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A study of serum c reactive protein in sickle cell disease patients with or without Vaso-occlusive crisis and its response to analgesic therapy

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Abstract

Introduction: Sickle cell anemia (SCA) is a hematological condition that runs in the family. SCA is accompanied by a number of acute and chronic consequences, the most clinically relevant of which is micro vessel blockage, commonly known as Vaso-occlusive crisis (VOC). Increased levels of pro-inflammatory markers, such as C-reactive protein (CRP), were found in the sera of SCA patients. The goal of the current study is to determine whether CRP values are elevated during a sickle cell crisis and whether this elevated level of CRP has any bearing on the severity of pain.

Material and methods: This hospital based observational study was conducted on 139 Patients with sickle cell disease aged above 12 years. All included patients of SCD with or without Vaso occlusive crisis were tested for CRP levels.

Results: Mean age in years was 25.4±1.2 years with male to female ratio of 2.15:1. Musculoskeletal, joint pain (83.45%) was most common form of presentation. Exhaustion and severe physical activity (73.38%) was most common precipitating factor. Mean VAS score was 8.41±1.4. Mean CRP level was 38.5±3.4. On analgesic administration there is significant reduction in CRP level. On Spearman's correlation coefficient between VAS and CRP, positive correlation was seen. R =0.73 and P value <0.00001*.

Conclusion: Strong positive correlation was seen between pain score and CRP levels, which indicates that as pain score increases the CRP levels are also spiked. It was even seen that as pain management was started early the CRP level also started to decline. So, pain management should be considered as an important part of treatment protocol of Sickle cell vaso-occlusive crisis. This can further help early discharge of the patient.

Keywords: Sickle cell Vaso-occlusive crisis, CRP levels, Analgesics, Pain management, Visual analogue score

Introduction

The more severe genotype of sickle cell disease is sickle cell anemia (SCA) (SCD). It stands for the beta S (S) globin allele's homozygous state. [1,2] In India, the prevalence of SCA is between 0.4% and 1% and that of Sickle cell trait is between 5% and 7%. [3-5] Sickle cell carriers are more common in distinct tribal populations and the Vidarbha region of Maharashtra state, with prevalence's ranging from 0.8% to 35.1%. [6]

When severe anemia, Vaso occlusive crisis (VOC), splenic sequestration, crippling avascular bone necrosis, osteomyelitis, or epistaxis arise, sickle cell disease is discovered to be apparent as early as 3 months of age. It can also go unnoticed for years. These difficult clinical occurrences demand prompt and expert clinical care. [7]

Hemolysis, acute and chronic inflammation, Vaso-occlusive consequences, numerous organ dysfunction, and decreased patient survival are clinical characteristics of SCA.[8] Mortality rates for this population remain high even with improved therapy, such as the early use of preventive antibiotic regimens, prudent blood transfusions, and the prescription of hydroxyurea in certain patients.[9]

Sickle cell disease (SCD) complications and symptoms are primarily brought on by crises (clinical and subclinical). Inflammation, the production of C-reactive protein (CRP) and other inflammatory mediators, and the ensuing increase of ischemia are caused by the activation and damage of endothelial cells along with the activation of adhesion molecules. [10]

The main clinical signs of SCD are unpleasant episodes of pain due to VOC, but subclinical events often happen. Stable state is the interval between painful crises when the patient is at ease.

The liver and adipocytes produce the plasma protein known as C-reactive protein (CRP), which is classified as an acute phase protein. Within six hours following the beginning of inflammation, the CRP level rises, culminating at about 48 hours. Compared to patients whose severe crises is resolved within 24 hours, patients whose pain persists for 4 days had higher CRP levels. [6]

For patients with sickle cell disease to be managed effectively, it is essential to identify, treat, and prevent Vaso-occlusive crises (VOCs) as early as possible. It's crucial to distinguish between pain brought on by VOCs and pain brought on by chronic pain, hyperalgesia, neuropathy, and neuropathic pain.

