EFFICACY OF DCBT 2345 – AN AYURVEDIC COMPOUND IN TREATMENT OF TYPE 2 DIABETIC PATIENTS WITH SECONDARY FAILURE TO ORAL DRUGS - RANDOMIZED DOUBLE BLIND PLACEBO CONTROL STUDY

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ABSTRACT

The objective of this study was to determine the efficacy of DCBT 2345 – an ayurvedic compound, in the management of diabetes of type 2 diabetic patients with secondary failure to oral hypoglycemic agents. A randomized, double blind, single center study of six months duration was carried out. 44 type 2 diabetic patients who satisfied the inclusion criteria were recruited for the study. Out of 44 patients, 30 completed the trial. 15 in the DCBT 2345 arm and 15 in the placebo arm. End points of the study included fasting and post prandial plasma glucose and glycosylated hemoglobin levels. There was no significant reduction in the fasting and postprandial plasma glucose levels in both the groups (placebo and DCBT 2345). However there was a significant reduction in the glycosylated hemoglobin levels ($p = 0.037$) in the DCBT 2345 group. No adverse events were noted in patients treated with DCBT 2345. Our study suggest that DCBT 2345 exerts a mild hypoglycemic action in type 2 diabetic patients with secondary failure to oral hypoglycemic agents.

KEY WORDS: DCBT 2345, Type 2 diabetes, Ayurvedic compounds, Gymnema sylvestre, Syzygium jambolinium and Cephalandra indica.

INTRODUCTION

Type 2 diabetes mellitus is a common disorder among Indians. Recent reports from the WHO indicate that India leads the world with the largest number of diabetic patients in the world (1). Therapeutic options for diabetes are dietary modification, oral hypoglycemic drugs (OHA) and insulin therapy.

Alternative medicines like ayurvedic preparations have attracted great interest in the management of diabetes. Various experimental and observational studies have shown that drugs like Vijayasar, Pterocarpus marsupium, Gymneme sylvestre and Tinospora cordifolia might be effective in diabetes management (2-5).

DCBT 2345, an ayurvedic formulation, has three herbal ingredients Gymnema sylvestre, Syzygium jambolinium and Cephalandra indica. These herbal extracts have been claimed to have some antidiabetic action. We have tried to study the effect of DCBT 2345 on diabetes management in type 2 diabetic patients with secondary failure to oral hypoglycemic agents.

MATERIALS AND METHODS

This was a six months, randomized, double blind, single centre study conducted at the Madras Diabetes Research Foundation, Chennai. The study group comprised of 44 type 2 diabetic patients with secondary failure to OHA, attending M.V. Diabetes Specialities Centre and satisfying the inclusion criteria. The ethical committee of the hospital approved this study and an informed consent was obtained from all the study subjects.

The inclusion criteria for the study were type 2 diabetes, with age greater than 30 years and secondary failure to OHA. The secondary failure to OHA was diagnosed if the patient's glycemic control was not responding to the maximal dose of oral hypoglycemic agents, which also indicated poor β cell reserve. Patients with ketosis, diabetic nephropathy, hepatic or renal disease, pancreatitis, cardiac failure, malnutrition and infections were excluded from the study.

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Protocol and Study Design

Care was taken to ensure that the drug and the placebo looked identical and were placed in different boxes coded A and B respectively. The investigator was blinded as to which of the boxes contained the drug and which the placebo, until the codes were decoded at the end of the trial. Patients were randomly allocated to either group A or B. The recommended dose was 2 tablets to be taken three times a day for six months. Patients in both groups received a standard High Carbohydrate High Fibre (HCHF) diet presented at our centre (6). The diet was kept constant throughout the study. A dietitian checked adherence to the diet at each visit to ensure that it was kept constant throughout the study. The tablets were allotted on a monthly basis to the patients. Each bottle containing 180 tablets, sufficient for a month, were given at each visit. Patients were asked to return the unconsumed tablets at the time of each visit to ensure that the tablets were taken regularly. The anti-diabetic treatment was continued as usual and other concomitant medication for hypertension and hyperlipidemia were also continued unchanged.

Clinical Investigations

Clinical history was recorded at the first visit. At each visit, the weight, blood pressure and pulse rate were recorded. The fasting and post prandial plasma glucose measurements were made on a monthly basis while the glycosylated hemoglobin, insulin measurements, C-peptide assays and lipid profile was done at the initial, third and final visits.

Fasting and postprandial plasma glucose (glucose-oxidase method) was estimated using kits supplied by Boehringher Mannheim, Germany. Glycosylated hemoglobin (HbA_{1c}) was estimated by HPLC method using the variant machine (Bio-Rad, U.S.A). Insulin and C-peptide assays were done by Elisa technique using DAKO kits (Dako Diagnositics Ltd., UK). The intra-assay and the inter-assay co-efficient of variation for insulin assay was 5.7% and 8.9% respectively and the lower detection limit was 0.5mIU/ml. The intra-assay and the inter-assay co-efficient of variation for C-peptide assay was 4.0% and 8.3% respectively and the lower detection limit was 0.02 pmol/ml.

