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Frequency and Distribution of ABO and Rh(D) Blood Groups in Glucose – 6 – Phosphate Dehydrogenase (G6PD) Deficient Neonates: A Hospital-Based Study in Uyo, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Author ISA contributed substantially to the conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content. Author ASB contributed substantially to acquisition of data, drafting of the article and revising it critically for important intellectual content. Author EEE contributed substantially to acquisition of data, drafting of the article and revising it critically for important intellectual content. Author EOK contributed substantially to acquisition of data, drafting the article and revising it critically for important intellectual content. Author EEOA contributed substantially to acquisition of data, drafting the article and revising it critically for important intellectual content. All authors read and approved the final manuscript.

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ABSTRACT

Background: Glucose-6-phosphate dehydrogenase deficiency, an X-linked recessive disorder, is the commonest inherited red cell enzymopathy affecting mankind. It is known to cause severe neonatal hyperbilirubinaemia that can result in permanent neurologic damage or death. Numerous

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associations have been reported between ABO and Rh blood groups and increased or decreased susceptibility to diseases, including G6PD deficiency. However, studies on the association between G6PD deficiency and ABO and Rh blood groups have been largely inconsistent and limited.

Aims and Objectives: To estimate the level of G6PD activity among icteric neonates delivered at University of Uyo Teaching Hospital with the view of determining the prevalence of G6PD deficiency as well as to examine the association, if any, between G6PD and ABO and Rh blood types.

Methods: One hundred and fifty neonates were recruited into the study over a period of two years. Screening for G6PD deficiency was carried out using a quantitative in vitro test (Assay Pro) while the ABO and Rh(D) blood group phenotypes were determined using the standard tube method. The data were analyzed with SPSS version 23.0. Chi-square was used for test of significance.

Results: The overall prevalence of G6PD deficiency in the icteric neonates was 26.0%. The prevalence in males was 27.0% and 23.1% in females. Majority of the patients were of the O and Rh (D) positive blood types, the frequency and distribution of these blood group phenotypes among the patients were not different from the pattern reported in the general population in our clime. There was no statistically significant association between GGPD deficiency and the ABO and Rh (D) blood types of the patients($p<0.05$).

Conclusion: There is a high prevalence of G6PD deficiency in icteric babies delivered at University of Uyo Teaching Hospital, Uyo, Nigeria. This justifies the need for routine neonatal screening for G6PD deficiency in all healthcare institutions in our environment. The association between G6PD deficiency and ABO and Rh (D) blood types was not statistically significant. However, we recommend that a large multicentre study be conducted in Nigeria and other African countries for the purpose of validating our results.

Keywords: Glucose-6-phosphate dehydrogenase deficiency; icteric neonates; ABO blood group; Rh(D) blood group; Uyo.

1. INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) is a cytoplasmic enzyme present in many cells and catalyses oxidation of glucose-6-phosphate to 6-phosphogluconate, the first step in the hexose monophosphate pathway, converting the coenzyme nicotinamide adenine dinucleotide phosphate (NADP) to its reduced form (NADPH). The NADPH is responsible for the generation of reduced glutathione (GSH) through reduction of oxidized glutathione (GSSG) by glutathione reductase. Reduced glutathione (GSH) protects the red blood cells from the harmful effects of reactive oxygen species [1].

The red blood cell (RBC) is prone to injury from several exogenous and endogenous oxidative agents thus, defects in the hexose monophosphate pathway or glutathione metabolism due to G6PD deficiency of impaired function, reduces the ability of the red cells to protect themselves against oxidative injuries. This results in haemolytic anaemia of varying severity including neonatal hyperbilinibinaemia, a principal cause of neonatal morbidity and mortality [1,2].

