COST EFFECTIVENESS OF GLIMEPRIDE PLUS METFORMIN PLUS VOGLIBOSE COMPARED WITH GLICLAZIDE PLUS METFORMIN PLUS VOGLIBOSE IN THE TREATMENT OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

Back ground: Diabetes mellitus is a chronic lifelong disease, requiring long term expensive treatment. Costly treatment is a limiting factor to medical adherence and therefore imposes a substantial economic burden on the society. In a developing country like India, it is important to make the treatment affordable to everyone irrespective of their socio-economic status. Cost effectiveness analysis is a pharmacoeconomic tool used to identify the treatment that represents the best outcome for the rupee spent.

Objectives: To assess and compare cost effectiveness of metformin plus voglibose plus glimepiride and metformin plus voglibose plus gliclazide.

Methodology: A prospective observational randomised comparative study was conducted for a period of six months across 2 diabetes centres. Out patients who consented to participate in the study were asked questions relevant to the study. The data collected were recorded in a data collection form and follow up was conducted after 3 months. The data was subjected to descriptive analysis using two independent sample t-test. With the results, cost effectiveness analysis was performed using ACER.

Results: Out of 109 patients, 58 (53%) were on glimepiride plus metformin plus voglibose therapy (group 1) and 51 (47%) were on gliclazide plus metformin plus voglibose (group 2). In group 1 the mean cost for reducing unit HBA1C was found to be 322.9, mean cost for reducing unit FBS was 73.12 and the mean cost for reducing unit PPBS was 5.24. In group 2, the mean cost for reducing unit HBA1C was 480.5, the mean cost for reducing FBS was 35.16 and the mean cost for reducing unit PPBS was 94.90.

Conclusion: Cost effectiveness analysis showed that the mean cost for reducing unit HBA1C and PPBS in glimepiride plus metformin plus voglibose group was less than that in the gliclazide plus metformin plus voglibose group. Whereas reduction in FBS was significantly less in the latter compared to the former.

Key words: Cost effectiveness, gliclazide, glimepiride, diabetes mellitus.

INTRODUCTION

Diabetes mellitus commonly known as diabetes is a group of metabolic disorders of multiple aetiology characterised by chronic hyperglycaemia (or elevated levels of blood glucose) accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins resulting from defects in insulin secretion, insulin sensitivity or both. The hormone insulin produced by beta cells of the pancreatic islets helps in controlling the blood glucose levels by signalling the liver, muscle, and fat cells to take in glucose from the blood to be used for energy. About 422 million people worldwide have diabetes, particularly in low- and middle-income countries, and 1.6 million deaths are directly attributed to diabetes each year.

Health economics is the application of economic theory, models, and empirical techniques to the analysis of decision making by individuals, health care professionals and government with respect to health and health care. It is fundamentally comparative and deals with choices between options. Pharmacoeconomics is a sub discipline of health economics that describes and analyses the costs (inputs) and benefits (outcomes) of pharmaceutical products and services in the healthcare system and society. It addresses the clinical, economic, and humanistic aspect of healthcare interventions. Pharmacoeconomic evaluations provide a basis for resource allocation and utilization. Pharmacoeconomic analyses are increasingly used to help decision-makers assess the value of health interventions. In healthcare, value can be defined as the patient health outcomes achieved per money spent. This value assessment promotes the effective and affordable use of healthcare products. To assess the value, both costs and benefits must be measured at the patient level. Pharmacoeconomics is used at all stages in the development of medicines by the pharmaceutical industry, when medicines are researched, produced, and marketed.

Objectives

General objectives:

- To carry out a cost effectiveness analysis.
- To assess and compare the cost effectiveness of metformin plus voglibose plus glimepiride with metformin plus voglibose plus gliclazide.

Specific objectives:

- To recommend cost effective alternatives based on the study results for improved medication adherence in patients prescribed with the above-mentioned drug combination for type 2 diabetes mellitus.
- To minimize the economic burden on patients associated with drug therapy.

MATERIALS AND METHODS

Study site:

The study was conducted at Dr. KVS Mahesh Diabetic Centre, Indiranagar, Bengaluru, Karnataka and Excel Care Hospital, Banashankari, Bengaluru, Karnataka, India.

Study design:

A prospective observational randomized comparative study.

Study period:

This study was carried out for a period of six months.

Sample size:

Sample size was estimated as 100 using the formula,

Sample size = $2SD^2 (Z_{\alpha/2}+Z_{\beta})^2/d^2$.

Inclusion criteria:

- Subject above 18 years of age.
- Subject with type 2 diabetes mellitus.
- Subject prescribed with either of two therapies of metformin plus glimepiride plus voglibose or metformin plus gliclazide plus voglibose.

Exclusion criteria:

- Pregnancy.
- Subject below 18 years of age.

Ethical approval:

The study was approved by Institutional Ethics Committee of PES college of pharmacy, Hanumanth nagar, Bengaluru, Karnataka.

Study procedure:

Two diabetic centres were identified and out patients from each centre who met the inclusion criteria and were in combination therapy with metformin plus voglibose along with either glimepiride or gliclazide were approached and briefed about the study. Subjects who were ready to volunteer were given the inform consent form.

Demographics, lab data such as FBS, HbA1c and PPBS levels and the medications in the treatment chart of the subjects who signed the inform consent form and consented to participate in the study were noted. They were also asked questions relevant to the study about their lifestyle such as about their diet, social habits, exercise schedule and plan etc. The data collected were recorded in a data collected form.

Follow up was conducted after 3 months and data from each record were compared for changes in recorded values. The changes in the lab value and therapy were noted in the data collection form. Collected data was analysed by using cost effectiveness analysis.

Statistical analysis:

The collected data was subjected to descriptive statistical analysis and Two-sample independent T-Test using Microsoft Excel 2013.

