

MORTALITY RISK FACTORS IN HOSPITALISED LATE ADOLESCENT AND ADULT SICKLE CELL DISEASE PATIENTS

Pradeep Kumar Mohanty¹, Srinibas Meher²

¹Associate Professor and Project Coordinator, Department of Medicine, Odisha Sickle Cell Project, National Health Mission, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Sambalpur, Odisha, India.

²Postgraduate Student, Department of Medicine, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Sambalpur, Odisha, India.

ABSTRACT

BACKGROUND

Odisha state of India has a high burden of Sickle Cell Disease (SCD) with high morbidity and mortality. Survival among patients with SCD has improved with the use of Hydroxyurea (HU) and better healthcare facilities, but is still below that of the general population. Morbidity and mortality in SCD is determined by various environmental factors in addition to genetic modifiers.

MATERIALS AND METHODS

Confirmed cases of SCD admitted to the Department of Medicine were included in the study. Factors that may lead to death were evaluated from history, clinical manifestations and laboratory investigations. Statistical analysis was done using statistical tool EPI INFO by Centre for Disease Control, USA, and Statistical Package for Social Sciences (SPSS) for windows software. A p value of <0.05 was considered significant. Comparison was made between those who survived and those who died.

RESULTS

Among a total number of 147 SCD patients studied, death occurred in 46 number of cases. Among these deaths, vaso-occlusive crisis was found in 38 number of cases (82.6%), infection in 20 cases (43.47%) and acute chest syndrome in 4 cases (8.69%) showing overlapping complications. Various precipitating factors associated with mortality include physical exertion (43.48%), cold exposure (4.35%), discontinuation of HU (56.52%) and pregnancy in 1 case. Lower level of oxygen saturation (SpO₂) ($90.19 \pm 7.4\%$), higher heart rate (97.21 ± 20.93), lower haemoglobin concentration (6.45 ± 1.76 g/dL), decreased platelet count (1.73 ± 0.96 lac/ μ L) and higher serum creatinine (2.08 ± 2.26 mg/dL) at the time of presentation were found to be significantly associated with mortality in patients with SCD.

CONCLUSION

In addition to the conventional precipitating factors, discontinuation of HU was found to be an important factor associated with mortality. However, larger number of deaths in SCD must be studied to test the strength of this association.

KEYWORDS

Sickle Cell Disease, Mortality, Hydroxyurea, Adolescents, Adults.

HOW TO CITE THIS ARTICLE: Mohanty PK, Meher S. Mortality risk factors in hospitalised late adolescent and adult sickle cell disease patients. J. Evid. Based Med. Healthc. 2018; 5(2), 135-139. DOI: 10.18410/jebmh/2018/30

BACKGROUND

Sickle cell haemoglobinopathy is characterised by sickle-shaped erythrocytes resulting from polymerisation of deoxygenated sickle haemoglobin (HbS). The HbS variant results from the point mutation that substitutes thymine for adenine in the sixth codon of the beta globin gene (GAG → GTG) and encodes valine instead of glutamic acid in the sixth position of the beta chain.^{1,2} Symptomatic forms of sickle cell haemoglobinopathy which include homozygous and compound heterozygous states are called "Sickle Cell

Disease" (SCD).¹ Earlier sickle cell disease was regarded as a disease of childhood due to high morbidity and high mortality in childhood.³ Due to advances in treatment and preventive measures, the life expectancy in patients with Sickle Cell Disease (SCD) has increased, but is still lower than the average normal population. The SCD patients suffer from multiple acute complications and chronic organ damage that may lead to death.

In adults, SCD presents variedly from asymptomatic state to painful crisis, acute chest syndrome, aplastic crisis, foetal loss, hepatomegaly, splenomegaly, haemolytic anaemia, jaundice, priapism, stroke, chronic renal failure, pulmonary hypertension, leg ulcer, avascular necrosis of femoral head, etc. The various recognised causes of death include severe vaso-occlusive crisis, acute chest syndrome, pulmonary hypertension, End-Stage Renal Disease (ESRD) and stroke, etc.

Haematopoietic stem cell transplantation is the only curative approach, but its less accessibility, toxicity as well

Financial or Other, Competing Interest: None.

