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A Comparative Study on Safety, Efficacy, and Cost of Glipizide versus Glimepiride as an Add-On Therapy to Metformin

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Abstract
Background: *Diabetes Mellitus (DM) is associated with abnormalities in carbohydrate, fat, and protein metabolism. Pharmacoeconomic studies are pertinent to the decision-making process when trying to balance the costs of specific alternatives.*
Objective: *To assess and compare the safety, efficacy, and cost of Glimepiride 2mg Vs Glipizide 5mg as an add-on therapy in patients receiving Metformin 500mg.*
Method: *A prospective comparative study was conducted for a period of 6 months on T2DM patients, subjects were recruited and grouped into 2 categories i.e. Group-A (metformin 500mg + glimepiride 2mg) and Group-B (metformin 500 mg + Glipizide 5mg). Efficacy of both treatments was assessed by using blood sugar levels data. The safety profile was assessed based on ADRs produced. Cost analysis was performed by using cost-effective analysis.*
Results: *The % of reduction achieves in both groups ('A' Vs 'B') from first follow up to final follow up was FBS 14.3% (17.4 Vs 14.9), PBS 13.7% (27.18 Vs 23.6) and RBS 29.9% (25.13 Vs 17.6). Based on the ICER (Incremental cost-effective ratio) formula, to achieve the Group A effectiveness, Group B requires more amount of 84 INR (FBS), 58.8 INR (PBS) and 27.9 INR (RBS) than the Metformin 500mg + Glimepiride 2mg. Among the 21 ADRs reported 10 were Metformin with Glimepiride and 11 were Metformin with Glipizide.*
Conclusion: *We conclude that the Glimepiride 2mg as add-on therapy with Metformin 500mg is little beneficial than Glipizide 5mg in terms of efficacy and cost. In terms of safety, both drugs are having similar safety profiles.*
Key Words: *Glipizide, Glimepiride, Metformin, Type2 Diabetes Mellitus, Safety, Efficacy.*

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I. Introduction

Diabetes Mellitus (DM) is associated with abnormalities in carbohydrate, fat, and protein metabolism [1]. According to the International Diabetes Federation (IDF) by 2030, India will become the largest number of diabetic people [2]. In 2010 the estimated Healthcare expenditures on diabetes are 11.6% of the total healthcare expenditure in the world [3]. Thus, pharmacoeconomic studies are pertinent to the decision-making process when trying to balance the costs of specific alternatives with their respective differences in clinical outcomes [4-5]. This study aimed to assess and compare the cost of Glimepiride 2mg Vs Glipizide 5mg as an add-on with Metformin 500mg along with the safety and efficacy assessment.

II. Materials And Methods

A prospective comparative study was conducted in a South Indian tertiary care teaching hospital for a period of 6 months on T2DM patients after Institutional Ethics Committee approvals. Type-II diabetes patients on treatment with study drugs, aged between 30-60 years old without any co-morbid conditions were recruited after obtaining Informed Consent from the study subjects, patients using other medication, pregnant and lactating mothers were excluded.

2.2 Data collection

The required information was collected in patient data collection Proforma by "Chart review method" which is well suited to assess the results. During the study, patient case records were received and patient demography, admitting diagnosis, past medical and medication history, physician medication order sheet and other special findings were collected.

In this study a sample of 60 patients was chosen and differentiated equally into two treatment groups; those were 30 patients were in Metformin500mg/ Glimepiride2mg and remaining 30 patients were in Metformin 500mg/ Glipizide 2mg.

During 6 months of the period we collected all patients' blood sugar level data, ADRs produced by the given antidiabetic medication.

Here we denote the Group (A) as Metfomin500mg/ Glimepiride 2mg and Group (B) as Metformin500mg/ Glipizide 5mg

The entire collected and documented patient's data were analyzed by the following parameters:

1. Efficacy was assessed by using blood sugar levels data.
2. The safety profile was assessed based on ADRs produced and causality was assessed by using Naranjo's scale.
3. Cost analysis was performed by using pharmacoeconomic model i.e. cost-effective analysis.

