TANG [HUMANITAS MEDICINE]

Research Article

Safety Evaluation of Sankhaholi (Evolvulus alsinoides Linn.) in the Management of Essential Hypertension: A Randomized Standard Control Trial

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ABSTRACT

Background: Hypertension is one of the major risk factors for stroke, heart attack, heart failure and kidney failure, thereby causing deaths and disability world-wide. The most predominant type of HTN is essential hypertension (HTN). Unani scholars have mentioned about the clinical manifestations and management of the hypertension and documented it in the context of 'Imtila'. The drug *Sankhaholi* (*Evolvulus alsinoides Linn.*) is one of the widely prescribed medicines for the management of essential hypertension in Unani medicine.

Material and Methods: The present clinical study was carried out to evaluate the safety of *Sankhaholi* (*Evolvulus alsinoides Linn.)* in the management of stage-1 essential hypertension. Newly diagnosed 41 patients of Essential Hypertension (22 patients were in the test group and 19 patients in the control group) were enrolled for the study. All the patients in the test group were given with the test drug 3 g powder of *Sankhaholi* twice a day for 6 weeks orally. Patients in the control group were given standard drug Ramipril 5 mg once a day for the same duration. Clinical as well as hematological parameters were recorded before and after the treatment.

Results: No significant changes are recorded in safety parameters viz. CBC, Haemogram, LFT and KFT. Clinically no adverse effect of the drug has been reported during the course of treatment. Also, significant effect on the systolic blood pressure ($p<0.001$) were recorded in test group. The drug *Sankhaholi* was also found effective on the symptoms associated with hypertension.

Conclusion: The finding of the study revealed that the test drug *Sankhaholi (Evolvulus alsinoides Linn.)* is safe and has substantial efficacy as an antihypertensive drug.

Keywords *Imtila*, *Sankhaholi*, Essential hypertension, *Evolvulus alsinoides Linn*

INTRODUCTION

Essential hypertension is a heterogeneous idiopathic disorder which accounts for about 90 to 95% of all cases of HTN (Victor, 2007). According to World Health Organization (WHO), the prevalence of hypertension is 29.3% and 25.2% in Indian men and women respectively (Gupta et al, 2007). Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths (Joshi, 2012). As per Joint National Commission (JNC 7) hypertension is said to be present if BP is persistently elevated at or above 140/90 mmHg. JNC classified BP (systolic/ diastolic) into normal (<120/ <80), pre HTN (120-139/ 80-89), stage 1 (140-159/ 90-99) and stage 2 (≥160/ ≥100) hypertension (Chobanian, Bakris and Black, 2003). Antihypertensive drugs such as diuretics, beta blockers, calcium channel blockers, ACE inhibitors, vasodilators etc. have been used in conventional system of medicine, but these agents may cause various adverse effects such as electrolyte imbalance, insomnia, bradycardia and liver dysfunction.

Unani scholars were quite familiar with the clinical manifestations of the hypertension under the entity '*Imtila*'. The description of *Imtila*' in which the body fluids are accumulated in different parts of the body particularly in the blood vessels, and could conceivably be referred to as "congestion" which exhibits symptoms like headache, vertigo, epistaxis etc. It has been further classified into "*Imtila*' *bi Hasbil Auiya* and *Imtila' bi Hasbil Quwa"* which are clinically observed in the hypertension (Bakar, 2010), (Ghai, YNM). Generally, *Imtila' bi Hasbil Auiya* (repletion in regard to vessels) is the condition, where increase in the blood volume occurs.

Unani drugs are known for safety and not association with any serious side effect. The test drug *Sankhaholi (Evolvulus alsinoides Linn.)* is mentioned in Unani literature for many therapeutic actions like diuretic, brain tonic, nervine tonic and as tranquilizer (Ghai, YNM). The evidence put forth by researchers through preclinical studies as well as in the light of above, an open, randomized, controlled clinical trial was carried out for evaluation of the safety of *Sankhaholi* in the management of stage 1 essential hypertension. This study is intended to re-affirm the safety as well efficacy of the *Sankhaholi* in the management of essential hypertension based on scientific parameters.

MATERIAL AND METHODS

The study was conducted for a period of one year from October 2015 to September 2016 in Majeedia Unani Hospital, New Delhi. Prior to the execution of the study, the protocol was

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approved by the Institutional Ethics Committee of Jamia Hamdard on 19/08/2015 and was implemented in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. A prior informed consent was obtained from each patient after providing the information sheet having the details regarding the nature of the study, the drugs to be used and the study procedure, etc.

