

Preventive potentials of Agada Yoga in Necrotic Effect of Pit Viper Envenomation: An open label, single arm clinical study

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ABSTRACT

Pit viper envenomation leads to local tissue damage, particularly necrosis of skin, has become more significant problem. *Sigrū sireeshadi Yogaas Lepa* along with *Lodhra sheethadi Kashaya pana* are mentioned in *Prayogasamuchaya* and *Visha Vaidya Jyothsnika* respectively found clinically effective in treating *Mandali sarpa Damsa* w.s.r. to Pit viper envenomation and found effective in preventing necrotic effect in post envenomation, but scientifically not proved. Hence the present study was planned to evaluate the combined effect of *Sigrū sireeshadi YogaLepa* and *Lodhra seethadi Kashaya pana* in prevention of necrotic effect in *Mandali sarpa Damsa* w.s.r to pit viper envenomation.

METHODOLOGY: An open labelled, single arm clinical study with the history of *Mandali sarpa Damsa* w.s.r to pit viper envenomation was planned. Total 30 subjects satisfying diagnostic criteria were selected by convenient sampling method from OPD & IPD of Papinissery Visha Chikitsa Kendra, Kannur District, Kerala. *Sigrū sireeshadi Yoga* was applied as *Lepa* 6 th hourly and *Lodhra seethadi Kashaya pana* 15 ml bd was administered orally for three days. Standard scoring of cardinal symptoms was used to measure the efficacy of treatment before and after. Statistical analysis was done by using student's paired t- test.

RESULT: The study showed statistically significant effect with $P < 0.001$ in cardinal symptoms like Oedema (95%), Erythma (81%), Pain (95%) and Burning sensation (85%).

CONCLUSION: The combined effect of *Sigrū sireeshadi YogaLepa* and *Lodhra seethadi Kashaya pana* is effective in prevention of necrotic effect in *Mandali sarpa Damsa* w.s.r to pit viper envenomation.

KEY WORDS: *Shigrū sireeshadi Lepa*, *Lodhara seethadi Kashaya*, *Mandali sarpa Damsa*, Pit viper envenomation.

INTRODUCTION:

Vipers are classified into two as pit viper and pit less (Crotalinae & Viperinae subfamily) based on the presence or absence of a pair of loreal pit. The pits are temperature sensing organ. Number of incidence of bites is from Viper and pit viper bites are not rare. No monovalent anti venom is available against Indian Pit Vipers. Systemic involvement has been rarely reported and symptomatic treatment is the mode in Modern system of Medicine.¹

Hump nosed pit viper(HNV) (*Hypnale hypnale*)and Malabar Pit viper (*Trimerasurus malabaricus*)bites are important yet under recognized cause of morbidity & mortality in southern India. In Srilanka, this small pit viper is known as '*kunakatutuwa*'(referring to the necrotic effects at the bite site) in Sinhala². HNV accounts for between 27 and 77% of venomous snake bite in south western India. *H. hypnale* was identified as a common and dangerous source of envenoming, second only to Russell's Viper³.

Although formerly thought to result only in minor or local envenoming characterised by oedema, pain, burning sensation and erythema. Clinical manifestations of systemic envenoming by this snake include acute kidney injury, haematological manifestations, and other organ involvement, in some cases leading to death⁴.

Pit viper variety of snake is having common features and clinical presentations that of *Mandali Sarpa*. The main symptoms of *Mandali Damsa* are *Swayadhu Vedana Twakpeetathwam*, and *Daha*⁵. A vast description regarding snakes, divisions, symptoms and treatments are mentioned in Malayalam regional treatises. *Prayoga Samuchaya* and *Visha Vaidya Jyotsnika* are the common Malayalam regional treatises which mention much yogas in *Mandalidamsa Chikitsa* with various methods of administration.

Lepa(tropical application) and *Aushada*are among the 24 types of *visha* managementsubsidies the inflammation from local envenomation⁶. Hence the present study was planned to evaluate the efficacy of *Shigru sireeshadi Yoga* as *lepahave* been taken along with *Sigru Shireesadi Kashaya pana* in the management of *Mandali Damsha Visha* (Necrotic effects of Pit Viper Envenomation).

