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RESEARCH ARTICLE

PLASMA LEVEL OF TOTAL ANTIOXIDANT AND FREQUENCY OF HBSC, HBSS, HBAA, HBAS, HBAC AND G6PD DEFICIENCY IN ICTERIC CHILDREN PRESENTING WITH ANAEMIA.

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Key words:-

Frequency, HbSC, HbSS, HbAA, HbAS, HbAC, G6PD, Deficiency, Icteric Children, Anaemia, total antioxidant

Abstract

Background:- Jaundice is a common clinical condition among anaemic children.

Aim and Objective:- This work was designed to evaluate the Plasma Level of Total Antioxidants and Frequency of HbSC, HbSS, HbAA, HbAS, HbAC and G6PD Deficiency in Icteric Children Presenting with Anaemia.

Materials and Methods:- One hundred icteric children aged 3-12 years presenting with anaemia were recruited for this work from the General Hospital, Oka-Akoko-Ondo state. Alkaline cellulose acetate membrane haemoglobin electrophoresis was carried out on the subjects to determine the haemoglobin types while immunochromatographic technique was adopted for qualitative determination of G6PD. ELIZA technique was used to determine HBsAg and anti-HCV in the subjects. Cyanmethaemoglobin method was used to determine haemoglobin concentration and capillary tube method was used to evaluate PCV. Total Antioxidant was determined in the subjects biochemically by spectrophotometry.

Results:- The result obtained in the icteric children presenting with anaemia showed a significant reduction in the haemoglobin concentration in the icteric children with G6PD deficiency than the haemoglobin concentration and PCV value obtained in icteric children with HbAS, HbAC and HbAA. The PCV value obtained in icteric children with G6PD deficiency was significantly higher than in HbSC. The frequencies of G6PD deficiency and electrophoretic types in the icteric children were found to be: 40(40%) G6PD deficiency, 28(28%) HbSC, 30(30%) HbSS, 2(2%) HbAS, 2(2%) HbAC, and 2(2%) HbAA respectively. While the pattern of gender distribution obtained from the study showed: Male: 30(30%) G6PD deficiency, 12(12%) HbSC, 16(16%) HbSS, 0(0%) HbAS, 1(1%) HbAC, 0(0%) HbAA and in female: 10(10%) G6PD deficiency, 16(16%) HbSC, 14(14%) HbSS, 2(2%) HbAS, 1(1%) HbAC and 2(2%) HbAA. G6PD deficiency and HbSS were more prevalent in icteric male children while HbAS and HbAA were more frequent in their female counterpart. There was a significantly lower plasma value of Total antioxidant in patients HbSS, HbSC and those with G6PD deficiency than the value obtained in subjects with HbAA, HbAS and HbAC with $p < 0.05$. There was a significantly lower plasma value of

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Total antioxidant in HbSS, HbSC than those with G6PD deficiency with $p < 0.05$.

Conclusion: G6PD deficiency, HbSS and HbSC with significant reduction in total antioxidant were more prevalent among the icteric children.

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Introduction:-

Haemolysis is the premature destruction of erythrocytes. A hemolytic anemia will develop if bone marrow activity cannot compensate for the erythrocyte loss. The severity of the anemia depends on whether the onset of hemolysis is gradual or abrupt and on the extent of erythrocyte destruction (Gallagher, 2013). Mild hemolysis can be asymptomatic while the anemia in severe hemolysis can be life threatening and cause angina and cardiopulmonary decompensation. The clinical presentation also reflects the underlying cause for haemolysis (Gallagher, 2013). For example, sickle cell anemia is associated with painful occlusive crises. Hemolytic anemia has multiple causes, and the clinical presentation can differ depending on the etiology. An array of laboratory tests are available for detecting hemolysis, and specialized tests may be indicated to diagnose the cause for haemolysis. There are differences in the management of various types of hemolytic anaemias. Hemolysis can be due to hereditary and acquired disorders. The etiology of premature erythrocyte destruction is diverse and can be due to conditions such as intrinsic membrane defects, abnormal hemoglobins, erythrocyte enzymatic defects, immune destruction of erythrocytes, mechanical injury, and hypersplenism (Gallagher, 2013).

