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Research Article

A CLINICAL EVALUATION OF THE EFFICACY OF "AMRITSAAR LOHOKTA DOSHANIWARAK DRAVYAS" IN THALASSAEMIA MAJOR PATIENTS WITH RESPECT TO ITS EFFECT ON IRON OVER-LOADING

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ABSTRACT

Background: Thalassaemia Major a hereditary blood disease, widespread in the Mediterranean countries, Asia and Africa and mortality is primarily due to iron overload. Here, we present a clinical study to evaluate the efficacy of 'Amritsaar Lohokta Doshaniwarak Dravyas' Thalassaemia Major Patients with respect to its effect on iron overload.

Methods:-In this study, Thalassaemia patients having age-group of 5 to 14 years were selected irrespective of their sex & religion. A total number of 40 patients were taken for the study and were randomly placed in Group A & Group B. The study was carried out for 21 days.

The Group A patients were administered Deferiprone 20mg/kg body weight and Lohadosh Niwarka Yogin the dose of 3gm / day. Trial was conducted for twenty one days and follow-up was taken after every seventh day. Patients of this group were told to eat '*Petha' two* pieces (approx 50gms) every day as a *Pathya.* The group B patients were administered Deferiprone20 mg/kg body weight. These patients were also told to follow the same dietary changes already advised by the Thalassaemia Day Care Centre.

Result: Effect on *Arochaka*, *Mandagni, Angamard, Fatigue,* Joint Pain, Abdominal Pain, Dyspnoea, Pallor, IBS, Recurrent URTI, SGPT, Sr. Urea, Sr. Creatinine in Group A were statistically highly significant and Group B showed statistically non significant results.

Effect on splenomegaly in Group A was statistically significant and in Group B was statistically non significant. Effect on Hepatomegaly in Group A and in Group B was statistically non significant.

Conclusion: The *Lohadosh Nivaraka yoga* shows distinct activity. It significantly improves the general condition, helps to reduce splenomegaly and ferritin levels, boosts immunity and reduces debility. Hence it can be concluded that *Lohadosh Nivaraka Yoga* is good complementary medication in Thalassaemia.

Keywords: *Amritsaar Lohokta Doshaniwarak Dravyas*, Thalassaemia, Iron overload, Deferiprone.

INTRODUCTION

Thalassaemia Major a hereditary blood disease, widespread in the Mediterranean countries, Asia and Africa, in which here is an abnormality in the protein part of haemoglobin molecule. For the successful treatment of Thalassaemia, it requires two key elements- Blood Transfusion and Iron Chelation. Regular blood transfusion considerably expands the life span of patients. Due to regular blood transfusions the iron accumulates in the body. The cause of death of these patients in 2nd and 3rd decades of life is the iron overload[1]. For this they have to depend on the iron chelating agents to reduce the iron overload due to disease or excess blood transfusion and also due to excess dietary absorption of iron from gut, to compensate the large turnover of red cell mass[2].

Desferrioxamine is the gold standard in the management of iron overload, besides this it has not become popular particularly in the developing countries and is being used in only 10% to 15% of thalassaemics in our country. This is mainly due to high cost and the need for continuous subcutaneous injection over 6 to 8

hours[3]. Hence, need is felt to formulate a dosage form which can reduce iron overload, cost effective and convenient to administer.

Need of the study

- A major problem encountered in the management of Thalassaemia is iron overload.
- The most common cause of death in 2nd and 3rd decade of life is iron overload.[1]
- There are around 65,000- 67,000 Thalassaemic patients in our country and about 1,00,000 children are born worldwide with Thalassaemia every year[14].
- The cost of iron chelators which are available is high and not easy to administer, some of them also have some side effects.

