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An Open Label Single Arm Prospective Clinical Study on *Kousheyashma Bhasma* in *Apasmara* (Epilepsy)

Chaithra G G[1]*, Suhas Kumar Shetty[2], Nidhin M M[3]

[1-3]Department of Manovijnanaevammanasaroga, PG. Scholar, Department of Rasashastra3, Shri Dharmasthala Manjunatheshwara college of Ayurveda, Hassan, India

ABSTRACT

Apasmara comes under the group of *Shareeramano Adhistitha Mahavyadhi* which bears a striking similarity with the disease epilepsy characterized by recurrent seizures, paroxysmal event due to chronic, abnormal, excessive, hypersynchronous discharges from central nervous system. Present antiepileptic drugs control the epilepsy but long term use generates adverse effects at Neurobiological psychological cognitive and social consequences. Pharmaceutico-analytical study of *Kousheyashma Bhasma* (Magnesium silicates with good amount of iron, calcium, aluminum), along with its toxicity and animal study has been done, the same has proved its anti-epileptic activity. As a continuation of the study this clinical work was planned. In the present study *Kousheyashma Bhasma* was administered after *Virechana* therapy in a dose of 125 mg with cow's ghee twice a day after food for 30 days. Results showed statistically significant improvement in convulsive movements, fall during attack, frothing from the mouth, chattering of teeth and post ictal confusion. The inter-ictal duration was increased from 15 days to 2 months and average duration of attack was reduced from 1 minute to an average 30 seconds. Moreover, as *Bhasma* was administered with ghee through the buccal route, the drug delivery was ensured to be rapid. This paper explains the study with its results and discussions.

KEYWORDS

Apasmara, Epilepsy, KousheyashmaBhasma, Virechana.

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INTRODUCTION

Apasmara is included under the group of disease affecting both the mind and body. It is defined as Apagama of Smriti associated with Tamahpravesha and Bibhatsacheshta due to the derangement of Dhi (intellect), Satwa and Smriti (memory) bears a striking similarity with the disease epilepsy is considered as a condition with recurrent seizures having paroxysmal event due to chronic, abnormal, excessive, hypersynchronous discharges from central nervous system (CNS) neurons in the brain[1] with a variety of clinical and laboratory manifestations. Approximately 50 million people worldwide have epilepsy making it one of the most common neurological disease globally and estimated that 2.4 million people are diagnosed with epilepsy each year and in India the prevalence is between 5 and 40 per 1000 persons[2].

Apasmara is mentioned as Mahavyadhi[3] Hence management remains difficult. Before advising *Shamana Aushadhi* (palliative therapy), *Shodhana* (purificatory) therapy is essential. From the results of the previous study, it is evident that *Virechana* eliminates all morbid Doshas from all micro to macro *Dhatu* (channels) and thus regulates the Vata Dosha .Hence this study is planned to observe and establish the effectiveness of *Kousheyaashma Bhasma* after *Virechana* in the management of *Apasmara*.

In this study 31 patients of *Apasmara* were registered, out of which 20 patients completed the full course of treatment. The patients were assessed on the basis of symptoms of epilepsy for last 6 months before the intervention, after *Virechana,* after giving *Kousheyashma Bhasma,* during follow up at 3 months of treatment and follow up at 6 months, following results were noted. Results showed statistically significant improvement in the signs and symptoms of *Apasmara.*

AIMS & OBJECTIVES

To assess the Kousheyasma Bhasma in the management of Apasmara (epilepsy) with special reference to severity of the attack, duration of the attack, frequency of the attack & ictal phase.

METHODS & MATERIALS

Source of data: Patients attending the OPD and IPD of Manasa Roga, Sri Dharmasthala Manjunatheshwara College of Ayurveda and Hospital, Hassan.

Ethical Committee Approval Number SDM/IEC/31/2017-2018

CRITERIA OF EVALUATION

Diagnostic criteria: Samanya Lakshanas mentioned in Ayurvedic texts like loss of

memory & consciousness, feel of entering into darkness, disgusting physical movement of limbs, fall after convulsion, frothing coming from the mouth, up ward rolling of eyeballs, post ictal confusion.

