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Real-World Experience with Hemoxin R Plus in Patients of Sickle Cell Anemia/ Disease Non Responsive To Standard Therapy (Comparison with the Standard of Care: A Retrospective Analysis)

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A B S T R A C T

Background*:** Sickle cell anemia (SCA) is amongst the most common genetic condition. It is the mutation of beta globin chain and has been acknowledged to have a global public health impact. This disease is common among many tribal and backward populations in India. In the central India its prevalence varies from 10-40%. It can be classified as two types of homozygous sickle cell disease and heterozygous sickle cell trait. Hand-foot syndrome (swelling), pain and anemia are some of the very common complications of the disease. In Sickle cell anemia, the number of healthy RBCs decrease which results in reduction of Oxygen in the tissues.Objectives*:** Currently available drugs do not seem to improve hemoglobin level of patients of Sickle cell anemia to considerable extent. Our experience with Hemoxin R Plus, an Ayurvedic medicine was very encouraging in improving quality of Life of SCA patients. Our aim of this analysis of the data available with us was to compare safety and efficacy of Hemoxin R Plus, with the standard of care in improving hemoglobin, RBC and Quality of life and in patients having SCA.***Materials and Methods*:** This was a retrospective analysis. Hospital records of the patients were used and reviewed for the analysis. Data was collected by the doctors from the medical records department, who treated the patients. Data analysis was done by applying Levene's Test for Equality of Variances. ***Results*:** Hemoxin R Plus was found to be better than the standard of care (hydroxyurea and folic acid) for every parameter considered for analysis, viz. Hemoglobin, RBCs and Sr. Creatinine. Hemoxin R Plus was found to be safe in the dose administered, as there were no adverse events reported, and liver markers and Sr. Creatinine did not go higher for any patient.***Conclusion*:** Capsule Hemoxin R Plus can be used for of the management of sickle cell anemia in improving hemoglobin, RBCs and in reducing pain and inimproving the quality of life.

Keywords: Sickle cell anemia, Hemoglobin, RBC, Hemoxin R Plus.

INTRODUCTION

Sickle Cell Anaemia (SCA) is the most common and severe form of SCD.It is most prevalent in malarial endemic areas in the tropics where outcomes are often poor due to resource constraints, resulting in most children dying before reaching the adulthood.

The World Health Organization recognized sickle cell anemia as a public health priority in 2006, and subsequently adopted a resolution on the prevention and management of birth defects, including sickle cell disease and thalassemia at the 63rd (2010) World Health Assembly [1].

Normal RBCs have a flexible biconcave disk-like shape that allows for unimpeded passage through microvasculature with an approximate 120 day life span [2]. SCA is a genetic haemoglobin path in which the 6th amino-acid of the beta chain of hemoglobin molecule (glutamic acid) is substituted by valine. The disease is characterized by

chronic hemolytic anemia accompanied often with fever, infections and unpredicted painful crises due to vaso-occlusion of sickle erythrocytes trapped in small vessels. This is the result of hemoglobin polymerization, which causes them is shape of erythrocytes (sickle erythrocytes) [3]. Those sickle shaped cells get stuck in the smaller blood vessels, and capillaries which further slows or block blood flow and hence oxygen supply to the body. Sickle cell disease (SCD) was first identified in 1910 by James Herrick [4]. Sickle hemoglobin was firstly illustrated in India by Lehman and Cutbush in the year 1952 in south India [5]. In India, prevalence of sickle gene is found to be 0-18% in north eastern part, 0-33.5% in western part, 22.5-44.4% in central part and 1-40% in southern part and the gene frequency of Hb-S varies between 0.031- 0.41. The prevalence varies considerably among different tribal groups ranging from 0-35%. In certain states like Madhya Pradesh, Orissa, Chattisgarh, Jharkhand, Gujrat and Maharashtra it forms a major public health problem. It has been detected more among tribal and scheduled caste populations [6].

