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RESEARCH ARTICLE

A CROSS-SECTIONAL STUDY OF RISK FACTORS ASSOCIATED WITH NEONATAL JAUNDICE

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(M)-male,(F)-female, (PT)-preterm, (AGA)-appropriate for gestational age, (SGA)-small for gestational age, (NW)-Normal weight -(2.5kg-3.99kg), (LBW)- low birth weight (1.5kg-2.499kg), (VLBW)- (1kg-1.499kg), (EONS)-early onset neonatal sepsis, (Inc)-ABO incompatibility, (TSH)-Thyroid Stimulating hormone, (IDM)-Infant of Diabetic Mother, (TSB)- Total Serum Bilirubin and (NNH)-Neonatal Hyperbilirubinemia.

ABSTRACT

In this study, the aim was to find out the risk factors associated with neonatal jaundice in a tertiary care hospital in Delhi, India. In our cross-sectional study of 661 neonates (601 term neonates and 60 preterm neonates), the results showed that almost all neonates had transient unconjugated hyperbilirubinemia in the neonatal period, with more than ninety percent affected during their first week of life. The prevalence of physiologic jaundice in neonates was 86.99% and the prevalence of pathologic indirect hyperbilirubinemia in neonates was 13.01%. In the present study, the Glucose-6-Phosphate Dehydrogenase (G6PD) activity was normal in all the neonates with pathologic jaundice. In our study, the risk factors like early onset neonatal sepsis, preterm gestation, low birth weight, very low birth weight, congenital abnormality (most commonly ventricular septal defect), serum TSH level (≥10mIU/L), polycythemia and infant of diabetic mother showed a strong association with pathologic indirect hyperbilirubinemia. Besides, the association of pathologic jaundice with other factors like male neonate, ABO or Rh incompatibility, anemia, primigravida mother and vaginal delivery was considered to be not statistically significant, in our study.

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INTRODUCTION

The word 'jaundice' comes from the French word 'jaune', meaning 'yellow' and 'jaunisse' meaning "yellow disease". (12) The medical term for jaundice is icterus. The word 'icterus' comes from the Greek word 'ikteros'.(8) The origin of the word icterus is quite bizarre, coming from an ancient belief that jaundice could be cured from looking at the yellow bird icteria.(12) The term icterus is sometimes incorrectly used to refer to jaundice specifically of sclera.(8)(12) Neonatal jaundice is a yellowish discolouration of mucous membranes and skin in a neonate (infant under 28 days of age), due to high bilirubin levels.(19) Other symptoms may include excess sleepiness or poor feeding. Complications may include seizures, cerebral palsy, or kernicterus.(19) Bilirubin was discovered by Rudolf Virchow in 1847.(17) The serum bilirubin level required to cause jaundice varies with skin tone and body region, but jaundice usually becomes visible on the sclera at a level of 2 to 3 mg/dL and on the face at about 4 to 5 mg/dL. With increasing bilirubin levels, jaundice seems to advance in a head-to-foot direction, appearing at the umbilicus at about 15 mg/dL and at the feet at about 20 mg/dL. (19)

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Under normal circumstance, the level of indirect bilirubin in umbilical cord serum is 1-3mg/dL and rises at a rate of <5mg/dL/24hr; thus, jaundice becomes visible on the 2nd or 3rd day, usually peaking between the 2nd and 4th days at 5-6mg/dL and decreasing to less than 2mg/dL between the 5th and 7th days after birth. Jaundice associated with these changes is designated *physiologic jaundice* (non-pathologic unconjugated hyperbilirubinemia) and is believed to be the result of increased bilirubin production from breakdown of fetal red blood cell breakdown combined with transient limitation in conjugation of bilirubin by the immature neonatal liver. In premature infants, the rise in serum bilirubin tends to be the same or somewhat slower but of longer duration than in term infants. Peak levels of 8-12mg/dL are not usually reached until the 4th-7th day, and jaundice is infrequently observed after the 10th day, corresponding to the maturation of mechanisms for bilirubin metabolism and excretion.(14)(15)(19) In general, factors suggesting a *pathologic jaundice* a search to determine the cause of jaundice should be made if it appears in the 1st 24 hours after birth, serum bilirubin is rising at a rate faster than 5mg/dL/24hr, total serum bilirubin is >12mg/dL in a term infant (especially in the absence of risk factors) or 10-14mg/dL in a preterm infant, jaundice persists after 10-14 days after birth, or serum direct bilirubin fraction is >2mg/dL at any time. Other factors suggesting a *pathologic jaundice* (unconjugated or conjugated hyperbilirubinemia) are family history of

hemolytic disease, pallor, hepatomegaly, splenomegaly, vomiting, lethargy, poor feeding, excessive weight loss, apnea, bradycardia, hypothermia, light coloured stools, dark urine positive for bilirubin, bleeding disorder, failure of phototherapy to lower the bilirubin level and signs of kernicterus.(15)(19) Persistent pathologic jaundice- that is, jaundice persisting beyond the first 14 days- is also seen in neonates, more commonly in breastfed babies.(14)

In young babies, unconjugated bilirubin (which is not carried by albumin) can penetrate the membrane that lies between the brain and the blood (the blood–brain barrier) because the blood–brain barrier has yet to develop fully, whereas more developed individuals with increased bilirubin in the blood are protected. Unconjugated bilirubin is potentially toxic to neural tissue (brain and spinal cord). The term kernicterus is used to denote the clinical features of acute or chronic bilirubin encephalopathy, as well as the yellow staining in the brain associated with the former. Kernicterus is also known to occur at lower levels of bilirubin in term babies who have risk factors, and in preterm babies.(14)(15) Kernicterus has been rising in recent years due to less time spent outdoors.(15) Jaundice and kernicterus are crucial global health issues, which must be addressed to reduce neonatal and child mortality globally and reach the sustainable development goals.

AIMS AND OBJECTIVES

In this study, the aim was to find out the risk factors associated with neonatal jaundice in a tertiary care hospital in Delhi, India. Our objective was to facilitate early diagnosis and reduce subsequent complications of neonatal jaundice.

MATERIALS AND METHODS

Study Setting and Period of Study: The study was conducted in the Department of Paediatrics, Rockland Hospital in Delhi, India during the period of 01 January 2012 to 07 August 2014.

Study Design: The study was a Cross-sectional Study, conducted at the Department of Paediatrics, Rockland Hospital in Delhi.

