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Original Research Article

A Study of Potential Comparison of N-Acetyl Cysteine with Metformin on Clinical Profile in an Ovulatory Infertile Woman with PCOS.

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Abstract

Aim: Comparison of the effects of metformin and N-acetylcysteine on the clinical, metabolic, and hormonal profiles in polycystic ovary syndrome patients.

Methods: For one year, a prospective, comparative study was carried out in the Obstetrics and Gynaecology Department at the M.G.M. Medical College in Kishanganj, Bihar, India. In this study, 120 women with PCOS (diagnosed using Rotterdam criteria) between the ages of 18 and 37 were enrolled. Enzyme immunological assay was used to evaluate serum levels of TSH, prolactin, follicle-stimulating hormone, luteinizing hormone (mIU/L), LH/FSH ratio, fasting insulin, fasting glucose level, fasting glucose/insulin ratio, and serum total testosterone (EIA).

Results: 20 of the 120 cases had follow-up lost. 50 cases in Group M and 50 cases in Group N were among the remaining 100 patients. Group M individuals were given a 500 mg tablet of metformin three times per day, while Group N cases were given a 600 mg tablet of N acetyl cysteine three times per day. Clinical characteristics, metabolic parameters, and hormonal profiles were reevaluated 24 weeks after starting treatment with metformin or NAC, depending on the individual case. After treatment, neither group's weight was significantly reduced, but Group N, who received NAC, saw a significantly lower BMI, WC, and WHR. Significant reductions in fasting insulin and glucose were observed in both groups. The fasting glucose/insulin ratio significantly improved in both groups. In Group N, total testosterone levels were noticeably lower.

Conclusions: In the N acetylcysteine group, the metabolic and hormonal profile improvement was more significant. NAC can replace insulin-sensitizing agents in the treatment of PCOS because it has less negative effects than metformin.

Keywords: Polycystic ovarian syndrome (PCOS), N acetylcysteine (NAC), Metformin

Introduction

Infertility, irregular menstruation, signs and symptoms of hyperandrogenemia, acanthosis nigricans, and a biochemical profile showing increased luteinizing hormone (LH) /follicle-stimulating hormone (FSH) ratio, increased androgen levels, hyperinsulinemia, dyslipidemia, and in many cases obesity are all

characteristics of polycystic ovary syndrome, which is the most frequently diagnosed endocrine disorder in reproductive women. According to the "Rotterdam criteria-2003" [1], which excludes other etiologies and includes any two of the following three features: (a) Oligo-ovulation or anovulation; (b) Clinical or biochemical signs of hyperandrogenism or both; and (c) Polycystic ovaries with at least 12 follicles or an increased ovarian volume >10 ml.

Early detection of PCOS is crucial since it raises the risk of metabolic syndrome, type 2 diabetes, and insulin resistance, all of which have long-term effects. Through a subliminal increase in LH-dependent ovarian androgen production, hyperinsulinemia may cause hyperandrogenism. Additionally, it reduces hepatic SHBG formation, which increases the bioavailability of free androgens in target tissues. Obesity significantly raises insulin resistance and has additively adverse effects on insulin resistance, anovulation, and hyperandrogenism.

The biguanide medicine class includes the oral anti-diabetic medication metformin (molecular formula C4H11N5). It is the first-line therapy option for type 2 diabetes, especially in those who are overweight, obese, and have normal renal function. It has also been researched for various disorders where insulin resistance may be a significant contributing factor. It is also used to treat polycystic ovarian syndrome. Metformin inhibits the liver's ability to make glucose, which is how it works.

The amino acid L-cysteine and reduced glutathione are both acetylated precursors of N acetylcysteine (NAC) [2]. Together with NAC, glutathione is a potent antioxidant that guards against free radical damage and is essential for maintaining a strong immune system. Accelerating the production of glutathione synthetase hormone (GSH) [3] results in the reduction of oxidative stress, which prevents the development of insulin resistance brought on by hyperinsulinemia and protects insulin receptors from oxidants [4]. In the current study, we assessed the impact of metformin and NAC on PCOS women's metabolic and hormonal parameters.

Methods

For one year, a prospective, comparative study was carried out at the Department of Obstetrics and Gynaecology, M.G.M. Medical College in Kishanganj, Bihar, India. In this study, 120 women with PCOS (diagnosed using Rotterdam criteria) between the ages of 18 and 37 were enrolled. Women with severe hepatic or renal disease, active peptic ulcers, severe hypersensitivity to metformin or NAC, pelvic organ pathologies, congenital adrenal hyperplasia, thyroid dysfunction, Cushing's syndrome, hyperprolactinemia, androgen-secreting neoplasia, diabetes mellitus, use of medication that affects carbohydrate metabolism within three months prior to the study, patients taking hormonal analogues other than progesterone, and patients.