Sickle haemoglobin (HbS) is a variant of normal adult haemoglobin, caused by a mutation in the HBB gene [7]. In this case inheritance is of recessive form. Those individuals with single globin chain defect are called carriers or traits or heterozygotes and they are generally symptomless. When the gene for sickle hemoglobin is inherited from both parents, it is called sickle cell anemia. Red blood cells (erythrocytes) with HbS become deformed under stress, forming a classic 'sickle' shape.

There is no proper mentioning of Sickle Cell Anemia as such in Ayurveda but the disease resembles with (one of the subtypes of) *Panduroga* [8]. In *Panduroga* there is depletion of blood, due to which, complexion becomes pale; and there are symptoms such as irritability, fatigue etc. The cause of *Panduroga* is the depletion of *Rasa*and*RaktaDhatu* with other *Dhatus* and vitiation of *Tridosha* [9].

The term *Beejadosha*is parallel to the 'genetic defects or abnormalities'. Symptoms associated with Sickle Cell Anemia are, difficulty in breathing, fatigue, pain etc. Essence of the *dhatus*(the tissue proper) is called *Ojas.* One can infer that in SCA, there is a depletion of *Ojas,* resulting in various debilitating symptoms and early death.

The difficulties associated with this disease are known to have serious negative impacts on the overall Quality of Life (QoL) of affected individuals. Therapies for sickle cell anemia are aimed to avoid/ reduce pain and preventing complications. Treatments available include medications, blood transfusions and at times, bone-marrow transplant. Other strategies include hypnosis, some exercises, meditation etc. Acupuncture and yoga can also be used as pain therapies. As the disease cannot be cured *per se,* with the oral medicines, this needs treatment which can maintain the quality of life of patients [10].

The Ayurvedic medicine considered here is Hemoxin R Plus. In a retrospective analysis of 150 SCA patients treated with Hemoxin R Plus was found to be effective in managing symptoms of SCA, and improving quality of life in 2022. Current analysis is the next phase of the earlier experience with the investigational product (IP), Hemoxin R Plus. This is the retrospective but comparative analysis, of control group receiving the standard of care.

