Original Article

Morbidity pattern and impact of hydroxyurea therapy among sickle cell patients in Raipur district of Chhattisgarh

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Abstract

Background: Sickle cell disease (SCD) is a disorder marked by a single-point mutation in the beta-globin gene. Hydroxyurea is a globally accepted disease-modifying agent that sounds to be effective in managing clinically and probably preventing complications of SCD. The current study aims to document the morbidity pattern and impact of Hydroxyurea therapy in the Outpatient Department of Sickle Cell Institute, Raipur. **Materials and Methods:** This cross-sectional study was conducted among randomly selected sixty-five patients (adults and children above six years). After obtaining informed consent, relevant data were collected in a predesigned pretested questionnaire. The appropriate statistical exercise was applied for the interpretation of results and inferences. **Results:** Acute febrile illness 54 (83%) and 53 (81.5%) reported pain crisis observed to have the most common morbidity among the study subjects, followed by 55.4% (36), 33 (50.8%) jaundice and difficulty breathing, respectively. Joint pain was the most commonly observed complaint, particularly at the knee joint (76.9%). Other complaints such as hand-foot syndrome (24.6%), epistaxis (27.7%), and acute chest syndrome (21.5%). Vaso-occlusive crisis (72.4%), difficulty in walking (60.0%) and eyesight (35.4%), leg ulcers (9.2%), and dactylitis (3.1%) were also documented as clinical manifestations among study participants. Less than half (44.46%) had an awareness about SCD. Hydroxyurea therapy was highly significant in improving the patient's clinical picture ($P < 0.01$), especially following the frequency of hospitalization and the requirement for blood transfusion. **Conclusion:** Pain crisis is the most common morbidity among study participants with a low level of knowledge about SCD with febrile illness. Hydroxyurea therapy was found to be quite effective as a disease-modifying therapy, especially for reducing the frequency of blood transfusion and lowering hospitalization rates among SCD patients.

Keywords: Acute chest syndrome, acute febrile illness, hydroxyurea, SCD

Introduction

In 1910, sickle cell disease (SCD) emerged as a "weird" or "new unknown sickness" in Western medicine.[1] A single-point mutation in DNA within the beta-globin gene is responsible for one of the most common hemoglobin genetic disorders.[2] The disease affects the people in Sub-Saharan Africa, the Middle East, India, the Caribbean, South and Central America, some Mediterranean countries, and the United States and Europe. Every year, around 300,000 children take birth with sickle cell anemia or its variants, out of which about 80 percent of the births occurred in low socio-economic countries.[3,4] The various clinical features of SCD result from two important pathological phenomena, which include occlusion of blood vessels and RBC

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breakdown. Sickle cell patients must deal with pain crises at regular intervals along with other manifestations. Sickle cell red blood cells (RBCs) have deviating adhesive properties, and leucocytes, plasma cells (mononuclear), and platelets attach themselves to the sickle-shaped RBC. Sickle RBCs also cling to the endothelium. Endothelial injury causes extensive hemolysis and disturbance in arginine metabolism, reducing the availability of nitric oxide (NO), which is responsible for vascular pathologies in this disease. This is followed by repetitive episodes of occlusion of vessels, resulting in chronic organ failure. Most clinical characteristics noticeably occur with time in the same person and among different patients.[5] Hydroxyurea therapy is the only available disease-modifying agent with promising improvement in the quality of life of SCD patients.

Need for study

Different sickle haplotypes exhibit a great deal of phenotypic and genetic variation, and the variances in patient features are due to geographical, environmental, and socio-economic distinctions between different provinces of Chhattisgarh. The aim of our study was to document morbidity patterns and impact of hydroxyurea therapy. The findings of the research may yield helpful information to overcome the morbidity among SCD patients as well as to support future planning and management of SCD in Chhattisgarh.

Materials and Methods

Study area

Outpatient department of Sickle Cell Institute Chhattisgarh (SCIC), Raipur.

Study settings

Department of Community Medicine, Pt. J N M Medical College, Raipur.

Study design

The observational, hospital-based study was conducted in the outpatient department (OPD) of Sickle Cell Institute Chhattisgarh (SCIC) Raipur.

Study duration

Two months (July 1 to August 31, 2022).

Sample size

65 sickle cell patients.

Inclusion criteria

The study participants had at least six months of Hydroxyurea therapy with a homozygous genotype.

Data collection method

A predesigned and pretested questionnaire was administered to the study subjects. The interview method was adopted for data collection.