Submission 21-12-2017, Peer Review 26-12-2017,

Acceptance 03-01-2018, Published 05-01-2018.

Corresponding Author:

Dr. Srinibas Meher,

Room No. 110, Resident Doctors' Hostel,

VIMSAR, Burla, Sambalpur, Odisha, India.

E-mail: srinibasmeh@yahoo.com

DOI: 10.18410/jebmh/2018/30



as high cost limits its use in developing countries.⁴ Hydroxyurea (HU) is the only approved pharmacological therapy for SCD.⁵ Various studies have found that HU is effective in both children and adults.⁶⁻⁸ Main mechanism by which HU decreases the severity of SCD includes increase in the foetal haemoglobin level and lowering of the concentration of HbS within the red blood cell that results in less polymerisation of abnormal haemoglobin (HbS).⁹ Other mechanisms include lowering of the neutrophil and platelet count.⁹

In India, Lehmann and Cutbush in 1952, first reported the presence of sickle cell trait among the aboriginal tribes of the Nilgiri Hills in the southern India. Dunlop and Mozumder in same year later reported 3 cases of sickle cell disease in tea garden workers of upper Assam whose origin was traced to Odisha and Bihar.¹⁰

SCD is a major public health problem in the state of Odisha, India. High prevalence of sickle cell haemoglobinopathy is seen in western Odisha ranging from 5 to 30%.¹¹⁻¹⁷ Veer Surendra Sai Institute of Medical Sciences and Research situated in Burla, Sambalpur, Odisha, caters treatment to majority of complicated cases and houses the nodal centre of Odisha Sickle Cell Project sponsored by National Health Mission, Government of Odisha, India, with state of art molecular biology laboratory. Presently, cases of sickle cell disease and trait registered at the nodal centre exceeds 16,000 and 19,000, respectively. Many a times, it has been observed that modifiable behavioural and other factors lead to acute decompensation from steady state and death. These risk factors are studied along with various other clinical, haematological and biochemical parameters to establish a link with mortality.

MATERIALS AND METHODS

Patients hospitalised to the Department of General Medicine, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Odisha, India, (situated on the geographical coordinates of 21.50°N and 83.87°E) were taken for study during the period from November 2015 to November 2017.

Study Design- Hospital-based prospective observational study.

Selection Criteria- Inclusion criteria were SCD patients with age ≥ 14 years, hospitalised in the Department of General Medicine and patients with or without hydroxyurea therapy. Exclusion criteria were patients with age < 14 years and patients who refused to be a part of the study.

Data Collection- Detailed history was taken regarding the patient's illness and precipitating factors that lead to hospitalisation; physical examinations and investigations were done to know the cause of illness and recorded. In addition to symptoms and signs, other study variables included are the conventional precipitating factors, hydroxyurea discontinuation, oxygen saturation, heart rate,

mean haemoglobin, serum creatinine, serum bilirubin, mean leucocyte and mean platelet count.

Definition of terms-

Late adolescents- 14 to 18 years of age.

Adults- > 18 years of age.

Sickle Cell Disease- Diagnosed by sickling slide test, alkaline agarose gel haemoglobin electrophoresis (pH 8.6) and cation-exchange High Performance Liquid Chromatography (HPLC) done sequentially. Those having sickle cells in slide test and S or SF band with or without any other variant in absence of blood transfusion within last 3 months on haemoglobin electrophoresis were diagnosed as sickle cell disease. High performance liquid chromatography (HPLC) was done using Biorad variant II, β -thalassemia short programme to categorize them to homozygous and compound heterozygous states.

Exertion- Included physical exertion in the form of playing outdoor games, walking to variable distance, cycling, driving vehicle to a long distance in case of drivers, working in the field, working indoor for a long time at a stretch.

Infection- When fever preceded bone pain, it was considered due to infection, but as vaso-occlusive crisis can present with pain and fever, fever developing after pain starts was not considered as due to infection.

Cold exposure- Exposure to cold conditions without protective clothing.

HU discontinuation- Patients who were previously taking HU, but not taking due to any reason for 7 days consecutively.