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked disorder, is the most common inherited enzyme disease in humans affecting approximately 400 million people globally with highest prevalence in Africa, India, the Mediterranean and South East Asia [3,4]. It was first described in black people in the 1950s when they were observed to exhibit variable susceptibility to haemolysis following administration of primaquine for the treatment of malaria [1,3]. Current ease of travel, migration and racial admixture have contributed to the worldwide distribution of G6PD deficiency with the prevalence varying among different ethnic groups. In the United States of America, the enzyme deficiency mostly of moderate severity is found among 2.5% of males and 1.6% of females. African- American males are frequently affected, with a prevalence of about 10% in the general population and 25.5% reported among jaundiced reonates. The prevalence of G6PD deficiency varies considerably from being rare in the indigenous populations of Northern Europe to frequencies of about 20% in parts of Southern Europe, 70% in Kurdish Jews, 5% in China, ranging from 3% to 6.9% in Pakistan and Southern Russian to as low as 0.1% in Japan [3-5]. The prevalence rate of G6PD deficiency in West Africa shows geographical variability. In Nigeria, the prevalence of G6PD deficiency ranges from 4-26% with 20-26% of males and 3-

5% of females being deficient [4,6]. Among jaundiced neonates in nigeria, though varies with the enzyme assay method employed, prevalence rate of 20.5-35.3% has been reported, which is much higher than what is obtained among Americans of African ancestry [6,7].

The enzyme deficiency is mainly reported in hemizygous males and homozygous females. However, low enzyme activity has been found in females with Turner's syndrome and 10% of heterozygous females which could put them at risk of developing haemolysis when they are exposed to oxidative agents such as drugs, with high redox potential, chemicals, infections, or 'fava' beans (Vicia faba) [7]. Clinical presentation of G6PD deficiency is variable ranging from asymptomatic cases to those with lifelong haemolytic episodes depending on the residual enzyme activity. The prominent mainifestations are drug-induced haemolysis, non- spherocytic haemolytic anaemia, favism, and neonatal hyperbilirubinaemia that is usually severe and protracted with a tendency to result in brain damage, or even death [7]. Development of jaundice in G6PD deficient neonates is as a result of several factors including immaturity of liver enzymes for bilirubin conjugation and excretion, method of feeding, presence of infection and exposure of the newborn to environmental agents such as clothes stored with naphthlene balls, herbal concoctions, or dressing the umbilical cord with antiseptic "mentholated" powders [7,8].

The ABO blood group is unquestionably the most important and antigenic of the blood group systems [9]. It is governed by a single gene located on chromosome 9 with three alleles (1A, 1B and 10). The antigens of this blood group system consist of complex carbohydrate moieties expressed on the surface of the red blood cell membrane [10]. However, these antigens are not confined to the erythrocyte membrane, but are expressed on the surfaces of a wide array of normal human cells and tissues as well as body fluids and some tumours [11,12]. Due to the presence of the carbohydrate moieties on the erythrocyte membrane, four blood groups, namely A, B, AB and O have been identified [11]. The ABO blood group system can be broadly classified as the O and non- O blood groups, the latter comprising blood groups A, B and AB. Furthermore, the A and AB blood groups have been further sub-classified. About 80% of blood type A or AB are classified as A1 or A_1 B, while the remaining 20% are either A_2 or A_2 B [13].

Rh blood group system, formerly referred to as Rhesus blood group system, is the second most clinically significant blood group system due to haemolytic disease of newborn. It is determined by a gene located on the short arm of chromosome 1 with two alleles (D and d). Individuals with D antigen on their red cells are known as Rh-positive (DD or Dd genotype) while those without D antigen (dd genotype) in their red blood cells are Rh-positve (DD or Dd genotype) while those without D antigen (dd genotype) in their red blood cells are Rh-negative. The Rh blood group system is by far the most polymorphic blood group system known in humans, comprising more than 60 antigens. These antigens (RhD and RhCE determinants) are composed of complex protein molecules expressed on the surface of the red cell membrane and those of their immediate precursors [14]. Its clinical relevance is attributed to the fact that the Rh antigens, particularly the D antigen, are highly immunogenic. Individuals who do not express D antigen on their red cell membrane will produce anti-D antibodies if they encounter the D antigen on transfused red blood cells causing a haemolytic transfusion reaction or on fetal red blood cells causing haemolytic disease of the newborn [15,16].

