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UTILITY OF *BHESHAJA SEVANA KALA* – OPEN END COMPARATIVE RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Background: *Bheshaja sevana kala* is the principle of time of administration of the medicine. Drug exhibits different actions when administered in different *bheshaja sevana kala* (time of administration of medicine). Actual aim of *bheshajasevanakala* is to provide the fulfillment towards desired action of drug administration in patient in order to pacify the disease. **Objective:** To evaluate the efficacy of *bheshaja Sevana kala (*time of administration of medicine*)* in the disease *prameha* (diabetes mellitus, type-II). **Methods:** A randomized clinical trial was outlined with a pre, mid and post test assessment of 30 patients satisfying the inclusion criteria. In the present study 15 patients were asked to consume 4gm of *Guduchi churna* (powder of *Tinispora cordifolia*) in *pragbhakta* (before food) and *pratah adhobhaktakala* (morning after food) with lukewarm water and another 15 patients were asked to take 4gm of *Guduchi churna* three times a day after food with lukewarm water for a duration of 30 days. After intervention, results were analyzed statistically. **Results:** In the present study, fairly good results were observed in all the parameters of the study. There was no much difference in the result between the groups with regards to subjective parameters i.e. *prabhootamootrata* (polyurea), *pipasa* (polydypsia), *kshuda* (polyphagia), *swedapravrutti* (excessive sweating), *karapadadaha* (burning sensation in palms and soles) *supti* (numbness) and *klama* (fatigue). In regards to FBS and PPBS patients of group A showed better result than group B, but it was statistically insignificant (P value > 0.05) between the groups. In case of *avilamootrata* (urine turbidity), also group A showed better result than group B and the result was statistically significant (P value 0.002). **Conclusion:** *Guduchi churna (*powder of *Tinispora cordifolia*) administered during appropriate time showed statistically significant result in subsiding the cardinal symptom of *prameha* i.e. avilamootrata (urine turbidity).

Key Words: *Bheshaja sevana kala*, Chronotherapy, *Prameha*, *Guduchi*.

INTRODUCTION:

Bheshajasevanakala is a unique principle explained in the science of Ayurveda. Author Vagbhata has stated that *kalobhaisajya yoga krt*[1], which means appropriate timefulfills the aim of administration of medicine. Thus medicine given at appropriate time is more efficacious than one given at inappropriate time. Here medicine is intended to be released into the blood stream at a specific time to obtain utmost efficiency for tackling the disease condition. The physiological variation of *doshas* like increase in *vata* during end of the day, end stage of digestion and old age and pathological condition like exacerbation of diseases like *jwara* (fever), *kasa* (cough) and so on shows the variation of *doshas* in 24 hour period. Thus consideration of that particular time for the administration of medicine will indeed helps to get the desired effect of the treatment. In present era also the time of administration of medicine has been given importance in the name of chronotherapy. Synchrinozing the drug therapies with body rhythms will indeed improve the result of treatment and that is studied presently under "chronotherapeutics". Thus an appropriate time of administration of medicine will be conducive to the recovery of the disease. Hence implementation of *bheshajasevanakala* in each and every disease will be helpful to treat it in an appropriate way.

Among the types of *bheshaja Sevana kalas* mentioned in the classical textbooks of Ayurveda, *pragbhaktha oushada kala* is one which is indicated in *apanavata*[2] vitiation, *prataha adhobhakta oushada kaala* is indicated for *vyanavata*[3] vitiation. According to Sushruta samhita, the disease *prameha* is *vyana* and *apana vata* vitiated disorder. [4]
Thus the disease *prameha* was selected to assess the role of *pragbhaktha, prataha adhobhakta bheshaja Sevana kala*. *Guduchi* is said to mitigate all types of *prameha*.[5] The drug *Guduchi* (Tinospora cordifolia) is proved in animal models as antidiabetic. *Guduchi* is having bitter and astringent taste

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which are said to mitigate *kapha* (bodily humor) and *medas* (fat); the main culprits in the disease *prameha.* The drug is selected in the form of powder in the dose of 12gm per day based on the classical reference.[6] Thus the drug of choice for present study was *Guduchi churna*. With this background a clinical study was planned to analyse the role of *bheshajasevanakala* in the disease *prameha* vis-à-vis diabetes mellitus (type II).

OBJECTIVE OF THE STUDY:

To evaluate the efficacy of *bheshaja Sevana kala* in the disease *prameha* (diabetes mellitus, type II).

MATERIALS AND METHODS:

Drug: The trial drug was *Guduchi churna* (powder of *Tinospora cordifolia*).

METHODOLOGY:

Sample: 30 patients fulfilling the inclusion criteria were selected for the study by random sampling method.

