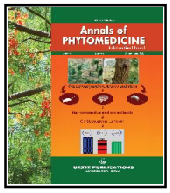
Annals of Phytomedicine 11(1): 595-600, 2022

DOI: http://dx.doi.org/10.54085/ap.2022.11.1.69

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885



Original Article : Open Access

A chronotherapeutic study of *Shalaparni Ksheerapaka* in prehypertension

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Article Info

Article history

Received 26 April 2022

Revised 14 June 2022

Accepted 15 June 2022

Published Online 30 June 2022

Keywords

Shalaparni

Ksheerapaka

Desmodium gangeticum (L.) DC

Prehypertension

Chronotherapy

Blood pressure

Abstract

Prehypertension is one of the major health concerns and has shown increasing epidemiology globally. The treatment of prehypertension using a safer and tolerable strategy, thus becomes a pressing priority. The purpose of the study was to evaluate the effect of *Shalaparni Ksheerapaka* based on chronotherapy in individuals as a treatment of prehypertension. Sixty patients were randomly allocated into three different groups according to the time of oral drug administration. All the patients performed the trial session for 30 days. Assessment of the results was done on the basis of pre-decided subjective (feeling of headache, dizziness and fatigue) and objective parameters (systolic and diastolic blood pressure) before and after the treatment. After 30 days of therapy, BP was normalized significantly with systolic BP as 123.1 ± 3.14 and diastolic BP as 81.2 ± 2.09 when *Shalaparni Ksheerapaka* was administered post lunch, *i.e.*, vyana vayu kala. Likewise, a significant improvement in subjective parameters of prehypertension was evident in groups that received *Shalaparni Ksheerapaka* post lunch and dinner. The present article emphasizes on the therapeutic value of *Shalaparni* in the treatment and control of prehypertension and unfolds the potential of *Shalaparni Ksheerapaka* as a promising drug for treatment of various other diseases.

1. Introduction

Hypertension or high blood pressure (BP) is one of the major health conditions faced by the majority of the population in the world due to the current lifestyle and different genetic factors (Niu *et al*., 2021). Hypertension is a serious condition when untreated, contributing to the increased risk of cardiovascular diseases, stroke and other heart and kidney related diseases. It is estimated that an overall 1.13 billion people worldwide have hypertension, most of them (two-thirds) living in low-and middle-income countries and affects around 30% of the adult population. BP is considered to be in a normal range when less than 120/80 mm Hg. BP between 120-139/80-89 mmHg is prehypertension and a condition which is ubiquitous, associated with increased risk of hypertension and cardiovascular diseases (Hisatomi *et al*., 2012). Extensive research and clinical trials are undertaken to treat this condition, albeit lacking the benefit in everyday practice owing to which the cases of well controlled prehypertension remain inconsequential world wide, instigating the search of novel drugs and methods. A collective treatment strategy considering the circadian variation of blood pressure, usage of antihypertensives, dietary interventions, weight reduction, tobacco cessation, physical exercise, stress management are ways of enhancing the management of prehypertension condition (Gupta and Guptha, 2010).

Chronotherapy is the study of biological rhythms and recommends medication by changing the time of dose that coincides an individual's circadian rhythm and psychological patterns. It combines chrono-pathological, chrono-pharmacological and chrono-toxicology knowledge which is accomplished by improving or increasing the effectiveness and tolerance of drugs according to administration of medication with respect to time (Kaur *et al*., 2013). This therapy has been reported to enable maximum benefits with minimum toxicity of the medicines (Lemmer and Labrecque, 1987). Further, chronotherapeutics have immensely contributed in comprehending the pathophysiological mechanisms of many diseases, thereby establishing effective and safer treatment modules in clinical settings (Portaluppi and Smolensky, 2010). *Matra* (dose) and *kala* (time of administration) are the two important factors that influence the pharmacodynamics of a drug (Jawanjal *et al*., 2020). Enhanced efficiency is achieved by administering drugs at specific time of the day and synchronizing particular concentration of drug with circadian rhythms in disease activity by way of chronoformulations (Kaur *et al*., 2013). In ayurveda, all pathological and physiological

