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SERUM BILIRUBIN LEVELS AS A DIAGNOSTIC INDICATOR FOR VARIOUS AILMENTS IN PATIENTS WITH HYPERBILIRUBINEMIA

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Abstract

This study examines the prevalence and clinical significance of hyperbilirubinemia across various diseases, including jaundice, hepatitis, malaria, anemia, and other conditions. A total of 171 patients from District Headquarters (DHQ) Hospital Timargara and private clinical laboratories were analyzed for bilirubin levels. The patients were grouped as follows: 77 with newborn jaundice, 19 with hepatitis B, 17 with hepatitis C, 17 with malaria, 9 with anemia, and 26 with miscellaneous diseases.

The results showed that 96.15% of newborn jaundice cases had elevated bilirubin levels ranging from 6 to 18 mg/dL, which normalized within 1 to 4 weeks. Among hepatitis B and C patients, elevated bilirubin levels were observed in 80% and 73.7% of cases, respectively, with the highest bilirubin level recorded at 6.8 mg/dL in hepatitis B patients. All patients with malaria and anemia presented with hyperbilirubinemia, though specific levels varied. In the miscellaneous diseases group, 30% exhibited elevated bilirubin. Interestingly, a subgroup of 4 patients showed asymptomatic hyperbilirubinemia, characterized by elevated bilirubin without clinical symptoms.

Statistical analysis revealed no significant correlation between bilirubin levels and other liver function tests (ALT, ALP), indicating that hyperbilirubinemia in conditions such as malaria and anemia may not always follow typical liver enzyme patterns. These findings highlight the importance of a comprehensive diagnostic approach, incorporating additional tests like liver imaging and genetic screening, to improve diagnostic accuracy and deepen understanding of the underlying causes of hyperbilirubinemia.

Keywords: *Anemia, Bilirubin, Hyperbilirubinemia, Jaundice, Malaria*

INTRODUCTION

Bilirubin is a yellow pigment produced as a byproduct during the breakdown of heme, a component of hemoglobin in red blood cells. The degradation of heme begins with its conversion to biliverdin by heme oxygenase, followed by the reduction of biliverdin to unconjugated bilirubin by biliverdin reductase. This unconjugated bilirubin, being lipophilic, cannot be directly excreted by the kidneys. Instead, it binds to serum albumin and is transported to the liver, where it undergoes conjugation with glucuronic acid by the enzyme UDP-glucuronosyltransferase (UGT1A1) in hepatocytes, forming conjugated (direct) bilirubin. Conjugated bilirubin is water-soluble, enabling its excretion into the bile and eventually the intestines. In the intestines, bilirubin is partly converted into urobilinogen, which is either excreted in the feces as stercobilin or reabsorbed into the bloodstream and excreted in the urine as urobilin (1).

Normal serum bilirubin levels range between 0.2 and 1 mg/dL, with most bilirubin existing in the unconjugated (indirect) form. Elevated bilirubin levels (hyperbilirubinemia) can result from various causes, including liver dysfunction, hemolysis, and bile duct obstruction. Disruptions in normal bilirubin

metabolism lead to the accumulation of either unconjugated or conjugated bilirubin, often presenting clinically as jaundice, characterized by yellow discoloration of the skin and sclerae. Hyperbilirubinemia has significant diagnostic value, as fluctuations in bilirubin levels can indicate underlying pathologies involving the liver, red blood cells, or bile ducts (2).

Hyperbilirubinemia is linked to numerous clinical conditions, such as liver diseases (e.g., hepatitis, cirrhosis), hemolytic disorders (e.g., anemia), and biliary tract diseases (e.g., cholestasis). In neonates, jaundice is commonly caused by the immaturity of the liver's conjugation capacity. Although bilirubin measurements are critical for diagnosing hyperbilirubinemia, they do not pinpoint its exact cause. Therefore, a comprehensive diagnostic approach that includes liver function tests (e.g., ALT, AST, ALP), imaging techniques (e.g., ultrasound, CT), and additional biochemical markers is vital to determine the underlying condition (3).