Hemolysis may be an extravascular or an intravascular phenomenon. Autoimmune hemolytic anemia and hereditary spherocytosis are examples of extravascular hemolysis because the red blood cells are destroyed in the spleen and other reticuloendothelial tissues. Intravascular hemolysis occurs in hemolytic anemia due to the following: Prosthetic cardiac valves, Glucose-6-phosphate dehydrogenase (G6PD) deficiency, Thrombotic thrombocytopenic purpura, Disseminated intravascular coagulation, Transfusion of ABO incompatible blood and Paroxysmal nocturnal hemoglobinuria (PNH) (Gallagher, 2013).

Hemolysis may also be intramedullary, when fragile red blood cell (RBC) precursors are destroyed in the bone marrow prior to release into the circulation. Intramedullary hemolysis occurs in pernicious anemia and thalassemia major. Hemolysis is associated with a release of RBC lactate dehydrogenase (LDH). Hemoglobin released from damaged RBCs leads to an increase in indirect bilirubin and urobilinogen levels (Packman and Leddy, 1995; Glader, 1999; Beutl et al., 2010; Gallagher, 2013).

A patient with mild hemolysis may have normal hemoglobin levels if increased RBC production matches the rate of RBC destruction. However, patients with mild hemolysis may develop marked anemia if their bone marrow erythrocyte production is transiently shut off by viral (parvovirus B-19) or other infections. This scenario would be an aplastic crisis since the bone marrow can no longer compensate for ongoing hemolysis. Skull and skeletal deformities can occur in childhood due to a marked increase in hematopoiesis and resultant bone marrow expansion in disorders such as thalassemia (Packman and Leddy, 1995; Glader, 1999; Beutl et al., 2010; Gallagher, 2013).

A wide range of causes of hemolytic anemia have been documented. Only the more commonly encountered hemolytic disorders are discussed in this article. Recent articles have noted that intravenous immunoglobulin G (IVIG) therapy given during pregnancy, the contrast medium iomeprol, and mitral valve replacement can cause hemolysis (Packman and Leddy, 1995; Glader, 1999; Beutl et al., 2010; Gallagher, 2013).

Hereditary disorders may cause hemolysis as a result of erythrocyte membrane abnormalities, enzymatic defects, and hemoglobin abnormalities. Hereditary disorders include the following: Glucose-6-phosphate dehydrogenase (G6PD) deficiency, Hereditary spherocytosis, Sickle cell anemia; Acquired causes of hemolysis include the following: Immune disorders, Toxic chemicals and drug, Antiviral agents (eg, ribavirin), Physical damage and Infections. Autoimmune hemolytic anemia (AIHA) can be due to warm or cold autoantibody types and, rarely, mixed types. Most warm autoantibodies belong to the immunoglobulin IgG class. These antibodies can be detected by a direct Coombs test, which also is known as a direct antiglobulin test (DAT). AIHA may occur after allogeneic hematopoietic stem cell transplantation. The 3-year cumulative incidence in this population has been reported at 4.44%. (Packman and Leddy, 1995; Glader, 1999; Beutl et al., 2010; Gallagher, 2013).

The antioxidant defense system has many components. A deficiency in any of these components can cause a reduction in the overall antioxidant status of an individual. Reduction in total antioxidant status has been implicated in several disease states, such as cancer and heart disease. Antioxidants play an important role in preventing the formation of and scavenging of free radicals and other potentially toxic oxidizing species. There are three categories of antioxidant species: enzyme systems (GSH reductase, catalase, peroxidase, etc.), small molecules (ascorbate, uric acid, GSH, vitamin E, etc.) and proteins (albumin, transferrin, etc.). Different antioxidants vary in their reducing power (Stanner *et al.*, 2004 ;Csepreghy *et al.*, 2016;).

Justification:-

Haemolytic anaemia is a common cause of death in children. Little has been reported about the aetiology of the cause of this fatal health illness in Oka-Akoko, Ondo state-Nigeria hence the need for this work in the area.

Aim and Objective:-

This work was designed to evaluate the Plasma Level of Total Antioxidants and Frequency of HbSC, HbSS, HbAA, HbAS, HbAC and G6PD Deficiency in Icteric Children Presenting with Anaemia

Methodology:-**Materials:-****Study area:-**

This work was carried out in Oka- Akoko which is in the Northern part of Ondo state that shares border with Kogi and Edo State in Nigeria.

