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CLINICAL EVALUATION OF TABLET *GOKSHURA* IN STAGE- I HYPERTENSION- AN OPEN LABEL RANDOMIZED CONTROL CLINICAL STUDY

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ABSTRACT

Background: High blood pressure (BP) is ranked as the third most important risk factor for attributable burden of disease in South Asia (2010). The term Stage-1 Hypertension is reserved for about 95% of hypertensive, in which no immediately evident underlying renal or adrenal cause can be found for the raised Blood pressure. It can be only detected on routine medical check-up or when patient goes to hospital. **Objectives:** This open randomized clinically controlled study was conducted to clinically evaluate the efficacy of Tablet *Gokshura* in Stage- I Hypertension. **Methods:** 72 subjects of either sex of Stage-I Hypertension in the age group of 30-60 years were enrolled for the present study. Registered patients were randomly divided into two groups. In Group-A (Clinical study) patients were managed with Tablet *Gokshura*. Group-B (Controlled study) patients were managed with Tablet *Tagara*. The duration of trial was 30 days with follow up 0^{th} day, 15^{th} day and 30^{th} day. **Interpretation:** After one month of therapy, statistically highly significant reduction in systolic B.P., diastolic B.P. mean arterial B.P. and pulse pressure was observed in both groups. Blood pressure was statistically significantly reduced in Group- A patients as compared to Group- B. **Conclusion:** On the basis of results obtained, it is clear that trial herbal *Gokshura* drug possess statistically significant anti-hypertensive activity with no observed side effects.

KEYWORDS: Hypertension, *Uccharaktachap*a, Blood pressure, *Gokshura*, *Tagara.*

INTRODUCTION

In the present times, life has been made easy for man with modernization every step of the way, but he has also paid for it by becoming prey to many lifestyle diseases. The diseases occur due to his faulty life style and stressful psychological conditions. These factors affect one's mind and homeostasis of the body by several psychosomatic mechanisms and lead to many lifestyle diseases such as hypertension and diabetes.[1]

World Health Organization (WHO) report, about 40% of people aged more than 25 years had hypertension in 2008. Today, chronic diseases are a major public health problem worldwide. In 2005, the World Health Organization (WHO) estimated that 61 per cent of all deaths 35 million and 49 per cent of the global burden of disease were attributable to chronic diseases. By 2030, the proportion of total global deaths due to chronic diseases is expected to increase to 70 per cent and the global burden of disease to 56 per cent. The greatest increase is anticipated in the African and Eastern Mediterranean regions.[2]

The term Stage-1 Hypertension is reserved for about 95% of hypertensive in which no immediately evident underlying renal or adrenal cause can be found for the raised Blood pressure. It can be only detected on routine medical check-up or when patient goes to hospital with its dangerous complications like stroke, angina, myocardial infarction etc. In medical parlance, this psychosomatic hemo-dynamic disease is also known as the 'Silent' or 'Hidden Killer' because of its end organ (*Trimahamarmas*) damages, having disastrous and menacing effects on human beings which ultimately leads to death of a person. Even Indian Council of Medical Research (ICMR) and All India Institute of Medical Science (AIIMS) study declared India a nation of Hypertension.[3]

The clinical entity of Hypertension is not available as such in the classical literature of *Ayurveda*. However, according to the directions of *Charaka* (Ch. Su 18/44-47) regarding the approach for the study of new diseases, various contemporary *Ayurvedic* scholars have been made efforts to find out the proper nomenclature, etio-pathogenesis and treatment of the disease. Various luminaries have tried to coin a name to the disease Hypertension i.e. *Uchharaktachapa, Raktadaba, Raktachapa, Raktavata, Dhamani-pratichaya, Raktagatavata, Dhamani-prapurana, Siragata Vata,*

Avrita Vata, Rakta Vikshepa, Vyana Prakopa, Raktamada, Vyana Atibala. etc.[4]

Therefore, considering it as challengeable malady, this project has been undertaken in order to find out a safe and effective medicament in *Ayurveda* without creating any adverse effects and to maintain the blood pressure in its normal ranges. Despite the huge public health burden and sustained research efforts focused on hypertension, we have seen slow progress in global control of hypertension. Transformation is urgently needed to reduce the global burden of hypertension.

