Predictive value of pain intensity in the clinical severity of painful crises in children and adolescents with sickle cell diseases

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ABSTRACT

Objectives: Painful crisis is a significant problem for patients with sickle cell diseases (SCD). We tried to understand whether or not there is an association between severity of pain and complication rate in hospitalized children and adolescents with SCD in the present study.

Methods: All hospitalized SCD patients with painful crisis between September 2012 and September 2013 were included into the study. The intensity of pain was assessed at the first visit. Pain scores were obtained using the Faces Pain scale and Verbal Descriptor Scale. Severity of pain was divided into three groups as mild, moderate, and severe according to the scales.

Results: Seventy-nine patients under the age of 18 years-old with SCD and 146 episodes of painful crisis were evaluated. Forty-five (57%) patients were women and mean age was 11.5 years. The white blood cell counts, aspartate aminotransferase and C-reactive protein (CRP) were significantly higher while erythrocytes, hemoglobin, hematocrit and albumin levels were significantly lower in the severe pain episodes group ($p<0.05$ for all). The number of patients transfused was significantly high in the severe pain episodes group than the other two groups ($p=0.006$, $p=0.001$). Most of severe pain episodes group had complicated vaso-occlusive crisis (acute chest syndrome 41.6 %, Hepatic sequestration crisis 6.7%), ($p<0.05$).

Conclusion: There may be an direct relationship between prevalence of complicated vaso-occlusive crisis and pain intensity of SCD. Patients with sickle cell anemia should be classified according to their pain scores during hospitalization, and patients with high pain scores should be closely monitored for complications.

Key words: Sickle cell diseases, Vaso-occlusive crisis, Severity of pain, Pain score

Introduction

Sickle cell disease (SCD) is inherited as an autosomal recessive disorder. It is now well established that SCD results from a single change of one amino acid, valine, instead of glutamic acid at the sixth position of the hemoglobin beta chain. The prevalence in Turkey as a whole is 0.3-0.6%, although this rises to 3%-44% in some parts of the Çukurova region.(1)

SCD is characterized by chronic hemolytic anemia, dactylitis, and acute episodic clinical events known as "crises." Vaso-occlusive (painful) crises (VOC) are the most common and start in infancy and early childhood. Other crises are acute chest syndrome, central nervous system crisis, sequestration crisis and aplastic crisis. The factors that precipitate or modulate the occurrence of sickle cell crisis are not fully understood, but infections, hypoxia, dehydration, acidosis, stress and cold are believed to play some role. Frequent episodes of crisis, infections and organ damage reduce the quality of life of patients with SCD. A high rate of VOC is an index of clinical severity that correlates with early death.(1,2) VOC is also the most prevalent complication of SCD. Pain is the insignia of SCD. Acute VOC is a common medical emergency in patients with SCD, necessitating hospitalization. Tissue damage due to vaso-occlusion releases numerous inflammatory mediators that initiate the transmission of painful stimuli and the perception of pain. Sickle cell vaso-occlusion, which may involve both the micro- and macrovasculature, is the most important pathophysiological event in SCD and explains most of its clinical manifestation.(3)

The decision to admit a patient with SCD requires multi-modal evaluation of severity of anemia, presence of infection, priapism, acute chest syndrome, acute stroke or another life-threatening complication.(4) The pain severity ratings Visual Analog Scale (VAS), Numeric Rating Scale (NRS), Verbal Descriptor Scale (VDS) and Faces Pain Scale (FPS) are used. The Verbal Descriptor Scale (VDS) is based on the patient selecting the most appropriate word to describe his/her condition. Pain is classified as mild, moderate or severe on a simple pain scale.(5-7) VAS and NRS are used with patients with SCD.(8) Jones et al.(6) converted pain-intensity scores associated with the Bieri FPS, NRS and VDS into four levels (none, mild, moderate, and severe) to analyze the effectiveness of a pain intervention.

Painful crisis is a significant problem for children with SCD, and there has been little progress to date in its management. There are insufficient studies concerning pain severity scores and prevalence of VOC complications in patients with severely painful crises, and also the management of these patients. The purpose of this study was to estimate the effect of initial pain severity ratings on progress, complications and management of hospitalized pediatric patients with SCD.

Methodology

This study comprised a retrospective chart review of a single-center series of 79 patients with SCD. The sample studied included all pediatric patients hospitalized at Antakya State Hospital, Turkey, between September 2012 and September 2013, with SCD with painful crisis. Data collected included demographic characteristics, clinical, hematological and biochemical data, and Verbal Descriptor Scale and Face Pain Scale scores. Data were obtained from patients' medical charts. The following clinical variables were recorded: age, gender, length of hospital stay (days), duration of pain (days), fever (axillary temperature equal to or greater than 38.0 ^{o}C), transfusion, exchange transfusion, type of pain crisis, factors triggering the painful crisis and intensity of pain.