Study Population:-

One hundred anaemic icteric children aged 3 to 12 years in Oka-Akoko classified using electrophoretic pattern and G6PD screening were investigated. The HbSS and HbSC studied were recruited from General Hospital, Oka-Akoko when in crisis.

Inclusion criteria:-

1. Only anaemic icteric children were investigated
2. Children who are not HbsAg and anti-HCV positive were recruited for the work
3. Children free from *Plasmodium spp* infection were recruited for the work.

Exclusion criteria:-

1. Anaemic but anicteric children were excluded from the work
2. Children who are HbsAg and anti-HCV positive were not recruited for the work
3. Children with *Plasmodium spp* infection were not recruited for the work.
4. Patients on antimalaria drugs were excluded

Biological specimen:-

Five millilitres of Venous Whole blood sample was obtained from each of the subjects and preserved in EDTA bottles for analysis.

Methods:-**Haemoglobin electrophoresis and *Plasmodium spp* detection:-**

Haemoglobin electrophoresis for haemoglobin electrophoretic pattern and *Plasmodium spp* detection using Giemsa thick film technique were carried out as described by Cheesbrough, (2002).

Qualitative Detection of G6PD using *CareStart™* G6PD Rapid Diagnostic Test:-

CareStart™ G6PD RDT. G6PD deficiency is a genetic disorder, resulting in no or low G6PD activity. People with G6PD deficiency should not take primaquine, an antimalarial drug, and other drugs with high oxidative stress because it could cause serious side effects such as acute hemolysis.

Determination of HbsAg and Anti-HCV:-

These were carried out by ELIZA using reagent kit of BIORAD.

Evaluation of Total Antioxidants:-

The Total Antioxidants was evaluated in the subjects using RANDOX kit.

Principle:- ABTS® (2, 2'-Azino-di-[3-ethylbenzthiazoline sulphonate]) is incubated with a peroxidase (metmyoglobin) and H₂O₂ to produce the radical cation ABTS®*+. This has a relatively stable blue-green color, which is measured at 600 nm. Antioxidants in the added sample cause suppression of this color production to a degree which is proportional to their concentration.

Identification of *Plasmodium spp* in the subjects:-

This was carried out by Giemsa-Thick film technique

Data analysis:-

The information obtained was subjected to statistical analysis using SPSS 17.0 to determine mean, standard deviation and level of significance of the differences at 0.05 using student's 't' test.

Ethical consideration:-

The proposal of this work was first presented to the Research and Ethical committee of the General Hospital, Oka-Akoko-Nigeria. The proposal was carefully reviewed and approved before sample collection.

Results:-

The overall frequency of G6PD deficiency, HbSC, HbSS, HbAS, HbAC and HbAA, obtained in this work among the icteric children include : 40(40%), 28(28%), 30(30%), 2(2%), 2(2%), and 2(2%) respectively. While the pattern of gender distribution obtained from the study showed: Male:30(30%) G6PD deficiency, 12(12%)HbSC,16(16%) HbSS, 0(0%) HbAS, 1(1%) HbAC, 0(0%) HbAA and in female: 10(10%)G6PD deficiency, 16(16%)HbSC, 14(14%) HbSS, 2(2%) HbAS, 1(1%)HbAC and 2(2%) HbAA. G6PD deficiency and HbSS were more prevalent in icteric male children while HbAS and HbAA were more frequent in their female counterpart (Tables 1,2,3,4 and figure 1,2, 3).

The results obtained showed a significantly lower PCV value in icteric children with G6PD deficiency than the results obtained from icteric children with HbSC, HbAS, HbAC and HbAA($p < 0.05$) (Tables 1,2,3,4 and Figure1). there was also a significantly lower PCV value in HbSC and HbSS compared with the results obtained in icteric children with HbAS, HbAC and HbAA ($p < 0.05$) (Tables 1,2,3 and Figure1). No significant difference was obtained in the value of PCV in icteric children with G6PD deficiency compared with icteric children with HbSS; HbSC compared with HbSS; HbAS compared with HbAA, HbAC and in icteric children with HbAC compared with HbAA($p > 0.05$) (Tables 1,2,3,4 and Figure1). There was no significant difference in the haemoglobin concentration obtained in icteric children with G6PD deficiency compared with HbSS, HbSC; HbSC compared with HbSS; HbAS compared with HbAC, HbAA and HbAC compared with HbAA($p > 0.05$) (Tables 1,2,3 and Figure1). However, there was a significantly lower haemoglobin concentration in the results obtained from icteric children who lack G6PD than the icteric children with HbAS, HbAC, HbAA($p < 0.05$) (Tables 1,2,3 and Figure1). A significantly lower in HbSS and HbSC than icteric children with HbAS, HbAC and HbAA($p < 0.05$) (Tables 1,2,3 and Figure1).