It was a randomized, open and standard controlled clinical study of one year duration while as, the duration of protocol therapy was for six weeks (42 days) with the follow-up at 2nd, 4th and 6th weeks. Patients of essential hypertension (Stage I hypertension based on JNC classification) has been enrolled. Patients of both sexes within range of 18-60 years who are not taking any anti-hypertensive drugs were enrolled in the study. While the patients of stage II essential hypertension, secondary hypertension, diabetes mellitus and other endocrine disorders, patients with systemic disorders like chronic liver, kidney or heart disease etc., pregnant and lactating mothers and terminally ill patients with infectious diseases like AIDS and Tuberculosis etc. were not included in the study. During the course of the study if patients fail to follow up or sudden increase in blood pressure level more than >160/100 mm Hg were noticed, withdrawal from the study was done.

Out of 60 screened patients, 47 patients who fulfilled the inclusion criteria were randomized in to two groups test group A and controlled group B by computer generated randomization chart. Drug *Sankhaholi* was given in powder form in dosage of 3g twice daily after meal in test group A, while, the standard drug Ramipril in dosage of 5g was given once daily for the same duration in control group. During the protocol therapy, patient in both the groups were asked to adhere to the diet according to the DASH eating criteria and daily brisk morning walk for 30 minutes. Out of 47 patients, 41 completed the study and six patients dropped out. One subject out of six drop out had systolic BP of more than 160 mmHg in the follow-up and the remaining five failed to report on specific time for follow-up. 41 completed the trial with 22 patients in test group and 19 patients in control group.

Assessment of safety was done on clinical and bio-chemical parameters before, in each follow-up and after the completion of protocol therapy as per the approved protocol. Haemogram, Liver function test and kidney function test were done before and after the study to record the safety and tolerability of the drug.

Blood pressure measurement was taken with standard mercury sphygmomanometers in sitting position, where patient's arm was fully bared and supported at the level of the heart. Cuff bladder encircled 80 percent or more of the patient's arm circumference. Mercury column was deflated at 2 to3 mm per second. The first and last audible sounds were recorded as systolic and diastolic pressure, respectively. For confirmation 2 sets of such readings on different occasions were recorded8. Effect on both systolic as well as diastolic blood pressure was assessed at each visit and subjected to the comparison and analysis statically on 0 day, 21st day and 42nd day.

Assessment of results were performed through Graph Pad Instat, Version 3.10, 32 bit for windows created on July 10, 2009 using t-test (unpaired & paired), repeated measures ANOVA, repeated measures analysis of variance and Tukey-Kramer multiple comparisons test. Test results were ranked as: ns- Non
significant, *p < 0.05 significant, **p < 0.01 very significant, ***p < 0.001 highly significant.

Characteristics	Test Group (n=22)	Controlled Group (n=19)
Age group %	20-29	2 (9.1%)	2 (10.52%)
	30-39	6 (27%)	6 (27.27%)
	40-49	10 (45.45%)	8 (42.10%)
	50-60	4 (18.18%)	3 (15.78%)
Mean ± SD		40.5±1.81	40.26±2.25
Monocyte	Female	08(36.3%)	08(42.1%)
	Male	14(63.6%)	11(57.8%)
Family history of Hypertension		10(45.4%)	05(26.3%)
Addiction	Positive	12(54.5%)	08(42.1%)
	Negative	10(45.4%)	11(57.8%)

Table 1. Baseline characteristics of the Patients

Parameters	Test Group (n=22)		Controlled Group (n=19)	
	0th day	42nd day	0th day	42nd day
TLC	7163.63± 408.75	7222.72± 351.00^{ns}	7837.89± 625.03	8242.10± 481.12^{ns}
Neutrophils	59.045±1 .61	61.77±1. 61^{ns}	62.42± 2.00	62.73±2. 18^{ns}
Eosinophils	3.63±0.4 5	4.18±0.3 4^{ns}	3±0.216	3.05±0.2 35^{ns}
Lymphocyte	35.45 ±1.50	33.27±2. 06^{ns}	32.15±1. 89	31.05±1. 60^{ns}
Monocyte	2.09±0.1 8	2.39±0.3 1^{ns}	1.89±0.1 05	2±0.132^{ns}

Table 2. Effect on CBC

Parameters	Test Group (n=22)		Controlled Group (n=19)	
	0th day	42nd day	0th day	42nd day
RBC (mill/mm3)	5.20+0.1 6	5.11+0.1 5ns	5.08±0.1 47	5.21±0.2 02^{ns}
PCV (%)	41.13+1. 25	42.63+1. 03ns	40.98±0. 147	40.24±0. 202^{ns}
PC (lacs/mm3)	2.18+0.2 3	3.53+1.6 3ns	2.11±1.1 2	1.82±1.4 2^{ns}
ESR (mm/1hr)	14.63+1. 27	12.09+1. 11ns	16.66±2. 08	14.46±1. 51^{ns}