Pharmacoeconomics analysis:

Cost effectiveness analysis was done using Average Cost Effectiveness Ratio (ACER).

RESULTS

A prospective observational study conducted over a period of 6 months. During the study 109 patients with type 2 diabetes mellitus were enrolled.

Table 1: Age distribution

Category	Number	Percentage (%)
30-39	14	12.84
40-49	25	22.94
50-59	37	33.95
60-69	26	23.85
70-79	7	6.42

From Table 1; the prevalence of T2DM is higher (33.95%) in age group of 50-59, followed by 23.85% in age group of 60-69.

Table 2: Gender distribution

Gender	Number	Percentage (%)
Male	58	53
Female	51	47
Total	**109**	**100**

Table 2, depicts that out of 109 subjects, 53% were found to be male and 47% were found to be female.

Table 3: Patients on medication

Medication Groups	No. of patients	Percentage (%)
Group 1- Glimepride + Metformin + Voglibose	58	53
Group 2 - Gliclazide + Metformin + Voglibose	51	47

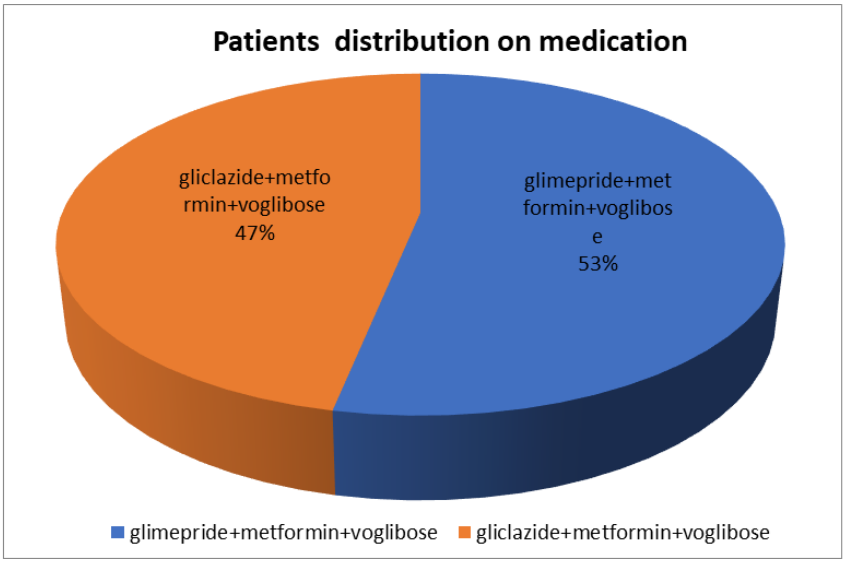

Figure 1: Patients distribution on medication

Table 3 and Figure 1 shows that out of 109 subjects 58 (53%) were on Group 1 therapy - glimepiride plus metformin plus voglibose and 51(47%) were on Group 2 therapy - gliclazide plus metformin plus voglibose.

Table 4: Baseline and follow up parameters for group 1

Glimepride + Metformin + Voglibose	**Baseline**	**After 3 months**	**P Value**
HBA1C %	9.157±1.47	7.684±1.66	0.0000000151***
FBS	188.25±76.38	145.13±38.83	0.00012***
PPBS	265.22±101.04	221±70.91	0.0037***

*P value: 0.05, *not significant, ***highly significant.*

Table 4 shows that the glycaemic parameters (HBA1C, FBS and PPBS) were improved significantly for group1 glimepiride plus metformin plus voglibose after the therapy.

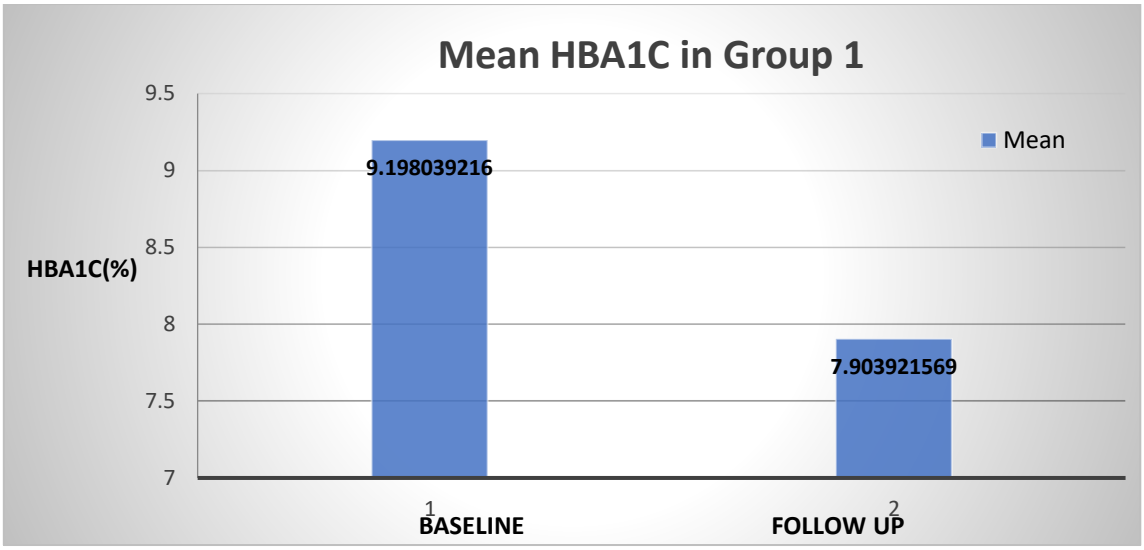

Figure 2: Mean of HBA1c in group 1

Figure no.4 shows that baseline HBA1C for group1 was 9.15% and Follow up after three months was found to be 7.68%. The difference between baseline and after 3 months was highly significant with p value of 0.000000051***.