The sufferers have excruciating agony in their back, stomach, and extremities. Patients experience an unpleasant and terrifying episode of sickle pain. In order to reduce pain and help patients achieve their highest level of functional capacity, pain management should be aggressive.

In the present study, an attempt is done to find out whether the CRP values are increased in sickle cell crisis and whether increased level of CRP has any relationship with the duration of pain and whether level of increased CRP can be one of the factors helpful in management of sickle cell VOC.

Materials and method

This hospital based observational case control study was carried out at Maharashtra, India, during period of October 2019 to December 2021. In the present study we included patients of homozygous sickle cell anemia (SS) as the heterozygous sickle cell hemoglobinopathy (AS) is usually results in benign condition. Total number of sickle cell anemia cases studied were 139. All the subjects were examined and investigated according to

proforma that was predesigned and pretested. Informed consent was obtained from all subjects enrolled in the study.

Inclusion Criteria

- Patients with >12 years
- Both gender
- Patients of painful vaso-occlusion sickle cell crisis under medicine ward

Exclusion Criteria

- Unwillingness of the patients, uncooperative subjects
- Renal failure
- Having overt infection (abscess/ skin infection)
- Known hypersensitivity to analgesics
- Respiratory insufficiency
- Pregnancy

Participants were told about the study and written informed consent was taken. Study participants coming to the department of medicine and showing the inclusion criteria were studied. Data was collected by using a pre designed questionnaire which consisted of standard questions related to clinical condition, socio demographic factors, addiction among family members, and so on, were interviewed. In addition, questions related to past and present medical history and health seeking behavior were also studied. Clinical examination, diagnosis, investigations details of previous operative procedure was done. All included patients of SCD with or without Vaso occlusive crisis were tested for CRP levels. Pain assessment was done by pain scale (visual analogue scale).

Pain assessment was repeated every 6 hourly. All concomitant treatment were entered. Analgesics were administered according to hospital protocol and pre and post analgesic administered response was observed.

Investigations

- 1. Hematological: Hb, TLC, DLC, ESR
- 2. Renal parameters: blood urea, serum creatinine
- 3. Liver function test
- 4. CRP (Normal: <10 mg/l)

Statistical analysis

All data was collected and complied in Microsoft excel. Results of continuous (quantitative data) measurement were presented on Mean +/- SD (min-max) and result on categorical (qualitative data) measurements was presented in percentage and proportions (%). Comparison of qualitative variable was analysed by chi-square test.

Wherever necessary between groups, comparison of quantitative variables was analysed by independent student t test according to distribution. A p value of 0.05 was taken as level of significance and was considered statistically significant. Data analysis was done using open epi version 2.3.1.

Results

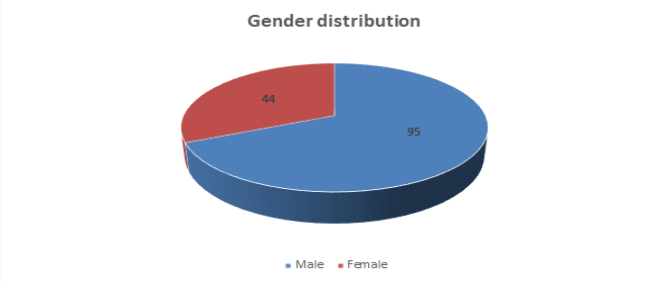
Out of 139 patients studied, majority belonged to age group 21 to 30 years old (59 cases, 42.44%); followed by 41 patients (29.49%) from age group 12 to 20 years old and 32 patients (22.02%) from age group 31 to 40. Least patients (7 cases, 5.03%) were found in age group more than 40 years old.

