Section: Paediatrics

Original Research Article

LEVELS OF TRANSAMINASES IN CHILDREN WITH SICKLE CELL ANAEMIA IN A STEADY STATE - A CROSS SECTIONAL STUDY

Pradeep Pazare[1], Aboli Dahat[1], Kritika Krishnakumar[2], Manish Chokhandre[3]

[1]Associate Professor, Department of Paediatrics, NKP Salve Institute of Medical Sciences and Research Centre and Lata Mangeshkar Hospital, Nagpur, Maharashtra, India
[2]Junior Resident, Department of Paediatrics, NKP Salve Institute of Medical Sciences and Research Centre and Lata Mangeshkar Hospital, Nagpur, Maharashtra, India
[3]Senior Resident, Department of Paediatrics, Datta Meghe Medical College and Shalinitai Meghe Hospital and Research Centre, Nagpur, India

Received : 13/12/2023
Received in revised form : 26/02/2024
Accepted : 12/03/2024

Keywords:
SCA, AST, ALT, hydroxyurea, blood transfusion.

Corresponding Author:
Dr. Pradeep Pazare,
Email: shilpadeep_160@yahoo.co.in

DOI: 10.47009/jamp.2024.6.2.178

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (2); 865-870

Abstract

Background: Sickle cell Disease (SCD) is one of the most frequent inherited hemoglobinopathy that is found mainly in the population of Indian, Americans, Arabian or African origin. The liver is one of the major organs contributing to multiorgan failure in children with Sickle Cell Anaemia (SCA). There is paucity of data on the liver function status of SCA subjects in most of the Indian hospitals, particularly in the Paediatric population of SCA in steady state. The purpose of this study was to measure the levels of the liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the children with SCA in steady state. **Materials and Methods:** It was an analytical, cross-sectional study conducted on children with SCA, at a single centre, in a tertiary care hospital in India. The study was conducted on 65 children diagnosed as SCA by HPLC method of either gender who fulfilled the criteria of steady state. Detailed history and physical examination were recorded. 2 ml of venous sample was obtained, and liver enzyme levels (AST, ALT) were estimated in these subjects. Data was collected based on laboratory investigations. **Result:** The mean age of the children in the study was found to be 10.13 ± 4.88 years, with a range of 6 months to 18 years. The mean AST was found to be 37.15 ± 19.8 mg/dl while the mean ALT was calculated to be 27.49 ± 22.74 mg/dl. The mean AST/ALT ratio was found to be 1.51 ± 0.81. Mean ALT was found to be significantly elevated in the group of children with history of hydroxyurea usage ($p<0.05$). Mean ALT as well as the mean AST/ALT ratio were found to be significantly higher in the group with history of blood transfusion ($p<0.05$). **Conclusion:** Hepatic impairment is well-known consequence of SCA. Present study indicates towards raised liver enzymes in children with SCA in steady state who were on hydroxyurea therapy as well as who received frequent blood transfusions in the past. Hence, it is suggested that liver functions should be monitored in all children with SCA who are on hydroxyurea therapy and who require frequent blood transfusions. However, further studies with larger sample size are needed in this field to obtain more accurate results.

INTRODUCTION

Sickle Cell Disease (SCD) is one of the most common hereditary hemoglobinopathy which is mainly found in the population of Indian, Americans, Arabian or African origin. The yearly number of SCD patients are increasing, with the sickle cell anaemia (SCA) patients expected to rise from about 3,00,000 to more than 4,00,000 between 2010 to 2050.[1] Hemoglobinopathies are especially important in India because they are responsible for the maximum number of hereditary ailments. According to recent data, India is ranked as the second worst affected country based on SCA births, with an estimated 42,016 babies born with SCA in the country in 2010.[2] Adult haemoglobin's beta chain is changed by the sickle cell mutation, which changes how sickle cell haemoglobin behaves. The normally benign sickle cell trait (AS genotype) is caused by having a single HbS gene; however, homozygous SCA (SS), which is typically a serious illness, is caused by inheriting the HbS gene from both parents. The SS disease is associated with rapid destruction of RBCs (red blood cells) and blockage of blood flow in the

