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ORIGINAL ARTICLE

Comparison of Metformin and *N* Acetylcysteine on Clinical, Metabolic Parameter and Hormonal Profile in Women with Polycystic Ovarian Syndrome

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Abstract

Objective Comparison of metformin and *N* acetylcysteine on clinical, metabolic parameter and hormonal profile in women with polycystic ovarian syndrome.

Design Prospective comparative study.

Setting Obstetrics and Gynecology department in Kamala Nehru Memorial Hospital Allahabad.

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Patient(s) On the basis of inclusion and exclusion criteria, 100 patients of PCOS were selected for study and assigned randomly in two groups to receive either metformin (1500 mg/day) (group M) or *N* acetylcysteine (1800 mg/day) (group N) for 24 weeks.
Intervention(s) Metabolic parameter and hormonal profile were determined before and after the treatment.
Main Outcome Measure(s) Metabolic parameters, fasting glucose, fasting insulin and testosterone changes.
Result(s) Forty-five patients of both groups were ultimately evaluated. There was a significant improvement of body mass index, waist circumference and waist–hip ratio in group N, but there was no significant difference found in weight reduction among two groups. The biochemical marker of insulin resistance like fasting insulin, fasting glucose/insulin ratio improved significantly in group N. Greater reduction of total testosterone was observed in group N.
Conclusion(S) Better improvement of metabolic and hormonal profile was observed in *N* acetylcysteine group. Because of its less side effect comparing to metformin, NAC can be used as a substitute for insulin-sensitizing agent in treatment of PCOS.

Keywords Polycystic ovarian syndrome (PCOS) · *N* acetylcysteine (NAC) · Metformin

Introduction

Polycystic ovary syndrome is a most commonly diagnosed endocrine disorder in reproductive women characterized by irregular menstruation, infertility, signs and symptoms of hyperandrogenemia, acanthosis nigricans, and biochemical profile showing increased luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio, increased androgen levels, hyperinsulinemia, dyslipidemia and in many cases, obesity. In India, more than 25% reproductive women are suffering from PCOS by the "Rotterdam criteria-2003" [1] which includes any two of the following three features:

- Oligo-ovulation or anovulation
- Clinical or biochemical signs of hyperandrogenism or both
- Polycystic ovaries, with the exclusion of other etiologies (either 12 or more follicles or increased ovarian volume > 10 ml).

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. Hyperinsulinemia may lead to hyperandrogenism by indirectly increasing LH-dependent ovarian androgen biosynthesis. It also inhibits sex hormone-binding globulin (SHBG) synthesis in liver, enhancing bioavailability of free androgens in target tissues. Obesity has an additive negative impact on hyperandrogenism and anovulation and substantially increases insulin resistance.

Metformin (molecular formula C4H11N5) is an oral anti-diabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function. It is also used in the treatment of polycystic ovary syndrome and has been investigated for other diseases where insulin resistance may be an important factor. Metformin works by suppressing glucose production by the liver.

N acetylcysteine (NAC) is the acetylated precursor of both the amino acid L-cysteine and reduced glutathione [2]. Glutathione along with NAC is powerful antioxidant, protect against free radical damage and a critical factor in supporting a healthy immune system. Through acceleration of glutathione synthetase hormone (GSH) synthesis [3], there occurs inhibition of oxidative stress and consequently the prevention of hyperinsulinemia-induced insulin resistance and preservation of insulin receptors against oxidant agents [4]. In the present study, we have evaluated the effect of metformin and NAC on metabolic and hormonal parameter in PCOS women.

Materials and Methods

This study was conducted on 100 women with PCOS (diagnosed by Rotterdam criteria) of age group 18–35 year, visiting OPD of obstetrics and gynecology department of Kamala Nehru Memorial Hospital, Allahabad. This was a prospective comparative study. The study period was May 2015 to May 2016.

Hypersensitivity to metformin or NAC, pelvic organ pathologies, congenital adrenal hyperplasia, thyroid dysfunction, Cushing's syndrome, hyperprolactinemia, androgen-secreting neoplasia, diabetes mellitus, consumption of medication affecting carbohydrate metabolism within 3 month before the study, patients taking hormonal analogue other than progesterone, severe hepatic or renal disease and active peptic ulcer were considered as exclusion criteria.

After taking informed consent, cases were randomly assigned to either group M or group N.

A detailed history was taken with special reference to age, parity, habitat, socioeconomic status, education and personal habits such as nutrition and exercise. Special focus was on menstrual pattern such as oligomenorrhea (interval between menstrual periods ≥ 35, amenorrhea (absence of vaginal bleeding for at least 6 months), clinical

hyperandrogenism (a Ferriman–Gallwey score ≥ 6) and/or biochemical hyperandrogenism (total testosterone (TT) ≥ 58 ng/dl or (2 nmol/l) to test for PCOS.