Youngest patient enrolled was 12 years old while oldest one was 45 years old. Mean age was to be 25.4 ± 1.2 years. Total males in cases are 95 (68.35%) and females are 44(31.65%). Male to female ratio was 2.15:1. (Table-1)

Table 1: Age wise distribution

Age (in years)	No of cases(n)	Percentage
<20	41	29.49%
21-30	59	42.44%
31-40	32	22.02%
>40	7	5.03%
Total	139	100%

Graph 1: Gender distribution

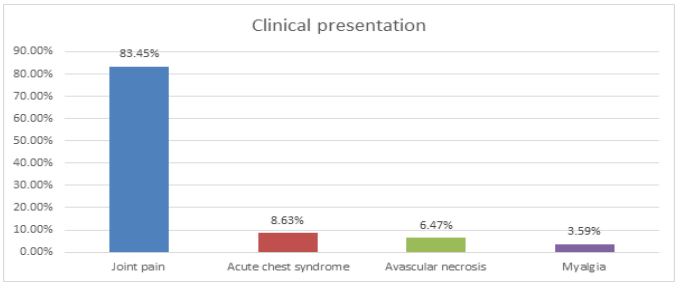


Common clinical presentations were joint pain, acute chest syndrome, avascular necrosis and myalgia. In majority of cases, joint pain (116 cases, 83.45%) was seen; followed by acute chest syndrome in 12 patients (8.63%), avascular necrosis in 9 patients (6.47%) and least common was myalgia seen in 5 patients (3.59%). (Table - 2)

Table 2: Clinical presentation

Clinical presentation	No of cases	Percentage
Joint pain	116	83.45%
Acute chest syndrome (Breathlessness, chest pain)	12	8.63%
Avascular necrosis	9	6.47%
Myalgia	5	3.59%

Graph 2: Clinical presentation



Most common aggravating factor was severe physical activity in 102 cases (73.38%). Next aggravating factors in decreasing order of frequency were exposure to cold in 15 cases (10.19%), damp weather in 9 cases (6.47%), stressful condition in 5 case (3.59%). In 8 cases (5.75%) the cause was unknown. (Table - 3)

Table 3: Symptoms aggravating factors

Aggravating factor	No of cases(n)	Percentage
Cold exposure	15	10.79%
Severe physical activity	102	73.38%
Damp weather	9	6.47%
Stressful condition	5	3.59%
No cause	8	5.75%

On laboratory investigation mean HB% was 7.3±1.2, ESR was 22.5±2.5, TLC was 5534±1234, polymorphs was 54.34±12.3, urea was 28.56±3.42, creatinine was 0.98±0.41, bilirubin was 1.3±0.1, SGOT was 32.76±9.45, SGPT was 28.9±6.5.

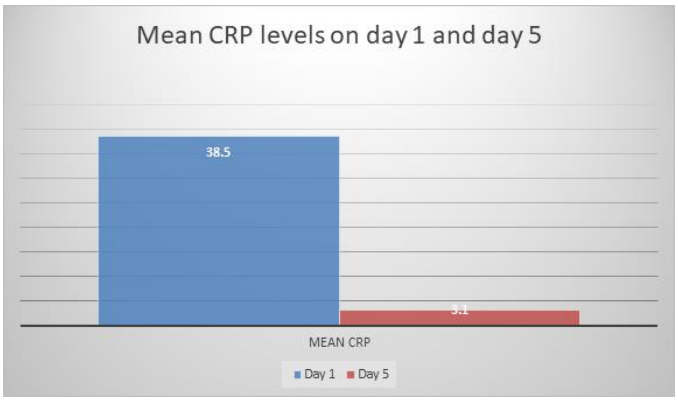
Mean CRP level on day 5 was 3.1±1.2. Statistical significance was seen ($p<0.0001$). On admission (day 1), baseline CRP was done. Then patients were started on analgesic medications according to hospital protocol. On day 5, again CRP level was tested and it was found to be drastically decreased which was statistically significant. (Table-4)

Table 4: Mean CRP levels on day 1 and day 5

CRP level	Mean
Day 1	38.5
Day 5	3.1

Applying t test, p value was <0.0001, shows statistical significance

Graph 3: mean CRP levels on day 1 and day 5



Most common analgesia used was NSAIDS in 90 cases, opioid in 33 cases and 16 used both. Majority patients required analgesia on day 1 as compared to day 5. Statistical significance was seen. On Spearman's correlation coefficient between VAS and CRP, positive correlation was seen. R =0.73 and P value <0.00001*.