METHODS

Aims and Objectives

1. To evaluate the effect of test drug *Lohadosh Niwaraka Yog* in iron overloading of Thalassaemic patients.

Contents of Trial Drug

The symptoms of iron overload in Thalassaemia closely resembles with the hazardous effects of improperly incinerated *Loha*.[4,5] While mentioning its treatment *Ayurved Prakash* advocates the use of *Agastipatrabhavita Vidang* with the *Anupana* of *Agastipatraswarasa* [6,7,8]. *Triphala*, *Trikatu* as told in '*Chakradatta Rasayana* Chapter under '*Amritsaar Loha'*[9] for minimizing the ill effects of iron on body. *Mustak* is also told in treatment of hazardous effects of *loha*[10]. As *Yavaksharais dipan, pachan* and *mutral* was also added[11]. *Kushmanda* is mentioned in the '*KakarashtakVarga*[12] and also in the *'Lohasevinam Varjaniyani'*[13] whose administration has been contra-indicated during the *lohabhasma* consumption and *Rasa aushadhi* consumption. The *Kushmanda* was given in this study with the *Lohadosh Niwarak Yog* as a *Pathya.* This study was conducted individually though it was related with one of the Thesis work.

Table 1: Contents of *Lohadosh Niwaraka Yog*

No.	*Ayurvedic Name*	Latin Name	Part Used
1	*Haritaki*	*Terminalia chebula*	Fruit
2	*Bibhitak*	*Terminalia bellirica*	Fruit
3	*Amalaki*	*Emblicaofficinalis*	Fruit
4	*Shunthi*	*Zinziberofficinale*	Ryzome
5	*Marich*	*Piper nigrum*	Fruit
6	*Pippali*	*Piper longum*	Fruit
7	*Vidanga*	*Embeliaribes*	Fruit
8	*Mustak*	*Cyperusrotundus*	Ryzome
9	*Agasti*	*Sesbania grandiflora*	Leaves
10	*Yava*	*Hordiumvulgare*	*Kshara*

Criteria for selection of patients

1. Patients having the signs and symptoms of Thalassaemia were selected irrespective of their sex, religion and occupation.
2. A detailed proforma was prepared and detailed history and physical examination was carried out.
3. An informed written consent of the patient was taken before the commencement of clinical trials.
4. Lab investigations like CBC and Hb count, LFT, RFT and Serum ferritin etc. were carried out before & after the study.

Exclusion Criteria

1. Patients suffering from cardiac disorders and anemia due to any other cause were debarred from the present study.
2. Those patients having complications like Hepatitis-B and other viral infections etc were also excluded.

Grouping

Selected patients were divided into two groups randomly with 20 patients in each group.

The study was conducted at Thalassaemia Unit, JK Lon Pediatrics Hospital, S.M.S Medical College Jaipur during the period of May 2010 to Jan 2011.

Group A: Trial Drug *Lohadosh Niwarak Yog* + The chelator advised by Thalassaemic Unit (Kelfer) Deferiprone.

Group B: The chelator advised by Thalassaemic Unit (Kelfer) Deferiprone.

Posology-Dose

Group A: 3 gm trial drug in suitable dosage form will be given + Kelfer

Group B: Kelfer

Anupana: Water

Pathya: *Kushmanda* will be told to be taken in the form of '*Petha'* as a *pathya* two pieces daily only in group A patients.

Duration: Twenty one days.

Follow up: Patients were reviewed after 7 days.

Criteria for Assessment: Assessment of the treatment was done on the basis of.

1. Relief in subjective and objective signs and symptoms and improvement in general health of Thalassaemic patients.

   a) Subjective improvement-All the patients registered for clinical trial were looked for any changes in their clinical manifestations and growing feeling of well being.

   b) Objective improvement was evaluated through laboratory investigations like CBC, Hb count, LFT, RFT and Serum Ferritin etc.

2. Statistical analysis

The information gathered on the basis of classical symptomatology was subjected to statistical analysis in terms of mean (X), standard deviation (SD) and standard error (SE). **Wilcoxon matched paired single ranked test** and **Student 't' test** was carried out at P<0.05, P<0.01, P<0.001 significance level. The obtained results were interpreted as.

Insignificant	:	P<0.05, P<0.1
Significant	:	P<0.01
Highly Significant	:	P<0.001

Scoring pattern

To evaluate the drug efficacy the following scoring pattern was adopted for the present study.

