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RESEARCH ARTICLE

CORROBORATION OF THE ETHNO PHARMACOLOGICAL USE OF A STANDARDIZED AYURVEDIC POLYHERBAL FORMULATION IN TYPE-2 DIABETIC PATIENTS; A PILOT CLINICAL STUDY

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ABSTRACT

Scientific validation of ethno-medicines and their use as therapeutic intervention in the management of chronic diseases like diabetes can provide more effective and less toxic drugs. The aim of this randomized pilot clinical study was to evaluate the safety and therapeutic efficacy of Polyherbal Formulation (PHF) in comparison to Metformin in newly diagnosed type-2 diabetic patients. 46 Patients, newly diagnosed with Type-2 diabetes mellitus (T2DM) were included in the study and randomized into 2 sex, age and BMI matched groups, Group 1 was administered with PHF (2-3 g/day) and group 2 received Metformin (0.5-1.5 g/day) for a period of 16 weeks. Fasting blood glucose (FBG) and post prandial blood glucose (PPBG) was measured every week and glycosylated hemoglobin (HbA1c) was measured before and after 3 months. 16 weeks treatment with PHF significantly reduced the PPBG by 20 % relative to 18 % decrease in Metformin. Significant improvement in blood glucose level was also depicted by the reduction in FBG and HbA1c in PHF group, compared to the baseline values. PHF is well tolerated, and the study confirms its antidiabetic activity by reducing the blood glucose in T2DM patients. A larger study is warranted for its use as an adjunctive therapy.

INTRODUCTION

According to the recent surveillance data, more than 370 million people across the globe are suffering from diabetes (Kahn *et al*., 2013). This prevalence is expected to increase by 49 % in year 2030, of which approximately 90 % will suffer from T2DM (Mootoosamy and Fawzi Mahomoodally, 2014). Progression of diabetes leads to micro and macro vascular complications, which are the major cause of mortality and morbidity. This increasing prevalence requires an immediate attention to develop the safer therapeutic intervention. While the current therapeutic drugs available for the treatment of diabetes reduces the FBG and HbA1c, but produces side effects too (Chen *et al*., 2011). Therefore, interest has been shifted in reviving the traditional Indian system of medicine, which has a unique holistic approach to cure a disease (Saravana Babu *et al*., 2012). As noted, the results from a meta-analysis supports the beneficial effects of the herbs prescribed in *Ayurveda* on glycemic control in randomized trials (Suksomboon *et al*., 2011).

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A polyherbal mixture composed of six herbal extracts (1:1:1:1:1:1, g/g) from *Berberis aristata DC., Cyperus rotundus L., Cedrus deodara (Roxb. ex D.Don) G.Don, Emblica officinalis Gaertn., Terminalia chebula Retz., Terminalia bellirica (Gaertn.) Roxb.* is mentioned in classical text Charaka Samhita for having a potent antidiabetic activity. Ethno medically, the preparation was prescribed for diabetes mellitus in the form of decoction (Satyanarayan Shastri *et al*., 1998). This traditional liquid dosage form has several disadvantages like physical, chemical and microbiological instability and it is also bitter in taste. Development of this preparation into a suitable drug delivery system in the form of capsule was sought to be of appropriate pharmacopoeial quality. In our previous study we used the lyophilized aqueous extract of the mixture instead of decoction and found that this mixture reduced the blood glucose level in Streptozotocin induced diabetic rats with no toxicity, suggesting that it may be useful for the prevention and treatment of hyperglycemia (Awasthi *et al*., 2013). Based on the previous findings concerning the clinical use of this polyherbal mixture in hard gelatin capsule, the present pilot study was carried out to assess the tolerability and efficacy of PHF in balancing blood glucose level in newly diagnosed T2DM patients.

MATERIALS AND METHODS

Preparation of the medicinal product

Herbal Medicinal Products Department, CSIR-Central Institute of Medicinal and Aromatic Plants, Lucknow (U.P), India, formulated the lyophilized aqueous extract of polyherbal mixture in hard gelatin capsules. Good agricultural and collection practice (GACP), good manufacturing practice (GMP) was followed during collection, manufacturing and packaging to ensure the quality and pharmacopoeial standards, which were maintained throughout. The product was standardized for its physiochemical parameters and HPLC fingerprinting (Awasthi *et al*., 2013). Each unit dose contains 500 mg of PHF in capsule dosage form and manufactured in a single batch to avoid batch to batch variation.

Study Design

In this single center, prospective randomized clinical study, the protocol and consent form was approved by the Institutional ethics committee of King George's Medical University (KGMU), Lucknow, Uttar Pradesh, India (Approval No. 56 E.C.M.11B/P12) and was conducted in line with Declaration of Helsinki and Good Clinical Practice.