Sample Size: For the present study, 661 neonates (645 singleton neonates and 16 twin neonates) were recorded and studied in Paediatrics Department in Rockland Hospital. These neonates were born alive to 653 mothers in Obstetrics and Gynaecology Department in Rockland Hospital, during the period 01.01.2012 till 07.08.2014.

Sampling Design: The study was done as Random Sampling of the neonates noticed to have deep yellow discolouration of whole body that were born in Rockland Hospital, Delhi. In this study, all the venous blood samples of neonates for Total Serum Bilirubin (TSB) and Direct Serum Bilirubin were collected during first 9 days of life, and in one case of persistent pathologic hyperbilirubinemia, the sample was again collected on Day 21 of life. These neonates were further investigated for hemoglobin estimation, hematocrit estimation, sepsis screen, Glucose-6-Phosphate Dehydrogenase (G6PD) activity and serum TSH levels. Besides, venous blood samples were collected for blood groups of about 516 neonates as well as blood groups of their mothers were also done.

Study Variables: Age and gender of neonate, physiologic jaundice or pathologic jaundice, tests of neonate (blood group of neonate and mother, total serum bilirubin level, indirect serum bilirubin level, direct serum bilirubin level, hemoglobin estimation, hematocrit estimation, Glucose-6-Phosphate Dehydrogenase (G6PD) activity and serum TSH level), maturity of neonate (term or preterm), weight of neonate (normal weight, low birth weight or very low birth weight), neonate with other risk factors (ABO or Rh incompatibility, anemia, polycythemia, early onset neonatal sepsis, congenital abnormality, infant of diabetic mother), mother (primigravida or multigravida), method of delivery (vaginal delivery or caesarean delivery), morbidity (hydrops fetalis, kernicterus or cerebral palsy) and mortality rate in a group of neonates born in Rockland Hospital, Delhi.

Inclusion Criteria/ Selection Criteria: Participants in the study eligible for inclusion were neonates of either gender, born alive in Rockland Hospital during the period 01.01.2012 till 07.08.2014. The mothers of these neonates were also included as participants after obtaining written consent from them. Neonates were included after obtaining proper informed written consent from their parent/guardian.

Intrauterine deaths were excluded from the study.

There were 7 neonates (3 males and 4 females) born in Rockland Hospital, Delhi and on Day 1 of life, these neonates were referred to the higher center. These 7 neonates were as follows:

- PT (28-29weeks) / Female /SGA/Very LBW
- PT (29-30weeks) /Male/ SGA/LBW
- PT (31-32weeks)/Male/SGA/Extreme LBW (920grams)
- PT (32 weeks) / Female /SGA/ LBW
- Term / Male / AGA
- Term / Female / AGA
- Term / Female / AGA (born by VAVD)

The further outcome of these 7 neonates is not known. These were born to 2 primigravida mothers and 5 multigravida mothers by emergency caesarean delivery in 6 cases and ventouse assisted vaginal delivery (VAVD) in one case. These 7 neonates were excluded from the study.

Study Characteristics: In this study, 661 neonates born alive in Rockland Hospital during the period 01.01.2012 till 07.08.2014, were recorded and studied. The demographic information, history, physical examination and investigations in the patient's questionnaire were recorded. Neonates that satisfied the inclusion criteria were selected and the neonates who did not meet the inclusion criteria were excluded.

Data Collection Methods and Tools: Neonates' history and investigations information was collected in questionnaires and the data was collected and reported, and then statistical analysis of data was performed using SPSS software. The calculations of odd's ratios were done using MedCalc statistical Software and calculations of P values were done using QuickCalcs-Graphpad Software.

Statistical Methods and Statistical Interpretation: The Chi-square test or Fisher's exact test was used to calculate the Two-tailed P values in our study. When presenting P values, it

was helpful to use the asterisk rating system as well as quoting the P value:

P < 0.05* , it is statistically significant,
P < 0.01 ** , it is very statistically significant,
P <0.001*** , it is extremely statistically significant.

RESULTS AND OBSERVATIONS

For the present cross-sectional study, 661 neonates (645 singleton neonates and 16 twin neonates) were recorded and studied in Paediatrics Department in Rockland Hospital. These neonates were born alive to 653 mothers (42.88% primigravida and 57.12% multigravida) by caesarean delivery in 70.75% cases and by vaginal delivery in 29.25% cases, in Obstetrics and Gynaecology Department in Rockland Hospital, during the period 01.01.2012 till 07.08.2014. (4) Hence, more than 70% neonates were observed in hospital for more than 72 hours before discharge, and the remaining healthy neonates with no risk factors were discharged after 24 hours of observation in Rockland Hospital, Delhi. In our study, all the 661 neonates after discharge were followed up for progress of jaundice in Paediatrics Out-Patient Department at Rockland Hospital, Delhi.

The various 645 singleton neonates (356 males and 289 females) were as follows:

Term, LGA and Macrosomia-9 males and 3 females
Term, AGA and NW - 299 males and 248 females
Term, SGA and LBW - 12 males and 19 females
PT, AGA and NW - 16 males and 07 females
PT, AGA and LBW - 14 males and 10 females
PT, SGA and LBW - 06 males and 01 female
PT, SGA and VLBW - 00 male and 01 female

The various 16 twins (9 males and 7 females) were as follows:

Term, AGA and NW - 1 male and 2 females
Term, SGA and LBW - 4 males and 4 females
PT, AGA and NW - 2 males only
PT, AGA and LBW - 1 male and 1 female
PT, SGA and LBW - 1 male only

Table 1: Table showing that the venous blood samples of 86 neonates with pathologic hyperbilirubinemia for serum bilirubin were collected during first 9 days of life, and in one case of persistent pathologic jaundice, the sample was again collected on Day 21 of life.

