EVALUATION OF SAFETY AND EFFICACY OF HYPONIDD, AN AYURVEDIC COMPOUND: A DOUBLE BLIND, PLACEBO CONTROLLED STUDY IN TYPE 2 DIABETIC PATIENTS WITH SECONDARY FAILURE TO ORAL DRUGS

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ABSTRACT

To determine the efficacy of an Ayurvedic preparation, Hyponidd in type 2 diabetic patients with secondary failure to oral hypoglycemic agents, a randomized double blind, single centre, study of 12 weeks duration was carried out. 40 type 2 diabetic patients who satisfied the inclusion criteria were recruited for the study. Out of 40 patients, 32 completed the trial, 16 in the Hyponidd arm and 16 in the placebo arm. There was a non-significant reduction in the fasting and postprandial plasma glucose levels in the group treated with Hyponidd. A significant reduction in the glycosylated haemoglobin levels was noted in the drug group ($p<0.05$). No adverse events were noted in patients treated with Hyponidd, except for one patient who had elevated liver enzymes.

Hyponidd exerts a mild hypoglycemic action in type 2 diabetic patients with secondary failure to oral hypoglycemic agents (OHA).

KEY WORDS: Hyponidd, Type 2 diabetes mellitus, Secondary failure to OHA, Ayurvedic compounds.

INTRODUCTION

Type 2 diabetes mellitus is one of the most common disorders seen all over the world. Recent projections from the WHO have indicated that the prevalence of diabetes is rising world wide, particularly in developing countries (1). India is reported to lead the world with the largest number of diabetic subjects. Type 2 diabetes being a multifaceted life long disorder, could lead to micro and macro vascular complications. A recent multi-centric, follow up study, on type 2 diabetes from the United Kingdom, has established that tight control of blood sugar can reduce the incidence of diabetes related complications (2). Diet, exercise and oral therapy are usually found to be effective for a period of 10 – 15 years following the diagnosis of diabetes. At this stage, due to declining pancreatic β cell reserve, oral therapy is no longer effective on its own, a stage known as secondary failure to OHA. Additionally, at this stage, the long-term complications due to diabetes, both microvascular and macrovascular begin to set in. Insulin therapy is the only option for control of diabetes when all oral hypoglycemic agents have failed.

Alternative medicines have been reported to be effective in controlling diabetes, but there are very few placebo controlled, randomized clinical trials. Hyponidd is a herbo-mineral formulation and has 12 blended ingredients including Vijaysar (Pterocarpus marsupium), Gurmar (Gymneme Sylvestre), Jambu Beej (syzigium Cumine), Amla (Emblica Officianale), Haldi (Gurcuma Longa), Neem (Melia Azadirachta), Trivang Bhasma and Shilajit. All these agents have been shown to have some anti-diabetic action. We report in this paper the results of a randomized, double blind, placebo control study aimed at assessing the efficacy of Hyponidd in type 2 diabetic patients with secondary failure to OHA.

MATERIALS AND METHODS

Study Subjects and Inclusion Criteria

Type 2 diabetic patients attending the outpatient division of M.V. Diabetes Specialities Centre and satisfying the inclusion criteria were recruited for the study. The ethical committee of the hospital approved the study and informed consent was obtained from all the study subjects.

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The inclusion criteria for the study were that the patients should be within the age range of 30 – 60 years and should have secondary failure to OHA. Secondary failure to OHA was diagnosed if the patient had HbA_{1c} levels > 8.5% even after supplementation of maximal dose of a combination of a sulphonylurea (15 mg glybenclamide or 160 mg gliclazide or 15 mg glipizide) and metformin 1500 mg/day. Patients with ketosis, diabetes related complications, hepatic or renal disease, pancreatitis, cardiac problems, uncontrolled hypertension, malnutrition and severe immune deficiency were excluded form the study.