Patients were initially screened by sickle slide test to find out sickle positive cases. Those found positive were subjected to alkaline agarose gel haemoglobin electrophoresis (pH-8.6). Presence of S or SF band and absence of A band in electrophoresis were considered diagnostic for sickle cell disease in absence of blood transfusion within last 3 months. High Performance Liquid Chromatography (HPLC) was done using Bio-Rad variant II, β -thalassaemia short programme to categorise them to homozygous and heterozygous states.

Consent- Informed consent was obtained from patients or their parents in case of minors.

Ethical Approval- Obtained from institutional ethical committee.

Statistical Analysis- Results were expressed as the mean ± 1 SD. For the calculation of p value, statistical tool EPI INFO by Centre for Disease Control, USA and Statistical Package for Social Sciences (SPSS) for windows software was used. Probability values of < 0.05 was considered significant.

RESULTS

During the study period, 746 number of patients with sickle cell disease were admitted to our hospital in the Department of General Medicine, of whom 147 were selected and data

collected. They were followed up during the hospital stay till discharge or death. The various parameters were compared between those who survived and those who died.

Of 147 SCD patients, 61% of patients were male and 39% were female. Thirty one percent patients died during hospitalisation. Among those who died, 67% were males and 33% were females.

The mortality among the patients was maximum in the age group of 15-25 years (47.83%) followed by those between 26-35 years (23.91%), 36-45 years (19.57%) and >45 years (8%). The mean age at death was 29.28 years (range 15 to 82 years).

SCD type was possible to characterise in 42 of the 46 patients who died. Among 42 patients who died during

hospitalisation, homozygous sickle cell disease was present in 40 cases (95.2%) and sickle beta thalassaemia in 2 cases (4.8%).

In patients who died during hospitalisation, the most common presenting symptom was bone pain suggestive of vaso-occlusive crisis (71.74%), followed by fever (52.17%), vomiting (30.43%), chest pain (17.39%), jaundice (13.04%), shortness of breath (13.04%) and abdominal pain (8.7%) in the decreasing order. Other symptoms were swelling of foot, abdominal swelling, loose stool, decreased urination and constipation. There was overlap of symptoms in many patients.

Precipitating Factors	Survival (n=101)		Death (n=46)		p value
	Number	Percentage	Number	Percentage	
Physical Exertion	49	48.51	20	43.48	0.28
Cold Exposure	0	0.00	2	4.35	0.04
Pregnancy	9	8.91	1	2.17	0.07
HU Discontinuation	33	32.67	26	56.52	0.003
Others	9	8.91	8	17.39	

Table 1. Precipitating Factors for Hospitalisation in Cases of Sickle Cell Disease (n=147)

Overall, physical exertion (46.94%) was the most common predisposing factor that led to hospitalisation followed by HU discontinuation (40.14%), cold exposure (1.36%) and pregnancy (in 10 cases). 12% patients had other factors for hospitalisation like wetting in rain, dilated cardiomyopathy, onset of avascular necrosis of femur bone, etc. (Table 1).

In patients who died, the most common precipitating factor was HU discontinuation (56.52%) followed by physical exertion (43.48%), cold exposure (4.35%) and pregnancy in one case. Pregnancy was a precipitating factor for hospitalisation, but only 1 died and 9 survived. There was overlap of precipitating factors in individual patients with

more than one factor present. The association of HU discontinuation and cold exposure with mortality was found to be statistically significant with 'p' value 0.003 and 0.04, respectively (Table 1).

Of 101 patients who survived, 63 (62.38%) were using HU of whom 33 discontinued HU accounting for 48.53% amongst users. Out of 46 patients who died, 38 (82.61%) were using HU of whom 26 had a history of discontinuation of HU accounting for 68.42%. Eight of the 46 patients who died were not using HU. Discontinuation of Hydroxyurea (HU) is thus found to be a risk factor for both morbidity and mortality in SCD.

Clinical Variables	Survival (n=101)	Death (n=46)	p value
Mean SpO ₂ in % (± SD)	97.59 (± 1.8)	90.19 (± 7.4)	0.0000001
Mean heart rate/minute (± SD)	91.47 (± 11.40)	97.21 (± 20.93)	0.03

Table 2. Mean Oxygen Saturation (SpO₂) and Mean Heart Rate in Hospitalised SCD Patients

The mean of oxygen saturation (SpO₂) at the time of admission to the hospital was lower in patients who died that was found to be statistically significant for mortality in SCD. Mean heart rate was higher in patients who died (97.21 ± 20.93) and also statistically significant (Table 2).