Inclusion criteria: Who follow the instructions and sign the informed consent,17 to 60 years of age irrespective of gender and socio-economic status and patients who are not benefitted by taking epilepsy medicines without disturbing the antiepileptic medications

Exclusion criteria: Subjects with uncontrolled diabetes mellitus and hypertension, congenital abnormalities, Mental retardation, infectious diseases of brain, vascular causes, substance dependence and metabolic causes of seizures, space occupying lesion, pregnant woman and lactating woman.

Study Design: The study was an Open label single arm prospective clinical study inpatients attending the Out patient and in patient department of Manasa Roga, Sri Dharmasthala Manjunatheshwara College of Ayurveda and Hospital, Hassan. Twenty patients fulfilling the inclusion criteria were selected by convenient sampling method.

DRUG ADMINISTRATION: Initially patient was administered Panchakola Phanta in the dose of 50 ml tid for 3 days before food or till the attainment of Niraama Lakshan as. Later Brahmighrita was given to the patients in Aarohanamaatra till the attainment of Samayak Lakshana next for 7 days.

During Vishrama Kaala, Abhyanga with Moorchita Taila and Naadi Sweda was given for two days. On the third day, Virechana was performed with Trivruttaleha 60 gms and as per classical method. Samasarjana karma was followed based on the type of Shuddhi achieved. Then Kousheyashma Bhasma is adviced in dose of 125 mg BD after food with cows Ghee for 30 days.

ASSESSMENT CRITERIA: Samanya Lakshana of Apasmara, Severity of the attack, Frequency of the attack, Duration of the attack, Ictal features. Patients were assessed before the treatment, after Virechana, after Administering the Kousheyashma Bhasma, Follow-up at 3 months, Follow-up at 6 months.

INVESTIGATIONS: Complete blood count, Magnetic resonance imaging, Electroencephalography.

FOLLOW UP: Follow up at every month till 6 months after *Virechana Karma* and giving *Kousheyashma Bhasma.*

STATISTICAL ANALYSIS: Cochran's Q is used to analyze the significance of change in nominal and dichotomous data and Repeated measure ANOVA compares means across one or more variables that are based on repeated observations.

OBSERVATION

In the present study, out of 20 subjects, maximum number of subjects (n-7, 35%) were from the age group of 20-25 years and predominance of males (n-12, 60%) over females was found. Religion wise distribution showed that more patients were Hindus (n-18, 90%). Major percentage (n-14, 70%) of patients were unmarried.45% of patients in this study were students and 75% (n-15,) were from lower middle class. Maximum (n-14, 70%) patients were accustomed to use mixed diet. Patients (n-12, 60%) had disturbed sleep and many (n-10, 50%) reported sleep deprivation as triggering factor. Most of study subjects were found to be addicted to coffee (n-14, 70%) while (n-10, 50%) said to be tensed. A considerable percentage of cases (n-19, 95%) had negative history of consanguinity. Most of the people (n-9,45%) are on regular medication for the disease in the form of AED, some of them had not initiated any therapies while rest of them are on medication and discontinued the same. In this study 17 subjects consumed *Snehapana* for 5 days. 12 subjects had the history of *Madyama* Shuddhi, 7 subjects had *Pravara Shuddhi*,1 subject had *Avara Shuddhi.* 19 subjects got *Kaphanta* as *Antiki Shuddhi*.

RESULTS

Cochran's Q test was run on symptoms, at time interval of before treatment (where before treatment is considered as the history of symptoms for the last 6 months before enrolling into the study),after giving *Virechana*, after giving *Kousheyashma Bhasma*, follow-up at 3 months and follow-up at 6 months.

Table 1- Cochran's Q test showing the Effect of *Kousheyashma Bhasma* on Symptoms

Symptoms	Before treatment	Follow-up at 6 months	Cochran's q	P value	Remarks
Hallucinations	1	0	4.00	0.406	NS
Loss of consciousness	20	2	59.304	0.001	S
Self-regaining from the attack	20	1	62.844	0.001	S
Convulsive movement	20	0	64.622	0.001	S
Bhruprasphurana	20	5	64.622	0.001	S
Jihwaprasphurana	20	0	64.622	0.001	S
Padavikshepana	16	1	47.982	0.001	S
Fall	16	0	51.67	0.001	S
Epileptic cry	4	0	12.00	0.017	NS
Akshi Prasphurana	16	1	54.941	0.001	S
Hasta Vikshepana	16	0	51.333	0.001	S
Chattering of the teeth	9	0	27.238	0.001	S
Froathing from the mouth	17	0	56.973	0.001	S
Post ictal confusion	12	0	44.480	0.001	S

