* *Study group members:*
R.S. Hariharan, S.Venkataraman, P. Sunitha and S. Rajalakshmi from Department of Diabetology, Madras Medical College, Chennai;
K.C. Samal and B.M. Routray from Department of Endocrinology, S.C.B. Medical College, Cuttack;
R.V. Jayakumar and K. Baiju from Department of Medicine, Medical College Hospital, Kottayam;
G.V. Satyavati, V. Muthuswamy, A.K. Gupta and N.K. Kumar from Central Technical Co-ordinating Unit, Traditional Medicine Research, ICMR, New Delhi;
M.D. Gupte, S. Radhakrishna, P. Jayabal, T. Venkatarao, Paul A. Tamby, B. Kishore Kumar, V. Selvaraj and A.K. Mathai from Central Biostatistical Monitoring Unit for Traditional Medicine Research, National Institute of Epidemiology, Chennai, India

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EFFICACY OF VIJAYASAR *(PTEROCARPUS MARSUPIUM)* IN THE TREATMENT OF NEWLY DIAGNOSED PATIENTS WITH TYPE 2 DIABETES MELLITUS: A FLEXIBLE DOSE DOUBLE-BLIND MULTICENTER RANDOMIZED CONTROLLED TRIAL

ICMR Study Group* on the Efficacy of Vijayasar in Type 2 Diabetes Meillitus

Key words: type 2 diabetes, Pterocarpus marsupium, clinical trial

SUMMARY

The aim of the study was to compare the blood glucose lowering effect of vijayasar (Pterocarpus marsupium), a traditional Indian plant, with a standard pharmacological agent tolbutamide, in the management of diabetes, and to determine adverse effects if any, of the plant remedy in a multicenter trial. The study was carried out at three diabetes centers attached to teaching medical institutions in different regions of the country, representing three different segments of the population in India. The trial was initiated in October 1995 and the intake was stopped in January 1998. A total of 365 newly diagnosed or untreated patients with type 2 diabetes mellitus (treatment-naïve) whose fasting blood glucose was <12.8 mmol/l were randomized to receive either the trial drug (n=182) or the standard pharmacological agent (n=183). The duration of treatment was 36 weeks with 4 weekly clinic attendance for review and collection of drug. It was a flexible dose trial, the dosage of Vijayasar being 2 to 4 g/day, and of tolbutamide 0.75 to 1.5 g/day. Any patient whose fasting blood glucose exceeded 12.8 mmol/l upon entering the trial was withdrawn from the study. A fasting glucose level of <7.8 mmol/l and postprandial blood glucose level of <11.1 mmol/l was taken to represent satisfactory glycemic control. If blood glucose was not controlled in either arm even after receiving the highest dose, the patient was withdrawn from the trial. Data were analyzed on the worst-case basis by including withdrawn cases, using the last observation carry forward principle. There were 172 patients in the vijayasar group and 177 patients in the tolbutamide group for the analysis. The mean decrease in either fasting or postprandial blood glucose showed no significant between group differences (p=0.2). Eighty six percent of patients in the vijayasar group and 94% in tolbutamide group attained glycemic control. There was no significant change in lipids and other laboratory parameters (p>0.05) during the course of the study. Analysis of the adverse effects reported revealed none of them to be specific to trial drugs. It is concluded that vijayasar is an effective blood glucose lowering traditional Indian plant agent, its glycemic effect being comparable to that of tolbutamide in treatment-naïve patients with type 2 diabetes and free from any significant side effects.

Correspondence to: M.D. Gupte, M.D., National Institute of Epidemiology, ICMR, Mayor V.R. Ramanathan Road, Chetput, Chennai - 600 031, India; *E-mail:* nieicmr@vsnl.com

INTRODUCTION

Diabetes mellitus has a significant impact on the individual's health and quality of life. It would also have implications for the health care system of a country as ever more cases are added for longterm management. Control measures are essential for individual patients to improve glucose homeostasis. Since the most important pathological process during the development of diabetes involves three key organs, i.e. pancreatic islets, liver, and skeletal muscle, almost all the conventional therapies are aimed at these organs. Although initial responses may be good, conventional oral hypoglycemic drugs may loose their efficacy in a significant percentage of patients (1). The usually associated side effect is hypoglycemia. Hence, there is an increasing interest among diabetic patients and health professionals in using alternative medicinal systems such as medicinal herbs. These natural products are available in abundance and can provide safe, stable, standardized and efficacious medicinal preparations (2).