Statistical Analysis: Paired 't' test was used to compare the data of the biochemical parameters before and after treatment with DCBT 2345. Independent t test was performed to test the significance of the mean difference between drug group and placebo group.

Of the 44 patients who entered the trial, there were 14 dropouts. Out of the 14 dropouts, six were due to associated illness (vomiting, hepatitis, abdominal tuberculosis, urinary tract infection and coronary artery disease), six patients had severe hyperglycemia and had to be put on insulin and two patients did not turn up for the follow-up.

The drug group had a mean (SD) age of 51 ± 9 years, body mass index 24.3 ± 3.1 kg/m^2 and males n (%) - 6 (40%) while the placebo group had a mean (SD) age of 59 ± 7 years, body mass index 23.9 ± 3.0 kg/m^2 and males n (%) - 5 (33%). There was no significant difference between the two groups with respect to any of the parameters.

Table 1: Results of the Diabetogenic Profile in the Study Patients.

Variables	Group	Baseline	End of study	p value
Fasting Plasma	Drug	198 ± 15.0	181 ± 12.1	NS
Glucose (mg/dl)	Placebo	180 ± 10.3	177 ± 14.0	NS
Post Prandial	Drug	303 ± 14.7	284 ± 17.6	NS
Plasma Glucose (mg/dl)	Placebo	297 ± 19.4	278 ± 23.5	NS
HbA_{1c} (%)	Drug	9.8 ± 0.54	8.6 ± 0.46	0.037
	Placebo	9.0 ± 0.44	8.5 ± 0.41	NS
Fasting Insulin (mIU/ml)	Drug	12.1 ± 1.5	131 ± 2.5	NS
	Placebo	13.7 ± 3.1	8.7 ± 1.2	NS
Stimulated Insulin (mIU/ml)	Drug	43 ± 4.7	42 ± 6.5	NS
	Placebo	50 ± 7.2	34 ± 6.2	NS
Fasting C-Peptide (pmol/ml)	Drug	0.7 ± 0.08	0.6 ± 0.08	NS
	Placebo	0.8 ± 0.1	0.5 ± 0.05	NS
Stimulated C-peptide	Drug	1.9 ± 0.18	1.7 ± 0.18	NS
(pmol/ml)	Placebo	1.8 ± 0.18	1.6 ± 0.15	NS

Values are expressed as mean ± SEM. Paired "t" test is used to test the significance among groups.

Table 1 shows the results of the study in 30 patients who completed the trial, 15 in drug and 15 in the placebo group. Paired 't" test analysis revealed significant reduction in the glycosylated hemoglobin levels (HbA_{1c}) (p = 0.037) in the DCBT 2345 group. However there was no significant difference in the fasting plasma glucose and postprandial plasma glucose levels both in the drug and placebo groups. Fasting insulin remained the same in the drug group whereas a 36% decrease was seen in the placebo group. Stimulated insulin again remained almost the same in the drug group whereas in the placebo group it fell by 32%. Stimulated insulin did not show any significant difference in either the drug or placebo groups. The fasting C-peptide showed a 37% drop in the placebo group in comparison with the drug group in which the values remained the same at the beginning and end of the study.

Fig 1 : Mean Fasting Plasma Glucose Levels in the Study Groups

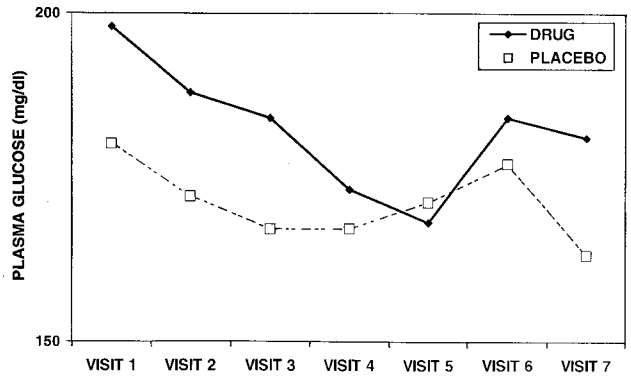


Figure 1 shows the mean fasting plasma glucose levels in the drug and placebo groups during all the visits. There was a slight decrease in the plasma glucose levels observed in both the placebo and drug group, but this did not reach statistical significance. There was also no difference between drug and placebo groups at any point of time.

Figure 2 shows the changes in postprandial plasma glucose levels. This was again not significantly different between the drug and placebo groups.

