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Original Article

Evaluating the Safety and Efficacy of Hydroxyurea in Adult Sickle Cell Disease: A Prospective Observational Study

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ABSTRACT

Background: Sickle Cell Disease (SCD) is characterized by recurrent hospitalizations and painful Vaso-Occlusive Crises (VOCs). VOCs are prevalent and often necessitate hospital admissions. **Aim and Objectives:** This study aims to comprehensively assess the role of Hydroxyurea (HU) in managing VOCs among adult patients with SCD. Specifically, it evaluates the efficacy and safety of HU therapy, its impact on hospitalization outcomes, and explores the prevalence of SCD across different patient groups. **Materials and Methods:** A total of 60 eligible patients were enrolled, and their medical records were systematically reviewed. Symptoms and clinical data were documented, followed by comprehensive statistical analysis. **Results:** Fatigue, a common symptom in SCD, was reported by 90% of patients. Joint pain was experienced by 61.7% of patients, with 54.6% of those exhibiting VOCs. Patients aged 18-35 years (*n*=54) outnumbered those over 35 years (*n*=6). The study displayed a balanced gender distribution (51.6% male, 48.3% female). Geographically, the majority were from rural (46.7%) and metropolitan (31.7%) areas, with suburban representation at 21.7%. **Conclusion:** The study demonstrated a favorable risk-benefit profile of HU treatment, yielding positive outcomes. Early detection and intervention significantly influence disease trajectory. Early screening and timely HU therapy in SCD patients, including new-borns, are recommended.

Keywords: Sickle Cell Disease Management, Hydroxyurea Therapy, Vaso-Occlusive Crisis, Adult Population.

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INTRODUCTION

SCD is a complex condition affecting multiple body systems and causing acute episodes of illness along with gradual organ damage. The global burden of disease study reveals that approximately 3.2 million individuals have SCD, while around 43 million carry the Sickle Cell Trait (SCT). Tragically, around 176,000 deaths annually are attributed to complications related to SCD. This disorder is among the most prevalent and severe single-gene disorders worldwide. Its prevalence has expanded significantly over time, driven by historical factors like the slave trade and modern population movements. SCD is on the rise globally, with estimates suggesting that nearly 300,000 new-borns are born with Sickle Cell Anemia (SCA) each year, characterized by having two copies of the sickle Hemoglobin Gene (HbS). This number could potentially reach 400,000 by the year 2050 (Kato *et al*., 2018; Rees *et al*., 2010). SCD is a genetic disorder characterized by the presence of abnormal sickle cell Hemoglobin (HbS) in red blood cells. The most common form occurs in individuals with two HbS alleles (SCD SS). Other variations include coinheritance with different globin gene alterations like C (SCD SC) and various forms of thalassemia (S/0thalassemia and S/+thalassemia). The disease is driven by three main biological processes: HbS polymerization, vaso-occlusion, and hemolysis-induced endothelial dysfunction. A fourth process, sterile inflammation, has more recently been recognized as well (Konotey-Ahulu, 1974, Okpala, 1998). SCD was initially observed in 1910 and labeled as a new, unknown condition referred to as black disease. It wasn't until 1949 that its molecular basis was recognized.a In 1958, Ingram identified the genetic cause as a substitution of valine for glutamic acid in the hemoglobin beta chain's sixth amino acid position. The mechanism of sickle formation was described by Hahn and Gillespie in 1927, noting the distinctive sickle shape of deoxygenated sickle hemoglobin, which led to the disease's name. A key therapeutic approach for SCD involves increasing fetal hemoglobin production by altering bone marrow proliferation kinetics, thereby shifting the balance

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away from sickle hemoglobin production (Arishi *et al.*, 2021). HU efficacy in treating SCD is often attributed to its ability to increase fetal hemoglobin levels. It functions as an S-phase-specific drug, inhibiting DNA synthesis and causing cell death. The drug directly inhibits the RR M2 subunit, leading to transient effects on RR due to its rapid absorption and excretion. HU effects in SCA include elevating HbF levels, increasing erythrocyte volume and hemoglobin content, reducing reticulocyte and white cell counts, altering red blood cell adhesion, and more. Clinically, HU has proven effective for many with SCA, leading to improved anemia, fewer vaso-occlusive events, and reduced hospitalizations. An ideal treatment for SCA would be low-cost, once-daily oral dosing that demonstrates laboratory and clinical efficacy, works across age groups, prevents acute events and organ damage, offers lasting benefits without resistance, and has minimal side effects. There are contraindications for HU use, such as pregnancy, liver disease, hypersensitivity, and non-compliance history. Prior to use, patients undergo evaluations including blood tests and kidney/liver function assessment. Common side effects include fever, cough, and back pain, while rarer effects involve changes in stool/urine color, nail discoloration, skin issues, and unusual bleeding or bruising (Arishi *et al.*, 2021; Inusa *et al.*, 2019; Lonergan *et al.*, 2001).