MATERIALS AND METHODS

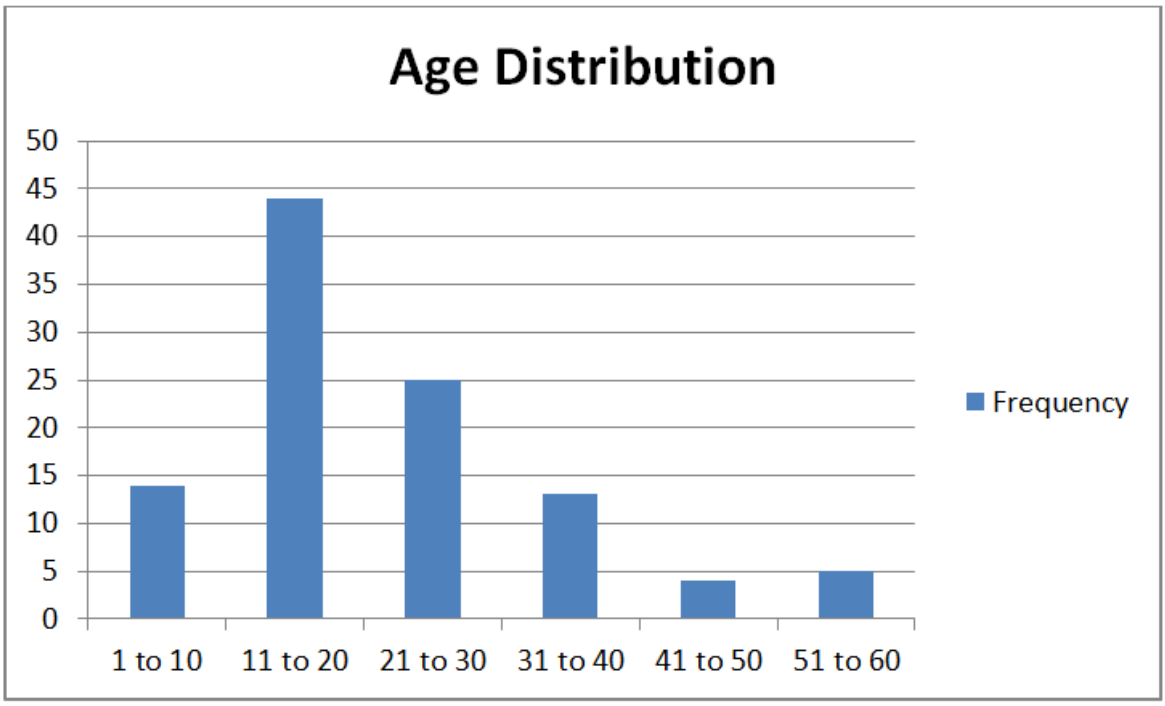
(a) Study Population

In this retrospective analysis, two groups were made based on the treatment received. 65 patients had received the contemporary modern drugs. 7 patients had received folic acid (age below 10 years), whereas 58 patients had received both, folic acid and hydroxyurea 500 mg. Total 40 patients had received the IP, of which 4 patients had received it of 300mg and 36 patients received the IP of strength 500 mg.

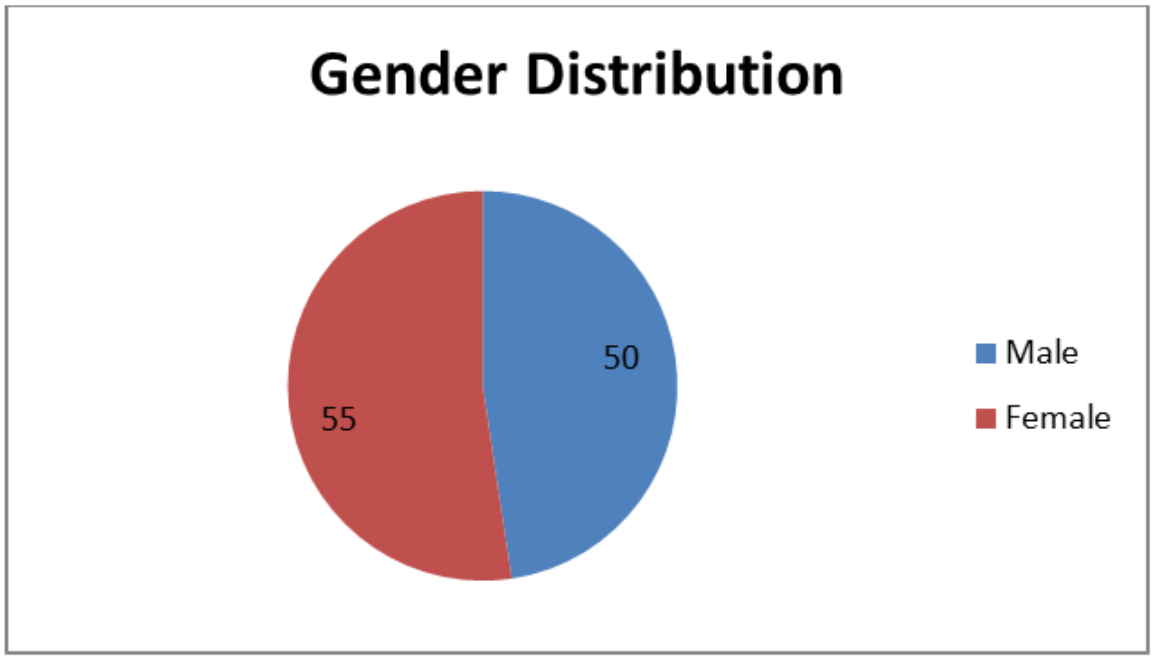
These were the known and confirmed cases of Sickle Cell anemia having complaints like abdominal pain, joint pain, backpain, total body pain, fatigue, breathlessness, difficulties in doing daily chores, attending school/job collected retrospectively by Doctors (Dr. Dexter Patel, Dr.PurvibenChoudhari) and assistants (Counsellor Mr.ChagganChoudhary. Coordinator: Nitin R Bhasin). All the patients in the study were of Sickle Cell Disease, diagnosed for more than a year and were on medication like Folic acid and/or a few on Hydroxyurea. Patients were having at least one or more symptoms/complaints described above.