A number of studies have documented a plausible association or relationship of blood types to some disease conditions, including infections, cancers, cardiovascular and thrombo-haemorrhagic disorders [17,18]. For instance, Wolpin et al. [19], in their study found that individuals with non- O blood group compared with those with blood group O were more likely to develop pancreatic cancer. Also, other workers have reported a higher prevalence of gastric and breast cancers in blood group A (a non-O blood group) patients [17,20-22]. Similar findings though with subtle differences in the distribution of the ABO blood types have been reported among the solid tumours by other researchers [23,24]. In addition, some studies have equally demonstrated an association between Rh blood group and the solid tumours and a range of other diseases and clinical entities [15,24-28].

Similarly, the frequency and distribution of ABO and Rh blood groups have been studied in G6PD deficient individuals [29-32]. A study that investigated the association between G6PD deficiency and the ABO and Rh blood types in American Negro males, found no significant association between he enzyme deficiency and the ABO blood groups, but in contrast found a

highly significant decrease in the frequency of gene E of the Rh system in deficient subjects which was in dissonance with what was observed in unaffected subjects [32]. In another study conducted to evaluate the distribution of these blood types among G6PD deficient and unaffected Chinese newborns, the authors reported that there was an increase in the frequency of blood group B as well as gene E of the Rh system in the enzyme deficient subjects when compared with the normal subjects [31].

There is paucity of data on G6PD deficiency in Nigeria. The prevalence of G6PD deficiency, frequency and distribution of ABO and Rh blood groups among G6PD deficient patients as well as the association between the enzyme deficiency and these blood types in our environment are unknown. Due to the numerous associations that have been made between the ABO and Rh blood groups and increased susceptibilty to diseases, we believe that if the local prevalence of G6PD deficiency as well as the risk of the enzyme deficiency is established for the different ABO and Rh phenotypes, it could serve as a prospective epidemiological marker to identify at risk persons in our population. Therefore, the study was aimed to determine the prevalence of G6PD deficiency, distribution of ABO and Rh blood groups in G6PD deficient newborns and to examine the relationship between the enzyme deficiency and these blood groups as seen in our locality.

2. MATERIALS AND METHODS

2.1 Study Location

This study was conducted at the Departments of Haematology and Paediatrics of the University of Uyo Teaching Hospital (UUTH), Uyo, Nigeria. The Teaching Hospital serves as a referral centre for the neighbouring states of Cross River, Rivers, Abia and Imo.

2.2 Study Population

This consisted of one hundred and fifty neonates with clinical and laboratory evidence of jaundice who were managed in the Department of Paediatrics from January 2018 to December 2019.

2.3 Study Design

This was a prospective cross-sectional study.

2.4 Inclusion and Exclusion Criteria

Jaundiced neonates admitted into the Special Care Baby Unit and Sick Baby Unit of University of Uyo Teaching Hospital whose parents gave written informed consent were recruited into the study. Newborns with jaundice whose parents failed to give consent, who had bleeding diathesis, birth asphyxia or any other conditions and those older than 28 days, were excluded.

2.5 Procedure

Three milliters of blood was collected from each study subjects into ethylenediamine tetracetic acid (EDTA) – anticoagulated bottles. The EDTA – anticoagulated blood was used for the screening of the subjects for G6PD deficiency using the Assay Pro G6PD quantitative in vitro test (Assay Pro, St. Charles, MO, USA). Its principle is based on reduction of NADP by G6PD present in red blood cells. The NADPH generated from the reaction fluoresces under ultraviolet light at a wave length of 340nm. Enzyme activity was determined by measuring the rate of absorbance change using the Hitachi U – 3010 UV/Vis spectrophotometer. Red blood cell G6PD activity of $\geq$2.9 u/gHb was regarded as normal [33]. Neonates with red blood cell G6PD values of <2.9Ug/Hb were regarded as moderately deficient, while those with values of <1.6U/gHb were considered to be severely deficient. Standard tube method as described by Dacie and Lewis [34] was used for the determination of ABO and Rh(D) blood groups using antisera obtained from Biotec Laboratory, United Kingdom.

2.6 Data Analysis

The data were collated, analyzed with Statistical Package for Social Sciences (SPSS) windows version 23.0 and presented in simple frequency tables. The comparisons were carried out with chi-square test as appropriate and statistically significant levels were set at $p>0.05$.

