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A CLINICAL STUDY TO EVALUATE THE EFFECT OF KRIMIMUDGARA RASA IN MANAGEMENT OF KRIMIROGA WITH REFERENCE TO INTESTINAL HELMINTHIASES

Neenu V. Kuzhikandathil¹, Sreejith Satheesan^{2*}, Sudharmini S³

¹PG Scholar, Department of PG Studies in Kaumarabhritya, Alva's Ayurveda Medical College, Moodbidri, Karnataka, India

²Assistant Professor, Department of Shalyatantra, Dharma Ayurveda Medical College, Sriperumbudur, Tamil Nadu, India

³Rtd. Associate Professor of Entomology, Department of Community Medicine, Government Medical College, Thiruvananthapuram, Kerala, India

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*Corresponding author

E-mail: dr.sreejith.satheesan@gmail.com

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ABSTRACT

The present study was undertaken to evaluate the efficacy of Krimimudgara Rasa, adapting Samshamana as the line of management of krimiroga (helminthiasis) in children, described by Acharya Charaka. A simple randomized controlled clinical trial was conducted among 40 randomly selected children of 6-12 years age, suffering from krimiroga and at least showing the symptom Udarashoola (abdominal pain) and presence of ova/cysts/worms of intestinal helminthes on microscopic stool examination. Krimimudgara Rasa 100mg (trial drug) was administered to 20 such children. Another set of 20 children were administered with Mebendazole 100mg (control drug). All children were subjected to clinical examination for signs and symptoms and parasite positivity, before treatment, on 7th day and 14th day after treatment. Krimimudgara Rasa and Mebendazole have produced almost same level of reduction of signs and symptoms in patients of both groups. There was no significant difference in the rate of reduction of clinical symptoms, as all the p-values of Unpaired t-test were >0.01. Patients of both groups became completely asymptomatic and negative for ova/cysts of worms on 14th day of treatment. The study has proved the efficacy and safety level of the trial drug and has established that Krimimudgara Rasa is found to be an effective safe alternative anthelmintic drug for soil transmitted intestinal helminthiasis.

Keywords: Krimiroga, Helminthiasis, Krimimudgara rasa, Mebendazole, Anthelmintic drug.

INTRODUCTION

Helminthiasis is infestation with one or more intestinal parasitic worms like Round worm (*Ascaris lumbricoides*), Whip worms (*Trichuris trichiura*) or Hook worms (*Necator americanus* and *Ancylostoma duodenale*)¹. World Health Organization (W.H.O) considers pre-school and school aged children as high risk population² for soil transmitted intestinal helminthes. Hence the agency has recommended for deworming once in every six months for every individual in childhood period. But many anthelmintic drugs used have developed resistance and have side effects like toxic or allergic reactions. Several herbal as well as herbo-mineral formulations in Ayurveda are described for the treatment of worm infections. But there is no clinical evidence about their efficacy and safety. Therefore Ayurvedic researches in this particular context can aid to achieve the global target³ of W.H.O to eliminate morbidity due to soil transmitted helminthiasis of children by 2020.

Samshamana⁴ (palliation) is one among the line of management of Krimiroga according to Acharya Charaka which is easier to be administered in children. Krimimudgara Rasa mentioned in Yogaratnakara⁵ being a rasa preparation, is potent-enough for short term administration which is comparable to that of Albendazole and Mebendazole in modern medicine. Moreover, all the ingredients of this yoga namely, Rasa⁶ (purified mercury), Gandhaka⁷ (purified sulphur), Ajamoda⁸ (*Trachyspermum roxburghianum*), Vidanga⁹ (*Embelia ribes*), Vishamushtika/ Kupeelu¹⁰ (*Strychnos nux-vomica*) and Palasa beeja¹¹ (*Butea monosperma*) are said to have Krimighna (anthelmintic)

property. This study has evaluated the efficacy of Krimimudgara Rasa in the management of Krimiroga especially intestinal helminthiasis, during the months of October-November 2015.

MATERIALS AND METHODS

In this clinical study the diagnostic criteria of Krimiroga and its treatment modality were assigned with reference to the classical literature from Ayurvedic and Allopathic Medicines. The diagnostic criteria included children having Udarashoola (abdominal pain) in association with two or more general features of Krimi¹² namely, Bhakthadwesa (aversion to food), Sadana (exhaustion), Jwara (fever), Vivarnatha (discoloration), Gudakandu (anal itching) and presence of ova/cysts/worm of *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus*, *Ancylostoma duodenale* or *Enterobius vermicularis*, in microscopic stool examination.

