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A Study on Assessment and Comparison of Anti Diabetic effect of Monotherapy and Combination Therapy involving in Metformin and Glimipride

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Abstract:

Diabetes mellitus (DM) is a complex metabolic disorder and which is one of the major health crisis the world facing today. There is no permanent cure for DM, however. It could be managed successfully with existing oral hypoglycaemic agents and insulin. Most of the time diabetic management will be unsuccessful in outpatients because of lack of health consciousness of the patients leading to noncompliance of advises given by physician and pharmacist. The main objective of the present study was to monitor three groups of Type-2 DM patients through frequent patient counselling and plasma glucose level monitoring using commercial self monitoring blood glucometer (SMBG). Patients were advised to take single or combination of Metformin or Glimipride for up to 24 weeks. Blood glucose levels were assessed at fasting and post prandial condition using SMBG. The results indicate that both single and combination therapy significantly reduces the DM complications. However the combination therapy provided better improvement of DM complications as compare to single drug treatment. More drugs related adverse effects were observed in combination therapy. The study reveals that the better clinical patient compliance of diabetic management could be achieved with proper and frequent patient counselling.

Keywords: Antidiabetic study, Metformin, Glimipride

1. INTRODUCTION

Type 2 Diabetes mellitus is a heterogeneous metabolic disorder characterized by relative deficiency in insulin secretion and peripheral insulin resistance, leading to hyperglycaemia. it is estimated more than 200 million people worldwide will have diabetes. The United kingdom prospective diabetes study has established that intensive blood glucose control is necessary for reducing the risk of diabetic complications in type 2 diabetic patients[1] Essentially, no glycemia thresholds have been observed for any type of diabetes complication: the lower the glycemia, the lower the risk of complications[2]. Self-monitoring of blood glucose (SMBG) has been recommended by the American Diabetes Association as a test for monitoring the glycemic status[3] but it is still controversially discussed as a tool for non-insulin treated type 2 diabetic patients[4] because methodologically meaningful studies into this question are lacking. The efficacy of structured, meal-related SMBG accompanied by brief counselling undertaken by the attending physician in a prospective, randomized group comparsion[5]. Patients using a blood glucose device showed significant improvements of glycemic control with marked improvements in quality of life. Recent findings studies positive association between the regular SMBG combined with continual health care consulation and glycemic control. Self- monitoring of blood glucose SMBG [6, 7] has become a recognized corner stone of diabetes care[8]. SMBG results are considered to be helpful for assessing the efficacy of hypoglycaemic treatments and adjusting dose in insulin therapy, while taking into account food intake, physical activity and various form of stress. In people with type2 diabetes taking insulin treatment. According to current and past French guidelines for diabetes care recommend at least two test a day[9,10]. Self-monitoring of blood glucose (SMBG)[11] has been widely accessible for people with diabetes for nearly 20 years. Early reports were hopeful, foreseeing better metabolic control as a possible target[11, 12]. Over the past10 years, new portable meters have been heavily marketed and new models are frequently introduced. The American Diabetes Association (ADA) recommends daily SMBG for all type 1 patients and for type 2 patients taking insulin or oral agents capable of inducing hypoglycemic[13] was needed. In a multicenter, randomized, double-blind, parellel-group study involving 372 patients with type 2 diabetes, combination therapy with glimipiride plus metformin was significantally more effective than monotheraphy with either agent in terms of Hba_{1c} reduction ($p<0.001$). Insulin is also important in type 2 diabetes mellitus once blood glucose levels cannot be controlled by diet, weight loss, exercise, and oral medicines. Insulin is indicated in the following situation **a)** when diet and oral hypoglycaemic drugs fail to control hyperglycaemia and achieve theraphy targets, **b)** diabetes during pregnancy when diet alone is inadequate and **c)** when oral hypoglycaemic agent drugs are contraindicated, during stressful condition such as infection and surgery[14,15,16].

