

**Neonatal hyperbilirubinaemia after induction of labour with oxytocin and cord serum albumin is compared with cord serum bilirubin as a risk indicator**

Shagun Gupta<sup>1</sup>, Virendra Kumar Gupta<sup>\*2</sup>, Jitendra Prasad Bhatnagar<sup>2</sup>, Prashant Agrawal<sup>3</sup>,  
Ankit Agarwal<sup>4</sup>, Sumit Bhatia<sup>4</sup>, Ravi Garg<sup>4</sup>, Kasturi Devatwal<sup>1</sup> and Narbir<sup>4</sup>

<sup>1</sup>Department of Obstetrics & Gynaecology, NIMS University, Jaipur, India

<sup>2</sup>Department of Pediatrics, NIMS University, Jaipur, India

<sup>3</sup>Department of Pediatric Cardiology, Medanta, Gurgaon, India

<sup>4</sup>Department of Pediatrics, NIMS University, Jaipur, India

**\*Correspondence Info:**

Dr. Virendra Kumar Gupta

Assistant Professor,

Department of Pediatrics,

NIMS University, Jaipur, India

E-mail: [vk.hindustani@gmail.com](mailto:vk.hindustani@gmail.com)

**Abstract**

**Introduction:** Jaundice is one of the commonest problems that can occur in a newborn. Many a times it is physiological in the newborn because liver is not mature enough to handle the bilirubin and there is an increased load of bilirubin due to a higher circulating erythrocyte volume, a shorter erythrocyte life span and a larger early labeled bilirubin peak.

**Objectives:** 1) To know the effect of oxytocin for induction of labour in neonatal hyperbilirubinaemia (NH). 2) Comparing Cord Serum Albumin level (CSA) with Cord Serum Bilirubin (CSB) in predicting neonatal hyperbilirubinaemia. 3) To know the sensitivity, specificity, Positive predictive value and negative predictive value of CSA and CSB in predicting neonatal jaundice in term neonates.

**Method:** Prospective study was performed on 789 healthy term neonates. Relevant maternal history is collected. Cord blood was collected from the healthy term neonates at birth, CSA and CSB measured. Neonate was assessed clinically every day. Total Serum Bilirubin (TSB) and blood group were assessed in neonate during 72-96 hours of life. TSB value  $\geq 17\text{mg/dl}$  is considered Neonatal Hyperbilirubinaemia (NH) which requires intervention like phototherapy (PT) or Exchange transfusion (ET).

**Result:** Out of 388 Infants born after oxytocin induced labour, 122 (56.48%) neonates developed NH ( $P=0.002$ ). Neonatal hyperbilirubinaemia was more significant in neonates with CSA levels  $\leq 2.8\text{g/dl}$  & CSB levels  $\geq 2.1\text{mg/dl}$ . At cord serum albumin level  $\leq 2.8\text{g/dl}$ , sensitivity, specificity, PPV and NPV are 75.93 %, 68.06 %, 47.26 and 88.24 % respectively, for predicting NH at birth. At cord serum bilirubin level  $\geq 2.1\text{g/dl}$ , sensitivity, specificity, PPV and NPV are 96.30%, 70.86%, 55.47% and 98.07% respectively, for predicting NH at birth.

**Conclusion:** Oxytocin should be used with caution in view of its ability to develop neonatal hyperbilirubinaemia by inducing hemolysis. Both CSA and CSB are equally effective in predicting NH at birth. These study variables can be considered as neonatal screening tools for NH for term neonates.

**Keywords:** Cord Serum Albumin; Cord Serum Bilirubin; Neonatal Hyperbilirubinaemia; Oxytocin

**1. Introduction**

Jaundice is one of the commonest problems that can occur in a newborn. Many a times it is physiological in the newborn because liver is not mature enough to handle the bilirubin and there is an increased load of bilirubin due to a higher circulating erythrocyte volume, a shorter erythrocyte life span and a larger early labeled bilirubin peak. Early prediction will help in early discharge and prevent hospitalization of babies and mothers. Albumin is synthesized by liver and it helps in transport of unconjugated bilirubin. The association between oxytocin-induced labour and neonatal hyperbilirubinaemia is well documented.[1-3] with suggested causes including hepatic glucuronyl transferase

immaturity.[4], anoxic liver damage.[5], enhanced placentofetal transfusion.[6], increased erythrocyte fragility.[7], and mechanical trauma to erythrocytes.[8].

