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Original Research Article

Efficacy of N acetylcysteine vs metformin on biochemical and clinical parameters in women with polycystic ovarian syndrome in a tertiary care hospital

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ABSTRACT

Introduction: Ovarian dysfunction syndrome, or PCOS, is characterised by hyperandrogenism, enlarged cystic ovaries, and persistent anovulation in women of reproductive age. These coexist with insulin resistance, dyslipidemia, and obesity. To enhance menstruation pattern, insulin sensitivity, and treat dyslipidemia, a metformin replacement that has few side effects is required.

Objectives: **Primary:** To study the effects of N acetyl cysteine in women with PCOS in and compare with commonly used Metformin. **Secondary:** To evaluate if N acetyl cysteine can substitute Metformin in treatment of women with PCOS in clinical parameters like BMI, menstrual pattern and biochemical parameters like FBS and lipid profile.

Materials and Methods: A prospective randomized control study was conducted in Obstetrics and Gynaecology department in Shri Sathya Sai medical college. 60 women (diagnosed by Rotterdam criteria) of age group 18 to 45 were included in this study. Subjects were randomly assigned into 2 groups. Group M received Metformin 500mg TDS and group N received N acetylcysteine 600mg TDS. Clinical and biochemical parameters contributing to metabolic syndrome such as menstrual pattern, BMI, Fasting blood sugars and lipid profile were noted before and after completion of the study along with side effects of the drugs.

Results: 30 women in metformin group and 30 in NAC group completed study. A statistically significant decrease in BMI, Waist hip ratio was noted in both metformin and NAC groups. The mean difference post treatment was (3.63 vs 4.16) in BMI and (0.014 vs 0.017) in waist hip ratio. Both treatments led to significant improvement in menstrual pattern, FBS and lipid profile. Group N showed statistically better results compared group M.

Conclusion: Metformin and N acetyl cysteine were efficient in improving BMI, menstrual pattern and the metabolic parameters. However, decrease in BMI, WHR, FBS, lipid profile and menstrual pattern were statistically more significant in NAC compared to metformin.

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1. Introduction

Polycystic ovary syndrome is the most common endocrine disorder in reproductive women. It is characterised by irregular menstruation, infertility, symptoms of hyperandrogenemia, acanthosis nigricans, and a biochemical profile characterised by an elevated luteinizing

hormone (LH)/follicle-stimulating hormone (FSH) ratio, elevated androgen levels, hyperinsulinemia, dyslipidemia, and, in many cases, obesity.¹

By the "Rotterdam criteria-2003",¹ which requires only two of the following three symptoms to be present: more than 25% of reproductive women in India suffer from PCOS.

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1. Ovulation abnormalities (oligo-ovulation or anovulation)
2. Hyperandrogenism (clinical or biochemical)
3. Polycystic ovaries (either 12 or more follicles or increased ovarian volume [10 ml] in ultrasound).

Early diagnosis of PCOS is important, because it is associated with increased risks of insulin resistance, type 2 diabetes mellitus and metabolic syndrome, all of which have long-term consequences. By increasing LH-dependent ovarian androgen biosynthesis, hyperinsulinemia may contribute to hyperandrogenism. To further increase the bioavailability of free androgens in target tissues, it also inhibits synthesis of sex hormone-binding globulin (SHBG) in the liver. Hyperandrogenism, anovulation, and insulin resistance are all worsened by obesity.¹

C4H11N5, or metformin, is a biguanide oral anti-diabetic medication. When it comes to treating type 2 diabetes, this drug is the gold standard, especially for those who are overweight or obese and have healthy kidneys. Also, it has been studied for diseases where insulin resistance is thought to play a role, such as polycystic ovary syndrome, which it is used to treat. Specifically, metformin slows the liver metabolism of glucose, which reduces blood sugar levels.¹

N-acetylcysteine (NAC) is an acetylated form of L-cysteine and a precursor to reduced glutathione.² Together, glutathione and N-acetylcysteine (NAC) are a potent antioxidant that shields cells from free radical damage and plays a crucial role in maintaining a robust immune system.³ Hyperinsulinemia-induced insulin resistance can be avoided, and insulin receptors can be protected from oxidative stress, through the acceleration of glutathione synthetase hormone (GSH) synthesis.⁴