Protocol and Study Design

This was a randomized, double blind, single centre study of 12 weeks duration. 40 type 2 diabetic patients who satisfied the inclusion and exclusion criteria were taken up for the study. 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 or 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 3 times a day for 3 months. Patients in both groups received a standard diabetic diet of High Carbohydrate High Fibre (HCHF) as described earlier (3). The diet was kept constant throughout the study. A dietitian checked the 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 contained 30 tablets and 6 such bottles 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 in case of hypertension and hyperlipidemia were also continued unchanged. Compliance to the drugs in the 32 patients were ensured by spot checks at patient's residence by SP and KK. 94% (30/32) of the patients adhered to the drug doses prescribed while one patient was irregular at consumption of drugs in the first week which was rectified thereafter and one patient was irregular while he was on a tour for a week.

Clinical Investigations

Patient's clinical history was recorded at the first visit. At each visit, the weight, blood pressure and pulse rate were recorded. ECG was done at the initial and final visit.

The fasting and post prandial plasma glucose measurements were made on a monthly basis while the glycosylated haemoglobin, insulin measurements, C-peptide assays and lipid profile were done at the initial and final visits.

Fasting and postprandial plasma glucose (glucose-oxidase method) were estimated using kits supplied by Boehringher Mannheim, Germany. Glycosylated haemoglobin (HbA_{1c}) was estimated by HPLC method using the variant machine (Bio-Rad, U.S.A). Serum cholesterol (CHOD-PAP method) and serum triglycerides (GPO-PAP method) were measured. HDL cholesterol was estimated by CHOD-PAP method after precipitating low-density lipoprotein and chylomicron fractions by the addition of phosphotungstic acid in the presence of magnesium ions and very low-density lipoprotein (VLDL). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula (4). 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 were 5.7% and 8.9% respectively and the lower detection limit was 0.5 mIU/ml. The intra-assay and the inter-assay co-efficient of variation for C-peptide assay were 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 most of the biochemical parameters obtained before and after treatment with Hyponidd.

RESULTS

The selection of subjects is shown in Figure 1. Of the 40 patients who entered the trial, there were 8 dropouts: 5 due to non-compliance, 2 patients had severe hyperglycemia and 1 patient showed a transient increase in the Serum Glutamate Oxaloacetate Transaminase (SGOT) and Serum Glutamate Pyruvate Transaminase (SGPT) levels.

Figure 1: Flow Chart Showing Subject Selection

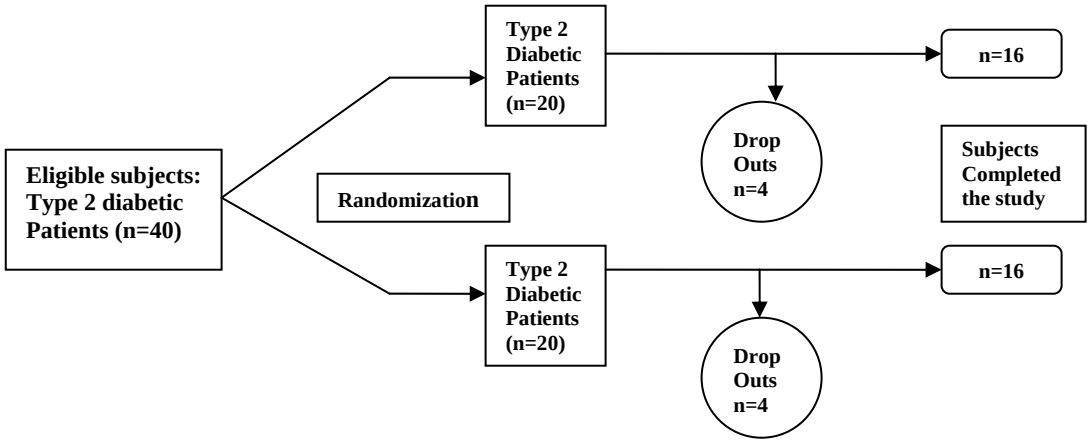


Table 1 presents the clinical features of the study groups. There was no significant difference in the age, body mass index, blood pressure, smoking rates or alcohol intake between the drug and placebo groups.

