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CLINICAL EVALUATION OF T-AYU-HMTM IN THE MANAGEMENT OF SICKLE CELL ANEMIA

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ABSTRACT: Sickle cell anemia is a hemoglobin disorder, which is an autosomal recessive type affects millions of children of underprivileged and tribal area every year. Because of its devastating complications sickle cell is considered a major health problem in India and the entire world. Since many years, majority of the tribal population in the South Gujarat region are suffering from this lifelong disorder, which is incurable till date. The study to clinically evaluate T-AYU-HMTM, a novel herbo-mineral preparation has been performed in patients with sickle cell anemia. The prior ethics approval for the study was obtained. This study was a non-randomized and efficacy comparative type study in which folic acid used as standard. The results were analyzed by using mean \pm SEM and one-way analysis of variance. Results from the study show the drug is effective in alleviating the clinical symptoms of patients. Results showed drug is able to sustain the level of red blood corpuscle. The drug also sustained hemoglobin level by reducing sickle hemoglobin balancing it with raising fetal hemoglobin. This sustained level might be responsible for alleviating the symptoms and better observational health-related outcome in sickle cell anemia patients as compared to folic acid treatment. The drug shows superior results on the clinical symptoms of sickle cell anemia patients as compared to folic acid treatment. As one has to tolerate the medicine for a lifetime in sickle cell anemia, T-AYU-HMTM might become the ultimate option in its management in future.

INTRODUCTION: As per epidemiological reports, each year over 300000 children are born affected by sickle cell anemia. Sickle cell anemia limits the affinity for oxygen of hemoglobin, resulting in the damaging or sickling of the red blood corpuscle. These irregularly shaped cells can get stuck in small blood vessels, which can slow or block blood flow and oxygen to part of the body.

This is the reason why this hemoglobin disorder affects all parts of the human body and exist different clinical appearances amongst the person to person. Lack of concern towards sickle cell anemia has created a barrier in health care. Even though many researches are going on management of sickle cell anemia, complications due to the sickling of the red blood corpuscle continue to be a significant issue in patients of sickle cell anemia and physicians in today's scientific modern world.

Physicians remain puzzled by the biological and clinical intricacies of sickle cell anemia, and researcher still trying to find the cure to reverse the sickling effect of the human body.

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Sickle cell anemia is broadly classified into its two types based on globin gene affected. Sickle cell trait (HbAS) in which the patients carry one normal and one defective globin gene. Patients with sickle cell trait are usually symptomless but mild anemia and various complications can occur under stressful conditions. Generally, people might have view on symptoms and complications of sickle cell disease only. But in real-world symptoms and complication in traits are not identified and remain undiagnosed throughout the lifespan of patients. On the other side if the both globin genes are affected then the condition is known as sickle cell disease (HbSS) ¹⁻¹¹.

Complication of sickle cell disease patients always remains challenging by causing various complications in organ functioning. Even though sickle cell genetics and pathogenesis is studied but till date treatment options are limited and symptomatic only. Sickle cell anemia patients present with clinical features like palpitation, pallor, dizziness, giddiness, fatigue, weakness, headache, anemia, painful episodes, splenomegaly and jaundice. In cases if delayed, inadequate evaluated or lacks of proper symptomatic management in sickle cell anemia patients may lead to develop further including gross hematuria, increased urinary tract infection in women, infarction with altitude hypoxia or exercise, heat illness (heat stroke, exertional rhabdomyolysis or kidney failure) or idiopathic sudden death. Splenic infarction at high altitude with exercise or hypoxemia can occur.

Isosthenuria (loss of maximal renal concentrating ability), fatal exertional heat illness with exercise can occur, hematuria secondary to renal papillary necrosis and early onset of end-stage renal disease from an autosomal dominant polycystic kidney ¹⁻¹².

T-AYU-HMTM novel formulation made up of extract of eight Indian origin herbal plants and three purified minerals. *In-vitro* anti-sickling effect of T-AYU-HMTM was evaluated at the Bombay College of Pharmacy Kalina, Mumbai. The results showed that T-AYU-HMTM has potent anti-sickling effects on sickle erythrocytes obtained from patients with sickle cell disease. The anti-sickling effect of T-AYU-HMTM is marked. In the absences of T-AYU-HMTM, the majority of red blood

corpuscles underwent sickling, while in the presence of T-AYU-HMTM, sickling of corpuscles is significantly inhibited. The *in-vitro* drepanocytic activity of the Herbo-mineral formulation (T-AYU-HMTM) was 44.89%, 49.24% and 61.16% at concentrations of 15µg/ml, 30µg/ml, and 45µg/ml respectively ¹³.