Cases were randomly allocated to either group M or group N after receiving informed permission. A thorough history was obtained, paying particular attention to details like age, parity, place of residence, socioeconomic status, level of education, and personal habits like diet and exercise. Menstrual patterns, including oligomenorrhea (interval between periods C 35), amenorrhea (absence of vaginal bleeding for at least 6 months), clinical hyperandrogenism (a Ferriman-Gallwey score C 6), and/or biochemical hyperandrogenism (total testosterone (TT) C 58 ng/dl or (2 nmol/l) to test for PCOS, were given special attention. Weight, body mass index (BMI), waist circumference, and waist-to-hip ratio were all measured clinically. The cutoff was a waist circumference of 85 cm or greater. With the measuring tape parallel to the floor, the

hip circumference should be calculated around the broadest part of the buttocks.

Enzyme immunological assay was used to evaluate serum levels of TSH, prolactin, follicle-stimulating hormone, luteinizing hormone (mIU/L), LH/FSH ratio, fasting insulin, fasting glucose level, fasting glucose/insulin ratio, and serum total testosterone (EIA). On the second or third day of menstruation, an ultrasonography examination (TAS and TVS) was performed.

Two treatment groups were randomly assigned to the subjects. Three times every day, 500 mg of metformin was given to group M. N acetyl cysteine, 600 mg, was given to group N three times every day. Each individual underwent the same technique as previously described after receiving treatment for 24 weeks. SPSS version 20 was used to examine the data that was obtained. Z test was used to compare the effects of metformin and NAC on PCOS patients. The paired Z test was used to compare the impact of metformin and NAC before and after therapy. Statistical significance was defined as a "P" value <0.05.

Results

Twenty of the 120 instances were not followed up on. 50 of the remaining 100 cases belonged to Group M, and 50 to Group N. Group N individuals received tab N acetyl cysteine 600 mg three times per day, while Group M cases received tab metformin 500 mg three times per day. After 24 weeks of the trial, the clinical features, carbohydrate metabolic parameters, and levels of reproductive hormones were once more assessed. In terms of their demographics (Table 1) and clinical characteristics, both groups were homogeneous (Table 3).

Table 1: Demographic evaluation of profile of patients

Parameter	NAC Group (n=50)	Metformin Group (n=50)	P- values
Age	27.86 ± 5.66	28.66 ± 5.19	0.4 (NS)
BMI	24.31 ± 2.53	24.54±2.64	0.3 (NS)
WHR	0.93 ±.06	0.91±.04	0.11 (NS)
SES (upper)	3 (7%)	3 (7%)	NS
(Middle)	40 (81%)	40 (81%)	NS
(Lower)	6 (11%)	6 (11%)	NS

Table 2: Effect of metformin and N acetyl cysteine on clinical, metabolic and hormonal parameters

	NAC (N=50)		Group	Metformin (N=50)		Group
Parameters	Pre t/t	Post t/t	P-Value	Pre t/t	Post t/t	P-Value
Weight	64.15 ± 9.10	62.525 ± 8.77	0.94 (NS)	66.73 ± 11.05	64.60 ± 9.73	>0.5 (NS)
BMI	24.54 ± 2.64	24.28 ± 2.43	0.34 (NS)	23.31 ± 2.53	23.93 ± 2.5	0.004 (S)
Fasting Insulin	23 ± 3.56	19.72 ± 2.78	0.05 (S)	24.25 ± 3.10	15.76 ± 4.25	0.05 (S)
Fasting Glucose	103.4 ± 13.22	88.4 ± 10.23	0.05 (S)	106.38 ± 10.87	85.4 ± 12.20	0.05 (S)
Ratio of Fasting Insulin/Glucose	4.50 ± 0.25	4.70 ± 0.25	0.05 (S)	4.55 ± 0.16	5.86 ± 1	0.05 (S)
Total Testosterone	1.95 ± 0.66	1. 82 ± 0.62	0.1 (NS)	1.6 ± 0.74	1.50 ± 0.59	0.05 (S)
WHR	0.909 ± 0.03	0.092 ± 0.04	0.25 (NS)	0.95 ± 0.07	0.86 ± 0.05	0.05 (S)
WC	90.6 ± 5.86	89.8 ± 5.51	0.28 (NS)	92.83 ± 4.73	89.25 ±4.87	0.002 (S)

Table 3: Comparison of pre-treatment and post-treatment in metformin and N acetyl cysteine on clinical, metabolic and hormonal parameter