Need of the study

The need for this study arises from several critical considerations: Divergent prognosis and outcome: SCD exhibits varying prognoses and outcomes across different geographical regions, with notable differences between foreign countries and India. This study aims to shed light on the distinctive role of HU within the Indian population, allowing for a nuanced understanding of its impact compared to foreign populations. Safety and efficacy in Indian population: While the safety and efficacy of HU have been explored in foreign contexts, there's a need to ascertain its performance within the adult Indian population. Factors like genetic diversity, healthcare practices, and socio-economic conditions can influence treatment outcomes. Thus, investigating the safety and efficacy of HU specifically in Indian adults is vital for informed clinical decision-making. Prevalence variation within India: India's diverse population includes both tribal and non-tribal communities. Understanding the prevalence of SCD within these groups is crucial for tailored healthcare interventions. This study intends to provide insights into the prevalence of SCD within both tribal and non-tribal populations, contributing to targeted strategies for disease management and prevention.

MATERIALS AND METHODS

The study employed an observational cross-sectional design and was conducted at the Department of General Medicine in Dhiraj General Hospital, Vadodara. Data was sourced from physician-prescribed prescriptions, and ethical approval was secured from the Sumandeep Vidyapeeth Institutional Ethics Committee (SVIEC). The sample size of 59 was determined using standard formulae, and the study duration was Six month. Inclusion criteria encompassed patients with HPLC-proven SCD above 18 years of age, admitted to various wards of the hospital, and receiving or having received HU. Exclusion criteria excluded non-consenting patients, those with sickle cell trait, or those with specific contraindications. The study materials included informed consent forms, proformas, and patient information sheets. The methodology entailed patient enrolment based on criteria and consent, comprehensive data and investigations review, specific testing, HU details recording, and assessment of patient satisfaction. Statistical analysis involved data validation, coding, and relevant tests. Ethical principles of informed consent, confidentiality, and participant freedom were maintained, and the study's feasibility was ensured within the hospital setting without interfering with treatment

RESULTS

Based on their residence, the study's participants were divided into several groups. There were 60 patients in all, of which 28 (46.7%) came from rural areas, 19 (31.7%) from cities, and 13 (21.7%) from suburban areas. Among the 60 patients, 28 (46.7%) were from tribal areas, and 32 (53.3%) were from non-tribal areas. Out of the 60 patients, 24 (40%) were from Gujarat, and 36 (60%) were from Madhya Pradesh. Among the 60 patients, 54 (90%) with SCD were in the age group of 18-35 years. Within this age group, 26 were female, and 28 were male. In the age group of 36 years and older, there were 6 patients with sickle cell disease, with 1 female and 5 males. Overall, out of the 60 patients, 29 were female, and 31 were male. In the dataset of 60 patients, the average age was 26 years, with a standard deviation of 8 years, denoted as (Mean age±SD, 26.483±7.97). The oldest patient in the dataset was 50 years old, while the youngest was 18 years old. Among the 60 patients, 39 (65%) required ward stay, while 21 (35%) required Intensive Care Unit (ICU) stay during their hospitalization. Based on the collected data, the average height was 1.65 meters with a standard deviation of 0.11 meters (1.65±0.11). The mean weight was 54.56 kilograms with a standard deviation of 9.62 kilograms (54.56±9.62). Among all the participants, 28.3% were classified as underweight (BMI ≤ 18.50), 70.0% were in the normal BMI range (BMI 18.50-24.99), and only 1.7% were categorized as pre-obese (BMI 25.00-29.99) based on their BMI group. Based on the collected data, the mean BMI (Body Mass Index) was 19.79 kg/m^2 with a standard deviation of 2.58 kg/m^2 (19.79±2.58). The lowest BMI observed was 13.96, while the highest was 27.34. Among the 60 patients, 29 of them were on regular medication, while 31 were not following a regular medication regimen. Among the patients, 38% (17 out of the total) had no history of crisis. There were 25 patients who experienced two or fewer episodes of crisis, and 18 patients had a history of more than two episodes of crisis. Among the 60 patients, 81.7% (49 patients) were non-smokers, while 18.3% (11 patients) were smokers based

