

Comparison of Three Biomarkers with Blood Culture Yield in Children with Sickle Cell Anaemia at an Acute Care Tertiary Setting of North-Western Nigeria

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Article Metrics

Date submitted: 02/25/2021

Date Accepted: 26/05/2021

Date Published: 30/07/2021



ABSTRACT

Background: Most acute presentations of sickle cell anaemia (SCA) mimic sepsis or a systemic inflammatory response syndrome (SIRS), but blood culture results take at least 48-72 hours, and usually of low yield. Therefore, a diagnostic marker differentiating sepsis from other acute presentations in SCA patients is needed. This study describes the performance of blood culture, C-Reactive Protein (CRP), high sensitive CRP (hsCRP) and Procalcitonin (Procal) in an acute care setting.

Methods and Material: Consecutive SCA patients with various acute presentations that attended the Emergency Paediatrics Unit of a tertiary hospital in north-western Nigeria were recruited; and their blood culture, CRP, hsCRP and Procal were evaluated.

Results: There were 25 acutely ill SCA patients recruited, with a mean±std age of 8.6±4.4 years. There were 2(8%), 11(44%) and 12(48%) patients in the category of no SIRS, with SIRS and with sepsis respectively. The means±std of biomarkers were CRP 126.7±62.4mg/L, Procal 4.38±11.6 ng/ml, and hsCRP 5mg/L respectively. Only 5(20%) of the blood cultures yielded growth of bacteria, P value 0.033. One subject in no SIRS group, four in SIRS group and nine in sepsis groups had elevated Procal levels. The CRP and hsCRP values were elevated in all the subjects across the groups, apart from one subject in the SIRS group with a normal CRP. These did not show any statistically significant differences.

All the 5(20%) subjects with positive blood culture had elevated levels of Procal while 9(36%) of the negative blood cultures had elevated Procal levels. This association was significant with a P value 0.026. C-Reactive Protein and hsCRP values were elevated in all blood culture categories, except for one negative culture which had normal CRP.

Conclusions: Procalcitonin performed most comparably to blood culture in differentiating sepsis and SIRS in patients with SCA during acute presentations; better than CRP or hsCRP.

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How to cite this article

Faruk JA, Aliyu S, Adebisi MN, Abubakar Y, Abdulrauf H A, Ibrahim M, *et al.*, Comparison of three Biomarkers with Blood Culture yield in Children with Sickle Cell Anaemia at an Acute Care Tertiary Setting of North-Western Nigeria. J Med Bas Sci Res 2021;2(1):37-43.

Access to the article



website: <http://www.jmbsr.com.ng>

doi: <https://doi.org/10.46912/jmbsr.35>

Keywords: Procalcitonin, C-reactive protein, sepsis, sickle cell anaemia.

INTRODUCTION

Many acute presentations of sickle cell anaemia (SCA) mimic sepsis and often times require admission and presumptive antibiotic treatment. Complications such as acute chest syndrome, stroke, mesenteric infarction and the ubiquitous bone pain crisis are usually accompanied by features of systemic inflammatory response syndrome (SIRS). Infection is frequent in SCA due to functional asplenia and abnormal humoral immunity; and it's a major cause of morbidity and mortality. Furthermore, infection can be a precipitant of other complications of SCA. As results of blood culture could take at least 48 – 72 hours, the dilemma of empirical treatment with antibiotics in the initial hours following hospital presentation is daunting. This dilemma may not be mitigated even later as bacterial yield from culture is quite low, due in part, to widespread pre-hospital use of antibiotics procured over the counter.

Many patients with these complications are treated presumptively with antibiotics, as the consequence of untreated bacterial infection in children with SCA could be dire. However, this approach is fraught with risk of over-medicalization. There has been worldwide outcry about spread of antimicrobial resistance from inappropriate use of antibiotics in recent times, which has led to institution of antibiotic stewardship. The search for a point-of-care diagnostic marker that may differentiate SCA patients with sepsis from those without infection, to guide antibiotics use, is ongoing. Several plasma biomarkers of inflammation and infection have been studied in SCA. Serum C-Reactive Protein (CRP) and, to a larger extent, Procalcitonin (Procal) have been speculated to offer some degree of

differentiation in such cases. While Procal has been shown to have a better diagnostic accuracy in detecting bacterial infection in SCA, there is a difference of opinion on its cut-off limit of negative predictive values. Some have opined that there is insufficient data on Procal to make a call on its utility in this regard. Other authors demonstrated higher CRP values in asymptomatic steady state subjects. Therefore, there is on-going discourse as to the utility and applicability of CRP, high sensitivity CRP (hsCRP) and Procal in the clinical settings of SCA management.

