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

BACKGROUND
Odisha state of India has 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 (43.48%) 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 ± 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/µL) 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.

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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
as high cost limits its use in developing countries. Hydroxyurea (HU) is the only approved pharmacological therapy for SCD. Various studies have found that HU is effective in both children and adults. 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). Other mechanisms include lowering of the neutrophil and platelet count.

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. 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%. 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 modificable 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.

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

<table>
<thead>
<tr>
<th>Precipitating Factors</th>
<th>Survival (n=101)</th>
<th>Death (n=46)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percentage</td>
<td>Number</td>
</tr>
<tr>
<td>Physical Exertion</td>
<td>49</td>
<td>48.51</td>
<td>20</td>
</tr>
<tr>
<td>Cold Exposure</td>
<td>0</td>
<td>0.00</td>
<td>2</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>9</td>
<td>8.91</td>
<td>1</td>
</tr>
<tr>
<td>HU Discontinuation</td>
<td>33</td>
<td>32.67</td>
<td>26</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
<td>8.91</td>
<td>8</td>
</tr>
</tbody>
</table>

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 r.

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.

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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survival (n=101)</th>
<th>Death (n=46)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SpO2 in % (± SD)</td>
<td>97.59 (± 1.8)</td>
<td>90.19 (± 7.4)</td>
<td>0.00000001</td>
</tr>
<tr>
<td>Mean heart rate/minute (± SD)</td>
<td>91.47 (± 11.40)</td>
<td>97.21 (± 20.93)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

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.

### Table 3. Haematological and Biochemical Parameters in Hospitalised SCD Patients

<table>
<thead>
<tr>
<th>Parameters (Mean)</th>
<th>Survival</th>
<th>Death</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>7.90 ± 2.05</td>
<td>6.45 ± 1.76</td>
<td>0.00017</td>
</tr>
<tr>
<td>Total leucocyte count (no./mm3)</td>
<td>12227 (± 12093)</td>
<td>13389 (± 9947)</td>
<td>0.6</td>
</tr>
<tr>
<td>Total platelet count (lac/mm3)</td>
<td>2.11 (± 0.88)</td>
<td>1.73 (± 0.96)</td>
<td>0.0285</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.84 (± 0.43)</td>
<td>2.08 (± 2.26)</td>
<td>0.0000044</td>
</tr>
<tr>
<td>Serum bilirubin total (mg/dL)</td>
<td>3.96 (± 7.39)</td>
<td>4.85 (± 6.18)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

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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=0.0000044). 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.\(^1\) females survived longer than males. However, in another study by Ogun GO et al.\(^2\) 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 al.\(^3\) and 21 years in another study (Ogun GO et al).\(^1\) 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% Sβ 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 Sβ0 thalassaemia.\(^1\)

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 al\(^2\) 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 ± 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 were haemoglobin level, total leucocyte count and total platelet count (Table 3). Patients who died had a lower mean haemoglobin concentration (6.45 ± 1.76 g/dL) compared to those who survived (7.90 ± 2.05 g/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 al\(^3\) and Maitra P et al\(^2\) 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 = 0.0000044) (Table 3). This is in accordance with observations by Platt OS et al,\(^1\) Maitra P et al\(^1\) and Darleen R et al.\(^1\)

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 were 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

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
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