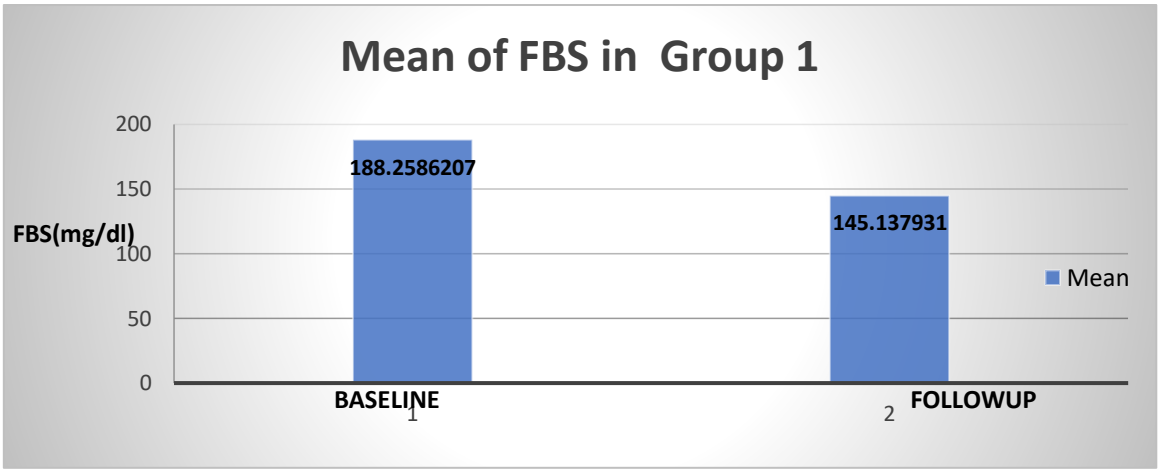

Figure 5: Mean of FBS Group 1

Figure no.5 shows that baseline FBS for Group 1 was 188.25 mg/dl and Follow up after three months FBS was 145.13mg/dl. %. The difference between baseline and after 3 months was highly significant with p value for Group 1 FBS was 0.00012***

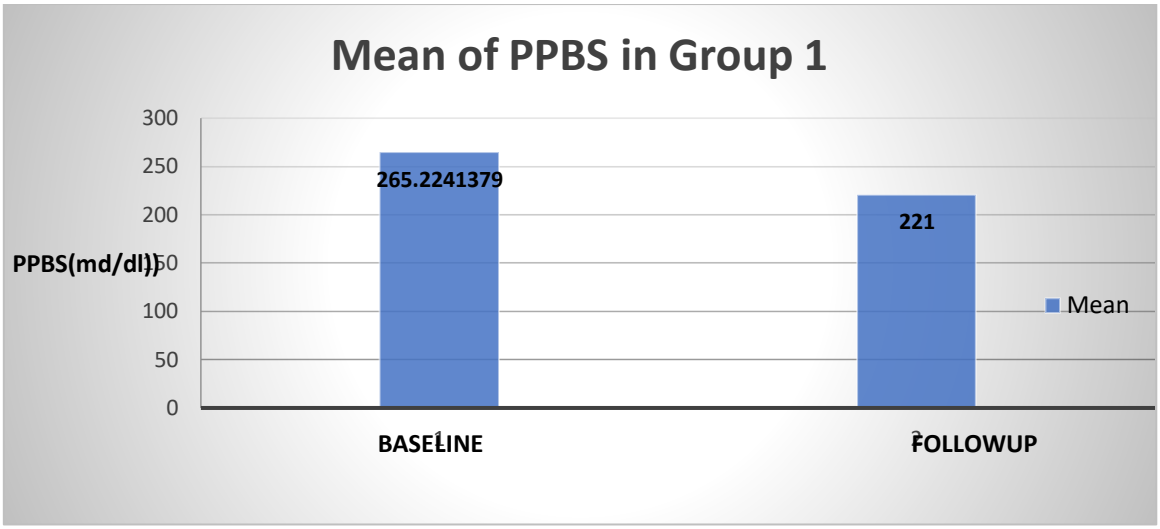

Figure 6: Mean of PPBS in Group 1

Figure no.6 shows that the baseline PPBS for group1 was 265.22 mg/dl and Follow up after three months PPBS was 221mg/dl. The difference between baseline and after 3 months was highly significant with p value for PPBS was 0.0037***

Baseline and Follow up Parameters for Group 2

GLICLAZIDE + METFORMIN + VOGLIBOSE	BASELINE	AFTER 3 MONTHS	P VALUE
sHBA1C %	9.198±1.649	7.903±1.117	0.00000606***
FBS	214.68±77.65	157.96±62.14	0.0000481***
PPBS	298.31±116.19	203.65±77.47	0.00000278***

P value: 0.05, *not significant, ***highly significant

Table 5: Baseline and Follow up Parameters for Group 2

From Table no.5, the glycaemic parameters (HBA1c, FBS, PPBS) after therapy improved very significantly as compared to the level before treatment for group2 that is gliclazide plus metformin plus voglibose