This study set out to describe the performance of blood culture, CRP, hsCRP and Procal in an acute care setting of a tertiary hospital in a developing country.

MATERIALS AND METHODS

This was an observational descriptive study of sickle cell anaemia children admitted at a tertiary hospital of North-western Nigeria. Ethical approval was obtained from the Health Research Ethic committee; certificate number ABUTH/PGO/COMM9. Informed written consent was given by all the caregivers, and assent was given, where appropriate by the children above seven years for their participation in the study. All the study procedures were carried out as per the guidelines given in Declaration of Helsinki 2013. Patients who were admitted with symptoms of fever and or bone pains into the emergency paediatric unit were consecutively recruited. Children who had received a blood transfusion in the three months prior to the study were excluded from participation. The

recruited patients had laboratory evaluations comprising white blood cell count, blood cultures and other relevant sepsis work-up; in addition to CRP, hsCRP and Procal. All cultures were performed according to standard laboratory procedures. The CRP, hsCRP and Procal levels were measured by Finecare™ rapid test using quantitative fluorescence immunoassay method. (Catalog No. W201, version: 06/02/2015 and Catalog No. W210, version: 06/01/2016 respectively). CRP > 10 mg/L, hsCRP > 1 mg/L and Procal > 0.5 ng/ml were defined as elevated levels based on the manufacturer's specifications. Systemic inflammatory response syndrome (SIRS), was defined as the presence of tachypnoea, tachycardia, fever and elevated leucocytes. Sepsis was defined as SIRS of infective origin, proven or suspected. The subjects were divided into three groups; those without SIRS, those with SIRS and those with Sepsis.

Data was collated and analysed using EPI INFO™ version 7.1.0.6., released 8/9/12. The results were presented in prose and tables. Categorical variables were summarized as simple proportions, means and ranges. Categorical variables were compared using Chi-square and Fisher's tests as appropriate. Significance was taken as a p-value < 0.05. Sensitivity, specificity, negative and positive predictive values were also calculated.

RESULTS

There were 25 patients recruited, comprising 14(56%) females and 11(44%) males; with a male to female ratio of 1:1.3. The symptoms manifested by the subjects at the point of recruitment, included fever 20(80%), bone pain 19(76%), pallor 7(28%), limb swelling 7(28%) and abdominal pain 5(20%). Others were cough, difficulty breathing, dysuria, headache, hemiplegia, convulsions in 2(8%) each, and oliguria,

abdominal distension in 1(4%) each. All the subjects except two, had multiple complaints with the commonest combination of symptoms being bone pain and fever with either limb swelling or pallor in 17 (68%).

The multitude of clinical diagnoses encountered in the study were vaso-occlusive crises 17(68%), anaemic crises 6(24%), infection/sepsis 6(24%), stroke 3(12%), acute chest syndrome 2(8%), then acute osteomyelitis and mesenteric infarction in 1(4%) each. The six diagnoses of infection comprised two subjects with urinary tract infections, three subjects with clinical suspicion of typhoid or other sepsis and one subject with hepatitis. There were at least two morbidities or diagnoses in 8(32%) of the subjects, the commonest combination being vaso-occlusive and anaemic crises. Only 5(20%) of the blood cultures yielded growth; comprising four *Staphylococcus aureus* and one *Escherichia coli*. There were no isolates from any of the urine, stool or cerebrospinal fluid (CSF) cultures done.

A summary of the descriptive parameters is given in Table I. All the subjects had oxygen saturations (SPO₂) of 95-99% in room air, and none of the subjects required volume expansion as they had good peripheral perfusion. High-sensitive-CRP values were >5mg/ml, which was the upper limit detectable by the test kit in all the 25 subjects.

