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Original Article

Biochemistry Section

Neonatal Hyperbilirubinemia- Evaluation of Total Calcium, Ionised Calcium, Magnesium, Lactate and Electrolytes

VANI AXITA CHANDRAKANT, VIDYA S PATIL, DEEPTI G INGLESHWAR, VIJAYETHA P PATIL, SHILPASREE A S

ABSTRACT

Introduction: A total serum bilirubin level above 5 mg/dL in neonates is defined as neonatal hyperbilirubinemia. In the first week of life around 60% of term and 80% of preterm babies develop jaundice, and at one month about 10% of breastfed babies are still jaundiced. This condition is associated with a wide variety of biochemical disturbances.

Aim: To study the biochemical disturbances in babies with indirect hyperbilirubinemia.

Materials and Methods: Eighty two babies with unconjugated hyperbilirubinemia were studied and compared with 82 normal healthy term babies. All birth details and biochemical investigations including serum bilirubin, lactate levels, total calcium, ionized calcium, magnesium, urea, and creatinine were recorded in a prestructured proforma. Descriptive statistics, Pearson's correlation and Student's 't' test was used for analysis of data.

Results: It was found that females were 42.7% and males were 57% indicating a male preponderance in the case group. Unconjugated hyperbilirubinemia was more common in babies born by caesarean section (65.8%) and babies born at gestation <35 weeks (52.43%). The average birth weight of these babies was 2.1 kg. Mean magnesium value in the control group was 2.12 mg/dL, compared to 2.13 mg/dL in babies with indirect hyperbilirubinemia. Lactate values were slightly higher than the reference range in these babies. Levels of urea, phosphorous, sodium potassium and chloride were significantly higher in hyperbilirubinemia babies. Level of total calcium was significantly lower. Ionised calcium and creatinine were found to be decreased and magnesium was increased in babies with indirect hyperbilirubinemia but results are not significant.

Conclusion: The total calcium was decreased significantly but changes in levels of ionized calcium and magnesium were not significant in babies with indirect hyperbilirubinemia.

Keywords: Biochemical disturbances, Jaundice, Unconjugated bilirubin

INTRODUCTION

Bilirubin is derived from breakdown of senescent Red Blood Cells (RBCs) in the reticuloendothelial system. This bilirubin is transported to liver for conjugation and excretion. Any defect in production, transport or degradation of bilirubin may result in accumulation of bilirubin in the skin and mucus membranes resulting in jaundice. A total serum bilirubin level above 5 mg/dL is defined as neonatal hyperbilirubinemia. In the first week of life around 60% of term and 80% of preterm babies develop jaundice, and at 1 month about 10% of breastfed babies are still jaundiced [1]. The risk factors for developing hyperbilirubinemia in newborn babies include maternal factors like blood type RH or ABO incompatibility,drugs like oxytocin, diazepam, ethnicity (native American, Asian), breast feeding, maternal illnesses like gestational diabetes and neonatal factors like birth trauma (instrumented delivery, cephalohematoma, cutaneous bruising), drugs (sulfisoxazole acetyl with erythromycin, chloramphenicol, ethylsuccinate), excessive weight loss after birth, infrequent feedings, infections (TORCH), polycythemia, male gender, prematurity and previous sibling with hyperbilirubinemia [2]. Bilirubin has a neurotoxic effect. When the levels of bilirubin ≥25 mg/dL it can cross the blood brain barrier and via apoptosis and necrosis it can produce irreversible damage. Choudhary and colleagues noted that among babies with neonatal hyperbilirubinemia ABO incompatibility was twice as common as Rh incompatibility [3].

A study found that from the third postnatal day till two weeks after birth, the concentration of ionized calcium in a retrospective selected reference population of healthy full-term and pre-term neonates significantly exceeded the upper 95% reference limit for adults [4].