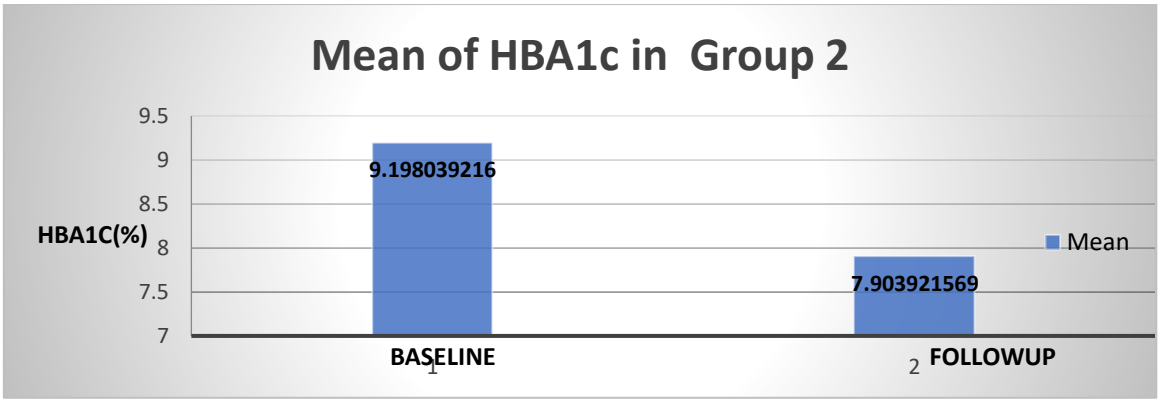

Figure 7: Mean of HBA1c for Group 2

Figure no.7 show that the baseline HBA1C for group2 was 9.19% and Follow up after three months HBA1C was found to be 7.9. The difference between baseline and after 3 months was highly significant with p value for Group 2 HBA1C was 0.00000606***

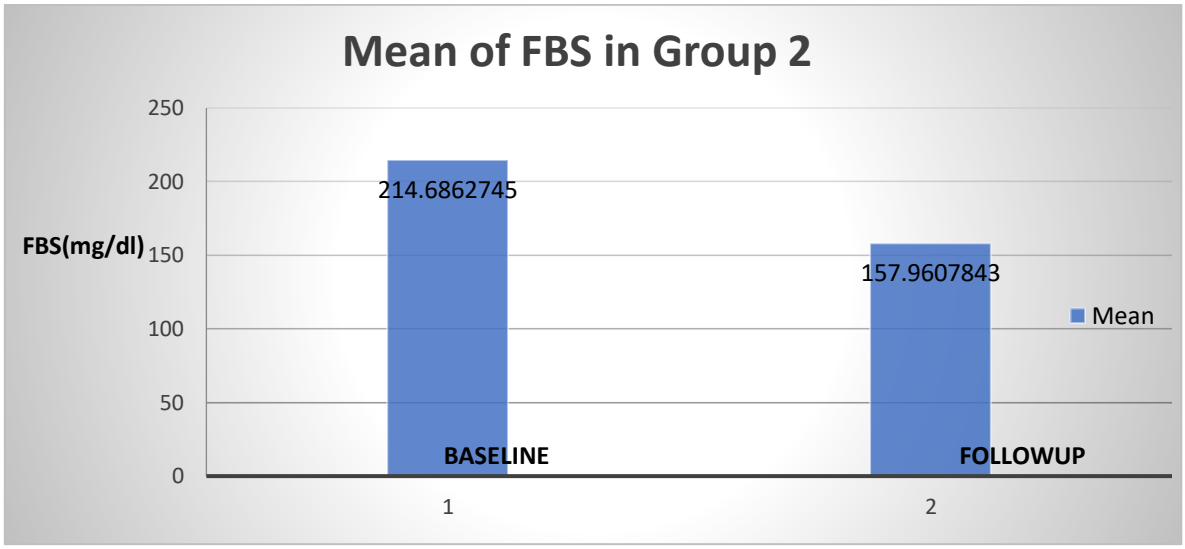

Figure 8: Mean of FBS in Group 2

Figure 8 shows that the baseline FBS for group2 was 214.68 mg/dl and Follow up after three months FBS was 157.96 mg/dl. The difference between baseline and after 3 months was highly significant with p value for Group 2 FBS 0.0000481***.

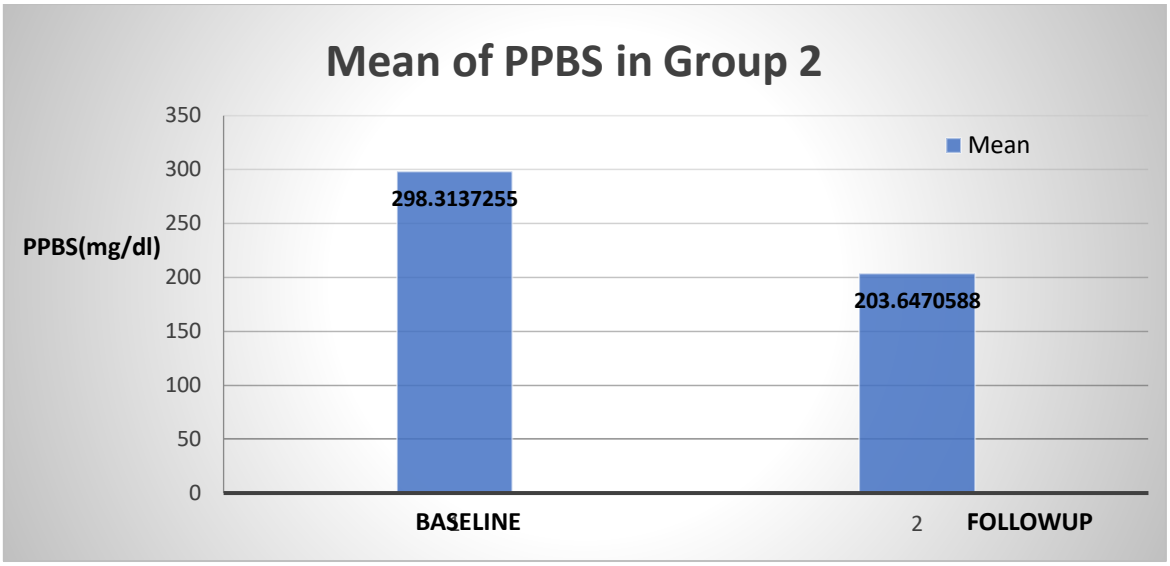

Figure 9: Mean of PPBS for Group 2

Figure no.9 show that the baseline PPBS for group2 was 298.3mg/dl and Follow up after three months PPBS was 203.64mg/dl. The difference between baseline and after 3 months was highly significant with p value for group2 PPBS was 0.00000278***.