Over 400 traditional plant treatments for diabetes have been reported, however, only a small number of these have received scientific and medical evaluation (3). In fact, the World Health Organization (WHO) Expert Committee on Diabetes has recommended that traditional medicinal herbs be further investigated (4). The hypoglycemic effect of some herbal extracts has been confirmed in animal and human models of type 2 diabetes. Vijayasar has a long history of use in India as a treatment for diabetes. It is a drug that is believed to have some unique features such as beta cell protective and regenerative properties apart from blood glucose reduction (5-6). Its bioactive constituents include (-) epicatechin (a flavonoid), marsupin (benzofuranone), and pterosupin (a dihydrochalcone) (7-8). Other active principles have also been shown to reduce blood glucose levels in hyperglycemia induced by streptozotocin in rats, which was comparable to the effect of metformin (8). The Indian Council of Medical Research (ICMR) conducted a multicenter flexible dose (2 to 4 g) open trial of vijayasar in patients with newly diagnosed mild type 2 diabetes (fasting plasma glucose from 120 to 180 mg/dl and postprandial plasma glucose from 180 to 250 mg/dl) (9). The results showed control of plasma glucose in 67 of 97 study patients. The mean decrase in 93 patients who completed the scheduled treatment of 12 weeks was 32 mg/dl (1.8 mmol/l) for fasting and 45 mg/dl (2.5 mmol/l) for postprandial plasma glucose. HbA_{1c} decreased from 9.8% to 9.4%. There were no significant changes in the mean lipid levels. No side effects were reported.

The evaluation of a drug is incomplete unless it is concurrently compared with a standard drug. Hence, as the next logical step, ICMR pursued further research on vijayasar by conducting a multicenter double-blind trial to evaluate the efficacy of vijayasar compared to tolbutamide in newly diagnosed/untreated patients with type 2 diabetes mellitus. The main objective of the trial was to compare the blood glucose lowering effect of vijayasar with a standard drug tolbutamide. It was also aimed to document the side effects, if any.

METHODS

Patient selection

The Expert Group constituted by ICMR for this trial finalized the trial design, protocol and proformae, drugs dosage, and other relevant aspects. The Group included experts in the field of traditional and allopathic medicine. Principal Investigators from the participating centers and statisticians were also members of the Group. The trial was started in October 1995 and the intake was stopped in January 1998. The participating centers were Madras Medical College, Chennai; SCB Medical College, Cuttack; and Medical College Hospital, Kottayam, India. Newly diagnosed or untreated patients with type 2 diabetes mellitus aged between 30 and 65 years were included in the trial. The exclusion criteria were a body mass index (BMI) <19 kg/m^2, significant nephropathy (serum creatinine 2.5mg% or more), retinopathy, neuropathy, hypertension, cardiovascular complications such as ischemic heart disease (IHD) and congestive cardiac failure, insulin requirement, fasting blood glucose >12.8 mmol/l, pregnancy and lactation. Free and written informed consent was obtained from each patient before entering the trial. Eligible patients entered a four-week diet-alone period. Their diet consisted of appropriate calorie intake depending on their present weight, which included 60%-65% of carbohydrates, 10%-15% of protein, and 25%-30% of fat. The calorie split up between various meals was 20% for breakfast and 40% for lunch and dinner each. At the end of diet therapy, patients with fasting blood glucose

between 7.8 mmol/l and 12.8 mmol/l, and postprandial blood glucose 11.1 mmol/l or more were admitted to the drug trial. The primary outcome measure were both fasting and postprandial blood glucose levels.