OBJJECTIVES

Primary Objectives

1. To Evaluate The Efficacy Of Tab *Gokshura* In Stage-1 Hypertension.

Secondary Objectives

1. To study the efficacy of a Tablet *Gokshura* in comparison with Tablet *Tagara* in the management of Stage-1 Hypertension.
2. To determine the existing level of Blood Pressure among clients with hypertension from experimental group and control group by using calibrated sphygmomanometer and stethoscope.
3. To provide a cost effective patient friendly treatment modality.

MATERIALS AND METHODS

Study Design

The study was undertaken as a part of post-graduation research work. It was open label comparative interventional study with 1:1 allocation ratio of the participants into two study groups. The study was conducted on 72 patients screened of Stage-I Hypertension selected from OPD and IPD of concerned institute.

Ethical Considerations

The study was approved by ethics committee of the study center. All participants underwent informed consent process before conducting any study related activity.

Study Participants- Eligibility Criteria

After signing informed consent, each patient was screened for eligibility to participate in study. Diagnosis was mainly based on readings of sphygmomanometer. With the help of sphygmomanometer, 3 consecutive readings of blood pressure in sitting position were taken. Thus final and initial value was taken. Their mean value was calculated and categorized the patients according to Joint National Committee (JNC) -7.

Inclusion Criteria

Patients of Stage-I Hypertension (JNC-7) in the age group of 30-60 years were registered irrespective of gender, caste and religion after obtaining their written informed consent.

1) Systolic blood pressure< 160 mm of Hg & > or = 140 mm of Hg. (In Sitting posture)
2) Diastolic blood pressure < 100 mm of Hg & > or = 90 mm of Hg. (In Sitting posture)
3) Age between 30 yrs. to 60 yrs.

Exclusion Criteria

1) Complicated hypertensive cases with Nephropathy, Left Ventricle Hypertrophy (LVH), Heart block, Congestive Heart Failure (CHF), Coronary heart disease (CHD) & Retinopathy.
2) Patients suffering with Uncontrolled Diabetes mellitus.
3) Accelerated & Malignant Hypertension.
4) Patients taking steroids, oral contraceptives pills, estrogen replacement therapy/ Hormonal Replacement Therapy (HRT) or Non-steroidal anti-inflammatory drugs (NSAID) groups of drugs.
5) Pregnant woman or planning pregnancy within six months and lactating mothers.
6) Patients with severe other illness hepatic/ renal failure.
7) Known Case of Gout.

Interventional Products/ Study Products

The study drug, *Gokshura* (T. terrestirs, Linn) tablets & controlled drug, *Tagara* (*Valleriana wallichi*) were prepared at GMP certified Pharmacy. Identical packing was used to ensure blinding of patients. The trial medicine containers were labelled as 'A' while controlled containers were labelled as 'B'. Manufacturing date and expiry date were put on each container. Each container contained 60 tablets of trial medicine & controlled medicine with labelled.

Study Procedures

Patients fulfilling the inclusion criteria were randomized by lottery methods.

After registration, patients were given the medicine and were followed up for 0, 15th & 30th day. Symptoms of Hypertension, such as *Shiroruka* (Headache), *Bhrama* (Giddiness), *Nidra-vikruti* (Disturbance of sleep), *Hridravata* (Palpitations) were examined and noted based on grade. [Table 1].

The selected patients were divided into two groups. [Fig 1]

- **Group A (Clinical Trial group)** - Total 36 patients were registered and completed the trial by administering them Tablet *Gokshura* 2 tab (250mg each) BD with *koshnajala* for 30 days.
- **Group B (Control group)** - Total 36 patients were registered and completed the trial by administering them Tablet *Tagara* 2 tab (250mg each) BD with *koshnajala* for 30 days.

Investigations: E.C.G, Lipid profiles were done.