Diagnostic criteria:

- Patients with FBS > 110 mg/dl and < 220 mg/dl
- Patients with PPBS > 140mg/dl and < 280 mg/dl
- *Prabhootamootrata*
- *Avilamootrata*

Inclusion criteria:

- Newly diagnosed patients of either sex between the age group 30 – 60 yrs with signs and symptoms of *prameha* (diabetes mellitus, type II) were selected for the study.
- Patients with FBS > 110 mg/dl and < 220 mg/dl.
- Patients with PPBS > 140 mg/dl and < 280 mg/dl.

Exclusion criteria:

- Patients of IDDM.
- Patients with other systemic ailments which interfere with the study.
- Pregnant women were excluded.

Sampling method: The patients who fulfilled the inclusion criteria were placed into two groups by random sampling method.

Table 1: Showing the intervention of the study.

Details	**Group 1**	**Group 2**
Drug	***Guduchi churna***	***Guduchi churna***
Time of administration	*Pragbhakta* → *Pratah*, *Sayam*; *Prataha adhobhakta*	Three times a day after food (TID)
Dose	4gm	4gm
Anupana (adjuvant)	Luke warm water	Luke warm water
No. of patients registered	15	15
Total duration of study is 30 days. Diet restriction was suggested for both the groups.		

Research design: An open ended randomized comparative clinical study.

Assessment tools: Investigations- FBS, PPBS, urine turbidity

Intervention: Patients coming under the inclusion criteria were grouped under two groups. The consent has been taken from each patient. The ethical clearance has been obtained from the ethical committee. Assessment was done on 0day, 15th day, and 30th day. (Table 1)

OBSERVATIONS:

In the present study among 30 samples, 14 patients were belonging to the age group of 41-50 (46.7%) years; 19(63.3%) and 11(36.7%) patients were belonging to the sex male and female respectively; 22 patients were non vegetarians; 16 (53.3%) patients were having *madhura rasa sathmyata* (habituated to sweet taste), 18(60%) patients were indulging in day sleep.

RESULTS:

Fasting blood sugar (FBS):

Table 2: Showing the results of mean FBS values on 0 day, 15th day and 30th day in both Group A and Group B.

	GROUP	**Mean**	**Std. Deviation**
FBS_0	Group A	144.2667	27.57708
	Group B	153.3333	31.51115
	Total	148.8000	29.45763
FBS_15	Group A	125.0000	23.47339
	Group B	136.3333	33.49129
	Total	130.6667	28.99505
FBS_30	Group A	111.6000	22.11270
	Group B	128.4667	25.71788
	Total	120.0333	25.07847

The improvement in the results of FBS in both group A and group B was highly significant (P value 0.000) but in between the group was insignificant (P value 0.643). (Table 2)

Post prandial blood sugar (PPBS):

Table 3: Showing the results of mean PPBS values on 0 day, 15th day and 30th day in both Group A and Group B.

	GROUP	**Mean**	**Std. Deviation**
PPBS_0	Group A	218.2000	37.90439
	Group B	237.8000	32.83552
	Total	228.0000	36.24153
PPBS_15	Group A	202.0667	43.48804
	Group B	222.3333	39.24951
	Total	212.2000	41.98719
PPBS_30	Group A	175.2000	35.87120
	Group B	204.8667	32.32837
	Total	190.0333	36.78782

The improvement in the results of PPBS in both group A and group B was highly significant (P value 0.000) but in between the group was insignificant (P value 0.570). (Table 3)

Urine turbidity

The intervention provided statistically significant (P value 0.002) results in urine turbidity in group A, but statistically insignificant results in group B (P value 0.123).

In the present study, fairly good results were observed in all the parameters of the study. There was no much difference in the result between the groups with regards to subjective parameters i.e. *prabhoota mootrata, pipasa, swedapravrutti, karapadadaha* and *supti, klama, kshuda*. In regards to FBS (53.3%), PPBS (13.3%) group A showed better result than group B but it was statistically insignificant (P value 0.643). Where as in the result of urine turbidity group A (60%) showed significant result than group B (P value 0.002). (Table 4)

Table 4: Showing effect of drug on urine turbidity.

GROUP		UT	
		Absent	Present
Group A	0 days	0	15
		0%	100.0%
	15 days	5	10
		33.3%	66.7%
	30 days	9	6
		60.0%	40.0%
Group B	0 days	0	15
		0%	100.0%
	15 days	0	15
		0%	100.0%
	30 days	2	13
		13.3%	86.7%

DISCUSSION:

Concepts narrated in Ayurvedic classics should be implemented in practice. One such concept is *bheshaja sevana kala* where in timely administration of medicine plays an important role in yielding the better result in treatment. The concept of *bheshajasevanakala* is applicable for all the diseases. But in classics particular *bheshajasevanakala* is mentioned only for few diseases. It is the duty of a physician to understand the core importance of this concept and implement in all the diseases after evaluating it. This is one such effort in bring out the most practically feasible *bheshajasevanakala* in a clinical condition like *prameha* to accelerate the recovery (maintaining the normal blood glucose level) of disease. The cardinal symptoms of *prameha* like *prabhootamootrata* (polyurea), *avilamootrata* (urine turbidity), *pipasa* (polydypsia), *kshuda* (polyphagia) , *swedapravrutti* (excessive sweating), *karapadadaha* (burning sensation in palms and soles) *supti* (numbness) and *klama* (fatigue) can be correlated with type II diabetes mellitus. In the disease type II diabetes mellitus the blood glucose level will be changing rhythmically within a day. Hence the disease seems more appropriate to test the efficacy of the medicine given at appropriate time.