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phenomena depend on delicate balance of doshas and to precisely regulate *doshas*, biological clocks adjustments are made in the form of *dinacarya* (daily regimen) and *ritucarya* (seasonal regimen). Ayurveda believes in administration of drugs in higher concentration during times of greatest need and in lesser concentration when the need is less (Arora and Kumar, 2000). In ayurveda, *aushadha sevana kala* is a classical concept that is presently studied as chronotherapy as it relates the intake of the food with the route of administration which is specified to the oral route. It is a vital concept for optimum efficacy of the drug (Hermida *et al*., 2007). *Ksheerapaka* is one of the unique preparations of ayurvedic pharmaceutics. Milk is used as a media for the formulation due its dietetic value which can be used as dietetic regimen, as well as medicine. It has an ability to dissolve water soluble, protein soluble and certain fat-soluble ingredients from the drugs which can be further used for *Ksheerapaka* preparation. Because of its palatability and other properties, it can be used easily for wide treatment purposes. Usually, *kasaya rasa dravyas* are used for the preparation of *Ksheerapaka*. Synergetic action of both milk and medicinal drugs proves to be more beneficial by means of this formulation (Sharma *et al*., 2018).

Herbal medicine has been used from the beginning of recorded human history. Several evidences exist to demonstrate that herbs derived from medicinal plants have been utilized for the treatment of various ailments, as well as for healing and enhancing physical and mental health in practically all ancient civilizations (Malik *et al*., 2020; Bushra *et al*., 2020). *Desmodium gangeticum* (L.) DC popularly called as *Shalaparni*, is grown and found throughout different parts of India. *Shalaparni* is traditionally used in ayurveda to treat various conditions in different formulations. The root of *D. gangeticum* is one of the constituents of famous ayurvedic preparation *dashamoola kvatha* which is an antipyretic, analgesic and bitter tonic. The therapeutic properties of this plant such as diuretic, anti-inflammatory, analgesic and aphrodisiac are well-established. Furthermore, *Shalaparni* is also used to treat complaints such as diarrhoea, cough, vomiting, asthma and chronic fever (Singh and Parmar, 2015). *Shalaparni* can also be used for preventing cardiovascular diseases and to protect the heart due to its antioxidant property. To the best of our knowledge, there are no reports on investigating the effect of the *Shalaparni* drug on patients when administered at different times of the day as per the body and further understanding the circadian rhythm of the drug. Also, prehypertension can be fairly correlated to *hridayagata vata* described by *Charaka* in *vatavyadhi* chapter *Shalaparni* in the form of *Ksheerapaka* has been advocated in the treatment of *hridayagata vata* (Adhikari *et al*., 2012). Hence, the present research aims at studying of chronotherapeutics (*bhaishajya sevan kala*) efficacy of *Shalaparni Ksheerapaka* in prehypertension and to evaluate the pharmacological actions of *Shalaparni*.

2. Materials and Methods

2.1 Drug collection and authentication

Shalaparni (*Desmodium gangeticum* (L.) DC) roots were collected from natural habitat through a botanist, Mr. Chellabery, Retd. Scientist, Regional Research Institute Siddha Medicine, Tirunelveli, Tamil Nadu during *grishma ritu*. The voucher specimen of the test drug has been retained and deposited for future reference. The roots were stored in air tight, clean and dry glass containers and were kept away from direct sun-light in a dust-proof room.

2.2 Drug standardization

The drug was standardized according to guidelines given by *Acharya Charak* in *vimansthan* 798/87, which is relevant with the monogram given by WHO. Study drug was compared with the standards mentioned in the ayurvedic text.