Table 1: Clinical Features of the Study Group

	Drug	Placebo	pvalue
Male n (%)	10 (62%)	11 (69%)	NS
Age (yrs)	53 ± 9	54 ± 10	NS
Body mass index (kg/m^2)	25.3 ± 2.8	24.6 ± 2.8	NS
Systolic blood pressure (mm Hg)	138 ± 12	137 ± 14	NS
Diastolic blood pressure (mm Hg)	82 ± 6	81 ± 6	NS
Smoking n (%)	2 (12.5%)	3(18.8%)	NS
Alcohol n (%)	1 (6.3%)	0	-

Table 2 shows the results of the baseline and final biochemical study in 32 patients who completed the trial, 16 in the drug group and 16 in the placebo.

Table 2: Effects on Glucose, HbA_{1c}, Insulin and C-Peptide Levels.

Variables	Group	At Baseline	At end of study	pvalue
Fasting plasma glucose (mg/dl)	Drug	182±11.5	157±14.5	NS
	Placebo	173±8	169±15	NS
Postprandial plasma glucose (mg/dl)	Drug	296±15	255±17	NS
	Placebo	281±14.8	263±22.3	NS
HbA_{1c} (%)	Drug	8.6±0.4	7.9±0.4	0.05
	Placebo	8.8±0.38	8.4±0.35	NS
Fasting insulin (mIU/ml)	Drug	9.7±2.42	10.1±2.13	NS
	Placebo	8.9 ± 0.78	9.0 ± 0.7	NS
Stimulated insulin (mIU/ml)	Drug	24.4±4.25	28.6 ± 5	NS
	Placebo	25.4±3.5	25.3±3.25	NS
Fasting C-peptide (pmol/ml)	Drug	0.6±0.075	0.7 ± 0.05	NS
	Placebo	0.6 ± 0.075	0.6 ± 0.05	NS
Stimulated C-peptide (pmol/ml)	Drug	1.2 ± 0.13	1.6 ± 0.2	NS
	Placebo	1.4 ± 0.13	1.5 ± 0.13	NS

Data are presented as Mean ± SEM

There was a non-significant reduction in the fasting plasma glucose in the drug group (25 mg/dl) compared to the placebo group (4 mg/dl). Similarly the reduction in the postprandial plasma glucose was more in the drug group (41 mg/dl) compared to the placebo group (18 mg/dl). However, the difference did not reach statistical significance (paired t test). Glycosylated haemoglobin levels decreased in the drug group by 0.7% ($p < 0.05$, paired t test) compared to 0.4% in the placebo group (NS).

Fig 2: Mean Fasting Plasma Glucose Levels in the Drug and Placebo Group

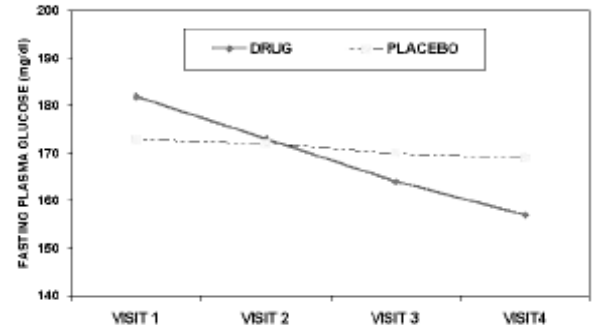
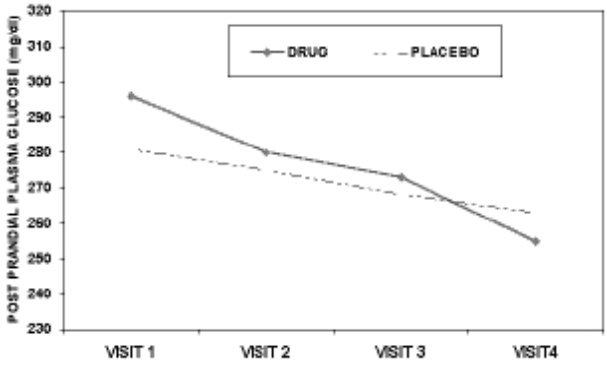


Fig 3: Mean Postprandial Plasma Glucose Levels in the Drug and Placebo Group



The drug group showed a slight but non-significant increase in both fasting and stimulated insulin levels and fasting and stimulated C-peptide levels. There was no significant difference either in insulin or C-peptide levels in the placebo group.

