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# Sickle Cell Disease: A Reality Check from A Prevalent Zone In India

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## Abstract

**Background:** Sickle cell disease is a major cause of morbidity and mortality in large tribal populations of India. States have created facilities for its diagnosis and for the supply of medication. The symptoms of acute crisis necessitate frequent medical visits, blood transfusions, and management of pain crisis

**Methods:** A cross-sectional prospective research design was used that involved the completion of questionnaires on socio-demographic characteristics and clinical characteristics. One hundred and fourteen individuals with Sickle cell disease who went to centers for outpatient visit were analyzed.

**Results:** The median age of the cohort was 19 years with Male: Female ratio of 1.5:1. Siblings were screened for 45.6% of individuals. Thirty-six (32%) individuals had multiple episodes of veno-occlusive crisis in the past 1 year. Only 16% of patients required >10 rounds of transfusion. Seven patients reported avascular necrosis of femur head. One hundred four patients with SCD were on Hydroxyurea and the majority of them (80%) had hemoglobin F in the desirable range of > 20%.

**Conclusions:** This study describes the high usage of hydroxyurea in the patients with sickle cell disease and 32% patients having multiple episodes of VOC in past 1 year

**Keywords:** Sickle cell disease, Fetal hemoglobin (HbF), Hydroxyurea

## Introduction

Sickle cell anemia (SCA) is a common genetic disorder in some regions of India, affecting millions of people [1]. Sickle cell disease (SCD) is caused by the homozygous inheritance of hemoglobin S (HbS) mutation or compound heterozygous inheritance of the HbS mutation with another beta globin chain abnormality. Another common blood-related disorder in the same regions of the country is beta thalassemia. These two disorders can manifest together [2] . SCD is the major cause of morbidity and early mortality in large tribal populations. With continuous care, medical support, and free medical assistance from the state, the survival rates are improving; however, SCD still remains a major health concern.

SCD is commonly associated with serious clinical conditions such as veno-occlusive disease-related pain crises, chest pain, stroke, bone necrosis, and hemolysis. The symptoms of acute crisis necessitate frequent medical visits and blood transfusions. Chronic events lead to gradual multiorgan damage resulting in permanent deterioration in the quality of life and mortality. The treatment involves the use of hydroxyurea, management of pain crises, transfusion support, and management of end-organ damage. Allogeneic

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hematopoietic stem cell transplantation is one of the curative options [3]. The aim of the study was to understand the socio-demographic and clinical profiles of patients with SCD. We also aimed to elucidate the real-world scenario, the clinical course of the disease, acceptability and availability of medical interventions, and the knowledge gap regarding the gravity of the disease. We investigated the local clinical scenario, as it actually is, in the real world and aimed to plan for large-scale interventions based on the needs of the patients.

## Methods

The following patients were included in the study: those with SCD who were registered with the sickle cell unit of the government district hospital of three predominantly tribal districts- Anugul, Sundergarh, and Jhasruguda. This was a cross sectional prospective study with patients of all age groups diagnosed with sickle disease included.

The study was planned at government run sickle cell units, after due permission from the government and in consultation with the state government. The study has been duly approved by the IRB of the Sarvodaya hospital and research Center.

All patients underwent a medical examination by a physician. All patient-related data were collected by the physician and recorded in a predesigned survey questionnaire. Data regarding the demographic part of the survey included age, height, weight, gender, family status, age at time of diagnosis of SCD, relatives with SCD, information on siblings, race, and education levels. The questions were used to assess the medical history including history of pain (veno-ocllusive crises), its frequency over time, site, and management. Medical history of admissions for surgical procedures, stroke, or other causes was also recorded. The history of short-term and life-long blood transfusions was specifically elucidated by physician. Patients were questioned about usage, frequency, regularity, and dosage of hydroxyurea. The accompanying medical records-diaries (if available) were also scrutinized.

Most of the patients carried the copy of the original-first report of Hb electrophoresis, generally performed using high-performance liquid chromatography (HPLC) at a centralized state unit. It clearly mentioned the percentage and variants of Hb. All surveyed patients, except for those with a history of recent transfusion, were offered a point of care cellulose acetate Hb electrophoresis, which was performed by trained personnel using fresh blood samples. The same information was used to compare with the old data. All data were statistically analyzed using standard statistical methods.

## Results

In total, 124 individuals with SCD were invited for clinical assessment and interactions; 114 patients were analyzed, and 10 were excluded due to insufficient information. There were 68 (59.6%) male and 46 (40.4%) female patients (Table 1). The median age of diagnosis was 5 years. One patient was diagnosed late with SCD at the age of 60 years. The median age at the time of presentation was 19 (range, 2–70) years. Most of the patients were young. Forty-four (38.5%) patients were in the <15-year age group, and 54 (47.3%) patients were in the 15–40-year age group. Only 14 (12.2%) patients were > 40 years of age. Only three individuals were > 50 years of age.