Magnesium is involved in maintaining bone health, carbohydrate metabolism, regulation of blood pressure, muscle contraction, energy transport and also serves a cytoprotective role [5]. Since, magnesium is required

for more than 300 biochemical reactions in the body, magnesium deficiency can cause various disturbances including hypocalcaemia, hypokalaemia and cardiac and neurological manifestations. Prakash CB and coworkers studied magnesium levels in 56 newborn and found that no appreciable changes occurred in the first week of life, cord blood values were somewhat higher than serum levels, no differences noted in breast as opposed to bottle feeding and no significant differences between venous and capillary blood [6].

Lactate can be produced by several mechanism. It is the end product of anaerobic glycolysis which usually indicates inadequate blood perfusion. It is nowadays being considered as a marker of strained cellular metabolism [7]. In conditions like sepsis or trauma, septic shock, blood loss, volume depletion, and systemic inflammatory syndrome, lactate levels can alter. Normally lactate is cleared by the liver and a small amount may be cleared by the kidneys. Any liver dysfunction can result in increased synthesis or decreased elimination. Lactate levels in babies with unconjugated hyperbilirubinemia was evaluated to try to establish a relation with indirect bilirubin. Moderate to high level of bilirubin in neonates may cause harm to developing Central Nervous System (CNS), particularly to cerebellum and basal ganglia causing severe motor symptoms and cerebral palsy [8].

MATERIALS AND METHODS

A two year retrospective analysis of data (January 2015 to December 2016) was carried out at SDM College of Medical Sciences and Hospital, Dharwad, Karnataka, India, in the Department of Biochemistry. Ethical clearance has been obtained from the Institutional Ethical Committee. A total of 82 newborn babies with unconjugated hyperbilirubinemia were included in the study and 82 age and sex matched healthy newborn babies were selected as control group. All birth details and results of biochemical investigations were recorded in a prestructured proforma. Babies with conjugated hyperbilirubinemia, inborn errors of metabolism, asphyxia, congenital defects, age >2weeks, congenital hypothyroidism, presence of history of drug exposure and sepsis were excluded from the study. Biochemical investigations like serum bilirubin, lactate levels, total calcium, magnesium, urea, and creatinine which were analysed by fully automated Siemens autoanalyser and ionised calcium by ABG analyser was noted down.

STATISTICAL ANALYSIS

All data was collected in a prestructured proforma containing all the variables of interest. Data was cross tabulated and processed. SPSS software was used for statistical analysis (version 20). The test statistics used for data analysis were descriptive statistics, Pearson's correlation, Student's 't' test with the level of significance set at 0.05 and a p-value of <0.05 was considered significant.

RESULTS

The sexwise distribution of controls and cases along with the demographic data of the study population is presented in [Table/Fig-1]. The values indicate a higher incidence of unconjugated hyperbilirubinemia in male babies (57.3%), babies born by caesarean section (65.8%) and in babies born at <35 weeks of gestation. Levels of urea, phosphorous, sodium, potassium and chloride were significantly higher in hyperbilirubinemia babies. Level of total calcium was significantly lower. Ionised calcium and creatinine were found to be decreased and magnesium was increased in babies with indirect hyperbilirubinemia but results are not significant [Table/Fig-2]. [Table/Fig-3] indicates that in jaundiced newborn the values of total bilirubin correlated negatively with ionized calcium and magnesium. In healthy neonates total bilirubin correlated negatively with magnesium, total calcium and ionized calcium.

	Cases (n=82)	%	Controls (n=82)	%
Sex of Baby				
Male	47	57.3	41	50.0
Female	35	42.7	41	50.0
Mode of Delivery				
Caesarean	54	65.8	41	50.0
Vaginal Delivery	28	34.1	41	50.0
Gestational Age				
<35 weeks	43	52.43	20	24.39
>35 weeks	39	47.56	62	75.61
Mean Birth Weight (in Kg)	2.1		3.18	

[Table/Fig-1]: Demographic data of study population.

DISCUSSION

In healthy term newborn, physiological jaundice follows a typical pattern where total serum bilirubin peaks at 5 to 6 mg/dL on third to fourth day of life and then slowly decreases during first week of life [1]. According to All India Institute of Medical Sciences NICU protocols 2007, in term neonate if Total Serum Bilirubin (TSB) concentrations on the first day of life >5 mg/dL, on 2nd day of life >10 mg/dL or > 13 mg/dL thereafter it is non-physiological and if TSB is > 17 mg/dL it should be regarded as pathological and investigated with possible intervention like phototherapy [9].