MATERIALS AND METHOD: The protocol was designed as per ethical guidelines and obtained the approval from ethics committee (code no: 10/12/01-MNC) in 2010.

Selection of Patients: Before commencing the study the general and medical information of the patients were assessed by the principal investigator. The patients were screened and recruited from the outdoor department of Dhanvantari Clinic, Vyara, Gujarat. Patients diagnosed with sickle cell anemia were first distributed in two groups. Total 20 patients were selected for the study based on the various inclusion-exclusion criteria and who have given consent for the participation for an open-label and non-randomized trial. During the study period supportive management and emergency support system is also kept ready during the study.

Patients were asked to visit the clinic every month for observational study. Complete blood count and clinical parameters were regularly evaluated during each follow up. The assessment of response to drug was based on improvement in sign and symptoms of the patients. Therefore clear observation and answering of patients helped in grading the symptoms by the doctor. Pain score given by the Principal investigator recorded the effect of test the drug on major and minor clinical symptoms.

This parameter can be considered as an indication of overall patient's health as well as overall therapeutic efficacy of test formulation. Eventually, the clinical benefit is worth more important in life long disease as compared to the statistical benefit.

Study Groups:

Group 1: T-AYU-HMTM tablets formulation 300mg tablet twice a day. In the study 10 patients of sickle cell disease were screened and selected.

Group 2: Folic acid 5 mg. Generally, folic acid is considered as standard because it has been the choice of drug in many blood related disorders. In

the study 10 patients of sickle cell disease were screened and selected¹¹⁻¹⁵.

Study Duration: Total duration for the study was four months as the one complete life cycle of red blood corpuscle is around 120 days and patients were followed up every 30 ± 7 days till four months. The assessment of the response was based on the hemoglobin and complete blood count picture before and after the study. The percentage change in hemoglobin level was analyzed by using HPLC, before and after the study. These results help in showing the effect of drug on types of hemoglobin level.

Source of Documents: Pathology reports, Case report form, Informed consent form

Statistical Analysis: Data were expressed by the mean \pm SEM. Data comparison was carried out using one way analysis of variance to compare means between the different treatment regimen. Difference between test and standard group with a P value of 0.05 was considered statistically significant.

RESULTS: As per methodology the results obtained from patients on every follow up were collected, analyzed and presented as below.

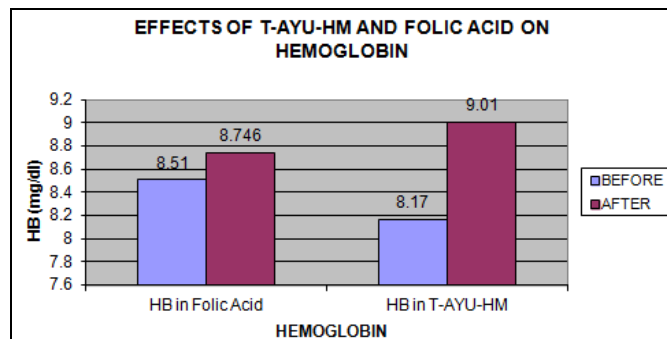


FIG. 1: EFFECT OF T-AYU-HM™ AND FOLIC ACID ON HEMOGLOBIN

Obtained results data suggests that both T-AYU-HM™ (8.17 ± 0.47 to 9.01 ± 0.59) and Folic acid (8.51 ± 0.37 to 8.74 ± 0.42) improved Hemoglobin (gm%) in sickle cell disease patients but the improvement was not statistically significant. However, rise in level of hemoglobin was comparatively more in the T-AYU-HM™ group than the folic acid group which can be seen in following figure.

