Original Article

Pre-Operative Screening for Biliary Atresia Using a Stool Color Card in Infants: In a Tertiary Care Hospital in Bangladesh

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Abstract

Aim of the study: To evaluate the accuracy of stool color card (SCC) for pre-operative diagnosis of biliary atresia in infants.

Materials and Methods: This cross-sectional descriptive study was conducted at the department of Pediatric Gastroenterology and Nutrition, BSMMU, Dhaka, Bangladesh. The stools of infants were compared with stool color card after collection for 3 consecutive days. Results were expressed as sensitivity, specificity, positive and negative predictive value. The study did not involve any social or legal risk to the subjects or any invasion of privacy.

Results: Forty neonatal cholestasis cases were studied. Among them, 33 babies (mean age, 75.7±34.5 days) were diagnosed as biliary atresia (BA) and 7 of them (mean age, 77.1±30.5 days) as non- biliary atresia (NBA) with male predominance 24 (60%). Ultrasonography of hepatobiliary system showed non-visualized gall bladder in 8 infants in BA group. Gallbladder contraction was absent in 32 (97%) cases of BA group (P =0.01). Hepatobiliary scintigraphy showed no excretion of radiotracer in 33 (100%) infants of BA group and 6 (85.7%) infants of non-BA group (P=0.17). The relation between the SCC diagnosis and the final diagnosis of BA significant relationship (
P <.05). The stool colour card showed sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of 90.9%, 77.1%, 90.9%, 77.1% and 85% respectively for the diagnosis of biliary atresia.

Conclusion: Stool color card was found highly sensitive with positive predictive value along with high diagnostic accuracy. So that stool color card can be a reliable screening tool of biliary atresia.

Keywords: Biliary Atresia, stool color card, infants

Introduction

Normal hepatobiliary function is adequate bile flow depended from the liver to the gallbladder through biliary channels, where bile is stored and concentrated and secreted to the duodenum when it is required for the digestive process. Interruption of this billiary secretion results in partial or complete cholestasis.[1,2]

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Cholestatic jaundice, characterized by elevation of serum direct bilirubin, is an uncommon but potentially serious condition that indicates hepatobiliary dysfunction[1]. It affects approximately 1 in every 2,500 infants.[2] Neonatal cholestasis is defined as direct hyperbilirubinemia occurring in the newborn as a consequence of diminished bile flow.[3] Direct hyperbilirubinemia in a neonate is defined as a serum direct bilirubin concentration of greater than 1 mg/dL if the total serum bilirubin (TSB) is <5 mg/dL or greater than 20% of TSB if the TSB is ≥ 5 mg/dL.[4]

The two most common causes of neonatal cholestasis

(NCS) are Biliary atresia (BA) and Idiopathic Neonatal Hepatitis (INH). It is important to differentiate between these two entities as early intervention in the form of Kasai portoenterostomy in BA improves the prognosis.[5] Biliary atresia is an idiopathic progressive inflammatory process of the extrahepatic bile ducts with obliteration and concomitant ongoing damage of the intrahepatic bile ducts resulting in chronic cholestasis, progressive fibrosis, and eventually biliary cirrhosis.[6] It occurs worldwide, affecting an estimated 1 in 8000-15000 live births.[7] A study was done in Bangladesh in 2005, showed that biliary atresia is a common cause of neonatal cholestasis in Bangladesh.[8] Although the pathogenesis of biliary atresia is still unclear, the disease is characterized by a complete inability to excrete bile as a result of sclerosing inflammation of the extra and possibly intra hepatic bile ducts.[9] Although cholestatic jaundice develops early, most of the cases patients present lately.[8] An easy method, which detects neonatal cholestasis in a simple way, particularly biliary atresia is to look at the baby's stool color. It is pale in cases of cholestasis, that is, grey, creamy or white and occasionally pigmented as a light caramel colour.[10] Thus, a screening programme with a stool color card, showing different normal and abnormal stool colors, to be compared with the baby's stool, was first introduced in Japan in 1987[11] and in 2002 in Taiwan[12]. This has led to a significant reduction in delay of biliary atresia diagnoses, and has allowed significantly earlier Kasai operations and thus reducing the need for hazardous liver transplantation at a young age.[13] Diagnostic tests (like- liver biopsy, MRCP) are costly, invasive and not available in all centers, especially in developing countries. No single test showed 100% sensitivity and specificity and it is well documented that the summation of different parameters will give more accuracy in diagnosis of BA.[14]