1. *Aruchi* (Anorexia)

Absent	:	0
Taking normal diet, without any interest	:	1
Taking the food without interest and unable to complete it all the time	:	2
Not interested in taking food, resisting or crying while feeding	:	3

2. Mandagni

Normal, feel hungry within 4 hrs. of food intake	:	0
Feel hungry after > 4 to 6 hrs. of food intake	:	1
Feel hungry after > 6 to 8 hrs. of food intake	:	2
Does not feel hungry even after 12 hrs. of food intake	:	3

***3. Angamarda* (Body ache)**

No body ache	:	0
Body ache after moderate work but relieved by rest	:	1
Body ache after mild work but relieved by res	:	2
Continuous body ache does not relieved by rest	:	3

***4. Balakshaya* (Fatigueness)**

Normal active child	:	0
Playing and activities are reduced	:	1
Feeling of tiredness while playing	:	2
Easy fatigability while playing	:	3

5. *Sandhi Shoola* (Joint pain)

No joint pain	:	0
Pain involve only one extremity	:	1
Pain involve both the extremity	:	2
Involvement of almost all the joints of body	:	3

6. *Udarshoola* (Abdominal pain)

No abdominal pain	:	0
Mild cramping pain only before blood transfusion	:	1
Moderate cramping pain before transfusion and lasting for few days after transfusion	:	2
Continuous abdominal pain with Irritable bowel syndrome	:	3

7. Dyspnoea

No sign of Dyspnoea	:	0
Slight Dyspnoea after heavy work relieved by rest	:	1
Dyspnoea on slight exertion like walking	:	2
Dyspnoea even at rest	:	3

***8. Panduta* (Pallor)**

No pallor	:	0
Pallor with shallow pink	:	1
Pallor with slight yellowish tint	:	2
Pallor with ash yellowish tint	:	3

9. *Pleehavriddhi* (splenomegaly)

Non palpable spleen	:	0
Mild splenomegaly (palpable up to 2 cm with mild tenderness)	:	1
Moderate splenomegaly (palpable up to 4 cm and tender)	:	2
Massive splenomegaly (palpable > 4 cm and tender)	:	3

10. *Yakritvriddhi* (Hepatomegaly)

Non palpable Liver	:	0
Mild Hepatomegaly (palpable up to 2 cm with mild tenderness)	:	1
Moderate Hepatomegaly (palpable up to 4 cm and tender)	:	2
Massive Hepatomegaly (palpable > 4 cm and tender)	:	3

11. Irritable bowel syndrome

Stool with normal frequency and consistency	:	0
2 to 3 normal motion / day with feeling of incomplete evacuation	:	1
3 to 4 normal motion / day with feeling of incomplete evacuation	:	2
> 4 per day which is unformed and watery	:	3

12. Recurrent respiratory tract infection

At interval one week or below	:	0
At interval between 7 to 15 days	:	1
At interval between 15 to 45 days	:	2
At interval > 45 days	:	3