The drugs used in the study were Krimimudgara Rasa 100mg tablet (trial drug) and Mebendazole 100mg tablet (control drug). Krimighna property of the Krimimudgara Rasa is also mentioned in Rasashastra classics like Rasakamadhenu¹³, Rasa Jala Nidhi¹⁴, Rasendra Sara Sangraha¹⁵ and Bhaishajyaratnavali¹⁶. Shodhana (purification) of all the six ingredients and preparation of 100mg tablet of Krimimudgara Rasa was carried out as per the methods adopted for its standardization and quality control¹⁷ of the formulation. The trial drug was prepared in the pharmacy facility of Nangelil Ayurveda Pharmacy, Kothamangalam, Ernakulam, Kerala.

The control drug used in this study i.e.:100 mg tablet of Mebendazole or (5-benzoyl-1H-benzimidazole-2-yl)-carbamic acid methyl ester) belongs to the organic compounds benzophenones. It is a synthetic broad-spectrum anthelmintic used in the treatment of intestinal helminths¹⁸. This drug required for the study was procured from pharmacist's counters.

Study Design and Sampling

The Simple Randomized Controlled Clinical Trial¹⁹ (RCT) was the study design adopted to envisage the present research work. The study population was from among those children who attended the Kaumarabhritya out-patient department of Alva's Ayurveda Medical College Hospital, Moodbidri, Karnataka, India and from health camps conducted among schools in and around Koothattukulam and Elanji, Ernakulam District, Kerala, India. A total of 40 children suffering from Krimiroga (infested with either Round worm, Whip worm, Hookworm or Pin worm) and fulfilling the inclusion criteria were randomly selected as study subjects. They were assigned into two groups: Group-A (control) and Group-B (trial), each group with 20 children who were recruited strictly adhering to the guidelines of Indian Council of Medical Research (ICMR)²⁰ and International conference of Harmonization - Good Clinical Practices Guidelines (ICH-GCP)²¹ with Institutional Ethical Committee Clearance (No. 25/96/2010-AWD dated 20/12/2012).

Inclusion Criteria

- Children of age group between 6-12 years irrespective of sex, religion, socio-economic status and food habits.
- Children having Udarashoola in association with two or more symptoms of Krimi.
- Children diagnosed with infestation of *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus*, *Ancylostoma*

duodenale and/or *Enterobiu svermicularis* by microscopic stool examination.

Exclusion Criteria

- *Ascaris* infestation with complication such as intestinal obstruction, pulmonary eosinophilia, cholecystitis and pancreatitis²².
- Microscopic stool examination positive to ova, cyst, or larval forms of intestinal protozoans (*Entamoeba histolytica*, *Entamoeba coli*, *Giardia lamblia*); Tape worms (*Taenia solium*, *Taenia saginata*, *Echinococcus granulosus*); and also Filarial worms (*Wuchereria bancrofti*, *Brugia malayi*).

Administration of Drug and Observation of Patients

Each child of control group (Group-A) was given one tablet of Mebendazole 100mg, twice daily for 3 consecutive days. In the trial group (Group-B) each child was given one tablet of Krimimudgara Rasa 100mg, twice daily for 3 consecutive days. Before starting the administration of the drugs, all the children of both the study groups were subjected to clinical examination. Subjects were further examined for clinical symptoms on 7th day after treatment. Follow up was done on 14th day after drug administration (i.e. 2 weeks after treatment) and all the subjects of both groups were observed for any clinical symptoms.

Laboratory Investigation

Stool samples of the subjects were examined²³ before starting treatment, and after 7th and 14th day of treatment.

Collection and Recording of Data

A pre-tested proforma was used to record the observations according to assessment criteria. Approximate grading was given for the variables in assessment criteria to correctly evaluate the outcome. Axillary temperature²⁴ was taken to record fever²⁵ of the patients.

