Original Research Article

A Comparative Study on N-Acetyl Cysteine and Metformin in Patients with Poly Cystic Ovarian Syndrome at a Tertiary Care Centre in Bihar

Sushma Shikha[1], Kumar Devashish[2*], Seema[3]

[1]Senior Resident, Department of Obstetrics and Gynaecology, Darbhanga Medical College and Hospital, Bihar, India

[2]Tutor, Department of Pharmacology, Darbhanga Medical College and Hospital, Bihar, India

[3]Associate professor, Department of Obstetrics and Gynaecology, Darbhanga Medical College and Hospital, Bihar, India

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Abstract

Introduction: 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. **Materials and Methods:** The study was prospective study to compare the effect of NAC and metformin. It was conducted in the Department of Obstetrics and Gynaecology, Darbhanga Medical College, Darbhanga, India. The study period was from February 2020 to September 2021. A total of 92 patients of PCOS diagnosed by Rotterdam criteria [2] were included in the study after obtaining written informed consent. It was approved by the Institutional Ethical committee. **Results:** Total 11 patients (7 from group M and 4 from group N) dropped out, due to intolerance of medication. Ultimately, evaluations were limited to 39 patients in group M and 42 patients in group N. Demographically both groups were comparable in terms of age, socio-economic status and BMI. **Conclusions:** Due to lack of adverse effects, NAC can be regarded as an appropriate substitute for insulin reducing medications in the treatment of PCOS patients.

Keywords: N-Acetyl Cysteine, Metformin, Poly Cystic Ovarian Syndrome

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: a) Oligomenorrhoea and/or anovulation, b) Hyperandrogenism, and c) 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]. Hyperhomo-cysteinemia 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.

Materials and Methods

The study was prospective study to compare the effect of NAC and metformin. It was conducted in the Department of Obstetrics and Gynecology, Darbhanga Medical College, Darbhanga, India. The study period was from February 2020 to September 2021. A total of 92 patients of PCOS diagnosed by Rotterdam criteria [2] were included in the study after obtaining written informed consent. It was approved by the Institutional Ethical committee.Hypersensitivity to either Metformin or NAC, presence of infertility factors other than anovulation, pelvic organic pathologies, congenital adrenal

*Correspondence
Dr. Kumar Devashish
Tutor, Department of Pharmacology, Darbhanga Medical College and Hospital, Bihar, India
E-mail: mail2drdev@gmail.com

hyperplasia, thyroid dysfunction, Cushing's syndrome, hyperprolactinemia, androgen secreting neoplasia, diabetes mellitus, consumption of medications affecting carbohydrate metabolism and taking hormonal analogues other than progesterone two months prior to enrollment, severe hepatic or kidney diseases and active peptic ulcer were considered as exclusion criteria. After the diagnosis, cases were randomly assigned to either Group-M or Group-N.In all the patients the main presenting complaint were noted and detail clinical examination was done. Patients' weight and height were measured and body mass index (BMI) calculated. All the patients underwent basic transvaginal pelvic ultrasonography for the diagnosis of poly cystic ovaries according to Rotterdam criteria. Baseline biochemical and hormonal tests were done on second day of cycle, after spontaneous menstruation or withdrawal bleeding with oral medroxy progesterone acetate. The samples were taken after over-night fasting.Patients were divided into two groups considering the similarity of compound confounding variables and randomized in order to minimize the effects of confounding factors through a randomized method. One group (Group-**M**), constituting 46 cases received treatment with Metformin (started with 500 mg once daily for one week, then 500 mg twice daily for one week, 500 mg three times daily thereafter). The other group (Group-**N**) constituting 46 cases received N-acetyl cysteine, 1.8 gm/day (600 mg three times daily).Patients presented for infertility were treated with Clomiphene Citrate along with Metformin or NAC. Dose of Clomiphene was 50 mg/day from day 2 to 6 and gradual increment in next cycle by 50 mg/day with maximum up to 150 mg/day.All patients were advised to avoid any change in their physical activity and nutrition and not to undergo any new pharmacotherapy during the study. Patients were asked to report any possible adverse effects. Each patient received the treatment for 3 months. At the end of treatment, they were evaluated for regression of main presenting complaints. Biochemical and hormonal tests were repeated again on 2nd day of menstruation. Transvaginal pelvic ultrasonography was repeated again. Data analysis was carried out by SPSS version 16. Comparison of the effects of Metformin and NAC on patients with PCOS was performed by Z test. Comparison of qualitative parameters before and after treatment with Metformin and NAC was conducted by Chi square test, withYates correction, if needed. A *'P'* value less than 0.05 was considered statistically significant.