Demographic information, family history and personal history were noted. Patients were of age from 4 years to 60 years.

Average age in the IP group was 27.2 years and that in the control group was 19.1 years. More than 70% of the patients were between 11 and 30 years.



Gender distribution:
Male: female distribution was almost equal, with 50 male and 55 female patients.



(b) Medication Used: Capsule Hemoxin R Plus (A proprietary Ayurvedic medicine)

Each Capsule Contains,

- SarjikaKshar (Sodium Bicarbonate and Sodium Carbonate)
- Lavang (*Syzygiumaromaticum*)
- Vijaysar (*Pterocarpusmarsupium*)
- Maricha (*Pipernigrum*)
- Jawar (*Sorghumvulgare*)
- Papaya (*Caricapapaya*)

Plus excipients
Dose: For, Adults: 500 mg capsule once a day; For children below 12 years of age, strength of the capsule was 300mg once a day
Other group of patients received Hydroxyurea and folic acid. Children below age 10 were given folic acid only.

(c) Investigations:
Following investigations were done in both the groups:
Hemogram: to know Hemoglobin and RBC
Liver Function Test: to know levels of SGPT and SGOT; and Sr. Creatinine to know the safety profile.

All the tests were done in the month of December 2023 and in May 2024. Thus, the results we see here are of five months' medication.

Following symptoms were observed before and after treatment

Sr. No		**Symptoms/ Complaints**
1.	Pain	Abdominal Pain
2.		Limb/ Joint pain
3.		Back pain
4.		Overall Body pain
5.	QoL	Fatigue
6.		Breathlessness
7.		Difficulty in Performing Daily Chores (Activities of Daily Life: ADL)
8.		Difficulty in Attending School/Job

RESULTS AND DISCUSSION

Clinical condition of patients with Sickle Cell Anemia worsens day by day if proper treatment is not given. In this study, the patients were on a particular Ayurvedic drug called Hemoxin R Plus to see its efficacy in increasing the level of Hemoglobin, RBCs; minimizing the symptoms and inimproving Quality of Life. The decline in symptoms was seen more in the IP group than the control group.

Below table mentions comparison between two groups (IP and Control) for Hemoglobin, RBC and Sr. Creatinine.

The increase in the mean of Hemoglobin and in RBCs was found more in the IP group than in the control group. Decline in the Sr. Creatinine level was found more in the IP group than in the control group.

Group Statistics					
Intervention		**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**
Hb	IP 300/ 500	40	1.69	0.62	0.10
	HU 500 + FAor FA	65	0.26	0.32	0.04
RBC	IP 300/ 500	40	0.80	0.36	0.06
	HU 500 + FAor FA	65	0.17	0.11	0.01
Creat	IP 300/ 500	40	-0.47	0.20	0.03
	HU 500 + FAor FA	65	-0.19	0.15	0.02

Below is the table depicting the statistical analysis of comparison of the two groups:

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Hb	Equal variances assumed	16.78	0.00	15.65	103.00	0.00	1.43	0.09	1.25	1.61
	Equal			13.59	51.86	0.00	1.43	0.11	1.22	1.64

	variances not assumed									
RBC	Equal variances assumed	36.39	0.00	13.42	103.00	0.00	0.64	0.05	0.54	0.73
	Equal variances not assumed			10.96	43.48	0.00	0.64	0.06	0.52	0.75
SrCreat	Equal variances assumed	2.06	0.15	-8.08	103.00	0.00	-0.28	0.03	-0.35	-0.21
	Equal variances not assumed			-7.63	67.95	0.00	-0.28	0.04	-0.35	-0.21

P value is less than 0.01 for both the efficacy parameters: Hemoglobin and RBC.