Table 1: Grading for the assessment parameters of the study

Udarashoola	Bhaktadwasha	Sadana	Gudakandu	Presence of Ova/Cyst/Worm
0 – Absent	0 – Absent	0 – Absent	0 – Absent	0 – Absent
1 – Present	1 – Present	1 – Present	1 – Present	1 – Present
Jwara ²⁵			Vivarnatha	
0 – Normal Body Temp. [36.1 - 37.2°C] or [97 - 99°F]			0 – Absent [Normal skin]	
1 – Fever [>37.5 or 38.3°C] or [99.5 or 100.9°F]			1 – Mild [Only on face]	
2 – Hyperthermia [>38.3 or 39.4°F] or [101 - 103°F]			2 – Moderate [Any half of the body]	
3 – Hyperpyrexia [>40 or 41.5°C] or [>104 or 106.7°F]			3 – Severe [All over body, distinct patches]	

Analysis of Data

The data collected according to the assessment criteria were analysed using Student's t-test. Paired t-test was done to find out the effect of drug after treatment within a same group. Unpaired t-test was applied to compare the effects of the two drugs, between control and trial groups. The outcome measurements of the study were calculated as the mean score of symptoms between before treatment and 7th and 14th day after treatment.

RESULTS

All the 40 children subjected to clinical trial had Udarashoola (abdominal pain) as a major sign and symptom of Krimiroga (helminthiasis) and all were found positive to ova/cyst when stool samples were examined prior to drug administration. Other signs and symptoms complained by them included Vivarnanatha (97.5%), Bhaktadwasha (95%) Sadana (85%), Gudakandu (37.5%) and Jwara (22.5%). Stool sample examination revealed that the subjects were infected with *Enterobius vermicularis* (37.5%), *Ascaris lumbricoides* (20%), *Trichuris trichiura*

(17.5%), *Ancylostoma duodenale* (15%) and *Necator americanus* (10%).

The p-values of the paired t-test for the symptoms excepting Jwara (fever) and Gudakandu (anal itching) remained <0.01. Hence the decrease in mean scores of these symptoms is found to be statistically highly significant. Decrease in the mean score of Jwara noticed among the patients treated with Mebendazole (Table 2) was found to be statistically significant as the p-values were <0.05. But among those treated with Krimimudgara Rasa (Table 3), they became symptom-free only on 14th day of treatment. The decrease in mean score of Jwara noticed on 7th day of treatment is not significant as p-value is >0.05. Patients of control and trial groups were noticed to have decrease in Gudakandu by one week after treatment, but this reduction was not statistically significant as the p-value of paired t-test was >0.01.

Results of the unpaired t-test applied to make a comparison of the effect of treatment between Group-A and Group-B on 7th day (Table 4) using the mean difference of before treatment and 7th

day after treatment (BT-7D) showed that the p-values for criteria Udarashoola (abdominal pain), Bhaktadwasha (aversion to food), Sadana (exhaustion), Jwara (fever), Vivarnata (discolouration), Gudakandu (anal itching) and Presence of ova/cysts/worms in microscopic stool examination are > 0.01. Hence the difference observed between the mean values of all the criteria appear to be statistically not significant while

comparing the effects of the two drugs on the 7th day after treatment. Similar results were obtained while unpaired t-test was applied to compare the effects of treatment between Group-A and Group-B on 14th day (Table 5). The unpaired p-values of the assessment criteria were >0.01.

Table 2: Effect of Mebendazole on Assessment Criteria (Group – A)

Mean of BT	Mean of		Mean difference	%	Paired 't'			
					SD	SE	t value	P - value
Udarashoola								
1	7 D	0.30	0.700	70	0.470	0.105	6.658	< 0.0001
1	14 D	0.10	0.900	90	0.307	0.068	13.077	< 0.0001
Bhaktadwasha								
0.95	7 D	0.30	0.650	68.42	0.489	0.109	5.940	< 0.0001
0.95	14 D	0.10	0.850	89.47	0.366	0.081	10.376	< 0.0001
Sadana								
0.95	7 D	0.25	0.700	73.68	0.470	0.105	6.658	< 0.0001
0.95	14 D	0.10	0.850	89.47	0.366	0.081	10.376	< 0.0001
Jwara								
0.35	7 D	0.05	0.300	85.71	0.470	0.105	2.854	0.0102
0.35	14 D	0	0.350	100	0.587	0.131	2.666	0.0153
Vivarnatha								
1.55	7 D	0.65	0.900	58.06	0.307	0.068	13.077	< 0.0001
1.55	14 D	0.15	1.400	90.32	0.502	0.112	12.457	< 0.0001
Gudakandu								
0.40	7 D	0.25	0.150	37.50	0.366	0.081	1.831	0.0828
0.40	14 D	0	0.400	100	0.502	0.112	3.559	0.0021
Presence of Ova/ Cysts/ Worms								
1	7 D	0.35	0.650	65	0.489	0.109	5.940	< 0.0001
1	14 D	0.10	0.900	90	0.307	0.068	13.077	< 0.0001

