

Uric Acid Concentration in Patients with Sick Cell Anaemia Presenting with Vaso-Occlusive Crises in Uch, Ibadan

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Abstract: Sick cell anaemia is a point mutation characterized by homozygous inheritance of HbS, the commonest presenting symptoms in patients with sickle cell anaemia is vaso-occlusive bone pain crisis; this is an acute exacerbation of chronic inflammatory state in them. Elevated serum uric acid is associated with increased oxidative state, inflammation, hyperhaemolysis and sickle cell nephropathy in adult patients with sickle cell disease. There are inconsistent findings on uric acid concentration during vaso-occlusive pain crisis in patients with sickle cell disease. This study compares uric acid concentration in sickle cell disease patients with bone pain crisis, steady state and HbA individuals. It also correlates uric acid concentration with the severity of vaso-occlusive crisis in patients with sickle cell disease using bone pain crisis as a prototype of a vaso-occlusive crisis. Thirty each of sex and age-matched adult patients with sickle cell anaemia in a bone pain crisis, steady state and HbA were recruited in this study. Total summary pain score was used for assessment of bone pain crisis severity, 23 parameters automated haematology analyzer was used to measure haematological parameters. Plasma uric acid concentration was determined by Uricase method using the Landwind LWC 100 plus automated analyzer machine. Data obtained were analyzed using the Statistical Package for the Social Science (SPSS) version 20. Results were considered statistically significant if $p < 0.05$. Biochemical parameters were correlated with the severity of bone pain crisis. Plasma uric acid concentration of mild BPC, moderate BPC and severe BPC were not significantly different from those of steady state group ($p = 0.523$, 0.543 and 1.000 respectively) There was also no significant correlation in the mean plasma uric acid concentration in mild BPC, moderate BPC and severe BPC (Correlation coefficient (r) = 0.212 , p -value = 0.372). In conclusion, this study established that though the uric acid concentration was higher in patients with SCA presenting with severe bone pain crisis than those with mild bone pain crisis and moderate bone pain crisis. However, there was no significant correlation between uric acid concentration and severity of bone pain crisis.

Keywords: Sick Cell Anaemia, Uric Acid Concentration, Bone Pain Crisis, Steady State, HbA

1. Introduction

Sickle cell anaemia (SCA) is the homozygous inheritance of haemoglobin S (HbS) [1]. It is the commonest monogenic disorder in the world with great impact in sub-Saharan Africa, particularly in Nigeria [2, 3].

Haemoglobin S results from a single codon mutation

characterized by the substitution of Guanine-Adenine-Guanine (GAG) to Guanine-Thymine-Guanine (GTG) in the sixth position of beta-globin gene codon on chromosome 11, this leads to an amino acid replacement of water-soluble glutamic acid to an insoluble valine [4]. In the deoxygenated, it forms polymers within the red cell, this result in physical deformation of the erythrocytes containing these polymerized

HbS to sickle red cells. The sickled red cells can occlude microvasculatures which is responsible for the crises and the chronic complications of patients with sickle cell anaemia [4]. The commonest crisis in patients with SCA is vaso-occlusive crisis (VOC) [5]. This occurs as a result of occlusion to blood vessels by sickled erythrocytes resulting in ischaemia of the tissues or organs supplied by these vessels.

In patients with SCA, oxidative stress is increased and has been implicated in the pathophysiology of SCA-related microvascular dysfunction and vaso-occlusion. Oxidative stress is the result of an imbalance between oxidants and antioxidants in favour of the oxidants. The oxidants include reactive oxygen species (ROS) such as superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radicals (OH^\cdot). An ischemia-reperfusion injury which accompanies vaso-occlusive crisis contributes significantly to increased production of reactive oxygen species. Uric acid is a byproduct of Xanthine oxidase activity which generates superoxide Xanthine oxidase (XO) derived from xanthine dehydrogenase (XD) is generated during the ischaemia producing two superoxides during the processes of conversion of hypoxanthine/xanthine to uric acid. The ROS produced causes oxidative injury to affected tissues during the early phase of reperfusion [6, 7].