Because of its effect on insulin and androgen levels, metformin is useful for treating PCOS. Some patients experience an increase in homocysteine levels and other gastrointestinal side effects, limiting their ability to take Metformin for an extended period of time. Heart disease, thrombophilia, preeclampsia, and repeat abortions are all increased risks associated with hyperhomocysteinemia. N-acetylcysteine (NAC) is a stable derivative of the amino acid cysteine that is necessary for the production of glutathione and has anti-oxidant properties in and of itself. Both glutathione and N-acetylcysteine are potent antioxidants that shield insulin receptors from free radical damage. The activity of insulin receptors may be affected by NAC.⁵

NAC is approved mucolytic for use in chronic obstructive pulmonary disease patients. NAC is safe and has no known side effects because it is not naturally occurring in the human diet but is instead sold as a nutritional supplement. As an insulin sensitizer, it has been shown to increase insulin secretion from pancreatic cells. Additionally, it protects the ovary from focal ischemia by inhibiting apoptosis. With NAC, plasma homocysteine levels are lowered.⁶

The current study was designed to compare the metabolic effects of metformin and NAC in PCOS patients because both are insulin sensitizers and may be helpful in PCOS patients in reducing the severity of long-term complications. NAC can be used instead of metformin because it doesn't cause side effects and is safe for long-term use.

2. Materials and Methods

This prospective randomized control trial study was conducted at Shri Sathya Sai Medical College & Research Institute, Chengalpet in its 300 bedded multispecialty tertiary hospital catering to both rural and semi-urban population. The study subject were women with PCOS diagnosed by Rotterdam criteria 2003, of age group 18 to 45 years.

After taking informed written consent, cases were randomly assigned to either group M or group N of 30 each by computer generated list of random numbers using simple randomization technique. A detailed history was taken with special reference to age, parity, socioeconomic status, education and personal habits such as nutrition and exercise. Special focus on menstrual pattern such as oligomenorrhea (interval between menstrual periods), amenorrhea (absence of vaginal bleeding for at least 6 months), clinical hyperandrogenism (a Ferriman–Gallwey score > 6) as diagnosis for PCOS.

Clinical assessment included weight, body mass index (BMI), waist circumference and waist-to-hip ratio. Waist circumference of 85 cm or more is used as cutoff. BMI is calculated by the following formula:

$$\text{BMI} = \text{mass (kg)} / \text{height (m square)}.$$

Fasting glucose levels and lipid profile were measured. Ultrasonography examination (TAS) was done preferably on day 2 or 3 of menstruation.

Group M received metformin 500 mg three times a day. Group N received N acetyl cysteine, 600 mg three times a day.

After 8 weeks of treatment each subject underwent clinical assessment again, which included weight, body mass index (BMI), waist circumference and waist-to-hip ratio. Waist circumference of 85 cm or more was used as cutoff. BMI was calculated.

Fasting glucose levels and lipid profile was measured again. Ultrasonography examination (TAS and TVS) was done again on day 2 or 3 of menstruation.

2.1. Inclusion criteria

Women 18–45 years of age diagnosed as PCOS fulfilling at least two of the following three criteria (Rotterdam criteria 2003), after exclusion of other etiologies.

2.2. Exclusion criteria

1. Pregnancy

2. History of cigarette smoking, alcohol consumption
3. Current or previous use (within 3 months) of oral contraceptives, antiandrogens, antidiabetics, statins, glucocorticoids or intake of any other hormone
4. Known case of diabetes mellitus or diagnosed diabetic during investigation by OGTT
5. Other factors for infertility like congenital adrenal hyperplasia, thyroid dysfunction, Cushing syndrome, hyperprolactinemia, androgen secreting neoplasia
6. Hepatic and kidney diseases and peptic ulcer
7. Hypersensitivity to either Metformin or NAC

2.3. Statistics and analysis of data

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables.

The association between categorical explanatory variables and quantitative outcome was assessed by comparing the mean values. Paired t-test was used to assess statistical significance.

P value < 0.05 was considered statistically significant. Data was entered in excel sheet and was analysed by using SPSS software, V.22.

3. Results

Total of 60 cases were included in the study. Subjects were randomly assigned to group M and Group N of 30 each. The mean age of women enrolled in the study were 32.67 ± 5.91 in group M and 32.16 ± 6.63 in group N. Difference was not significant ($p = 0.744$).

Table 1 gives menstrual pattern of women enrolled in the study. Before treatment 83.3% of women in group M and 83.3% of women in group N had oligomenorrhoea. After treatment menstrual complaints reduced to 43.3% in group M and 50% in group N. It was statistically significant.

