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Ayurvedic management of Thalassemia Major-A review of clinical researches conducted at IPGT & RA, Jamnagar

Review Article

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Abstract

Thalassemia Major is the most common single gene disorder which represents a major health burden worldwide. The available treatment modalities in conventional medicine i.e. blood transfusion (BT) and iron chelation therapies are associated with complications while bone marrow transplantation etc. are out of reach of many. Present study is aimed to highlight the effective role of *Ayurvedic* medicines i.e. *Dhatri Avaleha, Triphaladi Avaleha* and *Musta-Triphaladi Avaleha* in the management of Thalassemia Major. Till date total five clinical researches have been carried out on Thalassemia Major at PG level in the department of *Kaumarbhritya* at IPGT&RA, Jamnagar. In which a simple random sampling method was followed. Patients were divided into two groups, Group A (Trial group with Ayurvedic drug intervention and BT) and Group B (Control Group with BT and iron chelation therapy). Assessment was done based on the subjective and objective parameters after completion of treatment. The data obtained in clinical studies was analyzed by using suitable statistical tests. The trial drugs were found to be effective on subjective, objective criteria, BT interval and general health status of Thalassemic patients as well as clinically safe.

Key words: *Beejadushtijanya Pandu, Dhatri Avaleha, Triphaladi Avaleha, Musta-Triphaladi Avaleha.*

Introduction

Thalassemias are a group of inherited disorders of hemoglobin synthesis that results from an alteration in the rate of globin chain production.(1) It is an inherited autosomal recessive blood disease where in genetic defect (deletion) results in reduced rate of synthesis or no synthesis of one of the globin chains that makes up hemoglobin. This causes formation of abnormal hemoglobin molecules, thus causing anemia the characteristic presenting symptom of Thalassemia.

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Types:

On the basis of clinical manifestations, Thalassemia classified as Thalassemia Major, Thalassemia Intermedia and Thalassemia Minor.

1) **Thalassemia Major:** It is the most severe form of congenital hemolytic anemia. It is characterized by transfusion dependent anemia, splenomegaly, bony deformities, growth retardation and hemolytic faces.

Survival is depends on regular blood transfusion.

2) **Thalassemia Intermedia:** It is of intermediate degree of severity that does not require regular blood transfusion.
3) **Thalassemia Trait (Minor):** It is a mild asymptomatic condition in which there is moderate suppression of β-chain synthesis. Patients need very little medical care except for the genetic counseling.

Epidemiological features:

As per WHO estimate, 4.5% of the world populations are carriers of hemoglobinopathies. Over 180 million people in the world, more than 20 million in India carry β Thalassemia gene. Frequency of Thalassemic gene in Indian population varies from 0-17% in different ethnic groups with average of over 3%. It is prevalent among Gujarati (Lohana, Kachchhi, Bhanushali, Mahera), Punjabi, Sindhi, Agri (Mumbai), Goud Saraswat etc. communities.(2) The figure of Thalassemic patients in Gujarat is 3,000. The Thalassemia centre at GG Hospital, Jamnagar alone has a record of more than 250 Thalassemia Major children who are undergoing the conventional treatment.(3)

Present day medical approach and its limitations:

The various treatment modalities available for Thalassemia Major and their limitations are described below:(4)

- **Blood transfusion (BT) therapy:** The medical management of Thalassemia is aimed at maintaining Hb% level between 10-12 gm/dL. A post transfusion Hb level of 9.5 gm/dL is said to be sufficient to maintain active life. So for this, BT therapy is the only treatment which results in hemosiderosis (iron overload) as a complication. Other major complications are those related to transmission of infections i.e. Hepatitis B, C and HIV.
- **Splenectomy:** It should be considered when annual blood requirement exceeds 1.5 times the basal requirement for a patient maintaining pre transfusion Hb about 10 gm/dL, massive spleen enlargement posing a risk of splenic rupture or when splenic enlargement is associated with left upper quadrant pain. Splenectomy should be delayed till the patient is 5 years of age as there is a risk of overwhelming sepsis below this age.
- **Iron chelation therapy:** Iron chelators used in modern medicine are costly and associated with Adverse Drug Reactions (ADR) i.e. ophthalmological, auditory, allergic reactions, bone abnormalities etc.
- **Bone marrow transplantation:** It is recommended in patients receiving adequate chelation, without evidence of liver disease and who have HLA matched sibling. The problems often confronted are chronic graft versus host disease and unavailability of HLA matched donor as only 1 in 5 siblings are HLA identical. It is out of reach of poor due to cost factor and success rate (in terms of matching donor) is also limited.
- **Stem cell therapy:** It is an upcoming branch and again cost factor is the drawback. Poor outcome after stem cell transplantation correlates with the presence of hepatomegaly and with inadequate chelation prior to transplant.

