Randomized Controlled Trial of *Tinospora crispa* for Additional Therapy in Patients with Type 2 Diabetes Mellitus

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A randomized double blind placebo controlled trial was conducted to determine the efficacy of Tinospora crispa as additional treatment in patients with type 2 diabetes mellitus who did not respond to oral hypoglycemic drugs and refused insulin injection. Twenty patients were allocated to receive Tinospora crispa powder in capsule form at a dosage of 1 gram thrice daily for 6 months. Twenty patients received a placebo. The main outcomes were changes in fasting plasma glucose, glycosylated hemoglobin and insulin levels. The baseline characteristics of the patients in both groups were not significantly different. There were no significant changes in fasting plasma glucose, glycosylated hemoglobin and insulin levels among the patients within the group and between groups. Two patients who received Tinospora crispa showed marked elevation of liver enzymes that returned to normal after discontinuing Tinospora crispa. Moreover, patients in the Tinospora crispa group had significant weight reduction and cholesterol elevation while taking Tinospora crispa. It is concluded that there is no evidence to support the use of Tinospora crispa 3 grams a day for additional therapy in patients with type 2 diabetes mellitus who did not respond to oral hypoglycemic drugs. The patients receiving Tinospora crispa may have an increased risk of hepatic dysfunction.

Keywords : *Tinospora crispa, Diabetes mellitus*

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Tinospora crispa is a medicinal plant used as a remedy for patients with diabetes mellitus in Malaysia[1]. *Tinospora crispa* was found to have an anti-hyperglycemic effect in animals[2-4]. The hypoglycemic effect of *Tinospora crispa* is mediated by increasing insulin secretion from isolated rat and human islets of Langerhans[3]. *Tinospora crispa* is commonly used in diabetic patients in Thailand as well. Toxicological study of crude extract of *Tinospora crispa* revealed no obvious adverse effects[5]. However, animals of both sexes receiving the highest dose of *Tinospora crispa* extract had significantly higher alkaline phosphatase (ALP) levels, alanine aminotransferase (ALT) levels and liver weights than those of the water control and tragacanth control groups. Histopathological study of the liver indicated that male rats receiving the highest dose of the extract had significantly higher incidence of bile duct proliferation and focal liver cell hyperplasia than the two control groups. Blood chemistry studies revealed that both male and female rats receiving 1.28 g/kg. body weight of the extract had significantly higher cholesterol levels but significantly lower glucose levels than those of water control and tragacanth control groups. To our knowledge, there has been no controlled clinical trial of *Tinospora crispa* in patients with diabetes mellitus.

The objective of the study was to determine the efficacy of *Tinospora crispa* in patients with type 2 diabetes mellitus who did not respond to oral hypoglycemic drugs and refused insulin injection.

Patients and Method

The study was a randomized double blind placebo controlled trial conducted at Siriraj Hospital.

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The study was approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital. The eligible study subjects were patients with type 2 diabetes mellitus older than 35 years who had received an adequate dose of oral hypoglycemic agents for at least 2 months and still had a glycosylated hemoglobin of greater than 8.5% and refused insulin injection. Patients with liver disease, heart disease, renal impairment or those who previously received traditional medicine were excluded. Eligible patients were randomly allocated to the study group or the control group. All subjects received oral hypoglycemic agents. The study group received additional *Tinospora crispa* powder in a capsule form at a dosage of 1 gram thrice daily for 6 months. *Tinospora crispa* powder was prepared by the Department of Medical Sciences, Ministry of Public Health. The control group was given placebo in an identical capsule to be taken in the same fashion as the study drug. Compliance with the medication was made by a pill count at each visit. The patients were interviewed, examined and blood was taken for complete blood count, fasting plasma glucose, liver enzyme profile and renal function at entry and every month during the study. Blood for glycosylated hemoglobin and insulin determination was collected at enrollment and every 2 months during the study.

A sample size of 16 patients per group was estimated according to the assumption that baseline mean glycosylated hemoglobin was 10% with a standard deviation of 2% and post treatment mean glycosylated hemoglobin in *Tinospora crispa* group was 8% or less with type I error 5% and type II error 20%. The data were analyzed by descriptive statistics, student t test, repeated measure ANOVA and chi-square test where appropriate. A p value of ≤ 0.05 indicates a statistically significant difference.

