Original Research Article

Correlation of serum C-reactive protein in painful vaso-occlusive crisis in sickle cell disease and its response to analgesic therapy

Shweta P. Bijwe[1*], Mithil B. Ghushe[2]

[1]M.D. Pathology, IGGMC, Nagpur, Maharashtra, India
[2]M.D. Medicine, IGGMC, Nagpur, Maharashtra, India
[*]Corresponding author email: **dr.shwetabijwe@gmail.com**

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Abstract

Background: Sickle cell disease is characterized by chronic hemolysis, frequent infections and recurrent occlusions of microcirculations, which causes painful crisis and results in chronic organ damage and failure. Occlusion of microcirculation and infection are important factors that stimulates production of cytokines and acute phase proteins like C- reactive protein.

Aim: To estimate serum C-reactive protein levels in cases of painful vaso-occlusive crisis of sickle cell disease, to study correlation of level of serum C-reactive protein with duration of painful vaso-occlusive crisis of sickle cell disease, to study relation between level of serum C-reactive protein and treatment response of analgesic versus analgesic opioid in cases of painful vaso-occlusive crisis of sickle cell disease.

Materials and methods: This hospital based observational case control study was carried out at IGGMC, Nagpur, Maharashtra, India. Total 31 cases of sickle cell vaso-occlusive crisis, of age 12 years and above, admitted in hospital and 31 controls included in study. Study protocol was followed in each case.

Results: Musculoskeletal, joint pain (83.87%) was most common form of presentation. Exhaustion and severe physical activity (25.80%) was most common precipitating factor. Mean hemoglobin, bilirubin showed statistically significant difference in cases compared to control. 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 $p<0.0001$.

Conclusion: Serum C- reactive protein levels are higher in cases of painful sickle cell vaso-occlusive crisis than control. C- reactive protein levels correlate positively with duration of pain in cases of painful sickle cell VOC**.** Steady state C- reactive protein level is normal in cases of sickle cell anemia. Cases of painful sickle cell VOC in whom opioid had to be used in addition to NSAIDs for pain management had higher CRP levels than who responded to NSAIDs alone. The cases in whom serum C- reactive protein levels were >33.2mg/L required use of opioid for pain management of sickle cell VOC. However, sample size of the present study is small and will need further prospective study.

Key words

Sickle cell vaso-occlusive crisis, CRP levels, Analgesics, Pain management.

Introduction

Sickle cell disease (SCD) is the most extensively worked out genetic disorder. In fact sickle cell was the first human disorder to be understood at the amino acid level. Sickle cell anemia (SCA) alone is the most heritable hematological disease affecting humans [1].

The prevalence of sickle disease in Central India as per study of Shukla and Solanki (1985) is high in certain localities in Vidarbha region of Maharashtra [2].

Sickle cell is found to manifest as early as 3 months of age or may remain asymptomatic till the development of severe anemia, vaso-occlusive crisis (VOC), splenic sequestration, crippiling avascular bone necrosis, osteomyelitis or epistaxis. These are challenging clinical events deserving competent and urgent clinical management [3].

Sickle cell disease is characterized by chronic hemolysis, frequent infections and recurrent occlusions of microcirculations, which causes painful crisis and results in chronic organ damage and failure. Occlusion of microcirculation and infection are important factors that stimulates production of cytokines and acute phase proteins [4].

Intermittent painful crisis due to VOC are the major clinical manifestations of SCD, but subclinical episodes also occur [5]. The period between painful crisis, during which the patient feels well, is called steady state [4].

Acute phase proteins are defined as, any protein whose plasma concentration increases (positive acute phase proteins; fibrinogen, serum amyloid A, albumin, C-reactive protein) or decreases (negative acute phase proteins; albumin, transferring, insulin growth factor I) by at least 25% during an inflammatory disorder [6]. C-reactive protein (CRP) is a plasma protein, an acute phase protein, produced by the liver [7] and by adipocytes [8]. CRP level increases within 6 hours of onset of inflammation with peaking values at around 48 hours. CRP levels remains high in patients whose pain persist for 4 days than those in whom painful crisis is resolved within 24 hours [9].

