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REVIEW ARTICLE

STUDY OF VASO-OCCLUSIVE (PAIN) CRISES IN PATIENTS OF SICKLE CELL DISEASE (SCD) – ONE YEAR TMH EXPERIENCE

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ABSTRACT

Background: Sickle cell disease (SCD) is a chronic, potentially life-threatening, inherited hemoglobinopathy of which pain is (the) hallmark. Amongst the various complications of SCD, painful vaso-occlusive crisis (VOC) is the most frequent cause of hospitalization, impaired health-related quality of life with increased mortality. The painful crisis, manifests as pain in the extremities, back, abdomen, or chest. As sickle cell disease is prevalent in and around Jamshedpur with affection of both tribal and non-tribal groups and an important cause of mortality and morbidity, one year study was undertaken with the

Aim: To describe the clinical spectrum, laboratory parameters, efficacy of treatment and outcome in adults with pain crisis of sickle cell anemia admitted in Tata Main Hospital (TMH) over one year.

Methods and Materials: This was a retrospective cohort study done from 1st March 2015 to 28th February 2016 and included patients admitted in the medical wards, of TMH, Jamshedpur.

Results: A total of 32 patients were admitted with 50 pain episodes. The average pain rate was 0.492 patient-years. The average pain score was 8.9 ± 1.1 for males and for females was 8.6 ± 1.24. Most patients, 46.9% were in the age group of 21 to 30 years while only 2 patients (6.2%) were beyond the fourth decade of life. 25% of the patients had recurrent episodes. Sites of pain involvement were varied with involvement of knee being most common (78%). Length of stay (LOS) was maximum (7.12 ± 3.9) in patients with severe pain score. There was no mortality during the study period.

Conclusion: VOC represents a chaotic interval in the life of patients of SCD which needs immediate and appropriate treatment with counseling to avoid complications.

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INTRODUCTION

Sickle cell disease (SCD) is the most common single-gene hemoglobinopathy in the world, caused by a single point mutation at codon 6 of the β-globin gene on chromosome 11 resulting in the substitution of valine for glutamic acid (Steinberg *et al*., 2001). This genetic alteration yields mutated and defective haemoglobin (HbS) which is less soluble than adult haemoglobin and after deoxygenation undergoes polymerisation resulting in elongated, sickle cells and damage to red blood cell cytoskeleton (Steinberg, 2005). SCD is distributed widely in Africa, Mediterranean region, South and Central America, the Caribbean and South East Asia, the parts of the world where malaria is endemic (Piel *et al*., 2013). Nearly 20 million people suffer from SCD in India which accounts for 50% of world population (Mohanty and Pathare, 1998). Though it was first described among tribal groups in South India, it is now recognized to be widespread. In the eastern region, Odessa and Jharkhand are among the worst affected states. Acute, intermittent, self-limited episodes of musculoskeletal pain, often referred to as "pain crisis" is the hallmark of sickle cell anemia and is the most frequent and troublesome complication. It consists of pain in the extremities, back, abdomen, or chest and muscles (myalgias) and bones. Pain and SCD are so intimately intertwined, that the African workers named this disease "*chwechweechwe*" which means "repetitive, relentless chewing" in the Ga language of Ghana (Platt *et al*., 1991). It is also the most frequent cause of hospitalization and an important cause of absenteeism from work and impaired quality of life (QOL) (Ballas *et al*., 2005; Darbari *et al*., 2014; Olney, 1999; Houston-Yu *et al*., 2003). Pain crisis is a type of acute vaso-occlusive crisis (VOCs) caused by erythrocyte microvascular occlusion which leads to complex progressive cascade of tissue hypoxia and release of inflammatory mediators (acute phase reactants) that initiate the transmission of painful stimuli and the perception of pain (Odièvre *et al*., 2011; Ballas, 2011; Ballas, 2005). A triad of pathophysiologic factors initiates the acute painful crisis: vaso-occlusion, inflammation and nociception. Ballas *et al* described the crisis

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in 4 phases - prodromal, initial, established, and resolving phases (Odièvre *et al*., 2011). It may be precipitated by a variety of known and unknown factors. The severity of this complication varies from patient to patient and also in the same patient. An episode generally lasts for about 4 to 7 days and the intensity of pain varies from mild to excruciating. Each painful crisis is associated with residual inflammatory damage that accumulates with recurrent crises culminating in organ dysfunction and organ failure (Ballas, 2011). Frequent painful vaso-occlusive crises (VOCs) were associated with mortality in the Cooperative Study of Sickle Cell Disease (CSSCD) over twenty years ago (Darbari *et al*., 2014; Platt *et al*., 1994). Despite being of such clinical significance, there is hardly any data available on the epidemiological features, risk factors and outcomes of these patients in this part of the country, especially Jharkhand, where more than 9 lakhs tribals are suffering from the fatal disease and 60% of anemia in women is due to SCD. To address this issue, a retrospective analysis was undertaken to evaluate the clinical spectrum and outcome of the patients who were admitted in our tertiary care hospital with sickle cell pain crisis over 1 year period.