Table 3. Effect on Haemogram

Parameters	Test Group (n=22)		Controlled Group (n=19)	
	0th day	42nd day	0th day	42nd day
Total bilirubin (mg/dl)	0.79+0.0 3	0.73±0.0 2^{ns}	0.72±0.0 3	0.98±0.1 5^{ns}
SGOT (IU/L)	33.59+2. 16	35.72±2. 74^{ns}	39.42±3. 60	40.36±3. 53^{ns}
SGPT (IU/L)	38.40+3. 23	39.22±2. 71^{ns}	43.05±5. 88	40.42±4. 41^{ns}
Alkaline phosphatase (IU/L)	155.09+1 2.34	150.86±8 .18^{ns}	153.31±1 3.09	154.47±9 .09^{ns}

Table 4. Effect on Liver Function Test

Parameters	Test Group (n=22)		Controlled Group (n=19)	
	0th day	42nd day	0th day	42nd day
B. Urea (mg/dl)	21.86+1.9 1	22+1.55^{ns}	20.21+1. 44	19.84+1. 04^{ns}

Serum Creatinine (mg/dl)	0.83+0.04	0.79+0.03^{ns}	O.8+0.03	0.76+0.02^{ns}
S. Uric acid (mg/dl)	6.89+0.04	6.76+0.03^{ns}	5.21+0.33	4.72+0.22^{ns}
Total serum protein (g/dl)	7.01+0.09	7.16+0.09^{ns}	7.05+0.10	6.93+0.09^{ns}
Albumin (g/dl)	3.69+0.08	3.69+0.07^{ns}	3.8+0.11	3.66+0.39^{ns}
Globulin (mg/dl)	3.32+0.07	3.37+0.06^{ns}	3.32+0.06	3.37+0.08^{ns}

Table 5. Effect on Kidney Function Test

Effect On Systolic Blood Pressure			
Test Group	**Follow-up**	**Mean ± SEM**	**% change**
	Baseline	150.09 ± 1.64	
	MT (21st day)	142.18 ± 1.99*	5.27
	AT (42nd day)	136.86 ± 1.81***	8.81
Controlled Group	**Baseline**	143.78 ± 2.11	
	MT (21st day)	136.63 ± 1.91*	4.97
	AT (42nd day)	131.36 ± 1.87***	8.63
Effect On Diastolic Blood Pressure			
Test Group	**Baseline**	91.27 ± 1.04	
	MT (21st day)	87.90 ± 1.03*	3.69
	AT (42nd day)	86.18 ± 0.86**	5.57
Controlled Group	**Baseline**	92.36 ± 1.24	
	MT (21st day)	86.63 ± 1.11**	6.20
	AT (42nd day)	83.36 ± 0.83***	9.74

Table 6. Effect on Blood Pressure

RESULTS

Demographic Details

The highest incidence of hypertension of 44% was observed in the age group of 40- 49 years followed by 29 % in the age group of 30-39 years. 17 % incidence was observed in the age group of 50-60 years and 10 % incidence was observed in the age group of 20-29 years. The Mean age in the test group was 40.5±1.81 while in control group it was 40.26±2.25. In this study it was found that the incidence of hypertension was higher in males (60 %) than females (39 %). Most of the patients 63% had a negative family history of hypertension and 37% had positive family history of hypertension. These observations are different from the established findings, may be because of small sample size.

Effect on Safety Parameters

No significant changes are observed in parameters evaluated under CBC and Haemogram, before and after the intervention of Unani drug. As far as LFT is concerned, mean value of total bilirubin, SGOT, SGPT and Alkaline Phosphatase was 0.79+0.03, 33.59+2.16, 38.40+3.23 and 155.09+12.34 respectively which become 0.73+0.02, 35.72+2.74, 39.22+2.71 and 150.86+8.18 respectively after 42 days of protocol therapy. Statistically no significant changes are revealed in the value of parameters of liver function test. Mean value of B. Urea was 21.86+1.91 which becomes 22+1.55, Serum Creatinine was 0.83+0.04 which became 0.79+0.03, mean value of S. Uric acid was 6.89+0.04 which become 6.76+0.03. While assessing the value of total serum protein, it was 7.01+0.09 before treatment and 7.16+0.09 after treatment, mean value of Albumin and Globulin was 3.69+0.08 and 3.32+0.07 which become 3.69+0.07 and 3.37+0.06 respectively.