Trial drug

Vijayasar raw material was collected from Motinala, Mervai Range, Mekal Hills of Madhya Pradesh, India. Vijayasar, an extract (dried aqueous decoction) of the heartwood of *Pterocarpus marsupium*, was manufactured and capsulated by the ICMR Center for Advanced Research on Standardization, Quality Control and Formulation of Selected Natural Products, located at the Regional Research Laboratory, Jammu, India. Each vijayasar capsule contained 500 mg of drug. The same center also manufactured the matching capsule of tolbutamide. Each tolbutamide capsule contained 187 mg of tolbutamide and 313 mg of excipients (dibasic calcium phosphate).

Study design

It was a randomized double-blind trial. The duration of drug treatment was 36 weeks, with 4-weekly clinic attendance for assessment and drug collection. At each visit blood glucose levels were measured and adverse events, if any, were noted. The recommended dietary schedule was advocated to avoid any dietary aberration. The patients were instructed to avoid the use of other drugs for any ailment without consulting the treating physician. If a patient developed any major ailment that required institution of new treatment modalities, he/she was to be withdrawn from the trial. Serious side effects attributable to vijayasar or tolbutamide were also to be the reasons for withdrawal. Treatment duration was increased by another 36 weeks for 74 consecutive patients in both groups to study the sustainability of blood glucose control by vijayasar. Periodical site-visits were made by the monitoring team members for close monitoring of the progress of the trial.

The drugs were self-administered by the patients in two divided daily dosages, 30 minutes before meal. The starting daily dose was 2 capsules twice a day (i.e. vijayasar 2 g or tolbutamide 0.75 g a day). At the end of four weeks, if blood glucose control was not achieved, the daily dose was increased to 3+3 capsules for the next four weeks (i.e. vijayasar 3 g or tolbutamide 1.0 g). After 8 weeks, if blood glucose was still beyond control, the daily dose was further enhanced to 4+4 capsules (i.e. vijayasar 4 g or tolbutamide 1.5 g). At the end of 12 weeks, if blood glucose (both fasting and postprandial) was not controlled, the patient was labeled as "treatment failure". Such patients were switched over to oral hypoglycemic agents (OHAs) at the discretion of the Principal Investigators.

If at any time during the 36 weeks of treatment, a patient's fasting blood glucose exceeded 12.8 mmol/l (confirmed by another assessment a week later), the patient was considered as "treatment failure". On the other hand, if blood glucose was controlled by any dose during the treatment, that dose was continued for the rest of the treatment period until 36 weeks.

To study the adherence to dietary advice, a representative sample of 27 patients from Chennai Center, 29 patients from Cuttack Center, and 37 patients from Kottayam Center were surveyed independently by a Medical Officer (nutritionist) from the trial monitoring unit (Central Biostatistical Monitoring Unit (CBMU), Chennai). The 24-h recall method was adopted. Standardized cups were used to estimate calorie intake.

Randomization and blinding

Randomization was done separately for each trial center to equalize patients within a center in the treatment groups. Color, number of capsules and medication time were similar for both arms of the trial, so as to mask the identity of the drug from both the attending physician and the patient. Coded drugs (each code corresponded to one of the treatments) for individual patients were sent to the trial centers by CBMU.

Measurements

Primary measurements were fasting and postprandial blood glucose levels. Secondary measurements were HbA_{1c} and adverse effects. Additional secondary measurements were cholesterol, triglycerides, HDL, ALT and AST. All biochemical tests were carried out by specific enzymatic methods using Ranbaxy kits. Glucose was determined by GOD/POD method (10); urea by GLDH/kinetic method (11,12); creatinine

with alkaline picrate (13,14); HbA_{1c} was determined using BioSystems microcolumns (15); serum cholesterol and its subfractions were determined by Ranbaxy CHOD-PAP method (16); HDL was estimated by PEG method (17,16); serum triglycerides were determined by GPO/ESPAS kit method (18-20); serum transaminases were determined by IFCC/kinetic method (21,22); and serum alkaline phosphatase was determined by GSCC/kinetic method of Ranbaxy (23).