on their social history of smoking. Among the 60 patients, 81.7% (49 patients) did not use tobacco by chewing, while 18.3% (11 patients) were tobacco chewers. Among the 60 patients, 85.0% (51 patients) did not consume alcohol, while 15.0% (9 patients) were alcoholic. Among the 60 patients, 75% (45 patients) did not suffer from severe anemia, while 25% (15 patients) experienced severe anemia. In the study, a total of 60 patients were evaluated based on their reported symptoms. Among these patients, nearly half, constituting 48.3% (29 patients), experienced episodes of fever. Joint pain was another prevalent symptom, with 61.7% (37 patients) reporting this discomfort. Fatigue was a widespread complaint, with a significant 90% (54 patients) of the participants indicating they suffered from it. Respiratory symptoms were observed in 23.3% (14 patients), while 45% (27 patients) experienced gastrointestinal issues. A smaller portion of patients reported other symptoms, such as neurological (1.7%), ulcer (1.7%), breathlessness (1.7%), burning micturition (1.7%), and chest pain (11.66%). These findings provide insight into the diverse array of symptoms experienced by the patients under investigation. Based on the data collected from 60 patients, the mean ESR (Erythrocyte Sedimentation Rate) was 29 with a standard deviation of 17 (Mean ESR±SD 29±17). The highest ESR recorded from the data was 92, while the lowest CRP (C-reactive protein) was 4. For CRP, the mean was 68 with a standard deviation of 67 (Mean CRP±SD 68±67). The lowest CRP level observed was 1, and the highest was 307. These values represent the inflammatory markers in the patient population, providing insight into the levels of inflammation present in the study group. From the collected data of 60 patients, the mean HbF% (Hemoglobin F percentage) was 15.048 with a standard deviation of 7 (Mean HbF%±SD 15.048±7). The highest HbF% observed in the data was 30.8, while the lowest was 4.6. Regarding HbA% (Hemoglobin A percentage), the mean was 5.483 with a standard deviation of 5.2790 (Mean HbA%±SD 5.483±5.2790). The range of HbA% values varied from a minimum of 2 to a maximum of 38.9. For HbA2% (Hemoglobin A2 percentage), the mean was 3 with a standard deviation of 3 (Mean HbA2%±SD 3±3). The data showed a minimum HbA2% of 1.2 and a maximum of 5.4. Lastly, the mean S_Window% (Sickle Window percentage) was 67 with a standard deviation of 11 (Mean S_Window%±SD 67±11). The Sickle Window% ranged from a minimum of 40.3 to a maximum of 84.5. These values provide insights into the hemoglobin profiles of the patients in the study, particularly the distribution of different hemoglobin types and their percentages. In the dataset of 60 patients, the mean value for Mentzer's index was 22.59 with a standard deviation of 8.26 (22.59±8.26), and for Srivastav's index, the mean value was 7.37 with a standard deviation of 2.78 (7.37±2.78). Mentzer's index is used to assess whether a patient might have iron deficiency or beta thalassemia. A Mentzer's value greater than 13 suggests iron deficiency, while a value less than 13 suggests beta thalassemia. Srivastav's index is also used to evaluate iron deficiency or beta thalassemia. A Srivastav's value greater than 3.8 indicates iron deficiency, whereas a value less than 3.8 indicates the presence of beta thalassemia. These indices provide important diagnostic information about the potential underlying causes of anemia in the patient population under study. Among the 60 patients, 31.66% (19 patients) experienced hepatomegaly, while the remaining 68.33% (41 patients) did not have this condition. Among the 60 patients, 80% (48 patients) had splenomegaly, while 20% (12 patients) did not have splenomegaly. Additionally, hepatosplenomegaly was observed in 12 patients. In the study involving 60 patients, various medical conditions were observed among the participants. A total of 9 patients were diagnosed with AVN (Avascular Necrosis), 6 patients presented with Myelitis/Encephalitis, and 1 patient exhibited Bone marrow suppression. Pleural Effusion/Consolidation was found in 13 patients, while Auto splenectomy was noted in 9 patients. Additionally, 6 patients were diagnosed with Cholelithiasis, a condition characterized by the presence of gallstones in the gallbladder. These findings provide valuable insights into the diverse range of medical conditions and challenges faced by the patient population under investigation. Among the 60 patients receiving HU therapy, some experienced side effects. Specifically, 6.66% (4 patients) reported diarrhea, 3.33% (2 patients) had constipation, 5.00% (3 patients) experienced loss of appetite, 6.66% (4 patients) had nausea, and another 6.66% (4 patients) suffered from stomach upset due to the treatment. The majority, 71.66% (43 patients), did not report any side effects from HU therapy. Among the 60 patients, the majority, comprising 88.3% (52 patients), reported being fully satisfied with their treatment, while a smaller portion, 11.7% (7 patients), expressed average satisfaction. Additionally, one patient stopped treatment for an unspecified reason (Table 1).

DISCUSSION

SCD is a complex multisystem disorder characterized by acute bouts of illness and progressive organ damage over time. This condition is on the rise globally, leading to heightened hospitalization rates and frequent painful episodes. Fortunately, the use of HU has emerged as a promising therapeutic approach for mitigating the impact of sickle cell disease. Our study seeks to shed light on the significance of HU in managing SCD among adult individuals in the Indian population. We aimed to explore not only its effectiveness but also its safety profile in this specific demographic. Additionally, we will investigate the prevalence of this debilitating disease across various settings, including rural, urban, and tribal areas, to gain a comprehensive understanding of its impact on different communities in India. Through our research, we hope to contribute valuable insights that can enhance the management and care of individuals affected by SCD in India.