	Pre-Treatment			Post-Treatment		
Parameters	NAC	Metformin	P-Value	NAC	Metformin	P-Value
Weight	66.74 ± 11.04	64.16 ± 9.10	0.08	64.76 ± 5.84	63.15 ± 8.86	0.09
BMI	24.30 ± 2.52	24.53 ± 2.64	0.603	23.85 ± 2.96	24.57 ±2.42	0.001
Fasting Insulin	24.23± 3.09	24 ± 3.55	0.795	14.72 ± 4.26	17.83 ± 2.75	0.001
Fasting Glucose	106.37 ± 10.86	103.4 ± 13.21	0.284	85.3± 13.00	88.7 ± 10.75	0.001
Ratio of Fasting Insulin/Glucose	4.55 ± 0.16	4.50 ± 0.25	0.084	5.96 ± 1.09	4.70 ± 0.23	0.001
Total Testosterone	1.6 ± 0.74	1.95 ± 0.66	0.675	1.54 ± 0.58	1.83 ± 0.63	0.001
WHR	0.94 ± 0.06	0.911 ± 0.03	0.09	0.85 ± 0.05	87.35 ± 5.41	0.001
WC	92.82 ± 4.75	90.5 ± 5.83	0.603	23.85 ± 2.96	24.57 ± 2.42	0.001

After 24 weeks of treatment with either metformin or NAC clinical characteristic, metabolic parameter and hormonal profile were re-evaluated. 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

In the pathophysiology of PCOS, increased insulin resistance and compensatory hyperinsulinemia are crucial factors. Hyperinsulinemia and insulin resistance frequently coincide with anovulatory disorders, infertility, and hyperandrogenism. In this study, metformin and N-acetylcysteine were tested for their effects on PCOS patient's clinical, metabolic, and hormonal parameters. [9,10]

In this study, after 24 weeks of treatment, Group N receiving N acetyl cysteine showed a significant improvement in BMI, WC, and WHR. Similar results were obtained in a study by Gayatri et al. [5], which revealed no significant change in other clinical aspects including oligomenorrhea, amenorrhea, and infertility but found substantial improvement in several clinical features like weight gain, BMI, WHR, acne, and hirsutism in group N ($P < 0.05$). A prospective experimental clinical trial comparing NAC with a placebo was carried out by Salehpour et al. [6] in a 36-patient population.

In this study, both groups experienced a considerable decline in fasting plasma glucose and fasting insulin. The fasting glucose/insulin ratio significantly improved in both groups. Metformin had no discernible impact on the FBG/S.FI ratio, according to a research by Elnashar

et al. [7] and Gayatri et al. The extended treatment period identified in this study had a substantial impact on the FBG/S.FI ratio. The improvements in the parameters relating to the metabolism of carbohydrates in the present investigation are comparable to those in the study by Wei et al. [8], according to the results of both studies. Their research proved that metformin treatment can lower fasting blood sugar, fasting insulin, HOMA-IR, and AUC-Insulin in PCOS patients. N-acetyl steine had no appreciable impact on FPG, S.FI, or the FPG/S.FI ratio, according to Elnashar et al. Due to the study's longer duration, a significant improvement in FPG, FI, and the FPG/FI ratio was seen. NAC therapy enhanced insulin sensitivity, T levels, and lipid profile in women with polycystic ovarian syndrome, according to research by Fulghesu et al.16 in 2002. Similar to the current study, K Gayatri et al. (2010) compared the effects of metformin and N acetyl cysteine on PCOS patients and discovered that those taking N acetyl cysteine experienced significant improvements in FPG, S.FI, and FPG/S.FI.

In this research, Group M receiving N acetyl cysteine showed a significantly lower level of total testosterone. Fulghesu et al. in [4] examined the impact of NAC on hormonal parameters, insulin sensitivity, and lipid profile in individuals with PCOS and discovered a significant decrease in total testosterone, which is similar to the findings of the current investigation. [9,10]

In their studies on PCOS patients, Elnashar et al. in 2007 and Gayatri et al. in 2010 likewise discovered a substantial decrease in total testosterone after treatment with NAC. When comparing the ranges of the two groups, Group M receiving N acetyl cysteine showed a considerably higher decrease in BMI, WC, WHR, fasting glucose, fasting insulin, total testosterone, and an improvement in the glucose-insulin ratio. [11]

Conclusion

We came to the conclusion that the NAC, when compared to metformin, more effectively inhibits oxidative stress while also improving peripheral insulin, which in turn improves the clinical characteristics, biochemical markers of insulin resistance, hormonal levels, anovulation, and ultimately the long-term health status of women with PCOS. NAC can be used as a suitable alternative to insulin-reducing drugs in the treatment of PCOS patients due to the absence of side effects.

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