Discussion

The current investigation, which involved 139 patients who had SCD and VOC, was a hospital-based prospective study at a tertiary care facility. The high prevalence and global distribution of sickle hemoglobin (Hb S), a variant of hemoglobin (Hb), make it a variant hemoglobin (Hb) of significant clinical value. The main pathophysiological mechanism behind a number of Vaso-occlusive-like occurrences caused by the trapping of poorly deformable and fragile sickle red blood cells in narrow capillaries is the sickling of red blood cells (RBCs) in sickle cell anemia due to polymerization of HbS when deoxygenated. The type and frequency of problems that SCA patients experience, as well as the clinical severity of SCA, vary greatly. Recent research has indicated that SCA patients may frequently encounter Vaso-occlusive-like events, such as osteonecrosis, acute chest syndrome, and Vaso-occlusive crisis (VOC) (OTN).

In present study, out of 139 patients studied, majority belonged to age group 21 to 30 years old (59 cases, 42.44%). Mean age in years was 25.4±1.2 years. It is Ranging from 12 to 45 years. Male to female ratio was 2.15:1. Okocha C et al showed [11] that mean age 19±9.4 years, ranging 5 to 38 years. In their study, 30 patients were studied. Out of 30 patients, 9 patients were female and 21 patients were male. Male to female ratio was 2.33:1.Dr Kausik Goswami et al [12] showed that 54.73% were males and 45.26% were females. Shweta P. Bijwe et al [13] did a hospital-based study. In that study, total 31 patients were studied. Out of 31 patients, 23 patients were male and 8 patients were female. Male to female ratio was 2.88. Mean age in years was 18.64±3.56 years. It is Ranging from 12 to 29 years. Majority 70.96 % were in age group of 12 to 19 years.

In present study, on the basis of history given by the patients, Common clinical presentations were joint pain, acute chest syndrome, avascular necrosis and myalgia. In majority of cases, joint pain (116 cases, 83.45%) was seen; followed by acute chest syndrome in 12 patients (8.63%), avascular necrosis in 9 patients (6.47%) and least common was myalgia seen in 5 patients (3.59%). In present study, most common aggravating factor was severe physical activity and it was seen in 102 patients. Most common aggravating factor was severe physical activity in 73.38%, exposure to cold in 10.70%, damp weather in 6.47%, stressful condition in 3.59% and unknown or no cause in 5.75%. Shweta P. Bijwe et al [13] did a hospital based observational study in 31 cases

and found that Musculoskeletal joint pain was most common form of presentation. It was seen in 26 cases (83.87%). Acute chest syndrome was seen in 2 cases (6.45%) avascular necrosis in 3 cases (9.47%). They also found that Exhaustion and severe physical activity (25.80%) was most common precipitating factor and it was seen in 8 cases (25.80%). Other precipitating factors were exposure to cold, damp weather, stress and unknown cause. Exposure to cold was seen in 6 cases (19.35%), damp weather in 5 cases (16.12%), stress in 4 cases (12.90%), unknown cause in 8 cases (25.80%). Dr Kausik Goswami et al [12] showed that Diarrhoea (26%), LRTI (16%), URTI (14%) and malaria (12%) were more prevalent infection in sickle cell patients. In their study, total 95 patients were selected and grouped into three classes.Class one had 25 patients. Class two had 50 cases whereas class three had 20 cases. Most common precipitating factor was diarrhoea and it was seen in 25 cases.