In our study, we enrolled a cohort of 60 patients diagnosed with sickle cell disease, all of whom tested positive for sickling and had confirmed SCD based on a positive HPLC report. This

patient group consisted of 29 females and 31 males, reflecting an even distribution between genders, with males comprising 51.6% and females 48.3% of the total participants. The mean age of the patients included in our study was 26.483 years, with a standard deviation of 7.97 (Mean age±SD, 26.483±7.97). It is worth noting that a similar gender distribution was observed in a study conducted at the Franco and Piera Cutino-A.O.O.R. "Villa Sofia- Cervello" in Italy, which involved a larger sample size of 652 individuals. In that study, 56% of the participants were adults over the age of 18, and, like our study, it also exhibited an equal gender distribution. Furthermore, our findings indicated that SCD tends to affect younger individuals more than the elderly, as evidenced by the mean lifespan in our study of 24.5 years±6.8 years. Additionally, our study revealed that males had a higher susceptibility to sickle cell disease, aligning with the observations from the aforementioned research in Italy. In terms of Body Mass Index (BMI), the majority of our patients (70%) fell within the normal BMI range (18.5-24.9), while 28.3% were classified as

Table 1: Demographic Details of the participants.

Residential distribution of the patients				
Sl. No.	**State**			**Frequency (%)**
1.	Rural			28 (46.7%)
2.	Urban			19 (31.7%)
3.	Suburban			13 (21.7%)
Total				60 (100%)
Tribal area				
Sl. No.	**Tribal area**			**Frequency (%)**
1.	Yes			28 (46.7%)
2.	No			32 (53.3%)
Total				60 (100%)
State wise residential distribution of the subjects				
Sl. No.	**State wise distribution**			**Frequency (%)**
1.	Gujarat			24 (40%)
2.	Madhya Pradesh			36 (60%)
Total				60 (100%)
Age and gender distribution of patients				
Sl. No.	**Age Group**	**Gender**		**Frequency (%)**
		Male	**Female**	
1.	18-35	28	26	54 (90%)
2.	≥36	01	05	06 (10%)
Total		29	31	60 (100%)
Chi-square (χ2): 13.12, df:01 P:0.0001 S				
Distribution as per hospitalization				
Sl. No.	**State**			**Frequency (%)**
1.	Ward			39 (65%)
2.	ICU			21 (35%)
Total				60 (100%)
Distribution as per BMI groups				
Sl. No.	**BMI**			**Frequency (%)**
1.	Underweight (≤ 18.50)			17 (28.3%)
2.	Normal (18.50-24.99)			42 (70.0%)
3.	Pre-Obese (25.00-29.99)			01 (01.7%)

Total		60 (100%)

Patient compliance

Sl. No.	Patient compliance	Frequency (%)
1.	Compliant	29 (48.3)
2.	Non-Compliant	31 (51.6)
Total		60 (100%)

Past history of crisis according to patient

Sl. No.	No of crisis	No of patient	On irregular Hx
1	0	17	-
2	1	12	6
3	2	13	11
4	3	09	7
5	4	4	3
6	5	3	2
7	>6	2	2

Hospital stays according to patient compliance

Hospital Stay		
Patient compliance	Yes (27)	6.85±4.60 (01-20)
	No (33)	7.87±4.37 (03-22)

Patient distribution based on social history of smoke

Sl. No.	Smoker	Frequency (%)
1.	No	49 (81.7%)
2.	Yes	11 (18.3%)
Total		60 (100%)

Tobacco Chewer

Sl. No.	Tobacco Chewer	Frequency (%)
1.	No	49 (81.7%)
2.	Yes	11 (18.3%)
	Total	60 (100%)

Tobacco chewer with crisis

Type of crisis	No of pt.
Vo	3
Ss	2
Total	5

Patients Distribution based on alcohol consumption.

Sl. No.	Alcohol	Frequency (%)
1.	No	51 (85.0%)
2.	Yes	09 (15.0%)
	Total	60 (100%)

Hospital stay of addicted patients

	Hospital stays	
Addiction	Yes (24)	7.91±4.25 (03-20)
	No (36)	7.13±4.65 (01-22)

Reason for admission

Sl. No.	Infection	Frequency (%)	
1	Present	06 (10%)	
2	Absent		54 (90%)
	Crisis: Yes	36	
	Crisis: No	18	
Total		60 (100%)	

Patient distribution based on type of crisis

Sl. No.	Type of crisis	Frequency (%)
1.	ACS	07 (10%)
2.	SS	04 (13.3%)
3.	VO	25 (41.7%)
Total		36 (100%)

Patient distribution based on severity of anemia

Sl. No.	Severe anemia	Frequency (%)
1.	No	45 (75%)
2.	Yes	15 (25%)
Total		60 (100%)

Patient distribution based on symptoms

Sl. No.	Symptoms	Frequency (%)
1.	Fever	29 (48.3%)
2.	Joint Pain	37 (61.7%)
3.	Fatigue	54 (90%)
4.	Respiratory	14 (23.3%)
5.	GIT	27 (45.0%)
6.	Chest Pain	07 (11.66%)