Statistical method

Following data collection, relevant statistical exercises were used to arrive at a conclusion. The impact of Hydroxyurea therapy was also assessed based on the number of complaints with which the patients were hospitalized before and after the start of therapy with the help of the Wilcoxon signed-rank test.

Ethical consideration

Individual written consent has been obtained from the patient before the administration of the questionnaire. Ethical permission has been obtained from Institutional Ethics Committee Pt J N M Medical College No./MC/Ethics/2022/185, Raipur Dated 14/07/2022.

Results

Interviews were conducted with 63.1% (41) males and 36.9% (24) females. Among them were 58.5% (38) children and 41.5% (27) adults with SCD homozygous for the sickle cell gene. Most of the study participants were in the age group 11–20 years, while the least were in the age group of 41 years and above [Figure 1]. The demographic details of the study participants have been outlined in Table 1. According to the Modified B.G. Prasad Scale,[6] 29.2% (19) of the participants were from the lower-middle class.

Table 1: Socio-demographic details of study participants

Socio-demographic Variable		Frequency (*n*=65)	Percentage (%)
Place of residence	Urban	52	80.0
	Rural	13	20.0
Educational Status	Graduate and above	11	16.9
	Secondary School Certificate	03	4.6
	High School Certificate	50	77.0
	Illiterate	01	1.5
Occupation	Salaried Employee	05	7.7
	Daily Wage Worker	02	3.1
	Self Employed	10	15.4
	Students	46	64.6
	Unemployed	06	9.2

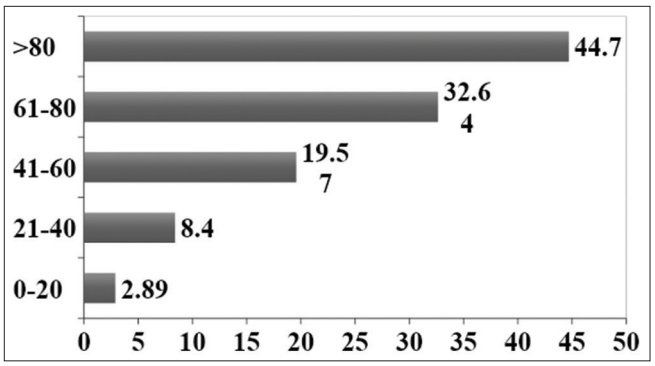

Figure 1: Age-wise mortality pattern of patients

Other Backward Classes (OBC) accounted for 61.5% (40), and the Teli (Sahu) community comprised 41.5% (27) of the population. Regarding SCD, the clinical findings have been outlined in Table 2. The patient's clinical profile was evaluated with the help of various clinical features peculiar to sickle cell patients. 55.4% (36) of participants experienced SCD-related jaundice. Breathing problems were reported by 50.8% (33) of individuals. The signs and symptoms have been elaborated in Table 3. All study participants (100%) were on hydroxyurea therapy with supplementary medication, for example, folate (65,100.0%), multivitamin (62, 95.4%), and antipyretics and analgesics if needed. The impact of hydroxyurea treatment was assessed on those subjects who were in therapy for at least 6 months prior to the study. History of blood transfusion was significantly reduced after hydroxyurea ($P \leq 0.01$). Similarly, the hospitalization rate among study participants also decreased significantly. However, 39 (73.6%) participants required hospitalization after therapy, probably due to the linking of health facilities for study participants who got proper referrals, which was lacking before the initiation of hydroxyurea therapy ($P \leq 0.01$) [Table 4]. The test results (Wilcoxon test −6.153, $P < 0.01$] showed that a 6-monthly hydroxyurea therapy elicited a statistically significant reduction in the number of complaints after therapy. Indeed, the median complaint score reduced from 2.00 to 1.00 [Table 5].

Table 2: Awareness and genotype status of parents and siblings of study subjects

Variable		Frequency (*n*=65)	Percentage (%)
Awareness about sickle cell disease (SCD)	Absent	36	55.4
	Present	29	44.6
Source of information about SCD	Doctor	28	43.1
	Internet/social media	03	4.6
	Book	01	1.5
	Unaware	35	53.8
Referral pattern to Sickle Cell Institute for treatment	ASHA worker	04	6.2
	Doctor	31	48
	School health camp	04	6.2
	Relative	23	35
	Self	03	4.6
Mother's genetic status for SCD	HBAS	32	49.2
	HBAS-Thalassemia	01	1.5
	HBSS	04	6.2
	Unknown status	28	43.1
Father's genetic status for SCD	HBAS	26	40.0
	HBSS	02	3.1
	Unknown status	37	56.9
Sibling's genetic status for SCD	Participants having sibling	50	76.9
	Sibling with HBAS	17	26.2
	Sibling with HBSS	49	75.4
	Sibling with unknown genetic status	15	23.1