Table 6: Parameters compared between two groups after 3 months follow up

Parameters	**Glimepride + Metformin + Voglibose**	**Gliclazide + Metformin + Voglibose**	**P Value**
Reduction in HBA1C %	1.47±1.43	1.29±1.40	0.255*
Reduction in FBS	43.12±71.06	56.72±71.45	0.161*
Reduction in PPBS	44.22±96.23	94.66±108.1	0.006***

*P value: 0.05, *not significant, ***highly significant.*

Table no.6 shows that both the treatment groups were comparable in efficacy in reducing HBA1c, FBS and PPBS without any significant differences

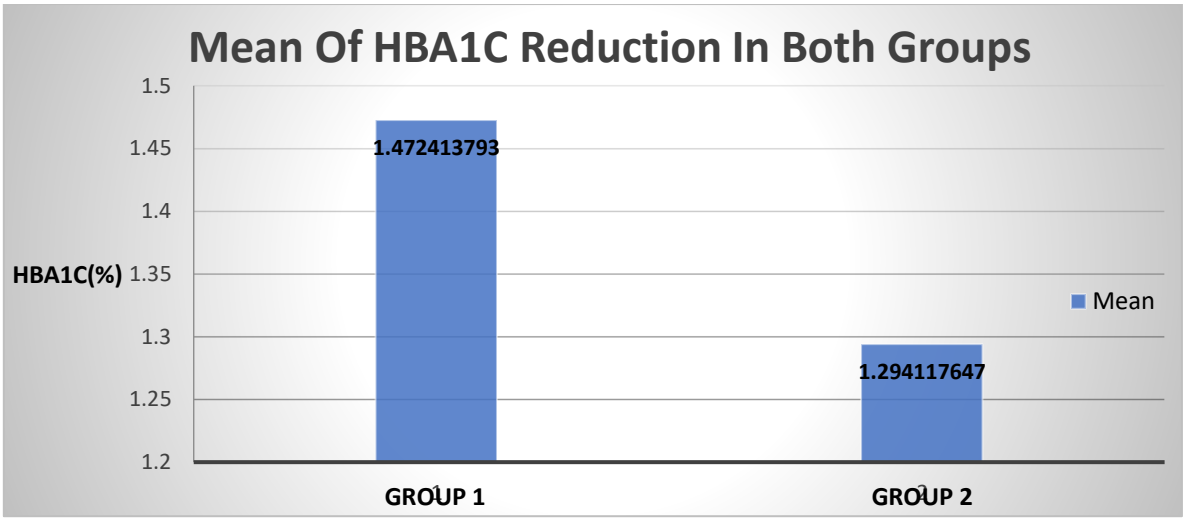

Figure 10: Mean of HBA1c for Both Groups

Figure no.10 shows that group1 showed better reduction in HBA1C 1.47% than group2 with a reduction of HBA1C 1.29%.

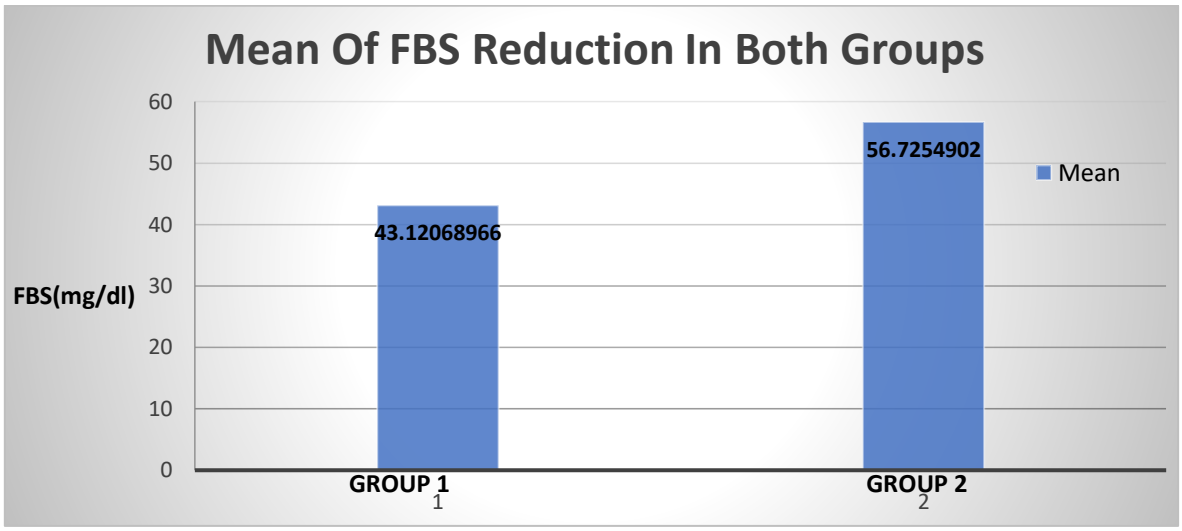

Figure 11: Mean of FBS for both groups

Figure no.11 shows that group2 showed reduction in FBS 56.72mg/dl than group1 with FBS reduction of 43.12mg/dl