2.3 Statistical Analysis:

Chi-square is a statistical test commonly used to compare observed data. According to the chi-square probability test if the calculated value is less than the tabulated value it indicates the significant difference between the two groups.

III. Results

A total of 60 patients were recruited for this study of which 7 were withdrawn from the study due to irregular follow-ups. The remaining patients were followed for 6 months.

3.1. *Demographics*:

The total study population (60patients) was divided equally into two treatment groups. In a group, A males were 12 (40%) and females were 18 (60%). In Group B males were 6 (20%) and females were 24 (80%). In the age wise distribution of group A, the most of the patients belong to the 41-45 years age group (40%) and followed by 36-40 years age group (26.6%). Similarly, in the age wise distribution of group B, the most of the patients belong to the 46-50 years age group (33.3%) and followed by 36-40 years age group (26.6%). In group A and B most of the subjects were suffering from type2 diabetes since 10-12 months [Table 1].

3.2. Safety results

In our study drug safety was assessed by assessing the ADRs which are produced by the antidiabetic medication during the study period and the causality assessment had carried by the Naranjo's causality assessment scale. We did not observe any significant difference in ADR occurrence in two groups ($p>0.5$). [Table 2]

3.3. Efficacy results

Patients were differentiated into two treatment groups (Group A and Group B). During the study period, we collected the blood sugar levels from each patient of each group and sent for investigation. For calculating the efficacy, we had considered % of reduction of RBS, FBS, and PBS from first follow-up to final follow-up. The % of reduction achieved in group A from first follow up to final follow up was 17.4 (FBS), 27.18 (PBS) and 25.13 (RBS). (Figure 1)

The % of reduction achieved in group B from first follow up to final follow up was 14.9 (FBS), 23.6 (PBS) and 17.6 (RBS). [Figure 2]

The observed % of the reduction in blood sugar values in both groups ('A' Vs 'B') from first follow up to final follow up was FBS 14.3% (17.4 Vs 14.9), PBS 13.7% (27.18 Vs 23.6) and RBS 29.9% (25.13 Vs 17.6). There was a significant difference between two treatment groups observed by comparing the tabulated and calculated values at 0.05 probability and 0.1 probability scales of the Chi-Square test. We observed the significant reduction in blood sugar levels in the group (A) than the group (B). [Table 3]

3.4 Cost Analysis Results

In this study, we had taken into the consideration of costs of the Metformin500mg, Glimepiride2mg, and Glipizide5mg. The costs of these drugs were obtained from the purchasing department of RIMS, Kadapa. According to the purchase department records present in the RIMS, throughout the study period, the purchasing

department purchased these study medication with the same costs. There is no any hike and fall in the costs of these study drugs during the study period.

The total therapy costs for group A and group B is 508.68 INR and 298.08 INR respectively. The % of the difference between the two therapy costs was 41.28. These values were represented in [Table 4].

3.4.1 Cost-effective analysis

We have calculated the total cost of the therapy of both the treatments for 162 days (5 follow-ups) and analyzed the results with the pharmacoeconomic formulae ICER (Incremental cost-effective ratio) ICER yields the additional cost required to obtain the additional effect gained by switching from drug B to drug A.

Based on the above ICER formula, to achieve the Group (A) effectiveness, Group (B) requires more amount i.e. 84 INR for FBS, 58.8 INR for PPBS and 27.9 INR for RBS than the Group (A). [Table 5]