ISSN (O): 2687-5365; ISSN (P): 2753-6556

blood vessels leading to severe and painful crisis which leads to significant morbidity if not intervened early.[3]

The term "steady state" refers to a situation in which a SCA patient is not undergoing any changes as a result of their therapy or an acute painful crisis in preceding 3 months. Characteristically, a steady state should satisfy numerous criteria stated in scientific literature that include lack of history of an acute, severe and painful event which required hospitalization, or the emergency room care for at least 3 weeks after the last clinical incident.[4] The absence of any history of blood transfusions during the three months prior to the point in time is another crucial requirement for the steady state.[5]

The liver is one of the major organs contributing to multiorgan failure in children with SCA. Dysfunction of hepatobiliary system is one of the frequent complications of SCA.[6] Children with SCA frequently experience hepatic impairment. Previous published reports described acute and chronic hepatitis, jaundice, hepatic infarcts, cirrhosis and choledocholithiasis.[7]

Various complications arising from the disease itself and its management can modify the functioning of the liver. According to published research, the clinical picture of SCA varies from minor abnormalities in liver function tests (LFTs) in children who are asymptomatic to substantial abnormalities in LFTs with apparent hyperbilirubinemia.[8] Deteriorating haemolysis associated with augmented sickling of red blood cells intra-hepatically causes sinusoidal dilatation, and perhaps leads to abnormal liver profile.[9]

There is paucity of data on the liver function status of SCA children in most of the Indian hospitals, particularly in the paediatric population of SCA in steady state. Hence, present study was undertaken to find out the liver function test in children suffering from sickle cell anaemia in a steady state. Further, association of liver function test in children with sickle cell anaemia in steady state with use of hydroxyurea and blood transfusion in past was also studied.

MATERIALS AND METHODS

This study was undertaken to assess the liver function test in children with SCA in steady state. It was a single centre, analytical, cross-sectional study of children diagnosed with SCA. The study was carried out in the department of Paediatrics, at a tertiary care centre in Maharashtra, India. Study was initiated only after obtaining the parent's or guardian's written informed consent and institutional ethics committee approval (IEC Number:21/2018). At any point of time, the patient's parents/guardians were given a choice to opt out of the study.

Children of both genders, between the age of 6 months and 18 years, attending the out-patient department (OPD) at the tertiary health care centre who were diagnosed as sickle cell anemia (SCA) by High Performance Liquid Chromatography (HPLC) and fulfilling the criteria of steady state were included in this study. The study excluded the children with sickle cell trait and SCD other than SCA as well as those children who did not comply with the criteria of steady state.

The study was carried out over the period of two years between October 2018 to September 2020. After enrolment of the children in the study, information was procured from parents/guardians of the children, and the details of demographic and clinical parameters were noted. Demographic data like name, age, sex, detailed history, and physical examination were recorded.

A structured interviewer-administered questionnaire that had been pretested and modified before being used in the study served as the data collection tool. Data was collected based on laboratory investigations. Sample was collected using Convenient Sampling Technique. 2 ml of venous sample was collected for immediate evaluation of AST and ALT. The blood specimen was collected in plain tubes (non-EDTA ones). The transaminases were measured on an Automated Analyzer Machine (Siemens Dimension Rx Max). The findings of the liver function test were noted down in the case record form of the study for each patient.

The sample size for this study was calculated with reference to statistical data [6] using the following formula:

$n = Z^2_{1-a/2}\, p(1-p)/d^2$.

Where $Z_{1-a/2}$ is the standard normal value at 5% (1.96) for two-tail, p is the proportion of cases with abnormal ALT levels (0.2), d is the tolerable error (0.1). According to this formula sample size calculated for this study was 65.

