated with PCOS [1,2]. The overall prevalence of insulin resistance among women with PCOS is between 50% and 70%, and greater in obese than in lean women with PCOS[2]. Hyperandrogenism is the key feature of PCOS. Increased circulating insulin level cause or contribute to hyperandrogenism in the women with PCOS. In our study we assessed insulin resistance by homeostatic model assessment of insulin resistance (HOMA-IR). It is calculated as[2]:

[glucose (mg/dl)] [insulin (µU /ml]/405.

Values greater than 3.2-3.9 generally indicate insulin resistance.

We assessed severity of hirsutism clinically by Ferriman-Gallwey score[3]. It is the most common method for grading the extent of hirsutism, assigning a score from 0-4 in each of 9 androgen sensitive areas. We considered a total score of 8 as threshold value. A total score more than 8 is defined as hirsutism.About 50% of PCOS patients are obese[4]. Women with PCOS have greater truncal abdominal fat demonstrated by higher waist circumference. Metformin, an insulin sensitizer, is an oral biguanide antihyperglycemic drug has been used extensively to treat insulin resistance, hyperandrogenism and oligo-ovulatory infertility in PCOS patients.

Recent studies show that statin (HMG-CoA reductase inhibitor) increases insulin sensitivity, decreases androgen level and improves lipid profile[5,6]in patients with polycystic ovaries. Our study is to determine the comparative efficacy of atorvastatin and metformin in reducing androgen level, enhancing insulin sensitivity and improving lipid profile.

II. Materials and methods

The prospective, randomised, single blind, interventional, unicentric study was conducted in Infertility Clinic and Gynaecology Out Patient Department and Endocrinology Out Patient Department of IPGME&R, Kolkata, West Bengal for one year. Study protocol, informed consent form and case report form were submitted to the ethical committee of IPGME&R, Kolkata for approval. Subjects recruitment commenced only after such approval was obtained.

15-40years aged women with modified Rotterdam criteria (at least two of the following criterias such as presence of clinical and/or biochemical evidence of hyperandrogenism after exclusion of other causes of hyperandrogenism, oligo-or anovulation and polycystic ovaries) were included in our study. Exclusion criterias were current pregnancy or lactation, current use of contraceptives, insulin sensitising medications, thyroid disease, type 1 or type 2 diabetes mellitus, congenital adrenal hyperplasia, cushing syndrome , deranged liver or kidney function tests. All eligible patients were randomised by randomisation table generated by computer. Then they had given single blind (patient) treatment either with atorvastatin or with metformin or with both according to randomisation done by computer generated randomisation table. Sample size was 108. They were divided into equal three groups- each comprising of 36 patients (A= atorvastatin=36, M=Metformin=36, AM=Atorvastatin+Metformin=36). Atorvastatin was given orally at a dose of 20mg once daily and Metformin was given orally 500mg twice daily. Combination treatment was given atorvastatin 20mg orally once daily and metformin 500mg twice daily. Baseline parameters such as total testosterone, fasting blood sugar, fasting insulin, USG lower abdomen and pelvis with folliculometry, serum lipid profile, BMI, Ferriman Gallwey hirsutism score, acne score were measured at the beginning and at the 3rd month. Collected data was tabulated, and then analyzed by software-Statistica version 6[Tulsa ,Oklahoma:Statsoft Inc,2001]. Numerical variables analysed by ANOVA test, Dunn's test, Student's paired test and Wilcoxon's matched pairs signed rank test. Categorical variables analysed by Chi-square test.

III. Results and analysis

Table 1 shows that the difference in the age distribution among the groups is not significant (p value 0.477). Most of the PCOS patients come to our institution are of 21-30 years of age. It is obvious that BMI has reduced significantly (p value<0.05) in each group after three months treatment with respective drug but when compared with each other at baseline and after treatment, they are comparable (p value 0.958 and 0.778 respectively).

With three months treatment with metformin, reduction of total testosterone level is significant (p value<0.05) but when treated with atorvastatin or both drugs(combined) the reduction is not significant (p value 0.574 and 0.065 respectively). Again the difference in reduction is not significant after treatment when compared with each others (p value 0.6844 after treatment).So this effect is comparable among the groups, as shown in table 2.We can see fasting insulin level has been decreased significantly in individual group after three months treatment (p value for metformin, atorvastatin and combined group is 0.000, 0.045 and 0.000). But there is no statistically significant difference at baseline and after treatment across the groups (p value- 0.3369 and 0.8576 respectively). From the table 2, we can see FBS level has been decreased in individual group after three months treatment (p value for metformin, atorvastatin and combined group is 0.000, 0.008 and 0.000). But there is no significant difference at baseline and after treatment across the group (p value- 0.1999 and 0.7315 respectively). In respect to HOMA-IR level, it has been decreased significantly in each individual group(metformin, atorvastatin and combibed group-p value 0.000,0.026 and 0.000 respectively).). But there is no significant difference at baseline and after treatment across the group (p value- 0.2355 and 0.8176 respectively).

