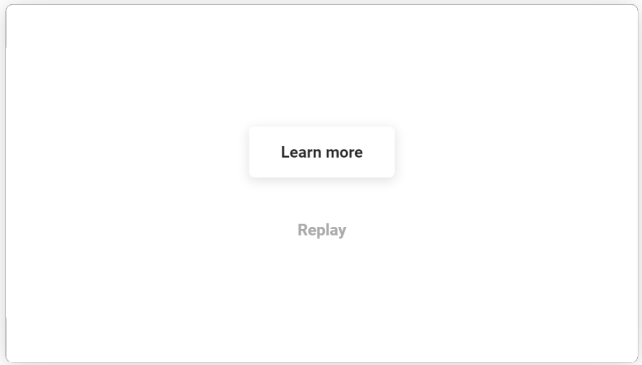

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India

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SUBJECT AREA AND CATEGORY

Environmental Science
Health, Toxicology and Mutagenesis

Medicine
Pathology and Forensic Medicine

Pharmacology, Toxicology and Pharmaceutics
Toxicology

Social Sciences
Law

PUBLISHER

Institute of Medico-legal Publications

H-INDEX

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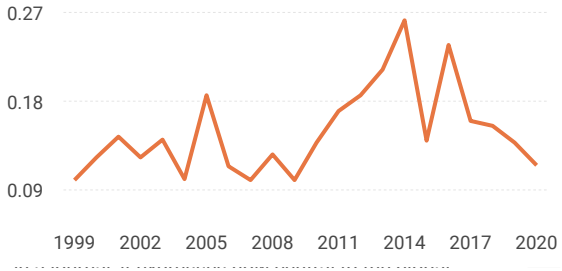
PUBLICATION TYPE

ISSN

COVERAGE

INFORMATION

SJR



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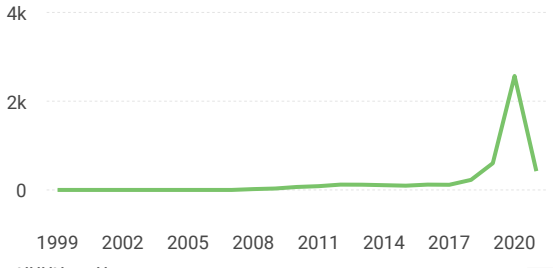

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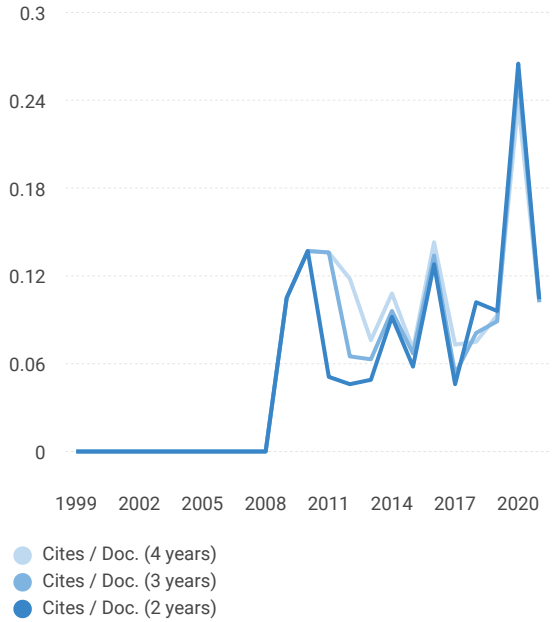

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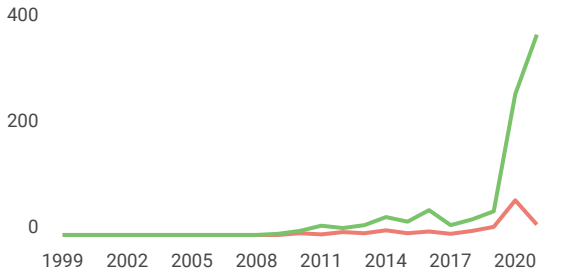