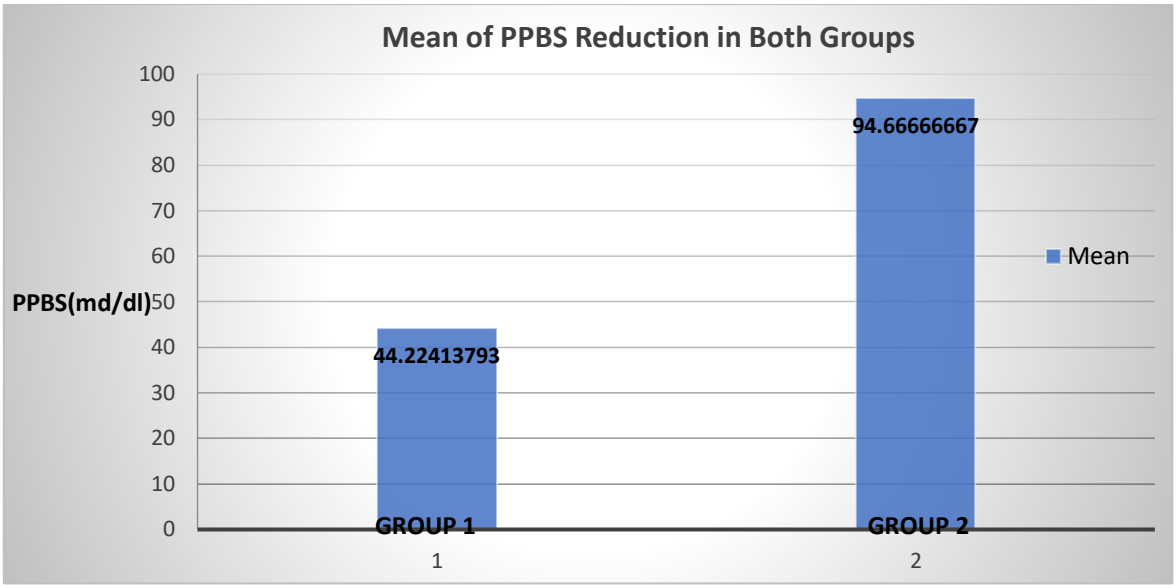

Figure 12: Mean of PPBS for Both Groups

Figure no.12 shows that for group1 reduction in PPBS was 44.22mg/dl and for group2 reduction in PPBS was 94.66mg/dl.

Table 7: Cost Effectiveness Compared Between Two Groups

Cost of Reducing Per Unit Parameter (In Rupees)	**Glimepiride + Metformin + Voglibose**	**Gliclazide + Metformin + Voglibose**	**P Value**
HBA1C %	322.9±413.03	480.5±541.39	0.047***
FBS	73.12±287.34	35.16±359.76	0.2739*
PPBS	5.24±137.72	94.90±349.65	0.0453*

*P value: 0.05, *not significant, ***highly significant.*

Table no.7 depicts that cost effectiveness analysis in mean cost (in rupees) of per unit reduction in HBA1c and PPBS in glimepiride plus metformin plus voglibose group was less than in the gliclazide plus metformin plus voglibose group.

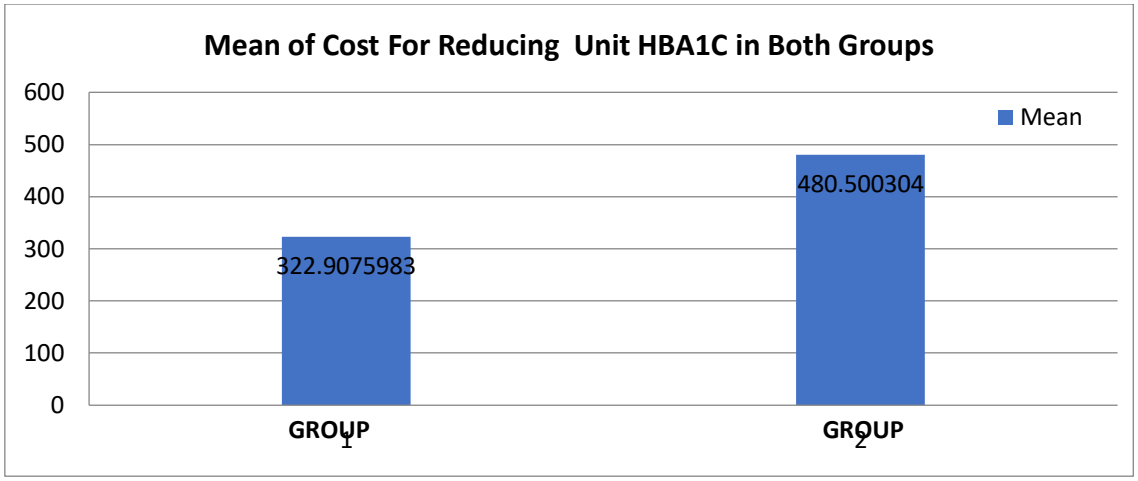

Figure 13: Mean of cost for reducing unit HBA1c in group 1 and group 2

Figure no. 13 depicts that for group1 cost for reducing unit HBA1C was 322.9and for group2 was 480.5. it shows that cost for reducing unit HBA1C for group1 was less when compared to group2 with highly significant P value 0.047***.