Among 147 SCD patients, hepatomegaly was seen in 10.88%, splenomegaly in 19.05% and both

hepatosplenomegaly in 2.72% of cases. Whereas, those patients who died had hepatomegaly in 4.35%, splenomegaly in 15.22% and both hepatosplenomegaly in 2.17% of cases. Splenomegaly was more common in survivors, but did not reach significance (p=0.22).

Out of 46 patients who died, 8 patients died before haematological investigations could be completed.

Parameters (Mean)	Survival	Death	p value
Haemoglobin (g/dL)	7.90 (± 2.05)	6.45 (± 1.76)	0.00017
Total leucocyte count (no./mm ³)	12227 (± 12093)	13389 (± 9947)	0.6
Total platelet count (lac/mm ³)	2.11 (± 0.88)	1.73 (± 0.96)	0.0285
Serum creatinine (mg/dL)	0.84 (± 0.43)	2.08 (± 2.26)	0.0000044
Serum bilirubin total (mg/dL)	3.96 (± 7.39)	4.85 (± 6.18)	0.52

Table 3. Haematological and Biochemical Parameters in Hospitalised SCD Patients

The mean haemoglobin concentration and mean platelet count at the time of presentation to the hospital in sickle cell disease patients were lower in those who died than in patients who survived and found to be statistically significant (Table 3). The mean leucocyte count was higher in patients who died, but did not reach statistical significance ($p=0.6$), (Table 3).

In 7 out of 46 patients who died, renal function test could not be done. The mean serum creatinine level at the time of admission was higher in patients who died. One patient among survivors and 5 patients who died had history of chronic kidney disease. The higher value of creatinine was found to be statistically significant for mortality in SCD (p value=0.000044). In 10 out of 46 patients who died, liver function test could not be done. Serum bilirubin was higher in patients who died, but is not significant ($p=0.52$) (Table 3).

DISCUSSION

In the present study, males predominated with difference, more marked among those who died (57.43% of males among survivors versus 67.39% males among those who died). In the study by Platt OS et al,¹⁸ females survived longer than males. However, in another study by Ogun GO et al,¹⁹ among 52 patients, death occurred to equal proportion in males and females. The higher death rate in male compared to female in the present study could be related to higher level of physical activity and exertion in case of males.

Mean age at death is 29.28 years in present study compared to a median age of death at 42 years in the study of Platt OS et al¹⁸ and 21 years in another study (Ogun GO et al).¹⁹ Our finding was closer to those by Ogun GO et al. Higher age at death noted by Platt OS et al maybe due to better healthcare facilities in USA than in our country. Our study was limited to adolescents and adults. Children dying with SCD were not included. In developed countries, age at death has shifted to adults following improved survival in children, which may not be the case in developing countries.

Homozygous sickle cell disease (SS) was the predominant type of sickle cell disease in the study subjects. Among those who died, 95.2% were SS disease and 4.8% S β thalassaemia. Due to uncommonness, other genotypes were not found. In the study by Platt OS et al with larger number of patients (3764 patients), 34% had sickle cell anaemia; 15% had sickle cell anaemia with coexistent alpha thalassaemia, 22% haemoglobin SC disease, 5% with sickle β^+ thalassaemia and 4% haemoglobin S β^0 thalassaemia.¹⁹

Bone pain was the commonest presenting feature in the present study among both groups, followed by fever. Other symptoms at presentation were vomiting, chest pain, jaundice, shortness of breath and abdominal pain. There was overlap of symptoms in many cases. Vichinsky EP et al²⁰ reported fever as the most common presenting symptom among those sickle cell disease patients who died.

The precipitating factors for hospitalisation were physical exertion (46.94%), followed by hydroxyurea discontinuation (40.14%). Others are exposure to cold,

pregnancy, wetting in rain and onset of avascular necrosis of femoral head. Other conditions were psychosis, chronic kidney disease, rheumatic heart disease, dilated cardiomyopathy, kyphoscoliosis and pulmonary hypertension (Table 1).