Ayurveda and Thalassemia Major:

Thalassemia is not found described as such in Ayurveda, but there are some *Ayurvedic* concepts highlighted below that help in understanding the etiopathogenesis of the disease.

- **Concept of *Beejadushtijanya Vikara* (~ genetic disorders):** Genetic basis of various diseases were

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known to ancient *Acharyas*. They described possible cause of *Beejadushti* (~ defected mutation) and also indicated the possible consequences in the form of *Tridosha Prakopa* (~vitiation of body humors), *Vikrita Avayava* (~ defected organ) formation corresponding to biochemical abnormalities or functional abnormalities and structural defects related to *Upatapti* of *Beeja* or *Beejabhaaga*. They described genetic basis for various diseases like *Arsha* (~ piles), *Prameha* (~ diabetes mellitus), *Kushtha* (~ skin disorders) and so on. All are *Asadhya* (~ incurable) in nature.(5) *Acharya* Charaka described *Beejadushtijanya Vikaras*,(6) wherein he explained that specific *Avayava* (~ organ) would be *Vikrita* (~ defected), if *Doshas* (~ humors) vitiate specific *Beeja* (~ sperm or ovum) or *Beejabhaaga* (~ chromosomes).

Table 1: Showing some classical terms, nearer terms in genetics and terms for Thalassemia

Terms in classics	Nearer terms in genetics	Terms for Thalassemia
Beeja	Sperm, Ovum and zygote	Sperm, Ovum and zygote
Beejabhaaga	Chromosomes	Chromosomes 16 & 11
Beejabhaagaavayava	Gene locus: Promoter region, Exons, Introns	α & β gene cluster

- **Concept of *Atulya Gotra Vivaha* (~ non consanguineous marriages):** It is also mentioned in *Ayurvedic* classics that *Tulya Gotra Vivaha* (consanguineous marriages) should not be done.(7) The reason for it is presumed that *Tulya Gotra Vivaha* will increase the chances of genetic and hereditary disorders. Hence, Ayurveda propagates *Atulya Gotra Vivaha*.

- **Concept of *Anukta Vyadhi* (~ unknown disease):** The methodology of understanding *Anukta Vyadhi* has been described in Charaka Samhita based on *Aaptopadesha Pramana* (~ words of the expert).(8) Following that Thalassemia may be correlated to ***Beejadushtijanya Panduroga***. The composite picture about this disease can be drawn considering points mentioned in classics in the light of knowledge available in the modern medical discipline.

Table 2: Showing Ayurvedic key points and similar terms in modern science for Thalassemia Major

Ayurvedic terminology	Nearer term in modern science (for Thalassemia Major)
Evam Prakopanam	Aggravating factors of the disease
Evam Yonim	Pathogenic material of the disease
Evam Utthaanam	Etiology of the disease
Evam Aatmaanam	Specific features of the disease
Evam Adhisthaanam	Location of the disease

Evam Vedanam	Knowledge of the disease
Evam Samsthaanam	Symptom of the disease
Evam Upadravam	Complication of the disease
Evam Vriddhi, Sthaana, Kshayam	Accumulation, stasis, diminution of symptoms
Evam Udarkam	Consequences of the disease, sequalae of the disease
Evam Naamam	Name of the disease
Evam Yogam	Treatment or management
Evam Pratikaara, Nivritti, Pravritti	Disappears and prevention of the disease

Samprapti (~etiopathogenesis) of Thalassemia according to Ayurveda:

In the case of Thalassemia the *Upatapti* of *Beejabhaagaavayava* is the main cause and consequent *Vishamaavastha* of *Dosha, Dhatu* and *Mala* (~ disequilibrium of humors, body constituents and proper excretion of waste products) which can lead to *Lakshanas* (~ sign and symptoms) of *Tridosha Prakopa*. *Pitta Pradhana Tridosha* (~ *pitta* dominant body humors) affects the functions of *Raktavaha Srotasa* (~ micro channels of blood n its indices) and ultimately the process of formation of *Rakta Dhatu* is affected and produces *Raktavikriti* (~ abnormality of blood indices). Persistent production of *Vikrita Rakta Dhatu* leads to various symptoms in the form of *Tridoshajanya Pandu.* As the disease Thalassemia is also compatible with life it can be considered as *Asadhya* in nature.

