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Original research article

To study the impact of insulin and glibenclamide combination therapy on insulin dosage and glycemic control in patients with type 2 diabetes mellitus on insulin therapy alone

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Abstract

Background and Objectives: Type 2 diabetes mellitus is a common metabolic disorder with immense social impact. Millions of patients are being treated with insulin either after primary failure or secondary failure with sulphonylurea therapy. Sulphonylureas have the potential to reduce the glucose levels by increasing the insulin secretion and insulin sensitivity. This study intends to know the effect on fasting and postprandial glucose levels on adding glibenclamide to daily insulin regimens and reduction of the dose of insulin requirement.

Methods: The study conducted at Department of General Medicine, Siddartha Medical College, Vijaywada, Andhra Pradesh, India from July 2021 to June 2022. In 50 patients who met the inclusion criteria the fasting and postprandial glucose levels were recorded prior to the addition of glibenclamide and after addition of glibenclamide FBG and PPBG were recorded again and following statistical tests i.e., Fisher's F test and Student's 't' test and Gaussian tests were used to find significance.

Results: At the end of study FBG decreased by 32.5%which was statistically significant (p<0.01) and the mean PPBG value decreased by 27.7% which was also statistically significant (p<0.05).

Conclusion: Combination therapy with insulin and glibenclamide results in a significant improvement in glycemic control compared to insulin therapy alone. Combination therapy has no significant effect on insulin dosage. Risk of hypoglycemia can be lowered if the dose of glibenclamide is tailored to each patient's requirement. Compared to other insulin sensitizers' traditional drug like glibenclamide is the cheapest and most economical option available currently in the Indian market.

Keywords: Diabetes mellitus; FBG; PPBG; Sulphonylureas; Glibenclamide.

Introduction

Diabetes mellitus is a set of metabolic disorders with a similar phenotype: hyperglycemia. Type 2 DM is a diverse group of disorders with varied levels of insulin resistance, decreased insulin secretion, and increased generation of glucose. All around the world, but notably in emerging nations, Type 2 DM prevalence is rising. In India, there were an estimated 19.4 million diabetics in 1995, and by 2025, there would likely be 57.2 million. The prevalence rates have been continuously rising since the ICMR research in 1970, which had found a prevalence rate of 2.3% in the urban population and 1.5% in the rural population [1].

To address metabolic abnormalities and restore carbohydrate and lipid metabolism to normal or close to normal is the driving concept in the treatment of patients with type 2 DM [2]. The goal of current pharmacological strategies for the treatment of type 2 DM patients is to increase insulin production, insulin action, or both. Unless weight loss to an optimal body weight is also achieved, dietary treatment alone seldom normalizes insulin secretion and action in type 2 DM patients. Sulphonylureas appear to work by both boosting insulin production and potentiating the effects of insulin when they are successful in reducing hyperglycemia. How to treat type 2 DM to the desired target range with diet and sulphonylureas is a problem that regularly confronts the doctor. This dilemma encountered in cases of increasing duration of the disease and increasing obesity of the person in consideration. Twenty percent of the patients of type 2 DM show no response to sulphonylureas from the very start of the treatment with these drugs which is called as the primary failure, while each year 5%-10% of the others develop failure to these agents which is called as secondary failure [3].

Sulphonylureas fail to work when these cells are unable to boost the production of the insulin from cells, whereas type 2 DM is characterized by both cell malfunction and insulin resistance [4]. Although the only logical course of action for patients who fail to respond to sulphonylureas is insulin therapy, this strategy

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may not always be successful. The insulin dosages needed for this might lead to weight gain and hyperinsulinemia; the latter is regarded to be a risk factor for atherosclerosis. Additionally, proper glycemic control is not always guaranteed by insulin treatment [5]. This failure of response to the, sulphonylureas and the suspected and the proved problems of the insulin therapy when used have raised the question of alternative therapeutic approach in which the combination of insulin and sulphonylureas is used.