No reliable objective index of pain exists. The provider solely depends on the patients report. As all the pain scales are subjective, estimation of serum CRP may be the first objective evidence for sickle cell crisis.

Pain episodes are among the most troublesome and frequent complications of sickle cell syndrome. The patients develop severe pain in the extremities, back and abdomen. A sickle pain episode is both uncomfortable and frightening to the patients. Therefore, pain management should be aggressive to ease the pain and enable patients to attain maximal functional ability.

Major barriers to effective management of pain are clinicians limited knowledge of SCD, inadequate assessment of pain and biases against opioid use. Biases are based on ignorance about

opioid tolerance, physical dependence and confusion with addiction.

Though these cases of SCD are managed on large scale at our institution, IGGMC, published studies regarding pain management and acute phase reactants in sickle cell crisis are very few. Therefore we undertook this study.

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.

Aim

- To estimate serum C-reactive protein levels in cases of painful vaso-occlusive crisis of sickle cell disease.
- To study correlation of level of serum C-reactive protein with duration of painful vaso-occlusive crisis of sickle cell disease.
- To study relation between level of serum C-reactive protein and treatment response of analgesic versus analgesic opioid in cases of painful vaso-occlusive crisis of sickle cell disease.

Materials and methods

This hospital based observational case control study was carried out at IGGMC, Nagpur, Maharashtra, India, during period of January 2007 to June 2008.

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 31 and equal number of age and sex match control were studied. 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

All consecutive cases of painful vaso-occlusive sickle cell crisis that admitted in medicine ward of IGGMC, of age 12 years or above age of 12 years, of both gender.

Exclusion criteria

- Subject with renal failure
- Cases having overt infection (abscess/ skin infection)
- Cases in which analgesics/ opioids are contraindicated/ known hyper sensitivity
- Cases having respiratory insufficiency
- Pregnancy
- Prior enrolment in study

Controls- Number of controls: 31

Definition of control- Age, gender matched individual having normal AA pattern on Hemoglobin Electrophoresis were included.

Study protocol

All consecutive cases of painful sickle cell crisis admitted in medicine wards of IGGMC were studied. Cases were clinically evaluated in details as per proforma which included complete history of patient, history of blood transfusion, general and systemic examination, all laboratory investigations, history of medical treatment and other important findings. Precipitating causes of painful crisis if any were mentioned. Sample of serum C-reactive protein were taken at the time of admission (within 30 minutes), 4^{th} day and on 14^{th} day from first day of crisis i.e. steady state of sickle cell disease.

Quantitative serum C-reactive protein were measured by immunotubidometric method on semiautomated biochemistry analyser. Cases were given treatment as per pain management protocol practiced at medicine wards of IGGMC, which was based on WHO guidelines for pain

management. Pain assessment was done by pain scale (visual analogue scale). Pain assessment was repeated every 6 hourly. All concomitant treatment were entered. Example; (antibiotics/ iv-fluids/ folic acid/ zinc). C-reactive protein was estimated in one group of healthy control age and sex match.

Biochemical measurement

Automated complete blood count- is done by the Sysmex KX-21.

Kidney function test:- blood urea is done by Berth lot method and serum creatinine done by Randox method.

CRP- done by LABKIT, SPAIN

Statistical analysis

Statistical analysis was done with the help of "SPSS version 12"version software. Probability value of $p<0.05$ were considered significant while $p<0.01$ taken as highly significant. Quantitative variable were described as mean ± SD. Paired and unpaired t test were applied.