Recent studies have investigated various aspects of bilirubin metabolism, such as the genetic regulation of bilirubin conjugation, and its association with disorders like Gilbert's syndrome and Crigler-Najjar syndrome, which are characterized by persistent unconjugated hyperbilirubinemia (4). The interplay between bilirubin metabolism and its levels in diverse disease states remains a crucial area of research, aimed at enhancing diagnostic precision and treatment outcomes.

Although extensive research has been conducted on the clinical significance of bilirubin, limited studies have analyzed its correlation with multiple diseases in a single cohort. Most existing studies have focused on specific conditions, such as neonatal jaundice or liver diseases like hepatitis and cirrhosis. Few investigations, particularly within local populations, have explored how bilirubin metabolism varies across a spectrum of diseases and demographic groups. This gap limits the understanding of bilirubin's diagnostic utility in multifaceted clinical contexts.

To address this gap, the present study evaluates the prevalence and diagnostic significance of hyperbilirubinemia across a range of diseases, including jaundice, hepatitis, malaria, anemia, and other miscellaneous conditions. By assessing the relationships between bilirubin levels and these diseases, this study aims to enhance diagnostic protocols for hyperbilirubinemia. Furthermore, it seeks to highlight bilirubin's role as a diagnostic marker, identify variations in its metabolism across diseases, and propose supplementary diagnostic tests to improve accuracy.

MATERIALS AND METHODS

STUDY DESIGN AND ETHICAL CONSIDERATIONS

This study was designed as a cross-sectional analysis of patients who presented to District Headquarters (DHQ) Hospital Timargara and nearby private clinical laboratories with signs or symptoms suggestive of hyperbilirubinemia, including jaundice, malaria, anemia, or liver disease. The study protocol was approved by the Graduate Research Committee (GRC) of Shaheed Benazir Bhutto University, Sheringal, Upper Dir, and ethical clearance was granted by the institutional ethics review board at DHQ Hospital Timargara.

Informed consent was obtained from all patients (or their guardians, in the case of minors), ensuring that they understood the nature of the study, the procedures involved, and the potential risks. All patient data were anonymized to maintain confidentiality, and the study was conducted according to ethical guidelines on human research.

INCLUSION AND EXCLUSION CRITERIA

Patients presenting with symptoms of jaundice, anemia, malaria, or other liver-related diseases, patients underwent bilirubin testing as part of their diagnostic workup, and patients of any age, including neonates, infants, and adults, were included in this study

Patients who did not provide informed consent, patients with a known history of chronic liver disease (e.g., cirrhosis, liver transplantation) or any condition that could affect bilirubin metabolism, such as drug-induced liver injury, and patients who were receiving medications known to alter bilirubin metabolism (e.g., rifampin, acetaminophen), were excluded from the study

These criteria ensured that the data collected accurately reflected the bilirubin metabolism in diseases related to hyperbilirubinemia and excluded any confounding factors that could skew the results.

SAMPLE COLLECTION AND LABORATORY TESTING

Blood samples were collected from all participants after obtaining informed consent. The standard procedures were used for sample collection. 5 ml venous blood sample was drawn from each patient. The samples were collected in two types of tubes: one for liver function tests (LFTs) and bilirubin testing (serum separation tubes) and another for complete blood count (CBC) testing (EDTA tubes).

BILIRUBIN TESTING

Total, direct, and indirect bilirubin levels were measured using the Jendrassik-Grof method, which is a colorimetric assay. This method involves reacting bilirubin with diazotized sulfanilic acid, producing a colored complex that can be quantitatively measured using a photometric system (Micro Lab 300). The bilirubin concentration was calculated using the Beer-Lambert law, which relates absorbance to concentration based on the sample's optical density at a specific wavelength according to the National Committee for Clinical Laboratory Standards, 2020 (6).

OTHER TESTS

Serum levels of alanine aminotransferase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST) were measured to assess liver function and to evaluate the degree of liver damage or inflammation. These enzymes are commonly elevated in conditions affecting the liver, such as hepatitis or cirrhosis. A full blood count was performed to evaluate hemoglobin levels, red blood cell count, and other parameters that can provide insight into anemia or hemolytic processes. Rapid diagnostic tests for hepatitis B (HBsAg) and hepatitis C (Anti-HCV antibodies) were performed to diagnose potential infections with these viruses. Malaria was diagnosed using either rapid diagnostic tests (RDTs) for Plasmodium antigens or peripheral blood smears for identifying malaria parasites.