Aim

To study the clinical spectrum, laboratory parameters and outcome of vaso-occlusive (pain) crisis in patients of sickle cell disease admitted in TMH over one year.

MATERIALS AND METHODS

A retrospective observational cohort study was done during a one year period from 1st April 2015 to 30th March 2016. The medical records of all SCD patients with pain crisis who were admitted in the medical wards of the Tata Main Hospital, Jamshedpur, Jharkhand, during this period were carefully analyzed. The study was approved by the ethics committee of the hospital.

Inclusion criteria

All confirmed cases of SCD aged above 12 years who fulfilled the criteria of pain crisis were included in the study. Diagnosis of SCD was based on the presence of sickle red blood cells (RBC) identified by sickling test with 1 drop of blood and 1 drop of 2% sodium metabisulphite. This was followed by demonstration of sickle hemoglobin (HbS) by hemoglobin electrophoresis on cellulose acetate membrane at pH 8.6 initially and later by high performance liquid chromatography (HPLC) method (when the technique became available in our hospital). Pain crisis was defined as the occurrence of the pain in the extremities, back, abdomen, or head that lasted at-least for 2 hours, led to hospital visit and could not be explained except by sickle cell disease (Platt *et al*., 1991). Episodes of pain that occurred within one week period was counted as a single episode.

Exclusion criteria:

(1) Cases of SCD with Hand-foot disease, acute chest syndrome, right hypochondrial pain and osteomyelitis
(2) Cases of combined SCD and other haemoglobinopathies like sickle-thalassemia, HbSC disease etc**.**
(3) SCD cases with chronic pain syndrome and/or severe co-morbid conditions
(4) Cases ≤ 12 years as they might differ substantially from adults in both their clinical course and healthcare utilization patterns.

The data analyzed included the demographic profile, clinical presentation, (site of pain, severity, pain score, duration, time to recovery, pain score at discharge), precipitating factors, relapse (readmission), laboratory profile, treatment strategy and clinical outcomes (length of hospital stay, mortality and complications). Other clinical events like haemolytic crises, surgeries, blood transfusions and other significant co-morbid condition were also noted. The laboratory profile included complete blood counts (done by automated cell counters), hemoglobin electrophoresis, blood urea, serum creatinine, liver function tests, chest x-ray (for chest infiltrates), and blood, sputum and urine cultures, serum lactate dehydrogenase, reticulocyte count, ambient room air arterial blood gas (to know the oxygen saturation of blood), and electrocardiogram (ECG).

Assessment of pain: Smiley-face pain score that was developed by Donna Wong and Connie Baker was used for grading the severity of pain into mild (score 1 to 3), moderate (score 4 and 6) and severe (7 to 10) on a scale of 1 to 10 as shown in the **Figure 1**. This score has been validated earlier in other studies. Patients were asked to choose the face that best described their pain feeling by the treating physician on admission.

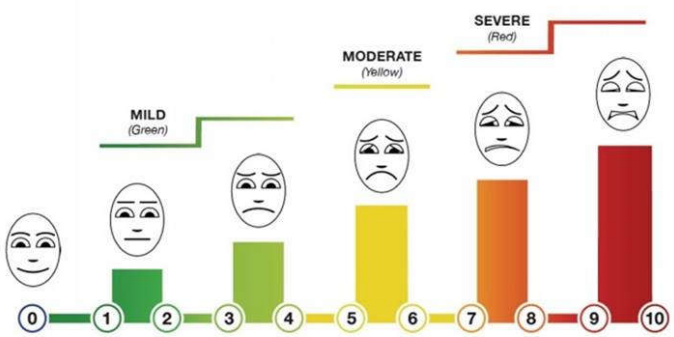

Figure 1: Wong-Baker Smiley-face pain score was used for grading the severity of pain

Treatment strategy

Analgesia used for pain relief – Assessment of the pain was done by the physician within 30 minutes of arrival to the ward. Drug selection was done based on patient's prior history and current pain score. Patients with mild pain with pain score 1 to 3 were treated with oral paracetemol (acetaminophen) 500 mg QID, tramadol 50 mg TID or diclofenac 50 mg BD. Those with moderate pain with pain score 5 and 6 were treated with the same medications intramuscularly. Patients with severe pain with pain score of 7 and 8 were treated with Tramadol infusion (100 mg in 500 ml of NS over 4 hours intravenously three times a day) while those with very severe pain with pain score of 9 and 10 were given fentanyl infusion (50 mcg in 500 ml of NS over 4 hours intravenously thrice a day).

Titration of analgesia: The effect of therapy was determined in 30-minute intervals after starting the infusion. Parenteral infusions were continued till pain reduced by at-least 50%. For

breakthrough pain that occurred between the scheduled doses, half of the maintenance dose was administered.