METHODOLOGY

Research design: An open labelled, single arm clinical study at outpatients and inpatients department in an Ayurveda hospital located in district headquarters southern Indian state of Kerala. Total 30 subjects satisfying diagnostic criteria were selected by convenient sampling method. *Sigru sireeshadi Yoga* was applied as *Lepa* 6thhourly and *Lodhra seethadi Kashaya pana* 15 ml bdwas administered orally for three days. Standard scoring of cardinal symptoms was used to measure the efficacy of treatment before and after. Statistical analysis was done by using student's paired t- test.

Source: 30 patients fulfilling the diagnostic and inclusion criteria was selected randomly from Papinissery Visha Chikitsa Kendram, Kannur, Kerala.

Ethical Clearance:The whole plan of study was approved by Institutional Ethics Committee (Approval no: PAMC/IECC/CT2012/dated 21.04.2012) prior to starting of work and an interim report on the status of research was also got approved in due course.

METHOD OF COLLECTION OF DATA

30 patients according to inclusion and exclusion criteria, diagnosed as Pit viper Envenomation were selected from out-patient and in patient department of *Pappinissery Vishachikitsa Kendram*, Kannur and were subjected to clinical study.

Diagnostic criteria: Subjects with Pit viper envenomation showing all four cardinal symptoms were selected.

Inclusion criteria: Subjects with essential symptoms of *Ruja*- pain, *Swayadu*-oedema, *Daha*- burning sensation and *Twakpeetathwam*, -erythema with pit viper envenomation after 2 hours were included. Subjects irrespective of age, gender, caste, religion and socio - economic status and normal BT & CT with negative 20 min WBC test were selected.

Exclusion criteria: Subjects having complications like coma, convulsions, unconsciousness and other systemic disorders with history of treatment for envenomation were excluded. Subjects having other skin lesions at the site of bite, trauma injury were also excluded. Subjects with abnormal BT & CT and positive 20 min WBC test were excluded.

Intervention: Selected subjects were treated in one group with *Sigru sireeshadi Yoga* was applied as *Lepa* 6th hourly and *Lodhra seethadi Kashaya pana* 15 ml bd was administered orally for four days, details of which are as below.

Drug: *Sigru sireeshadi Yoga*, *Lodhra seethadi Kashaya*

Source and authentication of raw drugs: The drug was selected from local areas and market after proper identification. Authenticity and preparation of *Sigru sireeshadi Yoga* and *Lodhra seethadi Kashaya* was done from PAMC, Parassinikadav

Method of preparation of Lepa choorna: The drugs *Sigru*, *Sireesha*, *Punarnava*, *Shunti* and *Aswagandha* were taken in equal quantity. 1 kilogram of each drugs were taken after expert authentication. These drugs are subjected to pulverization and made into fine powder and filtered and packed in 50 grams packs for easy dispensing. For 30 subjects 50 gms *Choorna* packs were given in 4 numbers each. (Table no 01)

Table 01: Intervention of Sigru Shireeshadi Lepa

PARTICULARS	DETAILS
Sample size	30
Drug application	0.5g/1cm ² of body area mixed with half of the quantity of thandulodakam
Temperature	Room temperature
Site	Over the area of oedema
Duration of lepa	From application to just before complete drying
Frequency	Four times with 6 hrs in between
Duration	3 days

Method of preparation of Kashaya: The drugs *Lodra*, *Seetha*, *Haridra*, *Daruharidra*, *Sarala*, *Manjishta Arka*, *Vilwa* And *Patala* were taken 300 gms each after authentication. These drugs were coarsely

powdered and 24 liters of water was added and heated and reduced to 6 liters. This *Kashaya* was bottled in 200ml bottles after adding allowed preservative to avoid spoilage.(Table no 02)

Table 02: Internal medicine-Lodraseethadi Kashaya

PARTICULARS	DETAILS
Drug	<i>Lodraseethadi</i>
Dosage form	<i>Kwatha</i>
Mode of use	Internal administration
Dose	15ml + 60ml boiled & cooled water bd
Duration between doses	12 hours
Time	Before food
Duration	3 days (6 doses)

Assessment: Assessment was done on the four cardinal symptoms: oedema, pain, burning sensation and erythema prior to treatment, after removal of first application 1st day 2nd day and 3rd day. After treatment assessment is made on 5th day. The overall relief obtained was assessed as follows. Subjective parameters: Graded in table 3; Assessment criteria: Described in table 4