2.3 Preparation of trial drug, *Shalaparni Ksheerapaka*

The *Shalaparni Ksheerapaka* (*Ksheera*-milk and *paka*-processing) was prepared by mixing one part of *Shalaparni* root powder, eight parts of cow milk and thirty-two parts of water (1:8:32) (Ragad and Gokhale, 2019). The mixture was boiled on low flame, *i.e.*, *mandagni* until only milk remained, *i.e.*, 50 ml by letting water evaporate. This was called as *Shalaparni siddha ksheera*, *i.e*., milk processed with *D. gangeticum* root. This was filtered and was further used for administering orally to the patients. The recommended dosage of *Shalaparni Ksheerapaka* was 50 ml taken orally at specific times of the day for 30 days.

2.4 Selection of patients

Patients attending the OPD, IPD and medical camps of Department of *Kayachikitsa*, *Panchakarma* of D. Y. Patil Ayurveda Hospital, Navi Mumbai, Maharashtra with signs and symptoms of *hridayagata vata* (Prehypertension), aged between 18 and 50 years were selected for the study. A regular/demographic record for all the study participants was maintained according to proforma prepared for the purpose. Persons fulfilling the inclusion criteria of systolic BP between 121-139 mmHg, diastolic BP between 81-89mmHg, age between 18-50 years, newly diagnosed patients of prehypertension or history of prehypertension less than one year, with no other medication were selected for the study. A well-informed consent was procured from all the patients and the study was approved by the Institutional Ethical Committee before the commencement of the work. Any subjects with medication, major systemic disorders (uncontrolled diabetes or uncontrolled hypertension), pregnancy and lactating women were excluded from the study.

2.5 Grouping/administration of drug and treatment schedule

A total number of 60 patients were registered and randomly divided into three groups (Group A, Group B and Group C with 20 patients in each group).

Group A (20 patients): Received *Shalaparni Ksheerapaka* (50 ml) orally at early morning, *i.e.*, *pratham kala* (*kinchitsuryodaye*).

Group B (20 patients): Received *Shalaparni Ksheerapaka* (50 ml) orally after lunch, *i.e*., *divas bhojne.*

Group C (20 patients): Received *Shalaparni Ksheerapaka* (50 ml) orally after dinner, *i.e*., *sayam bhojne* Participants of all the groups were observed for 30 days.

2.6 Study design and assessment criteria

Patients were analysed according to the readings of subjective and objective parameters before and after the treatment. A special scoring pattern was applied in symptoms and associated complaints.The patients were assessed for subjective parameters in terms of feeling of headache, dizziness and fatigue before and after treatment. A grading score was obtained to evaluate the efficacy of the treatment.

The objective parameters were evaluated on the basis of systolic and diastolic BP check-up.

2.7 Statistical analysis

The intra-group comparison was performed to observe the before and after effect of treatment using the Wilcoxon signed-rank test. The difference in quantitative parameters in post treatment was carried out using paired t-tests for intra-group comparison while for inter-group comparison ANOVA was applied. The results are expressed in terms of probability (p) as $p>0.05$-insignificant, $p<0.05$-significant, $p<0.01$, $p<0.001$-highly significant.

