e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(6); 1035-1039

Original Research Article

Comparative Study of N-Acetyl Cysteine with Metformin on Clinical Profile in Anovulatory Infertile Women with PCOS at Obstetrics and Gynaecology Department of SKMCH, Muzaffarpur, Bihar

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Received: 25-01-2024 / Revised: 23-02-2024 / Accepted: 26-03-2024

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Conflict of interest: Nil

Abstract:

Background: Polycystic ovary syndrome (PCOS) is defined as an ovarian dysfunction syndrome which affects the reproductive, endocrine and metabolic functions. Insulin resistance and hyperandrogenism is found to play a key role in the pathogenesis of polycystic ovarian syndrome.

Objective: To compare the effects of N-acetyl cysteine with metformin on clinical profile in anovulatory infertile women with PCOS.

Method: Study was performed as a randomized control trial on infertile anovulatory women with PCOS without additional endocrinopathy. Total 60 women were enrolled. In one group, oral NAC 600 mg, three times a day and in the other group, 500 mg oral metformin, three times a day were prescribed for 3 months. Menstrual pattern, ovulation and BMI were noted before and after completion of treatment along with the side effect profile of the drugs.

Results: 28 women in metformin group and 29 in N-acetyl cysteine completed the study. A statistically significant decrease in BMI was noted in both the metformin and NAC groups (25.36±2.15 kg/m^2 vs. 24.34±2.14 kg/m^2 respectively) with a p value of 0.00 for each group. Both treatments led to significant improvement in menstrual pattern and ovulation. The efficacy of the two drugs was equal. The side effects on NAC was significantly less (p = 0.02) compared to metformin.

Conclusion: Metformin and NAC appear to have equal effects on clinical profile in PCOS women. However NAC has better tolerability with fewer side effects.

Keywords: Polycystic ovary syndrome (PCOS), N-Acetyl cysteine (NAC), Body Mass Index (BMI).

Introduction

Polycystic ovary syndrome (PCOS) is defined as an ovarian dysfunction syndrome with combination of heterogeneous symptoms and signs manifesting as a wide spectrum of the disorder. PCOS is of uncertain etiology and is considered to be the most prevalent endocrinopathy affecting 5-10% of women.

PCOS affects the reproductive, endocrine and metabolic functions and manifests as infertility, oligomenorrhoea, amenorrhoea, acne, hirsutism, acanthosisnigricans, obesity, glucose intolerance dyslipidemia, deranged LH/FSH ratio etc. Various criteria have been proposed to diagnose this complex problem.

PCOS is diagnosed by Rotterdam criteria (2003) by presence of at least two of the following:

- Oligomenorrhoea and/or anovulation
- Clinical and/or biochemical signs of hyper-androgenemia
- Polycystic ovaries

The National Institute of Health (NIH) criteria include clinical and/or biochemical hyperandrogenism and chronic anovulation[1] for diagnosing PCOS whereas the most recent androgen excess and PCOS (AE–PCOS) Society criteria recommend that PCOS should be defined as clinical or biochemical hyperandrogenism associated with ovulatory dysfunction in the form

of oligo-anovulation or polycystic ovaries on ultrasound.

Insulin resistance and hyperandrogenism is found to play a key role in the pathogenesis of polycystic ovarian syndrome. Insulin resistance is seen in 30-40% of women with PCOS. Metformin, an insulin sensitizing agent have been found to have a promising effect in improving the clinical, hormonal and biochemical profile of women with PCOS. The mechanism of action of the metformin is by improving insulin sensitivity thereby lowering insulin levels resulting in increase in sex hormone binding globulin and hence decreases in androgens.

N-acetyl cysteine (NAC) a derivative of amino acid L-cysteine is an essential precursor used by the body to produce glutathione which is a powerful antioxidant and hence inhibit oxidative stress and consequently prevents hyperinsulinemia induced insulin resistance and preserves insulin receptors from oxidative stress.

Material and Method

Present study was conducted in the Department of Obstetrics and Gynaecology at Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar from December 2017 to May 2019.