Age of baby	Neonates with pathologic jaundice	% Neonates with pathologic jaundice
Day 1	01	0.15%
Day 2	05	0.76%
Day 3	20	3.03%
Day 4	12	1.81%
Day 5	17	2.57%
Day 6	15	2.27%
Day 7	09	1.36%
Day 8	05	0.76%
Day 9	02	0.30%
Day 21	01 Repeat neonate	--
Total	86 neonates	13.01%

Total Serum Bilirubin was calculated by adding Serum Indirect Bilirubin and Serum Direct Bilirubin. Normal values of Bilirubin are as follows:

Total Serum Bilirubin = 0.3 to 1.0 mg/dL
Serum Direct Bilirubin = 0.1 to 0.3 mg/dL
Serum Indirect Bilirubin = 0.2 to 0.7 mg/dL

Hyperbilirubinemia is a higher-than-normal level of bilirubin in the blood. In our study, the results showed that the Total Serum Bilirubin was more than 2 mg/dL and the Serum Direct Bilirubin level was less than 2 mg/dL, in all the 661 neonates. Thus, in our study of 661 neonates, the results showed that almost all neonates had transient unconjugated hyperbilirubinemia in the neonatal period. In our study, about 575 neonates had physiologic jaundice (non-pathologic unconjugated hyperbilirubinemia) and about 86 neonates had pathologic indirect hyperbilirubinemia.

Table 2: Table showing a comparison of prevalence of jaundice in a group of 661 neonates born in Rockland Hospital, Delhi.

Age at which neonates were diagnosed	Physiologic Jaundice	Pathologic jaundice	Total
1-7 days	575	79	654
8-28days	000	07	007
Total	575	86	661

In this study, it is evident that almost all neonates with physiologic jaundice and about 90.70% (78) neonates with pathologic jaundice were diagnosed from Day 2 till Day 7 of life. Besides, one neonate was diagnosed with pathologic jaundice on Day 1 of life. In the Table 2, the two-tailed P value was less than 0.0001***, in the Fisher's exact test. By conventional criteria, the association between rows and columns was considered to be extremely statistically significant. Hence neonates should be routinely followed for progress of jaundice in the first week of life.

The various TSB levels of the 86 neonates with pathologic indirect hyperbilirubinemia were as follows:

12 mg/dL-12.99mg/dL- 10 neonates were as follows:
Term/Male/AGA/NNH/EONS
Term/Male/AGA/NNH/EONS
Term/Male/AGA/NNH/EONS/Inc
Term/Male/AGA/NNH/EONS/Severe anemia /Inc
Term/Female/LBW/SGA/NNH/EONS/Polycythemia
Term/Male/AGA/NNH/Inc/(TSH on day2-11.19mIU/L)
PT/Male/LBW/NNH
PT/Twin/Male/LBW/SGA/NNH/EONS
PT/Male/LBW/NNH/EONS
PT/Female/LBW/NNH/EONS
13 mg/dL-13.99mg/dL- 8 neonates were as follows:
Term/Female/AGA /NNH/EONS -3 neonates
Term/Male/AGA/NNH/EONS/Inc
Term/Male/AGA/NNH/EONS
Term/Female/AGA /NNH
PT/Male/LBW/NNH/EONS
PT/Female/VLBW/SGA/NNH/EONS/Polycythemia/ (TSH on day5-13.4 mIU/L)
14 mg/dL-14.99mg/dL- 8 neonates were as follows:
Term/Male/AGA/NNH/EONS
Term/Male/AGA/NNH/EONS
Term/Male/AGA/NNH/IDM

Term/Female/AGA/NNH
Term/Female/AGA/NNH/Inc
Term/Female/AGA/NNH/EONS/Inc
PT/Male/NW/AGA/NNH/EONS/Inc
PT/Male/NW/NNH/EONS

15 mg/dL-15.99mg/dL- 13 neonates were as follows:
Term/Male/AGA /NNH/EONS/IDM
Term/Male/AGA /NNH/EONS/IDM
Term/Male/AGA /NNH/Inc
Term/Male/AGA /NNH
Term/Male/AGA /NNH
Term/Female/AGA/NNH/EONS
Term/Female/AGA/NNH/EONS
Term/Female/AGA/NNH/EONS/(TSHon day7-13.11 mIU/L)
Term/Female/AGA/NNH
PT/Male/NW/NNH/EONS
PT/Male/LBW/NNH/EONS/VSD/Inc
PT/F/NW/NNH/EONS/Mild anemia/(TSHday9-10.5 mIU/L)
PT/Female/LBW/NNH/EONS

16 mg/dL-16.99mg/dL- 15 neonates were as follows:
Term/Male/AGA/NNH/EONS -4 neonates
Term/Male/AGA/NNH/EONS/Inc
Term/Male/AGA/NNH/IDM/EONS/Inc/MMC (Sacral Meningomyelocele-size about 45 mm X 38 mm)
Term/Male/AGA/NNH/IDM/EONS/Inc
Term/Male/AGA/NNH/IDM
Term/Male/AGA/NNH/Inc
Term/Male/AGA/NNH
Term/Female/AGA/NNH
Term/Female/AGA/NNH/EONS/IDM
Term/Female/LBW/SGA/NNH/EONS
PT/M/LBW/NNH/EONS/VSD/(TSHday9-10.5 mIU/L)/Inc
PT/Female/LBW/SGA/NNH/EONS

17 mg/dL-17.99mg/dL- 10 neonates were as follows:
Term/Male/AGA/NNH/EONS -2 neonates
Term/Male/LGA/Macrosomia/NNH/IDM/Inc
Term/Male/AGA/NNH
Term/Female/AGA /NNH/IDM/Inc
Term/Female/AGA /NNH/EONS
Term/Female/AGA /NNH/EONS/Inc
PT/Male/NW /NNH/EONS/Inc
PT/Male/LBW /SGA/NNH/EONS/Polycythemia
PT/Male/LBW/NNH/EONS/Left Congenital Talipes Equinovarus (CTEV) /Inc

18 mg/dL-18.99mg/dL- 12 neonates were as follows:
Term/Male/AGA/NNH/EONS/Inc -2 neonates
Term/Female/AGA/NNH/EONS/Inc -2 neonates
Term/Female/AGA/NNH/EONS -2 neonates
Term/Male/AGA/NNH/EONS/(TSH on day 3-15.1 mIU/L)
Term/Male/AGA/NNH/EONS
Term/Male/AGA/NNH/EONS/IDM
Term/Female/AGA/NNH/EONS/Inc/Mild anemia
Term/Female/LBW/SGA/NNH/EONS
PT/Male/NW/NNH/EONS

19 mg/dL-19.99mg/dL- 2 neonates were as follows:
Term/Male/AGA/NNH/EONS
PT/Female/NW/AGA/NNH/EONS/Polycythemia