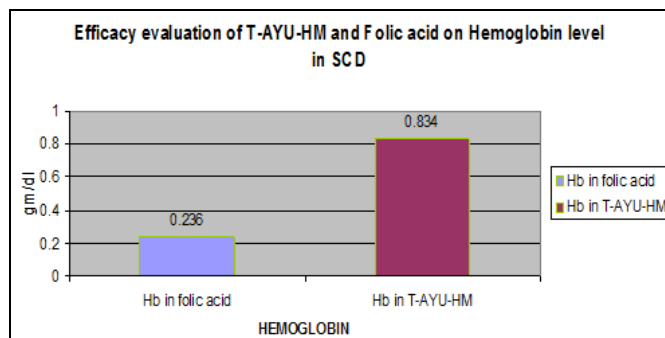


FIG. 2: EFFICACY EVALUATION OF T-AYU-HM AND FOLIC ACID ON HEMOGLOBIN

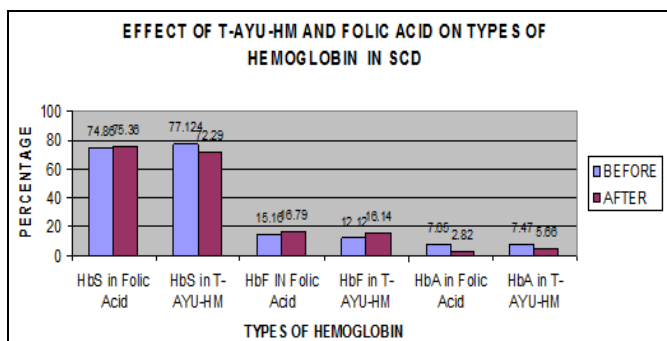


FIG. 3: EFFECT OF T-AYU-HM AND FOLIC ACID ON TYPES OF HEMOGLOBIN

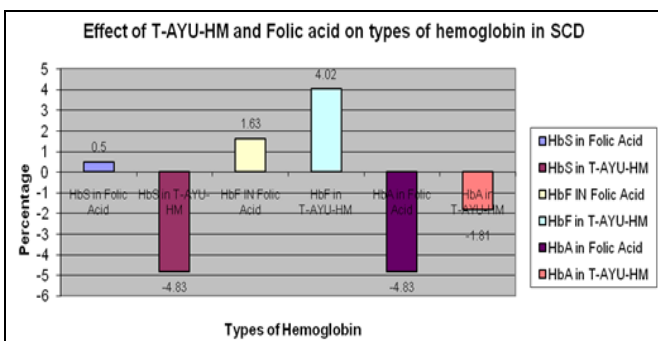


FIG. 4: EFFICACY EVALUATION OF T-AYU-HM AND FOLIC ACID ON TYPES OF HEMOGLOBIN

The sickle hemoglobin level (%) in sickle cell disease patients significantly declined after treatment with T-AYU-HM™ group whereas the sickle hemoglobin level increased folic acid group.

The fetal hemoglobin level significantly improved after treatment with T-AYU-HM™ and marginally in standard folic acid group. The adult hemoglobin level was declined after treatment in both groups.

The red blood corpuscles level in sickle cell disease patients improved marginally (0.197 millions/cmm) after treatment with T-AYU-HM™ compared to (0.043 millions/cmm) after treatment with standard

folic acid group. This could be a result of the less number of sickling cells and hence less chances of hemolysis.