During the neonatal period, metabolism of bilirubin is in transition from the fetal stage to the adult stage.[9]. Uridine diphosphoglucuronyl transferase (UDPGT) important liver enzyme for conjugation and excretion of bilirubin is detectable at 18–20 weeks of gestation. UDPGT levels in full term neonates are usually less than 0.1% of adult values. Adult value of this enzyme activity is demonstrable only by 6–14 weeks of postnatal life.[10].

Synthesis of albumin appears at approximately the 7th-8th wk. in the human fetus and increases in inverse proportion to that of  $\alpha$ -fetoprotein. Albumin concentrations are low in a neonate ( $\sim 2.5$  g/dL), reaching adult levels ( $\sim 3.5$  g/dL) after several months [11]. Albumin has been described as “the body’s tramp steamer, shuttling cargo of various kinds between ports of cell”. Its load includes bilirubin, free fatty acids, calcium, etc.[11] .

Bilirubin binds to albumin in an equimolar ratio. Free bilirubin is anticipated when the bilirubin- to- albumin (B: A) ratio is  $> 0.8$ . Around 8.5mg of bilirubin will bind tightly to 1 g of albumin.[12]. Serum bilirubin over 15 mg% is found in 3% of normal term neonates.[12].

Neonatal Hyperbilirubinemia (NH) is the most common cause for readmission during the early neonatal period (6.5%).[13]. American Academy of Pediatrics (AAP) recommends that neonate discharged should have a follow-up visit after 48 to 72 hours for any significant jaundice and other problems.[14]. This recommendation is not appropriate for our country due to poor access to health care facility. NH which may be over looked or delay in recognition by parents, because lack of knowledge.

By predicting the neonates at risk for significant NH early at birth, we can design and implement the follow-up programme in these risk groups, cost effectively.

There are studies to predict NH by measuring cord albumin and cord bilirubin individually.

### 1.1 The objectives of our study are:

- 1) To know the effect of oxytocin for induction of labour in neonatal hyperbilirubinemia.
- 2) Comparing Cord Serum Albumin level (CSA) with Cord Serum Bilirubin (CSB) in predicting neonatal hyperbilirubinemia (NH).
- 3) To know the sensitivity, specificity, positive predictive value and negative predictive value of CSA and CSB in predicting neonatal jaundice in term neonates.

## 2. Methods and Materials

### 2.1 Study area

The study was conducted in Departments of Pediatrics & Obstetrics & Gynaecology in NIMS Medical College, Jaipur, Rajasthan, India

### 2.2 Study population:

A total of 789 healthy newborn infants enrolled during period from November 2015 to June 2016.

### 2.3 Study design:

This is hospital based prospective cross sectional study.

### 2.4 Inclusion criteria:

Sequentially born term babies (gestational age  $\geq 37$  weeks) from any mode of delivery (normal and C-section), Birth weight  $\geq 2.5$ kg, and APGAR score of more than 7 at first and fifth minutes of life.

### 2.5 Exclusion criteria:

Preterm babies (gestational age  $< 37$  weeks), Rh incompatibility, Neonatal sepsis, Instrumental delivery (forceps and vacuum), Birth asphyxia, Respiratory distress, Meconium stained amniotic fluid, and Neonatal jaundice within 24 Hours of life.

Out of the 789 infants, 190 had been delivered after spontaneous labour and 388 after induction of labour by amniotomy and intravenous oxytocin (Syntocinon). The average dose of oxytocin used was 4500 mU (range 2500-7500 mU). In the cases selected for study the duration of labour was between 6 and 14 hours and analgesia was achieved with intramuscular pethidine. No patient was given epidural analgesia. In none of the cases was clinical or cardiotocographic evidence of fetal distress, and all mothers had vertex deliveries. The remaining 211 infants were delivered by caesarean section.