***Ayurvedic* drug intervention in Thalassemia:**

As iron overload is the main complication of Thalassemia Major which results as a consequence of repeated BT, excess iron should be removed from the body. This can be achieved by prolonging BT interval and searching for orally active iron chelators which should be palatable, inexpensive, non-toxic etc.

There are so many drugs (herbals and also minerals) mentioned in *Rasashastra* suggested for *Loha Sevanajanya Vikara Prashamana* (~ drugs for diseases/complications due to intake of iron/iron containing drugs and iron overload), *Lohashodhana Gana*,(9) *Lohamarana Gana*(10) and *Lohadravaka Gana*(11) (~ specific set of drugs used for purification of *Ashuddha Loha*- ~ impure iron) etc. which can be used as iron chelators to decrease the iron overload due to similarity of symptoms between *Ashuddha Loha Sevanajanya Vikara* (~ diseases produced by excessive/impure iron intake) and complications of Thalassemia i.e. iron overload.

In spite of these, some drugs mentioned in *Ayurvedic* classics in various diseases also can be used in the management of Thalassemia according to clinical manifestations of the disease. i.e. drugs used in *Panduroga Chikitsa* (~ anemia), *Yakrita Vikara Chikitsa* (~ hepatic disorders), *Pleehaa Vikara Chikitsaa* (~ splenic disorders), *Rakta Shodhana* (~purification of blood), *Srotoshodhana* (~ body channels cleanser), *Lekhana* (~ scraping property), *Bhedana* (~ piercing), *Tridoshahara* (~ normalize all body humors), *Rasayana* (~ adjuvant),

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Vayahasthapana (~ anti ageing), *Balya* (~ strengthening) drugs etc.

Details of research works on Thalassemia Major:

Till date a total of 5 research works have been carried out on Thalassemia Major in *Kaumarbhritya* department, Institute for Post Graduate Teaching & Research in Ayurveda (IPGT&RA), Gujarat Ayurved University (GAU), Jamnagar. Details are given in table 3.

Table 3: Showing details of clinical research works on Thalassemia Major conducted at *Kaumarbhritya* department, IPGT&RA, GAU, Jamnagar

Study No.	Name of Researcher	Year	No. of Pts. registered	Age Group
1.	Singh R. *et al* (12,13)	2007	19	1-15 Years
2.	Jadhav S. *et al* (14,15)	2009	30	1-15 Years
3.	Patalia A. *et al* (16,17)	2011	32	1-15 Years
4.	Rathod R. *et al* (18)	2013	41	6 Months-12 Years
5.	Rajgolkar S. *et al* (19)	2014	42	6 Months- 12 Years

In addition to these 2 research works have been carried out in department of RS & BK, IPGT&RA, Jamnagar on *Gandhakadi Yoga* on Thalassemic iron overload.(20,21) In which standardization, pharmaceutical, pharmacological, toxicological studies of *Gandhakadi Yoga* and also clinical observations on healthy volunteers were done. *Gandhakadi Yoga* has been evaluated for iron sorbitol induced iron overload in albino rats.(22) The quality control parameters of *Gandhakadi Yoga* tablets (microscopic and physico-chemical) have been published.(23,24)

Aims and Objectives

- To review previous clinical researches on Thalassemia Major conducted at IPGT & RA, Jamnagar.
- To highlight the effective role of *Ayurvedic* medicines (i.e. *Dhatri Avaleha, Triphaladi Avaleha* and *Musta-Triphaladi Avaleha*) in the management of Thalassemia Major.

Materials and Methods

Patients:

Diagnosed patients of Thalassemia Major attending the OPD of dept. of *Kaumarbhritya*, IPGT&RA, GAU, Jamnagar and additionally patients were registered from Thalassemia ward of G.G. Hospital, Jamnagar.

Inclusion criteria:

Diagnosed cases of Thalassemia Major.

Exclusion criteria:

Patients with HIV, HBV infection, hepatic failure, DM, TB etc., patient having BT interval for less than 12 days, patient undergone Splenectomy were excluded.

The selected patients were randomly divided into two groups, viz.

1. **Trial group (Group A):** In this group along with blood transfusion trial drugs (i.e. Avaleha) were administered orally with *Godugdha* (cow milk) as *Anupana*. Adult dose of *Avaleha* was taken 1 *Pala* (~ 48 gm)(25) and child dose was calculated according to Young's formula. [Table 4]
2. **Control Group (Group B):** In all the five studies, the standard treatment with blood transfusion and iron chelators as and when required served as **control**

group; no *Ayurvedic* intervention was done in control group.