Figures 2 and 3 present the mean fasting and postprandial plasma glucose levels during the visits. It can be seen that there was a greater reduction in the plasma glucose levels in the drug group compared to the placebo group but this did not reach statistical significance at any of the points studied.

Fig 4: Reduction in Fasting Plasma Glucose Levels in the Drug and Placebo Group.

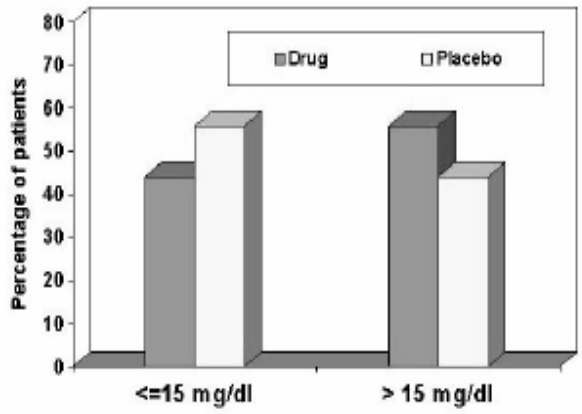


Fig 5: Reduction in Postprandial Glucose Levels in the Drug and Placebo Group

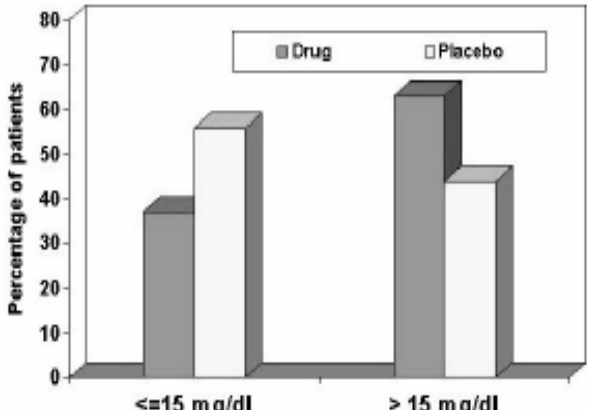


Fig 4 presents the percentage of patients (both in drug and placebo group) who had fasting plasma glucose reduced by 15 mg/dl or more after the 12 weeks of treatment. Similar percentages for postprandial glucose have been presented in Fig 5.

It can be seen that the 56% of the drug group showed a decrease in fasting plasma glucose by at least 15 mg/dl against 44% in the placebo group. 63% of the patients in the drug group had decrease in postprandial plasma glucose by at least 15 mg/dl compared to 44% in the placebo group.

Table 3 presents the results of the lipid profile. The drug showed a marginal reduction in serum cholesterol levels but this did not reach statistical significance. None of the other lipid parameters showed any difference in either the placebo or in the drug group.

Table 3: Lipid Profile, Liver Function Test and Kidney Function Test in the Study Patients

Variables	Group	At Baseline	At end of study	p value
Serum Cholesterol (mg/dl)	Drug	207±10.5	192±12.3	NS
	Placebo	196±8.5	193±8.8	NS
LDL Cholesterol (mg/dl)	Drug	157±8.8	120±10.5	NS
	Placebo	114±6.5	114±6.5	NS
Serum Triglycerides (mg/dl)	Drug	191±36.3	190±51.8	NS
	Placebo	210±3.5	222±30	NS
HDL Cholesterol (mg/dl)	Drug	44±2.5	40±1.8	NS
	Placebo	43±1.8	38±2.0	NS
SGPT (IU/L)	Drug	30.1±7.6	29.3±3.7	NS
	Placebo	28.9±3.8	26.6±1.9	NS
SGOT (IU/L)	Drug	24.3±2.7	25.6±2.0	NS
	Placebo	23.4±1.6	24.6±2.0	NS
Blood Urea (mg/dL)	Drug	22.8±1.6	26.5±2.4	NS
	Placebo	22.0±1.3	25.9±2.0	NS
Serum creatinine (mg/dL)	Drug	0.84±0.03	0.88±0.06	NS
	Placebo	0.88±0.03	0.91±0.04	NS

Data are presented as Mean ± SEM

There were no significant changes in liver or kidney function tests either in the drug or placebo group except for the one-drop out who had a transient elevation of serum transaminases in the drug group.