Results

There were 40 eligible patients. Twenty patients were in the study group and 20 in the control group. The baseline characteristics of the patients between the two groups were not significantly different as shown in Table 1. Six patients (3 in the *Tinospora crispa* group and 3 in the control group) were withdrawn from the study. One patient in the *Tinospora crispa* group had to receive insulin due to having active pulmonary tuberculosis. Two patients in the *Tinospora crispa* group had elevation of liver enzymes (SGOT and SGPT of greater than 200 u/L.) more than 3 times the baseline values after receiving it for 2 and 5 months. Liver enzymes in the aforementioned 2 patients returned to normal (less than 30 u/L.) after discontinuing *Tinospora crispa* for one month. One of them had evidence of hepatitis C infection. Two patients in the control group had to receive insulin due to having a subdural hematoma and being treated with prednisolone for Bell's palsy. One patient in the control group had to leave the study due to difficulty in returning to the clinic for follow up. Therefore, the authors were able to follow 34 patients until the end of the study. Fasting plasma glucose, glycosylated hemoglobin and insulin levels of the patients in both groups during 6 months were

Table 1. Baseline characteristics of the patients in the study

Characteristic	*Trinospora Crispa* Group(N=20)	Placebo Group(N=20)	P value
Gender, Male : Fema	7 : 13	5 : 15	0.7
Mean age, year (SD)	58.4 (9.2)	59.1 (10.7)	0.8
Mean body weight, kg (SD)	60.8 (10.0)	58.9 (10.0)	0.5
Mean BMI, kg./m^2 (SD)	27 (5.5)	26 (5.1)	0.7
Mean FPG, mg/dL. (SD)	214.9 (45.5)	227.3 (73.4)	0.5
Mean glycosylated Hb, % (SD)	10.4 (1.6)	10.0 (1.2)	0.4
Mean insulin level, uu/ml. (SD)	17.9 (9.5)	17.8 (13)	0.9
Mean hematocrit, % (SD)	38.7 (3.3)	39.7 (2.7)	0.3
Mean WBC (SD)	7,971 (2,072)	7,368 (1,586)	0.3
Mean BUN, mg./dL. (SD)	15.1 (5.2)	15.6 (4.9)	0.8
Mean creatinine, mg/dL. (SD)	1.0 (0.3)	1.0 (0.2)	0.6
Mean cholesterol, mg/dL (SD)	233.6 (51.9)	218.2 (31.7)	0.7
Mean triglyceride, mg/dL (SD)	204.8 (127.2)	183.9 (75.3)	0.5
Mean SGOT, u/L (SD)	28.36 (12.8)	25.8 (9.8)	0.4
Mean SGPT, u/L (SD)	30.3 (15)	27.5 (17.3)	0.6
Mean bilirubin, mg/dL (SD)	1.33 (0.26)	1.58 (0.27)	0.4

not significantly different as shown in Fig. 1 and Fig. 2. At the end of the study, all patients in the *Tinospora crispa* group had glycosylated hemoglobin values greater than 8.5% compared with 71% of the patients in the control group (p = 0.04). The body weight of the patients significantly decreased (approximately 2 kilograms) and the patients' cholesterol levels significantly increased (approximately 30 mg./dL.) after taking *Tinospora crispa*. Changes in hematocrit, white blood cells, triglyceride, renal function and liver profile of the remaining patients were not observed.

Discussion

This study was unable to demonstrate the efficacy of *Tinospora crispa* for therapy in patients with type 2 diabetes who did not respond to oral hypoglycemic drugs since there were no significant changes in fasting plasma glucose or glycosylated hemoglobin between those collected at baseline and during the study period in either group. Therefore, there is no evidence to support the use of *Tinospora crispa* in diabetic patients. However, there may be several explanations for being unable to detect any efficacy of *Tinospora crispa* in the present study. The authors recruited only type 2 diabetic patients who did not respond to an adequate dose of oral hypoglycemic agents. The insulin levels in the blood samples of the patients taking *Tinospora crispa* in the present study were not increasing. If the mechanism of action of *Tinospora crispa* is to stimulate insulin secretion, it is very unlikely that *Tinospora crispa* will be efficacious in these patients. A study that includes patients with mild diabetes who have never received oral hypoglycemic agents should be conducted in order to determine the efficacy of *Tinospora crispa*. Small sample size was not an explanation since 16 patients per group should be sufficient to detect the effect of at least 2% difference in glycosylated hemoglobin between the groups and there was no trend for any reduction in fasting plasma glucose or glycosylated hemoglobin in 17 patients who received *Tinospora crispa* for 6 months. In addition, all patients in the Tinospora crispa group still had glycosylated hemoglobin greater than 8.5% compared with 71% of those in the placebo group. An inadequate dosage or inadequate active ingredients of *Tinospora crispa* used in the study might explain the study results. A treatment duration of 6 months should be long enough to see the effect of treatment and this should not be the reason for negative results. Compliance with the medication was found to be satisfactory. Contamination was unlikely since this study included only patients who did not receive other traditional medicines. Co-intervention was considered insignificant since this study was double-blinded. *Tinospora crispa* is a well known appetite stimulant due to its bitterness and the patients in this group might consume more food after taking *Tinospora crispa* leading to uncontrolled diabetes and weight reduction. An explanation for the increase in cholesterol after taking *Tinospora crispa* is unclear. This observation was also found in animals[5]. Two patients (10%) who received *Tinospora crispa* at a dosage of 3 grams a day developed liver dysfunction and the study medication had to be discontinued. Although one patient had underlying chronic hepatitis, this