There was a significantly lower plasma value of Total antioxidant in patients HbSS, HbSC and those with G6PD deficiency than the value obtained in subjects with HbAA, HbAS and HbAC with $p < 0.05$ (Tables 1,2,3,4). There was a significantly lower plasma value of Total antioxidant in HbSS, HbSC than those with G6PD deficiency with $p < 0.05$ (Tables 1,2,3,4).

However, there was no significant difference in the plasma value of Total antioxidant subjects with HbSC compared HbSS; HbAS compared with HbAC; HbAS compared HbAA and HbAA compared with HbAC with $p > 0.05$ (Table 1,2,3,).

Table 1:- Overall Frequency, Mean and standard deviation of the electrophoretic pattern, PCV and haemoglobin concentration obtained in icteric children presenting with anaemia

	G6PD DEFICIENCY	HbSC	HbSS	HbAS	HbAC	HbAA
Frequency	40(40%)	28(28%)	30(30%)	2(2%)	2(2%)	2(2%)
PCV/%	9±2.0	16±1.0	12±3.0	39±3.0	40±0	42±0
Hb/g/dl	4±0.5	6±1.0	5±0.5	13±2.0	14±0	14±0
Total Antioxidant/µM	410±10.0	360±9.0	340±10.0	561±7.0	568±8.0	570±5.0

Table 2:- Gender distribution of the Frequency of G6PD deficiency, HbSC, HbSS, HbAS, HbAC and HbAA obtained in icteric children

	G6PD DEFICIENCY	HbSC	HbSS	HbAS	HbAC	HbAA
Frequency	40(40%)	28(28%)	30(30%)	2(2%)	2(2%)	2(2%)
Male	30(30%)	12(12%)	16(16%)	0(0%)	1(1%)	0(0)
Female	10(10%)	16(16%)	14(14%)	2(2%)	1(1%)	2(2%)

Table 3:- Comparative analysis of the Mean and standard deviation of the PCV and haemoglobin concentration obtained in icteric children with G6PD deficiency and anaemic icteric children with HbSC, HbSS, HbAS, HbAC and HbAA

		G6PD DEFICIENCY Vs.HbSC	G6PD DEFICIENCY Vs. HbSS	G6PD DEFICIENCY Vs. HbAS	G6PD DEFICIENCY Vs. HbAC	G6PD DEFICIENCY Vs. HbAA	HbSC VsHbSS
PCV	‘t’	-3.13	-0.83205.	-9.21425.	-14.31	-16.5.	1.27.
	‘p’	0.044	0.247	0.0058	0.0024	0.002	0.17
	Comment	P<0.05*	p>0.05	P<0.05*	P<0.05*	P<0.05*	p>0.05
Hb	‘t’	-1.79	-1.41	-4.37	-20.	-20	0.89
	‘p’	0.11	0.147	0.024	0.0013.	0.0012	0.23
	Comment	p>0.05	p>0.05	P<0.05*	P<0.05*	P<0.05*	p>0.05
Total Antioxidant	‘t’	3.71647	4.95	-12.37	-12.34	-14.31	1.49
	‘p’	0.03269	0.019238.	0.003236	0.003253	0.0024	0.14
comment		P<0.05*	P<0.05*	P<0.05*	P<0.05*	P<0.05*	P>0.05

Table 4:- Comparative analysis of the results obtained from icteric children with icteric children with HbSC, HbSS, HbAS, HbAC and HbAA

