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A double blind randomised placebo controlled cross over study of a herbal preparation containing *Salacia reticulata* in the treatment of type 2 diabetes

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Abstract

We conducted a randomised single centre double blind cross over clinical trial to investigate the effects of a herbal tea containing *Salacia reticulata* (Kothala Himbutu tea) in patients with type II diabetes mellitus. Fifty-one patients with type II diabetes mellitus for longer than 6 months and with evidence of stable glycaemic control over the preceding 6 months (as assessed by HbA_1C) participated in the study. They were randomised to receive a standard preparation of Kothala Himbutu tea for 3 months followed by placebo in similar tea bags for a further 3 months ($n = 28$) or in reverse order ($n = 23$). All patients received detailed advice on diet, exercise and lifestyle modification. HbA_1C was measured at recruitment, at 3 months and on completion of the study at 6 months. Liver and renal functions were assessed biochemically at baseline, at 3 and 6 months and adverse events were recorded. There were no significant differences between the two groups in age, body mass index, male/female ratio, glycaemic control and baseline laboratory tests. All patients completed both arms of the trial. The HbA_1C at the end of drug treatment was significantly lower than after treatment with placebo ($6.29 \pm$ S.D. 1.02 versus $6.65 \pm$ S.D. 1.04; $P = 0.008$). A statistically significant fall in HBA1c was seen with the active drug compared to a rise in HbA_1C with the placebo group ($0.54 \pm$ S.D. 0.93) versus $-0.3 \pm$ S.D. 1.05; $P < 0.001$. The daily mean dose of Glibenclamide fell by 1.89 (S.D. 6.2) mg in the drug treated group but rose by 2.25 mg in the placebo treated group ($P = 0.07$). The differences in the metformin dose were not significantly significant in the two groups. We conclude that Kothala Himbutu tea is an effective and safe treatment for type 2 diabetes.
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1. Introduction

Herbal medicines have been in use for millennia. In recent years, there has been increasing interest in herbal medicines as they have increased in popularity in the developed world. The use of self-prescribed herbal medicines in USA increased from 2.5 to 12.1% between 1990 and 1997 (Eisenberg et al., 1998) and frequency of consultations with practitioners of herbal medicine rose from 10.2 to 15.1%. A similar increase has been reported in Europe (Fisher and Ward, 1994). The evidence in favour of efficacy of these remedies is based on traditional use rather than clinical trials.

Many herbal preparations are used in the treatment of diabetes mellitus in Sri Lanka. As in Europe, many patients use them concurrently with prescribed medication such as Glibenclamide but do not tell their doctor about it (Mills, 2001). There is anecdotal evidence of such patients showing improved control and even an increased incidence of hypoglycaemia in such patients. There is some evidence from animal studies and non-randomised uncontrolled studies in humans for the efficacy of some of these remedies (Fernando et al., 1990; Welihinda et al., 1985). An alpha glucosidase in-

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hibitor kotalanol has been identified in one commonly used herb, *Salacia reticulata* (Yoshikawa et al., 1998). The alpha glucosidase inhibitor acarbose is used in clinical practice (Hoffman and Spengler, 1994). Data on the efficacy of the herbal preparation from randomised controlled clinical trials is not available. Traditionally this preparation is ingested as a herbal tea (Kothala Himbutu tea), where the herbal mixture is ingested in a cup of boiled water and in the form of a tea bag prepared using a formula passed on in an oral tradition to members of the family of the ayurvedic physician. We conducted a randomised double blind clinical trial to investigate the effects of herbal tea in patients with type II diabetes mellitus.

2. Methods

2.1. Plant material

The Kothala Himbutu tea was obtained from its manufacturer Siddhalepa Ayurveda Hospitals, Ratmalana, Sri Lanka, who prepared it in accordance with a patented formula (international patent application no. PCT/IB00/00405). The specimens of the collected materials used in its preparation were matched with voucher specimen numbers 0406043 PDA *Pterocarpus marsupium* Roxb., 0406042 PDA *Salacia reticulata* Wight, 0406044 PDA *Cinnamomum zeylonicum* Blume, 0406041 PDA *Artocarpus heterophyllus* Lam and 0406045 *Tinospora cordifolia* (Willd.) Hook F & Thoms at the national Herbarium of Peradeniya Botanical Gardens Peradeniya, Sri Lanka.