Table 3 shows despite some minor changes in lipid profile pattern among different groups, it is statistically significant at baseline and after treatment (Chi-square test p value 0.825 and 0.861 respectively).

From table 4 we can see that though there is minor differences in FG score distribution among different groups, it is not statistically significant at baseline and after treatment (Chi-square test p value 0.966 and 0.997 respectively). Table 5 shows that though there is minor difference in acne score distribution in different groups, it is not statistically significant at baseline and after treatment (Chi-square test p value 0.241 and 0.355 respectively). Overall complication rate is more in combined group (25%) as evidenced in table no. 6.

Discussion: In the present study, mean age (24.9, 24.3 and 25.3 in years respectively) and the baseline BMI of the selected subjects were comparable among all the groups. We found that BMI has reduced significantly in each group (metformin or atorvastatin or in combined group) after three months treatment (p

value 0.000, 0.013 and 0.000 respectively). In one comparative study (metformin, simvastatin and combined group) by Banaszewska et al concluded that BMI has declined after all treatments with no statistically significant difference between the treatment groups[7]. The total testosterone level decreased significantly after three months treatment with metformin (p value 0.001) but in atorvastatin and in combined group (atovastatin plus metformin) reduction of total testosterone level is not significant (p value 0.574 and 0.065 respectively) and also it is not statistically significant among the groups after treatment (p value after treatments 0.684). It is well established that metformin decreases androgen level[8].Banaszewska et al concluded that total testosterone level has declined after all treatments with no statistically significant difference between the treatment groups[7].In a study by Sathyapalan et al, it was shown that after 12 weeks of atorvastatin therapy there was statistically significant decrease in free androgen index and testosterone level in women with polycystic ovary[9].In another study[10] by Kaya C et al, it was concluded that both statins(atorvastatin and simvastatin) are effective in reducing hyperandrogenemia in women with PCOS . A randomized controlled study by Sathyapalan et al it was concluded that three months treatment with atorvastatin or metformin significantly decreased androstenedione and dehydroepiandrosterone sulphate concentration[11]. Fasting insulin has decreased significantly after three months treatment either with metformin or with atorvastatin or with atovastatin and metfomin (combined) [p value -0.000,0.045 and 0.000 respectively].But across the groups the fasting insulin level at baseline and after three months treatment are comparable (p value at baseline and after three months treatment 0.3369 and 0.8576 across the groups). In a study by Kaya C et al it was concluded that atorvastatin decreased fasting insulin level significantly in patients with polycystic ovary syndrome[10].In a study by Sathyapalan et al it was revealed that after three months treatment with atorvastatin there significant reduction of insulin resistance in the patients with polycystic ovary syndrome[9].Our study shows that statin decreases the fasting insulin level as other studies showed. But comparative efficacy between atorvastatin and metformin was not determined previously which was shown in our study. We can see FBS level has been decreased significantly in each of the treatment group after three months of therapy with respective drug (metformin ,atorvastatin and combined group- p value 0.000, 0.008 and 0.000 respectively). FBS level at baseline and at the end of study across the groups is comparable (p value 0.1999 and 0.7315 respectively. HOMA-IR level has been decreased significantly in each individual group (metformin, atorvastatin and combibed group- p value is 0.000, 0.026 and 0.000 respectively).). But there is no significant difference at baseline and after treatment across the group (p value- 0.2355 and 0.8176 respectively).Metformin is well known to decrease insulin resistance in PCOS patients[8].Few recent studies[9,10] show that atorvastatin decreases fasting insulin level and insulin resistance.

In one study[12] by Karimzadeh M. A et al showed that there was improvement of lipid profile with treatment with metformin.In a study[7] by sathyapalan et al lipid profile improved only in simvastatin and combined (simvastatin plus metformin) group but not in metformin group.In our study, we can see that lipid profile has improved in 9.44% of patients in atorvastatin and in combined group where as in metformin group it is 11.11%. Again across the group at baseline and after treatment result is comparable (Chi-square test p value 0.825 and 0.861 respectively). From table 4 we can see that though there is minor difference in improvement of hirsutism score (Ferriman Gallway score) in different groups after treatment, it is not statistically significant (Chi-square test p value 0.997 after treatment).In our study, from table 5 we can see that though there is some difference in improvement of acne score in different groups after treatment, it is not statistically significant (Chi-square p value 0.355 after treatment).Also there was no significant difference at baseline (Chi-square test p value 0.241). Four patients in metformin group and 5 patients in combined group suffered from minor gastrointestinal side effects that did not require discontinuation of treatment. No patient in atorvastatin group or in combined group suffered from musle pain/ myopathy. 3 patients in atorvastatin group and 4 patients in combined group suffered from minor elevation of transaminases (not more than three times of normal.