2. MATERIALS AND METHOD

The instuitional Human Ethical Committee of Annamalai University has been approved the study to been carried out at Raja Muthaih Medical College and Hospital (RMMC&H). A prospective cross- sectional study was conducted on 120 Type 2 diabetic patients which includes 69 males and 51 female were recruited as per the inclusion and exclusion criteria from the Department of medicine, RMMC&H,

AnnamalaiUniversity. Patients who are regulary visiting hospital for the treatment from March 2012 to May 2013. Has been taken as subjects for this study. Patients were recruited as per the inclusion and exclusion criteria as follows

Inclusion criteria :

Patients those are having the following categories only were recruited for the study

a. Patients who diagnosed with Type-2 diabetes complications
b. Patients with age of 30 years and above
c. Fasting glucose > 140mg/dl
d. Post prandial blood glucose level(at 2hr) >200mg /dl
e. Patients with associated diseases of Hypertension, Coronary artery diseases, Bronchial Pneumonia, Asthma

Exclusion criteria:

a. patients who diagnosed with outType-2 diabetes complications
b. Patients below the age group of 30 years.
c. Patients who are not willing to participate in the study.
d. Nursing or pregnant women.
e. Hepatic or renal diseases patients
f. Patients with History of Ketoacidosis

120 patients whose fasting plasma glucose level were greater than 140 mg/dl only was included in the study. Patients were divided into three group of 40 patients in each named as Group 1, 2 and 3. The **Group 1** patients were treated with Metformine 500 mg whereas **Group 2** was treated with Glimepiride 2mg and **Group 3** treated with combination therapy of Metformine500mg and Glimepiride 2mg. All the patients were instructed to take the prescribed drugs regularly, follow the diabetic diet as per the RMMCH's dietician recommendation and exercise like walking daily one hour two times a day. The Fasting plasma glucose(FPG) and post prandial (PPBS) blood glucose levels at 0^{th}, 4^{th}, 12^{th} , and 24^{th} weeks were recorded. Therefore 24th weeks of the treatment periods completed to educate the patients importance of SMBG in Management of diabetes mellitus To all the study participant Measures the random blood sugars using glucometer and to explain the adjustment of diet and physical exercise. By using SMBG questionary and ask the patients to encourage the patient's attitude in SMBG usage, Physician are more supported and encouraged. Manufactured for: Life scan INC. Mlipitas, CA 95035, 0336 USA made in china ONE TOUCH HORIZON AW 063-239-01A Rev:05/2004

Statically Analysis

One way ANOVA followed by Dunnet post test was done by Graph Pad prism4 using.

Table 1: Fasting plasma glucose (FPG), Two hour postprandial glucose (PPG) Baseline and end point patients receiving metformin, Glimepiride, combination of Glimepiride with metformin

Treatment	Blood sugar (mg/dl) levels							
	Fasting				*Post prandial*			
	0 week	**4th week**	**12thweek**	**24thweek**	**0week**	**4th week**	**12week**	**24th week**
Metformin 500mg	168.05 ± 23.81	162.42 ± 21.10	160.61 ± 20.10	145.11 ± 13.36***	248.10 ± 31.78	232.68 ± 32.66*	212.43 ± 21.42***	190.10 ± 13.85***
Glimepiride 2mg	158.16 ± 12.81	154.02 ± 19.31	150.09 ± 31.11	142.79 ± 18.66**	272.49 ± 19.89	263.89 ± 28.99	249.13 ± 39.62**	200.47 ± 24.59***
Metformin 500mg +Glimepiride 2mg	287.44 ± 37.92	279.79 ± 35.31	185.64 ± 26.56***	112.05 ± 11.15***	312.88 ± 58.16	296.08 ± 49.83	202.55 ± 30.86***	148.13 ± 20.88***

All values are Mean ± SD, N=40

One way ANOVA, repetatial analysis using Dunnet post test all values are compared with 0 week.

Where

***= P< 0.001- Extremely significant

** = p<0.01 - Highly significant

* = p< 0.5 - significant

RESULTS AND DISCUSSION

A prospective cross- sectional study was conducted on 120 patients with type2 diabetic mellitus where as male 69 (57.5%) and female 51(42.5%) more number of patients were in the age group of(51-60) 54 patients and (61-70) 32 patients the maximum number of patients had co morbidity condition. The most common which were Hypertension (27.5%) gastritis (17.5%) and LRTI (7.5%) who attended the diabetic OPD and in patients of Department of medicine Rajah muthiah medical college and hospital, Annamalai university. Those patients are treated with Metformin (500mg) termed as group1 and group 2 Glimipride (2mg)and group 3 combination therapy of Metformin plus Glimepiride