Hepatomegaly and condition seen as per patient compliance

Sl. No.	Hepatomegaly	Irregular Rx	Condition Seen	Frequency (%)
1.	Yes (19)	Yes (05)	Pleural Effusion/Consolidation	03
		No (14)	AVN	01
			Pleural Effusion/Consolidation	06
			Auto splenectomy	06
			Cholelithiasis	01
2.	No (41)	Yes (22)	AVN	05
			Myelitis/Encephalitis	03
			Pleural Effusion/Consolidation	04
			Auto splenectomy	01
			Cholelithiasis	03
		No (19)	AVN	03
			Myelitis/Encephalitis	03
			Bone Marrow Suppression	01
			Auto splenectomy	02
			Cholelithiasis	02

Inflammatory marker

		ESR	CRP
N	Valid	60	59
	Missing	0	1
Mean		28.88	67.89
Median		26.00	50.00
Std. Deviation		16.585	66.602
Minimum		4	1
Maximum		92	307

HPCL

		HbF%	HbA%	HbA2%	S_Window%
N	Valid	60	60	60	60
	Missing	0	0	0	0
Mean		15.048	5.483	2.892	66.655
Median		14.250	4.100	2.900	69.900
Std. Deviation		6.5832	5.2790	.8222	10.7418
Minimum		4.6	1.7	1.2	40.3
Maximum		30.8	38.9	5.4	84.5

Distribution as per Mentzer and Srivastav index

		Mentz Index	Sriva Index
N	Valid	60	60
	Missing	0	0
Mean		22.5987	7.3726
Median		20.9755	6.6714
Std. Deviation		8.26891	2.78803
Minimum		3.38	1.11
Maximum		51.64	16.81

Pearson's Correlation r:0.96 P: 0.0001

Patient distribution based on hepatomegaly

Sl. No.	Hepatomegaly	Frequency (%)
1.	Yes	19 (.66%)
2.	No	41 (68.33%)
3.	Total	60 (100%)

Patient distribution based on splenomegaly

Sl. No.	Splenomegaly	Frequency (%)
1.	Yes	48 (80%)
2.	No	12 (20%)
3.	Total	60 (100%)

Patient distribution based on condition seen

Sl. No.	Condition	Frequency (%)

1.	AVN	09
2.	Myelitis/Encephalitis	06
3.	Bone marrow suppression	01
4.	Pleural Effusion/Consolidation	13
5.	Auto splenectomy	09
6.	Cholelithiasis	06

Condition seen according to patient compliance

Conditions	Non-compliant patient	Compliant
AVN	5	4
Myelitis/Encephalitis	3	3
Bone marrow suppression	0	1
Pleural Effusion/Consolidation	7	6
Auto splenectomy	1	8
Cholelithiasis	3	3

Patient distribution based on side effect of HU therapy

Sl. No.	Side Effects	Frequency (%)
1.	Diarrhea	04 (06.66%)
2.	Constipation	02 (03.33%)
3.	Loss of Appetite	03 (05.00%)
4.	Nausea	04 (06.66%)
5.	Stomach Upset	04 (06.66%)
6.	None	43 (71.66%)
	Total	60 (100%)

Patient distribution based on satisfaction

Sl. No.	Score	Frequency (%)
1.	1.0	01 (01.7%)
2.	2.0	01 (01.7%)
3.	3.0	02 (03.3%)
4.	4.0	03 (5.0%)
5.	5.0	02 (03.3%)
6.	6.0	09 (15.0%)
7.	7.0	10 (16.7%)
8.	8.0	15 (25.0%)
9.	9.0	11 (18.3%)
10.	10.0	05 (08.3%)
	Total	59 (100%)

Patients Satisfaction

Sl. No.	Satisfaction	Frequency (%)
1.	Average	07 (11.7%)
2.	Fully Satisfied	52 (88.3%)
	Total	59 (100%)

underweight (18.5), and only 1.7% were categorized as pre-obese. The mean BMI in our study was 19.79, with a standard deviation of 2.58 (Mean BMI±SD, 19.79±2.58). These findings offer valuable insights into the demographic and health characteristics of individuals with SCD in our study population, indicating that maintaining a healthy BMI is an important aspect of managing the condition (Rigano *et al*., 2018).