Statistical analysis

A sample size of 150 patients was arrived at, based on our previous study suggesting that about 70% of patients with type 2 diabetes mellitus would be controlled by vijayasar, both in terms of fasting and postprandial blood glucose (9). Giving a 10% allowance for dropouts, the estimated sample size *per* arm was 170.

The CBMU scrutinized the filled-in proformae received from the trial centers every month. Inconsistencies, incompleteness and inaccuracies were rectified through correspondence, thus ensuring the quality of data.

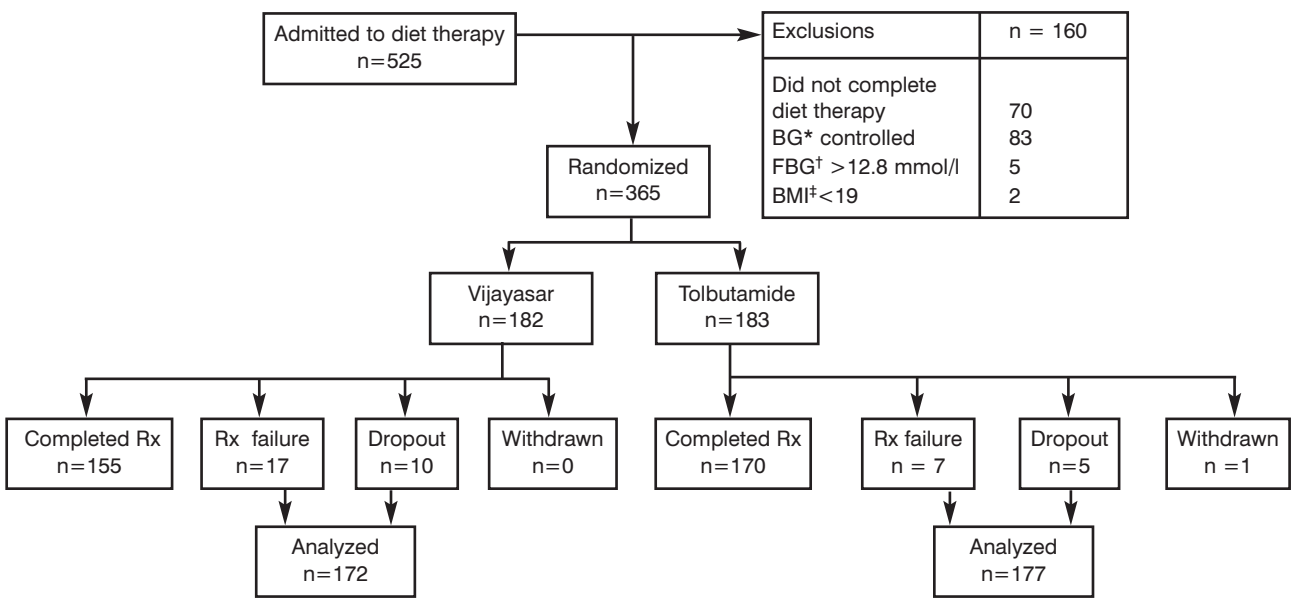
Computerized data base was maintained and standard softwares were used for validation and analysis of data. Student's unpaired t-test was used to assess the difference in the mean changes in blood glucose, lipids and other laboratory values between the two arms. Paired t-test was used to compare the initial and final values of blood glucose and other laboratory parameters within the arm. Statistical significance of difference in proportion was determined by χ^2-test with Yates' continuity correction. The 95% confidence intervals (95% CI) were constructed wherever appropriate. In the present study, statistical significance was set at $p<0.05$.

RESULTS

Patient flow

During the intake period from October 1995 to January 1998, 525 patients were admitted to the 4-week diet therapy. Of them, 160 were excluded for various reasons (Fig. 1). Hence, 365 patients were randomized, i.e. 182 to vijayasar and 183 to tolbutamide group. Over a period of 36 weeks of treatment, 10 patients dropped out in the vijayasar group for personal reasons. In the tolbutamide group, five patients dropped out and one more patient was withdrawn from the trial since this patient received insulin elsewhere. Analysis of dropouts showed that they were similar in all baseline characteristics to patients considered for analysis. Four of these five dropouts reported distance between their homes and

Figure 1. **Flow diagram of the trial progress**



*blood glucose; †fasting blood glucose; ‡body mass index

trial center as the reason for dropout, whereas dizziness on fasting was the reason in another patient. In total, 155 patients who completed the 36-week treatment and 17 failures were considered for analysis in the vijayasar group. In the tolbutamide group, the respective figures were 170 and 7. The profile of cases analyzed was similar in the two treatment groups (Table 1).