Table 4: Showing details of trial groups of research works

Study No.	Name of Trial drug	Duration of treatment	Follow Up
1.	*Dhatri Avaleha*	2 months	2 months
2.	*Triphaladi Avaleha*	2 months	2 months
3.	*Triphaladi Avaleha*	12 weeks	8 weeks
4.	*Triphaladi Avaleha*	12 weeks	8 weeks
5.	*Musta-Triphaladi Avaleha*	12 weeks	8 weeks

Methods of sampling: Simple random sampling method.
Method of research: Open clinical trial.
Drugs: All the trial drugs were prepared in the pharmacy of Gujarat Ayurved University, Jamnagar and pharmacognostical and analytical studies were done in laboratories of IPGT&RA, GAU, Jamnagar.

Criteria of assessment:

A special proforma was prepared to study the etiopathogenesis and response to the given treatment and any complications. The efficacy of therapy was assessed on the basis of suitable scoring pattern.

- **Objective Criteria:** Routine hematological investigations were performed along with biochemical investigations for assessment of liver function and iron overload.
- **Subjective Criteria:** The subjective criteria for assessment include the *Panduta* (~ pallor), *Daurbalya* (~ weakness), *Balakshaya* (~ chronic fatigue), *Akshikootashotha* (~ puffiness around the orbit), *Jwara* (~ fever), *Aruchi* (~ anorexia), *Udarashoola* (~ abdominal pain), *Pleehavriddhi* (~ splenomegaly), *Yakritvriddhi* (~ hepatomegaly), *Atisara* (~ loose motion), *Pindikodweshtana* (~ leg cramps) and *Sandhishoola* (~ arthralgia).
- **Criteria of assessing overall effect of therapy:** An assessment scale was made to assess the rate of improvement. At the end of treatment, the results in view of percentage of relief were classified.

Statistical analysis:

The data obtained in clinical studies was subjected to statistical tests and analyzed in to the following parts:

- Paired ‘t’ test was applied to evaluate the effect of therapy in individual group for subjective and objective criteria.
- Unpaired ‘t’ test was applied to the statistical data for evaluating the differences in the effect of two groups in improvement of subjective and objective criteria.
- Overall effect of therapy in each group was calculated with reference to percentage improvement in all cardinal features.

Results

Singh R. (2007) in her study (n=19) reported that *Dhatri Avaleha* provided insignificant results in all laboratory parameters. Statistically significant ($p<0.01$) result was found in BT interval in *Dhatri Avaleha* treated group in comparison to control group.

Jadav S. (2009) in his study (n=30) reported that *Triphaladi Avaleha* provided insignificant results in all laboratory parameters, except in total proteins ($p < 0.01$); in the control group all the laboratory parameters were unaffected.

Pataliya A. (2011) in his study (n=32) reported that *Triphaladi Avaleha* provided statistically highly significant decrease ($p<0.01$) in SGOT and significant decrease ($p<0.05$) in SGPT while

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statistically insignificant (p>0.05) result in rest of the parameters. Control drug provided statistically insignificant (p>0.05) result in all parameters.

Rathod R. (2013) in her study (n=41) reported that *Triphaladi Avaleha* provided better percentage of relief in Hb, S. TIBC and S. Ferritin. These comparative data were significant statistically. Statistically highly significant (p<0.01) decrease was found in SGOT, SGPT, S. Bilirubin, S. TIBC, S. Ferritin while insignificant (p>0.05) result on rest of the parameters. The effect of control drug on SGOT, SGPT, S. Bilirubin, S.TIBC was found statistically highly significant (p<0.01) and statistically insignificant (p>0.01) result was found in Hb, S. Iron, S. Ferritin.

Rajgolkar S. (2014) in his study (n=42) reported that *Musta-Triphaladi Avaleha* provided statistically significant (p<0.05) increase in Hb and S.TIBC while insignificant (p>0.05) increase was found in SGOT, SGPT, S. Bilirubin and S. Iron. While S. Ferritin was decreased which is statistically highly significant (p<0.001). Control drug provided statistically insignificant (p>0.05) increase in Hb, SGOT, SGPT, S. Bilirubin, significant (p<0.05) increase in S. Ferritin while highly significant (p<0.001) increase in S. Iron and S. TIBC. BT Interval was increased by a mean of 5.14 days in trial group while it was decreased by a mean of 1.45 days in control group.

All of the three trial drugs provided relief in all cardinal features of the disease. Comparative efficacy of trial group with control group was assessed on cardinal features and laboratory parameters. Overall effect of therapy in each study was assessed at the end of treatment course. Details are given in Table 5.