In the earlier retrospective analysis done in 2022, Hemoxin R Plus was found to be effective in decreasing the symptoms to a great extent. Pain (general body ache, limb and joints pain, abdominal pain and back pain) and four parameters that represent QoL viz. fatigue, breathlessness, difficulty in carrying out Activities of Daily Living (ADL) and difficulty in attending job / school were assessed. Ordinal scale (0 for best scenario / no symptom and 10 for worst case scenario) was considered for every parameter. Wilcoxon signed rank test was used to analyzed the before after data. For every parameter analyzed, *p* value was found to be < 0.05, defining there was significant difference after treatment, for patients having symptoms to some severity. Complaints in the SCA mainly affects Quality of Life (QoL) hence it was important to assess effect of the Hemoxin R Plus in improving quality of life of patients. In that study, QoL assessment was done before and after treatment and then the scores were compared for assessing improvement. SCD patients experience health related quality of life worse than the general population [11]. After this initial study, the investigator thought of checking if the blood parameters also are in line with the clinical results. Hence the current study of data available was planned.

Pain is the most common complication associated with the patients having SCD. It could be daily chronic pain as well as intermittent. When sickle cells travel through small blood vessels, they can get stuck and clog the blood flow to the chest, abdomen and joints. This causes pain that can start suddenly, be mild to severe, and can last for any length of time [12].There are unpredictable acute vaso-occlusive painful episodes called pain crises. These pain episodes often require emergency acute medical care. Due to unpredictability and subjective and varied nature of pain, managing pain crises is a challenge for both, patients and their healthcare providers[11]. Based on experience and on various studies it was crucial to include this as a clinical endpoint [13]. In a particular study it was found that pain episodes include pain in legs, back and abdomen[9]. Patients with sickle cell anemia, has a negative impact on the emotional, physical and occupational aspects of life. A study found that a higher percentage of Sickle Cell Anemia patients were unemployed compared to the other population [14].Attending jobs get difficult with Sickle Cell Anemia due to health complaints**.** In another study it was noted thatsickle cell pain resulted in over seven times increased risk of absenteeism from school [15]. Most of the patients in the IP group had a little to no pain that interfered with their routine activities. On the contrary, majority of the patients in the control group had pain as the most common symptom.

HPLC was done in 10 patients of IP group. Average percentage at the start was 53.9% which became 12.6% in 5 month timespan. This has a good prognostic value.

Below is statistics, where HPLC_1 denotes the baseline value and HPLC_2 denotes the value after 5 months of treatment.

Paired Samples Statistics					
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	HPLC_1	.5390	10	.11752	.03716
	HPLC_2	.1260	10	.05582	.01765

P value is statistically highly significant in before-after analysis for HPLC

Paired Samples Test									
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	HPLC_1 - HPLC_2	0.41	0.13	0.04	0.32	0.50	10.34	9.00	0.00

As discussed above the important factor in physiology of Sickle Cell Anemia is reduced amount of oxygen throughout body which affects the respiration rate and causes fatigue. A study in Curitiba showed that Sickle Cell Disease interferes with daily lives of patients, 62.5% physically with a potential limiting factor [16]. Patients in the control group reported breathlessness to a good extent.

All the parameters considered to assess efficacy thus were carefully chosen to understand the overall effect of Hemoxin R Plus in managing SCA. Increase in levels of Hemoglobin and RBC provided a solid scientific rationale for the symptom relief and for improvement in the quality of life. The increase was statistically highly significant, with *p value* less than 0.01. All the parameters were closely monitored during the medicine was being administered, as each of them was critical to assess clinical significance of Hemoxin R Plus. No patient exhibited any symptom of adverse drug reaction. The individual contents of the drug have good safety profile, and most of the contents are used as 'food' too. There was no increase in SGPT, SGOT and Sr. Creatinine values, confirming safety of the Investigational Product.

CONCLUSION

This was the retrospective analysis of the patients of sickle cell anemia treated with Hemoxin R Plus (IP) compared with hydroxyurea and folic acid. The study concludes that patients in the IP group were better off not only clinically, but also investigations-wise. Patients who received Hemoxin R Plus showed statistically significant increase in levels of Hemoglobin and also in RBCs. Relief from pain in limbs, abdomen, back and body was observed in the patients in the IP group. The IP was tolerated very well without any known adverse reaction, exhibiting safety of this Ayurvedic drug. Safety was further confirmed by Sr. Creatinine, SGPT and SGOT.