Table 2 depicts the change in anthropometric measurements in the study participants. The mean difference in BMI from the pre to post treatment period was 3.63 and 4.16 respectively in group M and N. It was statistically significant in both groups but the difference was higher in group N. The mean difference in WHR from the pre to post treatment period was 0.014 and 0.017 respectively in group M and N. It was statistically significant in both groups but the difference was higher in group N.

Table 3 shows mean difference in fasting blood sugars from the pre to post treatment period was 7.23 and 8.1 respectively in group M and N. It was statistically significant in both groups. The difference was higher in group N.

Table 4 shows assessment of lipid profile in the present study, it is shown that the mean difference of TCL (9 vs 5.93), TGL (19.5 vs 17.03), HDL (9.26 vs 8.3) and LDL (19.3 vs 13.03) in group N and M respectively. Though it is

statistically significant in both groups, the mean difference was significantly higher in group N than M.

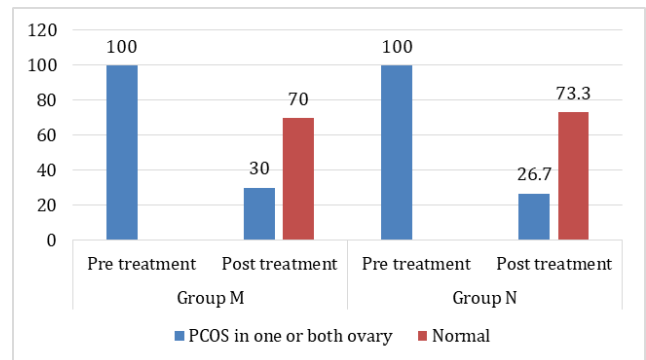


Fig. 1: Ultrasound among the study participants

Figure 1 shows documentation of ovulation on follicular monitoring after treatment in the study groups. In metformin group 70% of women ovulated compared to 73.3% in NAC group. The difference was statistically not significant. However on comparing with pre treatment ovulation status group N showed better results compared to group M.

4. Discussion

The most common gynaecological endocrinopathy in women of reproductive age is polycystic ovary syndrome (PCOS), which increases the risk of various metabolic and aesthetic conditions in addition to altering sexual and reproductive function. Increased ovarian and adrenal androgen production, irregular menstruation, anovulatory infertility, polycystic ovaries, and biochemical (increased androgens) and clinical (hirsutism, acne, and/or alopecia) hyperandrogenism are the main features of this multigenic condition.⁷

The present study was conducted with the aim to study the comparison of metformin and N acetyl cysteine on metabolic and clinical parameters in women with polycystic ovarian syndrome.

Our study showed that the mean age of the study participants was 32.67 ± 5.91 and 32.13 ± 6.63 in group M and N respectively. There was no significant difference between the groups. In a similar study done by Gayathri K et al.,⁸ it was shown that the mean age of the patients in metformin and NAC group was 22.6 ± 3.8 and 23.2 ± 4.1 respectively.

This study has shown that majority of the study participants in group M and N had moderate (56.7%) and sedentary lifestyle (53.3%) respectively. Recent research has shown that aerobic endurance exercise improves the body composition, metabolism, and cardiorespiratory performance in PCOS-affected women. It seems that the most effective therapy for overweight and obese women with PCOS is making lifestyle modifications that

Table 1: Menstrual complaints among the study participants

Menstrual complaints	Group M			P value	Group N		
	Pre treatment	Post treatment	Mean difference		Pre treatment	Post treatment	Mean difference
Present	25 (83.3)	17 (56.7)	3.63	0.024	25 (83.3)	15 (50)	4.16
Absent	5 (16.7)	13 (43.3)	0.014		5 (16.7)	15 (50)	0.017

Table 2: Anthropometric measurements among the study participants

Variable	Group M			P value	Group N		
	Pre treatment	Post treatment	Mean difference		Pre treatment	Post treatment	Mean difference
BMI	33.49 ± 3.1	29.86 ± 3.05	3.63	<0.001	31.96 ± 3.19	27.8 ± 3.04	4.16
WHR	0.87 ± 0.01	0.86 ± 0.02	0.014	<0.001	0.88 ± 0.021	0.86 ± 0.023	0.017

Table 3: Fasting blood sugar among the study participants

Variable	Group M			P value	Group N		
	Pre treatment	Post treatment	Mean difference		Pre treatment	Post treatment	Mean difference
FBS	92.20 ± 2.07	84.97 ± 2.44	7.23	<0.001	92.1 ± 2.23	84 ± 2.407	8.10