RESULTS

Table 2: Wilcoxon matched paired single ranked test

Variable	Group	Mean		Mean Diff.	% Relief	SD±	SE±	p	S
		BT	AT						
Arochaka	Gr. A	1.15	1.2	0.95	82	0.82	0.18	0.0001	HS
	Gr. B	1.25	1.15	0.10	8	0.30	0.06	0.5	NS
Mandagni	Gr. A	1.85	0.50	1.35	72.97	0.48	0.10	0.0001	HS
	Gr. B	1.75	1.60	0.15	8.57	0.36	0.08	0.25	NS
Angamard	Gr. A	1.7	0.5	1.2	70.58	0.41	0.09	0.0001	HS
	Gr. B	1.7	1.5	0.2	11.76	0.52	0.11	0.25	NS
Fatigue	Gr. A	2.25	0.9	1.35	60	0.67	0.15	0.0001	HS
	Gr. B	2.2	2	0.2	9.09	0.52	0.11	0.1563	NS
Joint Pain	Gr. A	1.75	0.65	1.1	62.8	0.64	0.14	0.0001	HS
	Gr. B	2	1.9	0.1	5	0.44	0.1	0.9999	NS
Abdominal Pain	Gr. A	1.55	0.4	1.15	74.19	0.67	0.15	0.0001	HS
	Gr. B	1.35	1.1	0.25	18.51	0.55	0.12	0.1250	NS
Dyspnoea	Gr. A	1.2	0.5	0.7	58.33	0.57	0.12	0.0002	HS
	Gr. B	1.25	1.15	0.1	8	0.30	0.06	0.500	NS
Pallor	Gr. A	2.1	1.1	1	47.61	0.64	0.14	0.0001	HS
	Gr. B	2.15	1.9	0.25	11.62	0.44	0.09	0.0625	NS
Splenomegaly	Gr. A	1.25	0.95	0.3	24	0.47	0.10	0.0313	S
	Gr. B	0.85	0.8	0.05	5.88	0.22	0.05	0.9999	NS
Hepatomegaly	Gr. A	0.85	0.6	0.25	29.41	0.44	0.09	0.0625	NS
	Gr. B	0.8	0.8	0	0	0.32	0.07	0.9999	NS
IBS	Gr. A	0.85	0.15	0.7	82.35	0.65	0.14	0.0005	HS
	Gr. B	0.9	0.8	0.1	11.11	0.30	0.06	0.500	NS
Recurrent URTI	Gr. A	1.35	1.55	0.8	59.25	0.41	0.09	0.0001	HS
	Gr. B	1.7	1.5	0.2	11.76	0.52	0.11	0.2500	NS

(HS: Highly Significant S: Significant NS: Non Significant)

Table 3: Intergroup Comparison Mann-Whitney Test

VARIABLE	Group	Mean Diff.	SD±	SE±	P	S
Arochaka	A	0.95	0.80	0.18	0.0001	HS
	B	0.10	0.30	0.06		
Mandagni	A	1.35	0.48	0.10	<0.0001	HS
	B	0.15	0.36	0.08		
Angamard	A	1.2	0.41	0.09	<0.0001	HS
	B	0.2	0.52	0.11		
Fatigue	A	1.35	0.67	0.15	<0.0001	HS
	B	0.2	0.52	0.11		
Joint Pain	A	1.1	0.64	0.14	<0.0001	HS
	B	0.1	0.44	0.10		
Abdominal Pain	A	1.15	0.67	0.15	<0.0001	HS
	B	0.25	0.55	0.12		
Dyspnoea	A	0.70	0.57	0.12	0.0004	HS
	B	0.10	0.30	0.06		
Pallor	A	1.00	0.64	0.14	0.0003	HS
	B	0.25	0.44	0.09		
Splenomegaly	A	0.30	0.47	0.10	0.0420	S
	B	0.05	0.22	0.5		
Hepatomegaly	A	0.25	0.44	0.09	0.0541	NS
	B	0.00	0.32	0.07		
IBS	A	0.70	0.65	0.14	0.0010	S
	B	0.10	0.30	0.06		
Recurrent URTI	A	0.80	0.41	0.09	0.0002	HS
	B	0.20	0.52	0.11		

Effect of Drug on Laboratory Parameters

Hematological Investigations

Patients were advised to go for lab investigation before & after Treatment. Data collected was analyzed & students **Paired t Test** was applied.

Table 4: Hematological Investigations

Variable	Group	Mean BT	Mean AT	Mean Diff	% imp	SD±	SE±	t	P	S
Hb%	A	7.34	7.375	0.03	0.4	1.78	0.39	0.07	0.10	NS
	B	6.79	6.95	0.15	2.28	1.51	0.33	0.458	0.10	NS
TRBC	A	2.66	2.85	0.18	6.83	1.04	0.23	0.78	0.10	NS
	B	2.47	2.53	0.065	2.63	0.51	0.11	0.563	0.10	NS
TLC	A	8.88	9.87	0.98	11.12	3.63	0.81	1.21	0.10	NS
	B	5.79	6.14	0.352	6.07	2.23	0.50	0.70	0.10	NS
N	A	45.66	46.32	0.66	1.44	9.62	2.15	0.30	0.10	NS
	B	46.99	49.08	2.09	4.45	13.86	3.10	0.67	0.10	NS
L	A	46.97	48.75	1.78	3.80	14.16	3.16	0.56	0.10	NS
	B	49.02	47.64	1.38	2.81	11.87	2.65	0.51	0.11	NS
M	A	3.81	4.66	0.84	22.14	3.20	0.71	1.17	0.10	NS
	B	3.68	4.42	0.74	20.10	2.48	0.55	1.32	0.10	NS
E	A	0.14	0.085	0.06	41.37	0.22	0.05	1.18	0.10	NS
	B	0.75	0.25	0.5	66.66	1.57	0.35	1.41	0.10	NS
PLT	A	308.9	284.2	24.75	8.011	73.59	16.45	1.504	0.10	NS
	B	201.4	244.4	43.05	21.37	161	36.09	1.19	0.10	NS
MCV	A	84.19	83.46	0.73	0.867	7.33	1.63	0.44	0.10	NS