		HbSC VsHbAS	HbSC VsHbAC	HbSC VsHbAA	HbAS VsHbAC	HbAS VsHbAA	HbAC VsHbAA	HbSS VsHbAS	HbSS VsHbAC	HbSS VsHbAA
PCV/%	‘t’	-8.36	-17.68	-26.	0.93	-1.4.	-1.	-6.79	-9.171	-10
	‘p’	0.01.	0.002	0.001	0.23.	0.148	0.211.	0.011	0.0058	0.005
	Comment	P<0.05*	P<0.05*	P<0.05*	p>0.05	p>0.05	p>0.05	P<0.05*	P<0.05*	P<0.05*
Hb/g/dl	‘t’	-3.13	-8.	-8.	-0.5.	-0.5.	0	-3.88	-18.	-18.
	‘p’	0.04	0.008	0.008	0.333	0.333	0	0.030	0.002	0.002
	Comment	P<0.05*	P<0.05*	P<0.05*	p>0.05	p>0.05	p>0.05	P<0.05*	P<0.05*	P<0.05*
Total antioxidant	‘t’	-17.63	-17.71	-20.40	-0.66	-1.05	-0.21	-18.11	-17.80	-20.57
	‘p’	0.002	0.002	0.0012	0.29	0.20	0.43	0.002	0.002	0.0012
comment		P<0.05*	P<0.05*	P<0.05*	P>0.05	P>0.05	P>0.05	P<0.05*	P<0.05*	P<0.05*

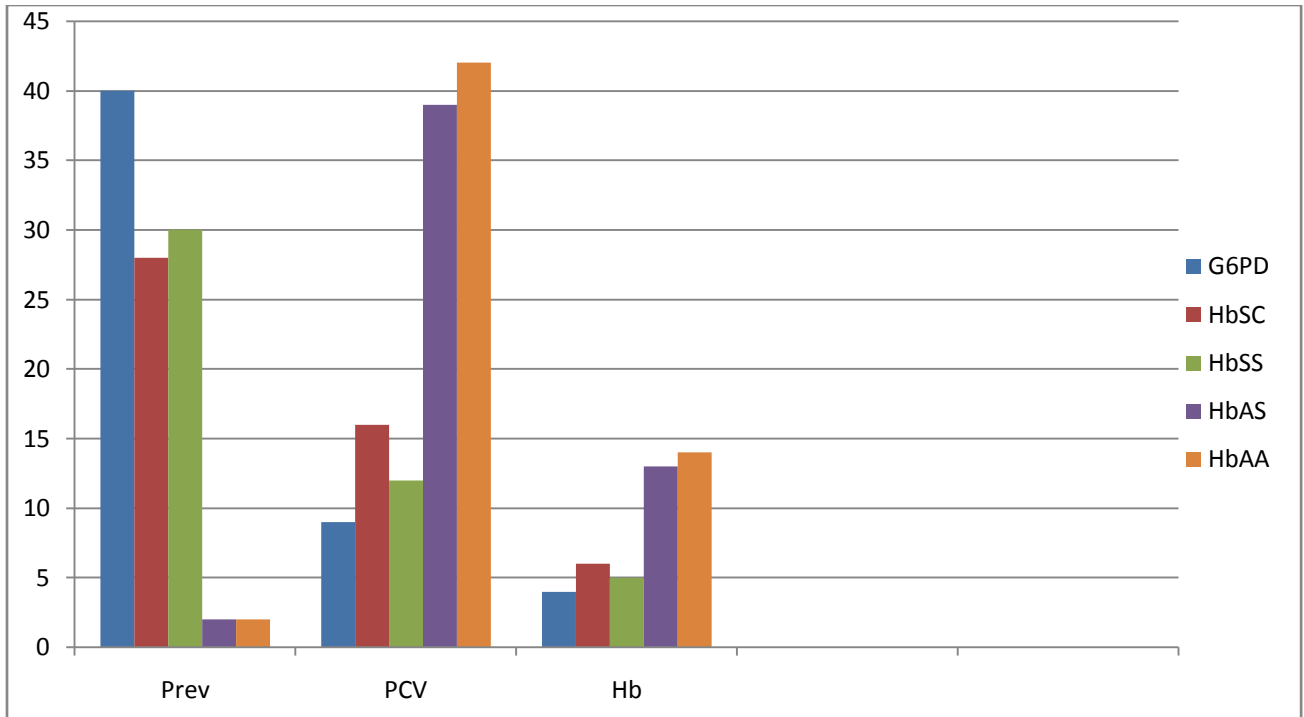


Figure 1:- Comparative analysis of the results obtained from icteric children with G6PD deficiency, HbSC, HbSS, HbAS, HbAC and HbAA.

