

Safety of Aqueous Extract of *Tinospora cordifolia* (Tc) in Healthy Volunteers: A Double Blind Randomised Placebo Controlled Study

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Received October 7, 2006; Revised January 24, 2007; Accepted April 25, 2007

This paper is available online at <http://ijpt.iuums.ac.ir>

ABSTRACT

It is a common misconception that ayurvedic medicines (traditional Indian system of medicine) are always safe. In fact, they also pose serious health risks either in the form of adverse reactions or in the form of drug interactions. Over 80% of our population takes ayurvedic medicines. The study was aimed to evaluate the safety profile of *Tinospora cordifolia* in healthy volunteers using a battery of haematological, and biochemical tests and open questionnaire method. Thirty healthy volunteers (males - 22 and females - 8) aged 18 - 30 years (mean 22.5 ± 0.28) who volunteered to participate were studied in a randomized, double - blind, placebo controlled design. The volunteers were provided with 21 days of medication (coded box) containing *Tinospora cordifolia* 500 mg or matching placebo. One tablet of *Tinospora cordifolia* of 500mg strength or placebo was taken once daily orally in the morning along with breakfast for 21 days. The safety assessment was done with the help of haematological and biochemical investigations which were assessed before and after the medication by unpaired t test. 'Unpaired t test' using SPSS computer software package. Analysis of the various lab values between the control and the test group before and after taking the drug/placebo by unpaired 't' test shows no significant difference between the groups ($p = > 0.05$). Hence it can be concluded that *Tinospora cordifolia* is safe at a dose of 500mg per day for a period 21 days in healthy volunteers for the parameters studied.

Keywords: Healthy volunteers, safety, *Tinospora cordifolia*

Over 80% of Indian population takes ayurvedic medicines – either self prescribed or through a 'Vaidya' [1]. It has to be emphasized that in the case of safety ends, no compromises must be made with ayurvedic medicine. It is a common misconception that ayurvedic medicines are always safe. In fact, they also pose serious health risks either in the form of adverse reactions or in the form of drug interactions. What is more important is the indirect risk associated with using an herbal remedy that is infact not efficacious. This may compromise, delay or replace an effective form of conventional treatment [2].

Tinospora cordifolia (Tc), an Indian medicinal plant, is known to be beneficial for the treatment of disorders like peptic ulcer, hepatobiliary disorders, rheumatism, infectious diseases etc [3, 4]. It has an immunostimulant activity [5]. Tc improves intelligence, power of retention and memory [6]. It enhances cognition in normal rats and successfully overcomes cyclosporine induced memory deficit [7].

The ayurvedic literature report that Tc can cause constipation, if taken regularly at high doses and it has no side effects and toxicity. Yet the safety and the potential in human beings have to be established using modern methods [8].

Hence the present study was undertaken to evaluate the safety profile of *Tinospora cordifolia* in healthy volunteers using a battery of haematological and biochemical tests and open questionnaire method.

METHODS

Thirty healthy volunteers (males - 22 and females - 8) aged 18 - 30 years (mean 22.5 ± 0.28) who volunteered to participate were studied in a randomized, double- blind, placebo controlled design. The protocol was approved by the institutional ethics committee and all participants gave written informed consent. The procedures followed were in accordance with the ethical standards of the responsible committee on human ex-

Table 1. Safety profile, Haematological and biochemical lab values before the treatment in control and drug groups

Tests	Pretreatment (Mean± S.E.M)	Values	95% C.I (Mean±S.E.M)		P value
	Control		Drug	Control	
1.Haemoglobin (Hb) (gm/dl)	14.98 ± 0.25	15.09 ± 0.25	14.45±15.52	14.57 ± 15.41	0.75
2. Total Leukocyte count (TLC/mm ³)	8151.87±121.14	8200.27± 138.42	7892-8411	7903 - 8497	0.79
3.Total red blood cell count (TRBC/mm ³)	5.53 ± 0.14	5.36 ± 0.21	5.22 – 5.84	4.92 – 5.81	0.51
4. Platelet count (PLC) (per mm ³)	332994.87±9175	366676.6 ± 18487	313314 – 352676	327023 – 406331	0.12
5. Alanine transaminase (ALT) (u/dl)	29.39 ± 1.69	28.61 ± 1.52	25.75 – 33.04	25.35 – 31.86	0.73
6.Aspartatetransaminase (AST) (u/dl)	32.15 ± 1.84	32.25 ± 1.59	28.21 – 36.08	29.83 – 36.67	0.65
7. Blood urea (mg/dl)	14.09 ± 0.24	14.29 ± 0.22	13.56 - 14.60	13.83 – 14.76	0.52
8.Serum creatinine (mg/dl)	0.97 ± 0.05	1.03 ± 0.04	0.86 – 1.08	0.94 – 1.13	0.34

perimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000.

The subjects who volunteered to participate in the study met the following inclusion criteria

- Healthy volunteers in the age group of 18 – 35 years
- Subjects with normal haematological and biochemical tests carried out before the start of the study

Subjects with the following were excluded from the study:

- History of cardiovascular, renal, hepatic, gastrointestinal, CNS disorders
- Currently on any type of medications

Thirty volunteers were randomized into two groups of 15 each and were provided with 21 days of medication (coded box) containing *Tinospora cordifolia* 500 mg or matching placebo. The subjects were randomized using a table of random numbers. (Simple randomization)

One tablet of *Tinospora cordifolia* of 500mg strength or placebo was taken once daily orally in the morning with breakfast for 21 days. The dose and the duration was based on pre-clinical study [7].