Fasting plasma glucose (mg./dL)

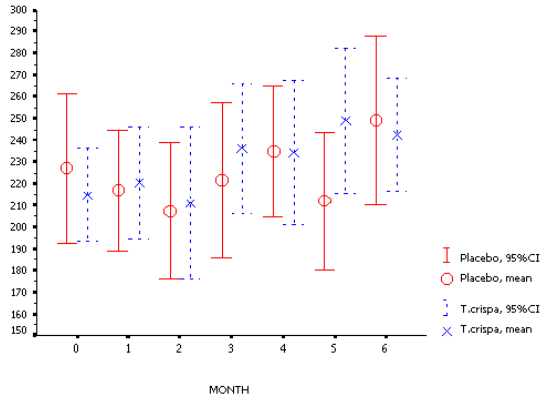

Fig. 1 Fasting plasma glucose in patients taking *Tinospora crispa* (X) and taking placebo (O)

Glycosylated Hemoglobin (%)

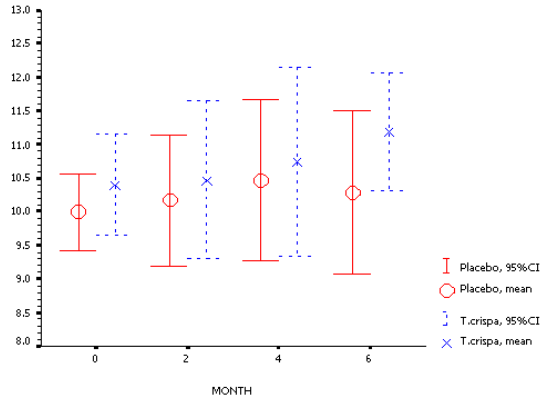

Fig. 2 Glycosylated hemoglobin in patients taking *Tinospora crispa* (X) and taking placebo (O)

observation suggests that hepatic dysfunction is an adverse effect of *Tinospora crispa*, and patients wanting to take *Tinospora crispa* and health care personnel who want to provide *Tinospora crispa* to the patients should be aware of this effect.

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ประสิทธิผลของบอระเพ็ดในการรักษาผู้ป่วยเบาหวาน

ชวัญญา แสงสุวรรณ, สุทธิพล อุดมพันธุรัก, สาธิต วรรณแสง , วิษณุ ธรรมลิขิตกุล

คณะผู้วิจัยได้ศึกษาประสิทธิผลของการรักษาโรคเบาหวานในผู้ใหญ่ที่ไม่ตอบสนองต่อการรักษาด้วยยารับประทานและไม่ยินยอมรับการรักษาด้วยอินสุลินจำนวน 40 คนโดยแบ่งผู้ป่วยออกเป็น 2 กลุ่มแบบสุ่ม ผู้ป่วยจำนวน 20 คนได้รับการรักษาเดิมที่เคยได้รับร่วมกับบอระเพ็ดขนาด 1 กรัมรับประทานวันละ 3 ครั้งติดต่อกันนาน 6 เดือน ส่วนผู้ป่วยอีก 20 คนได้รับการรักษาเดิมที่เคยได้รับร่วมกับยาหลอก ลักษณะของพื้นฐานและความรุนแรงของโรคในผู้ป่วยทั้งสองกลุ่มไม่แตกต่างกัน ผลการศึกษาพบว่าระดับน้ำตาลในพลาสมาและระดับของ glycosylated hemoglobin ภายหลังได้รับบอระเพ็ดไม่ลดลงจากระดับก่อนได้รับบอระเพ็ด และไม่น้อยกว่ากลุ่มที่ได้รับยาหลอก ผู้ป่วย 2 ราย (ร้อยละ 20) ที่ได้รับบอระเพ็ดมีผลทางซ้อนที่ตับ ผู้ป่วยที่ได้รับบอระเพ็ดมีน้ำหนักตัวลดลงและมีระดับโคเลสเตอรอลในเลือดเพิ่มขึ้น การศึกษานี้แสดงว่าบอระเพ็ดไม่มีประสิทธิผลในการรักษาโรคเบาหวานในผู้ใหญ่ที่ไม่ตอบสนองต่อการรักษาด้วยยารับประทานและไม่ยินยอมรับการรักษาด้วยอินสุลินโดยอาจมีผลข้างเคียงต่อตับ