Uric acid also induces oxidative stress by increasing the expression of hydrogen peroxides and 8-isoprostane in vascular smooth muscle [8]. Aside from this, Uric acid stimulates the proliferation of vascular smooth muscle [8]. Inhibitor of platelet-endothelial cell adhesions and vascular smooth muscle proliferation such as nitric oxide production is also reduced in the presence of uric acid [8]. All these culminate in increase oxidative stress that causes oxidative damage to the tissues and organs affected by the vaso-occlusion. This subsequently induces an inflammatory reaction in the damaged tissues which further generates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (another ROS) released by polymorphonuclear cell and monocytes. This further causes a progressive tissue injury in the late stage of reperfusion during VOC [9].

Only a few studies had been done on uric acid level in patients with sickle cell disease presenting with bone pain crisis: One of these showed a significant elevation in the plasma uric acid concentration in patients with sickle cell disease presenting with (bone pain crisis in steady state) [10]. Another study showed hyperuricaemia in patients with sickle cell disease both in steady state and during bone pain crisis [11]. Other studies have also demonstrated significantly elevated uric acid level in patients with sickle cell disease compared to uric acid level in HbA individuals [12-15].

However, none of these studies demonstrated the correlation between plasma uric acid concentration and severity of bone pains. Hence plasma uric acid concentration in patients with sickle cell disease presenting with vaso-occlusive crisis using (bone pain crisis as a prototype) and correlation of uric acid concentration with the severity of bone pain crisis was determined in this study.

2. Materials and Methods

This study was carried out in University College Hospital (UCH), Ibadan Nigeria between January 2018 and December 2018. Informed consent was obtained from each eligible participant before administering the questionnaire and blood sample collection. Ethical approval was obtained from the University of Ibadan / University College Hospital Ethics Committee.

2.1. Study Design

This is a cross-sectional study on the uric acid concentration of 90 adult participants. The participants were divided into 30 each age and sex-matched sickle cell anaemia in bone pain crises (BPC), sickle cell anaemia in steady state (SS) and normal HbA control. Interviewer administered questionnaires were administered to the participants to collect information on biographical data and significant previous and present medical history for the management of bone pain crisis. Height and weight of the participants were measured with physician mechanical beam scale with height rod for calculation of body mass index.

2.2. Inclusion and Exclusion Criteria

The criteria for inclusion of participants in this study were: (1). Participants whose alkaline pH Hb electrophoresis result showed HbS presenting with sudden onset of bone or joint pain; or multiple sites of bone pain which can only be attributed to sickle cell anaemia. This bone or joint pain necessitated clinic visit and analgesic administration (Patients with SCA in bone pain crisis) [16]. (2). Participants with alkaline pH haemoglobin electrophoresis results confirmed HbS and were feeling fine without any symptoms or signs of pain, overt infection, or any other acute episode suggestive of crisis in the last 3 months (Patients with SCA in steady state) [16]. The apparently healthy HbA adults were grouped as control (adult students and hospital workers whose haemoglobin electrophoresis at alkaline pH was confirmed as HbA).

The exclusion criteria included: (a) Refusal of the participant to give consent (b) Alcohol intake, (c) Cigarette smoking, (d) Presence of co-existing liver disease, (e) Presence of associated sickle cell nephropathy, (f) Presence of co-existing malignancy, (g) Ingestion of drugs such as cyclosporine, pyrazinamide, ethambutol, allopurinol and diuretics (h) Obesity (i) Presence of associated clinical features of hyperhaemolytic crisis such as the passage of dark coloured urine and increasing yellowness of the eye.

2.3. Assessment of Severity of Bone Pain

Clinical severity of bone pains in the bone pain crisis category of SCA patients was assessed using a Total Summary Pain (TSPS). Total summary pain score is a multidimensional scale that utilizes numerical rating scale, pain duration, patient's behaviour and analgesics used. It is simple and easy to use; it also takes into consideration

patient's and doctor's perception of pain as summarized below [17].

2.4. Sampling Technique

Adult patients with SCA who satisfied the inclusion, exclusion criteria and gave informed consent were consecutively recruited as they presented to the Haematology Day Care Unit (HDCU) during bone pain crisis (BPC) involving the spine, rib cage or limbs. They were stratified into different BPC groups. The SCA steady state participants were recruited consecutively as they presented for follow up during clinic visit after filling informed consent form. Age- and sex-matched apparently healthy individuals without clinical evidence of SCD whose alkaline pH haemoglobin electrophoresis done in University College Hospital Ibadan was HbA were recruited as the control group.