All patients from the respective districts were registered with the local sickle cell unit of the government hospital. All were from rural areas, and the majority belonged to the tribal population (commonly classified as scheduled class, scheduled tribe, and other backward class), and a few belonged to the general population. All patients were originally diagnosed using HPLC; therefore, the diagnosis and date of first reporting could be ascertained with certainty. Sibling testing was not performed in 18% of patients, and 36% of patients were unaware of the information. Only 45.6% of patients confirmed that their siblings were also tested for the disease.

Veno-occlusive crises were the most common symptoms reported by every patient. The symptoms reported ranged from single-site or multiple-sites pain to rather vague body ache. Further assessment revealed that most symptoms accounted for multiple episodes of pain crisis (Table 2). These could be elucidated only as subjective symptoms because no records of admission or physician evaluation were available for any patient.

Nearly one-third of patients never received any blood transfusion (Table 3). Only 16% of patients required >10 rounds of transfusion. In the preceding year, 86% of patients did not require transfusions, and only 6% underwent up to five transfusions.

**Table 1:** Sociodemographic data of 114 patients with SCD.

| Parameter | Number of patients | % |
|---|---|---|
| **Sex** | | |
| Male | 68 | 59.6 |
| Female | 46 | 40.4 |
| **Caste** | | |
| General | 23 | 20.17 |
| SC | 49 | 42.98 |
| ST | 35 | 30.7 |
| OBC | 7 | 6.14 |
| **Sibling(s) screened for SCD** | | |
| Yes | 52 | 45.6 |
| No | 21 | 18.4 |
| Do not know | 41 | 36 |

OBC, other backward class; SC, scheduled class; ST, scheduled tribe

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**Table 2:** Total number of episodes of veno-occlusive crises in patients with SCD.

| Number of episodes | Number of patients (%) |
|---|---|
| Multiple | 36 (31.5) |
| 5 | 5 (4.4) |
| 4 | 10(8.9) |
| 3 | 19 (16.7) |
| 2 | 23 (20) |
| 1 | 21 (18.5) |

**Table 3:** Number of transfusions in patients with SCD.

| Number of transfusions | Number of patients (%) who underwent transfusions for a lifetime | Number of patients (%) who underwent transfusions in the preceding year |
|---|---|---|
| 0 | 37 (32.45) | 98 (8) |
| 1 | 16 (14) | 9 (7.8) |
| 2–5 | 40 (35.08) | 7(6.2) |
| 6–10 | 2(1.75) | 0 (0) |
| >10 | 19 (16.66) | 0 (0) |

**Table 4:** The current pattern of HbF% in patients on hydroxyurea (n = 89).

| HbF level, % | Number of patients (%) |
|---|---|
| ≥ 41 | 8 (8.9) |
| 31–40 | 24 (26.9) |
| 26–30 | 15(16.9) |
| 30–25 | 23 (25.9) |
| ≤ 20 | 19 (21.4) |

Usage of hydroxyurea was specifically probed; 104 out of 114 patients were on regular hydroxyurea treatment. The supplies were replenished freely through district units. Patients reported irregularities in consumption, and this information was subjective, with no exact records. However, the usage could be established with certainty because the drug supply was documented with written records, and it was controlled.

In 89 patients, a random sampling of Hb electrophoresis, using gel, was performed on the date of examination (Table 4). Only 21% of these patients had a hemoglobin F (HbF) level of < 20%; the remaining patients had HbF levels > 20%. Nine patients had HbF levels > 40%, and approximately 27% of patients had HbF levels between 31% and 40%.

Importantly, seven of 114 patients had avascular necrosis of the femur head. There were occasional cases of cerebrovascular events.

## Discussion

SCD is covered under the National Program for Prevention and Control of Hemoglobinopathies in India [4] and is attracting focus from the state departments. The main focus is on early detection and prevention activities. However, the number of existing patients is very large; thus, it is important to focus on the care of this group. Every district hospital in notified districts has one sickle cell unit responsible for registering the patient and providing assistance for investigations, drugs, and transfusion support. All patients with SCD had some degree of complications. The frequencies of complications varied. No documented clinically significant sickling crises were observed. The only standard medication was hydroxyurea.