HBAS=hemoglobin AS, ASHA=Accredited Social Health Activist

Discussion

Less than half, 44.60% (29), of the respondents across the varied age-education matrix, knew anything about sickle cell illness. According to a study in Orissa, higher percentages were aware of SCD (58.5%). However, the respondent's thorough knowledge of the numerous SCD-related genotypes and the tests that need to be performed for genotype screening was poor.[7] In our study, genetic risk for SCD in their parents and siblings was also

Table 3: Details of signs and symptoms of study participants

History of ailments	Details of ailments	Status (Frequency, %)			
History of fever	Suffered from fever	Yes (58, 89.2%)		No (07, 10.8%)	
	Nature of fever	Continuous (33, 50.8%)		Intermittent (25, 38.4%)	
	Frequency of occurrence	<6 months (52, 80.0%)	6 month–1 year (5, 7.7%)	>1 year (1,1.5%)	
History of pain	Suffered from joint pain	Yes (53, 81.5%)		No (12, 18.5%)	
	Location of joint pain*	Knee (50, 76.9%) Wrist (42, 64.6%)	Shoulder (42, 64.6%)	Elbow (40, 61.5%)	Ankle (40, 61.5%) Hip (39, 60.0%)
	Onset of pain	Day (49, 75.4%)		Night (4, 6.1%)	
	Associated headache	Yes (33, 50.8%)		No (32, 49.2%)	
	Associated abdominal pain	Yes (24, 36.9%)		No (41, 63.1)	
	Pain Management	Prescribed medicine (48, 73.8%)	Visits to hospital (15, 23.1%)	Self-medication (2, 3.1%)	
History of leg ulceration	Occurrence	Present (6, 9.2%)		Absent (59, 90.8%)	
	Frequency	Once (5, 7.7%)		Twice (1, 1.5%)	
History of dactylitis	Occurrence	Present (2, 3.1%)		Absent (63, 96.9%)	
	Frequency	Once (1, 1.5%)		Twice (1, 1.5%)	
History of hand-foot syndrome	Occurrence	Present (16, 24.6%)		Absent (49, 75.4%)	
	Frequency	Once (15, 23.1%)		Twice (1, 1.5%)	
History of walking difficulty	Occurrence	Present (39, 60.0%)		Absent (26, 40.0%)	
History of eyesight difficulty	Occurrence	Present (23, 35.4%)		Absent (42, 64.6%)	
History of epistaxis	Occurrence	Present (18, 27.7%)		Absent (47, 72.3%)	
History of acute chest syndrome	Occurrence	Present (14, 21.5%)		Absent (51, 78.5%)	
History of vaso-occlusive crisis	Occurrence	Present (49, 75.4%)		Absent (16, 24.6%)	

*Multiple responses received

Table 4: Association of hospitalization and blood transfusion status before and after hydroxyurea therapy

Variable	History of hospitalization after therapy				*P*
	Response	Yes (Frequency, %)	No (Frequency, %)	Total	
History of hospitalization before therapy	Present	10 (83.3%)	2 (16.7%)	12 (18.4%)	<0.001
	Absent	39 (73.6%)	14 (26.4%)	53 (81.5%)	
Total		49	16	65	
History of blood transfusion before therapy	Present	13 (100%)	0 (0.0%)	13 (20.0%)	<0.001
	Absent	38 (73.1%)	14 (26.9%)	52 (80.0%)	
Total		49	16	65	

Table 5: Impact of hydroxyurea therapy and Wilcoxon signed rank interpretation

Number of complaints that lead to hospitalization	Number of participants	Mean±SD	Min	Max	Percentiles		
					25th	50th (Median)	75th
Before therapy	65	2.58±1.029	1.00	5.00	2.00	2.00	3.00
After therapy	65	1.28±0.484	1.00	3.00	1.00	1.00	2.00

Ranks

Number of complaints that lead to hospitalization		*n*	Mean rank	Sum of ranks	Wilcoxon signed rank test, *P*
Number of complaints before therapy− Number of complaints after therapy	Negative ranks	51[a]	27.04	1352.00	−6.153, <0.001 Highly significant
	Positive ranks	02[b]	13.00	26.00	
	Ties	13[c]			
	Total	65			