Criteria for Assessment
Assessment of the effects of therapy was done on the basis of various objective and subjective parameters. However the change in systolic, diastolic and mean arterial blood pressure was the main criteria. Sign and symptoms were graded according to severity.

Objective parameters
By noting down the alteration in blood pressure, pulse pressure, mean arterial pressure.

Outcomes
Symptoms observed in patients were measured to access subjective improvement according to four-point scale mentioned in table 1. Secondary efficacy parameters were Lipid profile, E.C.G. which were done at the 0^{th} day and 30^{th} day. Incidences of AE, SAE and ADR observed throughout the study period of 4 weeks were considered as safety parameters.

Sample Size
Sample size was calculated by formula given by Danniel. Total 72 numbers of known patient of Stage-1 Hypertension were screened for proposed study, was randomly selected from IPD & OPD of concerned institute.

Statistical Analysis
The collected data was compiled in Microsoft Excel 2016. Data describing quantitative measures was expressed as mean, median, mean +SD, standard deviation. Qualitative type of data was expressed as percentage or proportion. Data was analyzed using SPSS (Statistical Programme for Social Sciences) software 21 version, Open Epi Software version 2.3. For quantitative type of data test of significance applied was student t test and for Qualitative data Wilcoxon test & Whitman was applied.

- Data management and analysis was done using master chart.
- Parametric Test Such as paired t-Test etc.
- Non-Parametric such as sign rank test etc.
- On the basis of clinical study occurrence of various incidence & criteria for assessment of result was recorded as per case record form and statistical test for subjective criteria use Non-parametric Test like is Wilcoxon test and for objective criteria we have to use parametric test like, paired T- test etc.

Data Collection and Statistical Analysis:
Data generated from clinical study was collected and analyzed statistically. The improvement in the status of patient was assessed on the grades of various variables compared between pre-trial and post-trial values in terms of percentage and the student 't' tests was applied wherever it was felt necessary by using degree of freedom value. The results were interpreted at the level of $p<0.001$ as highly significant, $p<0.01$ as moderately significant, $p<0.05$ as significant and $p>0.05$ as insignificant.

RESULTS
Total 72 registered patients, 36 divided in each group were successfully completed the trial. In both groups the effect of therapy showed statistically highly significant reduction in systolic blood pressure, diastolic blood pressure, mean arterial pressure ($p<0.001$). In both groups the effects of therapy on the subjective and the intergroup comparison showed that therapy in Group A had statistically significant advantage over therapy used in Group B on palpitations and giddiness. [Table 2, 3, 4]

Table 1: Gradation of Symptoms- Subjective Parameters of Stage-I Hypertension.

Grade	*Upashaya*	Percentile
3 to 0	*Uttama* (Control of the disease)	75% & Above relief.
2 to 0 3 to 1	*Madhyama* (Markedly improved)	50%- 75% relief.
1 to 0 3 to 2 2 to 1	*Alpa* (Little improved)	25%- 50% relief.
No Changes in Gradation or Raised	*Anupashaya* (Unchanged)	25% & less relief.

Table 2: Showing statistical analysis of Subjective parameters in both groups.

Contents	*Shiroruka* (Headache)		*Bhrama* (Giddiness)		*Nidra-vikruti* (Disturbance of sleep)		*Hridravata* (Palpitations)	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
Day	30^{th}	30^{th}	30^{th}	30^{th}	30^{th}	30^{th}	30^{th}	30^{th}
Mean	0.06	0.36	0.17	0.64	0.11	0.53	0.06	0.69
S.D.	0.23	0.68	0.56	0.80	0.32	0.77	0.23	0.82
Test statistics	-2.54		-2.90		-2.90		-4.49	
p value	0.007		0.0025		0.0025		0.0000	
Significance rate	Significant	Significant	Significant	Significant	Significant	Significant	Significant	Significant

Table 3: Statistical analysis of objective parameters in both group.