After data collection, data entry was done in a Microsoft excel sheet. Data analysis was done with the help of statistical software GraphPad InStat.v3.0. Quantitative data, viz. the mean LFT parameters assessed (AST, ALT) was presented with the help of Mean and Standard deviation. Data provides an overview of the demographic distribution of the study participants based on gender. It outlines the number of males and females, along with relevant statistical comparisons. Liver function test results were compared between participants with raised AST levels and those with normal levels. It includes details on mean age, gender distribution, ALT levels, mean AST/ALT ratio, use of hydroxyurea, and history of blood transfusion. Similar comparison was made between participants with raised ALT levels and those with normal ALT levels.

We measured the impact of hydroxyurea on liver function tests. It included participants with a history of hydroxyurea usage and those without, focusing on mean AST, mean ALT, and mean AST/ALT ratio. Similarly liver function tests were compared in between participants with and without a history of blood transfusion. The correlation between transaminases and gender of children, and number of

ISSN (O): 2687-5365; ISSN (P): 2753-6556

blood transfusions in past was assessed using Pearson's correlation coefficient. The mean transaminase levels in sub-group of patients with and without hydroxyurea usage was compared using unpaired t test. P value of less than 0.05 was considered significant.

RESULTS

A total of 65 paediatric patients were enrolled in the study. The mean age of the children in the study was found to be 10.13 ± 4.88 years, with a range of 0.5 years (6 months) to 18 years. 27 of the enrolled children were males, while 38 were females.

The mean AST was found to be 37.15 ± 19.8 mg/dl while the mean ALT was calculated to be 27.49 ± 22.74 mg/dl. The mean AST/ALT ratio was found to be 1.51 ± 0.81.

Table 1 shows demographic characteristics of the study population. This table provides an overview of the demographic distribution of the study participants based on gender. It outlines the number of males and females, along with relevant statistical comparisons.

The liver function tests were compared between males and females' sub-groups of patients. It was found that mean AST and mean AST/ALT ratio in males was markedly elevated than that in females ($p<0.05$). On the contrary, mean ALT in males was found to be significantly lower as compared to that in females ($p<0.05$).

[Table 2] shows comparison of liver function test results between participants with raised AST levels and those with normal levels. It includes details on mean age, gender distribution, ALT levels, AST/ALT ratio, use of hydroxyurea, and history of blood transfusion.

Based on the status of the AST levels of children, 25 children had raised AST levels while 40 children had normal levels of AST. Significantly higher age was found in the normal AST sub-group ($p<0.05$) while higher number of females were found with normal AST($p<0.05$). Rise in ALT was significantly higher in subgroups of children with high AST ($p<0.05$). The mean AST/ALT ratio was markedly elevated in the higher AST subgroup ($p<0.05$). The use of hydroxyurea was significantly greater in the high AST sub-group ($p<0.05$). However, the number of children who received blood transfusion was comparable in both the sub-groups ($p>0.05$).

[Table 3] focuses on the comparison between participants with raised ALT levels and those with normal ALT levels. It includes similar parameters as in Table 2 i.e. mean age, gender distribution, ALT levels, AST/ALT ratio, use of hydroxyurea, and history of blood transfusion.

Out of 65 children, 8 children had raised ALT levels while 57 children had normal levels of ALT. Significantly high ALT was associated in the higher age sub-group ($p<0.05$). Similarly greater proportion of females were found to have high ALT, but this was not statistically significant ($p>0.05$). Rise in ALT was significantly higher in subgroup of patients with high AST also($p<0.05$). There was no significant correlation in raised ALT levels with use of hydroxyurea and those who received blood transfusion.