Clinical assessment included weight, body mass index (BMI), waist circumference and waist-to-hip ratio. Waist circumference of 85 cm or more was used as cutoff. Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor. BMI was calculated by the following formula:

$$\text{BMI} = \frac{\text{Mass (Kg)}}{\text{Height (m)}^2}.$$

Serum TSH, serum prolactin, serum follicle-stimulating hormone, luteinizing hormone (mIU/L), LH/FSH ratio, serum fasting insulin, serum fasting glucose level, serum fasting glucose/insulin ratio and serum total testosterone were measured by enzyme immune assay(EIA). Ultrasonography examination (TAS and TVS) was done preferably on day 2 or 3 of menstruation.

Subjects were randomly assigned into two treatment groups. Group M received metformin 500 mg three times a day. Group N received *N* acetylcysteine, 600 mg three times a day.

After 24 weeks of treatment, each subject underwent the same procedure as described above. The data obtained were analyzed by SPSS version 16. The comparison of the effect of metformin and NAC on patients with PCOS was made by Z test. The comparison of the effect of metformin and NAC before and after treatment was made by paired Z test. A "*P*" value < 0.05 was considered statistically significant.

Results

Out of 100 cases, 10 were lost to follow-up. In remaining 90 cases, 45 were in Group M, 45 were in Group N. The cases in Group M received tab metformin 500 mg three times a day, and Group N received tab *N* acetylcysteine 600 mg three times a day. The clinical characteristics, carbohydrate metabolic parameters and reproductive hormone levels were again measured after 24 weeks of study. Both groups were homogenous considering their demographic (Table 1) and clinical characteristic (Table 3).

After 24 weeks of treatment with either metformin or NAC clinical characteristic, metabolic parameter and hormonal profile were reevaluated. There was no significant reduction of weight in both the group after treatment, while a significant reduction of BMI, WC and WHR was found in Group N receiving NAC. Fasting glucose and fasting insulin were reduced in both groups significantly. There was a significant improvement of fasting glucose/insulin ratio in both groups. Total testosterone was significantly reduced in Group N.

Discussion

Increased insulin resistance and compensatory hyperinsulinemia play a key role in the pathogenesis of PCOS. Anovulation, infertility and hyperandrogenism often coexist with hyperinsulinemia and insulin resistance. This study has been conducted to evaluate the effect of metformin and *N* acetylcysteine on clinical, metabolic and hormonal parameter in women suffering from PCOS.

In this study, there was a significant improvement of BMI, WC and WHR seen in Group N receiving *N* acetylcysteine after 24 weeks of treatment (Table 2). Similarly in a study conducted by Gayatri et al. [5] found significant improvement in some of the clinical features like weight gain, BMI, WHR, acne and hirsutism in group N ($P < 0.05$), but there was no significant change in other features like oligomenorrhea, amenorrhea and infertility. Salehpour et al. [6] conducted prospective experimental clinical trial of NAC with placebo in a group of 36 patients. There was a significant reduction of weight, BMI, WC and WHR in NAC group as compared with placebo.

In this study, fasting plasma glucose and fasting insulin reduced significantly in both groups (Table 2). A significant improvement of fasting glucose/insulin ratio was observed in both groups (Table 2). A study conducted by Elnashar et al. [7] and Gayatri et al. found no significant effect of metformin on FBG/S.FI ratio. The present study found a significant effect on FBG/S.FI ratio due to longer duration of treatment. The results of the current study were comparable with the study done by Wei et al. (2012) [8] where the improvement in the carbohydrate metabolic parameters is similar to the improvements in their study. Their study confirmed that administration of metformin was able to reduce fasting blood glucose, fasting insulin, HOMA-IR and AUC-Insulin in patients with PCOS. Elnashar et al. found no significant effect of *N* acetylcysteine on FPG, S.FI and FPG/S.FI ratio. In this study, a significant improvement of FPG, FI and FPG/FI ratio was observed due to longer duration of study. In 2002, Fulghesu et al. [4] demonstrated that NAC treatment improved insulin sensitivity, T levels and lipid profile in women with polycystic ovary syndrome. Similar to the present study in 2010, K Gayatri et al. conducted a study to compare the effect of metformin and *N* acetylcysteine on PCOS patients and found a significant improvement of FPG, S.FI and FPG/S.FI in patients receiving *N* acetylcysteine.