The diagnostic applicability of the studied parameters to identify infections was evaluated using receiver operating characteristic curves (ROC) and corresponding area under curve (AUC) values and their 95% confidence intervals (CI). The ROC curves have been calculated by plotting the sensitivity versus 1- specificity for each possible cut-off value and then joining the points. The corresponding AUC values were obtained by using the SPSS statistical software. The test is ideal if its AUC value is 1.0, while a value of 0.5 does not differ from that obtained by chance.

Results

Age group range was from 12 to 29 years in 31 cases of study group. Mean age in cases was 18.64±3.56 years. 23 cases (76.66%) were in 12-19 age group range of which 11 are male and 12 are female, 8(25.80%) cases were in 20-29 age group range out of which 5 are male and 3 are female. Total males in cases are 16(51.61%) and females are 15(48.38%). Male to female ratio was 1.06 (**Table – 1**).

Table - 1: Age and sex wise distribution of cases (n=31).

Age group (years)	Male (%)	Female (%)	Total (n=31)
12-19	11 (35.48)	12 (38.70)	23(76.66)
20-29	5(16.12)	3(9.67)	8(25.80)
Total	16(51.61)	15(48.38)	31(100)

Table - 2: Age and sex wise distribution of control (n=31).

Age group (years)	Male (%)	Female (%)	Total (n=31)
12-19	10 (32.25)	12 (38.70)	22(70.96)
20-29	6(19.35)	3(9.67)	9(29.03)
Total	16(51.61)	15(48.38)	31(100)

Age group range was from 12 to 29 years in 31 control of study group. Mean age in cases was 18.48±3.65 years. 22 cases (70.96%) were in 12-19 age group range of which 10 are male and 12 are female, 9(29.03%) cases were in 20-29 age group range out of which 6 are male and 3 are female. Total males in cases are 16(51.61%) and females are 15(48.38%). Male to female ratio was 1.06 (**Table – 2**).

Table - 3 shows that Musculoskeletal, joint pain (83.87%) was most common form of presentation followed by avascular necrosis of femoral head (9.67%) and acute chest syndrome (6.45%).

Table - 4 shows that exhaustion and severe physical activity (25.80%) was most common precipitating factor of sickle cell crisis, followed

by exposure to cold (19.35%). In 25.80% cases no apparent cause could be found.

Table - 3: Presentation form in cases (n=31).

Presentation	Cases (%)
Musculoskeletal, joint pain	26 (83.87)
Acute chest syndrome	2(6.45)
Avascular necrosis	3(9.67)

Table - 4: Precipitating factors in cases.

Precipitating factors	Cases (%) (n=31)
Exposure to cold	6(19.35)
Exhaustion and severe physical activity	8(25.80)
Damp weather	5(16.12)
Stress	4(12.90)
none	8(25.80)

Table - 5 shows that mean hemoglobin, bilirubin showed statistically significant difference in cases compared to control.

Table - 6 shows 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.

Table - 7 shows that mean CRP level on day 14 was 3.22±1.02 mg/L with range of 1.2-5.2 mg/L in cases, while in control range was 2.3-5.3 mg/L with mean CRP level of 3.62±0.77 mg/L. There is no statistical significance (P=0.039).

Table - 8 shows that in cases mean CRP level on day 1 was significantly high[40.87±17.22 mg/L] as compared to mean CRP level on day 14 i.e. steady state of SCD (3.22±1.02 mg/L) with significant p(<0.0001) value.

Table - 9 shows that in cases mean CRP level on day 1 was 40.87±17.22mg/L, on day 4 CRP was 9.89±7.06 mg/L, on day 14 CRP was 3.22±1.02mg/L while CRP in control was 3.67±0.77 mg/L.

Table - 5: Biochemical investigations in cases and control.

Parameters	Cases	Control	Level of significance
Hb%	8.61±0.88	10.91±1.83	**P<0.0001**
ESR	19.48±3.57	10.25±1.82	**p<0.0001**
TLC	5512±1160	5434±822	P= 0.76
Polymorphs	55.41±3.58	54.83±3.85	p=0.541
Urea	28.35±3.85	28.64±5.06	P=0.80
Creatinine	0.73±0.21	0.67±0.17	P=0.22
Bilirubin	1.27±	0.62±0.16	**P=0.01**
SGOT	33.77±10.78	26.64±5.68	**P=0.001**
SGPT	30.90±7.39	26.32±4.56	**P=0.004**

Table - 6: Correlation of CRP in cases and control.