STATISTICAL ANALYSIS

The collected data were analyzed using descriptive statistics to determine the prevalence of hyperbilirubinemia across different diseases. This allowed for the categorization of bilirubin levels and the assessment of any patterns or trends across various disease states.

To evaluate whether bilirubin levels correlated with other clinical parameters (ALT, ALP, CBC), Pearson's correlation coefficient was calculated. This statistical test is used to measure the strength and direction of the linear relationship between two continuous variables. A p-value < 0.05 was considered statistically significant.

The data were entered into a statistical software program (e.g., SPSS or R) for analysis. Descriptive statistics, such as means, medians, standard deviations, and percentages, were used to summarize the demographic and clinical characteristics of the study population.

RESULTS

The patients studied in this research work were divided into different age groups with an age gap of 10 years. However, newborn babies were placed in a separate group (Fig. 4.2). Our results revealed that nonsymptomatic hyperbilirubinemia was most common (77 babies) in newborns. The patients included 5 children of age group 1 to 10 years. The patients whose age was between 11 and 20 years were 27. There were 27 patients aged between 21 and 30 years. Twenty-three patients were aged between 31 to 40 years. Patients in the age group of 41 to 50 years were 9. One patient was aged 55 years and was placed in the age group of 51-60 years. One patient was 63 years old, and one patient was 72 years old (Fig. 1).

The patients tested for hyperbilirubinemia in this study were diagnosed with various diseases including 17 patients of malaria. Among those patients, 3 were infected with Plasmodium falciparum, and 14 patients contained Plasmodium vivax suggesting that Plasmodium vivax is the most prevalent malaria parasite in malarial patients (Fig. 2).