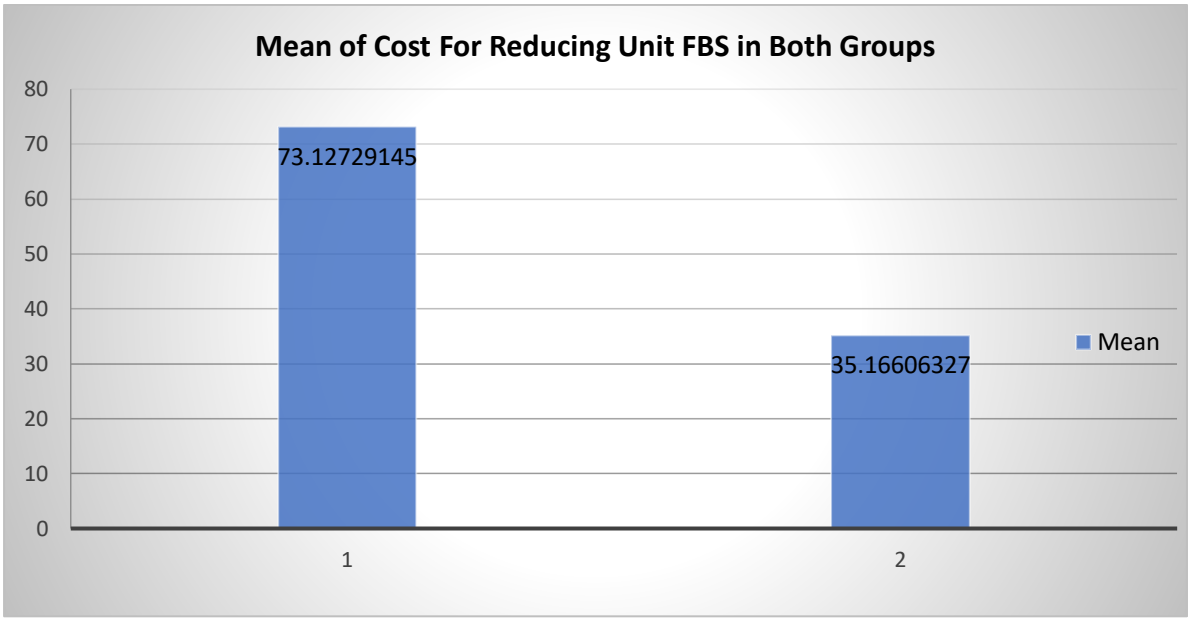

Figure 14: Mean of cost for reducing FBS by 1mg/dl in Group 1 and Group 2

Figure no.14 shows for group1 cost for reducing unit FBS was 73.12 and for group2 cost for reducing unit, FBS was 35.16. Thus, cost for reducing unit FBS was less for Group 2 when compared to group 1 and without significant with p value 0.27*.

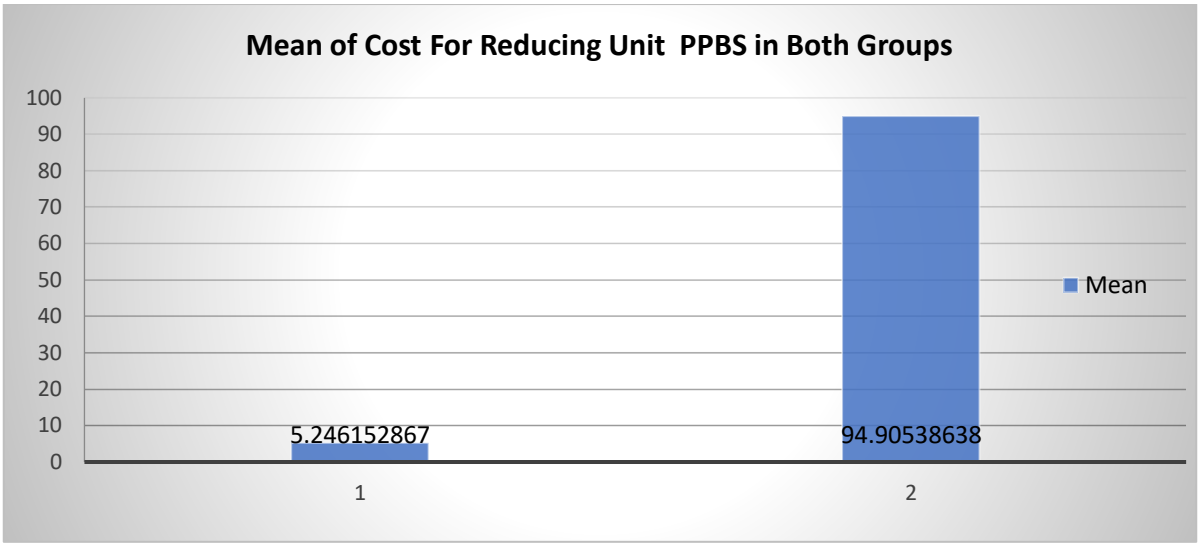

Figure 15: Mean of cost for reducing PPBS by 1mg/dl in group 1 and group 2

For group1 cost for reducing unit and PPBS was 5.24 and for Group 2 cost for reducing unit PPBS was 94.90. Cost for reducing unit PPBS was less for group1 when compared to Group 2 and highly significant with p value 0.045***.

DISCUSSION

There is a need to understand the relative cost-effectiveness of the prescribed drugs for chronic diseases like diabetes in planning to achieve the desired therapeutic goals more effectively without being a financial burden to the patient especially in a developing country like India. This comparative evaluation is based on scientific analysis rather than the apparent cost of therapy helps the decision-makers choose a more cost-effective treatment option, especially for patients in the socioeconomic backdrop of a developing country.

Diabetes is associated with significantly high lifetime medical expenditures while resulting in reduced life expectancy with substantial burden on the society. Combination therapies are commonly being used by many physicians, who believe in aggressive control of the blood sugar. Though the standard treatment guidelines in diabetes mellitus still advocate the addition of a second drug after initial trial of monotherapy, the practice of prescribing combination therapies as initial therapies has been advocated in many studies and has become an increasingly common practice.

In the present study 109 patients who were on either of glimepiride plus metformin plus voglibose treatment group or gliclazide plus metformin plus voglibose treatment groups were enrolled. The subjects were categorized into different age groups, among which, the individuals

aged over 50 were found to be more susceptible to T2DM because of decreased sensitivity of pancreatic beta cells and physical activity resulting in abnormalities in glucose metabolism in glucose metabolism with age. The study subjects were categorized on basis of gender where 53% were males and 47% were females. Out of 109 patients, 58 (53%) were on glimepiride plus metformin plus voglibose therapy and 51 (47%) were on gliclazide plus metformin plus voglibose.

