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APPLICABILITY OF THE INTEGRATED NEONATAL CHOLESTASIS CARD AT A TERTIARY CARE CENTRE FROM INDIA

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ABSTRACT **Objectives:** Delay in detection of Neonatal Cholestasis (NC) results in late referral of treatable causes of NC hampering the timely intervention. To overcome this by early detection of NC, an integrated NC card incorporating urine color was developed in India recently. This study was aimed to assess the applicability of integrated NC card. **Methods:** An analytical cross-sectional study was carried out at a tertiary care institute over a period of 18 months. Study participants were divided into 3 groups. Group A: infants with cholestasis, Group B: infants with unconjugated hyperbilirubinemia and Group C: healthy infants visiting the immunization clinic. Real-time stool and urine color of all study participants were assessed using integrated NC card by care-takers (mother) and the study investigator separately and documented for comparative analysis. **Results:** A total of 130 subjects (Group A: 30; Group B: 50; Group C: 50). were enrolled in study. The median age of children with in group A was 45 (28-125 days), Group B was 6 (2-50) days and Group C was 85 (40-185) days. Measure of agreement between investigator and care-takers: For dark yellow urine in group A: 93%, kappa=0.634; for normal urine in group B and C: 96%, Kappa= 0.648 and 98%, kappa=0.847 respectively. For pale stool in group A: 85%, kappa=0.550; for normal stool in group B and C: 93%, kappa= 0.623 and 96%, kappa=0.730 respectively. **Conclusion:** The integrated NC card was found useful in detection of NC based on urine color and differentiate it from unconjugated hyperbilirubinemia.

KEYWORDS : Hyperbilirubinemia, Newborn, Urine color, Infants, Cholestasis, Stool card

INTRODUCTION

Cholestatic jaundice in early infancy, better referred as Neonatal Cholestasis (NC) is characterized by the presence of dark yellow urine. Misdiagnosis of NC as physiologic jaundice which is characterized by unconjugated hyperbilirubinemia delays its identification and timely management. NC comprises of 19-33% of hepatobiliary disorders in children from India [1]. Biliary atresia is the most common cause of NC during the first three months of life and accounts for 40-50% of all liver transplants in the world [2,3]. Apart from this, other potentially treatable causes like neonatal infections, metabolic liver diseases (galactosemia, tyrosinemia) and genetic disorders (progressive familial intrahepatic cholestasis) constitute 45-69% of NC [1,4,5].

Over the years, late identification and referral of children with NC remains a problem worldwide delaying the treatment, thus adversely affecting the outcome. In low socioeconomic countries like India, the delay exists both at the community level as well as at primary care levels of health. Few years ago, Taiwan had developed an infant stool color card for use at their community level primarily for the early diagnosis of BA [6,7]. This card has six stool colors; of these, numbers 1–3 are abnormal pale stool and numbers 4–6 are suggestive of normal stool color.

However, a child with NC and pigmented stool based on Taiwan stool color card could be disregarded as normal child because icterus is difficult to appreciate in newborns. However, presence of dark yellow urine color staining the diapers is a reliable indicator of an underlying hepatobiliary disease. Utilizing this clinical indicator, Yachha et al from India developed an Integrated Neonatal Cholestasis card (NC Card) which included urine color along with stool colors [8]. This card has 2 urine colors:1- normal, 2- dark yellow; 7 stool colors: 1 to 4- abnormal pale and 5 to 7 as normal pigmented stool. This formed the derivation cohort for the integrated NC card. We aimed to study the applicability of this integrated NC card in a validation cohort at a tertiary care Centre from India.

METHODS

We conducted a prospective analytical cross-sectional study in the Department of Pediatrics at a tertiary care teaching hospital from India. Consecutive children up to 6 months of age who either presented with jaundice or developed icterus during hospitalization (especially neonates) were enrolled and classified into following groups: Group A: Infants with cholestasis characterized by conjugated hyperbilirubinemia (direct serum bilirubin of more than 20% of total serum bilirubin), Group B: Infants with unconjugated hyperbilirubinemia (direct serum bilirubin of less than 20% of total serum bilirubin). Normal healthy infants less than 6 months visiting for routine immunization to our hospital were also enrolled as a control group and classified as group C.

The clinical details like history and examination findings of study subjects in group A and group B were recorded in the study proforma. Salient laboratory investigations including blood or imaging or any other special tests were also recorded. The final clinical diagnosis along with the outcome at hospital discharge was noted. Demographic parameters of subjects in group C were recorded.