SD=standard deviation. a. After therapy < Before therapy. b. After therapy > Before therapy. c. After therapy=Before therapy

unknown to a significant portion of our research participants. The results mentioned above were caused by a lack of knowledge on the disease's etiology and pathogenesis. Also, some patients have misconceptions about SCD, such as not understanding its genetic basis, the role of each parent in hereditary transmission, or their search for a complete cure for SCD. On examination, 84.6% of the patients had pallor and typically have low blood hemoglobin (Hb) concentration and normal mean corpuscular volume (MCV), consistent with a study conducted by Adam *et al.*[8] Acute morbidity from SCD most frequently includes pain, which indicates underlying abrupt marrow ischemia or necrosis. The most frequent site of joint pain, according to 81.5% of the participants, was the knee, followed by other complaints such as headache (33, 50.8%) and abdominal pain (24, 36.9%). In homozygous cases, Mandot *et al.*[9] showed that 64% of people had musculoskeletal pain, 35% had abdominal discomfort, 7% had chest pain, and 71% had splenomegaly. Their hospital-based investigation could be the cause of the elevated occurrence. Sahu *et al.*[10] discovered abdominal discomfort in 4.7% of cases, musculoskeletal pain in 0.6%, and splenomegaly in 30% of cases. Their community-based investigation might be the reason for the lower occurrence. Most respondents manage their pain with the help of prescribed medications. Neither of the respondents used hydroxyurea therapy, nor were they aware of its use. Lack of knowledge regarding hydroxyurea therapy may be due to a lack of awareness of the genuine significance of the treatment and an underestimation of its value. Jain *et al.*[11] accounted for the most frequent morbid event for hospitalization was acute febrile sickness (31%), followed by severe anemia (30%) and acute painful episodes (20%). The remaining conditions were stroke (0.6%), acute chest syndrome (3.3%), splenic sequestration crisis (4%), and hand-foot syndrome (11%). There were no morbid occurrences such as priapism, leg ulcers, or avascular osteonecrosis. Our study reported 9.2% (6) leg ulcers, 3.1% (2) dactylitis, 24.6% (16) hand-foot syndrome, 27.6% (18) epistaxis, 21.5% (14) acute chest syndrome, and 72.4% (49) vaso-occlusive crisis. However, three patients throughout our investigation and 1 (0.03%) during our pilot study reported acute vascular necrosis of the hip joint. These results differed from those obtained in a tribal group in Chhattisgarh and could be attributed to a community-based study. The most frequent crisis was a vaso-occlusive crisis, which presented with musculoskeletal pain in 26 (26.8%), abdominal pain in 22 (22.6%), joint swelling in 9 (10.3%), acute chest syndrome in 2 (3%), dactylitis in 1 (2%), and central nervous system (CNS) crisis in 1 (2%) study subjects.[12] Tshilolo and colleagues examined the occurrence of epistaxis in 591 pediatric SCD patients in the Democratic Republic of the Congo and comparable to this study. They found that in children who reported to the OPD suffering from SCD, 26% had epistaxis in the past. Around 6.5% were from 3–5 years, 5.8% were from 6–12 years, and 17.4% of individuals aged above 13 years.[13] While Konotey Ahulu reported that 7.9% among SCD clinic in Accra, Ghana, had epistaxis.[14] Similar to this, our study, which was conducted at an institute specifically for sickle cell patients, reported epistaxis in (18, 21.5%) of patients. Adults who underwent hydroxyurea therapy for moderate-to-severe homozygous SCD showed substantial improvement in their quality of life. Patients receiving hydroxyurea medication show improved social roles, memory, and overall perception of health, in addition to a reduction in the occurrence of acute painful crises, acute chest syndrome, and blood transfusion episodes. In addition, in contrast to the placebo group and nonresponders, responders to hydroxyurea had pain scores of at least 5.00 and noticed a notable reduction in tension.[15] In our study, acute

chest syndrome, hand-foot syndrome, pain crisis, dactylitis, and blood transfusion frequency were all significantly less common after Hydroxyurea therapy.

Conclusion

A low level of knowledge about SCD was observed among participants. Febrile illness and pain crisis were the most common morbidity among study participants. Hydroxyurea therapy was quite effective as a disease-modifying therapy, especially for reducing the frequency of hospitalization, blood transfusion, and combating various clinical signs and symptoms of SCD.

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Conflicts of interest

There are no conflicts of interest.

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