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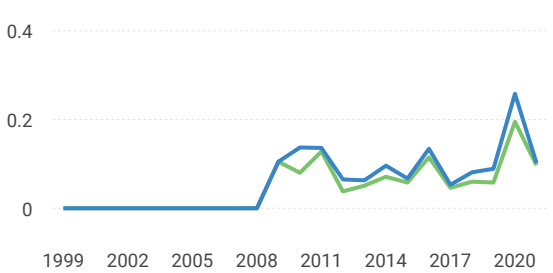

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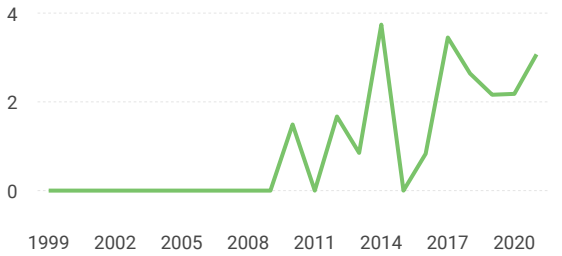

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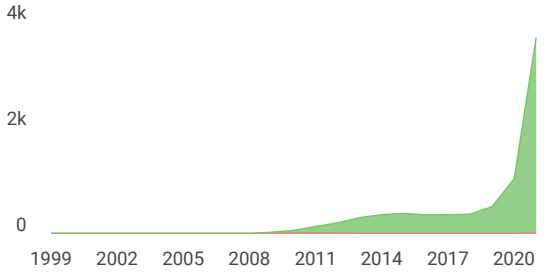

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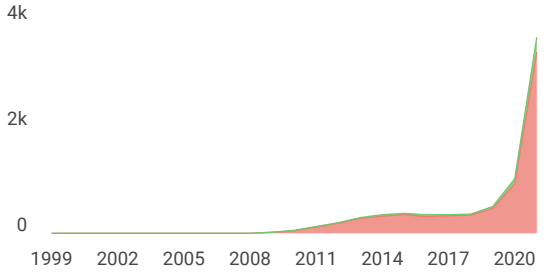

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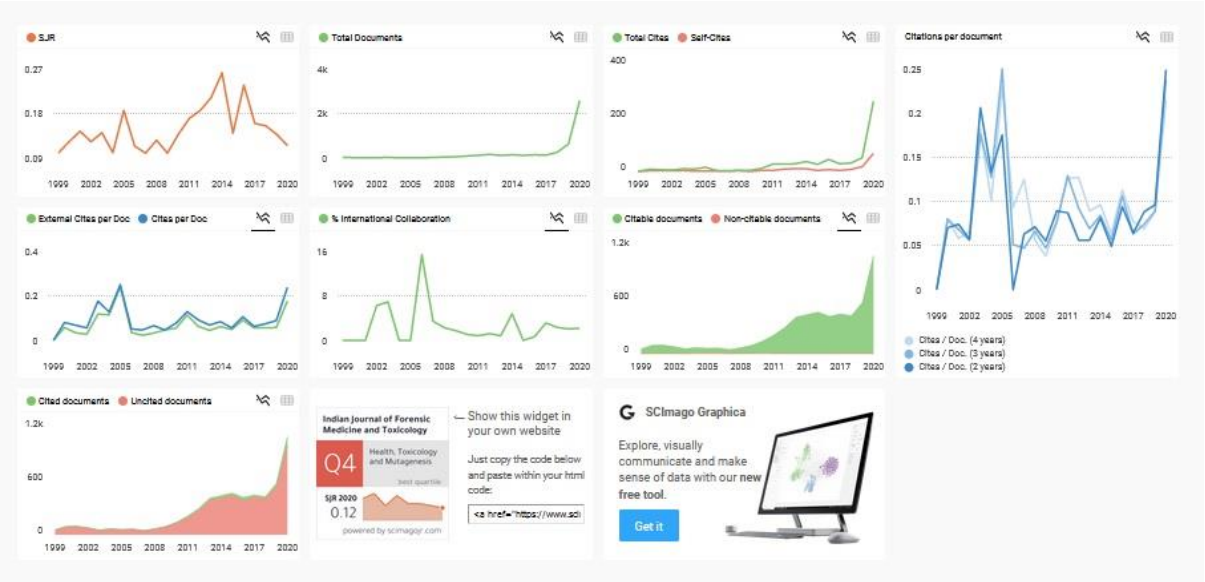
PUBLICATION TYPE	ISSN	COVERAGE	INFORMATION
Journals	09739122, 09739130	2008-2020	Homepage How to publish in this journal editor.ijfmt@gmail.com