Baseline values for hematological parameters, and liver and renal functions were recorded. Blood samples were collected in EDTA containing tubes for measurement of leukocyte (WBC), erythrocyte (RBC), hemoglobin (HGB), hematocrit (HCT) and platelet (PLT) levels. A complete blood count (CBC) was carried out on an automated hematology analyzer (Sysmex XT- 2000i, USA). Biochemical parameters (glucose, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, protein and albumin) were assessed in blood samples. All biochemical investigation was performed on a Modular Analytics P800 analyzer (Roche Diagnostics, Indianapolis, IN) using spectrophotometric methods. Concentrations of serum C-reactive protein (CRP) in 146 samples were measured by nephelometry using a BN II Nephelometer (Siemens). Serum CRP values were considered normal between 0 and 5 mg/dl.

Intensity of pain was assessed at the first visit, before any analgesia was administered. Pain scores were obtained using the Faces Pain Scale (FPS) and Verbal Descriptor Scale (VDS). Pain severity based on the Verbal Descriptor Scale was based on the patient selecting the most appropriate word for his/her condition. Pain was classified as mild, moderate or severe on the basis of FACES Pain Scale and VSD pain scores (VDS: no pain; slight and mild pain = mild pain; moderate pain; severe pain, very severe pain, and most intense pain possible = severe pain. Bieri FPS: face 1 = no pain, faces 2-3 = mild pain, faces 4-5 = moderate pain, faces 6 -7 = severe pain).(5-7) For statistical analysis, patients were divided into three groups: one group with mild pain, one group with moderate pain and one group with severe pain. Patients were compared according to severity of pain in terms of demographic, clinical, hematological and biochemical parameters.

Statistical analysis

Statistical analyses were performed on SPSS software, version 15. Data are expressed as arithmetic mean ± standard deviation (SD) for quantitative data and as percentages (%) for qualitative data. Values are presented as mean (minimum-maximum). The Mann-Whitney U test or Chi-square test was used for comparisons between groups, as appropriate. Categorical variables were assessed using the Pearson's chi-square test. A p value of <0.05 was considered significant.

Results

One hundred and forty-six episodes of painful crisis in 79 patients were evaluated. Forty-five (57%) patients were girls and 34 (43%) boys. Mean age was 11.5 years. Mean number of painful crises per year per patient was 1.8. Patients'

demographic characteristics are summarized in Table 1. Painful episodes most often involved vaso-occlusive crisis (n=91, 62.3%), followed by acute chest syndrome (n=35, 24%), splenic sequestration crisis (n=15, 10.3%) and hepatic sequestration crisis (n=4, 2.7%). Only one patient experienced central nervous system crisis (0.7%). Mean hospital length of stay for the 146 painful crisis episodes was 5.5±3.5 days, and mean duration of pain was 4.2±1.9 days.

The mild pain group experienced 15 (11%) episodes, the moderate pain episodes group 71 (48%) and the severe pain group 60 (41%). Age and gender distribution were similar between the groups. Mean length of hospital stay was significantly higher in the severe pain group than in the mild and moderate pain groups (p=0.001, p=0.001). Mean duration of pain was significantly longer in the severe pain group than in the other two groups (p=0.003, p=0.028). Fever was highest in the severe pain group ($p<0.05$). The number of patients transfused was also significantly higher in the severe pain group than in the other two groups (p=0.006, p=0.001). Eight patients were treated with exchange transfusion, six of whom were in the severe pain group ($p>0.05$). Most of the moderate pain group experienced VOC (77%), while most of the severe pain group had acute chest syndrome (41.6%) ($p<0.05$). Hepatic sequestration crisis occurred in four patients (6.7%) in the severe pain group. There were also significant differences between this group and the moderate pain group (p=0.027). Stress was the most common trigger of painful episodes in the mild pain group, and infection in the severe pain group (p=0.001, 0.002). Details of comparative values are given in Table 2.

Hematological and biochemical values were similar in the mild and moderate pain groups. Sickle cell anemia patients with severe pain episodes had significantly higher WBC and CRP levels compared with the other two groups (p=0.014, p=0.003, p=0.025, p=0.004, respectively). Erythrocyte count was significantly lower in the severe pain group than in the mild pain group (p=0.008). Sickle cell anemia patients with severe pain episodes had significantly lower HGB and HCT levels compared with the moderate pain group (p=0.002, p= 0.002). Aspartate aminotransferase levels were significantly higher in the severe pain group (p= 0.022) and albumin levels significantly lower (p=0.001) than in the moderate pain group. Normal range creatinine was higher in the severe pain group compared with the moderate pain group (p=0.04). The hematological and biochemical values of the groups are presented in Table 3 (page 32).