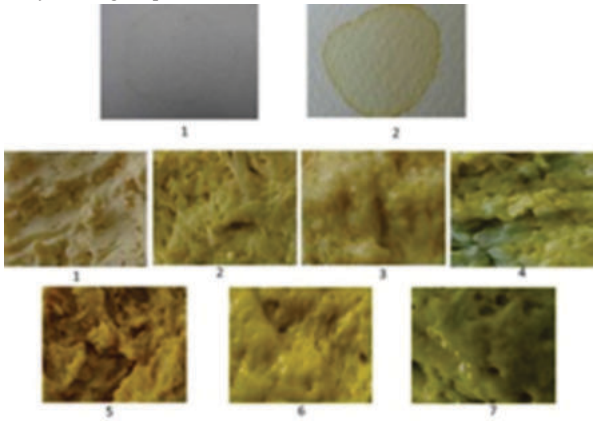

Figure 1: Integrated Neonatal cholestasis card. [urine color:1-

Normal; 2-dark yellow, stool color:1 to 4 -pale; 5 to7-pigmented]

Assessment of stool and urine color based on Integrated NC card.

A copy of integrated NC card was obtained for evaluation (figure 1). The study investigator (trained doctor) looked at the real time urine and stool color of the patients within 24 hours of getting admitted to the hospital or detection of icterus in an already admitted child.

At the time of this evaluation, the study investigator was not aware whether the study subject had conjugated or unconjugated hyperbilirubinemia. The urine and stool color were marked as per the integrated NC card (1 or 2 for urine and 1 through 7 for stool). At the same time, the care-taker (mother) of the study subjects was also asked to identify the urine and stool color based on NC card and the response was recorded and analysed to assess the agreement between them (study investigator and care-taker). The subjects in group C were enrolled from immunization clinic observation area following the vaccination. The urine and stool color evaluation was done by study investigator and care-taker in similar fashion, in those who passes urine and stool while in hospital. The target number of subjects to be enrolled in group C was to match the number of study subjects with hyperbilirubinemia.

The study was conducted after obtaining approval from the Institutional Ethics Committee (SAIMS/RC/IEC/2021/212) dated 02/06/2021. A written informed consent from the patient's parents or guardian was obtained.

Statistical Analysis:

Data was presented as median with range and proportions. The measurement of agreement between study investigator and care-taker was performed using Kappa statistics. A p-value of < 0.05 was considered significant. Statistical software SPSS version 20.0 was used for statistical analysis.

RESULTS

A total of 130 subjects (70 male, 60 female) were enrolled in study which comprised of 30 children in Group A, 50 in group B and 50 in group C. The median age of children with in group A was 45 (28-125 days), Group B was 6 (2-50) days and Group C was 85 (40-180) days. 110 out of 130 subjects belonged to lower socio-economic status. In group A, the causes of neonatal cholestasis included biliary atresia in 9/30 (30%), pre-term multifactorial in 8/30 (27%), idiopathic neonatal hepatitis 6/30 (20%), metabolic causes in 4/30 (13%), term sepsis in 3/30 (10%).

A. **Measurement of agreement between study investigator and care-takers in group A:** The details of stool and urine color identified by study investigator and caretaker are shown in table 1. Of the 28 dark yellow urine identified by study investigator, caretakers identified dark urine in 26 (93%) subjects with a Kappa value 0.634 ($P<0.05$) showing good agreement between them. For stool color, 20 were labelled as pale by study investigator of which 17 (85%) were also detected as pale by care-takers showing a moderate agreement between them with kappa value of 0.550 ($p<0.05$).

B. **Measurement of agreement between study investigator and care taker in group B:** The details of stool and urine color identified by study investigator and caretaker in group B are shown in table 2. Of 48 normal color urine identified by investigator, care-takers identified the normal color in 46 (96%) with a Kappa value 0.648 showing good measure of agreement ($P<0.05$). Similarly, 42 of 45 (93%) normal stool color was identified by caretakers with a Kappa value 0.623 confirming good agreement for stool color detection between them.

C. **Measurement of agreement between study investigator and care taker in group C**: The details of stool and urine color identified by study investigator and caretaker in group C are shown in table 3. Normal color urine was labelled in 47 subjects by study investigator and in 46 subjects by caretakers with strong agreement between them (Kappa value of 0.847, $P<0.05$). Similarly in case of stool color detection, a very good agreement was seen between the investigator and caretakers (Kappa value 0.730, $P<0.05$) as the agreement proportions were 96% and 100% for pigmented and pale color stools respectively (table 3).