The Researcher who was also the attending Physician filled the questionnaire and also assessed the clinical severity of the bone crisis as a tool used to assess Total Summary Pain Score. It also contains height and weight of participants which were measured with a physician mechanical beam scale with height rod. These were used to calculate the body mass index.

2.5. Sample Collection

Six millilitres of venous blood was collected at the antecubital fossa with a sterile needle from all participants. Out of the 6ml, 3mls of blood was withdrawn into an EDTA sample bottle for full blood count, reticulocyte count and peripheral blood film review. The remaining 3ml of blood was put into a lithium heparin bottle and separated into the plasma and cells with a swinging bucket centrifuge. The plasma was analyzed for uric acid and creatinine concentrations.

Total Summary Pain Score (TSPS):

This assesses both patient's and doctor's perception of pain as follows:

$TSPS = [\text{patient's pain score} \times \text{duration of pain}] + [\text{patients behavior}] + [\text{analgesia used}]$

Pain intensity of 1=Verbal numerical score 1-4,

Pain intensity of 2=verbal numerical score 5-6 and

Pain intensity of 3=verbal numerical score 7-10.

Duration of pain before the patient presents 1=pain less than 3 days,

Duration of pain before the patient presents 2=pain that lasted 4-7 days,

Duration of pain before the patient presents 3=pain that lasted more than 7 days.

Analgesic used to abate the pain of 1=PCM /NSAIDs

Analgesic used to abate the pain of 2=Opioids

Analgesic used to abate the pain of 3=Patient controlled analgesia / intensive care.

Patient's behaviour 1=for a patient who appears normal

Patient's behaviour of 2=for an agitated patient

Patient's behaviour of 3=for the very disturbed patient and

Patient's behaviour of 4=for a patient who was too quiet, Range of obtainable scores

The minimum score a patient can get in TSPS is 3 and the maximum score that can be accorded is 16

Interpretation of scores:

Mild total summary pain score=3-7,

Moderate total summary pain score=8-11

Severe total summary pain score=12-16

2.6. Processing of Sample

2.6.1. Haematological Parameters Assessment

Full blood count (FBC) was analyzed with SYSMEX analyzer (XS 1000i model). Microscopic examination of new methylene blue-stained freshly prepared smears was used for reticulocyte examination. Microscopic examination of May Grunwald Giemsa stained smears was used for irreversible sickle cells and nucleated red blood cells estimation.

2.6.2. Plasma Uric Acid and Creatinine Determination

Plasma uric acid concentration and plasma creatinine were determined according to the standard operating procedures described for the use of Landwind LWC 100 plus automated analyzer machine. The principle used to determine the uric acid was enzymatic (Uricase) method, while the principle used to determine the plasma creatinine was based on Jaffe method.

2.7. Statistical Analysis

Data were analyzed using SPSS version 20.0 (Statistical Package for Social Sciences, Inc., Chicago, Ill). The descriptive data were presented as means \pm standard deviation except otherwise stated. Frequencies were presented in tables. One-way ANOVA (Analysis of Variance) was used to compare means of the independent variables. Significant results were subjected to post-hoc analyses for pairwise comparisons. Spearman analysis was performed for correlation of plasma uric acid concentration with the severity of bone pain crisis. Results were considered statistically significant if $p < 0.05$.

3. Result

There was no statistically significant difference in the demographic characteristics of participants. Majority of the participants were young adults, with an age range between 21-30yrs constituting about 49% of the total participants. The average age of participants in HbA group, steady state group and BPC group were comparable ($p=0.620$). The mean body mass index (BMI) in the steady state, HbA and BPC group were 22.1kg/m², 22.7 kg/m² and 21.6kg/m² respectively, this was also not statistically significant.

The mean plasma uric acid concentration was not significantly different in the BPC group (4.04 \pm 1.21 mg/dL) and the steady state group (4.19 \pm 1.39 mg/dL) $p=0.641$. The plasma creatinine concentration was also not significantly different in the BPC group (0.97 \pm 0.37 mg/dL) and the steady state group (0.98 \pm 0.47 mg/dL) $p=0.613$ (table 2).

When comparing the uric acid concentration in the three different severities of bone pain crisis among each other, there was no significant difference in the mean uric acid concentration among the mild BPC group, moderate BPC group and severe BPC group. However, the mean uric acid concentration was slightly higher in severe BPC group than in mild and moderate BPC group (*table 3*). There was a trend of increasing plasma creatinine level with increasing severity of bone pains.