Table 3: SUBJECTIVE PARAMETER GRADING

Grading	Pain	Burning sensation	Oedema observational	Erythma
0	No pain	No burning sensation	No oedema	None
1	Pain on pressure	Burning sensation, not continuous	Slight oedema	Barely perceptible
2	Continuous mild pain not disturbing	Continuous burning sensation, not disturbing	Slight, involving surrounding area	Slight redness
3	Moderate pain disturbing	Continuous, disturbing	Moderate, involving surrounding area.	Moderate redness
4	Severe, continuous, disturbing	Severe, continuous, disturbing	Severe oedema involving area	Severe Redness

Table 4: ASSESSMENT CRITERIA

Range	Remark
100 % relief	Cured
>75 % to 99 %	Marked improvement
>50 % to 75%	Moderate improvement.
>25 % to 50 %	Mild improvement
0 % to 25 %	Unchanged

Statistical tests used: The collected data was tabulated and analysed using graph pad in stat software. Demographic data and other relevant information was analysed with descriptive statistics. Continuous data was expressed in mean+/- standard deviation, and nominal and ordinal data was expressed in percentage. Statistical analysis was done student’s paired t- test The changes with P value<0.001 was considered as statistically significant.

OBSERVATION: Observation of symptoms are depicted in the table 5, 6, 7, 8

Table 5: EFFECT ON OEDEMA

Mean of BT	Mean of		Mean difference	%	Paired t test			
					S.D	S.E	T Value	p value
3.333	AT-1	2.467	0.867	26 %	0.346	0.0631	13.730	<0.001
3.333	AT-2	1.767	1.567	47 %	0.504	0.0920	17.026	<0.001
3.333	AT-3	1.000	2.333	70 %	0.661	0.121	19.338	<0.001
3.333	FU-1	0.200	3.133	94 %	0.629	0.115	27.293	<0.001

Table 6: EFFECT OF PAIN

Mean of BT	Mean of		Mean difference	%	Paired t test			
					S.D	S.E	T Value	p value
3.267	AT-1	2.400	0.867	26%	0.346	0.0631	13.730	<0.001
3.267	AT-2	1.467	1.800	55%	0.407	0.0743	24.233	<0.001
3.267	AT-3	0.500	2.767	85%	0.430	0.0785	35.226	<0.001
3.267	FU-1	0.167	3.100	95%	0.481	0.0878	35.325	<0.001

Table 07: EFFECT ON BURNING SENSATION

Mean of BT	Mean of		Mean difference	%	Paired t test			
					S.D	S.E	T Value	p value
3.567	AT-1	2.833	0.733	21%	0.450	0.0821	8.930	<0.001
3.567	AT-2	1.900	1.667	46%	0.479	0.0875	19.039	<0.001
3.567	AT-3	1.100	2.467	69%	0.571	0.104	23.647	<0.001
3.567	FU-1	0.533	3.033	85%	0.615	0.112	27.017	<0.001

TABLE 08: EFFECT ON ERYTHMA

Mean of BT	Mean of		Mean difference	%	Paired t test			
					S.D	S.E	T Value	p value
2.733	AT-1	1.933	0.800	29%	0.484	0.0884	9.049	<0.001

2.733	AT-2	1.367	1.367	50%	0.490	0.0895	15.272	<0.001
2.733	AT-3	0.833	1.900	70%	0.712	0.130	14.617	<0.001
2.733	FU-1	0.500	2.233	81%	1.006	0.184	12.156	<0.001

RESULTS: The therapeutic interventions showed its efficacy in Odema, Pain, Burning sensation, Erythma with statistically highly significant results ($p < 0.001$). Overall assessment tabulated in Table 9.

Table 09: OVERALL ASSESSMENT OF RESULTS

EFFECT OF THERAPY	STUDY GROUP	%
100% relief - Cured	5	16.666
>75% <100% - Marked improvement	24	80
>50% to 75% - Moderate improvement	1	3.333
>25% to 50% - Mild improvement	0	0
>0% to 25% - Unchanged	0	0

DISCUSSION: An attempt has been made to understand Pit vipers (*Hypnale hypnale* & *Trimeresures Malabaricus*) in Ayurvedic version by analyzing morphological and clinical presentations of the snake. Pit vipers (*Hypnale hypnale* & *Trimeresures malabaricus*) are described with or without brown/black flecks forming a pattern. This pattern resembles with *Mandala* of *Mandali*.