Demographic profile and relevant maternal information was collected by interviewing the mother and from mother’s case sheet. With use of a wide-bore needle and gentle suction to avoid haemolysis 2.0 ml venous cord blood was collected as soon as the cord had been clamped and divided and before placental separation. The blood was anticoagulated with lithium heparin, and sent for analysis. Gestational age was assessed by New Ballard score. All the babies were followed up daily for first 4 postnatal days and babies were daily assessed for NH clinically and its severity. Total Serum Bilirubin (TSB) estimation was done at 72-96 hours of age for all neonates.

Cord blood collected at birth was analyzed by auto analyzer method (Erba EM 200) for Cord Serum Albumin and Cord Serum Bilirubin estimation. The main outcome of the study was inferred in terms of neonatal hyperbilirubinemia.

Serum bilirubin  $\geq 17$  mg/dl after 72 hours of life was taken as hyperbilirubinemia and treatment is advised, as per the American academy of pediatrics practice parameter, 2004.

### 2.6 Statistical analysis:

The qualitative variables were represented as absolute (n) and relative (%) frequency values. Quantitative variables were represented as mean and standard deviation.

## 3. Results

Data collected were analyzed using appropriate statistical software like namely SAS 9.2, SPSS 15.0. The table gives the haematological and biochemical values in cord blood from the 789 infants. There was no significant difference in any variable between infants delivered by caesarean section and those born after vaginal delivery.

The study was divided based on use of oxytocin for induction of labour into 2 groups (**Table -1**). Out of 388 Infants born after oxytocin induced labour, 122 (56.48%) neonates developed NH. Out of 401 infants 94 developed NH in which oxytocin was not used. (P=0.002).

According to cord serum albumin levels the study was divided into 3 groups (Table-2). Out of 216 infants who developed hyperbilirubinemia 164 (75.92%) were found having CSA levels  $\leq 2.8$  mg/dl (p value -  $<0.0001$ ).

Another division was made based on cord serum bilirubin level in 2 groups (Table-3). Out of 216 infants having hyperbilirubinemia 208(96.29%) had CSB levels  $\geq 2.1$  mg/dl(p value  $<0.0001$ )

The Demographic variables and the variables which influence the neonatal hyperbilirubinemia directly or indirectly were compared and shown in Table-4.

The diagnostical correlation of cord serum albumin and cord serum bilirubin is compared with neonatal hyperbilirubinemia is shown in Table-5

At cord serum albumin level  $\leq 2.8$ g/dl, sensitivity, specificity, PPV and NPV are 75.93 %, 68.06 %, 47.26 and 88.24 % respectively, for predicting NH at birth. At cord serum bilirubin level  $\geq 2.1$ g/dl, sensitivity, specificity, PPV and NPV are 96.30%, 70.86%, 55.47%and 98.07% respectively, for predicting NH at birth.

**Table 1: Use of Oxytocin and Neonatal Hyperbilirubinemia**

Oxytocin drug use	Neonatal Hyperbilirubinemia		P value
	Yes	No	
No	94(43.52%)	307(53.58%)	0.002
Yes	122(56.48%)	266(46.42%)	
Total	216(27.38%)	573(72.62%)	

**Table-2: Cord Serum Albumin and Neonatal Hyperbilirubinemia**

Cord Serum Albumin (mg/dl)	Neonatal Hyperbilirubinemia		P value
	Yes	No	
$\leq 2.8$	164(75.92%)	183(31.94%)	$<0.0001$
2.9-3.3	36(16.67%)	242(42.23%)	
$\geq 3.4$	16(07.41%)	148(25.83%)	
Total	216(27.38%)	573(72.62%)	

**Table-3: Cord Serum Bilirubin and Neonatal Hyperbilirubinemia**

Cord Serum Bilirubin (mg/dl)	Neonatal Hyperbilirubinemia		P value
	Yes	No	
$\leq 2$	08(03.70%)	406(70.86%)	$<0.0001$
$\geq 2.1$	208(96.30%)	167(29.14%)	
Total	216(27.38%)	573(72.62%)	