According to the study definitions of SIRS and sepsis, the subjects were retrospectively sub-classified into three groups. There were 2(8%), 11(44%) and 12(48%) patients in the no SIRS, SIRS and Sepsis groups respectively. The cut-off values for CRP, hsCRP and Procal were applied to further segregate the subjects as normal or high categories. Procal levels were above the cut off in 1(4%) patient from the no SIRS group, 4(16%) from the SIRS group and 9(36%) in the Sepsis group. The CRP

Table I: Descriptive parameters of the 25 study subjects.

Age – group(years)	Number (%)	Averages
0 – 5	7 (28)	8.4 ± 4.4 (Mean ± SD)
6 – 10	10 (40)	Range 2 – 16
.	8 (32)	
Category	Mean ± SD	Range
Heart rate (bpm)	112.3 ± 15.3	80 – 140
Respiratory rate (cpm)	34.5 ± 13.2	20 -68
Temperature (°c)	37.9 ± 0.87	36 – 40
Weight (kg)	19.9 ± 7.8	8.4 – 39
Height (cm)	116.3 ± 24.4	68 -155
WBC (x 10 ⁹)	16.3 ± 8.5	1.9 – 35
CRP (mg/L)	126.7 ± 62.4	9.6 – 200
Procal (ng/ml)	4.38 ± 11.6	0.1 – 53

Table II: Presenting symptoms in the 25 SCA subjects

Symptoms	Number of subjects (%)
Fever	20 (80)
Bone pain	19 (76)
Pallor	7 (28)
Limb swelling	7 (28)
Abdominal pain	5 (20)
Cough	2 (8)
Difficulty breathing	2 (8)
Dysuria	2 (8)
Headache	2 (8)
Hemiplegia	2 (8)
Convulsions	2 (8)
Oliguria	1 (4)
Abdominal distension	1 (4)

Table III: Clinical diagnoses of the 25 study subjects

Morbidity in SCA subjects	Number of subjects (%)
Vaso-occlusive crises (VOC)	17 (68)
Anaemic crises	6 (24)
Infection/sepsis	6 (24)
Stroke	3 (12)
Acute Chest Syndrome	2 (8)
Acute osteomyelitis	1(4)
Mesenteric infarction	1(4)

values were elevated in all the subjects across the groups, apart from one subject in the SIRS group. Likewise, hsCRP were elevated in all 25 subjects across all three groups. Table II shows the distribution of Procal among the clinical groups.

As further depicted in Table II, all the 5(20%) subjects with positive blood culture had elevated levels of Procal while only 9(36%) amongst the negative blood cultures had elevated Procal levels. This contrasts with 19(76%) of elevated CRP and 20(80%) of elevated hsCRP with negative blood cultures. Comparing the performance of the blood culture and biomarkers, positive blood cultures were found only in the sepsis group, with a statistically significant p-value of 0.033, whereas Procal, CRP and hsCRP did not show statistically significant differences between the three groups. On the other hand, there was a statistically significant association between blood culture and Procal, with a p-value of 0.026 whereas there was no significant association between blood culture and CRP or hsCRP.

Table IV: Distribution of subjects according to clinical groups and Procal tests values

Category n(%)	Procalcitonin levels		Chi square 6.592 P = 0.159
	Normal	High	
No SIRS 2 (8)	1 (4)	1 (4)	
SIRS 11 (44)	7 (28)	4 (16)	
Sepsis 12 (48)	3 (12)	9 (36)	
Total 25 (100)	11 (44)	14 (56)	
Blood culture			
Positive growth	-	5 (20)	Fisher's test 0.8361
No growth	11 (44)	9 (36)	P = 0.038
Total 25 (100)	11 (44)	14 (56)	