Use of adjuvant drugs: To counter the side-effects of opiates and other analgesics, anti-histaminics, anti-emetics, and other adjuvant drugs were given. All patients received intravenous fluids of 2 liters/day, to avoid dehydration and treat variable dehydration due to hyposthenuria. Additional fluids were given if they had fever and vomiting. Supplemental oxygen was given if they had SpO2 less than 92%. Blood transfusions were given only if patient had symptomatic anemia and a fall of hemoglobin by more than 2g/dl over the steady state. It was not routinely given for pain crisis. History of prior use of hydroxyurea, compliance and its dosage were noted.

Statistical methods: Results were analysed and presented as mean ± standard deviation (SD) for continuous variables. Student t test was used to compare means of continuous variables while Fischer's test was used to assess statistical differences between the groups. P value of ≤ 0.05 was taken as significant.

RESULTS

Profile of the patients – A total number of 65 patients of SCD were admitted with 94 events over one year period. Of these, 32 patients (49.2%) were admitted with 50 episodes of pain crises while 33 (50.8%) patients had other events, Figure 1. Most of the patients (70%) were from the tribal group. The average pain rate was 0.492 patient-year in SCD. The "pain rate" was calculated by dividing the number of episodes by the number of patient- year. There were 14 (43.7%) males and 18 (56.3%) females, giving a sex ratio of 0.7:1 as shown in Figure 2.

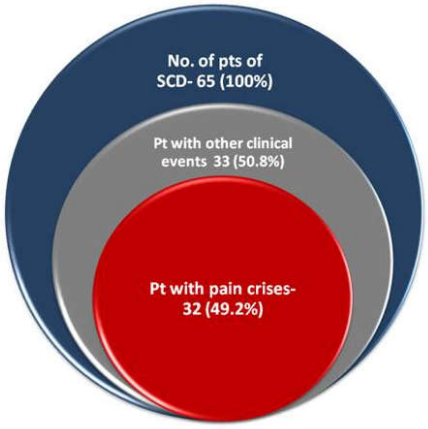

Figure 2: Distribution of patients with various events during one year

The age range of male patients was 16 to 36 years with average being 22.3 ± 9.8 while for the female patients, it was 16 years to 61 years with average being 29.5 ± 11.7. The average pain score was 8.9 ± 1.1 for males and for females was 8.6 ± 1.24. A total of 8 patients (25%) had recurrent episodes of which 3 were male patients, who had recurrent episodes (of a maximum 2 episodes/year) and 5 female patients who had recurrent episodes (up to a maximum of 9 episodes/year). Together they accounted for 34.04% of the pain episodes. The age and gender distribution of cases (n=32) was as depicted in Figure 3. Most patients, 46.9% including both males and females were in the age group of 21 to 30 years while only 2 patients (6.2%) were beyond the fourth decade of life.

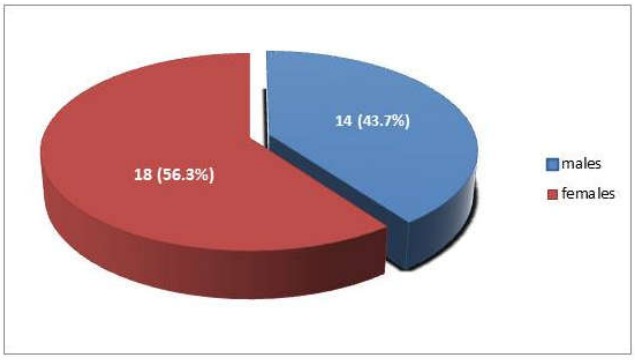

Figure 3: Shows the gender distribution of cases.

The severity of pain crises in the various age groups is shown in **Figure 4**. As seen, severe pain was most common in the age group of 21 to 30 years.

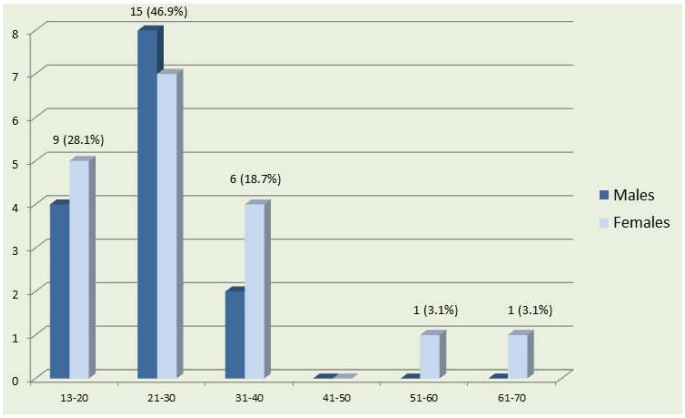

Figure 4: Age and gender distribution of the cases

Of the 50 episodes of pain, 2 episodes (4%) were mild (score 2 - 4) needing oral analgesics, 19 episodes (38%) were moderate (score 5 and 6) needing intramuscular analgesics, 17 episodes (34%) were severe (score 7 and 8), requiring intravenous tramadol while 13 episodes (26%) were very severe (score 9 and 10) and were treated with fentanyl infusion as shown in **Figure 5**. All analgesics were given as per the protocol mentioned above.