Table 4: Lipid profile among the study participants

Variable	Group M			P value	Group N		
	Pre treatment	Post treatment	Mean difference		Pre treatment	Post treatment	Mean difference
TCL	187.27 ± 14.24	181.33 ± 14.53	5.93	<0.001	193.47 ± 6.37	184.47 ± 6.51	9
TGL	138.8 ± 11.00	121.77 ± 10.70	17.03	<0.001	139.27 ± 11.41	119.77 ± 11.54	19.5
HDL	55.73 ± 4.83	64.03 ± 4.85	8.3	<0.001	55.5 ± 5.62	64.77 ± 5.62	9.26
LDL	127.17 ± 7.64	114.13 ± 7.80	13.03	<0.001	128.87 ± 7.96	109.57 ± 7.83	19.3

include regular exercise and calorie restriction for weight reduction.⁹

This study showed that 60% and 63.3% of the study participants in Group M and N had hirsutism respectively. Similarly, 90% and 96.7% of the study participants in Group M and N had acanthosis respectively. Similar effect was seen in a study done by Gayathri K et al.⁸

Present study has shown that, in group M, the percentage of patients with menstrual complaints have reduced from 83.3% in the pre-treatment period to 56.7% in the post treatment period. It was statistically significant. In group N, the percentage of patients with menstrual complaints have reduced from 83.3% in the pre-treatment period to 50% in the post treatment period. It was statistically significant. Similar finding was observed in a study done by Oner G et al.,¹⁰ which showed that menstrual irregularities were changed from 83% to 53% in metformin group and 71% to 47% in group N.

Present study stated that, the mean difference in BMI from the pre to post treatment period was 3.63 and 4.16 respectively in group M and N. The difference was higher in group N. Present study stated that, the mean difference

in WHR from the pre to post treatment period was 0.014 and 0.017 respectively in group M and N. It was found to be statistically significant. Similarly in a study done by Javanmanesh F et al.,¹¹ they showed that the mean difference in BMI was higher in group M than N (0.4 vs 1.2). In research by Salehpour S et al.¹² the NAC group significantly outperformed the placebo group in terms of weight reduction, BMI, waist circumference, and WHR after six weeks of therapy.

Present study has shown that the mean difference in FBS from the pre to post treatment period was 7.23 and 8.1 respectively in group M and N. The difference was higher in group N. On assessing the lipid profile in our study, it was shown that the mean difference of TCL (9 vs 5.93), TGL (19.5 vs 17.03), HDL (9.26 vs 8.3) and LDL (19.3 vs 13.03) was significantly higher in group N than M. Fulghesu AM et al.⁴ showed in 2002 that women with polycystic ovarian syndrome who received NAC therapy had better insulin sensitivity, T levels, and lipid profiles. In a study done by Oner G and Muderris II.,¹⁰ it was shown that Body mass index, hirsutism score, fasting insulin, HOMA index, free testosterone, and

monthly irregularity were significantly decreased with both therapies as compared to baseline values, and all treatments were equally effective. While metformin only reduced total cholesterol levels, NAC significantly reduced levels of both low-density lipoprotein and total cholesterol. The impact of NAC on hyperinsulinemic PCOS is likely due to an increase in insulin receptor activation, which has the side effect of reducing the responsiveness of β cells to the oral glucose tolerance test (OGTT). In individuals who were responding to therapy, the drop in circulating insulin was followed by a significant drop in T levels and free androgen index.

We found in our study that, ultrasound showed that presence of PCOS in one or both the ovaries was 100% in the pre treatment in group M and N. After treatment it has significantly reduced to 70% and 73% in group M and N respectively. Similarly, a study was conducted by E. Cheraghi et al.,¹³ to evaluate the effect of metformin and NAC on follicular parameters, oocytes and embryo quality in patients with PCOS. They concluded that NAC improves oocyte and embryo quality. It also improves anovulatory cycles compared to frequently used metformin.

5. Conclusion

The metabolic parameters, menstrual cycle, and BMI were all significantly improved by metformin and N-acetyl cysteine. However, NAC was statistically more significant than metformin in terms of the reduction in BMI, WHR, FBS, lipid profile, and menstrual pattern. Because NAC has less adverse effects than metformin, it is more easily tolerated, resulting in prolonged medication compliance. NAC can be used as a suitable alternative to metformin because to its absence of side effects. NAC, however, is more expensive than metformin.

6. Source of Funding

None.

7. Conflict of Interest

None.

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