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ORIGINAL ARTICLE

Comparative Study of Metformin and Voglibose Alone, and in Combination on Body Mass Index of Non-Diabetic Obese Subjects

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Abstract

The effect of Metformin and Voglibose alone and in combination on body mass index of non-diabetic obese subjects was observed. Sixty healthy human volunteers participated in the study, which was conducted as a single dose, randomized, open label, two-treatment parallel study. The effect of Metformin and Voglibose alone and in combination on BMI was compared by measuring body mass index (BMI) of non-diabetic patients at base line and after six months. Intergroup comparison between Voglibose and Metformin did not show any statistically significant difference. But, intergroup comparison between Voglibose and Metformin with the combination group (Voglibose + Metformin) showed statistically significant difference. As expected most common adverse effect in all three groups was gastrointestinal side effects like diarrhoea, flatulence, nausea and abdominal pain but there were very less ADR in Metformin group (10%) as compared to Voglibose (20%) and combination group (25%).

Keywords: ***Voglibose, Metformin, BMI, Non-diabetic.***

INTRODUCTION

Obesity is now a global problem[1] and is associated with a number of chronic conditions including osteoarthritis, obstructive sleep, apnea, gallstones, fatty liver disease, reproductive and gastrointestinal cancers, dyslipidemia, hypertension, type2 diabetes, heart failure, coronary artery disease, and stroke[2, 3]. Lifestyle modifications such as diet and exercise intervention are essential for both prevention and management of obesity, and Pharmacotherapy may be considered if the interventions are ineffective for individuals with a body mass index (BMI) ≥25 kg/m, when co-morbidities, such as hypertension or type 2 diabetes mellitus are present[4]. However, anti-obesity drugs are a frequent adjunct, because these interventions have limited long term success[5].

Therapeutic strategies for the non-diabetic obese patient include

(i) promoting weight loss, through lifestyle modifications (low-calorie diet and exercise) and anti-obesity drugs
(ii) treating common associated risk factors, such

as arterial hypertension and dyslipidaemia, to improve cardiovascular prognosis.

Many treatment options are available for overweight and obese adults: behavioral strategies, medications approved by the US Food and Drug Administration (FDA), and bariatric surgery for those at the greatest risk. Several anti-obesity medications like Sibutramine, Rimonabant, Orlistat have been approved by FDA. Sibutramine had been approved for long-term use. But, in October 2010, Sibutramine was withdrawn from the market because of its association with increased cardiovascular events and strokes[6]. The first selective CB1 receptor blocker, Rimonabant, was available as an anti-obesity drug in 56 countries, but it was also withdrawn from the market from 2006 because of an increased risk of psychiatric adverse events, including depression, anxiety and suicidal attempts[7]. Only Orlistat is a currently approved anti-obesity drug for long term use. It reduces intestinal fat absorption by inhibiting pancreatic lipase. Orlistat is notorious for its gastrointestinal side effects (sometimes referred to as *treatment effects*), which can include steatorrhea (oily, loose stools). However, though they are the most frequently reported adverse effect of the drug, but they tend to decrease with time. Over-the-counter approval was controversial in the United States, with consumer advocacy group Public Citizen repeatedly opposing it on safety and efficacy grounds.[8]

Metformin, a biguanide acts as an anti-hyperglycemic agent. It is the first-line drug of choice for the treatment of type 2 diabetes, particularly in overweight and obese people. It is most widely used for the treatment of non-diabetic obesity, for being useful in aiding weight loss[9,10,11]. It is also used in patients who did not have diabetes or PCOS. It improves hyperglycemia. The weight loss effects have been attributed by suppressing glucose production by liver and metformin's anorectic and lipolytic effects.[12] When prescribed appropriately, it causes few adverse effects (the most common is gastrointestinal upset) and is associated with a low risk of hypoglycemia.

Voglibose is a recent alpha glucosidase inhibitor; it is an N-substituted derivative of valiolamine which is a branched-chain amino cyclitol or pseudo-amino sugar and its N-substituted moiety is derived from glycerol. Voglibose is the pseudo-oligosaccharide, α-glucosidase inhibitor which has similar efficacy to acarbose even at lower therapeutic doses and has also the advantage of being non-hepatotoxic.[13] It has shown strong anti-obesity and anti-diabetic activities as it is new potent glucosidase inhibitor and is drug used for NIDDM in Japan, China and Korea. It has been found to significantly reduce postprandial blood glucose concentration in some animals and healthy volunteers[14,15]. It delays the digestion and absorption of carbohydrates, thereby inhibiting postprandial hyperglycemia and hyperinsulinemia and is aid in treatment of diabetes. Comparing with Acarbose in clinical trials, 58% of subjects on Acarbose had complained of gastrointestinal symptoms whereas Voglibose caused few adverse symptoms. Furthermore, there was a tendency for these side effects to decline over the course of Voglibose treatment.[16] Therefore, Voglibose is more effective and has fewer side effects than Acarbose.