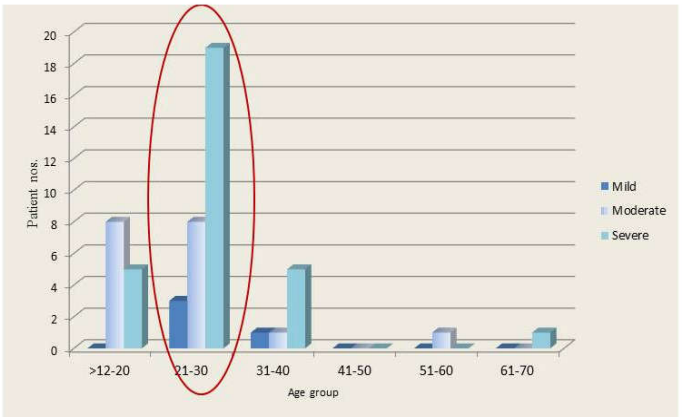

Figure 5: Severity of Pain crises in various age groups

Seasonal variation: The rate of pain crises was affected by the season of the year. While most of the episodes of pain occurred during the transition period from winter to summer and in winter season (69.8%), 20.2% occurred during rainy season and 10% of the cases were seen during summer. The same trend was seen in both the sexes.

Symptomatology: The various sites of pain described were large joints such as shoulder joint, knee joint with shin, elbow, small joints of hands, polyarthalgias (when multiple joints were involved), low backache, abdominal pain, chest pain (sternum and ribs) as shown in the pie-chart 6. It was associated with fever in 19 patients (38%) and weakness in 5 patients (10%). Knee joint was the most commonly affected joint in 78% of the cases.

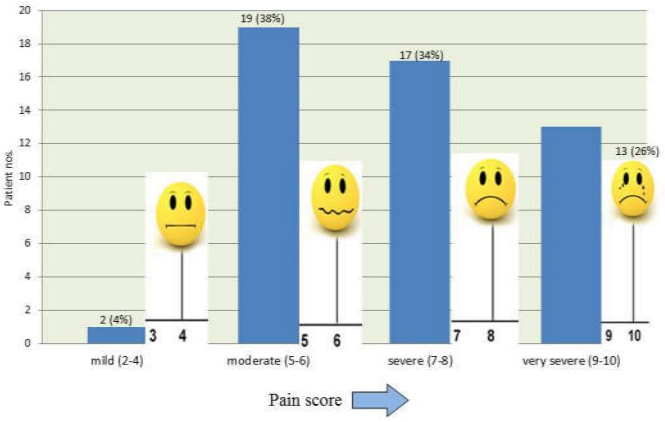

Figure 6: Bar graph showing the severity of pain crisis in various patients (n=50)

Precipitating factors: No obvious precipitating factors were found in 44 episodes (88%) while 6 episodes (12%) had precipitating factors, **Figure 7**. Three patients (6%) had psychological stress while urinary tract infection, pneumonia and viral fever were found in 1 patient (2%) each.

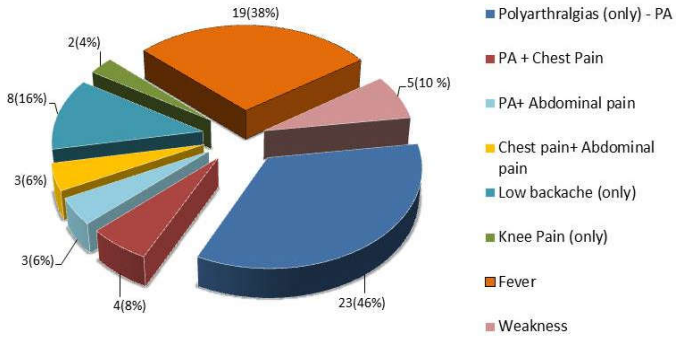

Figure 7: Pie chart depicting the distribution of site of pain

Use of hydroxyurea (HU): 19 episodes occurred in patients who reported taking hydroxyurea regularly while 31 episodes occurred in patients not using hydroxyurea. This difference was, however, not statistically significant (OR 1.22, (95% CI- 0.47 to 3.1) P - 0.67) (**Figure 8**). Only 2 of the 12 patients (16.7%) were using HU in the maximal doses of 15 mg/kg body weight. Rest of the 10 patients (83.3%) were taking below the maximum recommended dose due to various reasons.