BT – Before treatment; 7D – 7th day after treatment; 14D – 14th day after treatment; SD – Standard Deviation; SE – Standard Error

Table 3: Effect of Krimimudgara Rasa on Assessment Criteria (Group – B)

Mean of BT	Mean of		Mean difference	%	Paired 't'			
					SD	SE	t value	P - value
Udarashoola								
1	7 D	0.25	0.750	75	0.444	0.099	7.550	< 0.0001
1	14 D	0.20	0.800	80	0.410	0.091	8.718	< 0.0001
Bhaktadwasha								
0.95	7 D	0.20	0.750	78.94	0.444	0.099	7.550	< 0.0001
0.95	14 D	0.15	0.800	84.21	0.410	0.091	8.718	< 0.0001
Sadana								
0.75	7 D	0.30	0.450	60.00	0.510	0.114	3.943	0.0009
0.75	14 D	0.05	0.700	93.33	0.470	0.105	6.658	< 0.0001
Jwara								
0.20	7 D	0.10	0.100	50	0.447	0.100	1.000	0.3299
0.20	14 D	0	0.200	100	0.523	0.117	1.710	0.1036
Vivarnatha								
1.55	7 D	0.75	0.800	51.61	0.410	0.091	8.718	< 0.0001
1.55	14 D	0.20	1.350	87.09	0.587	0.131	10.283	< 0.0001
Gudakandu								
0.35	7 D	0.20	0.150	42.85	0.366	0.081	1.831	0.0828
0.35	14 D	0	0.350	100	0.489	0.109	3.199	0.0047
Presence of Ova/ Cysts/ Worms								
1	7 D	0.45	0.550	55	0.510	0.114	4.819	0.0001
1	14 D	0.20	0.800	80	0.410	0.091	8.718	< 0.0001

BT – Before treatment; 7D – 7th day after treatment; 14D – 14th day after treatment; SD – Standard Deviation; SE – Standard Error

Table 4: Comparison of Effects of Treatment Between Group - A and Group - B on 7th day

Assessment Criteria	Mean of BT – 7D		Mean Difference	Standard Deviation		t-value	Unpaired p-value
	Group A	Group B		Group A	Group B		
Udarashoola	0.70	0.75	0.500	0.470	0.444	0.345	0.7315
Bhaktadwasha	0.65	0.75	0.100	0.489	0.444	0.676	0.5027
Sadana	0.70	0.45	-0.250	0.470	0.510	1.611	0.1154
Jwara	0.30	0.10	-0.200	0.470	0.447	1.378	0.1761
Vivarnata	0.90	0.80	-0.100	0.307	0.410	0.871	0.3888
Guda Kandu	0.15	0.15	0.000	0.366	0.366	0.000	>0.9999
Presence of Ova/ Cyst/ Worms	0.65	0.55	-0.100	0.489	0.510	0.632	0.5309

BT – Before treatment; 7D – 7th day after treatment; Group-A – Control; Group-B – TrialTable 5: Comparison of Effects of Treatment Between Group-A and Group-B on 14th day

Assessment Criteria	Mean of BT – 14D		Mean Difference	Standard Deviation		t-value	Unpaired p-value
	Group A	Group B		Group A	Group B		
Udarashoola	0.90	0.80	-0.100	0.307	0.410	0.871	0.3888
Bhaktadwasha	0.85	0.80	-0.050	0.366	0.410	0.406	0.6867
Sadana	0.85	0.70	-0.150	0.366	0.470	1.125	0.2675
Jwara	0.35	0.20	-0.150	0.587	0.523	0.853	0.3990
Vivarnata	1.40	1.35	-0.050	0.502	0.587	0.289	0.7739
Guda Kandu	0.40	0.35	-0.050	0.502	0.489	0.318	0.7517
Presence of Ova/ Cyst/ Worms	0.90	0.80	-0.100	0.307	0.410	0.871	0.3888

BT – Before treatment; 14D – 14th day after treatment; Group-A – Control; Group-B – Trial

DISCUSSION

In this clinical study the most common parasitosis of patients was due to *Enterobius vermicularis* (pin worms) followed by *Ascaris* and Hookworms. Though the life span of the pinworms is brief, longstanding infections occur due to continuous reinfection²⁶. In addition to the presence of abdominal pain, other major clinical symptoms like aversion to food, discolouration and exhaustion were observed in majority of the children. These clinical findings also get support from samprapti (pathogenesis) proposed for Krimiroga²⁷.