CRP (mg/L)	Cases (n=31)	Control (n=31)	Level of significance
Day 1 (mean ±SD)	40.87±17.22	3.67±0.77	**P<0.0001**
Range	22.5-96.0	2.3-5.3	

Table - 7: Correlation of CRP in cases and control.

CRP (mg/L)	Cases (n=31) (i.e. steady state)	Control (n=31)	Level of significance
Day 14 (mean ±SD)	3.22±1.02	3.67±0.77	**P=0.039**
Range	1.2-5.2	2.3-5.3	

Table - 8: Correlation of CRP in cases.

CRP (mg/L)	Day 1 (n=31)	Day 14 (n=31)	Level of significance
Mean ±SD	40.87±17.22	3.22±1.02	**P<0.0001**
Range	22.5-96.0	1.2-5.2	

Table - 9: CRP estimation in cases and control (mg/L) (**Figure – 1**).

CRP 1 (mean ±SD)	CRP 4 (mean ±SD)	CRP 14 (mean ±SD)	CRP C (mean ±SD)
40.87±17.22	9.89±7.06	3.22±1.02	3.67±0.77

Table - 10: Correlation of visual analogue scale (VAS) in cases (**Figure – 2**).

VAS	Day 1	Day 4	Day14
Mean ±SD (cm)	8.70±1.03	2.41±1.60	0.0±0.0
Range	7-10	0-4	0
Level of significance	**P<0.0001**	**P<0.0001**	

Table - 11: Correlation between CRP level and pain scale.

Day	Day 1	Day 4	Day 14
CRP (Mean ±SD) (mg/L)	40.87±17.22	9.89±7.06	3.22±1.02
VAS (Mean ±SD) (cm)	8.70±1.03	2.41±1.60	0.0±0.0

Table - 12: Duration of pain in cases of sickle cell crisis.

Duration of pain (Hours)	Cases (%) (n=31)
≤96	20(64.51)
>96	11(35.48)

Table - 13: Correlation of CRP with duration of pain in cases.

Duration of pain (Hours)	CRP day 1 (mg/L)	CRP day 4 (mg/L)
≤96 (n=20)	33.36±8.57	5.96±2.61
>96 (n=11)	54.52±20.79	17.05±7.01
Level of significance	**P<0.0001**	**P<0.0001**

Table - 14: Correlation of CRP with treatment response.

CRP	Group A (n=17)	Group B (n=14)	Level of significance (A vs B)
Day 1 (mg/L)	29.47±8.25	54.71±17.98	**P<0.001**
Range	22.5-36.8	34.5-96.0	
Day 4 (mg/L)	5.72±2.85	14.95±6.97	**P<0.001**
Range	2.3-12.5	5.9-29.8	

Table - 10 shows that all cases had severe pain at the time of admission i.e. VAS score on day 1 was 8.70±1.03 cm, on day 4 mean was 2.41±1.60 cm and on day 14 i.e. steady sate of SCD none of cases had pain.

Table - 11 shows , in cases when CRP levels were high on day 1, VAS score was also high and as CRP levels decreases VAS score also decreases on day 4 and 14. It indicates that Mean CRP level and VAS score are proportional to each other.

Table - 12 shows that in 20 (64.51%) cases pain lasted for ≤96 hours, while in 11(35.48%) cases pain lasted for >96 hours.

Table - 13 shows that, the cases in which pain lasted for >96 hours (n=11) had higher mean CRP on day 1(54.52±20.79 mg/L) and on day 4 (17.05±7.01mg/L), than in cases in whom pain lasted for <96 hours [n=20] mean CRP on day 1 was 33.36±8.57mg/L and on day 4 mean CRP was 5.96±2.61mg/L with statistically significant p value (p<0.0001).