Table 5: Showing the overall effect of therapy (%)

Assessment of results	Study 1		Study 2		Study 3		Study 4		Study 5	
	G-A	G-B	G-A	G-B	G-A	G-B	G-A	G-B	G-A	G-B
Maximum improvement (>75%)	25	00	00	00	38.46	00	5	00	19.05	00
Moderate improvement (51-75%)	62.5	00	7.69	00	38.46	18.18	65	00	61.9	00
Mild improvement (26-50%)	12.5	00	84.61	00	15.38	36.36	25	00	19.05	00
No improvement (0-25%)	00	100	7.69	100	7.7	45.46	5	100	00	100

Discussion

Till date a total of five research works have been carried out on Thalassemia Major in dept. of *Kaumarbhritya*, IPGT & RA, Jamnagar. Among these 1 research work is on *Dhatri Avaleha*, 3 on *Triphaladi Avaleha* and 1 on *Musta-Triphaladi Avaleha.*

All of the three trial drugs provided relief in all cardinal features of the disease. Most of the drugs have properties like *Aamapachana* (~ digestives), *Deepana* (~

stomachic), *Rochana* (~ stimulate appetite) and *Srotoshodhana* which correct the *Agni* (~ digestive power) and help to improve appetite and digestion, as well as remove obstruction in the channels, so that the transformation of *dhatus* becomes undisturbed and thus, it relieves *Daurbalya*. *Anulomana Guna* (~ laxatives) helps in the correction of digestive process. In this way, *Aruchi*, *Udarashoola*, *Pindikodweshtana*, and *Sandhishoola* are relieved. *Triphala*,(26) *Katuki*,(27) *Guduchi*(28) and *Sharapunkha*(29) alleviate *Jwara* due to *Jwaraghna Guna* (~ antipyretic property). The drugs like *Triphala*,(30) *Katuki*,(31) *Haridra*,(32) *Guduchi*,(33) *Shweta Punarnava*,(34) and *Sharapunkha*(35) have *Pandughna* (~ hemetamic), *Bhedana*, *Pittasaraka* (~ excrete excess pitta), *Yakrita-Pleehaavriddhihara* (~ hepeto-spleno protective), *Raktashodhana* (~ blood purifier) and *Shonitasthapana* (~hemostatic) properties which relieve *Panduta*, *Akshikootashotha*, *Yakritavriddhi*, and *Pleehavriddhi*. *Tridoshahara*, *Rasayana*, *Vayahasthapana*, *Balya* drugs enhance *Bala* (~ strength) and general health status. Thus, improve the quality of life of Thalassemic patients.

While analyzing the effect of trial drugs on laboratory parameters *Musta-Triphaladi Avaleha* has shown better result in Hb, S. Ferritin and S. TIBC. The majority of the symptoms of Thalassemia are reported to be the result of iron overload in various tissues and organs. S. Iron and S. Ferritin level are the criteria for assessing iron overload in Thalassemic patients. The drugs like *Triphala*, *Haridra*, *Shweta Punarnava* belongs to *Lohashodhana Gana*,(9) *Guduchi*, *Vidanga*, and *Manjishtha* belongs to *Lohamarana Gana*(10) and *Kakamachi* belongs to *Lohadravaka Gana*(11) and They would have potential iron chelating activity and would have contributed to the reduction in S. Ferritin.

Some of the drugs like *Katuki*, *Triphala*, *Guduchi*, *Sharapunkha* etc. have hepatoprotective, splenoprotective properties which may have decreased SGOT, SGPT and S. Bilirubin level.

Both *Dhatri Avaleha* and *Musta-Triphaladi Avaleha* increased BT interval. This may be due to *Raktashodhana*, *Raktaprasadana* and *Shonitasthapana* properties of drugs which decrease the rapid destruction of RBCs, thus prolonging their life span and increases the BT interval. All these factors increase the expectancy of good life of Thalassemic patients.

Adverse drug reaction (ADR): All the trial drugs found clinically safe as no adverse drug reactions were reported during treatment period.

Conclusion

- There is no exact correlation to Thalassemia Major with any type of *Pandu*. But it can be co-related with *Beejadushtijanya Panduroga* and etiopathogenesis of the disease can be interpreted by the application of methodology described by *Acharya* Charaka in *Vimanasthana* in context of *Anukta Vyadhi*.
- Thalassemia Major being an incurable disease, improvement in the quality of life of the patient, minimizing the complications of the disease, as well as increasing the life span should be given due emphasis. *Ayurvedic* drugs improve the quality of life; maintain the patient fit for curative therapies like bone marrow transplant and stem cell therapy. Hence, *Ayurvedic* medicines are effective in management of diseases like Thalassemia Major as adjuvant drugs along with modern medical management.

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