Fig 2 : Mean Postprandial Plasma Glucose Levels in the Study Groups

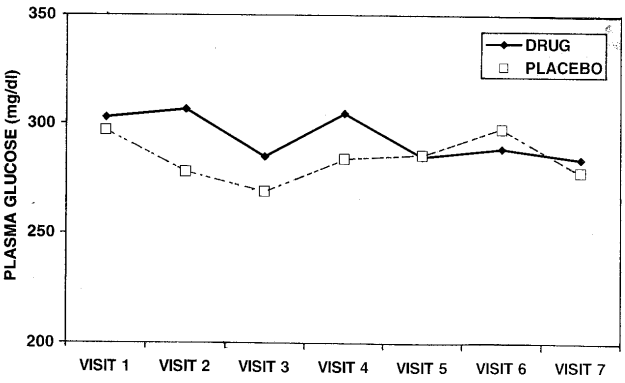
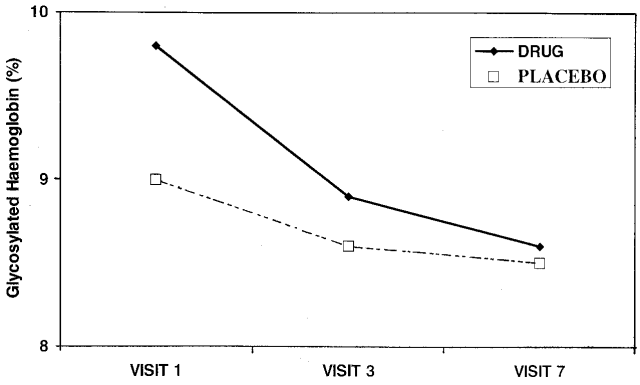


Figure 3 presents the mean glycosylated hemoglobin levels in the drug and placebo group. Glycosylated hemoglobin levels were reduced both in the drug and placebo groups but reached statistical significance only in the drug group.

Fig 3 : Mean Glycosylated Haemoglobin Levels in the Study Groups



DISCUSSION

Earlier studies have shown that the ingredients of DCBT 2345 Gymnema sylvestre, Cephalandra indica and Sygium jambolium have some antidiabetic action (7-9). In the current study we tried to study the effect of DCBT 2345 in the management of hyperglycemia in type 2 diabetic patients with secondary failure to OHA.

A decrease in the fasting plasma glucose and postprandial glucose levels was noted in the drug group; however, a similar effect was also noted in

the placebo group. Glycosylated hemoglobin however, decreased significantly in the drug group compared to the placebo group. It may appear paradoxical that while the fall in fasting and postprandial plasma glucose levels were not significantly different in the drug group and placebo group, there was a significant reduction in the glycosylated hemoglobin levels. The possible explanation is that the plasma glucose levels were tested only in the morning i.e. fasting and post breakfast while the HbA_{1c} reflects a mean of all the blood glucose levels. It is thus possible that the after lunch or after dinner blood sugars could have been lower in the drug treated group which could explain the significant lowering of HbA_{1c} levels in the drug treated group. This however, is purely speculative, as we have not measured these parameters. Even so, it is significant that there was a 1.2% lowering of HbA_{1c} in this group of patients with secondary failure to OHA. The mean lowering of HbA_{1c} with sulphonylurea and metformin is in the range of 1 - 1.5%, with the thiazolidinediones compounds it is around 1.5% while with acarbose, it is about 0.5%. Hence there appears to be some antidiabetic effect of this compound.

Review of literature provides interesting information on the herbal composition of DCBT 2345. Gymnema sylvestre, which is also known as "sugar buster" has been shown to reduce blood sugar levels in diabetic patients. The hypoglycemic nature of this drug was documented 70 years earlier (10). Later, extensive observational and experimental studies have shown that Gymnema sylvestre increases insulin production by regenerating islet cells and increasing cell permeability and it is also reported to decrease intestinal absorption of glucose (11,12).

Herbs that belong to the genera Syzygium have been shown to effectively reduce hyperglycemia (8). Syzygium cumini seed powder reduces the sugar in urine and ameliorates polydipsia (8). Extensive studies on experimental models have revealed that this herb promotes endogenous release of insulin. The glucoside jamboline has been shown to control polyuria and glycosuria equally well (13). Cephalandra indica is also referred to as an "Indian substitute: for insulin and has glucokenin, which has a property of reducing glucose in blood. Though, there are a few studies reporting no benefit with Gymnema and Syzygium (14-17) this double blind randomized placebo-controlled study on secondary OHA failure in type 2 diabetic patients shows some promise.

A more intensive study is called for, as the sample size was very small to bring out greater significance between drug and placebo groups. One of the limitations of the study is that herbal formulations could be slow acting and hence the study period should be a minimum of one year. The positive factors which have emerged from the study is the lowering of glycosylated hemoglobin and the maintenance of pancreatic beta cell function as assessed by plasma insulin and C-peptide estimations in the drug treated group, while there was a 30-37% deterioration in beta cell function in the placebo treated group. This might suggest that the drug helps to improve / maintain insulin secretion providing optimal stimulation of pancreatic beta cells. Alternatively, the drug may have improved insulin sensitivity thus resulting in less exhaustion of beta cells. Further studies are needed to assess the mechanism of action of DCBT 2345.

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