Cochran's Q test was run on loss of consciousness, it was significant with Cochran's Q value 59.304,self-regaining from the attack with cochran's Q value 62.844,convulsive movement with Cochrane q value 64.622,Bhrupraspurana at Cochrane value 51.590, *Jihwaprashpurana* with Cochrane q value 51.625,*Padavikshepana* at Cochran q value 47.982,Fall with Cochrane value 51.667,*Akshiprasphurana* with Cochran's Test value 54.941, *Hastavikshepana* with Cochran's Test value 51.333,chattering of the teeth with Cochrane value 27.238,frothing from the mouth with Cochran's Q value 56.973,Post ictal confusion at Cochran q value 44.480 and all these symptoms showing p value less than 0.001after follow-up of 6 months suggesting it is statistically significant.

Repeated measure Anova test was run on average duration of the attack, interval between the attack and number of attacks

Table 2 Repeated measure ANOVA test on average duration of the attack, interval between the attack and number of attacks

Symptoms		N	Mean	Green house geisser			Green House geisser Error df	Remarks
				Df	F value	P value		
Average duration ofthe attack	BT	20	2.05	2.373	22.897	0.001	52.460	S
	AV		0.00					
	KB		0.25					
	FU 3 MONTHS		0.50					
	FU 6 MONTHS		0.25					
Interval between the attack	BT	20	3.05	2.029	29.354	0.001	38.542	S
	AV		0.00					
	KB		0.05					
	FU 3 MONTHS		1.00					
	FU 6 MONTHS		0.10					
Number of attack	BT	20	3.10	1.117	31.436	0.001	21.219	S
	AV		0.00					
	KB		0.24					
	FU 3 MONTHS		0.57					
	FU 6 MONTHS		0.05					

It is found that mean value of the average duration of attack at BT is 2.05, from BT to after *Virechana* the mean value is reduced to 0.00, BT to after giving *Kousheyashma Bhasma*, it is 0.25 , BT to FU at 3 months is reduced to 0.50 and BT to FU at 6 months mean duration is reduced 0.25 seconds. It is also statistically significant with green house geisser value 52.460, at BT is 2.05, from BT to after *Virechana* the mean value is reduced to 0.00, BT to after giving *Kausheyashma Bhasma*, it is 0.25 , BT to FU at 3 months is reduced to 0.50 and BT to FU at 6 months mean duration is reduced 0.25 seconds. It is also statistically significant with green house geisser value 38.542 and p value less than 0.001, Number of attack at BT was 3.10, then from BT to

after *Virechana* is 0.00, BT To after giving *Kousheyashma Bhasma* mean value reduced to 0.224, BT to FU at 3 months it is 0.571 and BT to FU at 6 months mean duration reduced to 0.05 seconds. All these symptoms are statistically significant with p value less than 0.001.

DISCUSSION

Apasmara (Epilepsy) is a common neuropsychiatric disorder with major public health problem all over the world. Convulsive activities lead to neuronal cell loss; therefore, timely treatment is essential.Though advances in drug research introduced so many drugs for its management, but all remained anti-seizure rather than reverting the pathology, in this regard, to have an effective drug mentioned in classics for the easy management of *Apasmara*, this present clinical study has been conducted.

DISCUSSION ON RESULT

SEVERITY OF THE ATTACK: In the present study Cochran's Q & Repeated measure ANOVA test shows significant results in severity of the attack, at the end of follow up period at 6 months. Improvement was observed in loss of consciousness, convulsive movements, fall, epileptic cry, tongue bite, tingling of eyelids, frothing from the mouth chattering of teeth and post ictal confusion[5]. Most of the symptom like loss of consciousness, convulsive movements, fall, tingling of eyelids, found in *Vataja Apasmara*. The drug *Kousheyashma Bhasma* as wel *Ghrita* contains *Madhura Rasa* (*Sadindriya Prasadaniya*)[6] enables relative proportionality of both *Jnanendriya* as well as *Karmendriya* and (Prasadana) tranquilizes the mind thus pacify the *Prana, Udana & Vyana Vata*.