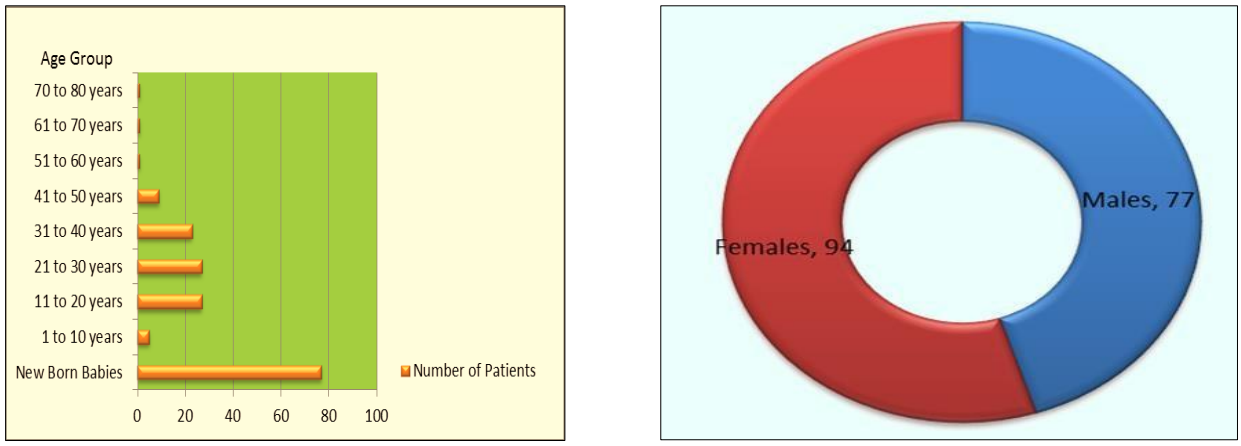

Fig. 1. Age and gender wise distribution of the patients

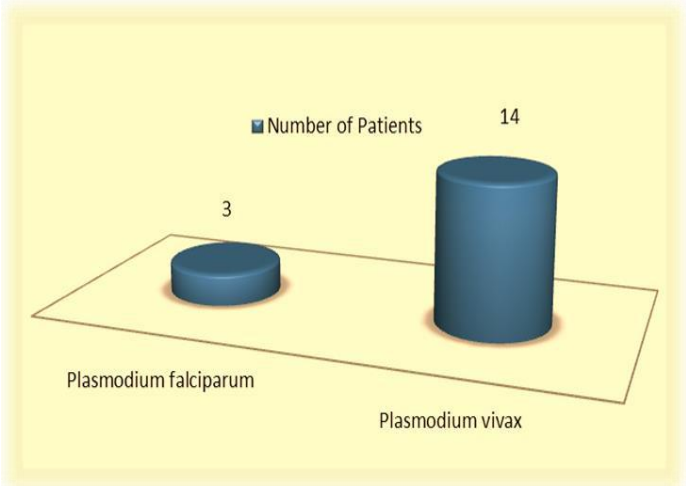

Fig. 2. Patients with malarial Types

HbsAg test revealed that six patients had Hepatitis B virus (HBV). Those patients included 4 male and 2 female patients aged 19-40 years. AntiHcv tests showed that 19 patients were positive for hepatitis C virus (HCV) which included 10 male individuals and 9 female individuals. The youngest patient with HCV was aged 12 years and the oldest patient in this category was 72 years (Table I).

Table I. Details of HCV patients

S. No.	Age	Gender	Disease
1	42 Years	Female	HCV
2	31 Years	Male	HCV
3	72 Years	Male	HCV
4	23 Years	Male	HCV
5	37 Years	Female	HCV
6	43 Years	Male	HCV
7	34 Years	Female	HCV
8	18 Years	Male	HCV
9	39 Years	Female	HCV
10	14 Years	Female	HCV
11	12 Years	Female	HCV
12	14 Years	Male	HCV
13	22 Years	Female	HCV
14	16 years	Female	HCV
15	31 Years	Female	HCV
16	27 Years	Male	HCV
17	28 Years	Male	HCV
18	38 Years	Male	HCV
19	32 Years	Male	HCV

*HGB (Haemoglobin), WBC (White Blood Cells), RBC (Red Blood Cells), PLT (Platelets Count), HCT (hematocrit), MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration), RDW (Red blood cell distribution width) Neu (Neutrophils), Ly (Lymphocytes), Mo (Monocytes), Eos(Eosinophils), Baso (Basophils)

Hyperbilirubinemia was observed in 9 females whose pregnancy tests were positive. Those females were 19 years to 41 years old. Three patients were anemic having low hemoglobin (8.1-9.1g/dL) and low RBC level (1.76-5.12x10^6 cells/µL). The patients included two teenage females and a 40-year-old man. Five patients including a 28-year-old male individual and four female individuals who were diagnosed with diabetes also showed a mild decrease in hemoglobin and hyperbilirubinemia. Jaundice with low hemoglobin levels and high levels of serum bilirubin were observed in 26 individuals.

Five individuals with different types of diseases (chest infection, high fever with headache, leukemia, and GIT problems) had hyperbilirubinemia. High levels of serum bilirubin were observed in four individuals who had normal ALT values, normal Hb levels, and normal red blood cell count. The overall details of patients present in each disease group are depicted in Fig. 3.

