European Journal of Molecular & Clinical Medicine (EJMCM)
ISSN: 2515-8260 Volume 07, Issue 10, 2020

Original research article

A prospective, comparative study of N-acetyl cysteine with metformin on clinical profile in an ovulatory infertile woman with PCOS

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Abstract

Aim: To compared the efficacy of Metformin and NAC on clinical, metabolic, hormonal, sonographic and fertility aspects among PCOS patients.

Material and methods: A prospective, comparative study was conducted in the Department of Obstetrics & Gynaecology, NSMCH, Bihta, Patna, Bihar, India, for 1 year. 120 women with PCOS (diagnosed by Rotterdam criteria) of age group 18–37 year were included in this study. 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* acetyl cysteine, 600 mg three times aday.

Results: Out of 120 cases, 20 were lost to follow-up. In remaining 100 cases, 50 were in Group M, 50 were in Group N. The cases in Group M received tab metformin 500 mg three times a day, and Group N received tab *N* acetyl cysteine 600 mg three times a day. 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.

Conclusion: we concluded that the better improvement of metabolic and hormonal profile was observed in N acetyl cysteine 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 acetyl cysteine (NAC) Metformin

Introduction

Poly cystic ovarian syndrome (PCOS) is defined as an ovarian dysfunction syndrome which manifests as a wide spectrum of disorder with the combination of heterogeneous symptoms and signs. It is considered to be the most prevalent endocrinopathy resulting from anovulation and affects 5%–10% of women.[1] Menstrual dysfunction typically occurs in PCOS, ranging from oligomenorrhoea to amenorrhoea. Other clinical features include obesity, infertility due

to chronic anovulation, hirsutism and acne due to hyperandrogenism. Long term risks include endometrial hyperplasia, endometrial cancer, type II diabetes, hypertension and dyslipidimia. According to Rotterdam criteria (2003),[2] PCOS is diagnosed, if there is presence of two out of the following three criteria: 1. Oligomenorrhoea and/or anovulation. 2. Hyperandrogenism (clinical and/or biochemical). 3. Polycystic ovaries, with the exclusion of other etiologies. To a great extent, etiology of the syndrome has remained unknown although it has been revealed that, synthesis of high levels of androgen and insulin-resistance (IR) lies at the core of its pathophysiology.[3] It has been proven that, IR results in a disturbed response of glucose to insulin stimulation in skeletal muscles and increase of hepatic glucose production as well as lipolysis.[4] While post-receptor dysfunction in the pathway of insulin activity has been introduced as the reason for insulin resistance, the underlying reason for such a dysfunction still remains equivocal.[5] Metformin, an insulin sensitizer, is being used for long time in the treatment of PCOS. Problems associated with Metformin include gastrointestinal side effects, fear of hypoglycemia and increase serum homocystine levels in some patients.[6] Hyperhomocysteinemia is a risk factor for cardiovascular diseases, thrombophilia, pre-eclampsia and recurrent abortion. However recent reviews of randomized control trials of Metformin in PCOS have not shown the promise suggested by the early observational studies.[7] NAC (N-acetyl-cysteine) is a stable derivative of the amino acid cysteine, which has antioxidant properties and is required for the body's production of glutathione. Glutathione along with NAC are powerful antioxidants. Through acceleration of glutathione synthetase hormone (GSH) synthesis,[8] there occurs inhibition of oxidative stress and consequently the prevention of hyperinsulinemia induced insulin resistance and preservation of insulin receptors against oxidant agents.[9] NAC probably influences insulin receptor activity[9,10] and results in an increase of glucose consumption, which is an indicator of the insulin sensitivity state. NAC is not found in the diet, but is available as a nutritional supplement. It has proven activity on insulin secretion in pancreatic cells, acting as an insulin sensitizer. It also has antiapoptotic activity, protective action against focal ischemia at level of ovary. Apoptosis is responsible for follicular atresia. Studies have shown that, taking N-acetyl cysteine (NAC) reduces plasma homocystine (Hcy) levels.[11] In the present study, we have evaluated and compared the efficacy of Metformin and NAC on clinical, metabolic, hormonal, sonographic and fertility aspects among PCOS patients.

Material and methods

A prospective, comparative study was conducted in the Department of Obstetrics & Gynaecology, NSMCH, Bihta, Patna, Bihar, India, for 1 year. 120 women with PCOS (diagnosed by Rotterdam criteria) of age group 18–37 year were included in this study. women with 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 excluded from this study.