Most patients are diagnosed in the early stage of the disease. Despite an inborn error, medical conditions are reported at various stages of life. The age distribution shows that most patients are young (< 40 years of age) [5], The non-reporting of patients aged > 40 years may indicate a bias owing to the increased mortality rates among patients in that age group. In a study conducted in Gujarat, only 13% of patients were > 30 years of age[6]. The overall median survival rate is low among patients with SCD. The cost of care is very high [7]. Allogeneic hematopoietic stem cell transplantation is the curative therapy used in adult patients with SCD internationally. There are no data on this therapy for Indian patients with SCD. The disease burden is high among the young age group; thus, most patients require medical assistance early in life. Further research is required regarding early interventions for SCD.

Hydroxyurea has proven clinical benefits and is approved by the US Food and Drug Administration for the treatment of SCD in children. Hydroxyurea augments HbF production, prevents sickling, and improves Hb levels. The full mechanism of action of hydroxyurea is not completely understood; however, it improves red blood cell hydration and decreases neutrophil and platelet counts, in turn improving blood flow and decreasing sickling. HUSTLE (NCT00305175) was a prospective observational study with the primary goal of describing the long-term clinical effects of hydroxyurea escalated to maximal tolerated dose in children with SCA. In 230 children (610 patient-years of follow-up), the mean HbF% attained at maximal tolerated dose was > 20% for up to four years of follow-up. When HbF% values were ≤ 20%, the children had twice the odds of hospitalization for any reason ($P<0.0001$), including vaso-occlusive pain ($P<0.01$) and acute chest syndrome ($P<0.01$), and more than four times the odds of admission for fever ($P<0.001$). Therefore, attaining HbF > 20% was associated with fewer hospitalization episodes without significant toxicity [8]. This data support the use of hydroxyurea in children and suggests that the preferred dosing strategy targets an HbF endpoint of > 20%. According to a 2014 expert panel report sponsored by the National Heart, Lung, and Blood Institute on the evidence-based management of SCA, hydroxyurea therapy

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should be administered among all children at nine months of age, regardless of symptoms [9].

One hundred and four patients with SCD were on hydroxyurea in our study. This percentage is higher than that reported by other studies conducted in Brazil and USA. [10,11,12] Free and controlled distribution of hydroxyurea by the state is a major reason for continued usage of hydroxyurea. Regular usage of hydroxyurea could be responsible for reduced number of cases of pain crisis and transfusion requirement. Patient education on pain management, which is self-driven, is required. The necessity of blood transfusion depends on the clinical conditions of the patients.

Characteristics of SCD in Indians might be different from those of other populations. This observation was reported in many previous studies. Transfusion requirement was very low, as revealed in the present study that 86% of the patients did not undergo a single transfusion in the preceding year.

Increased levels of HbF with hydroxyurea therapy were also reported previously. A study of 70 patients reported a statistically significant decrease in HbS levels and increase in HbF levels after one year of hydroxyurea therapy [13]. These levels might have been maintained with the regular usage of hydroxyurea. In the present study, high HbF levels were observed, and we found that nearly 80% of patients could maintain HbF levels above 20%. On average, there was prolonged usage of hydroxyurea. Once hydroxyurea therapy was started, the patients continued the treatment without visiting a physician. High HbF levels in the study population may be due to prolonged and consistent usage of hydroxyurea or may represent a different disease profile. This could be attributed to the low number of cases of pain crises and transfusions.

## Limitations

Limitation of the study was associated with cross sectional nature of the study involving single time interaction. Though the interaction was exhaustive, with analysis of medical history documents, clinical examination and personal interview, still there was no regular follow up data collected.

## Conclusions

Hemoglobinopathies in Indians represent a serious concern due to the high prevalence in an otherwise socio-economically deprived population. The clinical pattern of SCD and medical requirements of the patients are different from those reported in the western population remains a major clinical concern. Compared to world data, usage of hydroxyurea was very high (One hundred and four (91%) patients were on regular hydroxyurea). Desired levels of HbF were maintained in the surveyed population. Frequency of blood transfusions was low. Novel treatments including transplantation, gene therapy, and drugs for controlling the symptoms should be urgently researched and introduced.

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## Conflict of Interest

Dinesh Pendharkar, Garima Nirmal, Neha Gupta, and Abhishek Raj- all authors declare that they have no conflict of interest.

## Authorship Contribution

Dinesh Pendharkar contributed to conception and design, data acquisition , analysis, interpretation of the data, drafting article, revising and approval of final version

Garima Nirmal contributed to conception and design, data acquisition , analysis, interpretation of the data, drafting article, revising and approval of final version.

Neha Gupta contributed to conception and design, data acquisition, analysis, interpretation of the data, drafting article, revising and approval of final version.

Abhishek Raj contributed to conception and design, analysis, interpretation of the data, drafting article, revising and approval of final version.

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