DISCUSSION

The present study demonstrates the utility of blood culture, Procal, CRP and hsCRP in a sickle cell acute care setting of a resource-poor tertiary hospital setting. Although it employed a purposive

small and convenient sample size, the subjects were fairly distributed across the paediatric age groups. It can therefore be argued that the findings of the study are representative of the studied population. It can be further surmised that the studied population predominantly exhibited features of SIRS going by the average values of heart rates, respiratory rates, body temperatures and WBC. While this needs to be interpreted with caution due to the convenient sampling employed, it nevertheless amplifies what previous studies have reported whereby a lot of morbidities in sickle cell disease were found to mimic SIRS. The high preponderance of fever as a presenting symptom in the study, highlights the need to discern what proportion of these fevers require antibacterial therapy or not; because either under-treatment or over-treatment will have resounding consequences. Indeed, fever is a very common manifestation of infection, and infection has been established as a major cause of morbidity and mortality in SCA. In contrast to the high proportion of fever (80%), only a quarter of the study subjects had a clinical diagnosis of presumed infection. Therefore, the chances of overlooking an infection in the studied subjects was quite possible. Interestingly, using the study definitions, 92% of the subjects easily fell into either the SIRS or sepsis categories. This underscores the essence of the present study, whereby improving the precision with which these clinical decisions are based and made is crucial in avoiding further morbidity and/or mortality. However, it gives little or no comfort that only 20% of the blood cultures were positive from the study. Earlier studies already alluded to the low yields from blood cultures in emergency care settings, and the reasons advanced from those studies may not be different herein; although such data were not specifically elicited in the present study.

All subjects had hsCRP levels $>1\text{ng/ml}$, which was the upper limit detectable by the test kit, and signified elevation of the hsCRP. Thus, the hsCRP in the present study did not provide the desired benefit of

distinguishing which subjects had bacterial infection or not. Indeed, hsCRP is considered a marker of low grade systemic inflammation; and sickle cell disease is a condition known to be associated with inflammation even in the asymptomatic steady state. Thus, it is not surprising that all the subjects had elevated hsCRP given that these were sick patients with underlying inflammatory processes.

In tandem with the universal elevation of hsCRP in the present study, CRP was also elevated. This amounted to 96% of the study, and as such was equally not discriminatory between SIRS and sepsis. The reason for this finding is also not far-fetched, as CRP is commonly elevated in inflammatory conditions, including in asymptomatic steady state sickle patients.

As evident from Table II, a little over half of the study subjects had elevated Procal, and the single largest group with elevated levels was the sepsis group. Although this distribution did not show statistical significance, it at least indicates the promise of some utility for Procal in distinguishing between SIRS and sepsis. When blood culture results alone were considered as the basis for categorization of the subjects, Procal performed better at ruling out infection because no positive blood culture had normal Procal levels; all were elevated. In addition, this association was shown to have statistical significance. Therefore, amongst the three biomarkers tested in the present study, Procal has proven to be more useful in identifying sepsis, while CRP and hsCRP tended to over-diagnose sepsis or failed to discriminate SIRS from sepsis. This is in keeping with earlier studies where Procal was also shown to out-perform CRP in this function, with 100% sensitivity and negative predictive values for Procal in this role, although the specificity and positive predictive values differed. However, it is noteworthy that while the present study and that of Patel et al used $>0.5\text{ng/ml}$ as the cut-off point for elevated Procal, other studies chose higher values, with cut-offs as high as 2ng/ml sometimes used. These cut-off values were chosen

either to indicate presence of invasive bacterial infections or serious bacterial infections. Either way, elevation of Procal above the stated cut-off indicates the presence of bacterial infections, and as such it is a very useful biomarker in the setting of acute care for sickle cell patients especially in settings like the present study. These further underscores the need to have a uniform cut-off value of Procal for use across all healthcare settings.

The study is limited by the relatively small sample size and the lack of an asymptomatic control group for comparison. Patients admitted to hospital, were more likely to have elevated inflammatory and infection markers. However, this limitation was compensated for by the sub-group analysis of subjects with confirmed infection against those without bacterial isolates as initially intended by the study.

In the present study setting of acute care for sickle cell subjects admitted with SIRS or sepsis, Procal performed comparably to blood culture better than CRP or hsCRP in ruling out bacterial infections. Therefore, incorporating Procal into routine investigations for acutely ill sickle cell subjects, will help in the urgent decision-making process of antibiotic use at the early stages of admission.

CONCLUSION

In the present study setting, Procalcitonin performed most comparably to blood culture in differentiating sepsis and SIRS in patients with SCA during acute presentations; better than CRP or hsCRP. Therefore, incorporating Procal into routine investigations for acutely ill sickle cell subjects, will help in the urgent decision-making process of antibiotic use at the early stages of admission.

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