Patients on hydroxyurea (n=19)

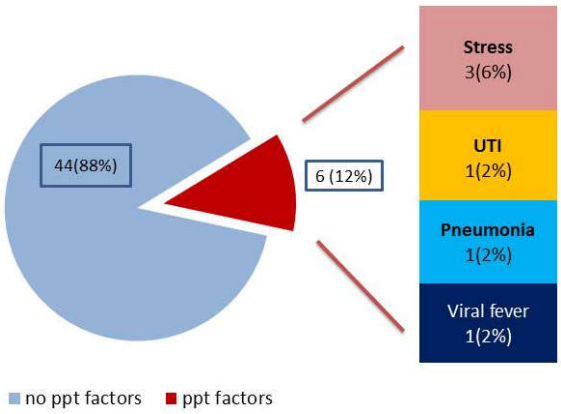

Figure 8: Precipitating factors of pain crises

Laboratory parameters: Hematological parameters like the haemoglobin, haematocrit, mean corpuscular volume (MCV), total leucocyte count and platelet counts between the three grades of pain crises were as shown in **Table 1**. As there was only one patient in the mild group, standard deviation (SD) was not calculated for the values. As is evident, haemoglobin and haematocrit values were higher in patients with severe pain crisis. Also of the 32 patients, only 20 patients (62.5%) had SCD, while 12 patients (37.5%) had sickle cell trait as per haemoglobin electrophoresis pattern.

Biochemical parameters: like the serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine between the three grades of pain crises were as shown in **Table 2.** SD was not calculated for these values for the mild pain score group as there was only one patient in this group. Serum creatinine value was higher in the severe pain score group.

Blood transfusions: A total of 59 compatible packed red blood cells were transfused in 21 patients (65.6%) as per the protocol while 11 patients (34.4%) did not receive any transfusion. 21 units (35.6%) were transfused in males. Their average hemoglobin value was 6.35 g/dl. 38 units (64.4%) were transfused in females whose average hemoglobin value was 5.14g/dl. Maximum of 4 units were transfused during 6 pain episodes (12%), 3 units during 5 pain episodes (10%) and 2 units during 10 pain episodes (20%) while 29 episodes of pain (58%) did not require blood transfusion as shown in **table 3**.

Outcome: included the length of stay (LOS), extent of recovery (partial or complete), complications during hospital stay, transfer to intensive care unit, mortality and quality of life.

Length of stay: LOS for patients with mild pain (3- 4) score was 5.72 days (SD ± 3.3), moderate pain (5-6) score was 6.82 days (SD ± 2.5) and those with severe pain (7 -10) score was 7.12 days (SD ± 3.9). Average LOS for male patients was 7.57 days (SD ± 2.96) while that for female patients was 6.13 days (SD ± 3.98).

Extent of recovery: 42 events (84%) were associated with complete recovery while 8 events (16%) were associated with partial recovery (reduction of pain score to 3-4).

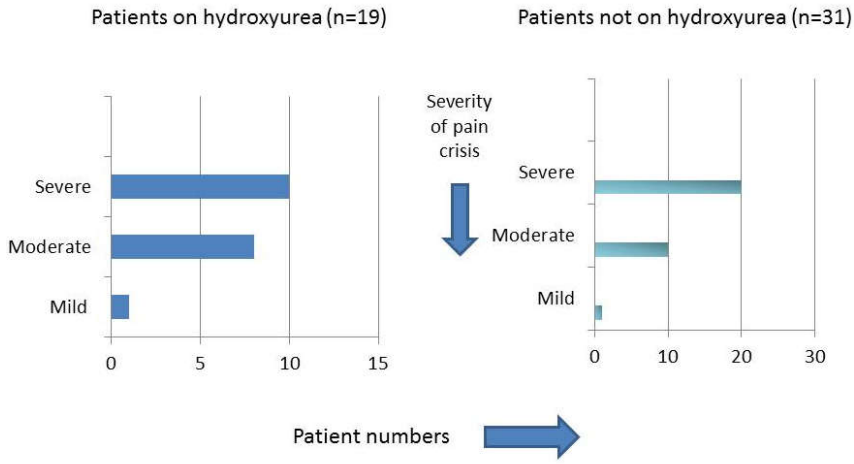

Figure 9: Comparison of severity of pain crisis between patients taking hydroxyurea and those not taking hydroxyurea (HU)

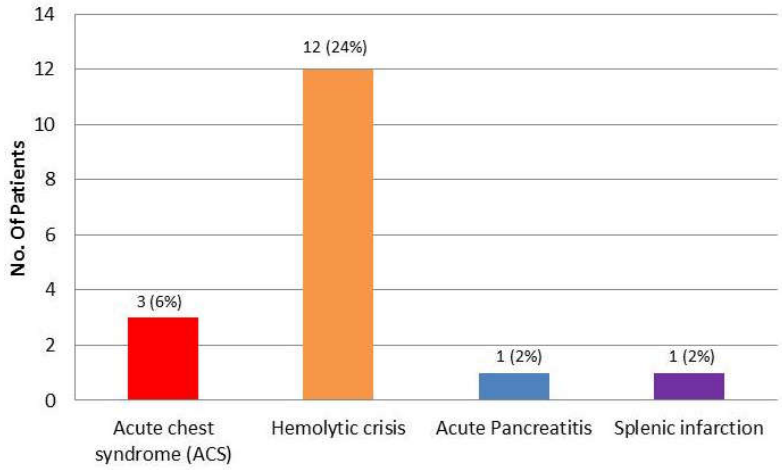

Figure 10: Complications during hospital admission (n=50)