Since sulphonylurea drugs stimulate endogenous insulin secretion and improve the glucose metabolism through extrapancreatic action, it is reasonable to ask whether the addition of sulphonylurea drugs to an insulin treatment program in a patient of type 2 DM has value [6]. The potential value of combining insulin and sulphonylurea therapies in patient with type 2 DM would be to achieve more normal glycemia in patients who are not well regulated and/or to achieve more normal glycemia without significant peripheral hyperinsulinemia. Recent studies have re-evaluated the possible advantages and drawbacks of combination insulin-sulphonylurea treatment using a variety of protocol designs. Despite the highly diverse findings, most trials demonstrated improved glycemic control and/or decreased insulin requirements, at least in certain individuals referred to as "excellent responders" [7]. A metaanalysis of all investigations on the effectiveness of the combination insulin-sulphonylurea treatment that are currently published in the literature has verified this [8].

Materials and Methods

The study conducted at Department of General Medicine, Siddartha Medical College, Vijaywada, Andhra Pradesh, India from July 2021 to June 2022. Seventy-six patients with type 2 DM who had failed on treatment with oral hypoglycemic agents were included in the study. Informed consent was taken before enrolment. Of these, only 50 patients (34 men and 16 women with ages ranging from 44 to 75 years) completed the entire 12-week study period. The rest were lost to follow up.

Selection criteria

This regimen included the addition of glibenclamide, and the dosage was changed to meet the needs of the patient and the patient's blood glucose level.

Prior to the inclusion of glibenclamide, baseline values for fasting and two hours after a meal were calculated.

Throughout the 12-week research period, there were four-week intervals where the individuals were followed up in the outpatient clinic. Utilizing fasting and two hours after a meal blood glucose readings, metabolic regulation was evaluated at each hospital visit and at the conclusion of the trial. Due to cost limitations, (HbA1C) was not estimated.

It may have been essential to change the dosage of insulin and/or glibenclamide based on the metabolic control, including the frequency of hypoglycemia episodes. The dosage of glibenclamide was either kept constant or, if necessary, increased by 2.5 to 5 mg based on the blood glucose level at each hospital visit. If the blood glucose level dropped, the insulin dose was decreased rather than the glibenclamide dose.

A significant response was taken as a decrease of fasting blood glucose level of >50 mg/dl.

The patients were instructed to continue eating the same diet they had been on without any dietary changes.

The patients received information about the potential for hypoglycemia as well as training in the identification and management of hypoglycemia symptoms.

A Technicon autoanalyzer was used to estimate blood glucose using the glucose oxidase-peroxidase technique.

Inclusion criteria

- All the patients with type 2 DM who were on insulin, regular insulin, lente insulin or in combination irrespective of sex were selected.
- The minimum dose used was 2.5 mg/day and maximum dose used was 10-mg/ day.

Exclusion criteria

- All patients with chronic renal failure, chronic liver disease, acute myocardial infarction, proliferative retinopathy and systemic illness were excluded.
- Follow up of weight was not included in the present study.

Statistical methods

Results are given as mean ± SE (standard error). Fisher`s F test (ANOVA) was used to determine significance of the effect of combination therapy on the fasting and postprandial blood glucose levels and the insulin dosage. The Student`s paired ‘t’ test and the Gaussian test were used to calculate the significance of the drop in fasting blood glucose and 2-hour postprandial glucose levels at the end of 4 weeks and 12 weeks.

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Results

Combination therapy lowered the mean fasting blood glucose concentration from 208.58mg/dl at the beginning of the study to 140.84 mg/dl at the end of 12 weeks resulting in a 32.5% decrease, which was highly significant statistically (p<0.01).

The mean 2-hr postprandial blood glucose value decreased from 296.12 mg /dl with a drop of 27.7% which was statistically significant (p<0.05).

The mean daily insulin requirement declined from 29.28 u/day, a fall of only 6.1% and the value did not reach statistically significant (p>0.05).