Group A consists of those who responded to NSAIDs alone while Group B of those who responded to opioid + NSAIDs. Mean CRP level on day 1 was significantly high in group B (54.71±17.98 mg/L) than group A, but CRP was reduced in both groups (p<0.001). In group A, mean CRP on day 1 was 29.47±8.25 mg/L and on day 4 was 5.72±2.85 mg/L (p<0.001). In group B, mean CRP on day 1 was 54.71±17.98 mg/L and on day 4 was 14.95±6.97 mg/L (p<0.001) as per **Table - 14**.

Area under the curve demonstrated that serum CRP level >33.2 mg/L showed maximum sensitivity and specificity. ROC- receiver operating characteristic curve was as per **Table – 15**.

Table - 15: ROC- receiver operating characteristic curve (**Figure – 3, 4**).

Variable	Value
Classification of variable	Criteria
Positive group	
B	Group B
Sample size	14
Negative group	
A	Group A
Sample size	17
Disease prevalence (%)	Unknown
Area under ROC curve	0.983
Standard error	0.025
95% confidence limit	0.857 to 0.990
Significance level p (Area=0.5)	0.0001

Criterion	**Sensitivity**	**95% CI**	**Specificity**	**95% CI**	**+ LR**	**-LR**
>=22.5	100	76.7-100.0	0	0.0-19.7	1	
>33.2	**100**	**76.7-100.0**	**88.24**	**63.5-98.2**	**8.5**	**0**
>36.2	85.71	57.2-97.8	88.24	63.5-98.2	7.29	0.16
>36.8	85.71	57.2-97.8	100	80.3-100.0		0.14
>96	0	0.0-23.3	100	80.3-100.0		1

Discussion

Even though SCA is prevalent in many parts of world, the clinical manifestations vary in different geographical area. As sickle cell crisis at time can be potentially life threatening, timely management of these cases can be certainly useful to reduce morbidity and improve quality of life. VOC in SCA is an acute presentation and one of the etiologies is thought to be inflammation, the acute phase reactants and marker of inflammation are known to be released in blood, raising their blood values. CRP is known to be raised in VOC. It is one of the most important, sensitive reliable marker, as an acute phase reactant. It is cheap and can be estimated by immunoturbidometric method, requires only venepuncture.

Age and sex distribution

In cases, age group range was 12-29 years. Mean age in cases was 18.48±3.65 years. In majority of

cases, 23 (76.66%) out of 31 were in 12-19 years of age group. Male to female ratio was 1.06. Similarly out of 31 controls, 22 (70.96%) were in age group of 12-19 years. Mean age was 18.48±3.65 years. Male to female ratio was 1.06. Similar ratio was found in study by Baum K F, et al. [10], 1987. Study done by Anil Pathare, et al., 2004 [4] found higher mean age 27.7±12.5 years. This variation as compared to present study can be explained by small sample size of present study.

Figure - 1: CRP estimation in cases and control (mg/L).

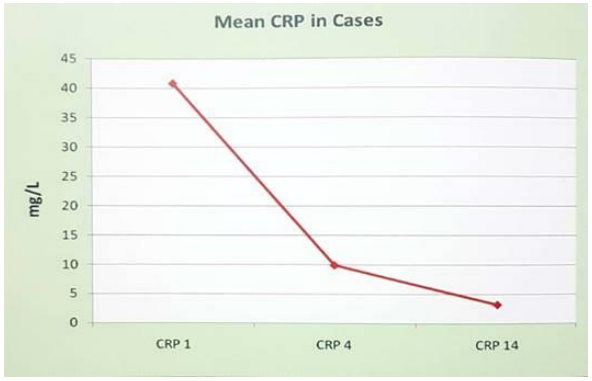
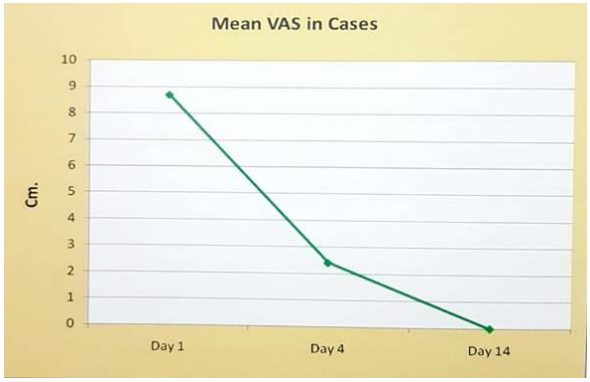