Table 2

Base line demography characteristics of patients

Gender	Number of patients	Percentage
Male	69	57.5
Female	51	42.5
Body mass index (Mean ± SD)	28.16 ± 2.15	ND

Duration of Diabetes (in years)

Years	Number of patients	Percentage
>5	43	35.8
6-10	59	49.1
11-15	18	15

Table;3 Co-morbidity condition of patients with type2 diabetic mellitus

Diagnosis	Number of patients	% of patients
Hypertension	33	27.5
Peripheral Neuropathy	21	17.5
Gastritis	6	5
UTI (Urinary tract infection)	7	5.8
Parkinsonism	2	1.6
LRTI (Lower respiratory tract infection)	9	7.5

Table-4 Adverse effects of Metformine, Glimepiride, combination of Metformine and glimepride in the treatment of type 2 diabetic mellitus

Types of ADR	Metformin (N=40)		Glimepiride(N=40)		Combination of Metformin and Glimepiride (N=40)	
	Monitored in(Weeks)					
	0-12	13-24	0-12	13-24	0-12	13-24
Nausea	Nil	Nil	6(15)	2(5)	7(17.5)	1(2.5)
Vomiting	Nil	Nil	Nil	Nil	5(12.5)	2(5)
Hypoglycaemia	Nil	Nil	Nil	Nil	Nill	12(30)
Metallic taste	Nil	Nil	Nil	Nil	4(10)	1(2.5)
Gastric irritation	9(22.5)	3(7.5)	2	Nil	Nil	Nil
Diarrhoea	13	Nil	Nil	Nil	Nil	Nil

1. **Effect of Metformin 500mg treatment on blood glucose level (group 1):**
   The blood glucose levels were measured up to 24th week post treatment of Metformine (500mg). The significant reduction in blood glucose level were observed at 24th week of treatment in fasting condition the 99% confidential interval found to be 9.707 to 36.17. Whereas, in post parental the significant level of reduction in blood glucose was found at 4th, 12th and 24th week of treatment, the 99% confidential interval found to be -1.170 to 33.37, 18.40 to 52.94 and 40.73 to 75.27 respectively.
2. **Effect of Glimepiride 2mg treatment on blood glucose level (group2):**
   The blood glucose levels were measured up to 24th week post treatment of Glimipride (2mg). The significant reduction in blood glucose level were observed at 24th week of treatment in fasting condition the 99% confidential interval found to be 1.114 to 29.63. Whereas, in post parental the significant level of reduction in blood glucose was found at 12th and 24th week of treatment, the 99% confidential interval found to be 4.123 to 42.60 and 52.78 to 91.26 respectively.
3. **Effect of combination of Metformin 500mg and Glimepiride 2mg on blood glucose level (group3):** As compare to Metformin and Glimipride alone treatment the combination of Metformin and Glimipride shows a drastic reduction in blood glucose levels in both fasting and post parental condition. The blood glucose levels were measured up to 24th week post treatment Metformin and Glimipride. The significant reduction in blood glucose level were observed at 4 week of treatment in fasting condition the 99% confidential intervals of 12 and 24th week was found to be 82.13 to 121.5 and 155.7 to 195.1 respectively. Whereas, in post parental the significant level of reduction in blood glucose was found at 12th and 24th week of treatment, the 99% confidential interval found to be 82.07 to 138.6 and 136.5to193.0 respectively.

A total 120 patients enrolled in the study 4 excluded in group 3 those patients were not coming for regular review visit to hospital not follow the study advice follow up the patients were difficult so they were excluded the final conclusion.During the study period all possible adverse effects were monitored at two phases of diabetic treatment (Table 4) are from 0 to 12 weeks and 13 to 24 weeks time period in the study. The highest possible adverse effects in combination treatment of Metformin and glimepiride treatments was found to be hypoglycaemia and that is consistent with Barton et al, 2003[17]. Ingle *et al*, 2012[18]. A group patients who has treated by the combination of Metformine and Glimepiride shows higher ADR as compare to alone treatment Metformin or Glimepiride. Around 12 patients were been diagnosed by hypoglycaemia after 24 week treatment hypoglycaemic related ADRs such as palpitation, confusion, irritability, behavioural and sweating. patients were observed with sever hypoglycaemic complications and they are immediately brought to the hospital for give the treatment with oral glucose was enough to relieve symptoms. whereas no patient has been diagnosed as hypoglycaemia in alone treatment of Metformin or Glimepiride. Metallic taste, Nausea and vomiting also observed in combination therapy. Mild abdominal disturbance (diarrhoea) was observed with Metformin treated patients however it was disappeared after initial course of treatment from 3 to 6 days. Mild gastric irritation was observed around two patients in Glimepride