3. Results

3.1 Demographic variables

Demographic data of the population under study provide imperative information on the variability in the population (Ramamoorthy *et al*., 2018). In our study, out of 60 patients randomized into three groups, most patients of prehypertension were detected in the age-group between 30-40 years (48%) probably due to contributing factors like occupational stress, erratic lifestyle, family responsibilities and frequent indulgence in outside food consumption (Bruno *et al*., 2016). On the basis of gender classification, 42% of subjects were male and 58% were female. In the current study, females seemed to be affected more than males with prehypertension, this is due to multitasking of women with regards to family and profession (Egan and Stevens-Fabry, 2015). Servicemen seemed to be most affected due to job related deadline pressures and sedentary lifestyle. Previous studies have well established the association of job-related pressure with increased BP (Markovitz *et al*., 2004). Further, 34 (57%) patients consumed a mixed diet while 26 (43%) were vegetarian. Earlier studies also affirmed the association of non-vegetarian groups with significantly higher BP in comparison to vegetarian groups (Varshney *et al*., 2005). The current dietary habits like excessive salty spicy diet coupled with late night sleep patterns may be directly influencing people with *pitta* and *vata prakriti* (Telles *et al*., 2015). When psychological factors were recorded, 26 patients detected with prehypertension had a history of anger (43%), 19 of anxiety (32%) and 15 of phobia (25%) making evident that emotions play predominant roles in aetiopathogenesis of prehypertension (Boutelle, 2014), Due to irregular dietary habits, most patients end up having disturbances in digestion *vishamagni* or *mandagni* which is said to cause most diseases (Kaviraj, 2011). Additionally, 24 patients (40%) in the current study had constipation. *Vata prakriti* patients have mostly are constipated which aggravates *vata* leading to *vaishamyata* or disturbance in circulation (Ragad and Gokhale, 2019). Pattern of food distribution unfolded those 24 subjects (40%) with prehypertension in this study were found to consume more of salt and spicy substances which clearly indicates the influence of salt in development of hypertension (Jawanjal *et al*., 2020). In line with digestion and exercise, those whose digestion was poor and could hardly sustain exercise were prone to prehypertension. Low appetite and little or no exercise could result in improper assimilation of metabolites resulting in disorders (Buttar *et al*. 2005).

3.2 Clinical assessment or effect of interventions

Patients were analysed according to the readings of subjective and objective parameters before and after the treatment. A special scoring pattern was applied in symptoms and associated complaints.

3.2.1 Subjective parameters

Subjective parameters like headache, dizziness and fatigue were assessed through gradation before (0^{th} day) and after intervention (30^{th} day). Elevation in blood pressure causes headache during hypertensive crisis and resolves after normalization of blood pressure. The development and frequency of headache along with blood pressure is considered to be a risk factor for heart attack and stroke (Mazdeh *et al*., 2016). The headache score recorded before and after treatment was found to be statistically significant in both group B and C (group B: $p= 0.0010$ and group C: $p= 0.0050$) whereas in group A, statistically significant difference ($p= 0.0039$) was observed. Dizziness is one of the symptoms of prehypertension and a forewarning to direct a patient to examine the possibility of hypertension. Unexpected increase in BP (e>180/120 mm Hg) can lead to symptoms such as dizziness that may be mild or severe (Lopes *et al*., 2013). Intra-group comparison unfolded a significant difference in the patient's score post therapy complaining for symptoms of dizziness and fatigue in group B and C albeit intra-group comparison of group A turned out to be statistically non-significant for the same parameters (Table 1). The rest of the patients were asymptomatic.

Table 1: Intra-group comparison of subjective parameters

		Group A		Group B		Group C	
		BT	AT	BT	AT	BT	AT
Headache	Mean ± SD	0.8 ± 0.8	0.3 ± 0.6	0.9 ± 0.9	0.3 ± 0.5	1.0 ± 0.9	0.3 ± 0.6
	p-value	0.0039		0.0010		0.0050	
Dizziness	Mean ± SD	0.5 ± 0.7	0.3 ± 0.6	0.6 ± 0.9	0.2 ± 0.4	0.8 ± 0.1	0.3 ± 0.6
	p-value	0.1250		0.0313		0.0039	
Fatigue	Mean ± SD	0.3 ± 0.4	0.1 ± 0.3	0.7 ± 1.0	0.3 ± 0.6	0.8 ± 0.9	0.3 ± 0.6
	p-value	0.2500		0.078		0.0039	

Table 2: Intra-group (within the group) comparison for systolic and diastolic BP values (mmHg)

		Group A		Group B		Group C	
		BT	AT	BT	AT	BT	AT
Systolic pressure	Mean ± SD	127.2 ± 3.58	120.4 ± 25.3	127.2 ± 3.58	123.1 ± 3.14	127.2 ± 3.58	127.1 ± 4.02
	p-value	0.2352		<0.0001		0.2885	
Diastolic pressure	Mean ± SD	84.8 ± 1.98	82.9 ± 2.10	84.8 ± 1.99	81.2 ± 2.09	84.8 ± 1.99	84.6 ± 2.06
	p-value	<0.0001		<0.0001		0.0813	

