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Original Research Article

Acarbose versus orlistat in weight management of infertile women with polycystic ovarian syndrome: a prospective randomized controlled trial

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ABSTRACT

Background: Polycystic Ovarian Syndrome (PCOS) affects about 4 to 12% of women worldwide. PCOS is the most common cause of anavulation in infertile women. The endocrine dysfunction of PCOS is aggravated by obesity. Weight management is the first line treatment of this condition. In this study, we tried to compare acarbose versus orlistat in weight management of infertile women with polycystic ovarian syndrome. The aim of this study was to compare the effects of acarbose and orlistat in weight management of infertile polycystic ovarian syndrome women.
Methods: This open label randomized controlled trial study was conducted in the Department of Reproductive Endocrinology and Infertility, BSMMU, Dhaka, Bangladesh. The study period was 1 year from July 2019 to June 2020. A total of 32 obese infertile women with PCOS were included in the study and randomized to two treatment arms: acarbose 100 mg tds for 3 months and orlistat 120 mg tds for 3-months.
Results: The response of adequate (>10%) weight reduction with acarbose was 67% of that with orlistat. The side effects with acarbose were 15% of that with orlistat. Acanthosis nigricans was reduced in 18.8% (n=3/16) of those receiving acarbose.Menstrual cycle regularized in 37.5% (n=6/16) in experimental (acarbose) group and in 18.8% (n=3/16) in control (orlistat) group.
Conclusions: The therapeutic potential of acarbose in reducing weight was relatively less than orlistat in obese infertile PCOS women.

Keywords: Acarbose, Infertile women and polycystic ovarian syndrome, Orlistat, Weight management

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders of women in the reproductive age group. The exact role that obesity plays in the development of PCOS remains to be determined. The theories put forward to explain the metabolic abnormalities associated with obesity may explain the role of obesity in the development of PCOS. The adipokine theory suggests that the adipose tissue is an endocrine organ that secrets several hormones (adipokines). Alteration in adipokines levels may lead to the development of PCOS.[1] In 1935, obesity was recognized as a common feature of the PCOS by Stein and Leventhal. Environmental factors such as lifestyle contribute to development of obesity in PCOS. Obesity exacerbates reproductive and metabolic abnormalities such as type 2 diabetes, hypertension and coronary heart disease associated in PCOS. Women with having a body mass index (BMI) of >25 kg/m^2 are reported to be overweight or obese and comprises 40-80% of those with PCOS[2.] The World Health Organization has declared obesity an epidemic. Fundamental treatment of obesity includes lifestyle intervention such as nutrition, physical activity and behavior therapy. However, effects of lifestyle intervention are not always satisfactory in all cases. Pharmacotherapy is used in many patients in conjunction with lifestyle intervention. Pharmacotherapy is indicated for individuals with a body mass index (BMI) >30 kg/m^{2}and for overweight women with a body mass

index (BMI) ≥27kg/m^2 with co-morbidities. It is obvious that the progression of pharmacotherapy for obesity treatment gives us chance to manage weight problem more effectively. In 25–60% of cases, patients with PCOS present glucose intolerance with consequent compensatory hyperinsulinaemia. Insulin resistance and hyperandrogenism are common.[3,4] PCOS is associated with defects in insulin sensitivity and secretion that are further exacerbated by obesity. Insulin resistance may lead to hyperandrogenism by various mechanisms such as a central action (pituitary), a direct ovarian stimulus, or by a hepatic action with a reduced production of steroid hormone-binding globulin (SHBG) and insulin-like growth factor binding protein-1 (IGFBP-1).[5] Anti-obesity medication are pharmacological agents that reduce or control weight. These medications alter one of the fundamental processes of the human body, weight regulation by altering either appetite, or absorption of calories. Acarbose is an anti-diabetic drug which is effective, safe and well tolerated in Asian patients with type 2 diabetes. Acarbose is significantly more effective in patients eating a relatively high carbohydrate diet. Acarbose, especially in combination with the low-calorie diet and exercise, seems to lose weight effectively in obese and overweight patients in communities that have a high carbohydrate intake. Acarbose, an overweight medication with mechanisms including appetite reduction and fat or calorie malnutrition especially in long time use. This drug is better tolerated in the Asians. It is shown to reduce weight with high carbohydrate diet. There are some drugs with confirmed effect on weight loss world widely with high cost for consumption. Acarbose is a non-expensive and reachable drug for patients. The cost of acarbose is less than the other anti-obesity drugs. The objective of this study was to compare the effects of acarbose and orlistat in weight management of infertile polycystic ovarian syndrome women.