There was no nucleated red blood cell seen in all the blood films of the participants. The mean irreversible sickle cell index was higher in HbS patient with BPC than steady state. However, the reticulocyte counts were not significantly higher in HbS

patient with BPC than steady state. (*table 3*). Also, there was no significant correlation between plasma uric acid concentration, haematological parameters and serum creatinine in all the clinical states of participants (*table 4*).

In patients with mild TSPS, the commonest site of bone pain was right lower limb constituting about 32% of site of BPC in this group. In the moderate TSPS group, left upper limb pain was the most common site, it occurs in 26% of participants in this group and severe TSPS group, 19% of them each had bone pain involving left upper limb, right lower limb and left lower limb. The mean number of site with BPC in mild TSPS group, Moderate TSPS group and severe TSPS group were 2.6, 2.3 and 3.1 respectively (*Table 5*).

Table 1. Demographic characteristics of Haemoglobin A, (HbA) and sickle cell anaemia patients in bone pain crisis (BPC) and during steady state (STEADY).

VARIABLES	HbA A N (%)	STEADY B N (%)	BPC C N (%)	TOTAL N (%)	P-Values B vs C
AGE (YEARS)					
18-20	5 (5.6)	5 (5.6)	5 (5.6)	15 (16.8)	
21-30	19 (21.1)	17 (18.9)	13 (14.4)	49 (54.4)	
31-40	3 (3.3)	5 (5.6)	6 (6.7)	14 (15.6)	0.933
41-50	2 (2.2)	2 (2.2)	5 (5.6)	9 (10.0)	
51-60	1 (1.1)	1 (1.1)	1 (1.1)	3 (3.3)	
GENDER					
M	14	16	14	44	
F	16	14	16	46	0.797

M, Male; F, Female.

Table 2. Plasma uric acid concentration and creatinine and some haematological parameters in Sick Cell Anaemia Patients in Bone Pain Crisis (BPC) and steady state (STEADY) and Haemoglobin A Controls (HbA).

Parameter	HbA A X±SD	BPC B X±SD	STEADY C X±SD	A vs B	P-value A vs C	B vs C
Uric acid (mg/dL)	4.04±1.21	3.85±1.17	4.19±1.34	0.882	0.892	0.641
Creatinine (mg/dL)	0.92±0.39	0.97±0.37	0.98±0.47	0.887	0.882	0.613
ISC (per HPF)		8.95 ±5.30	3.22 ±1.66			0.000*
Retic count (%)	1.60±0.71	2.36±0.72	2.43±0.84	0.000*	0.000*	0.922
NRBC (Cells/100WBC)	0.00	0.00	0.00			

*, statistically significant at $p < 0.05$; X, mean; SD, standard deviation; ISC, irreversible sickle cell index; Retic count, Reticulocyte count; NRBC, Nucleated red blood cells; HPF, high power field.

Table 3. Plasma uric acid and creatinine concentration of Different Bone Pain Crisis (BPC) severity groups in SCA patients.

PARAMETERS	Mild BPC A X±SD	Moderate BPC B X±SD	Severe BPC C X±SD	A vs B	P Values A vs C	B vs C
uric acid (mg/dL)	3.87±1.26	3.53±1.17	4.17±1.07	0.798	0.867	0.491
Creatinine (mg/dL)	0.85±0.38	1.00±0.43	1.06±0.29	0.892	0.789	0.998

*, statistically significant at $p < 0.05$; X, mean; SD, standard deviation.

Table 4. Correlation of uric acid with the haematological parameters and creatinine concentration in Haemoglobin A Controls (HbA) and Sick Cell Anaemia Patients in Bone Pain Crisis (BPC) and during Steady State (STEADY).