In this comprehensive study, our patient cohort encompassed a diverse range of geographical backgrounds, including individuals hailing from rural, urban, suburban, tribal areas, and city settings. Our research focused on two states in India, Gujarat and Madhya Pradesh, both of which are known as "sickle cell states," where SCD is notably more prevalent. Among the patients included in our study, the largest proportion resided in rural areas, accounting for 46.7% of the total, followed by metropolitan areas at 31.7%, and suburban regions at 21.7%. Additionally, our study revealed a higher representation of patients from the tribal zones of Madhya Pradesh as opposed to Gujarat. Specifically, Madhya Pradesh was responsible for 60% of the total cases (36 out of 60), whereas Gujarat contributed 40% (24 out of 60). These findings align with existing research. A study published in May 2016 by Roshan B. Colah and Malay B. Mukherjee, which focused on tribal populations in India affected by sickle cell disease, identified Madhya Pradesh as having the highest disease burden. This study noted that 27 out of 45 districts in Madhya Pradesh fall within the sickle cell belt, primarily inhabited by scheduled tribes. Additionally, another study conducted by Kaur *et al*., reported a prevalence range of 0-33.5% in western India and 22.5-44.4% in central India for sickle cell disease, further corroborating the regional distribution of the disease. In light of these established patterns and statistics, our study's findings provide valuable support and insight into the prevalence and distribution of SCD within these specific regions (Colah *et al*., 2015).

In our study, patients were admitted to either the Intensive Care Unit (ICU) or the general ward based on the severity of their disease. We observed that the length of hospital stays varied, with a decrease in hospitalization periods for patients who adhered to HU medication and an increase for those who were non-compliant. This underscores the critical importance of adhering to the prescribed treatment plan. Our investigation revealed that 33 out of the participants (55%) were compliant with their treatment regimen, while 27 (45.0%) were not. Additionally, we assessed the number of painful episodes (crises) experienced by patients in the past. We found that 14 patients (23.33%) had not experienced any crisis episodes, suggesting their compliance with therapy. Conversely, the majority of patients had experienced one episode (20%), two episodes (21.7%), or three episodes (15.0%), indicating non-consistency with therapy. Notably, one patient over the age of 36, who was not adhering to the treatment, had previously endured eight crisis episodes. Furthermore, three patients in our study had recently received a diagnosis of sickle cell disease. Additionally, we observed that the most common type of crisis among our participants was Vaso Occlusive Crisis (VO), affecting 24 patients (66%), followed by SS (Sickle cell disease) crisis in 7 patients (19%), and ACS in 5 patients (14%). Our findings are in line with a study conducted by Nabin Raj Karki at Augusta University's Division of Hematology/Oncology, Augusta, GA, USA. In their study, patients aged 18 to 50 years with SCD were either given a placebo or HU for six months to assess the frequency of painful crisis episodes. Their results indicated that patients who received a placebo experienced a higher frequency of painful crises compared to those on HU. Patients consistently taking HU showed fewer than two painful crisis episodes per year, providing supporting evidence for our study's conclusion that regular medication adherence is associated with a lower frequency of crises. Moreover, a study conducted by Oluwagbenga *et al*., in July 2019 on the clinical and biochemical manifestations of severe SCD in adult patients found that Vaso Occlusive Crises (VOC) were prevalent among patients. Their study revealed that 38% of patients experienced one VOC event annually, while 15% and 26% had two and three incidents per year, respectively. Hemolytic crises were observed in 50% of the patients, with 80% experiencing one incident and 12% having two incidents annually. The study also noted that none of the patients suffered from aplastic crisis, and a smaller percentage had hepatic or splenic sequestration crises. Additionally, 40% of the patients had received blood transfusions. These findings align with some aspects of our study, highlighting the variability in crisis frequency and the impact of medication adherence on crisis occurrence. In summary, our study's observations, in conjunction with the referenced research, emphasize the importance of treatment compliance in managing SCD and its influence on the frequency and severity of crises experienced by patients (Karki and Kutlar, 2021; Oluwagbenga *et al*., 2019).

In our research, we identified several factors contributing to non-adherence to HU therapy among patients. These factors include heightened concerns about the drug, apprehensions regarding potential long-term effects, dependency concerns, worries about disruption to their daily lives, the desire for immediate symptomatic relief, lack of sufficient knowledge about the medication, and the influence of low socioeconomic status. Our study results clearly demonstrated the impact of non-adherence to HU on hospitalization duration. Among the participants, 33 individuals (55%) were classified as non-compliant with their HU therapy regimen, and they had an average hospital stay of 7.87 days with a standard deviation of 4.37 days (ranging from 3 to 22 days). In contrast, the 27 patients (45%) who were adherent to their HU treatment had a shorter average hospital stay of 6.85 days, with a standard deviation of 4.60 days (ranging from 1 to 20 days). Our findings are corroborated by a quality study conducted by Hodges in September 2020, which investigated intentional and unintentional nonadherence to HU among individuals with sickle cell disease. This study identified 14 types of obstacles

contributing to nonadherence among those who had previously used HU but were not currently taking it. Notably, 64.3% of these barriers were categorized as accidental nonadherence, with the primary reasons being a lack of discussion about HU with healthcare providers and the absence of prescription recommendations. Among those currently using HU, 75.7% of the obstacles were attributed to inadvertent nonadherence, again stemming from the lack of awareness or early conversations about HU, depending on the age group. The study also found that intentional nonadherence was linked to fears about potential side effects, including cancer, observations of friends or family members experiencing negative outcomes or side effects from HU, and a general aversion to taking additional medications. In conclusion, our research underscores the multifaceted nature of non-adherence to HU therapy among SCD patients and its significant impact on hospitalization duration. The study by Hodges *et al*., provides valuable insights into the various barriers contributing to nonadherence, categorized as intentional and unintentional, shedding light on the complexities of medication adherence in this patient population (Hodges *et al*., 2020).