20 mg/dL-20.99mg/dL- 1 neonate was as follows:
Term/Female/AGA/NNH/EONS/Inc

21 mg/dL-21.99mg/dL- 1 neonate was as follows:
Term/Female/AGA/NNH/EONS

22 mg/dL-22.99mg/dL- 1 neonate was as follows:
Term/Female/AGA /NNH/EONS/Inc

23 mg/dL-23.99mg/dL- 2 neonates were as follows:
Term/Male/AGA/NNH/EONS/IDM/Inc
PT/Male/LBW/NNH/EONS/Inc/(TSH on day6-11.6mIU/L)

24 mg/dL-24.99mg/dL- 2 neonates were as follows:
PT/Male/NW/NNH/EONS/IDM/Inc
PT/Male/NW/AGA/NNH/EONS/Polycythemia (Day5-TSB-24.2 mg/dL, discharged after 3 days of phototherapy) and later again admitted for Persistent NNH (Day21-TSB-24.66 mg/dL, discharged after 3 days of phototherapy)

25 mg/dL-25.99mg/dL - 1 neonate was as follows:
Term/Female/AGA/NNH/EONS/Inc

In the present study, it is evident that the physiologic jaundice was seen in 86.99% (575) neonates {47.35% (313) males and 39.64% (262) females} and pathologic indirect hyperbilirubinemia was seen in 13.01% (86) neonates {7.87% (52) males and 5.14% (34) females}. The two-tailed P value was less than 0.0001***, in the Chi-square test. By conventional criteria, this difference was considered to be extremely statistically significant. Among these 13.01% (86) neonates with pathologic indirect hyperbilirubinemia, about 9.68% (64) neonates had TSB between 12mg/dL to 17.99mg/dL and 3.33% (22) neonates had TSB between 18mg/dL to 26mg/dL. All the neonates with TSB more than 18mg/dL were also associated with early onset neonatal sepsis. In the present study, a late preterm neonate was again admitted on Day 21 of life, for persistent pathologic indirect hyperbilirubinemia.

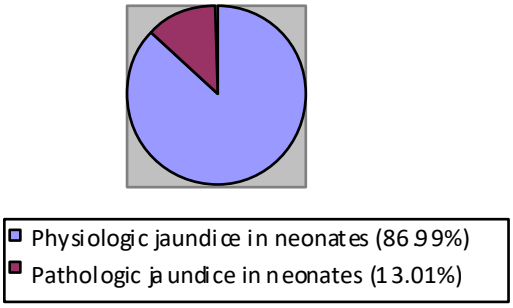

Figure 1: Pie diagram showing prevalence of jaundice in a group of 661 neonates born in Rockland Hospital, Delhi.

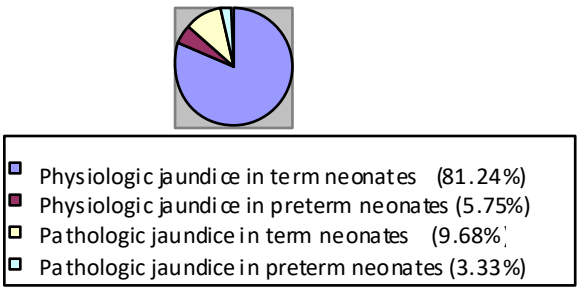

Figure 2: Pie diagram showing a comparison of prevalence of jaundice in term and preterm neonates in a group of 661 neonates born in Rockland Hospital, Delhi.

In the present study, it is evident that the physiologic jaundice was seen in 81.24% (537) term neonates (284 singleton males, 05 twin males, 6 twin females and 242 singleton females) and 5.75% (38) preterm neonates (21 singleton males, 13 singleton females, 1 twin female and 03 twin males). In the present study, it is also evident that the pathologic indirect hyperbilirubinemia was seen in 9.68% (64) term neonates (36 singleton males and 28 singleton females) and 3.33% (22) preterm neonates (15 singleton males, 6 singleton females and 01 twin male). In the Table 3, the odd's ratio was 4.8577.

The two-tailed P value was less than 0.0001***, in the Fisher's exact test. The association between rows (term and preterm neonates) and columns (neonates with physiologic jaundice and neonates with pathologic indirect hyperbilirubinemia) was considered to be extremely statistically significant. Thus, in our study, preterm gestation showed a strong association with pathologic indirect hyperbilirubinemia.

Table 3. Table showing a comparison of prevalence of jaundice in term and preterm neonates in a group of 661 neonates born in Rockland Hospital, Delhi.

Neonates	Physiologic Jaundice	Pathologic Indirect Hyperbilirubinemia	Total
Term	537 (81.24%)	064 (09.68%)	601
Preterm	038 (05.75%)	022 (03.33%)	060
Total	575 (86.99%)	086 (13.01%)	661

Table 4. Table showing a comparison of prevalence of jaundice in neonates with weight≥2.5kg and neonates with weight less than 2.5kg in a group of 661 neonates born in Rockland Hospital, Delhi

Neonates	Physiologic Jaundice	Pathologic Indirect Hyperbilirubinemia	Total
Weight ≥2.5kg	517	070	587
Weight <2.5kg	058	016	074
Total	575	086	661

In the Table 4, the odd's ratio was 2.0374, the two-tailed P value equals 0.0268* in the Fisher's exact test. The association between rows (neonates with weight≥2.5kg and neonates with weight less than 2.5kg) and columns (neonates with physiologic jaundice and neonates with pathologic indirect hyperbilirubinemia) was considered to be statistically significant. Thus, in our study, low birth weight (LBW) and very low birth weight (VLBW) neonates showed a strong association with pathologic indirect hyperbilirubinemia.

Table 5: Table showing a comparison of prevalence of jaundice in neonates with early onset sepsis and neonates with no sepsis in a group of 661 neonates born in Rockland Hospital, Delhi

Neonates	Physiologic Jaundice	Pathologic Indirect Hyperbilirubinemia	Total
No sepsis	447	017	464
Early onset neonatal sepsis	128	069	197
Total	575	086	661

In our study, the neonates with perinatal asphyxia, prolonged rupture of membranes (PROM), meconium stained amniotic fluid or neonates with sepsis screen positive (increased total leucocyte count, culture of blood or other body fluids positive for pathogenic bacteria growth, C Reactive protein (CRP) positive, etc.) were treated as early onset neonatal sepsis. In the Table 5, the odd's ratio was 14.1742 and the two-tailed P value was less than 0.0001*** in the Fisher's exact test. The association between rows (neonates with no sepsis and neonates with early onset sepsis) and columns (neonates with physiologic jaundice and neonates with pathologic indirect hyperbilirubinemia) was considered to be extremely statistically significant. All the neonates with TSB more than 18mg/dL were also associated with early onset neonatal sepsis, in our study. Thus, in our study, early onset neonatal sepsis showed a strong association with pathologic indirect hyperbilirubinemia.