Figure - 2: Correlation of Visual Analog Scale (VAS) in cases.



Presentation form of sickle cell crisis

In present study musculoskeletal, joint pain (83.87%) was most common form of presentation. Similar findings were seen by Dongre LR, et al. (2001) [11], Deshmukh, et al. (1979) [12] and Sheika Salim AI Arrayed (1995) [13]. However, Deshmukh, et al. (1979) [12] studied cases of SCD, while present study included cases of SCA painful vaso-occlusive crisis only.

Figure – 3: Receiver operating characteristics curve showing distribution of mean CRP on day 1 in cases.

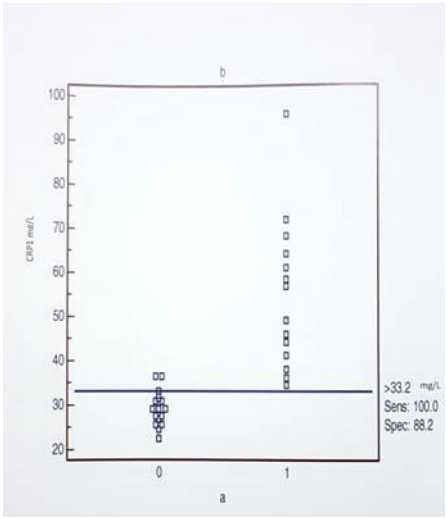
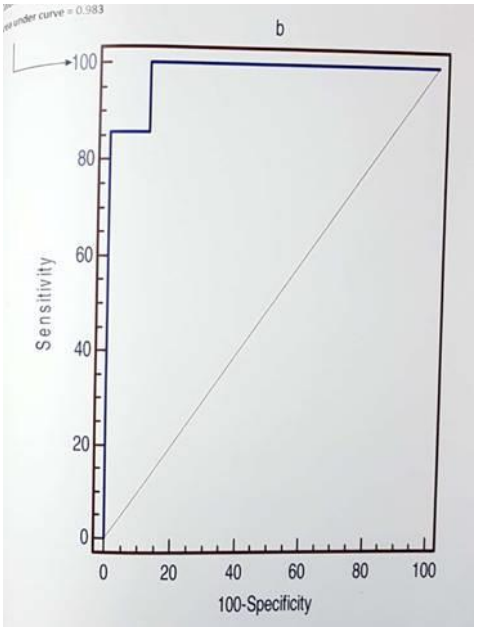


Figure – 4: Receiver operating characteristics curve showing area under curve.



Precipitating factors

In present study, exhaustion and severe physical activity (25.80%) was most common precipitating factor of sickle cell crisis, followed by exposure to cold (19.35%). In 25.80% cases no apparent cause could be found. Study done by Sheika Salim AI Arrayed (1995) [13] found exposure to cold (45%) as the most frequent precipitating factor. Others were fever (35%), exhaustion and severe physical activity (35%). This variation may be explained by geographical

variation and apparent cause of infection was excluded from our study.