	B	84.26	84.73	0.465	0.55	6.23	1.39	0.33	O.10	NS
MCH	A	27.46	27.47	0.015	0.054	2.89	0.64	0.023	0.10	NS
	B	27.55	27.16	0.39	1.41	1.72	0.38	1.01	0.10	NS
MCHC	A	32.63	32.41	0.215	0.658	2.30	0.515	0.416	0.10	NS
	B	32.09	32.00	0.085	0.264	1.47	0.33	0.257	0.10	NS

(HS: Highly Significant S : Significant NS: Non Significant)

Table 5: Table showing Results in Serum Parameters in both Groups

Variable	Group	Mean BT	Mean AT	Mean Diff	% imp	SD±	SE±	t	P	S
Sr. Ferritin	A	4006	3485	521	13.00	719.2	160.8	3.239	0.001	S
	B	4060	3546	513.7	12.65	803.2	179.6	2.86	0.01	S
SGPT	A	83.3	63.1	20.2	24.25	27.63	6.18	3.268	0.01	S
	B	96.2	87.1	9.1	9.45	17.69	3.95	2.29	0.05	NS
Sr. Urea	A	29.2	23.3	5.9	20.20	7.77	1.73	3.39	0.01	S
	B	30.35	26.4	3.95	13.01	6.54	1.46	2.70	0.02	NS
Sr. Creatinine	A	0.763	0.693	0.070	9.23	0.100	0.022	3.130	0.01	S
	B	0.774	0.747	0.027	3.55	0.149	0.033	0.825	0.10	NS

(HS: Highly Significant S: Significant NS: Non Significant)

- Effect on *Arochaka*, *Mandagni, Angamard, Fatigue,* Joint Pain, Abdominal Pain, Dyspnoea, Pallor, IBS, Recurrent URTI in Group A was statistically highly significant. In Group B showed statistically non significant results.
- **Effect on splenomegaly**: In Group the effect was statistically significant. In Group B statistically non significant.
- **Effect on Hepatomegaly**: In Group A and Group B the effect was statistically non significant.

DISCUSSION

Intergroup Comparison by Mann-Whitney Test

The present clinical trial is a comparative clinical study. So to access comparison between the efficacies of two therapies intergroup comparison was done. As the variables are nonparametric we used **Mann-Whitney Test** for statistical analysis & the obtained results are as follows.

The intergroup comparison showed that there is statistically highly significant difference in efficacy of both treatments on *Arochaka*, *Mandagni, Angamard, Fatigue,* Joint Pain, Abdominal Pain, Dyspnoea, Pallor and Recurrent URTI. It also showed that there is significant difference in efficacy of both treatments on splenomegaly and IBS. There is no statistical significant difference in efficacy of both treatments on hepatomegaly.

Effect of Drug on Laboratory Parameters

Hematological Investigations: Patients were advised to go for lab investigation before & after Treatment. Data collected was analyzed & students **Paired t Test** was applied. This showed that **No significant** change was observed on any haematological parameters.