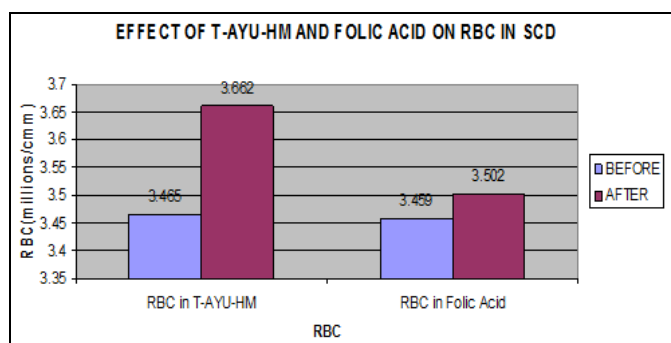


FIG. 5: EFFECT OF T-AYU-HM™ AND FOLIC ACID ON RBC

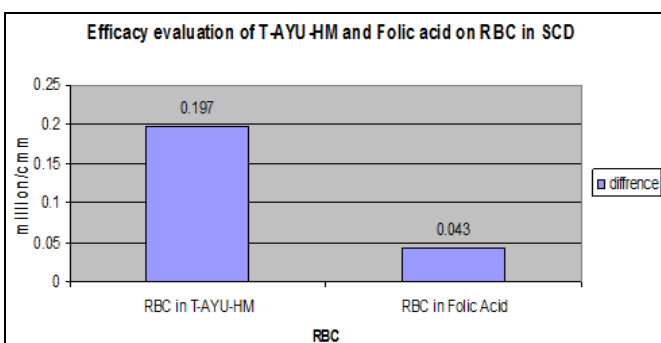


FIG. 6: EFFICACY EVALUATION OF T-AYU-HM AND FOLIC ACID ON RBC

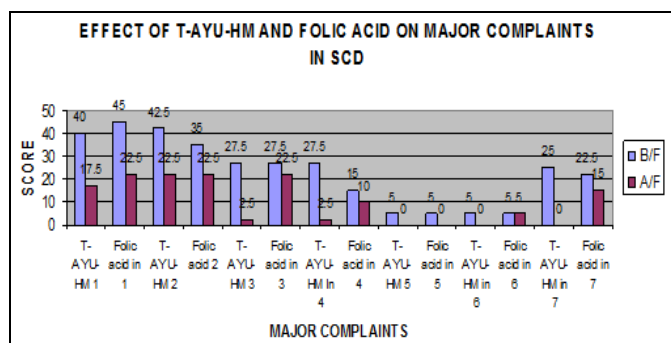


FIG. 7: EFFECT OF T-AYU-HM™ AND FOLIC ACID ON MAJOR COMPLAINTS

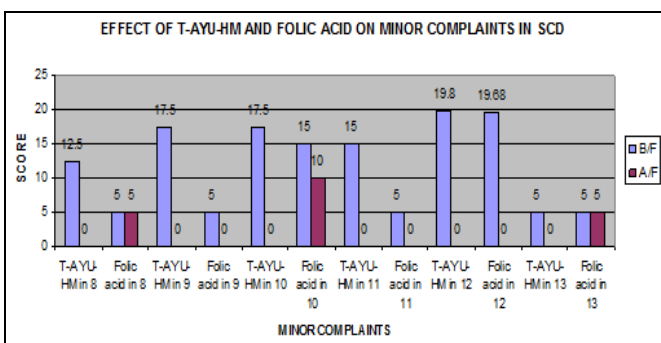


FIG. 8: EFFECT OF T-AYU-HM™ AND FOLIC ACID ON MINOR COMPLAINTS

The parameters given number in above explained graphs of complaints are as follow 1-Splenomegaly 2-Jaundice 3-Pallor 4-General weakness 5-

Palpitation 6-Fatigue 7-Bodyache 8- Backache 9- Puffiness on face 10-Abdominal colic 11-Loss of appetite 12-Fever and 13-Headache.

TABLE 5: EFFECTS OF T-AYU-HM™ ON HEMATOLOGICAL PARAMETERS

Test	Baseline value	Final visit value	Normal range
WBC (count/cmm ³)	8660 ± 765.53	9100 ± 962.10	4000-10000
Platelet (count/mm ³)	225660 ± 35197.60	218777.7 ± 21729	150000-450000
MCHC (gm/dl)	33.94 ± 0.49	34.82 ± 0.68	32 to 36
MCH (pg/cell)	24.19 ± 1.04	24.16 ± 0.90	27 to 31
MCV (fl/cell)	71.37 ± 3.36	69.94 ± 2.98	80 to 100
PCV (%)	24.31 ± 1.26	23.68 ± 1.67	39 to 51
Neutrophil (%)	56.63 ± 4.90	53.33 ± 4.04	40 to 80
Eosinophil (%)	1.9 ± 1.404	4.5 ± 1.40	0 to 5
Lymphocytes (%)	39.9 ± 3.89	42.11 ± 3.89	10 to 40
Monocytes (%)	0.2 ± 0	0 ± 0	4 to 10
Reticulocytes (%)	4.885 ± 0.47	5.63 ± 0.43	0.5-2.5
S. Bilirubin (mg/dl)	4.27 ± 0.47	4.29 ± 0.63	0-1.2
Direct Bilirubin (mg/dl)	1.87 ± 0.26	1.79 ± 0.43	0-0.2
Indirect Bilirubin (mg/dl)	2.4 ± 0.11	2.5 ± 0.54	0-1.2

TABLE 6: EFFECTS OF FOLIC ACID ON HEMATOLOGICAL PARAMETERS

Test	Baseline value	Final visit value	Normal value
WBC (count/mm ³)	8535 ± 1055.85	8470 ± 1492.50	4000-10000
Platelets (count/mm ³)	236800 ± 48069.35	222100 ± 28734	150000-450000
MCHC (gm/dl)	34.35 ± 0.62	35.12 ± 0.68	32 to 36
MCH (pg/dl)	24.78 ± 0.64	25.03 ± 0.66	27 to 31

MCV (fl)	72.43 ± 1.95	71.52 ± 1.84	80 to 100
PCV (%)	24.86 ± 1.19	25.05 ± 1.48	39-51
Neutrophil (%)	56.6 ± 4.50	60.2 ± 4.29	40 to 80
Eosinophil (%)	3 ± 0.88	1.9 ± 0.67	0 to 5
Basophil (%)	0	0	0 to 1
Lymphocytes (%)	39.3 ± 4.42	38.1 ± 3.91	10 to 40
Monocytes (%)	0.6 ± 0.6	0.8 ± 0.41	4 to 10
Reticulocytes (%)	6.445 ± 0.57	5.44 ± 0.70	0.5 – 2.5
S. bilirubin (mg/dl)	3.447 ± 0.64	2.47 ± 0.49	0.0-1.2
Direct (mg/dl)	1.2 ± 0.15	1.15 ± 0.24	0-0.2
Indirect (mg/dl)	2.066 ± 0.57	1.40 ± 0.28	0-1.0