Visual Analog Scale (VAS)

All cases had severe pain at the time of admission i.e. VAS score on day 1 was 8.70±1.03 cm. Mean pain score was reduced by day 4 to 2.41±1.60 cm with significant p value (<0.0001). On day 14 i.e. steady sate of SCD none of cases had pain i.e. pain score was 0. Minimum pain duration was 66 hours, while maximum pain duration was 240 hours in present study. There was successful pain relief in all cases. In the study done by Bernard L Loper, et al. (2007) [14], mean pain score on admission was 7.9 cm with 95% CI (75.99 to 82.95 cm). SK Ballas, et al. (1993) [15], mean pain score on admission was 9.5±0.63 cm that was comparable with our study.

Serum CRP Levels

In present study mean serum CRP in control was 3.67±0.77 mg/L that was comparable with the study done by Shapiro D (1989) [16]. Serum level of CRP was significantly high on admission i.e. day 1, with mean 40.87±17.22 mg/L than control with statistically significant p value (<0.0001). Mean CRP on day 4 in sickle cell VOC was 9.89±7.06 mg/L with statistically significant reduction as compared to day 1. 20 (64.51%) out of 31 had normal CRP value at 96 hours, while 11 (35.48%) had increased level of CRP at 96 hours. The cases in which pain lasted for >96 hours (n=11) had higher mean CRP on day 1 (54.52±20.79 mg/L) and on day 4 it was 17.05±7.01mg/L (p<0.0001).

In the cases in whom pain lasted for <96 hours (n=20) mean CRP on day 1 was 33.36±8.57mg/L and on day 4 mean CRP was 5.96±2.61mg/L with statistically significant p value (p<0.0001). Mean serum CRP in steady state i.e. day 14 was 3.22±1.02 mg/L with no statistically significant difference (p=0.039) when compared to control. Steady state was achieved in all cases. Thus mean CRP on day 1 was 40.87±17.22 mg/L and mean CRP on day 14 i.e. steady state was 3.22±1.02 mg/L (p<0.0001).

In a study done by J Stuart, et al. (1994) [9], they studied 14 episodes of painful crisis, 8 were treated at home and 6 at hospital. Patients with crisis that resolved within 24 hours in hospital demonstrated a minor rise in CRP compared with greater rise in patients admitted for 4 days or more. These findings are comparable with present study.

In study done by Anil Pathare, et al. (2004) [4] in Oman, 60 patients were enrolled 26 were in steady state i.e. Group A and 34 were in vaso-occlusive crisis i.e. group B. It was observed that CRP roses significantly (p<0.0001) in group B 114.61±15.2 mg/L, compared with steady state 7.25±2.1 mg/L. These findings are comparable with present study. Higher CRP on admission and steady state in Anil Pathare, et al. 2004 [4] study may be explained by more severe form of disease in Oman. However it needs further prospective studies on steady state CRP in SCD.

Pain management therapy

Pain management is the most important aspect of sickle cell VOC and two important group of drugs used in pain are NSAIDs and opioids. Each one is having advantages and disadvantages. Use of these drugs is mandatory in pain management of sickle cell VOC. NSAIDs used in study were Ibuprofen and Paracetamol. Opioid were Pentazocin and Tramadol which is known to be a weak opioid.

Practically it has been found that very little number of patients of sickle cell VOC develops addiction to these drugs if used for a short period. As such controversies exists, it was attempted in the present study whether there is difference in CRP level at the time of admission in cases who respond to NSAIDs alone , than those in whom opioids had been used in addition to NSAIDs.

In the present study, cases were distributed in 2 groups. In group A- cases who respond to NSAIDs (Ibuprofen + Paracetamol) and Group B – cases who responded to opioid + NSAIDs. In group A mean CRP on day 1 was

29.47±8.25 mg/L and on day 4 was 5.72±2.85 mg/L ($p<0.001$). In group B mean CRP on day 1 was 54.71±17.98 mg/L and on day 4 was 14.95±6.97 mg/L ($p<0.001$).