IV. Discussion

According to U.K. Prospective Diabetes Study Group 1998, in comparison with single-agent therapy, the therapeutic treatment goals for diabetes are not only reached satisfactorily but also maintained adequate control of blood glucose when using the combination therapy [6]. There are very few head-to-head studies that compare the effect of different combinations of antidiabetic agents. In our study, two fixed Metformin500mg Add-on therapy drugs were chosen: the first, with Glimepiride2mg a third-generation sulfonylurea that exhibits effects different from Glipizide5mg, including several extrapancreatic effects on muscle and adipose cells, elevating active glucose transport and increased insulin secretion (Muller, Satoh, & Geisen, 1995) [7] and the second with Glipizide5mg a second-generation sulfonylurea. There is no information about the comparison of the clinical effect of both sulfonylureas at specific doses; we used two common Add-on therapies that could not be equivalent and which could be a limitation of our study. The first clinical experience with the Glimepiride/Metformin combination was published in a study wherein Metformin failed as monotherapy; in the same study, a diminution of A1C of 0.7% was reached after 4 months of treatment (Charpentier, Fleury, Kabir, Vaur, & Halimi, 2001) [8].

In accordance with the new ADA-EASD guidelines, a sulfonylurea combined with Metformin constitutes an attractive option in the clinical practice (American Diabetes Association, 2008). This combination can reduce blood sugar levels concentration up to 2% (Krentz & Bailey, 2005) [9].

Our results showed similar reductions in the random, fasting and postprandial glucose levels for both antidiabetic combinations used in the study, reductions that were evident from the first follow-up of treatment. However, at the end of the study random, fasting and postprandial glucose levels were significantly lower in the Group (A) than the Group (B). Besides, it is worth mentioning that RBS, PBS, FBS is a better parameter to identify metabolic control because it evaluates the participation of both basal and postprandial glucose concentrations and their variability (Monnier, Colette, Dunseath, & Owens, 2007) [10]. Glimepiride is well-known to induce a higher frequency of hypoglycemia than other agents, and our results were in accordance with this fact (Rendell, 2004) [11] and not only that Glimepiride can also consider as a better second choice to Metformin Monotherapy in uncontrolled diabetic patient hongmei zhu also reported similar findings in their study [12].

Our results revealed that there is no significant difference in ADR occurrence in two groups ($p>0.5$) which is supported by Madhuri Chatterjee *et al*. [13]

V. Conclusion

We conclude that the addition of Glimepiride 2mg to Metformin 500 mg has modest beneficial than Glipizide 5 mg in terms of efficacy and cost. In terms of safety, both drugs are having similar safety profiles.

Tables:

Table 1: Demographics of the Study Subjects

	Total Number of subjects ***n=60***	
Gender	**Group A (30) Metfomin500mg and Glimepiride2mg**	**Group B (30) Metfomin500mg and Glipizide5mg**
Male	12(40%)	6(20%)
Female	18(60%)	24(80%)
Age		
30-35	2(6.6%)	2(6.6%)
36-40	8(26.6%)	8(26.6%)
41-45	12(40%)	8(%)
46-50	4(13.3%)	10(33.3%)
51-55	4(13.3%)	4(13.3%)
Duration of illness		
0-3 months	2(6.6%)	4(13.3%)

4-6months	2(6.6%)	2(6.6%)
7-9 months	8(26.6%)	6(20%)
10-12 months	18(60%)	18(60%)

Table 2: ADR data of Group A and Group B

S. No	Treatment Group	Reaction Observed	Causality Assessment (Naranjo's scale)	No. of Patients	Total
1	Group (A)	Weight Gain	Probable	1	10
		Dizzy	Possible	1	
		Excess Urination	Probable	2	
		Muscle Pain	Possible	1	
		Loss of Appetite	Possible	1	
		Headache	Possible	2	
		Itching	Possible	1	
		Drowsiness	Possible	1	
2	Group (B)	Headache	Possible	1	11
		Flu-like symptoms	Possible	1	
		Diarrhea	Possible	1	
		Feeling Weak	Possible	2	
		SOB	Probable	1	
		Muscle Pain	Possible	4	
		Hives	Possible	1	

Table 3: Chi-square test:

Treatment groups	FBS	PBS	RBS	Total
Group A(f_e)	17.4	27.18	25.18	69.71
Group B(f_0)	14.9	23.6	17.6	56.1
f_e-f_0	2.5	3.58	7.53	