This study compared efficacy of the treatment groups which showed that for glimepiride plus metformin plus voglibose treatment group the baseline HBA1C was 9.15%, FBS was 188.25 mg/dl and PPBS was 265.22 mg/dl. For gliclazide plus metformin plus voglibose treatment group the baseline HBA1C 9.19%, FBS was 214.68 mg/dl and PPBS was 298.31 mg/dl. After three months follow up HBA1C was found to be 7.68%, FBS 145.13mg/dl and PPBS 221mg/dl for Group1 and HBA1C was 7.9%, FBS 157.96mg/dl and PPBS was 203.65mg/dl for group 2. The difference between baseline and after 3 months for both groups was highly significant with p value for group1 HBA1C was 0.000000051***, FBS was 0.00012*** and PPBS was 0.0037*** and p value for group2 HBA1C was 0.00000606***, FBS was 0.000048*** and PPBS was 0.0000027***.

Reduction was determined for all parameters in both groups. For group 1 reduction in HBA1C was 1.47%, FBS was 43.12mg/dl and PPBS was 44.22mg/dl. For group 2 reduction in HBA1C was 1.29%, FBS was 56.72mg/dl and PPBS was 94.66mg/dl. Both the treatment groups were comparable in reducing HBA1C, FBS, and PPBS. Costs for reducing unit parameters were determined. For group1 cost for reducing unit HBA1C was 322.9, FBS was 73.12 and PPBS was 5.24. For group2 cost for reducing unit HBA1C was 480.5, FBS was 35.16 and PPBS was 94.90. Cost for reducing unit HBA1C for group1 was less when compared to group 2 and highly significant with p value 0.047***. Cost for reducing unit FBS was less for group 2 when compared to group1 and not significant with p value 0.27*. Cost for reducing unit PPBS was less for group1 when compared to group2 and highly significant with p value 0.045***.

None of the therapies produced significant change in mean BMI in the present study. The present study was of a shorter duration and both groups had comparable short-term effects of BMI which were not significant.

A study conducted by Memy Hegazy Hassan and Gamil Mohamed Abd-Allah showed similar results. It showed better glycaemic control was obtained with glimepiride treatment group than gliclazide treatment group.

The Present study shows drug acquisition costs are higher with gliclazide plus metformin plus voglibose compared with glimepiride plus metformin plus voglibose treatment. The mean cost for reducing a) HbA1c in latter was 322.9 rupees whereas the other was 480.5 rupees, b) FBS in group 1 was 73.12 and group 2 was 35.1 c) PPBS in group 1 was 5. 2 and group 2 was 94.9.

The results of this study differed from the study conducted by Raju Chipirishetti et. al. In the comparative study of glimepiride and gliclazide, gliclazide was found to be superior to glimepiride in terms of safety and efficacy and was shown to be a better option in diabetes treatment in contrast to our study results.

The study emphasizes the need to evaluate the cost effectiveness of treatment regimens as the primary care physicians dealing with economically backward patients need to know whether a particular regimen is also cost effective rather than just being an effective alternative. Sometimes a costly therapy is justified when judged in the context of superior efficacy or better tolerability, so scientific evaluations in the context of a prevalent disease like diabetes would highlight the comparative merits of the regimens to the primary care physicians for their patients.

As both the combination therapies were comparable in efficacy, the incremental cost effectiveness ratio (ICER) could not be applied in the current study. The small sample size and short-term evaluation in terms of cost effectiveness with mainly glycaemic indices as parameter are limitations of this study. The long-term adverse effects, costs incurred in treating such adverse effects and long-term advantages of these combination therapies with respect to life expectancy and quality adjusted life years on larger population need to be further evaluation.

CONCLUSION

A prospective observational study on the cost effectiveness of glimepiride plus metformin plus voglibose compared with gliclazide plus metformin plus voglibose was carried out in 109 patients with type 2 diabetes mellitus.

The present study showed that male (53%) subjects were predominantly diagnosed with T2DM compared to female subjects (47%) and an age group from 50-59 (37%) had higher incidence of T2DM. The glycaemic parameters (HBA1C, FBS, and PPBS) were improved for both treatment groups. The reduction in HbA1c after 3 months of treatment was found to be 1.47 in group 1 and 1.29 in group 2, the reduction of FBS was found to be 43.12 in group 1 and 56.7 in group 2 and the reduction in PPBS was found to be 44.22 in group 1 and 94.66 in group 2. The mean cost for reducing unit HBA1C was found to be 322.9, mean cost for reducing unit FBS was 73.12 and the mean cost for reducing unit PPBS was 5.24 in group 1 and the mean cost for reducing unit HBA1C was 480.5, the mean cost for reducing FBS was 35.16 and the mean cost for reducing unit PPBS was 94.90 in group 2. The cost effectiveness analysis showed that the mean cost (in rupees) per unit reduction in HBA1c and PPBS in glimepiride plus metformin plus voglibose group was less than that of metformin plus voglibose plus gliclazide group.

Thus, this study concludes that glimepiride plus metformin plus voglibose treatment strategy is more cost-effective compared to gliclazide plus metformin voglibose treatment strategy. This study helps the physicians to choose cost effective treatment option, so that the patients can access the treatment irrespective of their socioeconomic status and thus improve medication adherence.

Limitations

- ✓ The period of study was limited, to carryout observations in a wider aspect**.**
- ✓ Difficulty in follow-ups with the subjects, restricted the study to a smaller population.

Future Directions

- ✓ Long term study can be carried out in a larger population.
- ✓ The long-term adverse effects and its treatment costs need to be evaluated further.

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CONFLICTS OF INTEREST

The author declares that there is no conflict of interest to disclose.

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