Results in Serum Parameters in both Groups

Sr. Ferritin: Group A Mean Sr. Ferritin before treatment was changed from 4006 to 3485 having 13% improvement which is statistically **significant.** Group B Mean Sr. Ferritin before treatment was changed from 4060 to 3546 having 12.65% improvement which is statistically **significant.**

SGPT: Group A Mean SGPT before treatment was changed from 83.3 to 63.1 having 24.25% improvement which is statistically **significant.** Group B Mean SGPT before treatment was changed from 96.2 to 87.1 having 9.45% improvement which is statistically **non-significant.**

Sr. Urea: Group A Mean SGPT before treatment was changed from 29.2 to 23.3 having 20.20% improvement which is statistically **significant.** Group B Mean SGPT before treatment was changed from 30.35 to 26.4 having 13.01% improvement which is statistically **non-significant.**

Sr. Creatinine: Group A Mean Sr. Creatinine before treatment was changed from 0.76 to 0.69 having 9.23% improvement which is statistically

significant. Group B Mean Sr. Creatinine before treatment was changed from 0.77 to 0.74 having 3.55% improvement which is statistically **non-significant.**

Probable Mode of action

According to Ayurveda

This condition is caused by vitiation of *Tridosha.* The drugs *Haritaki, Aamalaki* are *Tridoshashamaka*, *Bibhitakikaphahara, Shunthi*, *Marich, Pippali, Vidanga* are *Kapha, Vatashamaka, Musta* and *Agasti* are *Kapha pitta shamaka, Kushmanada Vatapittahara* and *Yavakshara Kaphahara*. In this condition the *Angimandya* is also there, so *Dipan* is the *Chikitsa. Amalaki, Haritaki, Marich, Vidanaga* are *Agnidipan Dravyas.*[15] *Vidanga* and *Agasti* are helpful in reducing the *Lohadosh* by *Prabhava.*[7],[16]

According to modern science

- Polyphenolic compounds, tannins present in the herbal drugs and element calcium are supposed to inhibit the absorption of iron.
- Polyphenolic compounds reportedly have a wide range of effects in vivo and in vitro, including antioxidant and metal-chelating activities [17].
- They promote the healing of tissues and prevent free-radical oxidative damage.
- In present drug *Haritaki*[18], *Bibhitaki*[19] and *Vidanga*[20] contain tannins and thereby reducing the absorption of iron.
- It is reported that Embelline in *Vidanga* showed iron chelating activity in some of the *Lauha* preparations like *Vidangadi Lauha*, *Saptamrit Lauha* etc.[21]
- Apart from tannins the *Haritaki*[22] contains polyphenolic compounds which also help in inhibition of iron absorption from the food.
- *Kushmanda contains calcium. It a*cts as competitive antagonist to iron and therefore it also minimizes the absorption.
- The contents like *Pippali* and *Maricha* contain piperine as one of the constituent make the drugs like *Haritaki, Bibhitaki, Aamalaki* and *Kushmanda* biologically more available. The piperine may also help to improve the bioavailability of the modern iron chelators.[23]
- Antioxidants and essential nutrients enhance the chelation process by replacing the small losses of beneficial minerals that are removed during chelation. They promote the healing of tissues and prevent free-radical oxidative damage. As with the chelating agents, the antioxidants in test drugs help neutralize free radicals that are formed by a variety of oxidizing agents.

CONCLUSION

1. This preparation did not impart any side effect; *Lohadosh Niwaraka Yog* at the given dose was well tolerated by the patient without any undesirable side effect of Nausea, Vomiting etc.
2. In the experimental group the serum ferritin levels are reduced and no any adverse drug reactions were seen suggesting that the drug has not caused any drug interaction or have not interfered with the action of Kelfer.
3. From the results obtained it is concluded that the *Lohadosh Niwaraka Yog* used as a supportive treatment so that the general health of the patient should be maintained.
4. Splenomegaly is seen in many patients of Thalassaemia, as this drug has helped to reduce the spleen size it has to be recommended for this purpose in the regular treatment.
5. The associated symptoms like *Agnimandya, Arochak,* and recurrent URTI etc. are well managed with this treatment.
6. This type of integrated approach is helpful in treating diseases like Thalassaemia.
7. The lowering of SGPT implies that the drug has good action on liver. Also the serum urea, creatinine values are also reduced which shows that this trial drug has action on kidney function also.

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