Neonatal polycythemia is defined as a central hemoglobin or hematocrit exceeding 2 standard deviations (SD) above the normal value for gestational and postnatal age. A full-term infant was considered to have polycythemia when the hemoglobin concentration was ≥22g/dL or haemocrit was ≥65%. (16) In the Table 6, the odd's ratio was 7.0370. The two-tailed P value equals 0.0049**, in the Chi-square test. The association between rows (neonates with polycythemia and neonates with no polycythemia) and columns (neonates with physiologic jaundice and neonates with pathologic indirect hyperbilirubinemia) was considered to be very statistically significant. All the neonates with polycythemia were also associated with early onset neonatal sepsis, in our study. Thus, in our study, neonates with polycythemia showed a strong association with pathologic indirect hyperbilirubinemia.

Table 6. Table showing a comparison of prevalence of jaundice in neonates with polycythemia and neonates with no polycythemia in Rockland Hospital, Delhi

Neonates	Physiologic Jaundice	Pathologic indirect hyperbilirubinemia	Total
No polycythemia	570	81	651
Polycythemia present	005	05	010
Total	575	86	661

Table 7: Table showing a comparison of prevalence of jaundice in neonates born to mothers with no diabetes and neonates born to mothers with diabetes in Rockland Hospital, Delhi

Mothers	Neonates with Physiologic Jaundice	Neonates with Pathologic Indirect Hyperbilirubinemia	Total
Mothers with no diabetes	546	074	620
Mothers with diabetes	029	012	041
Total	575	086	661

In the Table 7, the odd's ratio was 3.0531 and the two-tailed P value equals 0.0036** in the Fisher's exact test. The association between rows (mothers with no diabetes and mothers with diabetes) and columns (neonates with physiologic jaundice and neonates with pathologic indirect hyperbilirubinemia) was considered to be very statistically significant. About 8 neonates of mothers with diabetes were also associated with early onset neonatal sepsis, in our study. Thus, in our study, neonates of mothers with diabetes showed a strong association with pathologic indirect hyperbilirubinemia.

Table 8. Table showing a comparison of prevalence of jaundice in neonates with serum TSH ≥10mIU/L and neonates with serum TSH less than 10mIU/L in Rockland Hospital, Delhi

Neonates with Serum TSH value after Day 1	Physiologic Jaundice	Pathologic jaundice	Total
Serum TSH<10mIU/L	196	79	275
Serum TSH≥10mIU/L	084	07	091
Total	280	86	366

In our study, at birth, there was an acute increase of TSH with peak serum concentrations reaching 70-160mIU/L in few term and preterm infants. A rapid decline to less than 10mIU/L was seen in most neonates over the next 7 days, in our study. There was no case of congenital hypothyroidism, in our study. About 6 neonates with Serum TSH≥10mIU/L were also associated with early onset neonatal sepsis, in our study.

The serum TSH levels were less than 16mIU/mL in all the neonates with pathologic jaundice in our study. In the Table 8, the odd's ratio was 0.2068 and the two-tailed P value was less than 0.0001***, in the Fisher's exact test. The association between rows (neonates with serum TSH<10mIU/L and neonates with serum TSH≥10mIU/L) and columns (neonates with physiologic jaundice and neonates with pathologic jaundice) was considered to be extremely statistically significant. Thus, in our study, neonates with Serum TSH≥10mIU/L showed a strong association with pathologic indirect hyperbilirubinemia.

Table 9: Table showing a comparison of prevalence of jaundice in neonates with congenital abnormality and neonates with no congenital abnormality in a group of 661 neonates born in Rockland Hospital, Delhi.

Neonates	Physiologic Jaundice	Pathologic jaundice	Total
No congenital abnormality	570	82	652
Congenital abnormality present	005	04	009
Total	575	86	661

In the Table 9, the odd's ratio was 5.5609 and the two-tailed P value equals 0.0201* in the Fisher's exact test. The association between rows (neonates with congenital abnormality and neonates with no congenital abnormality) and columns (neonates with physiologic jaundice and neonates with pathologic jaundice) was considered to be statistically significant. All the neonates with congenital abnormality were also associated with early onset neonatal sepsis, in our study. This shows that the association of pathologic jaundice with neonates with congenital abnormality (most commonly ventricular septal defect) (VSD) was considered to be statistically significant, in our study.

Table 10: Table showing a comparison of prevalence of jaundice in male neonates and female neonates in a group of 661 neonates born in Rockland Hospital, Delhi

Neonates	Physiologic Jaundice	Pathologic Indirect Hyperbilirubinemia	Total
Males	313	052	365
Females	262	034	296
Total	575	086	661

In the Table 10, the odd's ratio was 1.2802 and the two-tailed P value equals 0.3524 in the Fisher's exact test. The association between rows and columns was considered to be not statistically significant. This shows that the association of pathologic jaundice with male neonates was considered to be not statistically significant, in our study.

Table 11: Table showing a comparison of prevalence of jaundice in male neonates and female neonates of weight less than 2.5kg in a group of 74 neonates born in Rockland Hospital, Delhi.

Neonates	Physiologic Jaundice	Pathologic Jaundice	Total
Males (weight<2.5kg)	29	09	038
Females (weight<2.5kg)	29	07	036
Total	58	16	074

In the Table 11, the odd's ratio was 1.2857. The two-tailed P value equals 0.7800 in the Fisher's exact test. The association between rows (male neonates of weight less than 2.5kg and female neonates of weight less than 2.5kg) and columns (neonates with physiologic jaundice and neonates with pathologic jaundice) was considered to be not statistically significant. This shows that the association of pathologic jaundice with low birth weight male neonates was considered to be not statistically significant, in our study.

Table 12. Table showing a comparison of prevalence of jaundice in neonates with compatible blood groups and neonates with incompatible blood groups in a group of 516 neonates born in Rockland Hospital, Delhi.