Table 1: Demographic characteristics of study population

Parameter	Males (n=27)	Females (n=38)	P value
Mean AST	43.14 ± 21.11	32.89 ± 17.9	0.01*
Mean ALT	24 ± 10.26	29.97 ± 28.38	0.01*
Mean AST/ALT ratio	1.86 ± 0.92	1.25 ± 0.62	0.03*

*Statistically significant result was obtained in all 3 groups, mean AST, mean ALT and mean AST/ALT ratio using Unpaired t test. The p value was 0.01, 0.01 and 0.03 respectively.

Table 2: Liver Function Tests - Comparison based on AST levels.

Parameter	Raised AST (n=25)	Normal AST (n=40)	P value
Mean age (years)	9.46 ± 5.39	10.65 ± 4.56	0.01*
Number of males	15 (60%)	12 (30%)	0.01#
Number of females	10 (40%)	28 (70%)	
Rise in ALT	08 (32%)	0	0.01#
Mean AST/ALT ratio	2.09 ± 0.95	1.25 ± 0.62	0.01*
Use of Hydroxyurea	15 (60%)	28 (70%)	
No use of Hydroxyurea	10 (40%)	12 (30%)	0.04#
Blood transfusion received	11 (44%)	16 (40%)	
Blood transfusion not received	14 (56%)	24 (60%)	0.31#

*P value < 0.05 considered significant by Unpaired t test

#P value < 0.05 considered significant by chi-square test

Table 3: Liver Function Test- Comparison based on ALT Levels

Parameter	Raised ALT (n=8)	Normal ALT (n=57)	P value
Mean age (years)	12.4 ± 5.04	10.65 ± 4.56	0.01*
Number of males	2 (25%)	25 (43.86%)	0.45#
Number of females	6 (75%)	32 (56.14%)	
Rise in AST	08 (100%)	17(29.83%)	0.01#
Mean AST/ALT ratio	1.11 ± 0.31	1.25 ± 0.62	0.21*
Use of Hydroxyurea	5 (62.5%)	38 (66.67%)	

ISSN (O): 2687-5365; ISSN (P): 2753-6556

No use of Hydroxyurea	3 (37.5%)	19 (33.33%)	0.43#
Blood transfusion received	2 (25%)	25 (43.86%)	0.24#
Blood transfusion not received	6 (75%)	32 (56.14%)	

*P value < 0.05 considered significant by Unpaired t test
#P value < 0.05 considered significant by chi-square test

Table 4: Liver Function Test based on Hydroxyurea Use

Parameter	Hydroxyurea use present (n=43)	Hydroxyurea use absent (n=22)	P value
Mean AST	36.88 ± 19.92	37.68 ± 20.01	0.41
Mean ALT	28.34 ± 27.11	24.81 ± 10.08	0.04*
Mean AST/ALT ratio	1.49 ± 0.84	1.53 ± 0.78	0.23

* Statistically significant result was obtained in mean ALT group using Unpaired t test (p value of 0.04)

Table 5: Liver Function Test based on the history of blood transfusion.

Parameter	BT not given (n=38)	BT given (n=27)	P value
Mean AST	36.13 ± 19.23	38.59 ± 20.85	0.19
Mean ALT	24.37 ± 10.08	29.71 ± 28.15	0.04*
Mean AST/ALT ratio	1.43 ± 0.84	1.59 ± 0.77	0.03*

*Statistically significant result was obtained in mean ALT and mean AST/ALT ratio using Unpaired t test. The p value was 0.04 and 0.03 respectively.

[Table 4] explores the impact of hydroxyurea on liver function tests. It compares participants with a history of hydroxyurea usage and those without, focusing on mean AST, mean ALT, and mean AST/ALT ratio.
Out of 65, 43 children had been administered hydroxyurea while 22 children did not have history of hydroxyurea administration. On comparing the liver function tests between sub-groups of children classified based on hydroxyurea use, mean ALT was found to be significantly elevated in the group of children with history of hydroxyurea usage ($p<0.05$).
In the study, out of 65 children, 38 children did not have history of blood transfusion while 27 children had been administered blood transfusion.
[Table 5] shows liver function tests concerning participants with and without a history of blood transfusion. On comparing the liver function tests between sub-groups of children classified based on blood transfusion history, mean ALT as well as the mean AST/ALT ratio were found to be significantly higher in the group with history of blood transfusion ($p<0.05$).