Discussion

Patients with SCD with pain crises were hospitalized in this study. Patients were divided into three groups on the basis of pain assessment scales. Length of hospitalization and duration of pain, WBC, AST and CRP were significantly higher in the SCD group with severe painful episodes, while RBC, hemoglobin, hematocrit and albumin values were significantly lower. More complicated VOC was also observed in this group.

Patients with SCD suffer from acute, painful vaso-occlusion crises, infections and life-threatening acute chest syndrome. Vaso-occlusive crises are the most common causes of acute morbidity and medical emergency in sickle cell anemia patients requiring hospitalization.(9-11) Lionnet F et al.(12) reported prevalences of hospitalized painful VOC, acute chest syndrome and priapism of 36%, 20% and 20%, respectively. In our study frequencies of hospitalized painful VOC, acute chest syndrome, splenic sequestration crisis, hepatic sequestration crisis and central nervous system crisis were 62.3%, 24%, 10.3%, 2.7% and 0.7%, respectively. No priapism was observed in any patient. No patients died and all were discharged after treatment. Thirty-five painful crisis episodes exhibited acute chest syndrome in this study. Acute chest syndrome was recorded based on the current criteria: new infiltrate visible at chest X-ray associated with one or more symptoms, such as fever, cough, tachypnea, breathing difficulties or new-onset hypoxia.(12) Blood exchange was performed in 2 of the patients when no response to medical therapy was achieved. Twenty-five of the 35 patients with acute chest syndrome were in the severe pain group. VOC with complications (acute chest syndrome, splenic sequestration crisis, hepatic sequestration crisis and central nervous system crisis) was more prevalent in the group with severely painful crises. The prevalence of complications rose with severity of pain. Nine of the 15 patients with splenic sequestration crises, all of the 4 patients with hepatic sequestration crises and the one patient with central nervous system crisis were in the severe pain group. Hemorrhagic stroke was determined in our patients with central nervous system crisis. Primary hemorrhagic stroke is an uncommon complication of SCD, with reported mortality rates of 24% to 65%. Most reported cases are in adults, and little is known about the occurrence in children. The incidence of hemorrhagic stroke is greatly increased in patients with sickle cell anemia (HbSS) compared with the general population and affects children and young adults to a disproportionate extent.(13) All 4 episodes with hepatic sequestration were in the severe pain group. Acute hepatic sequestration is a rarely recognized complication of VOC. Patients with right upper quadrant hepatic syndrome generally report right upper quadrant pain and fever. Clinical examination is significant for jaundice and hepatic enlargement.(14) Right upper quadrant pain and fever, significant jaundice and hepatic enlargement were present in all our cases. Blood exchange transfusion was performed in all hepatic sequestration attacks when no response was obtained to medical therapy. Acute splenic sequestration crisis results from the rapid sequestration of red blood cells in the spleen. Splenic sequestration occurs in 10%-30% of children with SCD, most commonly between the ages of 6 months and 3 years, and may follow a febrile illness.(15,16) Similarly in this study, splenic sequestration crisis was determined at a level of 10.3%.

Infection is a major cause of morbidity and mortality in these patients. Patients with SCD have impaired immunity and are thus predisposed to infections which frequently precipitate VOC. Infection was also determined as the factor precipitating 82.2% of painful crisis episodes in this study. Many inflammatory markers of acute phase reaction are elevated in SCD patients. Routine laboratory tests including total leukocyte count and C-reactive protein are sensitive for infection.(9,11) SCD is considered an inflammatory

Table 1. Patients' demographic characteristics.

	(n; means/range) ms/range)
Number of patients	79
Age (years)	11.5±4.57 (1-18)
Gender (male/female)	34/45
The number of painful SCD crises	146
Number of painful crises per patient	1.8±1.13 (1-6)

Data are arithmetical means ± SD. SCD; Sickle cell disease

Table 2: Patients' clinical characteristics

Parameter	Mild pain group (n=15)	Moderate pain group (n=71)	Severe pain group (n=60)
Length of hospital stay (days)	3.40±2.61	4.56±2.44	7.08±3.99[a,b*]
Duration of pain (days)	2.6±1.12	4.14±1.12[a]	4.88±1.82 [a,b*]
Number of patients with fever (n,%)	8 (53%)	30 (42%)	50 (83%)[a,b]
Number of patients transfused (n,%)	3 (20%)	15 (21%)	36 (60%) [a,b]
Exchange transfusion (n,%)	0 (0%)	2 (2.8%)	6 (10%)
Vaso-occlusive crisis (n,%)	15 (100%)	55 (77%) [a]	21 (35%)[a,b]
Acute chest syndrome (n,%)	0 (0%)	10 (14%)	25 (41.6%)[a]
Splenic sequestration crisis (n,%)	0 (0%)	6 (9%)	9 (15%)
Central nervous system crisis (n,%)	0 (0%)	0 (0%)	1(1.7%)
Stress (n,%)	4 (27%)	7 (10%)	3 (5%)[a]
Effort or fatigue (n,%)	0 (0%)	8 (11.2%)	2 (3%)
Infections (n,%)	11 (73%)	54 (76%)	55 (92%)[b]
Cold (n,%)	0 (0%)	1 (1.4%)	0 (0%)
Dehydration (n,%)	0 (0%)	1 (1.4%)	0 (0%)

Data are arithmetical means ± SD (standard deviation). a Statistically significant at $p < 0.05$ compared to the mild pain group. b Statistically significant at $p < 0.05$ compared to the moderate pain group. *p-values were calculated by Mann-Whitney U test. Other p-values were calculated by Pearson's chi-square test.