Symptomatic hypoglycaemia was noted in one patient necessitating the stoppage of insulin (patient no. 1 in the master chart). This patient was known to have erratic control of blood glucose even before with at least one earlier episode of hypoglycaemia.

Table 1: Blood glucose levels and insulin dose before and after the addition of glibenclamide

	FBG (mg/dl)	PPBG (mg/dl)	INSULIN (u/day)
Beginning of the study	208.58±10.75	296.12±13.01	29.28±1.71
4th week	174.70±9.76	253.38±11.83	28.48±1.58
8th week	153.52±7.29	227.44±9.93	27.88±1.70
12th week	140.84±5.11	214.04±5.96	27.48±1.56
% of Decrease	32.5%	27.7%	6.1%
Test of significance "F"	24.32 p<0.01	11.60 P<0.05	1.43 p>0.05

Dose of glibenclamide

Of the 7 patients who were started on 2.5mg/day of glibenclamide, all had a modest reduction in the mean FBG (149.14 to 132.86) and mean 2-hr PPBG (209.86 to 191.14) values at the end of the study.

Nineteen patients were started on 5 mg/day of glibenclamide, 18 of whom showed a decrease in the mean FBG (135.37 to 124.11) and mean 2-hr PPBG (261.37to 203.39) values at the end of 12 weeks.

Two of the patient's who received 7.5mg/day of glibenclamide did not show a response in the blood glucose levels and had to be switched over to 10 mg/day.

Twenty-two patients received 10 mg/day of gibenclamide at the beginning of the study. The end of study added 3 patients added to this group. In this group, all had a drop in the mean FBG (182.82 to 156.04) and mean two-hour PPBG (359.18 to 226.32) levels.

Table 2: Dose of glibenclamide and FBG response

G'amide (mg/day)	0 week		4th week		8th week		12th week	
	n	FBG	N	FBG	n	FBG	n	FBG
2.5	7	149.14±17.98	7	139.71±8.87	7	127.00±4.66	7	132.86±4.86
5.0	19	135.37±6.54	18	144.47±6.64	18	131.11±5.15	18	124.11±6.80
7.5	2	244.00±71.99	2	158.50±38.50	1	316.00	0	-
10.0	22	182.82±12.82	24	200.75±17.04	24	171.46±11.80	25	156.04±5.66

Table 3: Dose of glibenclamide and PPBG response

G'amide (mg/day)	0 week		4th week		8th week		12th week	
	n	2-hr PPBG	n	2-hr PPBG	n	2-hr PPBG	n	2-hr PPBG
2.5	7	209.86±5.58	7	192.00±10.67	7	188.43±10.98	7	191.14±11.30
5.0	19	261.37±12.34	18	226.76±7.79	18	202.11±5.19	18	203.39±6.04
7.5	2	248.50±36.54	2	226.50±26.50	1	448.00	0	-
10.0	22	359.18±2074	24	292.38±21.32	24	248.63±16.30	25	226.32±6.54

Time taken for control

At the end of 4 weeks, 48 patients (96%) had a reduction in the FBG values with only 46 patients (92%) showing a sustained response at 8 weeks, but at the end of 12 weeks all 50 patients had a reduction in the blood glucose values.

The drop in blood glucose levels at the end of 4 weeks was statistically significant with an average drop in FBG of 37.30±5.05 (p<0.001) and 2-hr PPBG of 42.74±10.28 (p<0.001) and 2hr PPBG of 82.98±11.09 (p<0.001).

Despite this, at the end of 4 weeks only 8 patients (16%) had a drop in FBG levels of >50 mg/dl. This number increased to 22 (44%) at the end of 12 weeks. This increase in the number of people responding to continued treatment at the end of 12 weeks reached statistical significance (p<0.001).

The 2hr PPBG levels of 10 patients (20%) dropped by >50 mg/dl at the end of 4 weeks and 28 people (56%) had a significant reduction at the end of 12 weeks. The number of people responding to continued treatment again reached statistical significance (p<0.001).