Contents	Systolic Blood Pressure				Diastolic Blood Pressure			
	Group A		Group B		Group A		Group B	
	BT	AT	BT	AT	BT	AT	BT	AT
Mean	151.67	138.33	150.50	139.67	93.61	86	93.33	89
SD	4.82	8.26	4.49	8.51	3.57	4.7	3.31	5.33
SE	0.80	1.38	0.75	1.42	0.60	0.79	0.55	0.89
t table	9.93		7.46		7.63		4.38	
p	0.0000		0.0000		0.0000		0.0001	
Significant	Significant		Significant		Significant		Significant	

Table 4: Unpaired t- test.

Contents	Systolic Blood Pressure		Diastolic Blood Pressure	
	A	B	A	B
Mean	138.33	139.67	86	89
SD	8.26	8.51	4.76	5.33
SE	1.38	1.42	0.79	0.89
Df	70	70	70	70
t table	-0.67		-2.52	
p	0.2510		0.0070	
Significant	Insignificant		Significant	

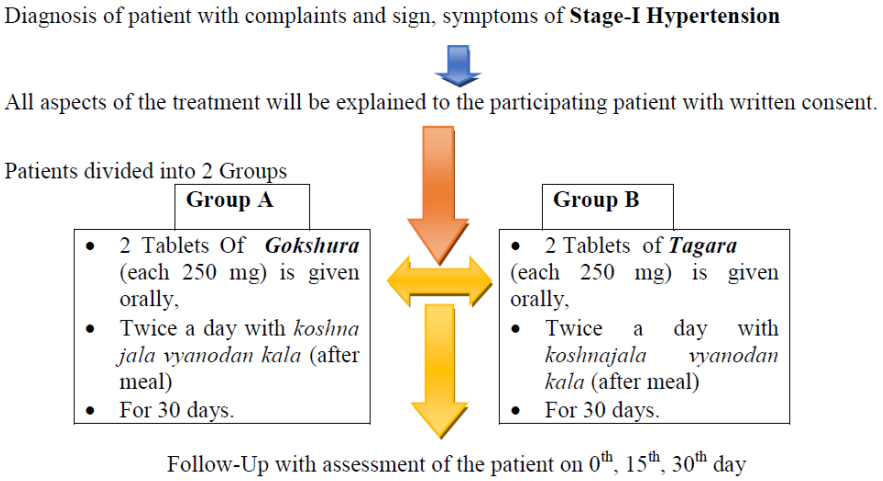

Figure 1: Flow Chart of Activities.

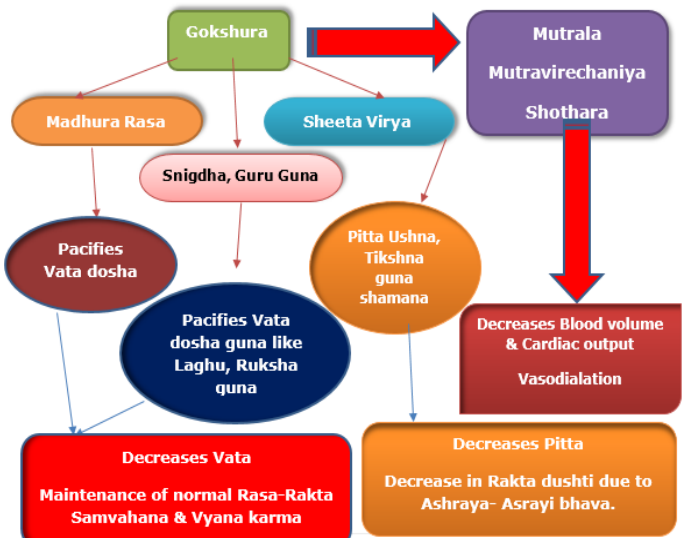

Figure 2: Showing Mode of Action of *Gokshura* in Stage-I Hypertension.