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 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. 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.

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 aday. Group N received *N* acetyl cysteine, 600 mg three times aday.

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 120 cases, 20 were lost to follow-up. In remaining 100 cases, 50 were in Group M, 50 were in Group N. The cases in Group M received tab metformin 500 mg three times a day, and Group N received tab *N* acetyl cysteine 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 demo-graphic (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 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.

Table 1 Demographic profile of patients

Parameter	**Metformin group (*n* = 50)**	**NAC group (*n* = 50)**	***P* value**
Age	28.67 ± 5.21	27.85 ± 5.65	0.4 (NS)
SES (upper)	4 (8%)	4 (8%)	NS
(Middle)	41 (82%)	41(82%)	NS
(Lower)	5 (10%)	5 (10%)	NS
BMI	24.55 ± 2.65	24.32 ± 2.54	0.3 (NS)
WHR	.911 ± .05	0.94 ± .07	0.11 (NS)

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

	Metformin=50			**NAC group=50**		
Parameter	**Pre –t/t**	**Post-t/t**	**P value**	**Pre –t/t**	**Post-t/t**	**P value**
Weight	64.17 ± 9.11	62.527 ± 8.78	0.95 (NS)	66.75 ± 11.07	64.62 ± 9.75	> .05 (NS)
BMI	24.55 ± 2.65	24.29 ± 2.44	.35 (NS)	24.32 ± 2.54	23.95 ± 2.7	.004 (S)
WC	90.7 ± 5.85	89.9 ± 5.52	.29 (NS)	92.84 ± 4.77	89.26 ± 4.88	.002 (S)

WHR	.911 ± .05	.904 ± .06	.25 (NS)	0.96 ± .08	.87 ± .06	\.05 (S)
Fasting glucose	103.6 ± 13.23	88.6 ± 10.25	\ .05 (S)	106.39 ± 10.88	85.5 ± 12.21	\.05 (S)
Fasting insulin	24 ± 3.57	19.72 ± 2.79	\ .05 (S)	24.25 ± 3.11	15.76 ± 4.26	\.05 (S)
Fasting glucose/insulin ratio	4.52 ± .27	4.72 ± .27	\ .05 (S)	4.57± .18	5.88± 1	\.05 (S)
Total testosterone	1.97 ± .68	1.84 ± .64	.1 (NS)	1.8 ± .76	1.52 ± .61	\.05 (S)

Table 3 Comparison of metformin and *N* acetyl cysteine 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	64.17 ± 9.11	66.75 ± 11.07	0.08	63.17± 8.88	64.77 ± 5.86	.09
BMI	24.55 ± 2.65	24.32 ± 2.54	0.605	24.59 ± 2.44	23.87 ± 2.98	\.001
WC	90.7 ± 5.85	92.84 ± 4.77	0.121	87.37 ± 5.43	87.95 ± 4.95	\.001
WHR	.911 ± .05	0.96 ± .08	0.09	.904 ± .07	.88 ± .07	\.001
Fasting glucose	103.6 ± 13.23	106.39 ± 10.88	0.284	88.9 ± 10.77	85.5 ± 13.01	\.001
Fasting insulin	24 ± 3.57	24.25 ± 3.11	0.797	19.85 ± 2.77	14.74 ± 4.28	\ .0001
Fasting glucose/insulin ratio	4.52 ± .27	4.57± .18	0.086	4.71 ± .25	5.98 ± 1.10	\ .0001
Total testosterone	1.97 ± .68	1.8 ± .76	0.677	1.85 ± .65	1.57 ± .60	\.001

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* acetyl cysteine 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* acetyl- cysteine after 24 weeks of treatment. Similarly in a study conducted by Gayatri et al.[12] 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.[13] 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. A significant improvement of fasting glucose/insulin ratio was observed in both groups. A study conducted by Elnashar et al.[14] 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)[15] 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* acetyl steine 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.[16] 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* acetyl cysteine on PCOS patients and found a significant improvement of FPG, S.FI and FPG/S.FI in patients receiving *N* acetyl cysteine.

In this study, a significant reduction of total testosterone was observed in Group M receiving *N* acetyl cysteine . 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.

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. While comparing difference between ranges of two groups, 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* acetyl cysteine .

Conclusion

We concluded that the 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.

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Received: 18-09-2020 || Revised: 06-10-2020 || Accepted: 20-10-2020