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Table 4: Mean drop in FBG and 2 hr PPBG

Week	Mean drop in FBG	Mean drop in 2-hr PPBG
0-4	37.30±5.05 t=7.38 p<0.001	42.04±10.28 t=4.15 p<0.001
0-12	67.38±7.52 t=8.95 p<0.001	82.98±11.10 t=7.47 p<0.001

Table 5: Percentage of drop in FBG and PPGB

Week	Drop in FBG > 50mg/dl	Drop in 2-hr PPBG> 50mg/dl
0-4	8(16%)	10(20%)
0-12	22(44%)	28(56%)
Significance	Z=3.21 p<0.001	Z=3.99 p<0.001

Discussion

The primary aim of the study was to determine, in type 2 diabetic patients with secondary sulphonylurea failure, whether metabolic control could be achieved under supervised insulin therapy combined with glibenclamide than insulin therapy alone and to also study the effect of combined therapy on the insulin requirement.

In the present study, there was a significant improvement in the fasting (p<0.01) and postprandial (p<0.05) blood glucose values. This was associated with a fall in insulin requirement that was statistically insignificant (p>0.05). The results obtained in the present study are comparable with the six studies quoted below:

Falko [9] demonstrated that the mean fasting blood glucose remained significantly lower compared with the base line values (p<0.05). HbA1C levels also decreased significantly (p<0.05) but no change in insulin dose was required.

Lardinois [10] reported that the fasting plasma glucose concentration fell an average of 57mg/dl associated with an approximately 25% reduction in postprandial glucose but no changes in insulin requirement were necessary. In another study by Groop [11], compared with insulin plus placebo, the fasting blood glucose values were lower during the insulin glibenclamide period (p<0.001). The mean insulin dose did not change significantly. Longnecker [11] presented data showing that tolazamide lowered the mean plasma glucose concentration (p<0.02). Postprandial glycemia also decrease but the change was not statistically significant. The dose of insulin did not vary during the study Groop demonstrated the combination of insulin and glibenclamide to more effective in lowering the fasting blood glucose (p=0.026) than the combination of insulin and placebo. This was associated with a reduction in insulin dose but was not statistically significant. Osei reported a significant reduction in fasting blood glucose values compared with base line values (p<0.005). HbA1c levels also decreased significantly (p<0.05). There was no change in insulin requirement.

Interestingly, in this study only one patient experienced symptomatic hypoglycaemia necessitating the withdrawal of insulin, whereas in the literature, hypoglycaemia is reported to be two to four times more common [3] in patients on combined therapy. This disparity could be due to the fact that in the present study, glibenclamide was added in varying doses depending on patient requirement; whereas in most of other studies, a fixed dose of glibenclamide was given to every patient in the study.

According to studies on the use of insulin and sulphonylurea together to treat type 2 diabetes, sulphonylurea added to the regular insulin regimen may lower glucose levels when compared to insulin monotherapy and, in certain situations, may reduce the amount of insulin needed. However, in individuals with secondary failure, this has not been shown to be preferable to optimum, maximal insulin administration alone. Regarding glycemic control, lipid profile, weight management, and complications of diabetes, it is yet to be determined if this combination medication provides any long-term benefits. The addition of sulphonylurea to insulin monotherapy in obese patients (C-peptide positive) who are insufficiently managed on insulin alone or require doses of insulin more than 100 u/day seems plausible since residual beta cell activity appears to be a requirement for a favorable outcome of combination treatment [3]. In type 2 diabetic individuals, a decrease in insulin needs and even peripheral insulin levels may have a long-term beneficial effect with regard to the atherogenic risk, however long-term research including numerous patients are necessary.

Conclusion

Glycemic control significantly improves with insulin and glibenclamide combination treatment. It has no effect on insulin dosage. Risk of hypoglycemia is less if the dose of glibenclamide is tailored to patient's requirement.

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Conflict of interest: None

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