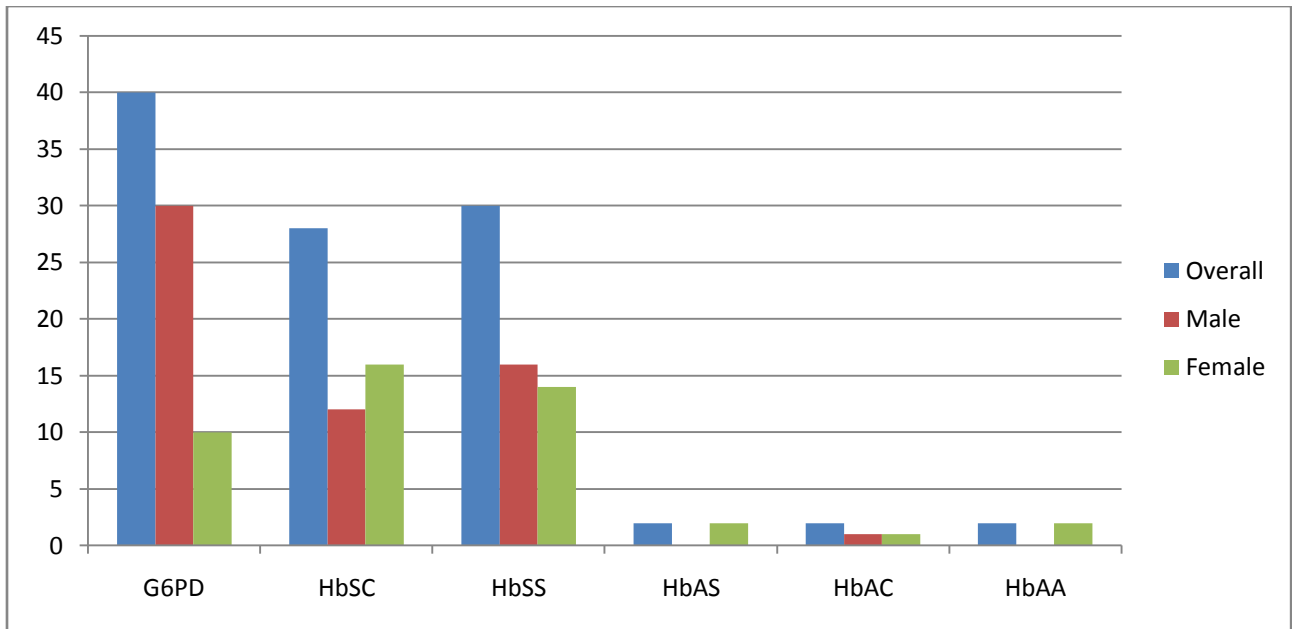
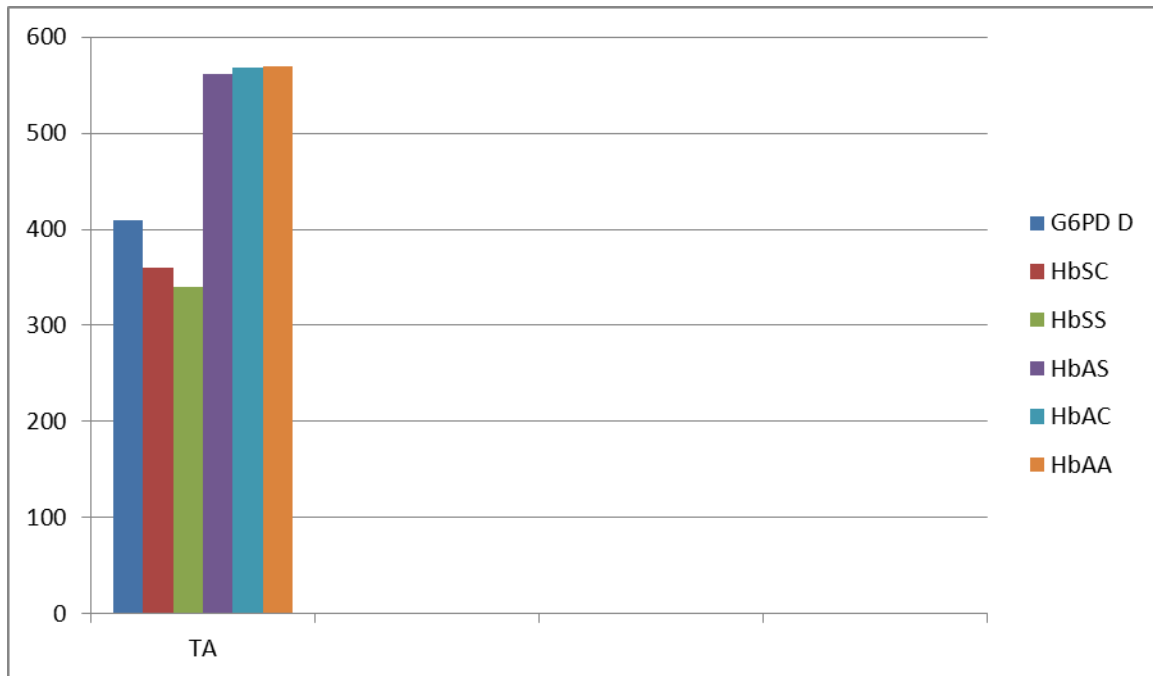