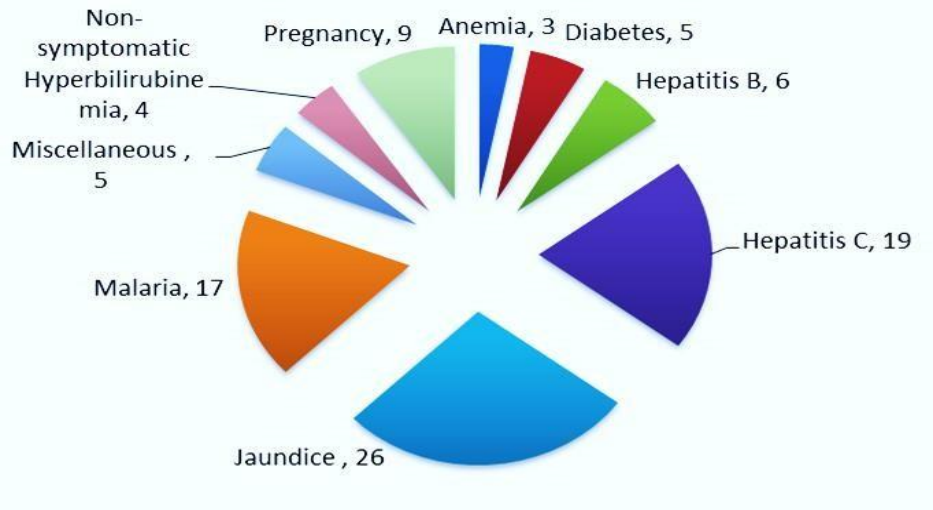

Fig. 3. Organization of patients in various disease groups

RELATIONSHIP OF SERUM BILIRUBIN WITH OTHER PARAMETERS

Hyperbilirubinemia in a total of 71 patients including 5 patients of hepatitis B, 14 patients of hepatitis C, 6 cases of pregnancy, 17 patients of malaria, 3 cases of anemia, 25 patients of jaundice, and one case of leukemia. On the other hand, 1 patient with HBV, 5 patients with HCV, 3 cases of pregnancy, and one patient with jaundice had serum bilirubin level lying in the normal range.

The results revealed that 80% of HBV patients, 73.7% of HCV, 96.15% patients of jaundice, 100% patients of malarial, anemia and leukemic patients had hyperbilirubinemia. Increased bilirubin level was noticed in 66.7% cases of pregnancy while hyperbilirubinemia was not observed in the patients with diabetes, chest infection and headache (Fig. 4).