Table 1. Hemtaological parameters according to the severity of pain score

Pain score	Hb (g/dl) (Avg ±SD)	Hct (%) (Avg ±SD)	MCV (fl) (Avg ±SD)	RDW (Avg ±SD)	TLC (/cumm)	Platelets (/cumm)
Mild (3-4)	6.3	18.9	85.2	18.4	11,000	91,500
Moderate (5-6)	7.5 ± 1.9	22.5 ± 1.8	88.7 ± 13.7	19.8 ± 3.41	11,432 ± 4,330	156,529 ± 104,738
Severe (7-10)	8.2 ± 1.83	24.6 ± 1.7	84.1 ± 14.5	18.7 ± 3.6	10,568.9 ± 5,271.9	184,344 ± 101,003

Table 2. Shows biochemical parameters according to the severity of pain score

Pain score	Serum Bilirubin (mg/dl)	ALT (U/L)	AST (U/L)	Creatinine (mg/dl)
Mild (3-4)	2.73	25.2	42.6	0.8
Moderate (5-6)	2.93 ± 2.3	51.6 ± 87.7	69.3 ± 57.1	0.9 ± 0.2
Severe (7-10)	2.68 ± 2.32	47.4 ± 84.4	60.9 ± 55.3	1.1 ± 0.43

Table 3. Frequency of blood transfusion in patients with pain crises

Units of PRBCs transfusions	No. of episodes (n=50)
Nil	29
2	10
3	5
4	6

Complications during hospital stay: Various complications observed during the pain crises were development of acute chest syndrome (ACS) in 3 patients (6%), haemolytic crisis in 12 patients (24%), acute pancreatitis and splenic infarction in 1 (2%) patient each **(figure 9)**.

Mortality: None of the admitted patients expired (mortality was zero). One patient fever and severe low back pain developed acute hemolytic crisis and was transferred to ICU. He subsequently improved and was transferred back to the ward.

Quality of life (QOL): Patients with recurrent crises had anxiety, depression, poor school performance, frequent absenteeism from school and work place, decreased participation in normal activities of daily living, and poor peer and family relationships.

DISCUSSION

The acute sickle cell painful episode is the insignia of the disease (Odièvre *et al*., 2011). Pain related to SCD can be acute or "crisis," which can last from minutes to weeks; chronic pain syndromes as a result of hypoxic tissue damage, lasting more than three months; or neuropathic pain caused by nerve damage or dysfunction (Ballas *et al*., 2012; Wang *et al*., 2010). Chronic pain may evolve into neuropathic pain with time. Acute pain, however, dominates the clinical picture and usually requires urgent treatment. Painful crisis is the commonest cause for hospitalization, and is associated with increased morbidity and mortality in SCD (Platt *et al*., 1994; Ballas and Lusardi, 2005; Darbari *et al*., 2013). US nationwide epidemiological survey data indicate that over half of sickle cell patients have 1– 2 pain episodes annually and 1 % of patients have more than 10 episodes (Platt *et al*., 1991; Wang *et al*., 2010). Nature of pain includes throbbing, sharp, pounding, dull, stabbing, cutting, and gnawing or like a generalized toothache (Ballas *et al*., 2012). The severe pain causes patients to grunt, groan, cry, twist and turn and to assume abnormal postures in the futile attempt to obtain relief (Ballas *et al*., 2012). Much of the devastation caused by the disease is due to the recurrent acute painful crises. Although knowledge about painful crisis is increasing, yet it is very difficult to establish the burden of this problem accurately in the absence of nationwide reporting system or registries. The present paper is a retrospective longitudinal study of all adult patients with SCA admitted to our hospital over a period of one year. This study allowed us to determine some unique features of the acute sickle cell episode with reference to its frequency, duration, pattern, and etiologies of recurrence within a short period of time and prognostic significance. This study showed slight predilection of pain crises for female patients as against other studies which showed male predominance. However, their average pain score was lesser than those of males and accordingly, their LOS was lesser than that of males (7.57 vs 6.13). This was against the observation made by Ballas *et al* in their study on the "Hospital Readmission for Adult Acute Sickle Cell Painful Episodes" in 2005, where the average length of stay for an acute painful episode, was significantly ($P<0.001$) longer for females than males. The average LOS in our study was 6.85 which was less than in a study by Ballas *et al*, where the average LOS was 7.7 days. In University Health System Consortium (UHC) Database which included patients with SCD in crisis over 1 year period, the mean length of stay was 6 days. There was a striking increase in painful crises in male patients between the ages of 15 and 25 years, whereas female patients showed little age-related change. The number of body areas that were painful was not significantly higher in either sexes. This was in accordance with what was reported previously regarding lack of gender differences by McClish *et al*. (2009) in the PISCES project done on 260 patients of SCD over 4 years (McClish *et al*., 2009).