The aims and objectives of the study were to compare the effects of N-acetyl cysteine with metformin on clinical profile in anovulatory infertile women with polycystic ovarian syndrome and also to compare the side effect profile of the two drugs. 60 women with PCOS and anovulatory infertility fulfilling the inclusion and exclusion criteria were enrolled in the study.

Inclusion criteria

- Anovulatory infertile with PCOS as per Rotterdam criteria (2003),
- Who gave consent

Exclusion criteria

- Diabetes mellitus, hypothyroidism and other endocrinopathy,
- hormonal therapy,
- Women who had not given consent.

Using computer generated random number these 60 women were divided into two groups of 30 each. A detailed clinical history was taken. General physical and clinical examination was done and followings were noted.

- Clinical evidence of hyerandrogenemia: Hirsutism (scored by Ferriman-Gallwey score), acne, androgenic alopecia, acanthosis nigricans
- Body mass index (BMI)
- Waist-hip ratio

The study subjects were then subjected to certain biochemical and hormonal tests as listed below:

Oral glucose tolerance test (OGTT), serum insulin: Fasting and two hour post prandial by Cobas et al [11], serum lipid profile including triglyceride and total cholesterol, day 2-5 hormonal assay: serum FSH, LH, Total testosterone using Cobas e 411 and sex hormone binding globulin by ELISA. HOMA-IR [S.glucose (mg/dl) × S. insulin (mg/dl)]/405 and Free Androgen Index (FAI) 100 × [S. total testosterone (nmol/l)/SHBG(nmol/l)] were calculated. The hormonal profile was performed on day 2 -5 of the spontaneous menstrual cycle or progesterone withdrawal bleeding. A baseline transvaginal ultrasound study was done using the machine Toshiba with a transducer frequency of 6 MHz starting from day2-3 of onset of menstrual cycle on every alternate day. On each visit type of endometrium whether differentiated or not and thickness of endometrium, size of the follicle and were looked upon to document ovulation.

The women enrolled were advised to avoid any change in their physical activity and diet. One group of women were given metformin in a dose of 500 mg thrice a day for three months duration and the other group received N-acetylcysteine 600 mg three times a day for a total of three months period. These women were followed monthly to look for compliance and any side effects of the medication were noted. Out of sixty women two were lost to follow up in metformin group and one woman in NAC group. At the end of 3 months, the clinical and biochemical evaluations were repeated. The statistical analysis was done using latest version of SPSS software and results were expressed as mean + standard deviation.

Results

The mean age of women enrolled was 25.43+2.13 years in metformin group and 25.93+2.49 in NAC group. The difference was statistically not significant (p= 0.203). Majority, 49 out of 60 had primary infertility while 11 of had secondary infertility. In the metformin group 83.33% of women had primary infertility and 16.67% had secondary infertility. In the NAC group 80% were cases of primary infertility and 20% of secondary infertility. The range of duration of infertility was 3 years to 11 years. Majority of the women (65%) had infertility of < 5 years duration, 63.66% (19/30) in metformin group and 66.67% (20/30) in NAC group had infertility ≤ 5 years. The mean of duration of infertility was 5.27+1.95 years in metformin group and 5.27+1.74 years in NAC group. The difference was statistically not significant (p=0.500).

The mean BMI before treatment was 26.40±2.30 kg/m^2 in metformin and 25.88±2.19 kg/m^2 in NAC group which was statistically not significant with p value of 0.187. A statistically significant decrease in BMI was noted in both the metformin and NAC

groups (25.36±2.15 kg/m^{2}Vs 24.34±2.14 kg/m^2 respectively) with a p value of 0.00 for each group. Unlike the pretreatment comparison of BMI in the two groups the post treatment BMI was significantly lower in NAC group as compared to metformin group (p=0.039). Table no.1 gives the menstrual pattern of women included in the study group. Before treatment 83.33% of women in metformin and 83.88% in NAC group had oligomenorrhoea. After treatment the regularity of menstrual cycle was restored in 41.37% of women in NAC group compared to 39.28% in metformin group which was statistically not significant (p=0.395). On intra group comparison there was no statistically significant improvement in menstrual pattern.