Table 1. **Baseline characteristics of study subjects according to treatment groups**

Characteristics	Vijayasar (n=172)	Tolbutamide (n=177)
Male (%)	54	60
Mean age (years)	46	46
Family history (%)	33	30
Physical activity (%)		
Heavy	1	1
Moderate	69	75
Sedentary	30	24
Cardinal symptoms (%)		
Polyuria	51	50
Polydipsia	53	49
Polyphagia	45	43
Mean body mass index	24.1	23.7
Mean lipids (mmol/l)		
Cholesterol	5.38	5.46
Total glycerides	3.08	3.08
High density lipids	1.19	1.19
Mean blood glucose(mmol/l)		
Fasting	9.4	9.4
Postprandial	13.9	13.8

Efficacy

At the end of 36 weeks of treatment, 86% of 172 patients in the vijayasar group and 94% of 177 patients in the tolbutamide group had their blood glucose (both fasting and postprandial) controlled, thus confirming the blood glucose lowering effect of vijayasar in newly diagnosed or untreated patients with type 2 diabetes mellitus. In the vijayasar group, among those having achieved blood glucose control, 35% were controlled with a daily dosage of 2 g; 37% with 3 g, and 28% with 4 g. The required dosage in the tolbutamide group, among those having achieved blood glucose control, was 0.75 g in 53%, 1 g in 37%, and 1.5 g in the remaining 10% of patients. The mean fall in fasting blood glucose was 2.4 mmol/l from the baseline of 9.4 mmol/l in the vijayasar group, compared to 2.7 mmol/l from the baseline of 9.4 mmol/l in the tolbutamide group (Table 2). The mean fall in the postprandial blood glucose was 4.3 mmol/l from the baseline of 13.9 mmol/l in the vijayasar group, compared to 4.4 mmol/l from the baseline of 13.8 mmol/l in the tolbutamide group. The observed differences in the mean decrease between the vijayasar and tolbutamide groups were similar and not reaching statistical significance (p=0.2).

Table 2. **Mean blood glucose levels at baseline and at the end of treatment**

		Blood glucose (mmol/l)		
Parameter	Drug group	At baseline	At 36 weeks	Mean fall (95% C.I.*)
Fasting	Vijayasar (n=172)	9.4	7.0	2.4† (2.2 - 2.7)
	Tolbutamide (n=177)	9.4	6.7	2.7 (2.4 - 2.9)
Postprandial	Vijayasar (n=172)	13.9	9.6	4.3† (4.0 - 3.6)
	Tolbutamide (n=177)	13.8	9.4	4.4 (4.1 - 4.8)

* C.I. = confidence Interval
† Not significant compared to tolbutamide

HbA_{1c} could only be studied in 90 patients (45 in the vijayasar and tolbutamide group each) using Biorad kit (used in the last lap of the trial) due to various reasons beyond our control. The mean decrease was 1.6(%) (p<0.001) in the vijayasar group, and 1.8(%) (p<0.001) in the tolbutamide group from the baseline value of 10.5 (%) (Table 3). The difference in the mean fall between the groups was similar and not statistically significant (p=0.5). At the end of the treatment, 22%

Table 3. **Mean HbA_{1c} at baseline and at the end of treatment**

	HbA_{1c}(%)		
Drug group	Baseline	At 36 weeks	Mean fall (95% C.I.*)
Vijayasar (n=45)	10.5	8.9	1.6* (1.3 - 1.9)
Tolbutamide (n=45)	10.5	8.7	1.8* (1.5 - 2.1)

* p<0.001

Table 4. **Blood glucose control according to stratum of baseline fasting blood glucose (FBG)**