METHODS

This is an open label randomized controlled trial conducted in the Department of Reproductive Endocrinology and Infertility, BSMMU, Dhaka, Bangladesh over a period of one year from July 2019 to June 2020 Approval from Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University was taken. A total of 32 obese (body mass index ≥30 kg/m^2) infertile women with PCOS aged from 18 to 40 years were included in the study. Women with hepatic impairment, diabetes mellitus and Intestinal diseases such as malabsorption, inflammatory bowel disease were excluded. The women who gave informed consent were allocated randomly to two treatment arms: one receiving acarbose 100 mg tds with meal for 3 months and orlistat 120 mg tds after meal for 3 months. The random sequence generation was done by permuted block randomization and allocation concealment was done by serially numbered opaque sealed envelopes. Weight related variables as well as other relevant clinical variables were measured at baseline and after 3 months. For statistical analysis SPSS version 23 was used.

Table 1: Sociodemographic profiles of the two groups.

Parameters		Acarbose (experimental)		Orlistat (control)		P value
		N	%	N	%	
Age (years) mean±SD		26.9±3.2 (n=16)		25.7±3.1 (n=16)		0.323
Residence	Urban	8	50	8	50	0.638
	Rural	8	50	8	50	
Education	Primary	8	50	6	37.5	0.859
	Secondary	4	25	4	25	
	Higher secondary	1	6.3	2	12.5	
	Graduate and above	3	18.8	4	25	
Occupation	Housewife	15	51.7	14	48.3	0.219
	Service Holder	1	100	0	0	
	Student	0	0	2	100	
Monthly income (in TK)	≤10,000	4	25	5	31.3	0.921
	>10000≤20,000	10	62.5	9	56.3	
	>20000	2	12.5	12.5	2	

RESULTS

A total of 60 infertile women with PCOS were approached, 40 women were randomized. Finally 32 women were included in analysis, as 8 women discontinued intervention or were lost to follow up because of corona pandemic. The women were allocated into two groups: acarbose (experimental) and orlistat (control). There were no significant differences in socio-demographic variable of experimental and orlistat group. There were decrease in weight, BMI, WC and WHR from baseline to post treatment observations in both experimental and control group. Percentage weight reduction was significantly more in the control (orlistat) group than in the experimental (acarbose) group. The effect size (standardized mean difference) was calculated as Cohen's d (d=0.2 indicates a small effect, d=0.50 indicates a medium effect and d=0.80 indicates a large

effect). The magnitude of difference or effect size as measured by calculated Cohen's d (0.26) was small to moderate. Adequate (>10%) weight reduction was achieved in 25% of those receiving acarbose compared to 37% of those receiving orlistat. Relative risk of adequate (>10%) weight reduction was 0.67 with acarbose compared to orlistat. Relative risk reduction =1-0.67=0.33. Side effects were higher in control (orlistat) group than in experimental (acarbose) group. Side effects were reported in 14.3% of those receiving acarbose compared to 81.2% of those receiving orlistat. Relative risk of side effects was 0.15 with acarbose compared to orlistat. Relative risk reduction of side effects with acarbose was 0.85.

The response of adequate (>10%) weight reduction with acarbose was 67% of that with orlistat. The side effects with acarbose were 15% of that with orlistat.

Table 2: Anthropometric measures of obesity baseline and post treatment.

Anthropometric parameters		Acarbose (Experimental)		Orlistat (Control)		P value
		Mean±SD	Median (Interquartile range)	Mean±SD	Median (Interquartile range)	
Weight* (Kg)	Baseline	77.2±10.4	73 (69-83.75)*	70.06±5.57	69 (66-74.5)*	<0.05
	Post treatment	70.4±10.9	69 (63-79.5)*	63.12±5.59	62.3 (58.25-68)*	<0.05
BMI*	Baseline	33.64±4.24	31.76 (31.17-35.94)*	31.44±1.53	30.86 (30.23-32.46)*	0.061
	Post treatment	30.62±4.15	29.56 (27.94-32.86)*	28.32±1.69	28.06 (27.26-29.5)*	0.051
WC (cm)	Baseline	102±7.8	103 (94.2-107.7)	97.4±6	98 (93.25-102)	0.067
	Post treatment	96.2±8.8	95.5 (90-104.7)	93.40±5.9	93.5 (89.2-98.7)	0.298
WHR	Baseline	0.96±0.05	0.95 (0.91-0.98)	0.95±0.07	0.94 (0.92-1)	0.93
	Post treatment	0.93±0.06	0.92 (89-0.97)	0.93±0.07	0.93 (0.91-0.98)	0.67

The variables which are not normally distributed and so better described by median (interquartile range) and analyzed by nonparametric tests.*

Table 3: Endocrine profile baseline and post treatment.