Table 1:

Cycle		**Metformin**		**NAC**		**p-value**
		Frequency (n=30)	%	Frequency (n=30)	%	
Before	Normal	5	16.67%	5	16.67%	0.500
	Oligomenorrhoea	25	83.33%	25	83.33%	0.500
		Frequency (n=28)	%	Frequency (n=29)	%	**p-value**
After	Normal	11	39.28%	12	41.37%	0.395
	Oligomenorrhoea	17	60.27%	17	58.63%	0.500

Ovulation on follicular monitoring after treatment in the study groups:

In metformin group 25% of women ovulated compared to 31.03% in NAC group. The difference was statistically not significant. However on comparing with pretreatment ovulation status the difference was statistically significant in both groups (p=0.002 in metformin and p=0.001 in NAC group).

Side-effect profile of the two drugs in the study groups. In metformin group 50% women had side effects compared to 20.69% in NAC group. The difference was statistically significant. Gastrointestinal side effects like nausea, abdominal cramps, dyspepsia, and diarrhea were most commonly observed in both the groups. In NAC group 79.31% of women did not show any side effects which was significant (p=0.008). Nausea was observed in17.85% women in metformin and 6.89% in NAC group. The difference was statistically not significant (p=0.114).

Discussion

In the study three months treatment of NAC and Metformin were compared for their effect on clinical parameters on anovulatory infertile PCOS female. The demographic and clinical profile of infertile women with anovulatory PCOS in NAC and metformin groups were matched with respect to mean age, type of infertility, duration of infertility, menstrual pattern and body mass index.

Obesity is seen in about 30% to 60% of women with PCOS. Obesity has indirect correlation with ovulation hence all interventions aimed at lowering the BMI increase the chance of conception. Moreover around 70% of obese women with PCOS have exaggerated insulin secretion. In the present study the mean BMI was comparable in both metformin and NAC groups at commencement of therapy (26.40±2.30 kg/m^2 in metformin vs 25.88±2.19 kg/m^2 in NAC, p=0.187). Post treatment the BMI decreased to 25.36±2.15 kg/m^2 in metformin and 24.34±2.14 kg/m^2 in NAC group. The difference was statistically significant in both groups with a p-value of 0.00. The decrease in BMI is probably because of improvement in insulin resistance by both the drugs individually. Although pretreatment the BMI was comparable in both the groups, post treatment the decrease in BMI was more marked in NAC group compared to metformin group and the difference was statistically significant (p=0.039). The decrease in BMI after treatment with NAC in present study is comparable to the study conducted by Salehpour S et al they observed a statistically significant decrease in BMI after treatment with NAC. The effect of metformin and NAC on BMI in the present study was not concordant with the study conducted by Oner G et al. They did not find significant decrease in BMI in both metformin and NAC groups after six months of treatment. Similar observation of no significant decrease in BMI was noted by Elnashar A et al.

Women with PCOS present with menstrual irregularity consequent to anovulation and increased androgen levels. Hyperinsulinemia leads to increased androgen production and abnormal LH and FSH secretion. All these factors lead to oligo or anovulation with resultant menstrual irregularity. In the present study 83.33% of women in each group had oligomenorrhoea before treatment. In metformin group 39.28% of women had restoration of normal menstrual pattern compared to 41.37% with NAC and the effect was statistically significant in both groups compared to pretreatment menstrual irregularity.

However no statistically significant difference in menstrual pattern was observed on comparing the two study groups post treatment. Oner G et al in their study found statistically significant improvement in the menstrual pattern after

treatment in both NAC and metformin groups. Menstrual regularity was restored in 47% of women in metformin group after treatment. Similarly menstrual cycle regularized after treatment in 53% of women compared to 29% before treatment in NAC group.

Anovulation is a common cause of infertility in women with PCOS. Of all women with anovulatory infertility 75% are because of PCOS. A significant correlation exists between insulin resistance and abnormal ovarian function in women with PCOS. It has been proposed that higher the insulin resistance in PCOS patients lower the probability of ovulation. Thus any intervention aimed at lowering the insulin resistance is likely to improve ovulation in PCOS women. In the present study statistically significant increase in ovulation was seen on follicular monitoring after treatment in both the study groups. Among all anovulatory women in metformin group 25% ovulated after treatment which was statistically significant with a p value of 0.002.