***Bheshajasevanakala* and chronotherapy:** [7]

Both these concepts are dealing with the biological rhythmicity in living organisms.The knowledge of rhythmic temporal patterns is essential for effective Ayurvedic treatments. In chronotherapy, the maximum blood level of the drug is optimized in such a manner that its peak activity will match the time of greatest discomfort in patients. The drug optimization can be achieved through *bheshajasevanakala* also. The *bheshajasevanakala* is mainly governed by dominance of particular *dosha* (bodily humors*)* which is responsible for biological rhythms and is targeted for the treatment. The physiological and pathological variations of the 24 hour period in humans had been well described in the Ayurvedic texts in terms of doshic regulations. Hence consideration of proper time for the administration of medicine tends to reduce the side effects and to make the drug more bio-available. The effectiveness of many drugs varies depending on the dosage, administration time associated with 24 hours biological rhythm under the control of circadian clock**.** Thus the principles in both the concepts can be correlated.

In the present study maximum number of patients belonged to the age group of 41-50 years (46.7%). This reflects the onset and prevalence of *prameha* in middle age of life; majority of the patients (73.3%) had the habit of taking mixed diet which implies the prevalence is more among the people who consume non vegetarian diet. Majority of the people (60%) were habituated to sleep at day time. These points to the role of day sleep in manifestation of *prameha.*16 (53.3%) patients were having family history of *prameha.* This observation points to a hereditary nature of *prameha.*

Among 15 patients of group A, 8 were having normal range of FBS and 2 were having normal PPBS value after the treatment. But in group B, 4 patients were having normal range of FBS and none had normal PPBS value after treatment. The result was more significant in group A due to antihyperglycemic activity of *Guduchi* which was given in consideration with *bheshajasevanakala.* But statistically the change in the results of FBS and PPBS in both group A and group B was highly significant but in between the group was insignificant.

Out of 15 patients of group A, in all patients the urine turbidity was present before treatment. By the end of the treatment in 9 patients the urine turbidity was absent. Out of 15 patients of group B, in all patients the urine turbidity was present before treatment. By the end of the treatment in 2 patients the urine turbidity was absent.This shows the significant effect of the drug on cardinal feature of *prameha.* Unique results are seen in Group A. No doubt, the results are because of consideration of appropriate time for administration of medicine.

Probable mode of action of *bheshajasevanakala* and drug *Guduchi* on *prameha:*

Time of administration of medicine in *prameha* are *pragbhakta (pratah* and *sayam)* and *pratah adhobhakta*. The medicine which is administered before food acts on *apana vata, kapha dosha* and *medas* which are involved in the pathogenesis of the disease *prameha*. The medicine which is administered after food at morning helps to tackle the involved *vyana vata* in *prameha.* Thus *Guduchi* administered in consideration with *bheshajasevana kala* in the disease *prameha* acts on the involved *vyana, apana* and *kapha dosha* and medas and helps in pacifying the disease symptoms. *Guduchi* has *tikta-kashaya rasa* (bitter and astringent taste), *ushnaveerya* (hot potency), *tridoshaghna* (mitigates bodily humors), *rasayana* (rejuvinative), *pramehaghna* (mitigates diabetes mellitus), *medorogahara* properties. Berberine present in *Guduchi* has been shown to inhibit hepatic gluconeogenesis in diabetic rats. Berberine also has

hypolipidemic action which substantiates the *medohara* property of *Guduchi*.

Limitation and scope of *bheshajasevanakala*

Bheshajasevanakalas are meant only for *shaman oushadhis*[8] (pacifying medicines). And *bheshajasevanakalas* cannot be implemented in the emergency conditions.[9] This unique concept has to be analysed in terms of advanced technologies where in the action of the drug can be specifically understood.

CONCLUSION:

Medicine given at the appropriate time will be conducive for the better treatment. The *bheshaja Sevana kala* (time of administration of medicine) is mainly governed by dominance of particular *dosha* which is responsible for biological rhythms and is targeted for the treatment. The drug optimization can be achieved by administering the medicine in an appropriate time. For management of *prameha* (diabetes mellitus) the ideal *bheshajasevanakala* is *pragbhakta* and *pratah adhobhakta kala* as per the textual and clinical evidence. *Bheshajasevanakala* is having its own scope and application in the management of diseases. By incorporating proper *bheshajasevanakala* one can enhance the bioavailability, target the disease site and relieve symptoms.

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