DISCUSSION

Hepatic impairment is a well-known consequence of SCA. It can be caused by a various factor such as excess iron deposition, bilirubin, gallstones, intrahepatic sinusoidal sickling, and transfusion-associated hepatitis infections.[10] The reason behind the hepatomegaly observed in SCA patients was the engulfment of sickle cells by phagocytes during their passage via hepatic sinusoids, which resulted in clinical evidence of hepatic dysfunction.[11] The term "sickle cell hepatopathy" (SCH) refers to the involvement of the liver in sickle cell disease. It is one of the frequent complications of SCA and if early intervention is not done it is associated with the significant mortality rate.[12]
Total 65 children were enrolled in our study. The mean age of the children was found to be 10.13 ± 4.88 years. 38 (58.46%) of the enrolled children were females, while remaining 27 (41.54%) were males. In the study by Akuyam et al., 60 SCA patients were enrolled, mean age was found to be 7 ± 3.61 years and the distribution of males and females were equal (50% each).[13] In an Egyptian study conducted by Saied et al in 2017, the mean age was found to be 11.81 + 5.1 years. There was a slight males preponderance noted, with 36 of the 70 patients being males (51.8%).[14] Another similar study by Yahouedehou et al. enrolled 22 paediatric SCA cases, with mean age being 8.5 + 3.4 years and slight female preponderance (n=12, 54.55%).[15]
Numerous tests are carried out in clinical and biochemical analysis which are helpful in evaluating liver function, diagnosing, monitoring, and comprehending the prognosis of liver disease.[11] In our study, 25 of the 65 children (38.46%) were found to be having raised AST while 7 out of 65 children (10.77%) had raised ALT levels. We assessed AST, ALT, along with the AST/ALT ratio. It was found that the mean AST was 37.15 ± 19.8 IU/L and the mean ALT was found to be 27.49 ± 22.74 IU/L. In a Nigerian study by Akuyam et al., the mean AST was found to be 40.98 ± 19.81 IU/L while the mean ALT levels were found to be 34.87 ± 17.94 IU/L. The findings of this study were similar to our study, as both the studies included children with SCA in a steady state.[13]
In a study by Nsiah et al., biochemical assessment in SCA children revealed that the SCA children had mean AST of 50 ± 20.11 mg/dl which was higher than that in our study. The mean ALT in this study was closer to that found in our study (22.8 ± 6.89 mg/dl). They concluded that in children with SCA, AST levels were significantly elevated than the ALT levels, indicating the release of AST via intravascular haemolysis.[16]
A study by Akuyam et al. found the mean AST to be 54.1 ± 2.64 IU/L while the mean ALT was found to be 27.05 ± 2.23 IU/L, these values were similar to our study findings.[13] The Egyptian study by Saied et al. found the mean AST and ALT findings which were

ISSN (O): 2687-5365; ISSN (P): 2753-6556

much higher than above mentioned studies.[14] Table 6 gives a comparison between studies based on the LFT levels. In many of the other studies, the mean ALT and AST values were higher than that seen in our study because they had included non-steady-state patients as well.