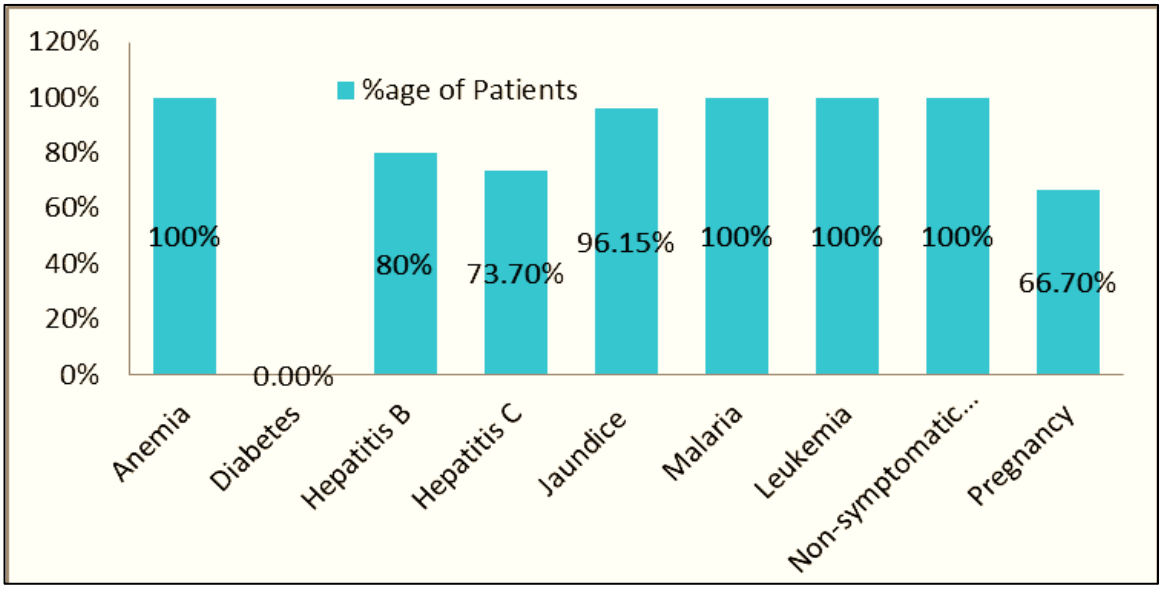

Fig. 4. Percentage of patients with hyperbilirubinemia in various diseases

CORRELATION BETWEEN BILIRUBIN AND BLOOD HEMOGLOBIN LEVEL

Out of 71 patients with hyperbilirubinemia, 52 patients had low blood hemoglobin levels. Among those patients 6 were diagnosed with HBV, 14 cases of HCV and 10 patients of malaria, 2 cases of pregnancy, 3 cases of anemia and 17 cases of jaundice revealed low hemoglobin with hyperbilirubinemia. The lowest Hb level (7.9 g/dL) was detected for a patient of anemia having serum bilirubin 5.1 mg/dL. In contrast, a patient with HBV showed the highest bilirubin level (6.8 mg/dL) whose Hb was 10.1 g/dL. Hence no direct relationship between high bilirubin and low Hb level was spotted.

RELATIONSHIP BETWEEN BILIRUBIN AND ALT

The highest value of hyperbilirubinemia (6.8 mg/dL) was observed for a patient with HBV. The patient had an Hb value of 10.1 g/dL and serum ALT level was 876 U/L. The highest value of ALT (2015 U/L) was observed for a jaundice patient having normal Hb (13.8 g/L) and a serum bilirubin level of 5.9 mg/dL. The results suggest that there is no direct relationship between blood bilirubin level and serum ALT level.

RELATIONSHIP BETWEEN BILIRUBIN AND ALP

Highest ALP value 915 U/L was detected for a patient with non-symptomatic hyperbilirubinemia having a bilirubin level of 4.3 mg/L and Hb 11.1 mg/L. However, the patient with the highest bilirubin had a normal (123 U/L) level of
ALT.

RELATIONSHIP BETWEEN BILIRUBIN AND RBC

On average, the normal value of RBC is 4.2-6.5 million cells/μL. In this study, the lowest value of 2.03 million cells/μL was observed for a jaundice patient having a bilirubin level of 3.1. The RBC value for the patient with the highest bilirubin level was normal (4.98).

RANGE OF HYPERBILIRUBINEMIA IN DIFFERENT DISEASES

The results of this study revealed that Bilirubin level increases in different diseases due to various reasons. Elevation in blood bilirubin level is not directly dependent on low hemoglobin level, high SGPT/ALT level, or increased hemolysis. Moreover, elevated bilirubin levels were observed in 19 out of 71 patients who had normal values of CBC and enzymes tested during liver function tests.

DISCUSSION

Bilirubin is the catabolic end product of heme-containing proteins such as hemoglobin, myoglobin, and cytochromes (7). Bilirubin binds with albumin for its circulation in the blood which is transported to the liver. The hepatocytes in the liver take up bilirubin from the blood where it gets conjugated with glucuronic acid by the action of an enzyme UDPglucuronyltransferase (8, 9). Conjugated bilirubin is water soluble and is secreted into bile. This process is highly regulated and keeps the serum bilirubin concentrations below 1.00 mg/dL in normal conditions (10). Hyperbilirubinemia refers to the conditions characterized by elevation in the levels of unconjugated and conjugated bilirubin (11, 12).

Hyperbilirubinemia is caused by several pathological conditions involving exaggerated rate of bilirubin production (hemolysis, dyserythropoiesis), decreased hepatic uptake of bilirubin (medications or portosystemic shunts), or reduced the rate of bilirubin conjugation (Gilbert syndrome) and abnormalities in bilirubin secretion (11). Elevations in the blood bilirubin levels are considered as significant apprehensions for various diseases such as cytomegalovirus (CMV) hepatitis, blood disorders, exposure to environmental hepatotoxins, acute fatty liver of pregnancy, inherited syndromes of bilirubin conjugation and hepatic ischemia (13). Thus, evaluating the serum bilirubin level is used as a diagnostic indicator for the diagnosis of several diseases including anemia, malaria, hepatitis, and hepatomegaly. Elevations in the blood bilirubin levels are considered as significant apprehensions for various diseases such as cytomegalovirus (CMV)

hepatitis, blood disorders, exposure to environmental hepatotoxins, acute fatty liver of pregnancy, inherited syndromes of bilirubin conjugation and hepatic ischemia (13).