Bilirubin Toxicity

Because of its affinity to membrane phospholipids, bilirubin inhibits uptake of tyrosine affecting synaptic transmission and inhibits N-methyl-D-aspartate (NMDA) receptor ion channels thus interfering with neuroexcitatory signals and nerve impulse conduction, particularly of auditory nerve. Warren BK has explained the selective toxicity of bilirubin

Variable	Group	N	Mean	Standard Deviation	Standard Error Mean	p-value	Significance
Total Bilirubin	Cases	82	10.652	4.306	0.476	<0.0001	HS
	Control	82	0.615	0.245	0.027		
Direct Bilirubin	Cases	82	0.915	0.972	0.107	<0.0001	HS
	Control	82	0.186	0.117	0.013		
Indirect Bilirubin	Cases	82	9.641	4.013	0.443	<0.0001	HS
	Control	82	0.418	0.185	0.020		
Magnesium	Cases	82	2.134	0.461	0.051	0.280	NS
	Control	82	2.123	0.432	0.047		
Total Calcium (mg/dl)	Cases	82	8.660	1.418	0.157	<0.0001	HS
	Control	82	9.571	0.405	0.045		
Ionised Calcium (mmol/L)	Cases	82	4.950	0.833	0.092	0.3461	NS
	Control	82	5.158	0.534	0.059		
Phosphorous (mg/dl)	Cases	82	5.952	1.864	0.206	<0.0001	HS
	Control	82	3.620	0.603	0.067		
Lactate*	Cases	82	2.998	2.871	0.317		
Urea (mg/dl)	Cases	82	32.890	12.505	1.381	<0.0001	HS
	Control	82	20.341	7.412	0.819		
Creatinine (mg/dl)	Cases	82	0.754	0.248	0.027	0.6841	NS
	Control	82	0.771	0.294	0.032		
Sodium (mmol/L)	Cases	82	138.098	5.115	0.565	<0.0001	HS
	Control	82	131.890	5.200	0.574		
Potassium (mmol/L)	Cases	82	4.756	0.775	0.086	<0.0001	HS
	Control	82	3.986	0.630	0.070		
Chloride (mmol/L)	Cases	82	103.854	6.352	0.701	0.0004	HS
	Control	82	100.549	5.354	0.591		

[Table/Fig-2]: Biochemical parameters in cases and controls.
*Lactate levels were not studied in the control group as present study is a reterospective analysis.
* Student t test used for comparison, HS: Highly significant, NS: Not Significant.

Parameters	Cases	Controls
Total Bilirubin-Magnesium	-0.111	-0.056
Total Bilirubin-Calcium	0.306	-0.121
Total Bilirubin-Ionised Calcium	-0.040	-0.222

[Table/Fig-3]: Relationship between bilirubin and other parameters.

to neonatal brain due to the immature blood brain barrier (BBB) of newborn,qualitative and quantitative differences in lipid composition of neonatal brain and inhibition of NAD dependant dehydrogenases by bilirubin, causing bilirubin to pass more readily into brain of neonates [10]. Although, increased free bilirubin may be predictive of kernicterus, in some infants other factors like low APGAR score, hypothermia, hypoglycemia, sepsis, acidosis, hypoxemia and hypercarbia may make the BBB more permeable to low levels of free bilirubin [11]. Bilirubin also serves as an antioxidant. Both conjugated and unconjugated bilirubin inhibits lipid peroxidation while biliverdin and bilirubin mediate a cytoprotective role through hemeoxygenase. Bilirubin also inhibits ion exchange and water transport in renal cells causing neuronal swelling in kernicterus. Bilirubin inhibits mitochondrial enzymes and interferes with DNA synthesis, produces strand breakage and inhibits phosphorylation and protein synthesis [12].