Neonates	Physiologic Jaundice	Pathologic Indirect Hyperbilirubinemia	Total
Compatible blood groups	284	056	340
ABO/Rh incompatibility	146	030	176
Total	430	086	516

In the Table 12, the odd's ratio was 1.0421 and the two-tailed P value equals 0.9011 in the Fisher's exact test. The association between rows (neonates with compatible blood groups and neonates with incompatible blood groups) and columns (neonates with physiologic jaundice and neonates with pathologic indirect hyperbilirubinemia) was considered to be not statistically significant.(5) There were about 145 neonates with physiologic jaundice, whose blood groups were not done, so these 145 neonates were excluded from this study. This study shows that the association of pathologic jaundice with neonates with ABO or Rh incompatibility was considered to be not statistically significant, in our study.

Table 13. Table showing a comparison of prevalence of jaundice in neonates with anemia and neonates with no anemia in Rockland Hospital, Delhi.

Neonates	Physiologic Jaundice	Pathologic jaundice	Total
Anemia	015	03	018
No anemia	560	83	643
Total	575	86	661

In the Table 13, the odd's ratio was 1.3494 and the two-tailed P value equals 0.7184 in the Fisher's exact test. The association between rows (neonates with anemia and neonates with no anemia) and columns (neonates with physiologic jaundice and neonates with pathologic jaundice) was considered to be not statistically significant, in this study. This shows that the association of pathologic jaundice with neonates with anemia was considered to be not statistically significant, in our study.

Table 14. Table showing a comparison of prevalence of jaundice in neonates born to primigravida mothers and neonates born to multigravida mothers in Rockland Hospital, Delhi.

Mothers	Neonates with Physiologic Jaundice	Neonates with Pathologic Jaundice	Total
Primigravida	238	042	280 (42.88%)
Multigravida	329	044	373 (57.12%)
Total	567	086	653 (100%)

In the Table 14, the odd's ratio was 1.3195 and the two-tailed P value equals 0.2437, in the Fisher's exact test. The association between rows (primigravida mothers and multigravida mothers) and columns (neonates with physiologic jaundice and neonates with pathologic jaundice) was considered to be not statistically significant.

This shows that the association of pathologic jaundice in neonates with their primigravida mothers was considered to be not statistically significant, in our study.

Table 15. Table showing a comparison of prevalence of jaundice in neonates born by vaginal delivery and neonates born by caesarean delivery in Rockland Hospital, Delhi.

Type of delivery	Neonates with Physiologic Jaundice	Neonates with Pathologic Jaundice	Total
Vaginal delivery	165	026	191 (29.25%)
Caesarean delivery	402	060	462 (70.75%)
Total	567	086	653 (100%)

In the Table 15, the odd's ratio was 1.0558 and the two-tailed P value equals 0.8988 in the Fisher's exact test. The association between rows and columns was considered to be not statistically significant. This shows that the association of pathologic jaundice with neonates born by vaginal delivery was considered to be not statistically significant, in our study.

Glucose-6-Phosphate Dehydrogenase (G6PD) activity: In the present study, the Glucose-6-Phosphate Dehydrogenase (G6PD) activity was normal in all the 86 neonates of Pathologic Indirect Hyperbilirubinemia and 214 neonates with physiologic jaundice. Remaining neonates with physiologic jaundice were not tested for Glucose-6-Phosphate Dehydrogenase (G6PD) activity. In our study, no neonate had a family history of G6PD deficiency. The two-tailed P value was less than 0.0001***, in the Chi-square test. By conventional criteria, this difference was considered to be extremely statistically significant.

Morbidity and mortality rate: In the present study, no neonate discharged from Rockland Hospital was reported to have hydrops foetalis, kernicterus or cerebral palsy during admission or on follow up. The two-tailed P value was less than 0.0001***, in the Chi-square test. By conventional criteria, this difference was considered to be extremely statistically significant. Besides, the neonatal mortality rate (NMR) was zero during the period 01.01.2012 till 07.08.2014, in the Paediatrics Department in Rockland Hospital, Delhi, India. The two-tailed P value was less than 0.0001***, in the Chi-square test. By conventional criteria, this difference was considered to be extremely statistically significant.

DISCUSSION

For the present cross-sectional study, 661 neonates (645 singleton neonates and 16 twin neonates) were recorded and studied in Paediatrics Department in Rockland Hospital. These neonates were born alive to 653 mothers (42.88% primigravida and 57.12% multigravida) by caesarean delivery in 70.75% cases and by vaginal delivery in 29.25% cases, in Obstetrics and Gynaecology Department in Rockland Hospital, during the period 01.01.2012 till 07.08.2014. (4) In our cross-sectional study of 661 neonates, the results showed that almost all neonates had transient unconjugated hyperbilirubinemia in the neonatal period, with more than ninety percent affected during their first week of life. The prevalence of physiologic jaundice in neonates was 86.99% (81.24% in term neonates and 5.75% in preterm neonates) and the prevalence of pathologic indirect hyperbilirubinemia in neonates was 13.01% (9.68% in term neonates and 3.33% in preterm neonates). Among these 13.01% neonates with pathologic indirect hyperbilirubinemia, about 9.68% neonates had TSB between 12mg/dL to 17.99mg/dL and 3.33% neonates had TSB between 18mg/dL to 26mg/dL. In our study, all the neonates with TSB more than 18mg/dL were also associated with early onset neonatal sepsis. In the present study, the Glucose-6-Phosphate Dehydrogenase (G6PD) activity was normal in all the neonates with pathologic jaundice. In our study, the risk factors like early onset neonatal sepsis, preterm gestation, low birth weight, very low birth weight, congenital abnormality (most commonly ventricular septal defect) (VSD), serum TSH level (≥10mIU/L), polycythemia and infant of diabetic mother showed a strong association with pathologic indirect hyperbilirubinemia. Besides, the association of pathologic jaundice with other factors like male neonate, ABO or Rh incompatibility, anemia, primigravida mother and vaginal delivery was considered to be not statistically significant, in our study. Thus, it is concluded that the hyperbilirubinemia in neonates was mostly the result of increased bilirubin production from increased red blood cell breakdown combined with transient limitation in conjugation of bilirubin by the immature neonatal liver and this neonatal hyperbilirubinemia became severe in presence of risk factors, most commonly neonatal sepsis. In our study, no neonate discharged from Rockland Hospital was reported to have hydrops foetalis, kernicterus or cerebral palsy during admission or on follow up. Besides, the Neonatal Mortality Rate was zero, in our study.