Different studies have shown the accuracy of stool color card. A recent study showed the sensitivity, specificity, positive predictive value, and negative predictive values of 76.5%, 99.9%, 12.7% and 99.9%, respectively.[15] In another study, the sensitivity and specificity of stool color card were found to be 80% and 99.9%, respectively, and the positive predictive value was 22.9%.[16] Regarding the reliability of stool color card showed the sensitivity, specificity, and positive predictive values of 89.7%, 99.9%, and 28.6% respectively, in their study.[17] Cholestasis may be present early, but it is rarely obvious to the clinician because it overlaps with the common physiologic jaundice seen in more than half of newborns during the first few weeks of life. In infants with BA, jaundice persists and the appearance of signs of cholestasis such as dark urine and pale stools follow. A provisional diagnosis is occasionally made before 4 weeks of life, but more typically not until 6 to 12 weeks and is based upon exclusion of other causes of neonatal cholestasis and typical liver biopsy findings. Major clinical challenges remaining are: (1) early diagnosis, so as to increase the percentage of successful HPEs, (2) prevention of the progressive liver injury and fibrosis that occur even after successful HPE.[18]

The aim of this study is to evaluate the accuracy of stool color card for diagnosis of biliary atresia by calculating its sensitivity, specificity, positive predictive value and negative predictive value

Methods

This cross sectional descriptive study was done from January 2020 to June2021 in the department of Pediatric Gastroenterology and Nutrition in Infants having clinically apparent jaundice developed before 3 months of age and persisted for more than 2 weeks and who fulfilled the following criteria of pale stool (either persistent or intermittent) with dark colored urine and direct bilirubin of ≥ 1 mg/dl, if total serum bilirubin is <5mg/dl (< 85 μmol/L) or direct bilirubin of >20 % of total serum bilirubin, if total serum bilirubin is ≥5mg/dl (≥85 μmol/L). Very sick infants (coagulopathy, encephalopathy, cardiopulmonary imbalance), infants suffering from severe co-morbid conditions (cirrhosis, sepsis, DIC) and parents not willing to be enrolled in this study were excluded from the study.

Procedure:

During recruitment, objectives of the study were explained to the parents and written consent was obtained. The detailed clinical history, physical examination findings and investigation reports were recorded in a predesigned standard data sheet. History was obtained from the parents, which included basic demography, perinatal histories, age at onset of jaundice, pattern of jaundice, colour of stool and urine, birth weight, parental consanguinity, maternal illness during pregnancy etc. Stool color was observed by the researcher himself to decide whether it was pigmented or pale stool. the infant stool was collected and compared with the infant stool colour card for 3 consecutive days and these SCC findings were compared between Biliary atresia and non-BA group