In present study, visual analog scale score was calculated. It was more than 5 in 112 patients (80.57%) and it was less than 5 in 27 cases (19.43%). Mean VAS score was 8.41$\pm$1.4. majority 80.57% had VAS score <5. In present study, duration of Vaso-occlusive crisis pain was measured. It was less than or equal to 96 hours in 89 patients (64.02%) while it was more than 96 hours in 50 cases (35.97%). Mean duration of pain in hours was 34.21$\pm$9.1. Majority 64.02% had duration <96 hours. In present study, most common analgesia used on day 1 was NSAIDS in 90 cases (64.74%). Opioid was used in 33 patients (23.74%) and in 16 patients (5.03%) used both. On day 5 only 10 patients out of 90 patients were on NSAIDS. 9 patients out of 33 patients were on opiod. 1 patient out of 16 patients was on both. Braga JA et al [14] showed that VAS (scores of 0–100) in 74 SCD adults with Vaso-occlusive crisis identified a mean score of 80 [95% confidence interval (CI): 75.99–82.95] on arrival at hospital. Shweta P. Bijwe et al [13] showed that out of 31 cases studied, mean duration of pain was less than 96 hours in 20 cases (64.51%) while it was more than 96 hours in 11 cases (35.48%). They also calculated visual analog scale score. Mean VAS score on day 1 was 8.70 ± 1.03 in most of the cases.SK Ballas and A Delengowski[15]studied in 23 hospitalized adult patients with sickle cell anemia during 60 acute painful episodes. The 10 cm Visual Analog Scale was used to measure the intensity of pain. The average pain severity score upon admission was 9.5 +/- 0.63 (mean +/- SD) and upon discharge was 4.8 +/- 0.97. They found that thedose or frequency of administering narcotic analgesics was reduced when the daily score of pain decreased by 2 or more on the scale.

In present study, on admission (day 1), baseline CRP was done. Then patients were started on analgesic medications according to hospital protocol. On day 5, again CRP level was tested and it was found to be drastically decreased which was statistically significant.Mean CRP level on day 1 was 38.5$\pm$3.4. Majority patients (71.94%) had CRP >20. Mean CRP level on day 5 was also calculated it was found to be 3.1$\pm$1.2. Statistical significance was seen ($p<0.0001$). Study by Mohammed FA et al [16] showed that higher hs-CRP levels were seen in VOC [median(range)=31.3(1.14-363.0)] than steady-state [median(range)=5(0.16-185.0)] groups ($P<0.001$). Shweta P. Bijwe et al [13]did a hospital based observational study and found that Mean CRP on day 1 (40.87±17.22 mg/L) was significantly high compared to control (3.67±0.77 mg/L) with statistical significance $p<0.0001$. Mean CRP on day 4 was 9.89±7.06. on day

14, mean CRP was 3.22±1.02**.** P Hernandez, Eva Svarch (2001)[17]studied 83 patients with sickle cell anaemia and they found increased C-reactive protein in 55% of them during the steady state and they found during the follow up of these patients that these 55% patients developed Vaso-occlusive crisis within 4-5 days of CRP positivity.

On Spearman's correlation coefficient between VAS and CRP, positive correlation was seen. R =0.73 and P value <0.00001*. Study by Mohammed FA et al [16] showed that on Spearman's correlation coefficient between hs-CRP and VOC was 0.65 (P<0.001) among unselected patients. The VOC crisis state is a phase where there is an acute increase of Vaso occlusion and tissue necrosis.

Conclusion

Present study concludes that Vaso-occlusive crisis in sickle cell anemia is a complex scenario requiring multimodal approach. Staring with prompt and adequate pain management which should be started at the earliest.

Strong positive correlation was seen between pain score and CRP levels, which indicates that as pain score increases the CRP levels are also spiked. It was even seen that as pain management was started early the CRP level also started to decline. So, pain management should be considered as an important part of treatment protocol of Sickle cell Vaso-occlusive crisis. This can further help early discharge of the patient.

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