	Mean AST (IU/L)	Mean ALT (IU/L)
This study	37.15 ± 19.8	27.49 ± 22.74
Akuyam et al,[13].	54.1 ± 2.64	27.05 ± 2.23
Saied et al,[14].	70 ± 139.5	53.4 ± 91.1
Nsiah et al,[16]	50 ± 20.11	22.8 ± 6.89

We assessed the impact of hydroxyurea on ALT and AST in steady state SCA cases. A total of 43 children in our study had been received hydroxyurea while 22 others never received hydroxyurea. We found that though mean AST was comparable in the two set of children, the mean ALT was significantly higher in the hydroxyurea treated children ($p<0.05$). This finding is in-line with the prescribing information of the drug, which does mention about elevated liver enzymes with hydroxyurea usage. Hence, paediatricians should do baseline liver enzyme assessment before starting hydroxyurea in SCA children.[17]

The study by Yahouedehou et al. had specifically tried to evaluate the impact of hydroxyurea on the liver enzymes. It was found that the mean AST levels in the SCA children decreased significantly after hydroxyurea treatment ($p<0.05$), from 57.50 ± 17.97 IU/L to 44.32 ± 16.50 IU/. However, mean levels of ALT did not significantly decrease after hydroxyurea treatment ($p>0.05$).[15] While in another study done by Joshi et al showed that both AST and ALT enzymes and bilirubin level returned to normal levels after hydroxyurea therapy.[18]

History of blood transfusion was also evaluated in the children enrolled in our study. It was found that 38 children had history of blood transfusion while the remaining 27 children did not receive blood transfusion. The mean AST was comparable in these two sub-groups ($p>0.05$), while the mean ALT as well as ALT/AST ratio was found to be significantly higher in those who had received blood transfusion ($p<0.05$). According to Comer et al,[19] that hemosiderosis and viral hepatitis, which are associated with repeated blood transfusions, are the most common causes of liver disease in children with SCA. Similar findings were reported by Traina et al,[20] and Mills et al.[21] In their study, these authors found that all sickle cell children with chronically elevated LFTs had evidence of hemosiderosis and erythrophagocytosis in their liver biopsies.

Our study is novel as it explored an important but often neglected topic of assessing liver function in SCA children in steady state. There is lack of data on the liver function status of SCA patients in most of the Indian hospitals, especially in the paediatric population of steady state in SCA. Moreover, there is a dearth in the studies which have evaluated the relation between liver function tests and factors like age of children, use of hydroxyurea and blood transfusions.

Likewise, it has few limitations also, as it was conducted only at one centre and on a limited sample of SCA cases. In addition, the other factors like iron overload or infections were not considered while evaluating the hepatic injury in SCA patients. Also, we evaluated the impact of SCA on serum ALT and AST only, while other hepatic function parameters like serum bilirubin, serum protein or enzymes like GGT or ALP were not taken into consideration.

CONCLUSION

Hepatic impairment is a well-known consequence of sickle cell anaemia. Present study indicates towards raised liver enzymes in children with SCA in steady state also. The correlation of the transaminases (ALT and AST) levels with the age of children, use of hydroxyurea and blood transfusions generate important evidence pertaining to the topic. This was thought to be an important step towards evidence generation for better management of the steady state in children with SCA in the Indian Setting. History of blood transfusion and use of hydroxyurea were found to be significant risk factors for raised liver enzymes in children with SCA in steady state. It is suggested that liver functions should be monitored in all children with SCA who are on hydroxyurea therapy and who require frequent blood transfusions. Hence, Serial LFT monitoring should be an integral part of management of children in SCA even in steady state. However, further studies with larger sample size are needed in this field to obtain more accurate results.