2.2. Study design

This single centre double blind randomised placebo controlled cross over clinical trial was conducted over a 6-month period. Patients were randomised into two groups using a system of computer-generated table of random numbers. One group (group A) received a standard preparation of Kothala Himbutu tea for three months followed by placebo in similar Tea bags for a further 3 months. The second group (group B) received placebo for the first three months and the Kothala Himbutu tea for the second 3 months. Specific written instructions were given for the preparation of the tea in the standard dosage (without sugar or other sweetening agent) and to drink it with each meal. Compliance was assessed by counting the unused bags at following visit. Adverse events were recorded on a standardised recording form. All patients received detailed advice on diet, exercise and lifestyle modification as indicated in the national guidelines for the management of type 2 diabetes (Sri Lanka Medical Association, 2000).

2.3. Ethical approval

Ethical clearance was obtained from the Ethical Review committee of the University of Sri Jayewardenepura. The Sri Lanka Medical Council does not encourage registered practitioners to prescribe alternative medicines. It is however common for patients receiving 'Western allopathic' medication to also be treated concurrently by ayurvedic practitioners. The ethical permission was granted to study such patients. The study participants gave written informed consent. The ayurvedic preparation and the placebo were administered by a qualified ayurvedic practitioner. Medical assessments and adjustments of prescribed medications were made by a registered medical practitioner.

2.4. Patients

Sixty-five consecutive patients with type II diabetes mellitus for a 6-month period or more from initial diagnosis, seeking ayurvedic treatment in addition to Western medical treatment were invited to participate in this study.

Inclusion criteria were an onset of diabetes mellitus after the age of 30 years, negative anti-GAD antibodies, normal or elevated fasting C peptide, aged between 40 and 65 years, and evidence of stable glycaemic control over the preceding 6 months as assessed by HbA_1C.

Exclusion criteria were an absence of long term complications of diabetes mellitus such as neuropathy, nephropathy, retinopathy, significant heart disease (cardiac failure, unstable angina), pregnant or lactating females, females of child bearing age who are not on a contraceptive method, if persons were currently or previously treated for any malignancy, those already on treatment with any preparation containing *Salacia reticulata* or another herbal product, those on treatment with other drugs known to effect carbohydrate metabolism (other than standard medications for diabetes mellitus) and those on insulin therapy.

2.5. Assessment of efficacy

A six point blood glucose profile (pre- and post-breakfast, pre- and post-lunch, pre- and post-dinner samples) was performed on a day during the week prior to each visit. HbA_1C was performed at recruitment, at 3 months and on completion of the study at 6 months. Fructosamine was measured at baseline and fortnightly thereafter. Medication prescribed for diabetes mellitus was continued and standardised criteria for changing dose of glibenclamide based on symptoms, plasma glucose and HbA_1C were used. The national guidelines for the management of diabetes was adhered to. According to the protocol, in the event that the clinical investigators felt that significant deterioration of glycaemic control occurred, the patient was to be withdrawn from the study.

2.6. Assessments of tolerability

At the time a complete history and clinical examination were done, blood and urine samples sent for baseline investigations (full blood count, liver function tests, urine for microalbumin, serum creatinine). Safety profile was assessed by comparing these baseline investigations when they were

repeated after 3 and 6 months. Adverse events were recorded and classified as mild (transient and easily tolerated), moderate (caused patient discomfort but did not interrupt activities) or severe (caused severe disruption or prevented usual activities) at each visit.

2.7. Statistical analysis

An intention to treat approach was used. The primary end point for efficacy studies was the end of treatment with either placebo or drug. The data were analysed as a within patient comparison of treatments using the *t*-test for paired differences (Pockock, 1984). The *t*-test was also used to test for period effect and carry over effect (Pockock, 1984).