The pain intensity score was highest on the day of admission and gradually plateaued till day four to five. There was significant correlation between the pain score on admission and the hospital length of stay ($P<0.05$). Thus, patients admitted with higher pain score were expected to have longer LOS. Similar observations was made by Ballas *et al* in his study on "Hospital Readmission for Adult Acute Sickle Cell Painful Episodes" in 2005 where 136 patients of SCD with pain crises were prospectively followed up for 4 years (Ballas and Lusardi, 2005). The frequency, location, duration, severity, and character of pain differed among patients. The pain was localized (20%), involved several areas (60%), diffuse (12%), and migratory (2%). It was associated with objective signs like fever (38%) and leucocytosis (15%). Joint tenderness was present in 45% of the patients. However, none of the patient had joint erythema, swelling or effusion clinically. No patient complained of jaw pain. Increasing age was associated more frequently with pain in the ankle/foot, shoulder, arm and hand. In general, pain in the legs and feet occurred more often than in the hand and arm which suggests that mechanism of pain in SCD may be more similar to diabetes and peripheral vascular disease.

According to the Pain In Sickle Cell Epidemiology Study (PISCES), adult patients reported SCD pain at home in about 55% of the 31,017 days surveyed (Smith *et al*., 2008). In a multicenter study of hydroxyurea by Ballas *et al*, at-home analgesics were used for SCD pain on 40% of diary days and 80% of two-week follow-up periods, with short-acting oxycodone and acetaminophen being the most frequently used analgesics (Ballas *et al*., 1989). In our study, oral analgesics were used by 42% of our patients for more than 15 days in a month. Platt and associates (Platt *et al*., 1991) reported that adult patients with SCD and high rates of pain episodes died earlier than those with low rates. 75% patients with recurrent admissions showed similar pattern of involvement of joints (stereotype) during subsequent admissions and went to develop same intensity of pain. 5 patients (15.6%) who had recurrent admissions experienced intermittent, mild to moderate pain episodes which were treated with oral analgesics taken from dispensaries attached to the hospital. Their average duration of pain prior to hospitalization was 2.4 days. Pain at certain sites like the chest, abdomen and back caused greater concern and hence, was an indicator of a higher likelihood of hospital admission in our patients. Also, the development of pain in these sites portended severe crisis. Most of the readmissions were after 2 months from the previous discharge date except for 2 out of 8 patients (25%). Both these patients had severe stressful factors and one was discharged prematurely without adequate pain relief against medical advice. The possible cause of re-admissions in our patients appeared to be true new acute painful episode except in the above mentioned two patients. None of the discharged patients were given oral opiates to be taken at home to avoid the problems of drug abuse and withdrawal symptoms. The male to female ratio was 0.6:1. The readmitted patients tended to be younger. In contrast to our study, the study by Ballas *et al* showed that about 50% of hospital readmissions occurred within 1 month of a previous discharge and about 16% occurred within 1 week of previous discharge with the readmissions being significantly higher for males than females (Ballas and Lusardi, 2005). Possible reasons for hospital readmission within 1 week after discharge

included premature discharge from a previous admission, opiate withdrawal syndrome, new acute painful episode, and aberrant behavior (Ballas and Lusardi, 2005). A recent study indicated that patient outcomes after hospital discharge could be improved if their post-discharge care was done by physicians who treated them in the hospital rather than with other physicians (van Walraven *et al*., 2004). Available data about the evolution of the sickle cell painful crisis show that about 10% of children and about 50% of adults with sickle cell disease continue to have mild to moderate pain between painful episodes (Ballas *et al*., 2012). Forster *et al*. reported that adverse events occurred in about 20% of patients in the peridischarge period (Forster *et al*., 2003).