Table 3: Inter-group (between the group) comparison for systolic and diastolic blood pressure values in all the groups

		Group A	Group B	Group C	*p-value*
Systolic pressure	Mean ± SD	125.90 ± 4.12	123.1 ± 3.14	127.1 ± 4.02	0.0048
Diastolic pressure	Mean ± SD	82.9 ± 2.10	81.2 ± 2.09	84.6 ± 2.06	<0.001

3.2.2 Objective parameter-systolic and diastolic BP

Objective parameters of prehypertension as systolic and diastolic BP were measured before (0^{th} day) and after (30^{th} day) therapy sessions. Prehypertension is considered to be the stage one of hypertension manifestation. High BP (130-139/85-90 mm Hg) can lead to higher risk of cardiovascular diseases and could prove to be fatal in nature (Svetkey, 2005). Systolic BP evaluates the amount of force exerted by the heart against walls of arteries. Elevated systolic BP in the range of 120-140 mmHg is known to be a danger zone which may result in various cardiovascular diseases (Fuchs, 2020). Table 2 represents the mean systolic and diastolic BP values before and after treatment in all the groups along with the statistical analysis of intra group comparison. Systolic parameters when measured before treatment had a mean of 127.20 in group A, 127.20 in group B and 127.20 in group C, post treatment, it was decreased to 120.40 in group A, 123.10 in group B and 127.10 in group C, respectively. Upon intra-group comparison of all three groups, significant difference (p<0.001) in the pre and post BP values was recorded only in group B, whereas systolic pressure value did not differ statistically in both group A and C (p>0.05). Increase in diastolic pressure defines increase in BP even when systolic BP is normal and can be caused by genetic and lifestyle factors (Franklin, 2007). Before treatment, diastolic pressure had mean values of 84.80 in group A and B with 84.80 value in group C which after treatment was normalized to 82.90 in group A, 81.20 in group B and 84.60 in group C. Intra-group comparison in values of pre and post diastolic pressure in all the groups suggests significant difference in group A and B (p<0.001) and non-significant difference in the mean value of group C (p=0.0813). Group B showed significant statistical results over group A and C on both systolic (123.10 ± 3.14) and diastolic values (81.20 ± 2.09). Inter-group comparison also showed significant difference in both systolic and diastolic BP values when compared between all the groups (Table 3).

Figure 1 represents the overall response of *Shalaparni Ksheerapaka* in prehypertension. Out of 60 patients selected for the clinical study, 9 patients in group A were observed to have a marked improvement, while 7 patients had a moderate improvement whereas 17 patients in group B had a marked improvement and 3 patients were found to have a moderate improvement. In group C, 12 patients were observed to have a moderate improvement than marked improvement observed in 3 patients. In both group A and C, 5 patients had no response towards the treatment. It was observed that no group achieved complete relief. Group B was observed to show 85% of major marked improvement in comparison with 45% of group A and 15% of group C. Moderate improvement was more observed in group C (60%) than group A (35%) and group B (15%). In both group A and C, 25% of patients showed no response. Previous studies have shown that risk of ischemia can be curtailed by decreasing the levels of both SBP and DBP, thus, preventing incidences of CVD. A reduction of about 3 mmHg in systolic decreases incidence of CHD by 5-9%, stroke by 8-14% while reduction in diastolic by 5 mmHg reduces ischemic heart disease by 20%, stroke by 32% (Satterfield, 1995).