3. Results

Of the 65 consecutive patients attending an ayurvedic clinic who were invited to participate, 14 were positive for anti-GAD antibodies. Therefore, 51 patients were randomised to take part in the trial. There were no significant clinical differences between the two groups in age ($53.2 \pm$ S.D. 7.5 versus $54.3 \pm$ S.D. 6.9), male/female ratio (16/12 versus 12/11), HbA_1C % ($6.8 \pm$ S.D. 0.9 versus $6.7 \pm$ S.D. 0.9), body mass index ($22.04 \pm$ S.D. 6.9 versus $22.07 \pm$ S.D. 3.09), the dose of glibenclamide ($8.8 \pm$ S.D. 7.1 versus $6.7 \pm$ S.D. 4.2) or dose of metformin ($928 \pm$ S.D. 583 versus $930 \pm$ S.D. 750). All 51 patients completed both arms of the trial.

3.1. Glycaemic control

The HBA1c at the end of drug treatment was significantly lower ($6.29 \pm$ S.D. 1.02) than after treatment with placebo ($6.65 \pm$ S.D. 1.04; $P = 0.008$). A statistically significant fall in HBA1c was seen in the active drug + glibenclamide/metformin arm of the study ($0.54 \pm$ S.D. 0.93) when compared to a rise in HBA1c the placebo + glibenclamide/metformin arm of the cross over study ($-0.3 \pm$ S.D. 1.05, $P \leq 0.001$). There was no evidence of period effect or carry over effect. The mean dose of glibenclamide fell by 1.89 (S.D. 6.2) mg daily in the drug treated group but rose by 2.25 mg daily in the placebo treated group ($P = 0.07$). The difference in dose of metformin was not significantly different in the two groups.

3.2. Safety and tolerability

The main adverse effect reported was dyspepsia and loose stools. The rates of adverse effects were similar in both groups with five patients in the drug group and four in the placebo group complaining of these symptoms. All those who complained of such symptoms were also being treated with metformin. Flatulence was reported in five patients in each group. None had severe adverse effects. No significant abnormalities in liver or renal function tests were recorded.

4. Discussion

Diabetes has been managed by ayurvedic practitioners for millennia. However, like most traditional and folk remedies these methods of treatment have not been subjected to rigorous scientific analysis. Ayurveda is derived from religious texts the vedas. Hence, it has been accepted on faith (Hardy et al., 2001).

Modern medical practice assumes all new treatments have no effect and try to disprove this hypothesis. Significant clinical observational research has been performed herbal usage in diabetes but very few randomised controlled clinical trials have been published (Hardy et al., 2001). We have conducted a study on an ayurvedic preparation using the experimental design and reporting quality expected of modern pharmaceuticals.

Our results confirm that the addition of Kothala Himbutu tea to conventional diabetes treatment produced significant falls in HbA_1C levels. In addition, it lowered the required dose of glibenclamide. The drug was well tolerated with comparable proportions of patients in placebo and drug treatment groups experiencing adverse effects. There were no increases in liver enzymes, serum creatinine or changes in haematological indices. There was a small but non-significant gain in weight in patients treated with the Kothala Himbutu tea when compared with placebo treated patients. This increase correlated with improved glycaemic control.

Salacia reticulata contains alpha glycosidase inhibitor kotalanol (Yoshikawa et al., 1998), which has an action similar to that of acarbose. The preparation of Kothala Himbutu tea we used also contains *Pterocarpus marsupium* (Gammalu) in addition to *Salacia reticulata*. Epicatechin, a flavinoid isolated from *Pterocarpus marsupium*, is reported to enhance insulin release from rat islet cells in vitro (Hii and Howell, 1985) but with no effect on glycaemic control in rodents (Kulb et al., 1982).

A recent review of ayurvedic interventions for diabetes highlighted the limitations of research into ayurvedic preparations (Hardy et al., 2001) as lack of placebo controlled double blind clinical trials, low sample size, inadequate description of method, lack of statistical analysis and short duration. It also recommended integration of ayurvedic diagnosis and assessments into the research method. On the evidence of this trial that has addressed all these limitations. We conclude that Kothala Himbutu tea is an effective and safe treatment for type 2 diabetes and that its hypoglycaemic action supports anecdotal reports of a risk of hypoglycaemia if used concurrently with sulphonylureas.

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