Table 3: Hematological and biochemical parameters of patients

Parameter	Mild pain group (n=15)	Moderate pain group (n=71)	Severe pain group (n=60)
White blood cell count (/mm³)	14000±4500	15400±6500	20737±10735[a,b]
Erythrocytes count (x 10⁶ /mm³)	3.39±0.67	3.15±0.77	2.74±0.84[a]
Hemoglobin (gr /dl)	8.37±1.50	8.88±1.75	7.67±2.05[b]
Hematocrit (%)	24.48±4.05	25.40±4.60	22.03±5.43[b]
Platelet count (x 10³/L)	360±192	402±232	348±217
Glucose (mg/dl)	103.54±15.37	99.83±18.06	104.16±22.24
BUN (mg/dl)	9.01±3.21	8.20±2.78	8.79±3.02
Creatinine (mg/dl)	0.31±0.08	0.33±0.14	0.29±0.11[b]
AST (U/L)	45.67±18.52	43.24±30.91	67.95±117.82[b]
ALT (U/L)	19.40±11.07	24.45±19.58	38.18±116.46
Total bilirubin (mg/dl)	2.67±2.32	2.63±1.86	3.66±3.72
Direct bilirubin (mg/dl)	0.57±0.11	0.76±0.68	1.29±2.62
Protein (g/dl)	7.50±0.87	7.58±0.56	7.26±0.71
Albumin (g/dl)	4.65±0.25	4.74±0.34	4.49±0.41[b]
CRP (mg/dl)	30.33±34.94	46.52±55.01	80.07±63.65[a,b]

Data are arithmetical means ± SD (standard deviation). a Statistically significant at $p < 0.05$ compared to the mild pain group. b Statistically significant at $p < 0.05$ compared to the moderate pain group. BUN; blood urea nitrogen, AST; Aspartate aminotransferase, ALT; Alanine aminotransferase , CRP; C-reactive protein. p-values were calculated by Mann-Whitney U test.

condition due to abnormally high leukocyte counts and increased levels of WBCs during and after VOC. Clinical studies show that leukocytosis is a risk factor for major sickle cell-related complications such as stroke, acute chest syndrome and early death.(17-19) This study demonstrates that patients with SCD have significantly high WBC levels in severely painful episodes. As a marker of inflammation, CRP has been used to predict prognosis and relapse in patients with some chronic diseases, as well as morbidity in others.(10) Akohoue et al.(10) reported higher serum CRP levels in patients with SCD than in healthy controls. In the present study, CRP levels were higher in SCD patients with painful crisis episodes. CRP levels were highest in patients with severe crises. Previous studies have shown that serum CRP levels are markedly increased in patients with SCD with VOC and that sequential measurements of CRP are useful in predicting the subsequent development of severe painful crisis in patients hospitalized for VOC.(20,21) Previous studies have also shown that CRP levels correlate well with VOC with fever in patients with SCD.(22)

Liver abnormality results in AST and ALT release, making this a useful test for detecting liver damage. Hemolysis also raises AST, ALT and bilirubin levels in SCD.(23) One recently published study reported elevated bilirubin, total protein random glucose AST and ALT levels in SCD.(23) Ojuawo et al.(24) reported significantly higher ALT, alkaline phosphatase and bilirubin levels during crisis than at

recovery, especially in young patients. However, total protein and albumin levels between crisis and at recovery were not significantly different. In this study, AST levels were significantly high and albumin significantly low in the severe pain crisis group. Koh et al.(25) reported that increased hospital stay was associated with lower albumin and hemoglobin/hematocrit levels. In agreement with Koh et al.(25) we determined low albumin, hemoglobin and hematocrit values in the severe pain SCD group, that with the longest hospitalization. This shows the presence of greater hemolysis and hepatic damage in this group.

In conclusion, SCD continues to represent a major public health problem in Turkey, and especially in our region. Patients are mostly admitted to the emergency department with VOC. This analysis of 146 painful crisis episodes suggests that VDS and FPS should be used in determining the severity of painful episodes in patients with SCD, and that patients with high pain intensity scores should be monitored closely in terms of complicated VOC.

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