Results

Total 11 patients (7 from group M and 4 from group N) dropped out, due to intolerance of medication. Ultimately, evaluations were limited to 39 patients in group M and 42 patients in group N. Demographically both groups were comparable in terms of age, socio-economic status and BMI. Mean age in group M was 25.6 with a SD of 3.6 while in the group N, it was 23.4 with SD of 4.5. BMI was 26.6 kg/m^2 with SD of 3.6 in group M and 28.3kg/m^2 with SD of 3.3 in group N. Clinical components have been shown in Table 1. Both the groups were also similar in biochemical and hormonal profile (Table 2).

All the patients in both groups had ultrasonographic features of poly cystic ovaries (PCO) and no changes was noted post treatment. But clinically patients improved in terms of weight management, and hirsutism in group N. Other clinical components showed no changes. Considering laboratory parameters, fasting blood sugar level improved in both the groups, but it was more significant in group N. Fasting Insulin level as well as the fasting glucose/fasting Insulin ratio also had a significant decrease in group N. Same goes for serum LH level, serum FSH, LH/FSH ratio and TT was significant in group N. Nevertheless, no significant change was observed in serum FT, TT/FT ratio and SHBG in both the groups (Table 2).

Table 1: Mean and standard deviation of percentages of patients with various clinical feature before and after intervention

Clinical character	Group M		P value	Group N		P value
	Before	After		Before	After	
Weight gain	7.2%	4.3%	>0.05	5.8%	3.2%	<0.05*
Oligomenorrhea	53.6%	49.3%	>0.05	58.4%	47.8%	>0.05
Amenorrhea	4.7%	2.3%	>0.05	9.2%	5.6%	>0.05
Hirsutism	2.6%	1.9%	>0.05	5.3%	2.1%	<0.05
Infertility	23.4%	16.7%	>0.05	18.5%	12.4%	>0.05
BMI	26.6, 3.6#	25.3, 2.2	>0.05	28.3, 3.3	25.1, 2.7	<0.05

Table 2: Mean and Standard Deviation of various biochemical and hormonal parameters before and after intervention among the study participants

Lab finding	Group M		P value	Group N		P value
	Before	**After**		**Before**	**After**	
FBS (mg/dl)	86.3, 4.6	84.4, 4.1	<0.05	86.6, 3.3	82.6, 4.3	<0.05
Fasting Insulin (mU/ml)	30.1, 9.6	29.2, 9.5	>0.05	27.8, 4.4	24.8, 3.2	<0.05
HOMA-IR	4.9, 2.1	5.3, 1.1	>0.05	5.2, 1.6	4.9, 1.3	<0.05
LH (mIU/ml)	12.1, 2.2	10.7, 1.6	<0.05	13.1, 2.1	11.1, 1.5	<0.05
FSH (mIU/ml)	4.4, 1.1	4.5, 0.9	>0.05	4.9, 0.8	4.8, 0.8	<0.05
TT (ng/ml)	2.2, 0.4	1.3, 0.2	<0.05	1.5, 0.2	1.1, 0.2	<0.05
FT (pg/ml)	3.1, 2.2	3.0, 2.1	>0.05	3.5, 2.1	3.3, 2.1	>0.05
SHBG (nmol/l)	63.3, 20.3	64.6, 19.2	>0.05	62.3, 20.4	63.1, 20.2	>0.05