DISCUSSION

Hypertension is directly responsible for 57% of all stroke deaths and 24% of all Coronary Heart Disease (CHD) deaths in India. Hypertension is a major public problem worldwide, though there is difference in developed and developing countries. India is a very large populated and typical developing country, community surveys have documented that between three and six decades, prevalence of hypertension has increased by about 30 times among developers, and about 10 times among rural inhabitants. Cardiovascular diseases contributed to 2.3 million death in India in 1990 and is projected to double by the year 2030.[5]

Vata is prominent *Dosha* in this disease and circulating *Rakta* (*Ras-Rakta complex*) is main *Dushya* and *Srotasa-Rasavaha*, *Raktavaha* together with *Manovaha Srotasa* are involved. *Pitta lakshana* are also seen because of association of *Rakta* with *Pitta* (*Ashraya- Aashriya Bhava*). The symptomatology quoted under *Raktapradoshaja Roga* by *Acharya Charaka* almost coincides with essential Hypertension symptomatology among those *Anidra, Sirashoola, Bhrama, Hridadrava* etc., are common, hence *Rakta* is considered as a main *Dushya*, in this disease. Ageing is one of the main factors for essential hypertension. *Vata* is stated as dominant in old age and signs of premature ageing are mentioned under *Pitta-Prakuti.*[6]

In this study 66.67% of sufferers were found to be male and the rest 33.33% were female. The higher incidence in male is due to more stressful lifestyle, job, addiction, genetic. Hence the difference in percentage is observed.

Maximum numbers of patients were worker 37.5% followed by 14% were Housewives & government servants. The increased incidence in workers and in government servants may be due to their stressful lifestyle, *Ratrijagarana* and shift duties for workers and daily up downs to different workplaces through different vehicles and among housewives due to their sedentary habits, *chinta, diwaswapa, vegavarodha* and exposure to cold water.

In this study 40% patients had no addiction, where as 18% patients were having addiction of tobacco, 8% patients having addiction of cigarette or bidi and 6% patients having addiction of alcohol. Though the large % of patient was not having addiction but addiction of tobacco, alcohol, cigarette definitely causes the hypertension.

Goshura accounts *Madhura rasa, Snigdha guna, Guru guna* & *Sheeta virya*. Due to its *madhura rasa* & *snigdha, guru guna* it pacifies *vatadosha*, and also it decreases other qualities of *vatadosha* like *laghu* and *ruksha guna*. Owing *sheeta virya* it pacifies vitiated *Pittadosha* and normalizes *pittadosha* that leads to *Mandagninasha*. Also due to *sheeta virya*, the *gunas* of *pitta* like *ushna* and *teekshna* are decreases and leads to *Teekshnagninasha*.[7] Overall *Gokshura* acts on vitiated *vata* and *pitta dosha* and their associated properties which is usually aggravated in *Uccharaktadaba*. [Fig 2].

Gokshura is documented to have beneficial effect on dyslipidemia and also has diuretics effects. It decreased sympathetic tone & A.C.E. inhibitors activities. The preliminary phytochemical study of *Gokshura (Tribulus terrestris)* revealed the presence of saponins, flavonoids, glycosides, alkaloids, and tannins. Due to this lipid lowering activity the atherosclerotic changes are reduced and hence the peripheral resistance resulting from atherosclerotic changes is reduced resulting into decrease in blood pressure.[8]

Tagara drug has good control on stress factor as it directly effects on I-GABA receptors and shows vasodilators properties.[9]

CONCLUSION

From the clinical trial conducted for the study it can be concluded that Tablet *Gokshura* & Tablet *Tagara* are equally effective on the Stage-I hypertension which was statistically significant, and both decreased systolic, diastolic blood pressure and mean arterial pressure considerably. Both medicines are having effect on headache but Tablet *Gokshura* decreases headache earlier than Tablet *Tagara*. Tablet *Gokshura* reduces giddiness more effectively than Tablet *Tagara*. Both medicines reduce the disturbance of sleep but the action of Tablet *Gokshura* starts after 3 weeks use. It is noted that when data is subjected to unpaired t test, the clue regarding the supremacy of the drug of group A upon group B cannot observed. It means the difference between the efficacies within both groups is very less and hence it is concluded that both drugs Tablet *Gokshura* & Tablet *Tagara* are equally effective on Stage- I hypertension.

Registration

The study is registered in Clinical Trial Registry of India vide number CTRI/2020/09/027960 (Date: 22/09/2020).

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