Effect on Blood Pressure (BP)

Before treatment, mean SBP in the test group was 150.19±1.641 which decreased to 142.27±1.991 with ($p<0.05$) at mid-treatment and further declined to 139.22±1.731 with extremely significant change with ($p<0.001$) after treatment. In control group, before treatment SBP mean was 143.78±2.11 which fell to 136.63±1.91 with ($p<0.05$) at mid-treatment and was further decreased to 131.36±1.87 with ($p<0.001$) after treatment.

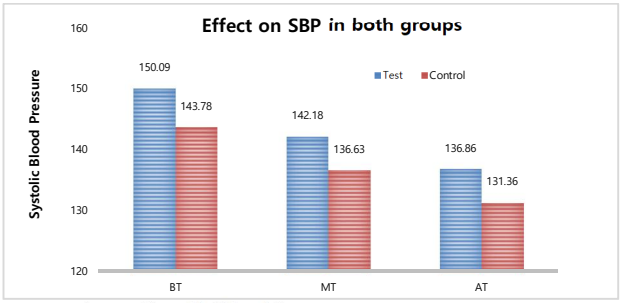

Fig. 1 Effect on Systolic Blood Pressure

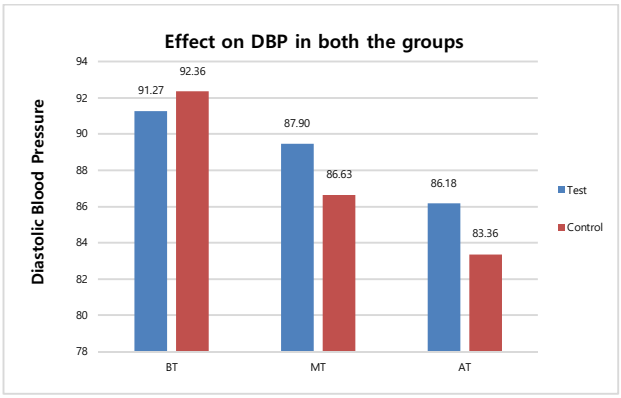

Fig. 2 Effect on diastolic blood pressure

Before treatment, mean DBP of the test group was 91.27±1.04 which was reduced significantly to 87.90±0.90 with ($p<0.05$) at mid-treatment and further reduced to 86.18±0.86 after treatment with ($p<0.01$). In the control group, before treatment, mean DBP was 92.36±1.24 which decreased significantly to 86.63±1.11 with ($p<0.05$) at mid-treatment and further reduced to 83.36±0.83 with ($p<0.001$) after treatment. The result was comparable in both the test and control group at mid treatment and after treatment. However, the control group was better in reducing DBP than test drug after treatment but at mid treatment results were similar ($p<0.05$) in both the groups.

DISCUSSION

Sankhaholi has significantly reduced the systolic and diastolic blood pressure in patients of stage 1 hypertension in the present study but control drug Ramipril controlled better the diastolic blood pressure. The control drug is an established antihypertensive drug falling under the category of ACE

inhibitors. The improvement in the test group can be attributed to its different pharmacological actions such as the diuretic effect of *Sankhaholi* (Ghani, YNM), antihypertensive and anti-anxiety effect of *Sankhaholi* (Joshi, 2012), (Kiran et al, 2005), (Shamsi, Ahmad and Khan, 2007). Mainly the antihypertensive mechanism of the test drug is most likely through its ACE inhibitor like activity as suggested by a study carried out by Umang H. Joshi, in which anti-hypertensive mechanism of *Evolvulus alsinoides Linn* herb was evaluated by using DOCA salt induced hypertensive model.

On the safety parameters, the test dug did not exhibit any side effects. The test drug did not raise any significant safety parameters during the study as no significant changes were observed in hematological parameters, liver function test and kidney function test. Similar findings have been attributed to the test drug *Evolvulus alsinoides Linn* viz a viz safety profile by other researchers also (Shamsi, Ahmad and Khan, 2007), (Saranya et al, 2015). As far as controlled drug is concerned, no safety issues were reported in control group too.

CONCLUSION

It could be inferred that the test drug *Sankhaholi* is safe and effective in managing the essential hypertension. During the study, clinically no significant side effects of test drug were observed nor reported by patients. Thus, *Sankhaholi* can be used as a monotherapy or as an adjuvant with the other antihypertensive drug for the management of essential hypertension. Further studies can be done to explore the mechanism of action of *Sankhaholi* in reducing blood pressure.

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CONFLICT OF INTEREST

The authors have no conflicting financial interests.

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