Bilirubin, Gestational Age and Birth Weight

Compared to term infants, late preterm infants are physiologically immature, and pose limited compensatory responses to extra uterine environment. Out of 82, 43 babies (52.43%) were less than 35 weeks of gestation and the mean birth weight was 2.1 kg of jaundiced babies and 3.18 kg of control group. These findings are similar to another study by Mahmud H and coworkers, where serum bilirubin was found to be negatively correlated with gestational age and birth weight, where preterm and low birth weight babies developed severe and very severe jaundice compared to

term babies (p<0.001) [13]. Another worker also found that late preterm infants (gestational age 34-36 weeks) have a higher incidence of hyperbilirubinemia along with respiratory distress, temperature instability, feeding difficulties, hypoglycemia, apnea and late onset sepsis [14]. William AK et al., also noted higher morbidity and mortality in late preterm infants as diagnosed by hypoglycemia, temperature instability, respiratory distress, apnoea, jaundice and feeding difficulties. Risk factors for hospital re-admission or morbidity included being first child, being breast fed at discharge, having a mother with labor complications and being of Asian/ Pacific island descent [15].

Bilirubin and Magnesium

After calcium, magnesium is the second most important divalent cation in serum, with approximately 1% of total magnesium being extracellular. Magnesium ion is an important antagonistic regulator of the NMDA receptor ion channel [16]. It protects central nervous system against hypoxia and exerts neuroprotective effect by blocking excitotoxic and NMDA receptor mediated neuronal injury. Magnesium physiologically acts against or compensates for the neurotoxic effects of bilirubin. 25% of total serum magnesium is bound to albumin and 8% to globulins. In this study, it was noted that magnesium levels are non-significantly increased (p=0.280) in babies with indirect hyperbilirubinemia and a negative correlation was observed between total bilirubin and magnesium (r = -0.111). Abdel-Azeem ME et al., noted that neonates with indirect hyperbilirubinemia had higher magnesium levels. In addition they found higher copper and lower zinc values than healthy babies which were not related to their maternal serum values [17]. Similarly, Imani M et al., noted that magnesium levels are elevated in babies with moderate and severe hyperbilirubinemia. They noted a positive correlation between magnesium levels and bilirubin before and after phototherapy [18]. Contrary to this study, Mohamed SE et al., noted a positive relation between magnesium and bilirubin and that phototherapy decreases serum magnesium and bilirubin levels [19]. Sarici and colleagues demonstrated a positive correlation between severity of hyperbilirunemia and Ionised Magnesium (IMg) and significantly higher plasma IMg levels in severe hyperbilirubinemia group than group with moderate hyperbilirubinemia. This elevation in plasma IMg may be observed due to extracellular movement of intracellular magnesium resulting from cellular injury of neurons and red blood cells [20].

Bilirubin and Calcium

Direct measurement of ionsed calcium rather than total calcium, is the method of choice when accurate knowledge of active concentration of calcium is required [21]. Capillary blood sample may be used but ionised calcium in capillary blood may be slightly higher than in arterial blood. Light induced hypocalcemia (following phototherapy) results from increased calcium uptake by bone when inhibitory effect of melatonin declines after pineal inhibition by transcranial illumination [22]. In this study mean total calcium in the control group was 9.57 mg/dL and 8.66 mg/dL in case group. The mean ionised calcium level was 5.15 mmol/L in control group and 4.95 mmol/L in case group. Total bilirubin correlated negatively with total and ionized calcium in control babies but in jaundiced babies total bilirubin correlated positively with total calcium and negatively with ionized calcium. These findings are similar to a study by Reddy AT et al., who found higher incidence of hypocalcaemia and hyponatremia in Low Birth Weight (LBW) babies and preterm neonates with jaundice [23]. Similarly, Dushyant R et al., found hypocalcaemia more common in preterm and term newborn having higher TSB [24]. Statistically significant difference was noted in total calcium levels between TSB group15.1-20.0 mg/dL and TSB group 20.1-30.0 mg/dL. Preterm babies developed more hypocalcaemia symptoms than term babies. Hosny and coworkers found plasma bilirubin and plasma IMg levels to be significantly higher in hemolytic and non-hemolytic jaundiced cases. Ionised calcium was significantly higher in hemolytic cases and not significant in non hemolytic cases in each group of full term, preterm and LBW babies [22]. Amit J et al., found that after exchange transfusion total bilirubin decreased, but levels of calcium and phosphorous remained unchanged in jaundiced newborn [25]. Hypomagnesemia also causes a defect in synthesis and release of Parathyroid Hormone (PTH) and end organ resistance to PTH leading to hypocalcaemia. Magnesium therapy appears to have an important role in rectifying not only hypomagnes aemia but also hypocalcaemia. Bernard LS et al., have concluded that prophylactic administration of continuous intravenous calcium gluconate at 35 mg/kg/24hr limits the postnatal depression of serum calciumin LBW infants during first 24 hours of life [26]. Findings of several studies suggest that hypermagnesemia and hypocalcaemia may be critical factors in development of tissue injury [27-30].