based on sensitivity, specificity, positive predictive value and negative predictive value. Stool color was defined as pale (completely and uniformly devoid of any green or yellow pigments), slightly pale (contained mixture of pale and normally pigmented stools, or uniform in color but not normally pigmented), or normally pigmented (uniformly and normally pigmented). Physical examinations of all cases were done by researcher himself on the day of admission or afterwards whenever possible. The following data were obtained during physical examination: growth parameters, presence of associated physical anomalies and any signs of systemic diseases. Other significant physical findings were also recorded. For all patients, serum bilirubin (total and direct) were done by photometric method, serum alanine aminotransferase by kinetic rate method, gamma glutamyl transpeptidase by enzymatic rate method, prothrombin time by viscosity clot detection method. For diagnosis of causes, the following investigations were done according to need: complete blood count by spectrophotometry, flow-cytometry and impedance methods, urine routine microscopic examination by fluorescence flow cytometry, thyroid function tests (FT4, TSH) and TORCH (IgM) antibodies by ELISA techniques. These investigations were done from Microbiology, Virology, Biochemistry and Molecular Biology, Hematology and Clinical Pathology departments of BSMMU. Ultrasonography of the hepatobiliary system, hepatobiliary scintigraphy and percutaneous liver biopsy were done in all cases. For ultrasonography of hepatobiliary system, the infants were kept on fasting state for 3-4 hours then abdominal sonography was done by the same radiologist using Philips, Affiniti 30 ultrasound system with either 2-5 MHz convex transducer or 7.5-12 MHz linear transducer at the department of Radiology and Imaging, BSMMU. The findings of triangular cord sign, gall bladder length, gall bladder volume were recorded. During the fasting state, infants were given intravenous fluid as required. Again, an hour after feeding, sonography was done to see the volume of contraction of gall bladder. Then triangular cord sign, gall bladder length and gall bladder contractility in ultrasonography findings were compared between biliary atresia and non-BA group. The sensitivity, specificity, positive predictive value and negative predictive value and diagnostic accuracy of the accuracy of stool colour card for diagnosis of biliary atresia were determined. Scintigraphy of hepatobiliary system was done after giving phenobarbitone (5 mg/Kg/day orally in two divided doses) for at least 3-5 days and was done in Institute of Nuclear Medicine and Allied Science, BSMMU. After ensuring normal coagulation parameters, platelet counts, and taking informed consent of parents, percutaneous liver biopsy was done using a Trucut liver biopsy needle by a trained, expert resident of the department and histopathology report was obtained from Pathology department, BSMMU. Liver biopsy was taken as gold standard for diagnosis of biliary atresia and idiopathic neonatal hepatitis. Results of investigations were collected and recorded in a structured questionnaire.

Statistical analysis:

After collection, data were manually checked and analyzed by using Statistical Package for Social Science (SPSS 22.0 Chicago, Illinois) for Windows XP. Fisher exact test and Chi-Square test were used for categorical data, while independent t-test and Mann-Whitney U test were used for comparison of continuous data. For all statistical tests, p value of less than 0.05 was considered as statistically significant. Results were expressed as sensitivity, specificity, positive predictive value, negative predictive value of stool colour card (SCC) which was used as a diagnostic marker for Biliary Atresia (BA).

Results:

Total 40 children fulfilled the study criteria were included in the study of which 24 (60%) babies were males and 16 (40%) females. Among them, 33 (83%) infants were diagnosed as BA and 7 (17%) as non-BA with a mean age of 75.7±34.5 days and 77.1±30.5 days respectively.

Figure-I shows among the studied subjects, 33 (83%) infants had persistent pale stool for consecutive 3 days whereas, 7 (17%) infants did not have persistent pale stool.

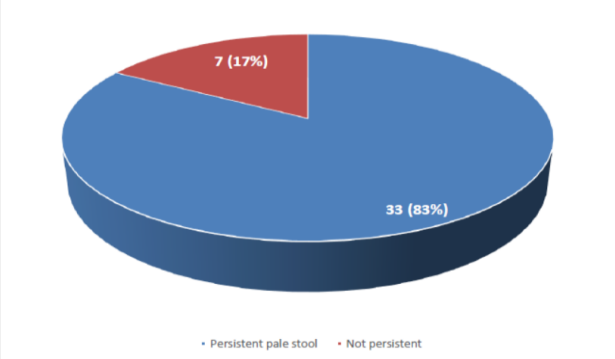

Figure-I: showing persistent pale stool (present or not) by stool colour card (N=40)

Table-I shows no excretion of radiotracer activity even after 24 hours in 33 (100%) infants in BA group, whereas it was 6 (86%) in non-BA group. The *P* value (p=0.17) is statistically not significant. Only 1 infant in non-BA group had excretion of radiotracer into the intestine.