Discussion

This study has been conducted to evaluate the therapeutic effects of NAC and Metformin on clinical, biochemical, hormonal and fertility aspects of the disease, as well as a comparison of the therapeutic effects of the two drugs in women suffering from PCOS. The results illustrate the fact that, after 12 weeks of treatment with NAC, patients showed a significant decrease in weight gain and hirsutism. Weight gain is an important predictor of insulin resistance[12]. In a study conducted by SagharSalehpour et al, there was significant improvement in weight loss and BMIin NAC group[13]. In another study conducted by Fulghesu, 31 out of 37 women, who were enrolled, were obese. In this study, the administration of NAC did not result in any significant change in BMI[9]. In the study conducted by Elnashar on 64 women suffering from CC- resistant PCOS, patients were divided in to two groups, one receiving NAC and the second Metformin for a period of six weeks. Here again, no significant change was reported in BMI[14]. Studies on other insulin sensitizing agents, such as Thiazolidinediones and Pioglitazone have reported weight gain in patients[14]. The significant weight loss in our study may be due to longer duration of treatment as compared to Elnashar et al.In our study, there was insignificant decrease in other clinical features like oligomenorrhoea and amenorrhoea, these findings are similar to the findings of Salehpour et al[13] in a prospective experimental clinical trial of NAC with placebo in a group of 36 patients. Probably longer duration of treatment is required for improvement in menstrual problems. There was improvement in infertility due to anovulation in both the groups, but it was not significant. In the study by Salehpour et al[13] ovulation rate following consumption of NAC was reported to be higher as compared to the control group. In our study, also the ovulation rate was better in NAC group. Through a five day treatment of obese CC-resistant PCOS patients with NAC, Rizk et al has reported a

significant increase in ovulation rate (49.3%) and pregnancy rate (21.3%) as compared to the control group[15]. Meanwhile, after a six week treatment course, Elnashar reported the ovulation rate to be 6.7% in the group receiving NAC as compared to 51.7%among patients treated by Metformin[15]. He concluded that, NAC per se cannot be considered an effective medication in ovulation induction among women with CC- resistant PCOS.

Significant decrease in biochemical markers of insulin resistance like, fasting insulin, fasting blood sugar, fasting glucose/insulin ratio and HOMA-IR index was also found in other studies. In the study by Salehpour et al [13] there was significant drop in serum fasting plasma glucose (FPG), fasting insulin levels and HOMA-IR index, but the rise in glucose/ insulin ratio was not found to be statistically significant. Thus, it seems that, NAC consumption has been accompanied with an improvement in insulin sensitivity and glucose utilization. While, Elnashar reported that, FPG and serum insulin levels dropped significantly among patients who received Metformin and such a change was not significant in the group of patients being treated with NAC. In his study, the glucose/insulin ratio did not show a significant change in the two groups[14]. But in our study, it was significant and better as compared to Metformin. The significant decrease in serum LH, FSH and LH/FSH ratio in our study was not observed in the study by Salehpour et al[13]. They compared NAC with Placebo, but in our study the comparison was with Metformin. In Metformin group, there was decrease in serum LH, but there was insignificant decline in serum FSH and LH/FSH ratio.

The decline in TT in both the groups and more so in NAC group was also observed by different studies, e.g. Salehpour et al [13] Fulghesu et al [9] Elnashar et al[14] Kilic-Okman et al[16] and Peterson SW et al[17]. The insignificant change in FT, FT/TT ratio and SHBG before and after treatment in each group and in between the two groups was also reported by previous studies in this regard[9, 13, 14, 16]. Hyperandrogenism interferes with follicular maturity in women with PCOS and results in anovulation[18]. It seems that, for future ovulation induction, NAC preserves more follicles in the ovary through its anti-apoptotic mechanism[19]. Various studies have concluded that, Metformin does not result in an improvement of the hyperinsulinemic and excessive testosterone state[14, 20]. It seems that, the beneficial effects of Metformin are manifested in some special groups. Overall, as compared to the long course of treatment (24–36 week) with other insulin reducing medications, the highly significant changes brought by a 12 weeks course of treatment with NAC suggest the hypothesis that, longer treatment with NAC may result in more desirable outcomes, such as more effective control of clinical hyperandrogenism, menstrual irregularities and sonographic findings.

Conclusion

It can be concluded from the results of the present study that, NAC improves some of 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. Due to lack of adverse effects, NAC can be regarded as an appropriate substitute for insulin reducing medications in the treatment of PCOS patients.An assessment of the therapeutic effects of the medication (NAC) when combined with behavioral modification can also be considered for future studies. It will be more helpful if future studies are conducted with a greater number of patients and for a longer period of treatment.

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