3. RESULTS

A total of 150 neonates comprising 111 (74%) males and 39 (26%) females were screened for G6PD deficiency. Of this number, 111 (74%) had normal G6PD activity while 39(26%) were G6PD – deficient. The overall mean G6PD value was 4.82 $\pm$ 2.39 U/gHb (range 0.85 – 13.00 U/gHb) (Table 1). Among those with normal G6PD values, males had a mean G6PD value of

5.58±2.01 U/gHb and females had a mean value of 6.34 ± 1.90 U/gHb. Thus, normal females had a mean G6PD value that was higher than that of normal males, however the difference was not statistically significant (p = 0.07). Enzyme levels in babies with G6PD deficiency was 2.02± 0.58U/gHb in males and 2.23±0.21U/gHb in females, P = 0.09 (Table 2).

Babies with O Rh D positive blood group were the majority with a total of 80 subjects (53.3%) and mean G6PD value of 4.71 ± 2.24 u/gHb while babies with the A Rh D negative and B Rh D negative blood groups were the least common with 1 subject each (0.7%) and mean G6PD values of 6.04 and 3.65 u/gHb, respectively. Collectively, subjects with the O blood group were more than the non- O blood group Table 3.

Table 4 shows the relationship between the G6PD activity levels in the subjects and their ABO and Rh (D) blood groups. There was no statistically significant difference between the enzyme activity levels and the blood groups (P > 0.05).

Table 1. Mean G6PD levels of study subjects

G6PD status	Frequency	Percentage (%)	Mean	Standard deviation
Deficient	39	26.0	2.07	0.53
Normal	111	74.0	5.79	2.00
Total	150	100	4.82	2.39

Table 2. Glucose – 6 – phosphate dehydrogenase levels in normal and deficient neonates according to sex

Classification	NO	Mean	t-value	p-value
Normal				
Male	81(73.0)	5.58±2.01	1.8	0.07
Female	30(76.9)	6.34±1.90		
Deficient				
Male	30(27.0)	2.02±0.58	1.69	0.09
Female	9(23.2)	2.23±0.21		
	Male (%)	**Female (%)**	χ^2	**p-value**
Normal	81(73.0)	30(27.0)	0.23	0.63
Deficient	30(76.9)	9(23.2)		

Table 3. Distribution of G6PD values among the ABO and Rh (D) blood groups of subjects

Characteristics	Frequency	Percentage (%)	Mean	Standard Deviation
ABO and Rh(D) Blood Groups				
A^+	42	28	5.04	2.54
A^-	1	0.7	6.04	0.00
B^+	19	12.7	5.14	2.93
B^-	1	0.7	3.65	0.00
AB^+	4	2.7	3.94	0.93
O^+	80	53.3	4.71	2.24
O^-	3	2	3.87	2.97
Non- O and O Blood Groups				
Non – O Rh D Positive	65	43.3	5	2.58
Non – O Rh D negative	2	1.3	4.85	1.69
O Rh D Positive	80	53.3	4.71	2.24
O Rh D negative	3	2	3.87	2.97

Table 4. Relationship between the G6PD status of the subjects and their ABO and Rh (D) blood groups

Blood Group	G6PD Normal (%)	Deficient (%)	χ^2	P-value
ABO and Rh(D) Blood Groups				
A^+	31(73.8)	11(26.2)	1.88	0.98
A^-	1(100)	0(0)		
B^+	13(68.4)	6(31.6)		
B^-	1(100)	0(0)		
AB^+	3(75.0)	1(25.0)		
O^+	60(75.0)	20(25.0)		
O^-	2(66.7)	1(33.3)		
Non- O and O Blood Groups				
Non – O Positive	47(72.3)	18(27.7)	0.9	0.96
Non – O negative	2(100)	0(0)		
O Positive	60(75.0)	20(25.0)		
O negative	2(66.7)	1(33.3)		