Table I: Comparison of Scintigraphic findings of BA and non-BA group (N=40)

Radiotracer excretion into the intestine	Froup A (n=74)		Non-BA (n=7)		P –value
	N	%	N	%	
Presint	0	0	1	14	0.17[ns]
Absent	33	100	6	86	

Table II: Relation between SCC diagnosis and final diagnosis of biliary atresia by liver biopsy (N=40)

Occupation	Final diagnosis (Biopsy)		Toatal	P -value
	BA (n=33)	Non BA (n=7)		
BA	30 (90.9%)	3 (42.9%)	33 (82.5%)	0.01[ns]
Clinical diagnosis	(True positive)	(False positive)		
Non BA	3 (9.1%)	4 (57.1%)	7 (17.5%)	
(SCC)	(False positive)	(True positive)		
To	**33**	**7**	**40**	

Table-III shows the comparison of the SCC diagnosis with the final diagnosis by liver biopsy. The sensitivity and specificity of the SCC were 90.9% and 77.1% respectively. The positive predictive value was 90.9% and the negative predictive value was 77.1%. The overall accuracy of the SCC was 85%.

Table-III: Comparison of the SCC diagnosis with the final diagnosis by liver biopsy (N=40)

Statistic	Value
Sensitivity	90.9%
Specificity	77.1%
Positive Predictive Value	90.9%
Negative Predictive Value	77.1%
Accuracy	85%

Discussion:

The diagnosis of neonatal cholestasis in infants is still difficult as many differentials have to be excluded until a firm diagnosis is reached. The major diagnostic challenge is to distinguish biliary atresia from idiopathic neonatal hepatitis. Biliary atresia, common and correctable cause of cholestasis, should be diagnosed as early as possible, because early diagnosis of this condition positively affects the outcome. Among different diagnostic tools, biliary atresia can be diagnosed by ultrasonography and successfully treated by surgical correction. Cholestasis is defined as impairment in the excretion of bile, which can be caused by defects in intrahepatic-transmembrane transport of bile, or mechanical obstruction to bile flow. Elevated conjugated bilirubin is the predominant characteristic features in most of the causes of neonatal cholestasis.[19] In biliary atresia the body accumulates an excess of bilirubin, it turns yellow (jaundice), passage of conjugated bilirubin through urine causing dark urine, due to lack of bile pigment the stools are pale.[20] With the aim to evaluate the accuracy of infant stool colour card for diagnosis of biliary atresia by calculating its sensitivity, specificity, positive predictive value, negative predictive value, this cross-sectional study was carried out in 40 infants with neonatal cholestasis due to Biliary atresia and non-BA attending Pediatric Gastroenterology and Nutrition Department of BSMMU, Dhaka on 40 study cases aged 14-90 days). In this study, among total of 40 cholestatic cases, 24 were males and 16 females. Among the studied subjects, highest frequency (n=24) was seen in 31-60 days age group. Maximum patients 33 and 7 in BA and Non-BA group showed age at admission (days) 73 mean±SD 75.7±34.5 and 77.1±30.5 respectively. There was no significant difference of age between two groups (p>0.05). In accordance reported mean age at presentation was 48.25 days, majority of the subjects 52.6% were found in the age group of 42-56 days.[20] There were 55.3% male and 44.7% female babies and male to female ratio was 1.2:1. Other findings were similar with that of common epidemiological background of neonatal cholestasis. Previous report revealed that neonatal cholestasis had slightly more male predominance.[8] History of persistent pale stool was significantly higher in BA group than non-BA (97% vs 0.0%). History of intermittent pale stool significantly higher in non-BA than BA infants (100% vs 3.0%). p value was calculated by Fisher's exact test, which is statistically significant (p=0.00). In accordance analyzed the clinical course of 29 infants with BA detected by stool color card registry.[17] Twenty three (79.3%) infants and 26 (89.7%) infants were found to have pale-colored stool before 30 and 60 days of age, respectively. Hsiao et al. (2008) reported among 148 infants in 2004 and 131 infants in 2005 as having pale-colored stool (colors 1-3) before 60 days of age. Among them, 29 (19.6%) in 2004 and 34 (26.0%) in 2005 were diagnosed as having BA. Previous studies showed that the detection of cholestasis rests on the clinical recognition of jaundice, pale stool, and/or dark urine