Table 1: Identification of urine and stool color by study investigator and care-takers in Group A

Urine color	Observations		
Study investigator / Care taker	Normal	Dark Yellow	Total
Normal	2	2	4
Dark yellow	0	26	26
Total	2	28	30
Stool Color			
Study investigator / Care taker	Pale	Pigmented	
Pale	17	3	20
Pigmented	3	7	10
Total	20	10	30

Table 2: Identification of urine and stool color by study investigator and care-takers in Group B

Urine color	Observations		
Study investigator / Care taker	Normal	Dark Yellow	Total
Normal	46	0	46
Dark yellow	2	2	4
Total	48	2	50
Stool Color			
Study investigator / Care taker	Pale	Pigmented	
Pale	4	3	7
Pigmented	1	42	43
Total	5	45	50

Table 3: Identification of urine and stool color by study investigator and care-takers in Group C

Urine color	Observations		
Study investigator / Care taker	Normal	Dark Yellow	Total
Normal	46	0	46
Dark yellow	1	3	4
Total	47	3	50
Stool Color			
Study investigator / Care taker	Pale	Pigmented	
Pale	3	2	5
Pigmented	0	45	45
Total	3	47	50

DISCUSSION:

The stool color card developed in Taiwan is an established method for early detection and referral of children with BA [6]. It was found that the hospitalization and mortality rates of BA cases were significantly reduced after the launch of the stool color card in Taiwan [9]. However, presence of pigmented stool can be disregarded as normal and newborns with NC and pigmented stool could be missed. In recent study from India, Authors demonstrated that parents were able to differentiate dark yellow urine from normal color with an extremely high accuracy [8]. Based on this, they developed integrated NC card by adding urine color to the stool color card [8]. In our study, we assessed the measure of agreement for different colors of stool and urine using integrated NC card between study investigator who was a trained doctor and care-taker (mother) who represents general public, thus

establishing the validity of integrated NC card. This was important to get an insight about the wide applicability of recently developed integrated NC card in India [8].

Among children with NC, we found a substantially good agreement between doctor and parents for the identification of dark yellow urine. Since, a dark yellow urine is a sure indicator of conjugated hyperbilirubinemia, utilizing the integrated NC card at primary care level for early detection and referral of NC appears a useful tool. The agreement for stool color between the doctor and parents was moderate implying that a small but significant proportion of parents may not identify the pale stool correctly.

The Need for early detection and referral of BA is known for years. In India, the median delay observed in BA is 4 ± 2 months and in neonatal hepatitis is 2.2±1.3 months [10]. Consensus report of the year 2000 showed an average delay of NC cases referral by 4.5 weeks [4]. Other life-threatening causes of NC leading to neonatal liver failures also requires timely recognition and referral for treatment. Neonatal herpes simplex virus infection is associated with high mortality if anti-viral therapy is delayed as compared its early institution [11]. Similarly, liver failure due to galactosemia or tyrosinemia can be reversed if the diagnosis and treatment is initiated timely. Likewise, studies on neonatal hemochromatosis have shown that delay in diagnosis and treatment is associated with increased mortality [12,13]. Thus, this integrated NC card will help in early referral of non-biliary atresia causes of NC also.

Unconjugated hyperbilirubinemia in newborn is a common occurrence seen in 60-80% of term and pre-term babies. The best way to differentiate between unconjugated and conjugated hyperbilirubinemia is urine color. In our study, there was a good agreement between doctors and parents in identifying normal color urine in infants with unconjugated hyperbilirubinemia. This further substantiate the usefulness of integrated NC card in distinguishing unconjugated from conjugated hyperbilirubinemia. However, in 2 subjects, study investigator labelled urine as dark yellow against the expected normal. This could have been due to either presence of some dehydration at the time of evaluation or some concurrent medicine altering the urine color transiently.

We also included normal infants in our study as a control to study the measure of agreement for urine and stool color between doctor and parent. Here again, urine color of 3 subjects was labelled as dark yellow by study investigator and the reason could be due to some ongoing medication which was not recorded in our study protocol. However, the results showed a very good agreement for both urine and stool color between the two. Thus, we can confidently say that the results of our study can be extrapolated to the community level use of the card.

Our study strengths include its prospective nature and real time evaluation of urine and stool color by a single study investigator. However, there were certain limitations as well in our study. Firstly, the number of study subjects in NC group were less given the rarity of the clinical condition we included and short time frame of the study. Secondly, we evaluated only single urine and stool color. Dehydration and certain medications can give rise to dark yellow urine transiently. Thus, evaluation of multiple urine samples and if found persistently dark yellow would be a more reliable marker of cholestasis. Similarly, it is recommended to evaluation of three or more stool sample to assess pale or pigmented stool in a more accurate way. Thirdly, majority of patients in our study were from low socio-economic status. A homogenous representation of patients from a varied class of socio-economic status would give a more practical insight in the applicability of integrated NC card.

In conclusion, the integrated NC card showed a good agreement for early detection of NC and distinguishes it from unconjugated hyperbilirubinemia, thus establishing the validity of this card. There is need to implement this at community and primary care level for early detection of NC and timely management.

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