In our study, we examined the impact of smoking, tobacco chewing, and alcohol consumption on the prognosis of sickle cell disease. Out of the 60 patients studied, 11 (18.3%) were smokers, 11 (18.3%) were tobacco chewers, and 9 (15.0%) reported alcohol use, while the remaining patients had no history of these habits. Regarding smoking, 11 patients in our cohort were smokers. While there is no conclusive data on the direct influence of smoking on the frequency of painful crises in sickle cell disease, our study observed that 7 of these smokers experienced severe crises. Furthermore, a retrospective study conducted in the USA in 2019 titled "Tobacco associated with an increased risk of acute chest syndrome and pain among adults with sickle cell disease" revealed that patients addicted to tobacco had a higher risk of experiencing painful crisis episodes or acute chest syndrome. This study, involving 300 patients, found that 201 of them, who were active smokers, had painful crisis episodes. This suggests that tobacco addiction may elevate the risk of painful crisis episodes in individuals with sickle cell disease. Additionally, we found that patients with addiction to smoking, tobacco, or alcohol had longer hospital stays, averaging 7.91 days with a standard deviation of 4.25 days (ranging from 3 to 20 days), compared to patients without these addictions, who had an average hospital stay of 7.13 days with a standard deviation of 4.65 days (ranging from 1 to 22 days). Therefore, our study suggests that patients with SCD who are addicted to these substances tend to have prolonged hospital stays compared to non-addicted patients (Cohen *et al*., 2010).

In our research, various reasons led to hospital admissions, including infection, crisis, severe anemia, pregnancy, and others. Notably, more than 36 individuals were hospitalized due to medical emergencies. Severe anemia accounted for 25% of admissions, infection for 10%, and pregnancy (at 36 weeks) for 8.3%. We collected data on the signs and symptoms present among these patients, which included fever, joint discomfort, fatigue, respiratory issues, gastrointestinal symptoms, neurological symptoms, pallor, splenomegaly, and anemia. Our findings revealed that splenomegaly was prevalent in 85% of patients, often attributed to sickle-shaped red blood cells blocking the spleen's veins. Anemia was present in 80% of patients, while 68.3% exhibited pallor, a common consequence of anemia. Fatigue, a common symptom in sickle cell disease, was reported by 90% of patients, and joint pain was experienced by 61.7% of them. Among those with joint pain, 54.6% had Vaso occlusive crises, which aligns with a study by Robyn T. Cohen in May 2016, showing a similar association between Vaso occlusive crises and joint pain. In our study, fatigue emerged as the most prevalent symptom, followed by joint pain. Gastrointestinal symptoms were observed in 27% of patients, while chest pain was reported by 11%. These findings provide supporting evidence for the prevalence of these symptoms in sickle cell crisis, with fatigue and joint pain being the most frequently encountered symptoms in our study (Cohen *et al*., 2016).

In our study, we employed Mentzer's and Srivastava's indexes as diagnostic tools to differentiate between thalassemia and SCD. The Mentzer index categorizes individuals with values greater than 13 as having Iron Deficiency Anemia (IDA), while those with values below 13 are considered at risk of developing -Thalassemia. Similarly, Srivastava's index designates individuals with a score exceeding 3.8 as part of the IDA group, and those with a score of 3.8 or below are at risk of developing -Thalassemia. Our study yielded a mean value for Mean Corpuscular Volume (MCV) of 76.87, with a standard deviation of 10.21 (76.87±10.21). Based on this data, our mean Mentzer index value was 22.59, with a standard deviation of 8.26 (22.59±8.26), while the mean Srivastava index value was 7.37, with a standard deviation of 2.78 (7.37±2.78). These results indicate that the majority of the patients in our study fell into the IDA category. Of note, two patients exhibited Mentzer index values below 13, specifically 3.38 and 11.13, placing them at risk of thalassemia. Interestingly, the patient with a Mentzer index value of 3.38 also had a Srivastava's index value of 1.18, indicating the presence of both thalassemia and SCD in this individual. Our findings are consistent with a study published in 2020 by Lakhani on blood indices in sickle cell disease, which reported a mean Mentzer's index of 24.46±13.56 and a mean Srivastava's index of 7.94±4.28. These findings provide valuable context and validation for the diagnostic indices used in our study to differentiate between different hemoglobinopathies.