IV. Conclusions

Treatment with atorvastatin and combination of drugs (metformin and atorvastatin) are as effective as metformin in reducing BMI, total testosterone level, fasting insulin level, FBS, PPBS, insulin resistance though treatment with atorvastatin and combination of drugs do not have significant effect on total testosterone level. There is no difference in efficacy of metformin, atorvastatin and combination of these drugs in improvement of lipid profile, hirsutism or acne in patients with polycystic ovary syndrome and atorvastatin is as effective as metformin in treatment of polycystic ovary syndrome. Further studies with large number of patients with longer follow up needed to establish the role of atorvastatin as an alternative to metformin in the treatment of polycystic ovary syndrome.

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Table 1: Showing age, BMI distribution in different groups

Parameters (Mean±SD)	Metformin group	Atorvastatin group	Combined group	P value
Age in years	24.9±3.28	24.3±3.85	25.3±3.31	0.477
Baseline BMI	25.4 ± 3.09	25.2±2.71	25.2±2.40	0.958
BMI at the End of study	24.5 ± 2.66	24.9±2.65	24.6±2.12	0.778

Table-2: Testosterone level (ng/dl) at baseline and after treatment(after three months) in different groups

Parameters(Mean±SD)	Metformin	Atorvastatin	Combined	P value
Baseline testosterone level (ng/dl)	65.6±20.70 67.8	59.9±23.57 52.8	68.3±18.88 74.9	0.3489
End of study testosterone level (ng/dl)	62.4±19.14 67.6	58.5±22.07 52.8	65.3±15.94 69.6	0.6844
Baseline Fasting insulin level (µu/ml)	18.2±7.22 15.9	18.1±6.58 17.4	19.8± 7.45 23.5	0.3369
End of study Fasting insulin level (µu/ml)	16.4±6.32 15.1	16.8±6.18 14.4	17±5.50 18	0.8576
Baseline FBS level (mg/dl)	102.7±15.70 101	100.1±15.69 96	105±16.06 114.5	0.1999
End of study FBS level (mg/dl)	96.8±12.73 98.5	98±14.18 96	99.3±12.38 100.5	0.7315
Baseline HOMA-IR	4.8±2.45 3.5(7.2-2.7)	4.6±2.30 4.2(6.7-2.5)	5.3±2.61 6.7(7.8-2.6)	0.2355
End of study HOMA-IR	4±1.94 3.3(5.4-2.5)	4.2±2.11 3(5.7-2.4)	4.3±1.84 4.5(5.7-2.6)	0.8176

Table -3: Comparison of improvement of lipid profile among the groups

	Lipid_0m Normal	Lipid_0m Abnormal	Row Totals	Lipid_3m Normal	Lipid_3m Abnormal	Lipid_3m Improved
Metformin group(%)	28(77.78%)	8(22.22%)	36	28(77.78%)	4(11.11%)	4(11.11%)
Atorvastatin group(%)	26(72.22%)	10(27.78%)	36	26(72.22%)	3(8.33%)	7(19.44%)
Combined group(%)	26(72.22%)	10(27.78%)	36	26(72.22%)	3(8.33%)	7(19.44%)
Totals	80	28	108	80	10	18

Table-4: Comparison of Ferriman Gallwey Score at baseline and after treatment in different groups.

	Hirs_ 0m FGS 9	Hirs_ 0m FGS 10	Hirs_ 0m FGS<8	Hirs_ 3m FGS 9	Hirs_3m FGS 10	Hirs_3m FGS <8
Metformin group(%)	6(16.67%)	5(13.89%)	25(69.44%)	6(16.67%)	1(2.78%)	29(80.56%)
Atorvastatin group(%)	6(16.67%)	3(8.33%)	27(75%)	5(13.89%)	1(2.78%)	30(83.33%)
Combined group(%)	6(16.67%)	4(11.11%)	26(72.22%)	5(13.89%)	1(2.78%)	30(83.33%)
Total	18	12	78	16	3	89

Table 5: Comparision of acne score at baseline and after treatment in different groups.

	Acne Sc_0m 0	Acne Sc_0m 1	Acne Sc_0m 2	Acne Sc_3m 0	Acne Sc_3m 1	Acne Sc_3m 2
Metformin(%)	31(86.11%)	0	5(13.89%)	31(86.11%)	5(13.89%)	0
Atorvastatin(%)	32(88.89%)	3(8.33%)	1(2.78%)	34(94.44%)	1(2.78%)	1(2.78%)

Combined(%)	31(86.11%)	2(5.56%)	39(8.33%)	33(91.67%)	2(5.56%)	1(2.78%)
Total	94	5	9	98	8	2

Table 6: Showing different complications following treatment

Side effects	Metformin group	Atorvastatin group	Combined group
GI (nausea/ vomiting/ anorexia/diarrhoea/Flatulence	4 (11.11%)	0	5 (13.88%)
Increase in transaminases	0	3 (8.33%)	4 (11.11%)
Muscle pain/ myopathy	0	0	0
Abnormal renal function	0	0	0

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