Subjects

Study subjects were newly diagnosed (within 6 months) with diabetes as per the definition set in Standards of Medical Care in Diabetes-2012 by American Diabetes Association. Patients having an age between 20-60 years, of either sex and not taking any medicine were enrolled in the study from outpatient department, Department of Medicine (MOPD), KGMU. Patients with Type-1 diabetes, cardiovascular disease, hepatic dysfunction, seizure disorder, pregnancy and having contraindication of Metformin and serum creatinine level > 1.2 were excluded. An informed consent was taken from all enrolled patients.

Study protocol

The patients were randomly allocated to either of the following two groups:

Group A included 20 patients of both sex, given orally 1-1.5 g Metformin tablet (500 mg tablet GLYCOMET®, USV India Ltd twice or thrice daily) (Longo *et al*., 2012) for a period of 16 weeks.

Group B included 20 patients of both sex, given orally 2-3 g PHF (500 mg, 2 capsules twice or thrice daily) (Anonymous., 2003) for a period of 16 weeks. Dose was escalated as per the blood glucose level of the patients on subsequent visits (Patients were followed up every week) till 16 weeks. All the examinations were performed in the presence of physicians at the MOPD at KGMU.

Outcome measures

Baseline evaluation included FBG, PPBG and HbA1c. Thereafter, FBG and PPBG were done at each visit and HbA1C was done at 3 months. The clinical measurements were done using Cobas integra (400plus) analytical system (Roche Professional Diagnostics).

Statistical Statistics

SPSS 20 was used for statistical analysis. Differences between groups were analyzed by independent Student's *t*-test. Comparison from the baseline in the respective groups was analyzed with the paired *t*-test. P-value ≤ 0.05 was considered to be statistically significant.

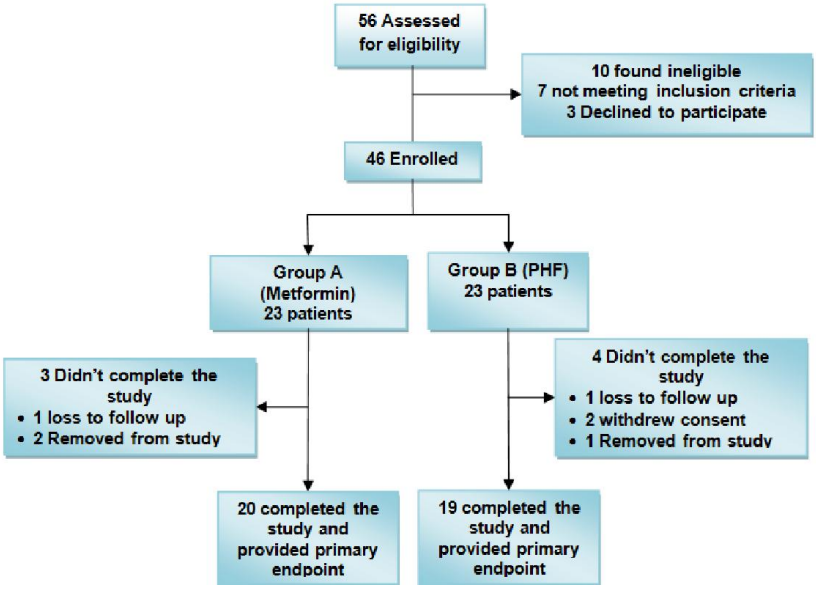

Fig. 1. Study subjects flow diagram

RESULTS

Subjects

56 patients were screened with newly diagnosed diabetes out of which only 46 were enrolled in the study. 20 patients completed the study in group A (Metformin) and 19 in group B (PHF). Baseline characteristics were similar in both the groups.

Fasting, postprandial blood glucose and HbA1c

FBG (Figure 2) decreased at 4 months in both the groups (PHF group: $p < 0.05$; Metformin group: $p < 0.01$). After 4 months treatment with Metformin and PHF, a progressive decrease occurred in PPBG level ($p < 0.01$ at 3 and 4 months in PHF group; $p < 0.01$ at 4 months in Metformin group). HbA1c decreased by 1% in PHF group and 3% in Metformin group. Though the decrease was non-significant in PHF group ($p = 0.096$ in PHF group; $p = 0.04$ in Metformin group).

Safety and tolerability

Intervention was well tolerated with no side effects. Though, complaints of gastritis were received in both the group.

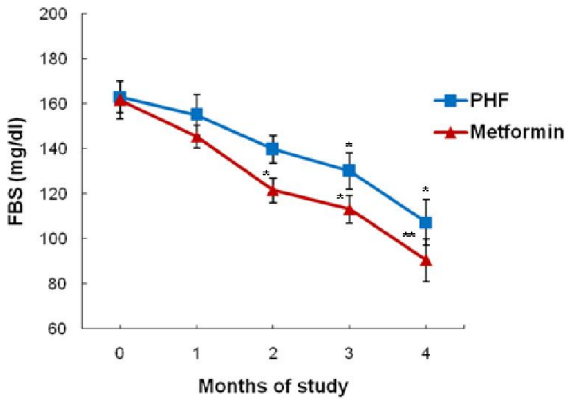

Fig 2. Effect of PHF and Metformin on fasting blood glucose. *p < 0.05, **p < 0.01; compared to baseline values in the respective groups.