4. DISCUSSION

The overall prevalence of G6PD deficiency in this study was 26%. This value is comparable with prevalence rates of 26%, 26.7% and 28.4% previously reported in Nigeria [5,35,36]. Similarly, prevalence of 29.3%, 30.2% and 32% have been documented in studies conducted in Pakistan, Egypt and India respectively [37-39]. However, much lower rates of 1.57%, 1.62% and 2.1% have been reported in highly developed countries [40]. Also, in sharp contrast to the present study, figures as high as 40%, 43%, 47.7% and 62%, have emanated from studies carried out in Nigeria [41-44]. The substantial variation between the prevalence figures from this study and earlier studies may be attributed, largely, to the marked differences in the study population. Furthermore, methods of enzyme assay and sensitivity of the methods used may have also considerably contributed to the variation in the prevalence rates [45]. For instance, the quantitative method which was used in this study measures the actual enzyme activity whereas the less reliable qualitative or semi-quantitative method like the fluorescent spot test used in some of the cited studies particuarlly those done in Nigeria [46], demonstrates enzyme activity by a colour change representing lower cut off value of <2.1 U/gHb. The latter test method is based on the visual assessment of fluoresced reduced NADPH when exposed to ultraviolet light such that, the sample is considered to be G6PD enzyme “deficient” when it does not fluoresce, and “normal” when it fluoresces [47]. Studies have shown that false negative results may occur with the use of the fluorescent spot test in female heterozygotes and male homozygotes following acute haemolythic events [8,39,47]. This underscores the importance of utilizing a universally acceptable, most sensitive and specific assay method that will guarantee the infallibility of every report regardless of where it is produced.

Other factors that may have been responsible for the variation in prevalence rates across countries, cultures and ethnic groups could include frequency of carrier individuals, genetic and racial diversity of human populations as well as malaria endemicity pattern. Strong relations between malaria and G6PD deficiency has been widely documented, and with malaria being holoendemic in Nigeria [48], the higher prevalence of the enzyme deficiency in the country compared to developed countries is not unexpected. In addition, the babies enrolled into most Nigerian studies already had jaundice [48-50]. Enzyme assays done during acute haemolytic episodes will likely demonstrate enzyme activity in reticulocytes [5]. Considering the enzyme variant responsible for deficiency in the West African sub-region, GdA [36], its activity is known to decrease as the cells age so that reticulocytes have normal or near normal enzyme activity [8]. Thus, earlier studies conducted in this region would have under-reported the prevalence of G6PD deficiency in neonates [41].

The mean G6PD activity level of the subjects in this study was 4.82±2.39 U/gHb while the

deficient icteric neonates had mean activity of 2.07±0.53 U/gHb. These values are relatively much lower than 12.43±2.28 U/gHb reported by Azma et al. [51] in Malaysia and 10.6U/gHb observed by Reclos et al [52] in Greece. It should however be noted that these studies were conducted using different test kits and in different geographical regions which could have been responsible for the variation in the mean G6PD activity levels compared to the findings in the present study. Similarly, George et al. [53] in Port Harcourt, Nigeria reported a higher mean G6PD level of 17.3±10.9U/gHb in deficient neonates, however our figure is higher than the finding of 1.50± 0.02U/gHb documented by Uko et al. [54] in Calabar. These findings are not surprising as it has been reported in sub-Saharan Africa, that three different G6PD variants with polymorphic gene frequencies exist [36]. G6PD B is the most common with normal enzyme activity and it is not known to be associated with haemolysis [5]. G6PD A^+ is the next in frequency, but has a slightly reduced enzyme activity and it is not associated with haemolysis [36,40]. The third variant $G6PDA^-$ is characterized by mild to moderate enzyme deficiency which is associated with haemolysis especially when the deficient persons take certain foods, chemicals or drugs [5,36,40]. The difference in enzyme activity and resultant variable reference ranges may be attributed to the enzyme variant prevalent in the geographical location as well as increase frequency of carrier individuals in the population resulting in further population heterogeneity. G6PD reagents used in these studies were from different manufacturers and had variable reference intervals which may have also accounted for the varying G6PD activity levels.

The prevalence of G6PD deficiency among males in this study was 27.03% while the females had a G6PD prevalence rate of 23.08%. A male to female ratio (M:F) of 3:1 similar to the finding in an Iraqi study and studies in other parts of the world, was observed in this series [7,8,47,55]. This therefore reaffirmed the X-linked recessive inheritance pattern of the disorder. Female offspring of a G6PD – deficient father would all be carriers (heterozygotes) of the trait, with a variable range of G6PD activity, except for rare cases of female homzygotes or hemizygotes as in Turner's syndrome who are often affected. Female heterozygotes could however be G6PD deficient if the phenomenon of X-chromosome inactivation occurs in keeping with the Lyon – Hypothesis [56]. Each male offspring of a carrier or affected (homozygote) mother usually has a 50% - 100% chance of being G6PD deficient [57].