In our study, we identified hepatomegaly (enlarged liver), splenomegaly (enlarged spleen), and hepatosplenomegaly (enlargement of both liver and spleen) in certain individuals, which was confirmed by Ultrasound (USG) reports. Specifically, we observed hepatomegaly in 19 patients (31.66%), splenomegaly in 48 patients (80%), and hepatosplenomegaly in 12 patients. These

findings highlight that splenomegaly is a more prevalent condition among individuals with sickle cell disease. Splenomegaly's higher occurrence in SCD can be attributed to the spleen's role as the primary organ for Red Blood Cell (RBC) destruction. In sickle cell disease, the abnormally shaped RBCs can obstruct blood flow within the spleen, leading to its enlargement as a result of increased workload and congestion.

In our study, we identified several infectious etiologies that coexisted with sickle cell disease, reflecting the compromised immune system of patients and their increased susceptibility to infections. Specifically, we observed respiratory system infections such as pleural effusion and consolidation in 13 patients. Avascular necrosis and auto-splenectomy were found in 9 patients, while infections of the central nervous system (myelitis/encephalitis) and cholelithiasis were present in 6 patients. Additionally, bone marrow suppression was identified in just one patient. These findings underscore the complex health challenges that individuals with SCD may face, including a heightened vulnerability to various infections and related complications.

In our study, only one mortality occurred in a patient with SCD who was admitted to the ICU for a crisis episode while taking HU. The cause of death was determined to be cardiorespiratory arrest with acute chest syndrome and sepsis, but it was not attributed to the adverse effects of HU. Our findings provide evidence that HU is a safe treatment option with a high benefit-to-risk ratio, and mortality in SCD is primarily driven by the disease itself rather than the medication.

In our study, we identified several common side effects of HU treatment in a subset of patients, although most did not experience these effects. These side effects included diarrhea (6.66%), constipation (3.33%), lack of appetite (5.00%), nausea (6.66%), and stomach upset (6.66%), while the majority reported no adverse effects (71.66%). Our findings suggest that some patients may experience increased nausea, stomach discomfort, and diarrhea after initiating HU therapy.

In our current study, we found that patients who underwent HU (HU) therapy reported satisfactory outcomes. Using a scoring system ranging from 0 to 10, a significant majority (88.3%) of patients expressed high levels of satisfaction, giving scores in the range of 5 to 10, indicating their full satisfaction with the therapy. Conversely, a smaller portion (11.7%) expressed average satisfaction, scoring between 0 and 5. These results suggest that a large proportion of patients experienced high levels of satisfaction with their HU therapy, indicating its effectiveness.

CONCLUSION

In conclusion, our study highlights the high effectiveness and safety of HU in the management of sickle cell disease, particularly during sickle cell crises. This medication significantly reduces the incidence of crises during non-crisis periods and minimizes additional complications associated with the disease. Importantly, our research revealed no significant adverse effects, with only mild to moderate side effects that were self-limiting and did not necessitate treatment, typically resolving within two days. Furthermore, HU is an affordable and widely accessible treatment option, making it suitable for basic healthcare facilities. It is crucial to note that in our study, patient mortality was not attributed to SCD or HU therapy, further affirming its safety profile. In light of these findings, HU emerges as a secure and beneficial medication for individuals with sickle cell disease, offering a favorable benefit-to-risk ratio.

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ABBREVIATIONS

ACS: Acute Chest Syndrome; **AVN:** Avascular Necrosis; **BMI:** Body Mass Index; **CNS:** Central Nervous System; **CRP:** C-reactive Protein; **DNA:** Deoxyribonucleic Acid; **ESR:** Erythrocyte Sedimentation Rate; **HbA%:** Hemoglobin A Percentage; **HbA2%:** Hemoglobin A2 Percentage; **HbF:** Fetal Hemoglobin; **HbF%:** Hemoglobin F Percentage; **HbS:** Sickle Hemoglobin; **HPLC:** High-Performance Liquid Chromatography; **HU:** Hydroxyurea; **ICU:** Intensive Care Unit; **IDA:** Iron Deficiency Anemia; **MCV:** Mean Corpuscular Volume; **RBC:** Red Blood Cell; **RR:** Ribonucleotide Reductase; **S/0thalassemia:** Sickle Cell/Zero Beta Thalassemia (S/β^0-thalassemia); **S/+thalassemia:** Sickle Cell/Plus Beta Thalassemia (S/β^+-thalassemia); **S_Window%:** Sickle Window Percentage; **SCA:** Sickle Cell Anemia; **SC:** Hemoglobin SC Disease (Coinheritance of HbS and Hemoglobin C); **SCD:** Sickle Cell Disease; **SCT:** Sickle Cell Trait; **SVIEC:** Sumandeep Vidyapeeth Institutional Ethics Committee; **USG:** Ultrasonography; **VOCs:** Vaso-Occlusive Crises.

CONFLICT OF INTEREST

Regarding the content of this manuscript, the authors state that they have no conflicts of interest. All affiliations and interests, both financial and non-financial, that can be viewed as possible sources of bias have been declared. This covers any associations, sources of financing, or personal ties that could have an impact

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