The Pitta located in the *Hridaya* known as *Sadaka Pitta*en ables the *Manas to* perceive the things clearly helps to overcome the post-ictal confusion (*DhiSatwasamplava*)[7].*Buddhivaisheshika* type of *Alochaka Pitta* concerned with intellectual faculties and these are regulated by *Sheeta Veerya* of *Kousheyashma Bhasma* and *Ghrita*[8].

Kousheyashma Bhasma on single and repeated administration is effective against MES induced seizures as indicated by the reduction in the duration of hind limb extension and clonic convulsions. The efficacy of *Kousheyashma Bhasma* against MES seizure is more pronounced on chronic administration suggesting that the drug has cumulative effect. These results are comparable to the effects produced by the standard drug sodium valproate. This indicates that, as *Kousheyashma Bhasma* is

effective in generalized tonic-clonic seizures in human beings[9].

DURATION OF ATTACK: In the present study decrease in the duration of attack was found like before the treatment patinets had histroy attack for average of 1 minute which ws reduced 15 minutes with minimal ictal & postictal symptoms. It significant after administering *Kousheyashma Bhasma* after *Virechana*. The proven anticonvulsant action of the drug helps in reducing the duration of the attack.

***FREQUENCY OF ATTACK*:** number of attack was reduced after administering *Kousheyashma Bhasma* after *Virechana*

Along with these observations there is considerable changes found in headache, sleep pattern, quality of life, social and personal adaptations among the subjects.

DISCUSSION ON PROBABLE ACTIONS OF THE DRUGS

Apasmara is mentioned as *Mahavyadhi* Hence management remains difficult. Before advising *ShamanaAushadhi*, *Shodhana* therapy is essential. From the results of the previous studies,it is evident that *Virechana* eliminates all morbid *Doshas* from all micro to macro *Dhatu* (channels) and thus regulates the *Vata Dosha*[10].Hence in this study, After *Deepana Pachana* with *Panchakola Phanta, Brahmi Ghrita* was given to the patients in *Aarohanamaatra* till the attainment of *Samyak Snigdha Lakshanas,* later *Virechana* was performed. *Samsarjana Krama* was followed according to the type of *Shuddhi* achieved. After *Samsarjana Krama, Kousheyashma Bhasma* in a dose of 125 mg with cow's Ghee two times a day after food for 30 days and the effect was observed on different signs & symptoms.

Brahmi Ghrita-The drug Brahmi extract is believed to reduce the rate of seizures as well increase the level of serotonin and gamma-aminobutyric acid. These two chemicals in the brain that are thought to regulate pyramidal neurons and interneurons that initiate epileptic activity[11].

Virechana- Virechana helps in cleansing other *Dosha* in the body. In the patients of *Apasmara*, *Virechana* has the quality to eliminate both vitiated Pitta and *Kapha* and thus removes *Avarana*, which obstructs the path of *Vata* .During *Virechana* process, the inflammation of intestinal mucosa leads to hyperemia and exudation resulting into increased passage of protein-rich fluids through vessel walls to intestinal lumen. Increase in fluid volume also results in the dilution of toxic material. Evacuation of the fluid from *Rasa-Rakta* by *Virechana* is the direct process that leads to evacuation of toxins[12].

Kousheyashma Bhasma is given with Cow's Ghee in the study. Bhasma is a nanoparticle and ghee has the Samskaraanuvartana Guna which is rich in lipid soluble active principles. Water soluble drugs is usually distributed in the extracellular spaces and it may not readily diffuse in to CSF and other body cavities, while the lipid soluble drugs are rapidly distributed throughout the intra and extra cellular spaces. Ghrita contains DHA (docosahexaenoic acid) and omega 3 long chain poly unsaturated fatty acid. It is known to have antioxidant property which acts upon the degenerative brain cells and balance the neurotransmitter[13].

Along with the lipid soluble molecules, Bhasma also have the capacity to cross the Blood Brain Barrier thus increasing the availability of active principles in the brain. It is observed even more with change in the route of administration, the availability is made fast that is the buccal route was utilised. This might be the probable reason that the medicine worked so effectively in reducing the severity, duration and frequency of attack with short span of time[14].