Haematological Parameters	HbA			STEADY			BPC		
	X±SD	r	P	X±SD	r	P	X±SD	r	p
Haematocrit (%)	44.21±3.49	0.279	0.136	23.20 ±3.29	0.185	0.249	27.65±3.78	-0.164	0.386
WBC ($\times 10^3/\mu\text{L}$)	5.81±2.15	-0.100	0.598	10.00±2.26	-0.105	0.580	12.34±3.87	-0.210	0.265
Neutrophils ($\times 10^3/\text{L}$)	2.94±1.70	-0.106	0.577	5.53±2.08	-0.352	0.056	7.91±3.51	-0.190	0.316
Lymphocytes ($\times 10^3/\text{L}$)	2.19±0.76	-0.060	0.753	3.16±0.90	0.047	0.805	3.18±1.20	-0.171	0.365
Monocytes ($\times 10^3/\mu\text{L}$)	0.48±0.15	0.088	0.645	0.89±0.49	0.250	0.184	0.97±0.68	0.087	0.649
Eosinophils ($\times 10^3/\mu\text{L}$)	0.18±0.14	0.111	-0.297	0.23±0.14	0.008	0.965	0.17±0.07	-0.115	0.544
Basophils ($\times 10^3/\mu\text{L}$)	0.04±0.20	-0.347	0.060	0.08±0.04	0.146	0.443	0.07±0.03	-0.128	0.499
Platelets ($\times 10^3/\mu\text{L}$)	259.79±65.81	-0.088	0.645	329.08±123.96	-0.044	0.816	379.85±124.71	-0.313	0.093
ISC (per HPF)	0.00			3.22 ±1.66	-0.002	0.982	8.95 ±5.30	0.039	0.839
Reticulocyte count (%)	1.60±0.71	-0.032	0.869	2.43±0.84	0.019	0.920	2.36±0.72	0.154	0.417
NRBC (Cells/100WBC)	0.00			0.00			0.00		
RBC indices									
MCV (fL)	83.93±7.20	-0.76	0.691	83.23±5.82	0.025	0.894	81.32±9.56	-0.282	0.131

Haematological Parameters	HbA			STEADY			BPC		
	X±SD	r	P	X±SD	r	P	X±SD	r	p
MCH (pg)	27.79±2.69	-0.145	0.444	29.89±2.83	-0.042	0.827	27.65±3.78	-0.194	0.304
MCHC (g/dL)	31.49 ±1.69	-0.143	0.451	32.95±1.46	0.026	0.906	33.36±1.41	-0.126	0.500
Creatinine (mg/dL)	0.92±0.39	-0.072	0.705	0.98±0.47	-0.183	0.333	0.97±0.37	-0.163	0.389

*, statistically significant; MCV, mean cell volume; MCH, mean cell haemoglobin; MCHC, mean cell haemoglobin concentration; RBC indices, Red blood cell indices; X, mean; SD, standard deviation; r, Pearson correlation coefficient; ISC, irreversible sickle cell index; Retic count, Reticulocyte count; NRBC, Nucleated red blood cells; HPF, High power field; p, p-value.

Table 5. Site of bone pain in Sickle cell anaemia patients during bone pain crisis according to total summary pain score patient group.

Site of bone pain	TSPS Patient group (frequency [%])		
	Mild X (%)	Moderate X (%)	Severe X (%)
Right Upper Limb	4 [16]	3 [13]	5 [16]
Left Upper Limb	4 [16]	6 [26]	6 [19]
Right Lower Limb	8 [32]	4 [17]	6 [19]
Left Lower Limb	6 [24]	5 [22]	6 [19]
Spine	1 [4]	3 [13]	5 [16]
Chest	2 [8]	2 [9]	3 [11]

Note: There were multiple involved bone pain sites per patient at presentation.
X=number of sites involved in bone pain crisis.

Correlation of uric acid concentration with total summary pain score (TSPS)

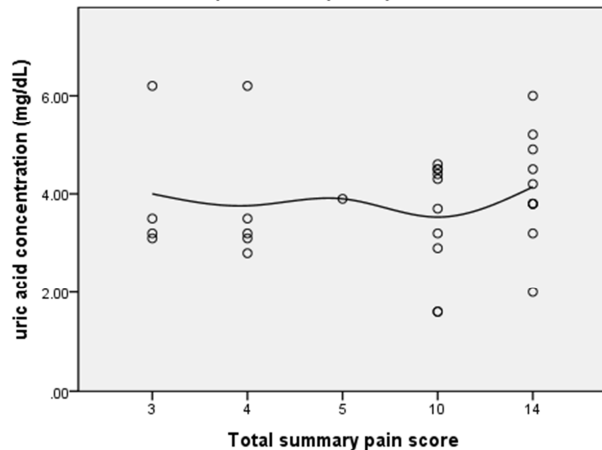


Figure 1. Correlation of uric acid concentration with total summary pain score in sickle cell patients with bone pain crisis: n=30.