The most common precipitating factor among hospitalised SCD patients who died was discontinuation of hydroxyurea therapy reaching statistical significance (Table 1). Hydroxyurea discontinuation as a precipitating factor for crisis and risk factor for death has not been mentioned earlier, although adherence of hydroxyurea was studied. Three recent studies on mortality, which were undertaken elsewhere in 'hydroxyurea era' do not mention hydroxyurea discontinuation as a risk factor for mortality.^{19,21-24} The underlying mechanism leading to decompensation after HU discontinuation presumably maybe related to reversal of its effects, but not exactly known and needs further study.

We analysed the association of oxygen saturation (SpO₂) and heart rate at admission with mortality comparing these variables between patients who survived and those who died. It was found to be significant ($p=0.0000001$ in case of SpO₂ and $p=0.03$ in case of heart rate) with a lower SpO₂ ($90.19 \pm 7.4\%$) and higher heart rate (97.21 ± 20.93) associated with mortality. Their presence can predict worse outcome and should warn the treating physicians to be more careful to avert death.

It was found that splenomegaly (20.79%) was associated with survival, although not reaching significance level ($p=0.22$), this might be related to preserved splenic function protecting against infection.

Haematological parameters studied are haemoglobin level, total leucocyte count and total platelet count (Table 3). Patients who died had a lower mean haemoglobin concentration (6.45 ± 1.76 gm/dL) compared to those who survived (7.90 ± 2.05 gm/dL) with a 'p' value 0.00017. Similarly, a lower mean platelet count had a significant association with mortality (p value 0.0285).

Platt OS et al¹⁸ and Maitra P et al²¹ also reported lower haemoglobin level to be associated with mortality. We found an association between lower platelet count and mortality, which was not observed by Platt OS et al and Maitra P et al.

Biochemical parameter associated significantly with mortality was a higher serum creatinine level (2.08 ± 2.26 mg/dL; p value = 0.000044) (Table 3). This is in accordance with observations by Platt OS et al,¹⁸ Maitra P et al²¹ and Darleen R et al.²²

Although, mean serum bilirubin level was higher in those who died, it did not reach statistical significance ($p = 0.52$). But, considering the small number of cases, this association cannot be commented upon as it has been found to be significant in other studies (Platt OS et al, Maitra P et al).

The causes for which the SCD patients were hospitalised and died are vaso-occlusive crisis (52.15%), infections including malaria (32.67%), acute chest syndrome (8.69%) and chronic kidney disease (10.86%). Overlapping of conditions were also noted. Other studies reported severe vaso-occlusive crisis and acute chest syndrome as the most

common cause of mortality in SCD (Platt O S et al, Ogun G O et al).

CONCLUSION

This study brings out certain modifiable risk factors, which are found to be associated with mortality and include discontinuation of HU therapy, lower oxygen saturation (SpO₂) and higher heart rate at presentation, lower haemoglobin concentration, lower platelet count and higher value of serum creatinine at presentation. Adherence to hydroxyurea must be given importance and need to be practiced not only to reduce complication, but also to avoid mortality risk because of discontinuation. Portable pulse-oximeters can be utilised to monitor oxygen saturation from time to time in non-ICU setup so that supplemental oxygen therapy can be initiated when SPO₂ falls and to provide intensive care if available to those at risk. Similarly, monitoring heart rate can also be useful.

Acknowledgement

We are deeply indebted to the patients and their family members without whose consent this study could not have been possible. We are also thankful to Mr. Satyabrata Meher, Research Assistant, Odisha, Sick Cell Project; and Dr. Kulwant Lakra, Assistant Professor, Community Medicine Department of VSS Institute of Medical Sciences and Research, Burla, for their help in statistical analysis.