With the above background the studies comparing Metformin and Voglibose are limited and no clinical studies comparing Metformin and Voglibose in head to head comparison have been reported for non-diabetic obesity. Therefore, the present study is planned to compare and evaluate the effect of Metformin and Voglibose on BMI in non-diabetics.

AIMS AND OBJECTIVES

- To study the effect of Metformin alone on body mass index of non-diabetic obese subjects.
- To study the effect of Voglibose alone on body mass index of non-diabetic obese subjects.
- To study the effect of combination of Metformin and Voglibose on body mass index of non-diabetic obese subjects
- To compare safety profile of Metformin & Voglibose as per se in terms of patients reported adverse effect.

MATERIALS AND METHODS

Clinical Phase

1. The study initiated from the informed consent process. All subjects had given their written consent before participation by filling the ICF approved by IERC. The ICF was provided in English as well as in Hindi and Marathi to suit the language choice of the patients.
2. Then, details of each patient that included their demographic data, past medical history and physical examination (vital signs) were recorded in the CRF.
3. The patients were admitted and housed in the clinical facility for 1 hour before dosing. They were discharged at the end of the study if not suffering from any adverse events. In case of any adverse events, the volunteers were kept under observation.
4. They were divided into three groups A, B and C, each group contained 20 volunteers.
5. Group A was administered with Tab Metformin 500 mg, Group B was administered with Tab Voglibose 0.3 mg and Group C with Tab Metformin (500 mg) + Tab Voglibose (0.3 mg). The study duration was six months.
6. This study was carried out as per the ICH (Step 5), "Guidance for Good Clinical Practices (GCP)" and the principles of declaration of Helsinki (Scotland, October 2000).

ELIGIBILITY CRITERIA

Inclusion Criteria

- Willing to participate in the study
- Must be able and willing to give written informed consent prior to any study-related procedures and to comply with the requirements of the study protocol.
- Age group of 20-60 years of either gender.
- Obese or overweight determined by a BMI of > 25 kg/m^2 .

Exclusion Criteria

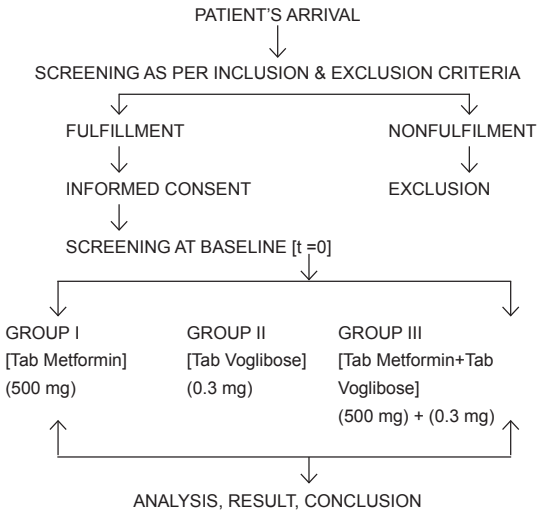
The patients with

- Diabetes Mellitus and pre-diabetes HbA1c level of 5.7%
- Pregnant and lactating women.
- Known allergic to drugs and sensitive to drugs.
- Patient concurrently taking other medication which is known to affect the obesity.
- Smoker, alcoholic and tobacco chewer.
- Presence of gastrointestinal disorders like inflammatory bowel disease, gastric deranged liver function test, and kidney function test.
- Patient with hypothyroidism.

STUDY PERIOD: 6 months

STUDY DRUGS: Metformin: 500 mg
Voglibose: 0.3 mg

STUDY FLOW CHART:



ASSESSMENT AT EACH VISIT

1. General physical examination
2. Laboratory investigations at base line : HbA1c level
3. BMI

Experimental phase

Volunteers were assessed at baseline for HbA1c for screening. Healthy non-diabetic volunteers were enrolled and assessed at baseline and at end of study for Body Mass Index.