Correlation coefficient (r)=0.212, p-value=0.3

4. Discussion

This study showed that the mean uric acid among the patients with sickle cell anaemia in BPC, steady state group and HbA control were comparable. This was in contrast to the report from Nduka *et al.* that reported significantly higher uric acid concentration during BPC in their 30 HbS participants with sickle cell anaemia presenting with bone pain crisis and 110 HbS participants in steady state [10]. This might be due to increased cell turn over as a result of hyperhaemolysis in some of their participants with bone pain crisis as hyperhemolysis was not excluded. Hyperhemolysis was absent in patients in this study as evidenced by the absence of a significant difference in the mean reticulocyte count and absence of nucleated red blood cells on peripheral blood film review. This might also suggest that vaso-occlusive crisis inferring indirectly to ischaemia – reperfusion injury may not significantly cause an increase in uric

acid level in SCA patient. In view of the normal creatinine level which was comparable for all the study groups, the comparable uric acid concentration in all study participants is not surprising because a previous study reported that patients with sickle cell anaemia were often normouricemic due to increased renal urate clearance and hyperuricemia occurs only in patients who develop altered renal tubular function with diminished urate clearance secondary to diminished urate secretion [18]. Our study does not support our hypothesis that uric acid will contribute to increased reactive oxygen species consequent to its overproduction during the process of ischaemia/perfusion injury. The mean uric acid level in sickle cell anaemic patient in steady state and bone pain crises were within normal reference limit of uric acid. This finding was similar to the mean uric acid concentration of 4.40 ± 2.02 mg/dL reported by Cerqueira *et al.* but lower than the value reported by Gupta *et al.* in 2015, who reported mean uric acid of 8.62 ± 2.97 mg/dL. The factors that contribute to hyperuricaemia in the study by Gupta were obesity (BMI as high as 43.6 kg/m^2), use of hydroxyurea, presence of gout in some of the participants and possibility of use of diuretics in the hypertensive participants in the study group [11]. In contrast, none the patients in this study were obese, neither was on hydroxyurea nor had clinical features suggestive of gout.

The relatively similar mean uric acid levels among the patients with sickle cell anaemia in BPC, steady state group and HbA control contrast with the report from Nduka *et al.* that reported significantly higher uric acid concentration during crises in their participants with sickle cell anaemia [10]. This may be attributed to increased cell turn over as a result of hyperhaemolysis in some of their participants.

The lack of difference in the mean plasma uric acid concentration of the patient with sickle cell anaemia and HbA control in this study agrees with the reports of Pandey *et al.* and Nduka *et al.* but is in contrast to the finding of Obeagu *et al.* Imo state, Nigeria, Rasheed *et al.* in Zaria (Kaduna) Nigeria and al-Naama *et al.* amongst Iraqi children and Khalid *et al.* in Western Sudan [10, 13, 15, 19]. The contrasting results might be due to the

difference in exclusion criteria used for selection of study population. The studies did not exclude the presence of hyperhemolysis and sickle cell nephropathy. Hyperhaemolysis leads to high erythropoietic cell turn over and elevated uric acid concentration. Sick cell nephropathy results in impaired excretion of uric acid due to recurrent infarction and hypoxia resulting from sickling of erythrocytes [10, 12, 13].

This study has improved on previous studies by excluding them from the study population, those with evidence of hyperhaemolysis using the reticulocyte count, nucleated red blood cells in the peripheral blood and patient with known sickle cell nephropathy were also excluded

The irreversible sickle cell index was significantly high in patients with SCA presenting BPC that in steady state in this study. This might suggest that the high level of the sickled erythrocytes is responsible for the vaso-occlusion responsible for bone pain crisis they have [20].

5. Conclusion

This study shows that there was no significant change in serum uric acid in sickle cell anaemic patients either in BPC or steady states and uric acid concentration does not correlate with bone pain crisis severity in them. Therefore, the measurement of plasma uric acid concentration is not an objective means of determination of the severity of bone pain crisis in patients with sickle cell anaemia.

6. Limitation of This Study

1. Being a cross-sectional study, some of the confounding factors in the participants of this study which were not measured e.g tumour markers might affect uric acid concentration, unlike longitudinal study.
2. The participants in this study might not completely represent the study population as the sample frame is only limited to those people that can assess health care.
3. Inability to objectively measure some of the confounding factors such as red meat ingestion and glomerular filtration rate study participants might affect uric acid concentration.

Conflict of Interest Disclosure

All the authors do not have any possible conflicts of interest.

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