Table 4: Total cost of the therapy in both the groups

S. No	Combination therapy	Cost per unit INR (A)	Total units (B)	Therapy Cost(A×B)	% of Difference
1	Group A	3.14	162	508.68	41.28
2	Group B	1.84		298.08	

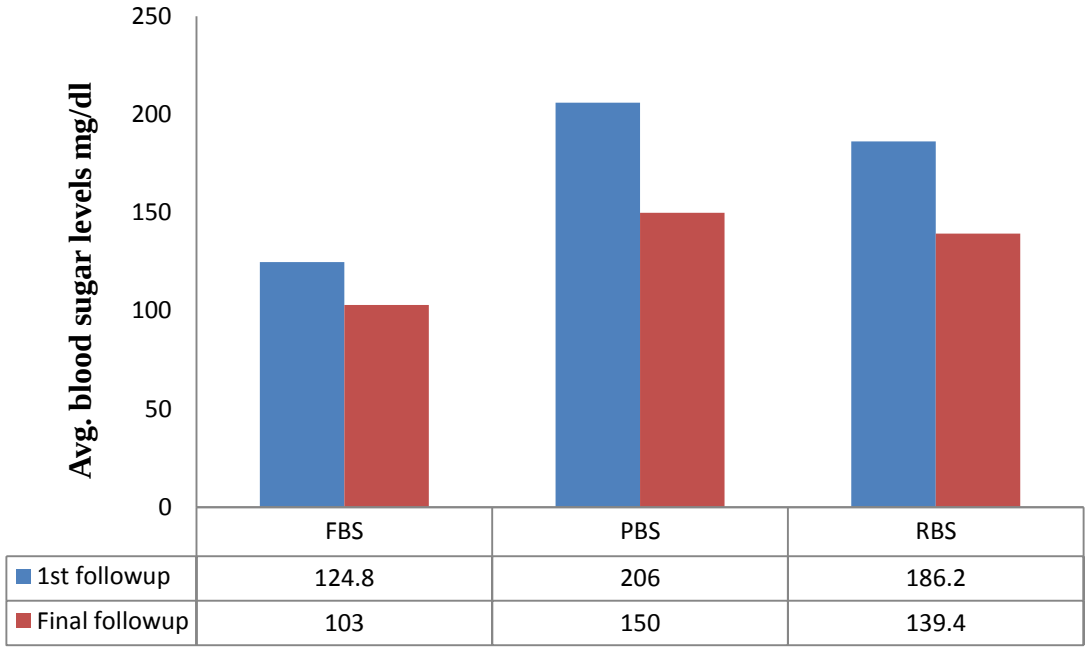
Table 5: Calculation of ICER

S. No	Study group	Cost	DC	Effect		DE	ICER= DC/DE	Result (ratio)
1.	Group (A)	508.68	210.6	FBS	17.4-14.9	2.5	210.6/2.5	84
				PBS	27.18-23.6	3.58	210.6/3.58	58.8
2.	Group(B)	298.08		RBS	25.13-17.6	7.53	210.6/7.53	27.9

E= Effect (% of reduction of blood sugar levels of group A -% of reduction of blood sugar levels of group B);
C= Cost in rupees; DC= Difference in cost (Group A - Group B); DE= Difference in effect (Group A- Group B)