with a palpable liver in most of the cases.[12,21] Our present study showed that persistent pale stool in BA patients was present in 97%. Sarker et al. (2021) reported 78.5% subjects had pale colored stool, three (7.9%) had yellow colored and five (13.6%) had greenish colored stool. 74 In the present study ultrasonography of HBS in the studied infants showed absent or non-visualized gall bladder in 8 (20%) cases. Triangular cord sign was seen in 4 (12%) babies of BA group and absent in non-BA group (p=1.00). The p value (p=0.00) of gall bladder contraction in both the groups is significant. Kanegawa et al.[22] described that in neonatal cholestasis, "triangular cord" sign was one of the important signs of cholestasis. Lee et al.[23] found that there were nonvisualization of gall bladder or bile duct in infants subjects with neonatal cholestasis. Similar comparable results was shown[20] where it was seen that the common sonographic findings of the studied subjects were non visualization of gall bladder 60.5%, non visualization of common bile duct 50%, hepatomegaly 92%, and triangular cord sign at portahepatis 7.9%. In the present study final diagnosis seen by using the SCC was positive for BA in 30 (90.9%) cases and negative for BA in 3(9.1%) cases. The relation between the results of the SCC diagnosis and the final diagnosis of the study group had a p value 0.01, which was statistically significant. The SCC positively predicted BA in 30 cases out of 33 cases of proven BA (90.9%); also, the SCC excluded BA in 4 out of 7 cases who were proved not to have BA (57.1%). In accordance with this study[20] reported that out of 38 subjects 30 had pale-colored stool and 8 subjects had normal colored stool. Among the pale-colored stool 29 subjects were diagnosed as biliary atresia and 1 other than biliary atresia. Among the normal colored stool 3 were diagnosed as biliary atresia. Brown and Househam[24] also found similar findings in their study. 75 Presence of bile pigment in biliary atresia may be explained by the fact that in early stages of biliary atresia child may pass intermittent pale colored and normal colored stool. If bilirubin level is high it may ooze from gut wall and can pigment the stool. In female child pale stool sometimes mixed with dark urine and may give false impression of pigmented stool.[25] El-Shabrawai et al. demonstrated that the diagnosis using the SCC was positive for BA in 49 (45.4%) cases and negative for BA in 59 (54.6%) cases. On comparison of the SCC diagnosis with the final diagnosis, the SCC positively predicted BA in 43 cases out of 46 cases of proven BA (93.48%); also, the SCC excluded BA in 56 of out of 62 cases who were proven not to have BA (90.32%). The present study showed that the sensitivity and specificity of the SCC were 90.9% and 77.1% respectively. The PPV was 90.9% and the NPV was 77.1%. The overall accuracy of the SCC was 85%. Sarker et al.[20] reported sensitivity of stool color in the diagnosis of biliary atresia was 90.6%, specificity 83.3%, accuracy 89.5%, positive predictive value 96.7% and negative predictive value 62.5%. Rouzrokh et al.[26] observed that detection of neonatal cholestasis by examining the color of the stool had a sensitivity and specificity of 100% and 83% respectively with positive predictive value and negative predictive value of 81% and 100% respectively. Chen et al.[17] analyzed the reliability of stool color card and showed the sensitivity, the specificity, and positive predictive values of 89.7%, 99.9%, and 28.6%, respectively. El-Shabrawai et al. reported, the SCC had true results in 91.67% of cases and false results in 8.33% of cases. The sensitivity and specificity of the SCC were 93.48% and 90.32%, 76 respectively. The PPV was 87.76% and the NPV was 94.92%. The overall accuracy of the SCC was 91.67%. Thus, among all the diagnostic tools available for biliary atresia, stool colour card can play an important role in the diagnosis of biliary atresia, when stool samples are preserved and compared with SCC for 3 consecutive days. So from the findings of the study, it can be concluded that stool colour card can play an important role in the diagnosis of biliary atresia and is a reliable indicator for screening neonatal cholestasis namely biliary atresia.

Conclusion:

Stool color card is found to have high sensitivity and positive predictive value along with high diagnostic accuracy. Therefore, it can be concluded that stool color card can be a reliable screening tool for diagnosis of biliary atresia.

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