Following references support our observations:

- Almost all hyperbilirubinemia in the immediate neonatal period is unconjugated. Physiologic hyperbilirubinemia occurs in almost all neonates. Shorter neonatal RBC life span increases bilirubin production; deficient conjugation due to the deficiency of UGT decreases clearance; and low bacterial levels in the intestine combined with increased hydrolysis of conjugated bilirubin increase enterohepatic circulation. Bilirubin levels can rise up to 18 mg/dL by 3 to 4 days of life (7 days in Asian infants) and fall thereafter. Physiologic jaundice generally lasts less than seven days. The condition affects over half of babies in the first week of life. Of babies that are born early about 80% are affected.(19)

- Transient neonatal jaundice is one of the most common conditions occurring in newborns (children under 28 days of age) with more than eighty percent affected during their first week of life.(17)
- Jaundice is observed during the 1st week after birth in approximately 60% of term infants and 80% of preterm infants.(14)(15)
- The prevalence of neonatal jaundice in healthy term babies at National District Hospital in Bloemfontein was 55.2%. Although 52% of sampled infants had jaundice on the Bilicheck® meter, only 17% appeared clinically jaundiced. The consequence of a missed diagnosis and delayed treatment may cause serious morbidity (kernicterus).(3)
- The incidence of neonatal hyperbilirubinemia in a retrospective study done in a tertiary care hospital was 13.47%. Preterm gestation showed a strong association with neonatal hyperbilirubinemia.(27)

- The neonatal morbidity was studied in 7015 neonates born at the All India Institute of Medical Sciences Hospital, New Delhi. Neonatal hyperbilirubinemia occurred in 5.9 per cent, most of whom were premature.(28)

- Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. Overall, 6-7% of full term infants have indirect bilirubin levels >13mg/dL, and <3% have levels >15mg/dL.(15)

- A blood type incompatibility between the mother and baby is also a reason to track the newborn's jaundice more closely. This exists when a mother has the blood type O (and therefore has antibodies against A and B cells) and her newborn is of blood type A or B. This *may* cause the newborn's red blood cells to break down more quickly due to maternal antibodies that have leaked into the baby's bloodstream. A blood type incompatibility also exists if the mother has Rh (Rhesus) factor negative blood type and the newborn is Rh factor positive. This had been a common cause of severe neonatal jaundice, but is now very uncommon because Rh immune globulin (Rhogham) is given to mothers at risk before delivery.(9)

- Alloimune hemolytic disease from RhD antigen incompatibility is approximately 3 times more common among whites than among blacks, because of differences in Rh allele frequency. Indirect-reacting bilirubin content rises rapidly to high levels in the 1st 6-12 hour of life. The risk of initial sensitization of Rh-negative mothers has been reduced to less than 0.1% by the routine administration of Rh-immunoglobulin (RhoGAM) to all mothers at risk for Rh alloimmunization.(16)

- In about a third of all ABO incompatible pregnancies maternal IgG anti-A or IgG anti-B antibodies pass through the placenta to the fetal circulation leading to a weakly positive direct Coombs test for the neonate's blood. However, ABO HDN is generally mild and short-lived and only occasionally severe because: (1) IgG anti-A (or IgG anti-B) antibodies that enter the fetal circulation from the mother find A (or B) antigens on many different fetal cell types, leaving fewer antibodies available for binding onto fetal red blood cells. (2) Fetal RBC surface A and B antigens are not fully developed during gestation and so there are a smaller number of antigenic sites on fetal RBCs.(1)

- In a study, majority of new-borns with ABO incompatibility, developed hyperbilirubinemia between 3-5 days. It shows, hemolytic disease due to ABO incompatibility, becomes severe in presence of aggravating conditions or with risk factor. Hyperbilirubinemia due to ABO incompatibility resolves naturally in most cases (56%), as there is very mild hemolysis. In cases, who required treatment, most of them were cured only by phototherapy (43%).(22)

- In a cross-sectional study, about 200 mothers and neonates were examined. Our findings depicted that mother's WBC, Hb, PLT, and gestational age were associated with jaundice ($P < 0.05$). Furthermore, there were significant relationships between different degrees of bilirubin with TSH, T4 levels and G6PD ($P < 0.05$). In fact, TSH, T4 levels and G6PD were found to be linked to neonatal hyperbilirubinemia. The risk factors for jaundice in our study population comprise some predisposing factors such as WBC, Hb, PLT, gestational age, TSH, and T4 levels, as well as G6PD. Neonates at risk of jaundice are linked to some maternal and neonatal factors that can provide necessary interventions to reduce the burden of the disease. Therefore, identification of associated factors can facilitate early diagnosis, and reduce subsequent complications.(18)

- The tragedy of occurrence of kernicterus is compounded by the fact that, if newborn jaundice and neonatal hyperbilirubinemia are detected early, kernicterus is completely preventable. All newborn infants are at risk for newborn jaundice, which when unmonitored or untreated can progress to excessive bilirubin levels.(26)

- In a retrospective study on 1020 patients admitted at a hospital during one year period 1st January 2012–31st December 2012, in 260 there was a diagnosis of indirect hyperbilirubinemia, associated pathology consisted of urinary tract infection in 15 cases, piodermatitis in 12, otitis media in 7, acute diarrhea in 14 cases and severe dehydration in 9 cases. Only one case complicated with kernicterus.(10)

- Neurotoxicity is the major consequence of neonatal hyperbilirubinemia. An acute encephalopathy can be followed by a variety of neurologic impairments, including cerebral palsy and sensorimotor deficits; cognition is usually spared. Kernicterus is the most severe form of neurotoxicity. Although it is now rare, kernicterus still occurs and can nearly always be prevented.(19)

- Common complications of preterm birth are high rates of respiratory distress syndrome, sepsis, periventricular leucomalacia, seizures, intraventricular hemorrhage, cerebral palsy, infections, pathologic jaundice, kernicterus, hypoxic ischemic encephalopathy, and visual and hearing problems. Complications of preterm birth were the leading cause of death in children younger than 5 years of age globally in 2016, accounting for approximately 16% of all deaths, and 35% of deaths among newborn babies. Preterm neonates who survive are at greater risk of a range of short-term and long-term morbidities.(30)