In this study, a significant reduction of total testosterone was observed in Group M receiving *N* acetylcysteine (Table 2). Similar to the present study, Fulghesu et al. in 2002 evaluated the effect of NAC on hormonal parameters, insulin sensitivity and lipid profile in patients with PCOS and found a significant reduction of total testosterone.

Table 1 Demographic parameters

	Metformin group (n = 45)	NAC group (n = 45)	P value
Age	27.64 ± 5.11	26.82 ± 5.42	.4 (NS)
SES (upper)	4 (8.8%)	4 (8.8%)	NS
(Middle)	36 (80%)	36 (80%)	NS
(Lower)	5 (11.11%)	5 (11.11%)	NS
BMI	24.48 ± 2.57	24.21 ± 2.43	.3 (NS)
WHR	.908 ± .04	.92 ± .06	.13 (NS)

Table 2 Effect of metformin and *N* acetylcysteine on clinical, metabolic and hormonal parameters

	Metformin group (n = 45)		P value	NAC group (n = 45)		P value
	Pre-t/t	Post-t/t		Pre-t/t	Post-t/t	
Weight	63.14 ± 9.07	61.47 ± 8.23	.81 (NS)	65.52 ± 10.26	63.52 ± 9.26	> .05 (NS)
BMI	24.48 ± 2.57	24.29 ± 2.44	.35 (NS)	24.21 ± 2.43	22.81 ± 2.6	.004 (S)
WC	90.0 ± 5.66	89.3 ± 5.43	.27 (NS)	91.71 ± 4.50	88.84 ± 4.93	.002 (S)
WHR	.908 ± .04	.901 ± .05	.23 (NS)	.92 ± .06	.86 ± .05	< .05 (S)
Fasting glucose	102.6 ± 13.17	87.6 ± 10.88	< .05 (S)	105.39 ± 10.96	84.5 ± 12.01	< .05 (S)
Fasting insulin	23 ± 3.51	18.77 ± 2.72	< .05 (S)	23.19 ± 3.04	14.76 ± 4.65	< .05 (S)
Fasting glucose/insulin ratio	4.47 ± .25	4.68 ± .24	< .05 (S)	4.55 ± .16	5.99 ± 1	< .05 (S)
Total testosterone	1.99 ± .67	1.82 ± .62	.1 (NS)	1.9 ± .74	1.54 ± .60	< .05 (S)

Table 3 Comparison of metformin and *N* acetylcysteine on clinical, metabolic and hormonal parameter (pre treatment and post treatment)

Parameters	Pre-treatment			Post-treatment		
	Metformin	NAC	P value	Metformin	NAC	P value (diff)
Weight	63.14 ± 6.92	65.50 ± 5.81	.08	62.15 ± 8.79	63.50 ± 5.96	.09
BMI	24.48 ± 2.57	24.21 ± 2.43	.605	24.39 ± 2.44	22.81 ± 2.60	< .001
WC	90.0 ± 5.66	91.71 ± 4.50	.116	89.37 ± 5.43	88.84 ± 4.93	< .001
WHR	.908 ± .04	.92 ± .06	.09	.901 ± .05	.86 ± .05	< .001
Fasting glucose	102.6 ± 13.17	105.39 ± 10.96	.277	87.6 ± 10.88	84.5 ± 12.01	< .001
Fasting insulin	23.00 ± 3.51	23.19 ± 3.04	.784	18.77 ± 2.72	14.76 ± 4.65	< .0001
Fasting glucose/insulin ratio	4.47 ± .25	4.55 ± .16	.076	4.68 ± .24	5.99 ± 1.00	< .0001
Total testosterone	1.99 ± .67	1.92 ± .74	.639	1.82 ± .62	1.54 ± .60	< .001

Elnashar et al. in 2007 and Gayatri et al. in 2010 also found in their study on PCOS patient, a significant reduction of total testosterone after treatment with NAC (Table 2).

While comparing difference between ranges of two groups (Table 3), significantly greater reduction of BMI, WC, WHR, fasting glucose, fasting insulin, total testosterone and improvement of glucose-insulin ratio was seen in Group M receiving *N* acetylcysteine (Table 3).

Conclusion

It can be concluded from the results of the present study that NAC improves the clinical features, biochemical markers of insulin resistance, hormonal levels, anovulation and consequently the long-term health status of women with PCOS through inhibition of oxidative stress and improvement of peripheral insulin more effectively when compared with metformin. Due to the lack of adverse effects, NAC can be regarded as an appropriate substitute for insulin-reducing medications in the treatment of PCOS patients.

Compliance with Ethical Standards

Conflict of interest There are no conflicts of interest in research involving human participants.

Ethical Approval This study was approved by ethical committee and scientific committee of Kamala Nehru Memorial Hospital, Allahabad, where this study was conducted.

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