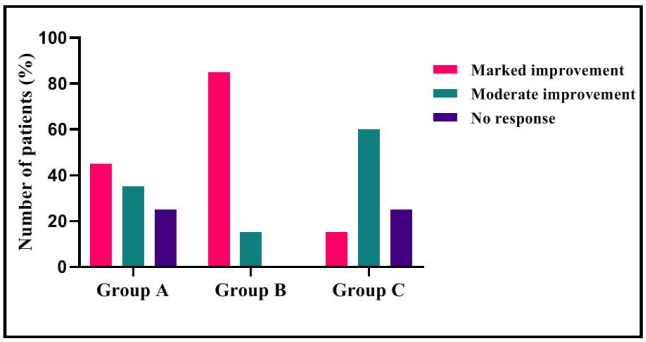

Figure 1: The bar graph shows the percentages of patients in all the groups who exhibited different levels of improvement after treatment with *Shalaparni Ksheerapaka* at different times of the day.

4. Discussion

Chala property, *i.e.*, movement of *vata* is responsible for circulation. *Shalaparni* has the synonym *sthira* which corrects any *vaishamyata* or abnormality of *chalaguna* of *vata*. Flavonoids detected in *Shalaparni* (*D. gangeticum*) have been reported to exert beneficial

effects in hypertension by restoring endothelial function (Clark *et al*., 2015). *Ksheerapaka kalpana* dosage form (processing the drug in milk) has been advocated in the classics. Water soluble, fat soluble and protein soluble active principles are extracted in *Ksheerapaka* increasing the efficacy and potency of drugs (Dube *et al.*, 2016). Milk is a nutrient with fat soluble vitamins A, D, E, and K. Vitamin D deficiency is associated with hypertension, cancer, inflammation, increased risk of CVD, a reason why *Ksheerapaka kalpana* must have been suggested for better efficacy (Tsugawa, 2015).Overall, the data suggests that consumption of *Shalaparni Ksheerapaka* during morning, post-lunch or post-dinner can ameliorate headache, but supplementation post-lunch and dinner was found to minimize the occurrence of dizziness and fatigue. Upon intra-group comparison data analysis, we can comprehend that group B and C who received *Shalaparni Ksheerapaka* (50 ml) orally at *divas bhojne* and *sayam bhojne* respectively had a better relief with subjective parameters compared to the group A.

5. Conclusion

Conventional antihypertensive medicines are usually dosed in the morning. Currently, owing to the cardiovascular events mostly observed in the morning hours, time of dosing of these medicines for better plasma concentration are studied. An optimum pharmacological utility of drugs is obtained from administration of medicine at specific time, and thus *aushadha* employs a proper *kaala* which results in expected *kaarya*. On the basis of different observations and results, it can be concluded that *Shalaparni Ksheerapaka* is a promising drug for the prevention of prehypertension. *Shalaparni Ksheerapaka* can be correlated with prehypertension as mentioned in the context of *hridayagata vata*. The groups when treated with *Shalaparni Ksheerapaka* were found to be statistically significant as there was change in gradation shown in subjective parameters which includes headache, dizziness and fatigue before and after treatment. Subjective parameters were found to show an improved result with post dinner administration of the drug. It was observed that *Shalaparni Ksheerapaka* was highly effective in maintaining the systolic and diastolic BP (p<0.001) in B group when administered post lunch. The reduction, thus found in objective parameters indicates normalization of BP and a possible treatment modality of prehypertension. *Shalaparni Ksheerapaka* with modified lifestyle can prove to be a safer option for the management of patients with prehypertension. Additionally, combining *Shalaparni* with milk may ameliorate the vitamin D deficiency which is known to be a risk factor for hypertension and can prove to be immensely beneficial in clinical settings when supplemented at *divas bhojne* or *sayam bhojne*, *i.e*., post lunch or post dinner, respectively.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Citation **Rajkumar Gupta, Rajashree Jadhav, Shirish Patil, Shraddha Nayak, Avni Cherieth, Kanchanlata Tungare, Mustansir Bhori, Shishira Bharadwaj and Ritu Wadhwa (2022). A chronotherapeutic study of *Shalaparni Ksheerapaka* in prehypertension. Ann. Phytomed., 11(1):595-600. http://dx.doi.org/10.54085/ap.2022.11.1.69.**