Precipitating factors were not found in most patients (88%) while infections resulted in crisis in 6% of patients and psychosocial factors were detected in 6% of patients. Interestingly, 3 out of the 5 patients (9.4%) reported to developing pain crisis during the change of season, though literature describes pain crises typically as unpredictable in nature. In a study of risk factors of painful crisis of SCD by Baum *et al*, painful crisis was more in winter season (Baum *et al*., 1987). Similar observation was made by us, with maximum cases (69.8%) occurring in winter and the transition period from winter to summer. However, we did not find more distal joints involvement in patients admitted during cold months as compared to other months. This was also observed by McClish *et al*. (2009) in the PiSCES project (McClish *et al*., 2009). The apparent risk factor for painful crisis which emerged from our study was higher hemoglobin and hematocrit values in the steady state. The Jamaican study by Baum *et al* in a retrospective study of epidemiology of Painful Crisis of Homozygous Sickle Cell Disease in 995 patients, observed that patients whose anemia was severe had fewer episodes of pain as the lower blood viscosity with more severe anemia may ameliorate the severity of vaso-occlusion (Baum *et al*., 1987). Thus, high hemoglobin levels (Hb>8.5g/dl) appeared to be an important risk factor for painful crises by promoting micro vascular sludging and vaso-occlusion. Similar observations were made by Platt and his associates in their landmark study of pain crisis in SCD involving 3,578 patients from newborn up to 66 years in 1991 (Platt *et al*., 1991), Darbari *et al* in 2013 and in CSSCD. Other strong protective factors which emerged in various studies was fetal hemoglobin (HbF) level. Fetal hemoglobin has effect on both the kinetics and extent of hemoglobin S polymerization (Platt *et al*., 1991). Charache *et al* proposed that even a modest increase (>4%) in fetal hemoglobin reduced the pain rate and ultimately improved the survival (Charache *et al*., 1995). Similar observations were noted by Platt and his associates (Platt *et al*., 1991). We did not have HbF levels in all our patients and hence could not study the relationship. In a study of rheologic predictors of the severity of the painful sickle cell crisis by Ballas *et al*, lower percentage of dense cells, irreversibly sickled cells (ISC) and increased deformability of RBCs were associated with severe painful crisis (Ballas *et al*., 1988). In addition, higher serum ferritin ($p = 0.005$), and HDL cholesterol ($p = 0.01$) were independently associated with one or more painful VOCs requiring an hospitalization for acute pain in a Contemporary Adult Sickle Cell Anemia Cohort Study by Darbari *et al*. (2013). Unlike the traditional teaching that patients with sickle call trait have a benign course, in our study 12 patients of the 32 (37.5%) with sickle cell trait (AS pattern) had pain crisis. Most of them (10 patients) had mild to moderate pain crisis. There was no mortality during the study period. However, Platt and associates reported that adult patients (> 20 years) with sickle cell disease and high rates of pain episodes (3 episodes or more per year) tended to have higher mortality rates than those with less than 3 episodes in a year (Platt *et al*., 1991). The association between painful VOC hospitalizations and mortality was first reported by the CSSCD 20 years ago. Also, in a study of painful vaso-occlusive crises by Dardari *et al* in 2010, individuals with severe pain crisis were at a higher risk of death independently of other risk factors (Darbari *et al*., 2014). Acute multiorgan failure (MOF) (Hassell *et al*., 1994) and sudden death (Manci *et al*., 2003) during painful crises has been reported in literature. Most of these serious complications usually occur during day 1-5 of pain crisis. The pain crises is, thus, the measure of clinical severity of SCD (Platt *et al*., 1991).

Use of antimetabolite, hydroxyurea (HU) in SCA reduces the prevalence of VOCs and is associated with significant reduction in hospitalizations for pain (Platt *et al*., 1991; Charache *et al*., 1995; Steinberg *et al*., 2010). One of the proposed mechanisms of action is increased fetal hemoglobin production, which in turn reduces sickle hemoglobin polymerization and vaso-occlusion (Darbari *et al*., 2013; Ballas *et al*., 1989; Charache *et al*., 1995). Other mechanisms of the anti-sickling effect of hydroxyurea are increased water content of red cells, with secondarily increased deformability (Charache *et al*., 1995), and decreased adhesion of red cells to endothelium (Adragna *et al*., 1994). We did not find a significant difference of pain crises between the group taking hydroxyurea and the one not taking HU (p value 0.67). This was possibly due to the potential confounding variables which were not assessed in this study which included the adequacy of HU dosing, duration of HU therapy and compliance with its use. Similar observations were made from the adult contemporary cohort study of painful vaso-occlusive crises by Dardari *et al*. (2013). However, in a study by Charache *et al* in 1995 on the effect of hydroxyurea on the frequency of painful crises in sickle cell anemia, there was 44 % reduction in the median annual rate of painful crises (Charache *et al*., 1995). The difference began to emerge within about two months of the initiation of treatment and was clearly evident at four months. The analgesics we used in our study were acetaminophen, diclofenac, tramadol and opiate fentanyl. We did not come across any major complication except for mild hypotension in 2 patients on fentanyl infusion, which was promptly corrected with intravenous fluids. Although there are no controlled trials to compare the safety and efficacy of different analgesics in the management of acute pain crises, patient safety can be maximized by obtaining a detailed history, understanding drug pharmacology, its side effects, carefully monitoring patients and individualizing care. The choice of opioid, its dose and route of administration has to be individualized with frequent monitoring for possible side effects and to minimize risks of abuse, misuse or diversion. Concerns of treatment of pain episodes with opiates include that of drug abuse, disbelieving patient's pain perception and reluctance to prescribe pain medication resulting in under treatment.

Conclusion

The acute painful crisis is the hallmark of SCD. It is associated with anxiety, depression, suffering and interruption in the activities of daily living. It is unpredictable and may be precipitated by known or unknown risk factors and triggers. The pain may be localized or migratory, involving various

joints and may be associated with systemic features. If the acute painful crisis is treated aggressively at its beginning, it would be of short duration with little or no complications. Also as each episode of pain results in hypoxic damage, aborting the acute painful episode at the prodromal phase could potentially prevent or minimize the tissue damage. Opiates can be safely given under supervision to treat the painful crisis.

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