treatment, hence those patients are advised to take the antidiabetic medicine along with suitable supportive therapy like vitamin sublimation or H2 receptor antagonist to avoid gastric irritation. The patient compliments was observed after 6 to 12 week of Glimipride treatment along with either vitamin sublimation or H2 receptor antagonist.

CONCLUSION

The present study was concluded that both alone and combination of oral hypoglycaemic therapy has significantly reduces the blood sugar level after 24 week treatment. The combination treatment shows higher adverse reaction as compare to alone treatment of Metformine or Glimepiride. Whereas the observed adverse effect were overcome by frequent patient counselling. The usage of a glucometer improved glycaemic control, possibly due to the encouragement of greater self-care management. Hence, the study was reveals that the frequent patient counselling is needed in diabetic management for better clinical outcomes.

REFERENCES

1) UK Prospective Diabetes Study Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53
2) Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. Br Med J 2000; 321:405–12.
3) American Diabetes Association. Tests of glycemia in diabetes. Diabetes Care 2004;27(Suppl. 1):S91–S93.
4) Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R. Selfmonitoring in type 2 diabetes mellitus: a meta-analysis. Diabetic Med 2000;17:755–61.
5) Schwedes U, Siebolds M, Mertes G. Meal-related structured selfmonitoring of blood glucose: effect on diabetes control in noninsulin- treated type 2 diabetic patients. Diabetes Care 2002;25: 1928–1932.
6) Sonksen PH, Judd SL, LowyC.Homemonitoring of blood glucose. Method for improving diabetic control. Lancet 1978;1:729–32.
7) Walford S, Gale EA, Allison SP, Tattersall RB. Self- monitoring of blood glucose improvement of diabetic control, Lancet 1978: 1:732-5.
8) Agence nationale d' accrediation et d' evaluation en sante (Anaes). follow up of the type2 diabetic patient excluding follow- up of complications. Recommendations of Anaes, Diabetes Metab 1999:25:1-64.
9) Agence francaise de securite sanitaire des produits de sante (AFSSAPS), Haute autorite de sante (HAS) . type2 diabetes treatment : french recommendations for good practice . Diabetes metab 2006:;32:643-8.
10) Norris. SL, Engelgau MM, Narayan KMV . Effectiveness of self-management training in type 2 diabetic . A Systemic review of randomized controlled trials, Diabetic care 2001; 24; 561-87
11) American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Position statement. *Diabetes Care* 1999;21(Suppl 1):S32-S41.
12) Evans J, Newton R, Ruta D, MacDonald T, Stevenson R, Morris A. Frequency of blood glucose monitoring in relation to glycemic control: observational study with diabetes database. *BMJ* 1999;319:83-86. Abstract/FREE Full Text.
13) Charpentier G,Fleury F, Kabir M, etal. Improved glycaemia control by addition of glimepi to metformin monotheraphy in type 2 diabetic patients . Diabet med, 2001;18;828-834.
14) Bastaki S., Diabetes mellitus and its treatment, Int J Diabetes & Metabolism, 2005, 13, 111-134.
15) Dipirio J.T., Talbert R.L., Yee G.C., Wells B.G., Pharmacotherapy: A pathophysiologic approach, 6th ed., Mc. Graw Hill Medical publishing division,1999. 1333-1364.
16) Sundaram A. Anand Moses C. R., and Seshiah V., Newer antidiabetic drugs, Int.J. Diab. Dev. Countries, 1998, 18, 24-30.
17) Ingle P V, Talele G S, Adverse Effects Of Metformin In Combination With Glimepiride And Glibenclamide In Patients With Type 2 Diabetes Mellitus, Asian J Pharm Clin Res, Vol 5, Suppl 1, 2012.
18) Barton frenchman, Rph, CCP. FASCP Treatment and treatment related adverse events of type2 diabetes mellitus in residents of long- term care facilities: A retrospective study.