Similarly among anovulatory women in NAC group 31.03% of women ovulated after treatment which was statistically significant (p=0.001). In the study by Elnashar A etal a significantly higher percentage of women that is 51.6% in metformin group ovulated as compared to only 6.6% in NAC group after treatment. Salehpour S et al in their study also found statistically significant improvement in rate of ovulation in NAC plus clomiphene group as compared to placebo plus clomiphene group. The ovulation rate in NAC plus clomiphene was 45.12% as compared to 28% in placebo group with a p value of 0.02.

Conclusion

This study was conducted to compare the effect of N-acetyl cysteine with metformin on clinical profile namely BMI, documentation of ovulation and change in menstrual pattern of anovulatory infertile women with PCOS and to see for the side effect profile of the two drugs if any. Both the drugs were effective in improving BMI, menstrual pattern and ovulation status. Both NAC and Metformin resulted in improvement in BMI; however decrease in BMI was statistically more significant in NAC compared to metformin. On comparing the side effect profile NAC appeared to be a better tolerated with lesser side effects. However NAC is costlier as compared to

References

1. Azziz R, Woods KS, Reyna R. The prevalence and features of polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab. 2004; 89(6):2745-9.
2. Bu Z, Kuok K, Meng J, Wang R, Xu B, Zhang H. The relationship between polycystic ovary syndrome, glucose tolerance status and serum preptin level. Reprod Biol Endocrinol. 2012; 10:10.
3. Elnashar A, Fahmy M, Mansour A, Ibrahim K. N-aectyl cysteine vs metformin in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective randomized controlled study. Fertil Steril. 2007; 88(2):406-9.
4. Franks S. Polycystic ovary syndrome: A changing perspective. Clin Endocrinol. 1989; 31:87-120.
5. Fulghesu AM, Ciampelli M, Muzj G, Belosi C, Silvaggi L, Ayale GF et al. N-acetyl cysteine treatment improves insulin sensitivity in women with polycystic ovary syndrome. FertilSteril. 2002; 77(6):1128-1135.
6. Fulghesu AM, Cucinelli F, Pavone V, Murgia F, Guido M, Caruso A. Changes in luteinizing hormone and insulin secretion in polycystic ovary syndrome. Hum Reprod. 1999; 9:2242-6.
7. Gorry A, White DM, Franks S. Infertility in polycystic ovary syndrome: focus on low-dose gonadotropin treatment. Endocrine. 2006; 30(1):27-33.
8. Oner G, Muderris II. Clinical, endocrine and metabolic effects of metformin vs N-acetyl cysteine in women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Bio. 2011; 159:127-31.
9. Robinson S, Kiddy D, Gelding SV, Willis D, Niththyananthan R, Bush A et al. The relationship of insulin insensitivity to menstrual pattern with hyperandrogenism and polycystic ovaries. Clin Endocrinol. 1993; 39:351-55.
10. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on Diagnostic criteria and long term health risks related to polycystic ovary syndrome. FertilSteril. 2004; 81(1):19-25.
11. Salehpour S, Sene AA, Saharkhiz N, Sohrabi MR, Moghimian F. N-acetylcysteine as an adjuvant to clomiphene citrate for successful induction of ovulation in infertile patients with polycystic ovary syndrome. J ObstetGynaecol Res. 2012; 38(9):1182-86.
12. Salehpour S, Tohidi M, Akhound MR, Amirzargar N. N-acetyl cysteine, A novel Remedy for Polycystic Ovarian Syndrome. Int J FertilSteril. 2009; 3(2):66-73.
13. Schuring AN, Schulte N, Sonntag B, Kiesel L. Androgens and insulin – two key players in polycystic ovary syndrome. Recent concepts in pathophysiology and genetics of polycystic ovary syndrome. Gynakol Gebutshilfliche Rundsch. 2008; 48(1):9-15.
14. Sills ES, Perloe M, Palermo GD. Correlation of hyperinsulinemia in oligoovulatory women with clomiphene resistant polycystic ovary syndrome: a review of therapeutic rationale

and reproductive outcomes. Eur J Obstet Gynecol Reprod Biol. 2009; 91(2):135-41.
15. Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Hum Reprod. 2012; 27:3067-73.