The difference in gender prevalence in this study was not statistically significant (P=0.63). This observation is in consonance with findings from other studies [33,52,58,59]. However, the results of Kaplan et al. [60] in the USA, sharply contrasts the above with a higher G6PD deficiency prevalence found in females compared to males, though the difference was not statistically significant. This finding is contrary to what would be expected of an X-linked disorder. It would naturally be perceived that the enzyme deficiency would occur more in males owing to the fact that they posses only on Xchromosome. Unlike their male counterparts, the females are in the peculiar position of having 3 genotypes: normal homozygous, heterozygous and deficient homozygous. Due to the random X chromosome inactiviation [56], the heterozygous female has two red cell populations: G6PD deficient and G6PD normal. In most instances, the female heterozygote still has normal enzyme activity, though the total G6PD activity of the heterozygous female can range from near normal to near deficient [61,62]. It has been postulated that in geographical areas where G6PD deficiency is prevalent, female newborns might be homozygous for the trait, thus presenting with clinical features typically seen in the hemizygous G6PD deficient male newborns [62]. A DNA analysis, which would have subserved the role of a tie-breaker, was beyond the scope of this study due to financial concerns.

Overall, enzyme levels in normal and deficient females were higher than the levels in normal and deficient males. The former finding is similar to what was reported by Obasa et al. [33]. This can possibly be explained by the fact that the gene for the G6PD enzyme is located on the Xchromosome and so, because the female has the luxury of being doubly endowed, she should demonstrate higher enzyme levels. However, because of the influence of Lyonization [56] enzyme levels in the female should not be overtly higher than in males. This will serve as grounds for further research in the nearest future.

Given that distribution of several diseases has been linked to certain blood groups, we tried to determine the association between G6PD deficiency and ABO and Rh (D) blood groups. In this study, majority of the patients were of the O blood group while those of the non- O blood group were less than 50%. Of the Rh(D) blood

type, over 95% of the subjects were Rh(D) positive while the Rh (D) negative blood type constituted the minority. The observed pattern is in tandem with the ABO and Rh (D) distribution and frequency in the general population in Nigeria [63]. Subjects with the non-O blood type were found to have a higher mean G6PD activity level than those with the O blood type, however this difference was not statistically significant (P = 0.96). Our finding is consistent with previous report by Ufelle et al [64]. The current investigation did not demonstrate any statistically significant association between the (ABO) blood group and G6PD deficiency. This observation is in agreement with that of Tarlov et al. [32] but conflicts with those of Adam et al [65], Saha et al [31] and Saha and Banerjee [66] who found evidence for ABO blood group association in a cohort of G6PD deficient Asian subjects. The only earlier references to the possible association of the Rh blood group system with G6PD deficiency are those of Tarvo et al. [32] and Saha and Wong [31]. In both cases a decrease in the frequency of gene E was observed in the enzyme deficient subjects compared with the normal subjects. In the present study, no association was established between the Rh (D) blood group and G6PD deficiency (P>0.05). The inconsistencies in the various studies conducted across the globe could largely be ascribed to environmental, genetic and ethnic differences in the study populations. However, further studies including a nationwide survey are needed to examine, the relationship between G6PD deficiency and ABO, Rh and other blood group systems.

5. CONCLUSION

In view of the high prevalence of G6PD deficiency in icteric neonates in our environment, we advocate that a policy for routine neonatal assessment of G6PD activity be instituted in all healthcare institutions to aid in the prompt diagnosis and care of babies with this condition. Family studies and prenatal diagnosis should be done to enhance identification of affected individuals so that management can be commenced early in those so identified. The principal limitation of this study is the small sample size of the patients. We hereby recommend that a large multicentre or community-based study be conducted to evaluate the influence of ABO, Rh and other blood group systems on the risk of occurrence of G6PD deficiency for the purpose of validating our findings.

CONSENT

As per international standard, parental written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Ethical approval was obtained from the Health Research Ethical Committee of the Hospital before the commencement of the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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