Figure 2:- Gender distribution of G6PD deficiency, HbSC, HbSS, HbAS, HbAC and HbAA in icteric children.



Key: TA – Total antioxidant; G6PD D – G6PD deficiency

Figure 3:- Showing comparative plasma level of Total antioxidant in the subjects.

Discussion, conclusion and recommendation:-

Discussion:-

The overall frequency of G6PD deficiency, HbSC, HbSS, HbAS, HbAC and HbAA, obtained in this work among the icteric children include : 40(40%), 28(28%), 30(30%), 2(2%), 2(2%), and 2(2%) respectively. While the pattern of gender distribution obtained from the study showed: Male:30(30%) G6PD deficiency, 12(12%)HbSC,16(16%) HbSS, 0(0%) HbAS, 1(1%) HbAC, 0(0) HbAA and in female: 10(10%)G6PD deficiency, 16(16%)HbSC, 14(14%) HbSS, 2(2%) HbAS, 1(1%)HbAC and 2(2%) HbAA. G6PD deficiency and HbSS were more prevalent in icteric male children while HbAS and HbAA were more frequent in their female counterpart. The frequency of distribution of 28%HbSC and 30%HbSS found among the icteric study as indicated above was higher than the report of Nubila *et al.*, (2013) that found HbSS (5.5%) and HbSC (1.1%) among Yorubas in Ibadan, south western Nigeria in a pilot study and SCD frequency of 2.39% reported by Nwogoh *et al.*, (2012) in Benin City, South-South Nigeria.

These differences could be attributed to the fact that haemolytic anaemia is associated with HbSS and HbSC which was the major inclusion criteria for the recruitment of test subjects for this work. In addition all HbSS and HbSC icteric children were studied during crisis which accelerates massive haemolysis of red blood cells (Serjeant, 1997; Serjeant and Serjeant, 2001; Madigan and Malik, 2006; Lal and Vinchinsky, 2011; Nwogoh *et al.*, 2012 ; Serjeant, 2013) leading to decreased PCV and haemoglobin concentration.

The results obtained showed a significantly lower PCV and haemoglobin concentration in icteric children with G6PD deficiency than the results obtained from icteric children with HbAS, HbAC and HbAA and in the value of PCV in G6PD deficiency than in icteric children with HbSC. This could be attributed to the fact that Hereditary disorders may cause hemolysis as a result of erythrocyte membrane abnormalities, enzymatic defects, and hemoglobin abnormalities such as Glucose-6-phosphate dehydrogenase (G6PD) deficiency, HbSS and HbSC (Gallagher, 2010). These findings with respect to G6PD deficiency do not agree with the report of Williams *et al.*, 2013 that there was not association between vital parameters or hematocrit and G6PD deficiency but in agreement with their report that history of scleral icterus may increase the odds of G6PD deficiency, though did not exclude other common causes of icterus such as sickle cell disease or malarial infection.