Bilirubin and Other Electrolytes

In present study electrolytes sodium, potassium and chloride levels were significantly elevated in babies with indirect hyperbilirubinemia. These findings are consistent with those of another study [31]. But in the study by Reddy and colleagues, incidence of potassium and chloride changes following phototherapy was nonsignificant irrespective of gestational age, birth weight and duration of phototherapy [23]. Similarly, a study by Amit J and coworkers found that after exchange transfusion total hemoglobin and bilirubin decreased, but levels of urea, potassium remained unchanged in jaundiced newborn [25]. Sunil KP and Yadav showed that premature and LBW babies are at a higher risk of developing hyponatremia if they receive phototherapy [32]. It was found that levels of urea were significantly higher in the case group. But difference in creatinine levels between case and control group was non significant.

Bilirubin and Lactate

In clinical practice elevated levels of lactate are indicative of any form of shock or tissue hypoperfusion. Lactate is elevated in a variety of situations which include sepsis and septic shock, cardiogenic, obstructive and hemorrhagic shock, cardiac arrest, trauma, seizure, excessive muscle activity, regional ischemia, burns and smoke inhalation, diabetic ketoacidosis, thiamine deficiency, malignancy, liver dysfunction, inborn errors of metabolism, drugs like metformin and alcohol. In this study lactate levels were found to be slightly higher than the reference range in babies with indirect hyperbilirubinemia. However, this was not compared with healthy control group as it is retrospective analysis of data.

LIMITATION

A wide variety of biochemical disturbances are seen in babies with indirect hyperbilirubinemia but the exact mechanisms leading to these disturbances need to be elucidated. As this is a retrospective analysis of hospital data, lactate levels could not be determined in control babies, which is the limiting factor of current study. The study can be improvised by studying changes in the levels of biochemical parameters before and after initiation of appropriate treatments.

CONCLUSION

Unconjugated hyperbilirubinemia is a common condition seen in newborn babies. It was noted that total calcium was decreased significantly but changes in levels of ionized calcium and magnesium were not significant in babies with indirect hyperbilirubinemia. Further, studies can be carried out on larger population samples to firmly establish the relationship between biochemical markers and neonatal hyperbilirubinemia.

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AUTHOR(S):
1. Dr. Vani Axita Chandrakant
2. Dr. Vidya S Patil
3. Dr. Deepti G Ingleshwar
4. Dr. Vijayetha P Patil
5. Dr. Shilpasree A S

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Biochemistry, SDM College of Medical Sciences and Hospital, Dharwad, Karnataka, India.
2. Professor and Head, Department of Biochemistry, SDM College of Medical Sciences and Hospital, Dharwad, Karnataka, India.
3. Assistant Professor, Department of Biochemistry, SDM College of Medical Sciences and Hospital, Dharwad, Karnataka, India.
4. Associate Professor, Department of Biochemistry, SDM College of Medical Sciences and Hospital, Dharwad, Karnataka, India.
5. Assistant Professor, Department of Biochemistry SDM College of Medical Sciences and Hospital Dharwad, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Vani Axita Chandrakant,
Associate Professor, Department of Biochemistry,
SDM College of Medical Sciences and Hospital, Sattur,
Dharwad-580009, Karnataka, India.
E-mail: draxitacvani@gmail.com

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