Statistical Phase

The statistical evaluation was done by ANOVA with the help of SPSS (Statistical Package for Social Service) value less than $p < 0.05$ was taken as significant.

Results and Observations

In present study, sixty non-diabetic (n = 60) volunteers completed the study. A comparative evaluation of Voglibose and Metformin alone and in combination of BMI was done. All the groups were matched in baseline characteristics, i.e. age, sex and weight. The BMI decreased significantly when compared to baseline value in all three groups

Comparative effect of Voglibose Metformin alone and in combination on BMI in non- diabetic (before and after therapy)

Group	BMI		P value
	Mean value ± SD		
	Before therapy	After Therapy	
I	28.89 ± 0.6959	27.72 ± 0.6771**	P < 0.001
II	29.05 ± 0.7801	27.51 ± 0.7895**	P < 0.001
III	27.98 ± 0.7083	22.66 ± 0.3263**	P < 0.001

Note: P < 0.001**: Statistically highly significant
Group I: Voglibose, Group II: Metformin, Group III: Combination (Voglibose + Metformin)

Intergroup Comparison

A. Voglibose and Metformin

Inter-group comparison between Voglibose group (27.72 ± 0.6771) showed no statistical difference in BMI when compared with Metformin (27.51 ± 0.7895) by using unpaired t-test and was found to be statistically non-significant with a *p* value 0.8411.

B. Voglibose alone and in combination (Voglibose and Metformin)

Inter-group comparison between Voglibose group (27.72 ± 0.6771)alone showed statistical difference in BMI when compared to combination group (Voglibose + Metformin) 22.66 ± 0.3263 by using unpaired t–test and was found to be statistically significant with *p* value < 0.0001.

C. Metformin alone and in combination (Voglibose and Metformin)

Inter-group comparison between Metformin group (29.05 ± 0.7801) alone showed statistical difference in BMI when compared to combination group (Voglibose + Metformin) 22.66 ± 0.3263 by using unpaired t–test and was found to be statistically significant with *p* value < 0.0001.

Adverse Effects

Most common adverse drug reaction reported in all the three groups were related to gastrointestinal disturbances. In the Voglibose group 4 patients (20%), Combination 5 patients (25%) and 2 patients (10%) in Metformin group had shown adverse drug reactions. In Voglibose group, gastrointestinal adverse drug reaction seen were, nausea in 1 patient (5%), flatulence in 1 patients (10%), diarrhea in 1 patient (5%) and abdominal pain in 1 patient (5%). In Combination group, adverse drug reaction seen were, nausea in 1 patient (5%), flatulence in 2 patients (15%), diarrhea in 1 patients (10%) and abdominal pain in 1 patient (5%). In Metformin group, adverse drug reaction seen was Nausea in 2 patients (10%)

Discussion

Nowadays, the number of patients of Diabetes Mellitus has been ever increasing because of too factors like sedentary lifestyle, genetics etc. BMI is considered to be major contributory factor for macro- and micro-vascular complications. So there is need of effective drugs which can control this culprit parameter.

The objective of the present study, therefore, was to compare the effect of Metformin and Voglibose alone and in combination on BMI in type-2 diabetes patients.

The present study showed that when Voglibose 0.3 mg and Metformin 500 mg was given BD to the subjects for six months, it showed reduction in BMI. But more significant reduction in BMI was seen when Voglibose and Metformin were given in combination.

The inter-group comparison between Voglibose and Metformin did not show any statistically significant difference. But, the inter-group comparison between Voglibose and Metformin with the combination group (Voglibose + Metformin) showed statistically significant difference.

As expected the most common adverse effect in all three groups was gastrointestinal side effects like

diarrhoea, flatulence, nausea and abdominal pain. But there were very less ADR in Metformin group (10%) as compared to Voglibose (20%) and Combination group (25%).

CONCLUSION

In the present study, all three treatment arms - Voglibose, Metformin and combination – have proven efficacy in reducing BMI. Metformin and Voglibose have equal efficacy in reducing BMI. The clinical benefit of Metformin was its better safety profile as compared to Voglibose. Thus, to conclude, the present study recommends use of Metformin looking at its efficacy and safety profile amongst the available anti-diabetic drug as preferential choice in the management of BMI and type-2 Diabetes Mellitus.

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"You can never be overdressed or overeducated."
— Oscar Wilde