Mean CRP level on day 1 in cases of sickle cell VOC who responded to group B was higher than those who responded to group A, however further prospective studies are needed to confirm this. Mean CRP value of group B on day 1 was 54.71±17.98 mg/L while mean CRP value of group A on day 1 was 29.47±8.25 mg/L.

CRP was reduced in both groups. Similar results were found in study done by Bull soc. (1993) [17].

Prasad K (2006) [18] shown that use of NSAIDs reduce serum level of CRP. Elvan Erhan MD (2006) [19] shown that Tramadol infusion combined with a non-opioid drug was effective to relive moderate to severe pain due to VOC. Statistically significant difference of CRP on day 1 in group B (analgesic and opioid) was explained on the basis of severe form of crisis in whom opioids are needed for pain management than those who responded to analgesics.

Role of mean serum CRP level in Prediction of crisis

As opioids may be necessary for pain relief in severe form of crisis, in the present study an attempt was made, whether CRP at certain level can predict crisis severity and may strongly indicate need to use opioid for pain management. For this purpose various CRP levels were tested for maximum sensitivity and specificity by plotting ROC.

Area under the curve demonstrated that serum CRP level >33.2 mg/L showed for maximum sensitivity and specificity. Therefore it can be postulated that, if serum CRP is more than 33.2 mg/L, cases of sickle cell VOC may need opioid invariably for successful pain management. However this needs to be confirmed further by large sampled size prospective randomized controlled studies, as on extensive literature no parallel study could be found out which studied serum CRP level in sickle cell VOC between cases treated by analgesic and/or opioids.

In bivariate analysis between CRP and duration of pain showed that CRP on day 1 correlates positively with duration of pain ($r=0.387$). These findings are comparable with study done by J Stuart, et al. (1994) [9]. Therefore, this can be postulated from present study that CRP is useful acute phase reactant associated with sickle cell crisis.

As diagnosis of sickle cell VOC is clinical, increased CRP level can be a useful adjunct as one of the objective evidence in sickle cell VOC. As visual analog scale (VAS) for pain is subjective and may vary from patient to patient, increased CRP level can be a useful adjunct as one of the objective evidence associated with painful sickle cell VOC.

CRP is simple, cheap investigation and can be performed easily and needs only venepuncture. It can be one of the important investigations that can support the management of SCA.

CRP levels are normal in steady state in present study. If CRP levels can be monitored, normal CRP can be one of the important parameters which can help to document achievement of steady state in SCD. Persistent elevation of CRP in sickle cell crisis would be suggestive of severe form of VOC and needs more intensive management as for as pain is concerned.

High CRP value >33.2 mg/L at the time of admission in present study signified that these cases had severe crisis and may need opioid invariably.

Hence it can be postulated from present study, CRP level >33.2 mg/L at the time of admission in painful VOC may be treated with opioid right from the beginning of treatment. However sample size of the present study is small and will need further prospective study.

Study limitations

- Small sample size.
- Only painful VOC cases were included.
- Other acute phase reactants are not studied.

Conclusion

Serum C-reactive protein levels are higher in cases of painful sickle cell vaso-occlusive crisis than control. C- reactive protein levels correlate positively with duration of pain in cases of painful sickle cell VOC. Steady state C- reactive protein level is normal in cases of sickle cell anemia. Cases of painful sickle cell VOC in whom opioid had to be used in addition to NSAIDs for pain management had higher CRP levels than who responded to NSAIDs alone. The cases in whom serum C- reactive protein levels were >33.2 mg/L required use of opioid for pain management of sickle cell VOC. Musculoskeletal and joint pain was the most common presentation. Exhaustion and sever physical activity is the most common precipitating factor.

Thus serum C- reactive protein estimation is one of the objective evidences associated with painful crisis. Increased level of serum C-reactive protein correlates with duration of pain and may also helpful in planning management of VOC. Normal C- reactive protein value may be helpful to document steady state in sickle cell anemia. By avoiding precipitating factors VOC may be avoided. Effective management reduces morbidity and improves quality of life in patients of sickle cell crisis.

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