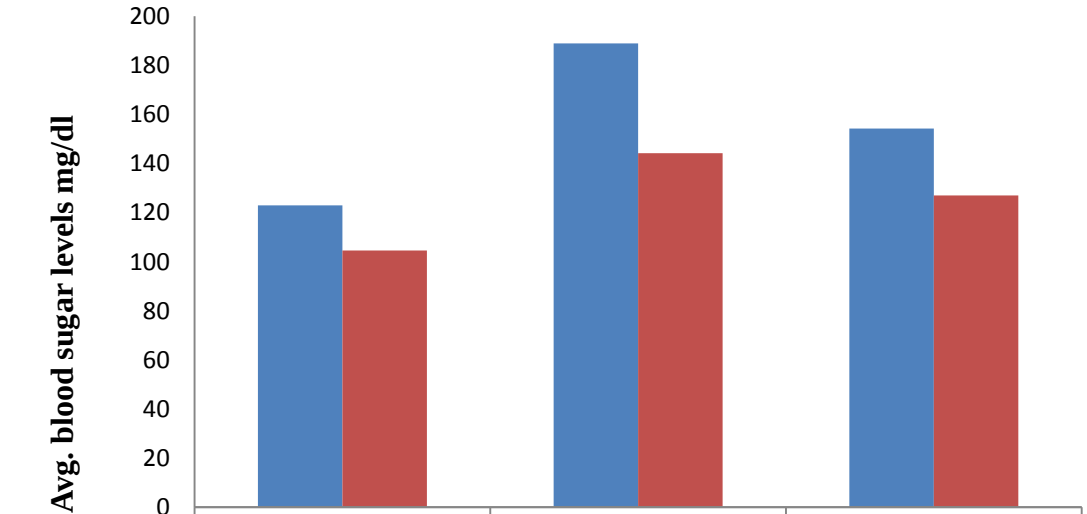
Figures

Figure 1: Comparison of Blood Sugar values from 1st follow-up to final in Group A



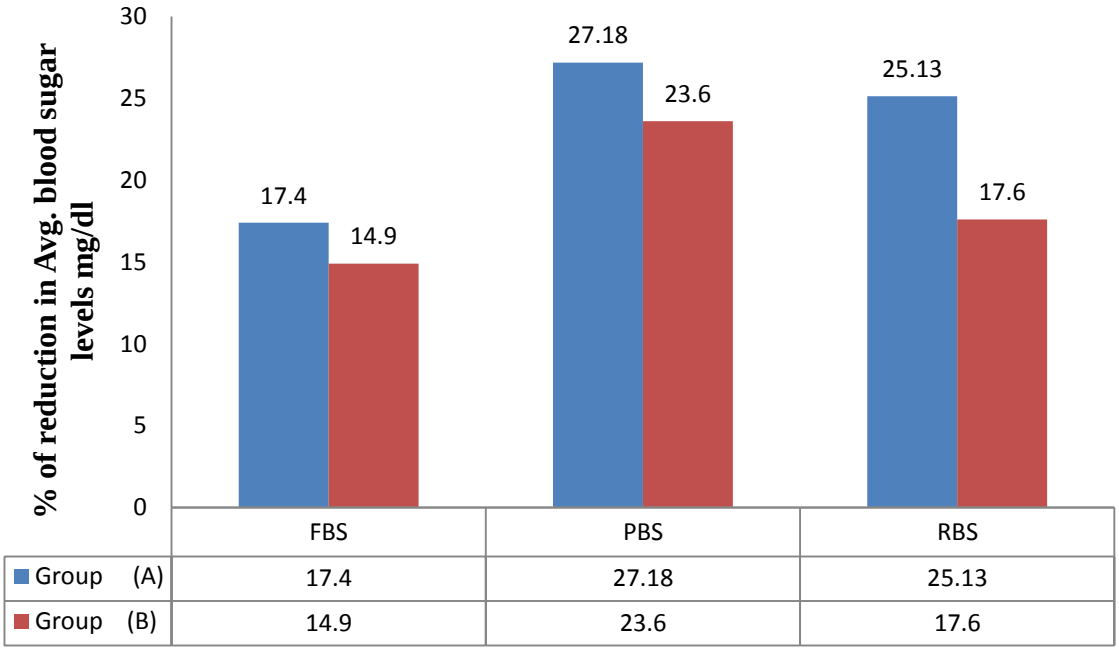
	FBS	PBS	RBS
1st followup	124.8	206	186.2
Final followup	103	150	139.4

Figure 2: Comparison of Blood Sugar values from 1st follow-up to final in Group B



	FBS	PBS	RBS
1st followup	123	188.9	154.3
Final followup	104.6	144.2	127

Figure 3: Comparison of % reduction of blood sugar level between two groups after final follow-up



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