The present study revealed that the signs and symptoms due to worm infestation among the children were significantly reduced by the effects of treatment with trial drug (Krimimudgara Rasa) and control drug (Mebendazole). Both these drugs were found to be equally effective in decreasing the symptoms Udarashoola, Bhaktadwasha and Sadana. Due to Shoolaghna (analgesic) property of Ajamoda (*Trachyspermum roxburghianum*) and Vidanga (*Embelia ribes*) present in Krimimudgara Rasa, worms are made immobile and dead later, which are gradually eliminated, thereby reducing the pain. This drug has Krimighna²⁸ (anthelmintic), Kandughna, Shoola Prashamana (analgesic), Deepana²⁸ (stomachic) as well as Pachana²⁸ (digestive) properties owing to its ingredients. All the contents are helpful in increasing digestive power by improving Agni and also creating a hostile environment inside the gastro intestinal tract (GIT), later removing the parasites and reducing the symptoms of Krimiroga.

Strychnine and Embeline are the characterising compounds which are biologically or therapeutically active principles in Krimimudgara Rasa²⁹. Strychnine strengthens the muscles of stomach and expels worms from the body. Embeline is responsible for anthelmintic activity exhibited by this drug. In the case of control drug, it is established that the principal mode of action for Mebendazole³⁰ is by its inhibitory effect on tubulin polymerization, which results in decreased production of adenosine triphosphate (ATP). Due to diminished energy production, the parasites are immobilized and eventually die. In

the light of these modes of actions of both the drugs, it is also understood that the effects of trial drug and control drug were almost similar in reducing clinical symptoms and decreasing parasitic load in stool samples of treated patients.

Effect of Krimimudgara Rasa in reducing Jwara (fever) was not found satisfactory on 7th day after treatment, even though the drug produced good effect on 14th day of treatment. In contrast, the drug Mebendazole could make a significant reduction in Jwara (fever) from before treatment to 7th and 14th day after treatment. Gudakandu (anal itching) was persisting among patients of both groups still on 7th day of treatment. All those patients became symptom-free on 14th day of treatment only. This could be due the fact that in pinworm infection, adult female worm^{31,32} oviposits around 11,000 to 16,000 eggs at a time at the perianal region resulting in autoinfection. This leads to more new generations of young worms which are also resistant^{33,34} to drugs.

As the unpaired t-test showed no significant difference between the effects of treatment among children administered with Mebendazole and Krimimudgara Rasa, it can be inferred that the trial drug (Krimimudgara Rasa) is also effective as the control drug (Mebendazole), which is an established anthelmintic drug recommended by WHO.

CONCLUSION

Treatment with Krimimudgara rasa has produced striking effects in reducing all the clinical symptoms assessed in the study except fever. The trial drug also proved beneficial in eliminating the ova/cysts/worms of helminths which was evident in microscopic stool examination. These findings also established that Samshamana (palliative) method is also effective in treating Krimiroga, which has been described by Acharya Charaka along with Apakarshana (extraction), Prakriti Vighata (disruption of pathogenesis), Nidana Parivarjana (avoiding causative factors) and Samshodhana (evacuation of doshas). Since no significant difference was noticed in the unpaired t-test between the effects of treatments with Krimimudgara Rasa and Mebendazole, it can

be inferred that Krimimudgara Rasa (trail drug) is found to be as effective as Mebendazole (control drug) in treating Krimiroga. The trial drug is also found to be absolutely free from any sort of side effects or adverse reactions in its therapeutic dose and duration. Thus the present clinical study proves that Krimimudgara rasa can be used as a safe and effective alternative anthelmintic drug for soil-transmitted intestinal helminthiasis. It can also be used therapeutically for short durations just like the well-established anthelmintic drug Mebendazole.

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