DISCUSSION: Sickle cell anemia is an autosomal recessive type of disorder where the red blood corpuscles may acquire a sickle shape, particularly on exposure to hypoxia. These may lead to complications arising out of destruction of the sickle cells or reduced perfusion due to clogging of vessels as a result of clumping of sickle cells or due to toxic effects arising out of processing of ruptured red blood corpuscles. The common signs and symptoms seen in patients of sickle cell anemia include – pallor and weakness, jaundice, pain (due to vascular clogging), splenomegaly¹¹⁻¹⁵. The drugs used so far, provide either symptomatic relief from pain (analgesics) or help in restoring red blood corpuscles (hematinics). None of these can provide a long term relief from the complications of the disease or reduce the need for hospitalization and blood transfusion.

Some of the newly introduced drugs like hydroxyurea are claimed to improve fetal hemoglobin but have not yet been able to establish themselves as a safe and effective therapeutic option. Actually the toxicity of hydroxyurea may outweigh any therapeutic benefit¹⁶⁻¹⁷. The results showed potential of T-AYU-HMTM in reducing sickle hemoglobin and also raising the fetal hemoglobin level. In the management of sickle cell anemia many treatment options might have proved effectiveness on raising the fetal hemoglobin level but no drug till date have potential to reduce the sickle hemoglobin and simultaneously increase the fetal hemoglobin level¹¹⁻¹³.

In current study, the formulation showed fundamental proposed mechanism of action was preventing red blood corpuscles to become sickle and thereby prevent pain and complications in patients¹³. Though, there is no significant increase in RBC count in study, but it was sustained is more important for the prognostic outcome in sickle cell

anemia patients. Reason for importance in sustained value of red blood corpuscle is rise in red blood corpuscles lead to rise in hemoglobin level, which will eventually lead to viscosity based complications in sickle cell anemia. On analyzing the major and minor complaints of patients of Sickle cell anemia it was found that there was a significant alleviation in T-AYU-HMTM compared to patients who received standard folic acid treatment. A major benefit of T-AYU-HMTM was that most of the patients reported significant reduction in the severity and frequency of pain episodes. This in turn would bring about a significant improvement in the day-to-day functionality of the patients. Also, the occurrence of splenomegaly was found to reduce significantly.

Overall, the results suggest that T-AYU-HMTM is as effective as folic acid in improving the hemoglobin (gm %) and in fact significantly superior than folic acid in improving the clinical status of sickle hemoglobin and Fetal hemoglobin in patients of Sickle cell anemia. In addition to this, T-AYU-HMTM was also found to be significantly better in alleviating the complications of sickle cell anemia like episodes of Pain and splenomegaly.

Currently, there is a great need of any drug that can be safe, effective, and easily available in the management of sickle cell anemia. T-AYU-HMTM is an alternative system class of formulation so patients' compliance can be better expected. Therefore, further research work and development of this medicine can become a great boon for the patients of sickle cell anemia.

CONCLUSION: The present study provides an important data about the efficacy of the T-AYU-HMTM in sickle cell anemia patients with comparison of standard folic acid. In the absence of any oral medicine with reasonable efficacy in

sickle cell anemia, T-AYU-HMTM is as a good candidate for therapeutic management of sickle cell anemia compared to folic acid. However, further studies will be performed in a larger population to ascertain its multi-centric potential in the therapy of sickle cell anemia and optimize the dose regimen. The study has obtained significant results in terms of alleviating the clinical symptoms. T-AYU-HMTM sustained the level of red blood corpuscle, hemoglobin and eventually able to control various complications. This is indicative of a good quality of life can be possible in sickle cell anemia patients with T-AYU-HMTM.

Many herbal drug researches are going on for management of sickle cell anemia but T-AYU-HMTM showed potential to increase the quality of life in patients of sickle cell anemia by reducing the sickle hemoglobin through its drepanocytic activity. Not all formulations have the tendency to maintain the level of hemoglobin including control over percentage of sickle hemoglobin.

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CONFLICT OF INTEREST: The authors affirm no conflict of interest associated with this work.

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