The cardinal symptoms selected for this study were Oedema, Pain, Burning sensation and Erythema induced from *Pit Viper* (*Hypnale hypnale* & *Trimeresures malabaricus*) bite. All four cardinal symptoms were tried to compute by using appropriate grading scale. In Ayurvedic classics also *Svayadhu* (oedema), *Daha* (burning sensation) *Twak Peethatwam* (erythema) and *Vedana* (pain) are explained as local manifestations of *Mandali Damsa*.

The overall effect shows both internal and external drugs will be reducing the cardinal symptoms due to pit viper envenomation significantly. Among the 30 participants 5 patients (17% approx.) had 100% relief from the cardinal symptoms. 24 patients (80%) had marked improvement, 1 patient (3%) had moderate improvement from the envenomation.

Swelling and bruising of the bitten limb result from increased vascular permeability induced by proteases, phospholipases, membrane damaging polypeptide toxins, hyaluronidase etc. Hyaluronidase splits acidic mucopolysaccharides and promotes the distribution of venom in the extracellular matrix of connective tissue⁷. Snake venom often contains various phospholipases A₂. These are esterolytic enzymes that break down membrane phospholipids such as lecithin i.e. phosphatidylcholine into fatty acids and lysolecithin. This causes cellular membrane damage in human beings; all these enzymes cause oedema, blister formation and local tissue necrosis⁸. The enzymes and toxins of venom cause local tissue destruction which itself is painful. Proteases and esterases release Bradykinin from plasma which is causative of pain⁹. Irritation of superficial sensory nerves causes burning sensation over the bitten area. Vaso dialation of the area causes redness⁸.

The *Lepa yoga* of *Sigru Punarnavadi Choorna* is aimed mainly on the treatment of *Sopha* due to the envenomation. The external medicine *Sigrusireeshadi Lepa Yoga* has five ingredients. Among them *Sigru*

is *Thikta Rasa Pradhana*, *Kaphavatahara* and has *Vishahara* property, acting on reduction of *Sopha* and *Ruja*. *Sireesha* is the best *Vishagna* drug and has *Sothahara* and *Vedanasthapana karmas*. *Punarnava* is *Kaphavatahara* with *Vranaropana Vrana Sodhanating* property there by reducing *Sopha*. The combined action will act on oedema and erythema. *Aswagandha* is a drug which posses *Madhura Rasa* and *Madhura Vipaka* and has the action of *Jwaraghna* and *Sophahara*. Since *Mandali* is having *Dosha* predominance of *Pitta* and *Aswagandha* will have an obvious influence on the symptoms of *Daha*. The drug *Shunti* has *Kaphavatahara* properties. Hence it will alleviate *Sopha* and *Ruja*.

The internal medicine is *Lodraseetaadi Kashaya* contains nine ingredients, they are *Tikta – Kashaya Rasa* predominant, *Tikta Rasa* itself is *Vishahara* by nature more or less pit viper (*Sopha Mandali*). *Visha* is *Pitta* predominant. Majority of the ingredients possess *Sophahara Karma*. On *Doshas* it shows predominantly *Kapha- Vaatahara* property. All these properties can be attributed to its *vishahara*, *Sophahara* and *Rujahara* properties. More or less in the text it is told that these combinations have anti snake venom property (*Kshelasaanthaye*).



FIGURE01:BITE MARK OF PIT VIPER



FIGURE 02:ERYTHMA



FIGURE 3: SWELLING



FIGURE 4:APPLICATION OF LEPA



FIGURE 5: BEFORE TREATMENT



FIGURE 6: AFTER TREATMENT

CONCLUSION

Combined action of *Lepa yoga* of *Sigru Punarnavadi Choorna* and *Lodraseetaadi Kashaya* has been found beneficial in three days treatment of Pit viper envenomation. The therapeutic action showed better results in cardinal symptoms like pain and swelling. The combined therapy has seized the progression of Pit viper envenomation necrotic changes that leads to loss of tissue by anti-inflammatory response. Hence, we can conclude the study that the therapy has preventive potentials on pit viper envenomated necrosis.

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