DISCUSSION

Ayurvedic preparations have been used for the treatment of various diseases including bronchial asthma, ischemic heart disease, hyperlipidemia and diabetes (5). However, evidence-based studies on the efficacy and safety of traditional Indian medicines are limited. This study reports on the anti-diabetic effect of an ayurvedic drug Hyponidd

in patients with secondary failure to oral hypoglycemic agents.

Hyponidd showed a non-significant reduction in both the fasting plasma and postprandial plasma glucose while the glycosylated hemoglobin levels reduced significantly which is in agreement with earlier reports (6).

Various experimental studies have shown that the various ingredients of Hyponidd have antidiabetic action. *Gynmnema Sylvestre* and *Gurmar* increases insulin secretion probably by regeneration of pancreatic beta cells (7,8). In vitro trials on experimental models with *Gynmnema Sylvestre* have proved that this herbal drug increases insulin release by increasing the cell permeability (9). *Jambu beej* and *Neem Paan* are reported to have antidiabetic action (10,11). Gurmar is also reported to have stress reducing effect (12). Moreover, *Amla,* which is a rich source of vitamin C, has been reported to reduce free radical production, which is considered to be the most important causative factor for diabetes -related complications. Additionally *Haldi* and *Shilajit* also have antioxidant property (13). *Vijaysar* has been proved to be effective in reducing HbA_{1c} levels in newly diagnosed type 2 diabetic patients (14). *Pterocarpus marsupium* is effective in reducing levels of blood glucose and glycosylated haemoglobin in type 2 diabetic patients (5). *Tinospora cordifolia,* a widely used herb in Indian Ayurvedic medicine, has been shown to have antidiabetic and hypolipidemic action (15). Similarly, *Momordica charantia* seeds have been reported to have insulin like bioactivity (16).

Antidiabetic drug could have three sites of action: reducing insulin resistance, increasing insulin secretion or decreasing the absorption of glucose from the intestine. Most of the ayurvedic drugs claim to influence all the three sites of action. Some of the ingredients of Hyponidd have been reported to influence the production of insulin and reduce the deleterious effects of glucose, like peroxidation (13). It is also claimed that Gynmnema Sylvestre increased the production of insulin, decreases its destruction and thus normalizes blood sugar (17). In our study, we found a slight (but non-significant) increase in both insulin and C-peptide levels suggesting that the drug probably works by stimulating beta cells. However, further studies are needed to prove this effect.

The hypolipidemic action of Hyponidd has been reported in earlier studies (6). In the current study Hyponidd showed a slight reduction in serum cholesterol levels compared to the placebo. *Jambu beej* and *Neem Paan* have been reported to have hypolipidemic action (10,11). Whether this effect is secondary to its effect on blood glucose or an independent effect needs further study.

None of the earlier studies or our own study showed any significant adverse effects for Hyponidd implying that the drug is safe.

In conclusion, the results of this double blind randomized trial shows that Hyponidd, a herbal anti-diabetic drug reduces fasting and postprandial plasma glucose slightly and the HbA_{1c} levels slightly, in a group of type 2 diabetic patients with secondary failure to oral hypoglycemic agents. One could argue that this is a group of patients in whom one would not expect dramatic results as they are already in a stage of secondary failure. The effect of the drug might be more impressive if used in newly diagnosed type 2 diabetic patients. Moreover another limitation of the study is that the sample size is small. More studies are clearly needed to determine the efficacy and mechanism of action of Hyponidd in different groups of type 2 diabetic patients.

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