Endocrine parameters		Experimental (acarbose) (Mean±SD)	Orlistat (control) (Mean±SD)	P value
Basal FSH (IU/l)	Baseline	4.73±1.64	4.84±1.02	0.821
	Post-treatment	4.93±0.93	5.03±0.65	0.726
Basal LH (IU/l)	Baseline	6.45±3.85	6.11±4.14	0.813
	Post- treatment	4.55±1.59	4.77±2.62	0.778
LH FSH ratio	Baseline	1.35±0.67	1.27±0.76	0.766
	Post-treatment	0.95±0.25	0.93±0.49	0.89
Fasting insulin (IU/l)	Baseline	15.59±5.96	11.66±3.77	<0.05
	Post-treatment	12.74±4.73	9.90±2.99	0.052
Percentage reduction in fasting insulin	(baseline levels–post-treatment levels)/baseline levels	0.17±.07	0.14±.06	0.21

Table 4: Side effects in experimental (acarbose) and control (orlistat) group.

Side effects	Experimental (acarbose)	Control (orlistat)
Bloating	6.30%	-
Abdominal pain	6.30%	-
Oily stool	-	62.50%
Fecal Soiling	-	25%
Increased defecation	-	31.30%

Table 5: Weight reduction in experimental (acarbose) and control (orlistat) group.

Weight parameters Median (Interquartile range)	Experimental (Acarbose)	Control (Orlistat)	P value
Weight baseline (kg)	73 (69.2-83.7)	69 (66-74.5)	<0.05
Weight post treatment (kg)	69 (63-79.5)	62.50 (58.25-68)	<0.05
BMI baseline	31.76 (31.17-35.94)	30.86 (30.23-32.46)	0.061
BMI post treatment	29.56 (27.94-32.86)	28.06 (27.26-29.50)	0.051
Percentage weight reduction*	7.4 (6.4-9.7)	9.1 (8.6-10.8)	<0.05

Table 6: Adequate weight reduction (≥10% of baseline) achieved in experimental (acarbose) and control (Orlistat) group (per protocol analysis).

Adequate weight reduction in obese infertile women with PCOS	No		Yes		Relative risk	95% confidence interval of RR
	N	%	N	%		
Acarbose	12	75	4	25	0.667	0.231-1.922
Orlistat	10	63	6	37		

Table 7: Side effects in experimental (acarbose) and control (Orlistat) group (per protocol analysis).

Side effects of drugs in obese infertile women with PCOS	No		Yes		Relative risk	95% confidence interval
	N	%	N	%		
Acarbose	14	87.5	2	14.3	0.154	0.041-0.576
Orlistat	3	18.7	13	81.2		

Acanthosis nigricans was reduced in 18.8% (n=3/16) of those receiving acarbose. Menstrual cycle regularized in 37.5% (n=6/16) in experimental (acarbose) group and in 18.8% (n=3/16) in control (orlistat) group. Spontaneous pregnancy occurred in three women of experimental group. Two women had menstrual cycle regularized and conceived after completion of 3 months treatment. One continued acarbose on her own and conceived. Two pregnancies ended in blighted ovum, while the other continued.

DISCUSSION

This randomized controlled clinical trial is carried out with an aim to evaluate the effect of acarbose versus orlistat in weight management of infertile women with polycystic ovarian syndrome. The percentage weight reduction was significantly more in the control (orlistat) group than in the experimental (acarbose) group. The response of adequate (>10%) weight reduction with acarbose is 67% of that with orlistat. The side effects with acarbose are 15% of that with orlistat. In a trial on 56 males in Israel acarbose did not change BMI significantly.[6] Their diet was very different and low calorie diet was not administered for the subjects.Present study showed minimal side effects of acarbose such as bloating, abdominal pain similar to other studies.[7] Other side effects e.g., diarrhea, flatulence, abdominal distention, meteorism have been reported by others.Side effects such as flatulence, meteorism and abdominal distention are dose dependent, so with a daily dose of 300 mg there is a 100% rate of side-effects initially, which is reduced to 47% within 2 months[8]. Two randomized controlled trials compared metformin with orlistat in obese women with polycystic ovarian syndrome. They reported that weight loss achieved by metformin is similar to that with orlistat.[9,10] However, they did not define the clinically important outcome as more than 10% reduction as done in the present study. Acarbose represents a good therapeutic option for patients with PCOS and insulin resistance. The first study of acarbose in the normal weight patients with PCOS was carried out in 2001 by Ciotta L. et al. which showed improvement in insulin sensitivity.[11] Geisthovel F. et al. have shown that serum glucose, insulin levels were decreased after acarbose treatment in premenopausal women with hyperinsulinemia.[12] However, there was no significant difference in percentage reduction of fasting insulin in women receiving acarbose or orlistat in the present study. According to present study menstrual cycle regularized in 37.5% in acarbose group and in 18.8% in orlistat group. Penna I. et al. demonstrated that the patients taking acarbose tended to have regular menses, with a 2.67-fold higher chance during the last 2 months of treatment.[13] Ciotta L. et al. also reported regularity of menstrual cycles in 60% of the patients in the acarbose group.[11] This tendency to regular menstruations seems to be related to weight reduction, which favors increased SHBG production, reduction of the fraction of free androgens, a lower peripheral estrone conversion, and a lower action on ovarian androgens.Present study reported spontaneous pregnancy following regularized menstrual cycle in three women after completion of acarbose treatment for three months.In present study, acarbose was able to reduce serum LH levels in obese patients with PCOS. Acarbose treatment decreased LH/FSH ratio. Other studies (Ciotta L. et al 2001, Penna I.et al 2005) found that acarbose was able to reduce serum LH.[11,13] Reduction of LH seems to be related to decreased insulin levels during acarbose therapy. Decreased LH