LIMITATIONS

Our study shows that Hemoxin R Plusissafe and effective in treating SCA patients, compared with the current Standard of Care. However, this was not a planned study, but a retrospective analysis. A larger, prospective randomized multicentric trial would confirm the findings further.

REFERENCES

1. World Health Organization Fifty-ninth World Health Assembly: resolutions and decisions, annex 2010. WHA59/2006/REC/1. Geneva: World Health Organization.
2. Nurain, I. O., Bewaji, C. O., Johnson, J. S., Davenport, R. D., & Zhang, Y. (2017). Potential of three ethnomedicinal plants as antisickling agents. *Molecular pharmaceutics*, *14*(1), 172-182.
3. Nsimba, M. M., Lami, J. N., Hayakawa, Y., Yamamoto, C., &Kaji, T. (2013). Decreased thrombin activity by a Congolese herbal medicine used in sickle cell anemia. *Journal of ethnopharmacology*, *148*(3), 895-900.
4. Herrick, J. B. (1910). Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. *JAMA*, 312, p 1063.
5. Colah, R. B., Mukherjee, M. B., Martin, S., &Ghosh, K. (2015). Sickle cell disease in tribal populations in India. *Indian J Med Res*, *141*(5), 509-515. doi:10.4103/0971-5916.159492
6. Gorakshakar, A. C. (2006, October). Epidemiology of sickle hemoglobin in India. In *Proceeding of the National Symposium on Tribal Health* (pp. 103-108).https://www.nirth.res.in/publications/nsth/14.AC.Gorakshakar.pdf
7. Ware, R. E., de Montalembert, M., Tshilolo, L., &Abboud, M. R. (2017). Sickle cell disease. *The Lancet*, *390*(10091), 311-323.
8. Gupta, A., &Raskar, S. An Ayurvedic Management of Sickle Cell Anemia in Children: A case study. *International Journal of Ayurvedic Medicine*, *12*(3), 714-717.
9. Bhalkar, C. A., Bhaskaran, J. K., &Sheshagiri, S. (2020). Ayurveda treatment modalities for improving the quality of life in Sickle Cell AnaemiaA case study. *Journal of Research in Traditional Medicine*, *4*(5), 121-121.
10. Moody, K., Abrahams, B., Baker, R., Santizo, R., Manwani, D., Carullo, V., ...& Carroll, A. (2017). A randomized trial of yoga for children hospitalized with sickle cell vaso-occlusive crisis. *Journal of pain and symptom management*, *53*(6), 1026-1034.

11. McClish, D. K., Penberthy, L. T., Bovbjerg, V. E., Roberts, J. D., Aisiku, I. P., Levenson, J. L., ... & Smith, W. R. (2005). Health related quality of life in sickle cell patients: the PiSCES project. *Health and quality of life outcomes*, *3*, 1-7.
12. Centers for Disease Control and Prevention. (2019, June). *Complications and treatments of sickle cell disease*.https://www.cdc.gov/ncbddd/sicklecell/treatments
13. Farrell, A. T., Panepinto, J., Carroll, C. P., Darbari, D. S., Desai, A. A., King, A. A., ... &Zempsky, W. T. (2019). End points for sickle cell disease clinical trials: patient-reported outcomes, pain, and the brain. *Blood Advances*, *3*(23), 3982-4001. DOI: 10.1182/ bloodadvances.2019000882.
14. Farber, M. D., Koshy, M., Kinney, T. R., & Cooperative Study of Sickle Cell Disease. (1985). Cooperative study of sickle cell disease: demographic and socioeconomic characteristics of patients and families with sickle cell disease. *Journal of chronic diseases*, *38*(6), 495-505.
15. Fuggle, P., Shand, P. A., Gill, L. J., & Davies, S. C. (1996). Pain, quality of life, and coping in sickle cell disease. *Archives of disease in childhood*, *75*(3), 199-203.
16. de Souza Freire, M. H., Pereira, R. A., Ramos, E. J. The Impact of Sickle Cell Disease on The Daily Routine of Adolescents.