- Preterm birth is the most common cause of death among infants worldwide. Complications from preterm births resulted in 0.81 million deaths in 2015 down from 1.57 million in 1990.(2)(11) The chance of survival at 22 weeks is about 6%, while at 23 weeks it is 26%, 24 weeks 55% and 25 weeks about 72%.(6) The chances of survival without any long-term difficulties are lower.(14) Approximately 0.5% of births are extremely early periviable births, and these account for most of the deaths (11)

- By pathologic criteria, kernicterus develops in 30% of infants (all gestational ages) with untreated hemolytic disease and bilirubin levels >25-30 mg/dL. The incidence at autopsy in hyperbilirubinemic preterm infants is 2-16%.(15)

Following references don't support our observations:

- Bilirubin in LBW infants is significantly higher in males when compared with females.(29)
- Globally over 100,000 late-preterm and term babies die each year as a result of jaundice.(21)
- Neonatal mortality rate of India fell gradually from 85.2 deaths per thousand live births in 1969 to 22.7 deaths per thousand live births in 2018.(13)
- In the present study, the neonatal mortality rate was zero.(4)

SUMMARY

In this study, the aim was to find out the risk factors associated with neonatal jaundice in a tertiary care hospital in Delhi, India. Our objective was to facilitate early diagnosis and reduce subsequent complications of neonatal jaundice. The study was a cross-sectional study, conducted at the Department of Paediatrics, Rockland Hospital in Delhi. For the present study, 661 neonates (645 singleton neonates and 16 twin neonates) were recorded and studied in Paediatrics Department in Rockland Hospital. These neonates were born alive to 653 mothers in Obstetrics and Gynaecology Department in Rockland Hospital, during the period 01.01.2012 till 07.08.2014. The study was done as Random Sampling of the neonates noticed to have deep yellow discolouration of whole body that were born in Rockland Hospital, Delhi. In this study, all the venous blood samples of neonates for Total Serum Bilirubin (TSB) and Direct Serum Bilirubin were collected during first 9 days of life, and in one case of persistent pathologic hyperbilirubinemia, the sample was again collected on Day 21 of life. These neonates were further investigated for hemoglobin estimation, hematocrit estimation, sepsis screen, Glucose-6-Phosphate Dehydrogenase (G6PD) activity and serum TSH levels. Besides, venous blood samples were collected for blood groups of about 516 neonates as well as blood groups of their mothers were also done. Participants that satisfied the inclusion criteria were selected and the participants who did not meet the inclusion criteria were excluded. Neonates' history and investigations information was collected in questionnaires and the data was collected and reported, and then statistical analysis of data was performed using SPSS software. The calculations of odd's ratios were done using MedCalc statistical Software and calculations of P values were done using QuickCalcs-Graphpad Software. The Chi-square test or Fisher's exact test was used to calculate the Two-tailed P values in our study.

In our cross-sectional study of 661 neonates (601 term neonates and 60 preterm neonates), the results showed that almost all neonates had transient unconjugated hyperbilirubinemia in the neonatal period, with more than ninety percent affected during their first week of life. The prevalence of physiologic jaundice in neonates was 86.99% (81.24% in term neonates and 5.75% in preterm neonates) and the prevalence of pathologic indirect hyperbilirubinemia in neonates was 13.01% (9.68% in term neonates and 3.33% in preterm neonates). Among these 13.01% neonates with pathologic indirect hyperbilirubinemia, about 9.68% neonates had TSB between 12mg/dL to 17.99mg/dL and 3.33% neonates had TSB between 18mg/dL to 26mg/dL. In our study, all the neonates with TSB more than 18mg/dL were also associated with early onset neonatal sepsis. In the present study, the Glucose-6-Phosphate Dehydrogenase (G6PD) activity was normal in all the neonates with pathologic jaundice. In our study, the risk factors like early onset neonatal sepsis, preterm gestation, low birth weight, very low birth weight, congenital abnormality (most commonly ventricular septal defect), serum TSH level (≥10mIU/L), polycythemia and infant of diabetic mother showed a strong association with pathologic indirect hyperbilirubinemia. Besides, the association of pathologic jaundice with other factors like male neonate, ABO or Rh incompatibility, anemia, primigravida mother and vaginal delivery was considered to be not statistically significant, in our study. In our study, no neonate discharged from Rockland Hospital was reported to have hydrops foetalis, kernicterus or cerebral palsy during admission or on follow up. Besides, the Neonatal Mortality Rate was zero, in our study.

CONCLUSION

From this cross-sectional study of 661 neonates (601 term neonates and 60 preterm neonates), it is concluded that almost all neonates had transient unconjugated hyperbilirubinemia in the neonatal period, with more than ninety percent affected during their first week of life. The prevalence of physiologic jaundice in neonates was 86.99% and the prevalence of pathologic indirect hyperbilirubinemia in neonates was 13.01%. Among these 13.01% neonates with pathologic indirect hyperbilirubinemia, about 9.68% neonates had TSB between 12mg/dL to 17.99mg/dL and 3.33% neonates had TSB between 18mg/dL to 26mg/dL. In our study, all the neonates with TSB more than 18mg/dL were also associated with early onset neonatal sepsis. In the present study, the Glucose-6-Phosphate Dehydrogenase (G6PD) activity was normal in all the neonates with pathologic jaundice. In our study, the risk factors like early onset neonatal sepsis, preterm gestation, low birth weight, very low birth weight, congenital abnormality (most commonly ventricular septal defect), serum TSH level (≥10mIU/L), polycythemia and infant of diabetic mother showed a strong association with pathologic indirect hyperbilirubinemia. Besides, the association of pathologic jaundice with other factors like male neonate, ABO or Rh incompatibility, anemia, primigravida mother and vaginal delivery was considered to be not statistically significant, in our study. Thus, it is concluded that the hyperbilirubinemia in neonates was mostly the result of increased bilirubin production from increased red blood cell breakdown combined with transient limitation in conjugation of bilirubin by the immature neonatal liver and this neonatal hyperbilirubinemia became severe in presence of risk factors, most commonly neonatal sepsis. In our study, no neonate discharged from Rockland Hospital was reported to have hydrops foetalis, kernicterus or cerebral palsy during admission or on follow up. Besides, the Neonatal Mortality Rate was zero, in our study.

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