REFERENCES

1. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN: Global burden of sickle cell anaemia in children under five, 2010-2050: modelling based on demographics, excess mortality, and interventions. PLoS Med. 2013, 10:1-14.
2. Hockham C, Bhatt S, Colah R: The spatial epidemiology of sickle-cell anaemia in India. Sci Rep. 2018, 8:1-10.
3. Habara AH, Shaikho EM, Steinberg MH: Fetal hemoglobin in sickle cell anemia: The Arab-Indian haplotype and new therapeutic agents. Am J Hematol. 2017, 92:1233-1242.
4. Nader E, Skinner S, Romana M, Fort R, Lemonne N, Guillot N, et al: Blood Rheology: Key Parameters, Impact on Blood Flow, Role in Sickle Cell Disease and Effects of Exercise. Front Physiol. 2019, 10:13-29.
5. Akinola NO, Stevens SM, Franklin IM, Nash GB, Stuart J: Subclinical ischemic episodes during the steady state of sickle cell anemia. J Clin Pathol. 1992, 45:902-906.
6. Kotila T, Adedapo K, Adedapo A, Oluwasola O, Fakunle E, Brown B: Liver dysfunction in steady state sickle cell disease. Ann Hepatol. 2005, 4:261-263.
7. Issa H, Al-Salem AH: Hepatobiliary Manifestations of Sickle Cell Anemia. Gastroenterology Res. 2010, 3:1-8.
8. Maher MM, Mansour AH: Study of Chronic Hepatopathy in Patients with Sickle Cell Disease. Gastroenterology Res. 2009, 2:338-343.
9. Shah R, Taborda C, Chawla S: Acute and chronic hepatobiliary manifestations of sickle cell disease: A review. World J Gastrointest Pathophysiol. 2017, 8:108-116.
10. Kakarala S, Lindberg M: Safety of liver biopsy in acute sickle hepatic crisis. Conn Med. 2004, 68:277-9.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

11. Obi C, Aladeyelu O, Agbiogwu I, Agu CN, Arusiwon JA, Udeh MO: Enzyme activities of liver function (Bio-makers) in sickle cell anaemic patients attending Sickle Cell Anaemic Centre, Benin City, Edo State, Nigeria. Int J Blood Res Disord. 2020, 7:1-5.
12. Kyrana E, Rees D, Lacaille F: Clinical management of sickle cell liver disease in children and young adults. Arch Dis Child. 2021, 106:315-320.
13. Akuyam SA, Abubakar A, Lawal N, et al.: Assessment of biochemical liver function tests in relation to age among steady state sickle cell anemia patients. Niger J Clin Pract. 2017, 20:1428-1433.
14. Saied DA, El-Raziky MS, El-Ghamrawy MK, Mahmoud MA: The pattern of hepatobiliary complications among Egyptian sickle cell disease children. Journ Adv Medicine Med Res. 2017, 65:54-59.
15. Yahouedehou SCMA, da Guarda CC, Figueiredo CVB, et al.: Hydroxyurea alters hematological, biochemical and inflammatory biomarkers in Brazilian children with SCA: Investigating associations with βS haplotype and α-thalassemia. PLoS One. 2019, 14:1-13.
16. Nsiah K, Dzogbefla VP, Ansong D, Akoto O, Boateng H, Ocloo D: Pattern of AST and ALT changes in Relation to Hemolysis in sickle cell Disease. Clin Med Insights Blood Disord. 2011, 4:1-9.
17. Agrawal RK, Patel RK, Shah V, Nainiwal L, Trivedi B: Hydroxyurea in sickle cell disease: drug review. Indian J Hematol Blood Transfus. 2014, 30:91-96.
18. Joshi N, Jain N, Ramawat P: Impact of hydroxyurea therapy on clinicohematological parameters in children with sickle cell anemia. Indian J Child Health. 2021, 8:99-102.
19. Comer GM, Ozick LA, Sachdev RK, et al.: Transfusion-related chronic liver disease in sickle cell anemia. Am J Gastroenterol. 1991, 86:1232-4.
20. Traina F, Jorge SG, Yamanaka A, de Meirelles LR, Costa FF, Saad ST: Chronic liver abnormalities in sickle cell disease: a clinicopathological study in 70 living patients. Acta Haematol. 2007, 118:129-35.
21. Mills LR, Mwakyusa D, Milner PF: Histopathologic features of liver biopsy specimens in sickle cell disease. Arch Pathol Lab Med. 1998, 112:290-4.

ISSN (O): 2687-5365; ISSN (P): 2753-6556