		Vijayasar (V)		Tolbutamide (T)		
Stratum	**Baseline FBG (mmol/l)**	Number of patients	Number controlled (%)	Number of patients	Number controlled (%)	**(V) vs (T) p-value**
1	< 8.9	53	45 (85)	58	55 (95)	0.15
2	8.9-9.9	62	58 (94)	60	59 (98)	0.38
3	10.0-12.8	57	45 (79)	59	52 (88)	0.28
p-value for trend		p=0.3		p=0.1		–

(n=10) of patients in the vijayasar group and 29% (n=13) of patients in the tolbutamide group had controlled levels of HbA_{1c}(<8.5%). These proportions were not significant.

The proportion of patients who had glucosuric symptoms varied from 43% to 53% in the two groups. Ninety-nine percent of them were relieved of these symptoms by 36 weeks of treatment in both groups. There was no change in the mean levels of cholesterol, high-density lipoprotein (HDL) and triglycerides (TG). There were no significant changes in AST and ALT either. None of the patients reported any side effects attributable to trial drugs.

Diet survey showed that average calories derived from carbohydrates were higher by 15-100 kcal than recommended, whereas calories derived from proteins were lower than prescribed. Also, the calories derived from fat were lower than advised except for one center. In all, the average excess calories intake ranged from 8% to 25%.

Thirty-five patients in the vijayasar group and 39 patients in the tolbutamide group could continue the treatment for another 36 weeks. The blood glucose values remained controlled throughout that period in both study groups, indicating control sustainability.

DISCUSSION

This double-blind trial with tolbutamide control has ascertained the blood glucose lowering effect of vijayasar in newly diagnosed treatment-naïve patients with type 2 diabetes mellitus. The results showing 86% of vijayasar patients to have their blood glucose controlled (fasting blood glucose <7.8 mmol/l and postprandial blood glucose 11.1 mmol/l) over 36 weeks confirmed the usefulness of vijayasar, as reported earlier (9). Glucosuric symptoms were also controlled. There was no episode of hypoglycemia in either group, which might be owing to the flexible dose design.

The safety aspect of the drug vijayasar was also established with the dosage to up to 4 g *per* day. The study also demonstrated sustainability of the blood glucose control for up to 72 weeks.

To find out whether the absolute reduction in the blood glucose level was related to baseline blood glucose values, a subgroup analysis by stratifying the patients according to baseline blood glucose was carried out (Table 4). For this purpose, strata were defined according to the baseline fasting blood glucose of <8.9 mmol/l, 8.9-9.9 mmol/l, and 10.0-12.8 mmol/l. The proportion controlled in both fasting and postprandial state in the three strata showed no statistically significant differences in either vijayasar or tolbutamide group. The difference in the proportion controlled between the vijayasar and tolbutamide groups was not statistically significant in any stratum either, inferring that the proportion controlled was not related to baseline blood glucose level in either study group.

A pertinent question that has to be answered is whether diabetes control could be achieved with vijayasar if patients were on other hypoglycemic drugs irrespective of their diabetes control status. Yajnik et al. (24) report that 80% of 43 patients treated with oral hypoglycemic drugs were able to reduce their usual drugs when treated with a compound of vijayasar. Encouraged by these results, ICMR has planned a new study by including already treated patients (taking other hypoglycemic agents) into the trial. To avoid complications with multiple hypoglycemic agents, patients treated (either controlled or not) with no

more than one of the prespecific oral hypoglycemic agents have been included in the study. This is an open trial and is in progress at four different centers in India.

CONCLUSION

Among the controlled patients, 72% of them achieved blood glucose (fasting and postprandial) control with 3 g of vijayasar. The mean blood glucose decrease was similar in both arms. All additional secondary parameters remained stable. The sustainability of the blood glucose control with vijayasar for up to 72 weeks was also similar to that recorded with tolbutamide. There was no side effect specific for trial drugs. Vijayasar has a property to lower blood glucose level, and can be used as a safe therapy for newly diagnosed patients with type 2 diabetes mellitus.

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