**Table-4: Correlation of Clinical Variable With Neonatal Hyperbilirubinemia**

Variables	Neonatal Hyperbilirubinemia		P value
	YES	NO	
<b>Gender</b>			
Male	124(57.41%)	302(52.71%)	0.237
Female	92(42.59%)	271(47.29%)	
<b>Mode of delivery</b>			
Cesarean Section	53(24.53%)	158(27.57%)	0.390
Vaginal route	163(75.46%)	415(72.43%)	

**Table-5 Sensitivity, Specificity, PPV, NPV of CSA & CSB Level**

	Sensitivity	Specificity	PPV	NPV
Cord serum Albumin level $\leq 2.8$	75.93%	68.06%	47.26%	88.24%
Cord serum bilirubin level $\geq 2.1$	96.30%	70.86%	55.47%	98.07%

#### 4. Discussion

Oxytocin is an important therapeutic agent in obstetrics and probably its effect on erythrocytes cannot be prevented other than by keeping the total dose used to a minimum. The use of prenatal drug treatment with either phenobarbitone or antipyrine to activate fetal hepatic glucuronyl transferase and so increase the neonate's ability to eliminate bilirubin has been suggested, but it would be more logical to prevent the hyperbilirubinemia by reducing the dose of oxytocin rather than treat it with potentially toxic drugs.

Our study result is similar with the studies of Awasthi *et al.*[2] (1998) and Rostami *et al.*[3] (2005), regarding oxytocin effect on neonatal hyperbilirubinemia which showed significant correlation between the neonatal hyperbilirubinemia with the oxytocin induction of labour(P=.002).

Albumin is the major binding protein in the human neonate. Low production of albumin will lower its transport and binding capacity.[15]. Albumin binds to potentially toxic products like bilirubin and antibiotics. Sahu *et al.*[16](2011), showed that 70% (14/20) neonates who developed significant NH had cord serum albumin level  $< 2.8$  g/dl, 30% (6/20) neonate had CSA level 2.9-3.3 g/dl and none of neonates with CSA level  $\geq 3.4$ g/dl developed NH. There is statistical significance noted between low CSA with development of NH (p value  $<0.001$ ).Our study results correlated well with Sahu *et al.*[16] that 75.92 % of neonates developed hyperbilirubinemia who had albumin levels  $\leq 2.8$ g/dl requiring phototherapy(PT) and about 11% needed exchange transfusion. At higher levels of albumin that is 2.9- 3.3 gm/dl ,16.67% needed PT and neonates with cord blood albumin  $> 3.3$  gm/dl, 07.41% need intervention for hyperbilirubinemia.

Sun *et al.*[17] (2007), Rudy Satrya *et al.*[18] (2009) studies are in correlation with the present study. So the cord bilirubin level of  $\geq 2.1$ mg/dl can be used as an early predictor of neonatal hyperbilirubinemia.

Trivedi *et al.*[19] (2013), studied correlation of cord serum albumin level with cord serum bilirubin to predict the risk for hyperbilirubinemia in term newborns. 33.88% babies developed significant NH. Babies with cord serum bilirubin  $>2.0$ mg/dl, 76.3% developed significant NH in first seven day of the life. Among 33.88% babies who developed significant NH, 53.53% babies had cord serum albumin  $\leq 2.8$ g/dl. In our study, 27.34% (216/789) developed NH, among these 96.30% (208/216) had a cord serum bilirubin level  $\geq 2.1$ mg/dl and 75.92% (164/216) had cord serum albumin  $\leq 2.8$ g/dl.

#### 4.1 Limitations of the study

Only full term healthy neonates were taken for the study, sample size is less and further study with larger sample is required.

#### 5. Conclusion

Oxytocin should be used with caution in view of its ability to develop neonatal hyperbilirubinemia by inducing hemolysis. Cord serum bilirubin level  $\leq 2\text{mg/dl}$  are considered safe while  $\geq 2.1\text{mg/dl}$  are highly suggestive of babies who will develop neonatal hyperbilirubinemia. Cord blood albumin levels  $\geq 3.4\text{ gm/dl}$  is probably safe for early discharge of baby. The study variables, cord serum albumin and cord serum bilirubin are equally effective in predicting neonatal hyperbilirubinemia at birth. These variables can be used as screening test for neonatal hyperbilirubinemia for term neonates and is cost effective in individualizing the follow-up and planning for early discharge.

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