REFERENCES

- [1] Serjeant GR, Serjeant BE. Sick cell disease. 3rd edn. New York: Oxford University Press 2001.
- [2] Hankins JS, Wang WC. Sick cell anemia and other sickling syndromes. In: Greer J, Arber D, Glader B, et al, eds. Wintrobe's clinical hematology. 13th edn. Philadelphia: Lippincott Williams & Wilkins 2014:823-926.
- [3] Dacie JV. The haemolytic anaemias, congenital and acquired. Part 1, the congenital anaemias. 2nd edn. New York: Grune & Stratton 1960.
- [4] Vermynen C. Hematopoietic stem cell transplantation in sickle cell disease. Blood reviews 2003;17(3):163-166.
- [5] Green NS, Ender KL, Pashankar F, et al. Candidate sequence variants and fetal hemoglobin in children with sickle cell disease treated with hydroxyurea. PLoS One 2013;8(2):e55709.
- [6] Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the multicenter study of hydroxyurea in sickle cell anemia. New Engl J Med 1995;332(20):1317-1322.
- [7] Charache S, Terrin ML, Moore RD, et al. Design of the multicenter study of hydroxyurea in sickle cell anemia. Investigators of the multicenter study of hydroxyurea. Control Clin Trials 1995;16(6):432-446.
- [8] Wu DY, Ugozzoli L, Pal BK, et al. Allele-specific enzymatic amplification of beta-globin genomic DNA for diagnosis of sickle cell anemia. Proc Natl Acad Sci 1989;86(8):2757-2760.
- [9] Platt OS, Orkin SH, Dover G, et al. Hydroxyurea enhances fetal hemoglobin production in sickle cell anemia. J Clin Invest 1984;74(2):652-656.
- [10] Dunlop KJ, Mozumder UK. The occurrence of sickle cell anaemia among a group of tea garden labourers in Assam. Ind Med Gaz 1952;87(9):387-391.
- [11] Purohit P, Mashon RS, Patel S, et al. Clinical and molecular characterization of Hb Hofu in eastern India. Intl J Lab Hematol 2014;36(1):71-76.
- [12] Meher S, Patel DK, Patel S, et al. Epidemiology of beta thalassemia trait in eastern India. Odisha Physician Journal 2012;9:24-29.
- [13] Purohit P, Dehury S, Patel S, et al. Prevalence of deletional alpha thalassemia and sickle gene in a tribal dominated malaria endemic area of eastern India. ISRN Hematology 2014;2014:1-6.
- [14] Patel DK, Mashon RS, Patel S, et al. β -Globin gene haplotypes linked with the Hb D-Punjab [β 121 (GH4) Glu Gln, G AA> C AA] mutation in Eastern India. Hemoglobin 2010;34(6):530-537.
- [15] Mohanty D, Colah RB, Gorakshakar AC, et al. Prevalence of β -thalassemia and other haemoglobinopathies in six cities in India: a multicentre study. J Community Genet 2013;4(1):33-42.
- [16] Nanda BK, Panda GK, Naik UP, et al. Haemoglobin-S in Agharia community of Orissa. J Ind Med Assoc 1967;48(4):150-152.
- [17] Kar BC, Kulozik AE, Sirr S, et al. Sick cell disease in Orissa state, India. Lancet 1986;2(8517):1198-1201.
- [18] Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. New Engl J Med 1994;330(23):1639-1644.
- [19] Ogun GO, Ebili H, Kotila TR. Autopsy findings and pattern of mortality in Nigerian sickle cell disease patients. Pan Afr Med J 2014;18:30.
- [20] Vichinsky EP, Styles LA, Colangelo LH, et al. Acute chest syndrome in sickle cell disease: clinical presentation and course. Cooperative study of sickle cell disease. Blood 1997;89(5):1787-1792.
- [21] Maitra P, Caughey M, Robinson L, et al. Risk factors for mortality in adult patients with sickle cell disease: a meta-analysis of studies in North America and Europe. Haematologica 2017;102(4):626-636.
- [22] Powars DR, Elliott-Mills DD, Chan L, et al. Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality. Ann Intern Med 1991;115(8):614-620.
- [23] Thomas AN, Pattison C, Serjeant GR. Causes of death in sickle cell disease in Jamaica. Br Med J 1982;285:633-635.
- [24] Arduini GAO, Rodrigues LP, Marqui AB. Mortality by sickle cell disease in Brazil. Rev Bras Hematol Hemoter 2017;39(1):52-56.