G6PD deficiency was found to be more frequent in male than female icteric children. This finding agrees with the report of Williams *et al.*, 2013 who found that the overall frequency of G6PD deficiency was 15.3% (24.1% in males, 6.6% in females). In addition G6PD deficiency is inherited as an X-linked recessive disorder. G6PD deficiency is polymorphic, with more than 300 variants (Nkhoma *et al.*, 2009; Olusanya *et al.*, 2015).

The frequency of G6PD deficiency (40%) found in this work among the icteric children in Oka-Akoko was lower than the frequency rate of 43% found among children presenting with jaundice in Ilorin, Nigeria by Amiwero and Olatunji, (2012). They reported that children in the age group one day to 15 years presenting with jaundice at Ilorin have an overall 43.0 percent [males (50 percent) and females (28.1 percent) chance of having G6PD deficiency, as the underlying cause of their jaundice and that this justifies the need for G6PD screening in children presenting with jaundice.

There was also a significantly lower PCV and haemoglobin concentration in HbSC and HbSS compared with the results obtained in icteric children with HbAS, HbAC and HbAA. The significant reduction in the haemoglobin concentration and PCV obtained in icteric children with HbSS, HbSC and G6PD deficiency in this study could be attributed to haemolytic anaemia associated with enzymopathy (G6PD deficiency) and the genetic defect (HbSS and HbSC). Their pathophysiology is characterized by massive red blood destruction which usually leads to reduced RBC count, haemoglobin concentration and PCV which was also reported in this work. HbSS and HbSC contains sickling haemoglobin types which include HbS and HbC. These could greatly be responsible for the reduction in PCV and haemoglobin concentration found among the icteric children studied (Serjeant, 1997; Serjeant and Serjeant, 2001; Madigan and Malik, 2006; Lal and Vinchinsky, 2011; Nwogoh *et al.*, 2012; Serjeant, 2013).

There was a significantly lower plasma value of Total antioxidant in patients HbSS, HbSC and those with G6PD deficiency than the value obtained in subjects with HbAA, HbAS and HbAC. There was a significantly lower plasma value of Total antioxidant in HbSS, HbSC than those with G6PD deficiency. This significant reduction in total antioxidant could be associated with oxidative stress induced by the crisis associated with the clinical condition and also as a result of massive destruction of red blood cells causing over utilization of antioxidants to reduce the cellular damage because antioxidant molecule inhibits the oxidation of other molecules. Oxidation is a chemical reaction that can produce free radicals, leading to chain reactions that may damage cells. Oxidative stress can be considered as either a cause or consequence of some diseases (Stanner *et al.*, 2004; Dabelstein *et al.*, 2007).

Conclusion:-

The result revealed a significant reduction in the haemoglobin concentration and PCV in the icteric children with G6PD deficiency than the haemoglobin concentration and PCV value obtained in icteric children with HbAS, HbAC and HbAA. The PCV value obtained in icteric children with G6PD deficiency was significantly higher than in HbSC. The frequencies of G6PD deficiency and electrophoretic types in the icteric children were found to be: 40(40%) G6PD deficiency, 28(28%) HbSC, 30(30%) HbSS, 2(2%) HbAS, 2(2%) HbAC, and 2(2%) HbAA respectively. While the pattern of gender distribution obtained from the study showed: Male: 30(30%) G6PD deficiency, 12(12%) HbSC, 16(16%) HbSS, 0(0%) HbAS, 1(1%) HbAC, 0(0) HbAA and in female: 10(10%) G6PD deficiency, 16(16%) HbSC, 14(14%) HbSS, 2(2%) HbAS, 1(1%) HbAC and 2(2%) HbAA. G6PD deficiency and HbSS were more prevalent in icteric male children while HbAS and HbAA were more frequent in their female counterpart. Total antioxidant was lower in subjects with HbSS, HbSC, G6PD deficiency than in subjects with HbAS, HbAC and HbAA.

Recommendation:-

Routine investigation of children with jaundice (haemolytic anaemia) should include haemoglobin electrophoresis, determination of G6PD and evaluation of total antioxidant for effective management

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