concentrations contribute to the decline in LH-dependent adrenal androgen secretion. The studies showed a reduction in free androgen index and an increase in SHBG, with improvement of hirsutism and acne. The present study did not study hyperandrogenism, and the time period was too short to see an effect on hirsutism and acne. PCOS is a complex disorder presenting most commonly with oligomenorrhea or amenorrhea, infertility, hirsutism, acne, and obesity. Acarbose is an anti-hyperglycemic agent in type II diabetes mellitus and lower the weight of many diabetic patients. Acarbose (α glucosidase inhibitors) is a promising therapy for PCOS because of its effects on postprandial insulin levels. In multiple clinical studies, acarbose improved hirsutism, acne, and menstrual irregularities through reduction in androgen concentrations and through increased androgen binding. Obesity aggravates insulin resistance and hyperinsulinaemia in PCOS women. South Asian women are more insulin resistant compared to Caucasian women of comparable BMI.[14] Therefore, different cut off values of BMI have been suggested for South Asian women.[15] Obesity is ≥27kg/m^2 and morbid obesity is ≥30kg/m^2. Pharmacotherapy is indicated for patients with BMI ≥30 kg/m^2 or ≥ 28 kg/m^2 in association with risk factors such as hypertension, diabetes.[16] Acarbose has been proposed for weight reduction in diabetic and nondiabetic obese patients. Regarding carbohydrate metabolism, acarbose leads to a 20% reduction of the postprandial peak of glycaemia. This effect may last for as much as 5 hr, with an increase in the time of glucose absorption that prevents glucidic toxicity and the consequent hyperinsulinaemia.[17] Through the action of GLP-1, acarbose produces a reduction of appetite with a consequent reduction of BMI.[18] Acarbose has been explored as an alternative to orlistat for weight reduction in obese women with polycystic ovary syndrome. This is a non-inferiority trial comparing acarbose with orlistat in obese PCOS women. The clinically meaningful outcome we defined was more than 10% reduction in weight. The NNT (number needed to treat) as calculated from absolute risk was 9. The clinical implication of NNT is, if 9 patients are treated with acarbose, one fewer patient will have adequate weight loss than if they all received the standard treatment of orlistat. The use of NNT is valuable in daily clinical practice at assisting physicians in selecting therapeutic interventions by benefit risk assessment. The Consolidated Standards of Reporting Trials (CONSORT) statement recommends the use of both relative and absolute risk (measures of effect) for randomize controlled trials (RCT's) with binary and time to event outcomes. The British Medical Journal (BMJ) requires that whenever possible, absolute rather than relative risks and NNT's with 95% confidence interval (CI) are to be reported in RCT's.[19] In present study, there was no fixed diet or exercise program. This is representative of a true clinical setting rather than a controlled environment. It may also improve patient compliance.[20] The present study was a randomized controlled trial. The selection bias and confounding bias was eliminated by random allocation of the women to acarbose or orlistat. However, information bias could not be eliminated by blinding, single (patient) or double (both investigator and patient).Generalizability or external validity is limited as it was a single center study with small sample size.

CONCLUSION

This study demonstrates that the therapeutic potential of acarbose in reducing weight is relatively less than orlistat in obese infertile PCOS women. However, the cost and side effects are far less with acarbose than orlistat. Considering this and the additional effects of reducing insulin resistance and favoring pregnanc, acarbose can be a suitable alternative to orlistat in obese infertile women with polycystic ovary syndrome. Double blind RCT's with multicenter, larger sample size is recommended to increase reliability and generalizability of clinical decision making.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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