Route of Administration of the drug- According to the modern point of view, buccal administration applied in the buccal area diffuse through the oral mucosa and enter directly into the bloodstream. buccal administration may provide better bioavailability of some drugs and a more rapid onset of action compared to oral administration because the medication does not pass through the digestive system and thereby avoids first pass metabolism[15].

Haritamanjari- Acalyphaindica as a *Bhavanadravya*- Studies suggest that the *Acalyphaindica* leaf extract has shown significant decrease in the duration of tonic hind limb extension suggesting the anticonvulsant effect. The performance results indicate that methanolic extract of *Acalyphaindica*f rom leaf have potential anticonvulsant activity. It has been suggested that convulsions are associated with oxidative damage. Acalypha also has strong antioxidant property[16].

PROBABLE MODE OF ACTION OF KOUSHEYASHMA BHASMA - AYURVEDIC PERSPECTIVE

Apasmara is a disease in which mainly *Manas* is afflicted by deranged rajas and *Tamas* and the major *Dosha* involved is *VataD osha*. All kind of *Chesht as* mainly *Bhibhatsa Cheshta* caused due to *Vata. Kousheyashma Bhasma* brings down Vata due to its *Madhura rasa*.The vitiation of *Sadhaka* and *Alochaka Pitta* are regulated by *Sheeta Veerya* of *Kousheyashma Bhasma. Tarpakakapha* resides in Shiras does *Snehana* and Tarpana of Indriyas. The reference of *Snehana* and *Tarpana* has been

interpreted by *Dalhana* as "*Sneha* means *Majja* of the *Mastaka* and *Tarpaka Kapha* nourishes the *Indriya.* By applying the theory of similarity, *Sneha* quality of *Ghrita* helps in pacifying the *Lakshanas of Apasmara*[17, 18].

By these *Kousheyashma Bhasma* regulates Vata & Pitta and thereby breaking the Samprapti of *Apasmara.*

MODERN PERSPECTIVE:

Kousheyashma mineralogically identified as asbestos and studies proven that it contains magnsesium silicate, calcium an iron as chemical elemen.

Magnesium is one of the essential elements required in normal diet. studies have shown that people with epilepsy have low systemic Mg concentration. Low Mg concentration can produce spontaneous ictal-like events consisting of a tonic firing phase and a phase of clonic-like discharges. Magnesium is a potential modulator of seizure activity because of its ability to antagonize the excitatory calcium influx through the N-Methyl-D-aspartate (NMDA) receptor[19].

Hypocalcemia enhances neuromuscular excitability throughout the body. Calcium concentration may inhibit zinc potentiation of AMPA current which in turn inhibits excitatory response from glutamate transmitters[20].

Iron deficiency may play an important role in inducing seizures as it decreases the GABA inhibitory neurotransmitter due to change in its metabolism. Reduces enzymes such as monoamine and aldehyde oxidases and Impairs oxygenation and energy metabolism of the brain[21].

Table:3 Action of drugs

Drug	Rasa	Guna	Veerya	Vipaka	Action
KousheyashmaBhasma	*Madhura*	*Sheeta*	*Sheeta*		Epilepsy,paralysis,fever, headache,anemia,urinary diseases.
Haritamanjari (*Acalyphaindica*)	*Tikta*	*Laghu, Ruksha*	*Ushna*	*Katu*	*Shirashoola,Vibandha,* Anti-convulsant activity, methanoicextract act as CNS depressant and induces the sleeep
Ghrita	*Madhura*	*MruduSnigda*	*Sheeta*	*Madhura*	*VataPittaShamaka, Agni Deepana, Medhya, Svarya, Balya, Vrushya, Chakshushya, Rasayana*

CONCLUSION

The following conclusion is drawn in respect to the results obtained from the present stud. *Kousheyashma Bhasma* in a dose of 125 mg with cow's ghee two times a day after food for 30 days After *Virechana* therapy is statistically significant in most of the symptoms like convulsive movements, fall during attack, frothing from the mouth, chattering of teeth and post ictal confusion and the inter-ictal duration was increased for example from 15 days to 2 months and average duration of attack was decreased from 1 minute to an average 30 seconds. Moreover, as *Bhasma* administered with ghee at the buccal route, the drug delivery was ensured to be rapid.

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