The pure aqueous extracts of *Tinospora cordifolia* (500 mg tabs) were procured from Sami labs, Bangalore. Placebo (lactose - 450 mg + starch 50 mg) similar in

size, shape and taste was obtained from pharmacy manufacturing unit of the institution.

The safety assessment was done with the help of haematological and biochemical investigations which were assessed before and after the medication in the hospital lab [Table 1]. The various tests used for the testing of the safety profile of *Tinospora cordifolia* were as follows:

Hematology Haemoglobin (Hb), Total Leukocyte Count (TLC) and Total Red Blood Cell Count (TRBC) – give an idea of the effect of Tc on blood elements and bone marrow.

Liver Function Tests (LFT) includes ALT and AST – shows the effects of Tc on the liver.

Renal Function Tests (RFT) includes blood urea and serum creatinine – shows the effects of Tc on the kidney.

Possible untoward effects after taking the medication were detected by ‘open questionnaire method’ (Table 3)

Statistical analysis was carried out using ‘Unpaired t test’ (Mann – Whitney test) using SPSS computer software package. Level of significance (p-value) was considered more than 0.05.

Table 2. Safety profile, Haematological and biochemical lab values after the treatment in control and drug groups

Tests	Posttreatment (Mean± S.E.M)	Values	95% C.I (Mean±S.E.M)		p value
	Control		Drug	Control	
1.Haemoglobin (Hb) (gm/dl)	15.01 ± 0.22	15.12 ± 0.24	14.45 – 15.51	14.57 – 15.63	0.75
2. Total Leukocyte count (TLC) (per mm ³)	8182.13±128.96	8224.87 ± 139.95	7905 – 8458	7942 - 8525	0.79
3.Total red blood cell count (TRBC) (per mm ³)	5.57 ± 0.19	5.53 ± 0.18	5.16 - 5.99	5.15 – 5.90	0.86
4. Platelet count (PLC) (per mm ³)	332994.87±9271.9	36692.87±18599	313314 – 352676	327023 - 406331	0.14
5. Alanine transaminase (ALT) (u/dl)	29.63 ± 1.76	28.74 ± 1.48	25.87 – 33.39	25.58 – 31.90	0.7
6.Aspartatetransaminase (AST) (u/dl)	32.35 ± 1.85	33.36 ± 1.52	28.39 – 36.31	30.10 – 36.61	0.68
7. Blood urea (mg/dl)	14.09 ± 0.26	14.29 ± 0.23	13.45 – 14.65	13.79 - 14.79	0.58
8.Serum creatinine (mg/dl)	1.03 ± 0.04	1.04 ± 0.03	0.94 - 1.12	0.96 – 1.12	0.9

RESULTS

Of the 30 (Males - 22; females - 8) volunteers enrolled in the study all 30 completed the study. Average age of the volunteers is 22.5 ± 0.28 years. Sixteen volunteers were from North India, eight from Karnataka,

Table 3. Adverse drug reaction monitoring form(Open questionnaire). Does the individual have any symptoms? Yes ----- No -----

Adverse experience	1	2	3	4
Date start				
Date stop				
<u>Pattern</u>				
Isolated				
Intermittent				
Continuous				
<u>Severity*</u>				
Mild				
Moderate				
Severe				
<u>Outcome</u>				
With sequelae				
Without sequelae				

* Mild – does not interfere with routine activity

Moderate – interferes with routine activity

Severe – unable to do any activity

four from Kerala and two from Maharashtra (south Indian states)

No dropouts were recorded in the study.

Volunteer compliance was noted by asking the volunteers to return the empty boxes in which the tablets were dispensed. None of the boxes given back by the volunteers contained any drug or placebo. Hence the compliance was assumed to be 100%.

Analysis of the various lab values of the control and the test group before taking the drug/placebo by unpaired 't' test shows no significant difference between the groups ($p = > 0.05$) [Table 1] .

Analysis of the various values of control and the test group after taking the drug/placebo by Unpaired t test shows no significant difference between the groups ($p = > 0.05$) [Table 2]. No volunteer complained of any ad-

verse effects during and after the period of drug intake at the given dose and duration.

DISCUSSION

The data from the results section before giving the drug shows no significant difference between the groups ($p = > 0.05$). This shows that the two groups are similar and comparable in all matters except for the medication. Similarly the data after giving the drug also does not show any significant difference between the groups ($p = > 0.05$). This shows that there is no difference between the two groups and hence the effect of Tc is similar to the placebo or in other words, Tc does not affect the above parameters at dose of 500mg for a duration of 21 days.

Considering long term safety studies, twenty days may not look a very adequate duration, but the duration was selected on the basis of the pre-clinical study. We sincerely feel the need for a study of much longer duration and with different strengths. But this study clearly indicates that *Tinospora cordifolia* is safe at dose of 500mg per day for a period 21 days in healthy volunteers for the parameters studied. This study is an attempt to do a scientific study on an herbal medication with regard to safety since safety issues are overlooked for herbal drugs.

ACKNOWLEDGEMENT

The authors acknowledge the support extended by the Dean of the institution for carrying out the work. We also acknowledge SAMI LABS, B'lore for providing pure aqueous extract of *Tinospora cordifolia*.

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