The present study was aimed to investigate the levels of bilirubin in patients having different types of ailments. In total, clinical data of 700 patients were examined from 171 were selected for further analysis. Those patients were categorized into different groups based on age, sex, and type of the disease. Among those samples, 77 were newborn babies who showed a very high level (8-18mg/dL) of bilirubin with normal ALT and ALP levels. The babies manifested characteristic features of jaundice including yellow discoloration of the eyes and skin. Medical records showed that infants with hyperbilirubinemia recovered after a short period of treatment, usually one week to four weeks.

The rest of the 94 samples comprised 26 patients of jaundice, 29 patients of hepatitis C, six patients of hepatitis B, 17 members having malaria, 3 anemic patients, 9 cases of pregnancy, five cases of diabetes, 5 patients of miscellaneous, and four patients with non-symptomatic hyperbilirubinemia. Hyperbilirubinemia in infants occurs as a result of physiologic jaundice in which the baby's liver is not so strong to effectively excrete bilirubin. It can also be caused by poor breastfeeding or the substances present in the breast milk which stimulate reabsorption of the bilirubin. This condition is called breast milk jaundice. But the most risky form of infantile jaundice is hemolytic jaundice caused by ABO incompatibility or hemolytic disease of the newborn (14).

Phototherapy is the use of visible light for the treatment of hyperbilirubinemia in the newborn. This relatively common therapy lowers the serum bilirubin level by transforming bilirubin into water-soluble isomers that can be eliminated without conjugation in the liver. The dose of phototherapy is a key factor in how quickly it works; the dose in turn is determined by the wavelength of the light, the intensity of the light (irradiance), the distance between the light and the baby, and the body surface area exposed to the light. The use of phototherapy lowers hyperbilirubinemia in newborns. In this type of treatment, the baby is exposed to visible light emitting from light-emitting diodes, halogen quartz lamps, or fluorescent bulbs. As bilirubin is photosensitive so the light converts serum bilirubin to a water-soluble isomer that can be easily excreted without conjugation. The reaction involves the addition of oxygen to the bilirubin in a process called photooxidation (15).

Further analysis of the results revealed that hyperbilirubinemia was common in all malarial patients, anemic patients and the only one case of leukemia included in this study. Hyperbilirubinemia was observed in 96.15% of jaundice patients, 80% of hepatitis B patients, 73.7% of patients with hepatitis C, 66.7% of cases of pregnancy, and 0.00% of cases of diabetes. Besides, no direct proportionality was conceived between hyperbilirubinemia and other laboratory parameters such as ALT, ALP, and CBC. However, the patients with hyperbilirubinemia in the cases of anemia and hepatitis showed decreased Hb levels. These results signify that elevation in the serum bilirubin level is not dependent upon liver damage or hemolysis only. As the pathway of bilirubin formation, transportation, and excretion is a complex process and involves multiple mechanical and physiological factors.

Since, overproduction of bilirubin is attributed to hemolysis or injury so the tests of RBC count and serum hemoglobin level are commonly used.

However, hyperbilirubinemia can also occur due to impaired transportation in plasma. Transport of bilirubin in plasma needs its binding with albumin. Deficiency of plasma albumin level results in an increase of free bilirubin in in the blood. Therefore, assessment of plasma bilirubin is necessary for the investigation of hyperbilirubinemia without hemolysis and liver diseases. Failure of bilirubin uptake by hepatocytes also increases the level of bilirubin. So, evaluation of the proteins involved in this process is also necessary. Conjugation of bilirubin with glucuronic acid is essential for its solubility and excretion. Genetic deficiency of the bilirubin-UDP-glucuronosyltransferase enzyme leads to unconjugated hyperbilirubinemia. Obstruction in the bile duct and gale stones block the excretion of bilirubin and ultimately cause hyperbilirubinemia.

For that reason, this study recommends additional clinical tests for the detection of the exact causes of hyperbilirubinemia in patients with high bilirubin levels to reach a specific diagnosis of certain disease.

This study will support clinicians and patients as well as researchers in the precise evaluation of hyperbilirubinemia and accurate diagnosis of myriad ailments

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