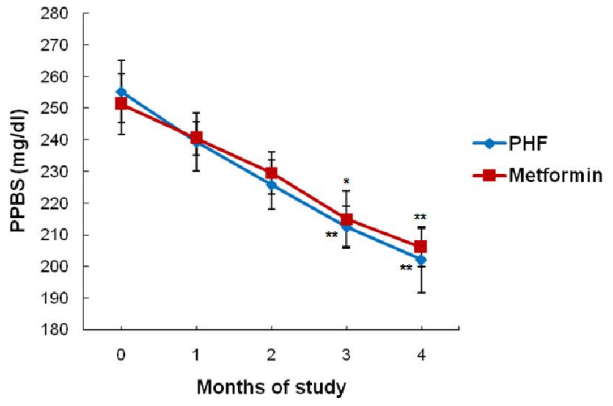

Fig 3. Effect of PHF and Metformin on post prandial blood glucose. *p < 0.05, **p < 0.01; compared to baseline values in the respective groups

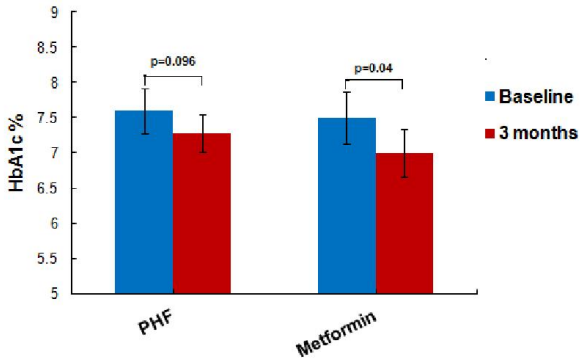

Fig 4. Effect of PHF and Metformin on Glycosylated hemoglobin; *p < 0.05; compared to baseline values in the respective groups

DISCUSSION

In traditional Indian system of medicine many plant extracts are used alone or in combination to treat various disorders. Since time immemorial these combinations are in use, and many of them are found to be safe. However, scientific validation to prove their therapeutic efficacy is still needed (Sahib, 2013). A large number of people worldwide are using complementary and alternative medicine to manage the glycemic control (DiNardo *et al*., 2012). In the present study, the therapeutic efficacy of a polyherbal formulation was evaluated in reducing the blood glucose level in T2DM patients. The results obtained, clearly showed that this herbal combination improves the glycemic control in patients with T2DM. In fact, the overall improvement caused by PHF is almost comparable to Metformin. Moreover, no complaints regarding the side effects were reported during the study, which supports its efficacy, safety and tolerability. Therapeutic benefit of *Berberis aristata DC.* in diabetes has already been proved in clinical study. It is in fact, well known that berberine, an isoquinoline alkaloid is the active principle constituent in *Berberis,* responsible for its antihyperglycaemic activity (Di Pierro *et al*., 2013). In the present study, extracts of *Berberis aristata DC* was used in combination with other herbal extracts and therefore, it may have contributed to some extent in reducing the blood glucose in T2DM patients. *Cyperus rotundus L.,* another herb used in this PHF was reported to inhibit α-amylase and α-glucosidase) (Tran *et al*., 2014). *Cedrus deodara,* the third herbal component used in PHF has also been reported to exhibit antihyperglycaemic activity (Patil *et al*., 2011). However, no clinical study has been conducted to date to evaluate the efficacy of *Cedrus* and *Cyperus* in management of T2DM. Similarly, *Emblica officinalis* (D'Souza *et al*., 2014), *Terminalia chebula* (Rao and Nammi, 2006) and *Terminalia bellerica* (Latha and Daisy, 2013) possess anti hyperglycemic activity. In the present study, the significant reduction in blood glucose level of T2DM patients caused by PHF may be due to the presence of more than one anti-hyperglycemic principle and their synergistic effects. Elevated blood glucose in diabetes puts strain on every organ of the body and leads to micro vascular and macro vascular complications. Within 16 weeks, PHF brings the blood glucose level from pathological to physiological

acceptable limit, without causing any episode of hypoglycemia. A greater reduction in PPBG by administration of PHF revealed that it is superior to the standard pharmacological agent Metformin in controlling the post prandial glucose which is as an important determinant for cardiac diseases (Cavalot *et al*., 2006). In conclusion, this study confirms the beneficial effects of the herbal formulation PHF on fasting and postprandial glucose levels and can be given in mild to moderate T2DM patients or as an add-on therapy with other established drugs, but it warrants further more elaborative investigations on other biochemical parameters in large sample size population.

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