SCOPE

"Indian Journal of Forensic Medicine & Toxicology " is a double-blind peer reviewed international journal. The frequency is quarterly. It deals with Forensic Medicine, Forensic Science, Toxicology, DNA fingerprinting, sexual medicine, environmental medicine, Forensic Pathology, legal medicine and public health laws.



ISSN-0973-9122 (Print) ● ISSN-0973-9130 (Electronic)

Volume 15 / Number 4 / October-December 2021

Indian Journal of Forensic Medicine & Toxicology

Website: www.ijfmt.com

Official Organ of Indian Association of Medico-Legal Experts (Regd.)

Indian Journal of Forensic Medicine & Toxicology

Print-ISSN:0973-9122 Electronic - ISSn: 0973-9130

Website: www.ijfmt.com

Editor

Dr. R.K. Sharma
Institute of Medico-legal Publications
Logix Office Tower, Unit No. 1704, Logix City Centre Mall, Sector- 32, Noida - 201 301 (Uttar Pradesh)

Printed, published and owned by

Dr. R.K. Sharma
Institute of Medico-legal Publications
Logix Office Tower, Unit No. 1704, Logix City Centre Mall, Sector- 32, Noida - 201 301 (Uttar Pradesh)

Published at

Institute of Medico-legal Publications
Logix Office Tower, Unit No. 1704, Logix City Centre Mall, Sector- 32, Noida - 201 301 (Uttar Pradesh)

"Indian Journal of Forensic Medicine & Toxicology" is peer reviewed quarterly journal. It deals with Forensic Medicine, Forensic Science, Toxicology, DNA fingerprinting, sexual medicine and environment medicine. It has been assigned International standard serial No. p-0973-9122 and e- 0973-9130. The Journal has been assigned RNI No. DELENG/2008/21789. The journal is indexed with Index Copernicus (Poland) and is covered by EMBASE (Excerpta Medica Database). The journal is also abstracted in Chemical Abstracts (CAS) database (USA. The journal is also covered by EBSCO (USA) database. The Journal is now part of UGC, DST and CSIR Consortia. It is now offical publication of Indian Association of Medico-Legal Experts (Regd.).

Indian Journal of Forensic Medicine & Toxicology

Contents

Volume 15, Number 4 October-December 2021

Article Type: Research Article

Risk Factors of Rebound Hyperbilirubinemia in Post Phototherapy Hyperbilirubinemia Infants

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Abstract

Background: Post phototherapy rebound hyperbilirubinemia is a cause for readmission in some infants. However, this phenomenon data of rebound hyperbilirubinemia is lacking from Indonesia. Our study aims to describe the risk factor of post phototherapy rebound hyperbilirubinemia in the infant.

Method: Cross-sectional study of all infants with indirect hyperbilirubinemia who were treated phototherapy according to standard guidelines in neonate intermediate unit Dr. Soetomo hospital for 6 months from June 2017 until December 2017. Bilirubin was measured 24 hours after phototherapy. Bilirubin rebound is considered as increasing total serum bilirubin that needs reinstitution of phototherapy.

Result: A total of 53 (44.9%) infants developed rebound hyperbilirubinemia. We revealed the following risk factor for rebound hyperbilirubinemia was the onset of jaundice on < 3 days, (10 babies, p <0.05). Other results are 30 (56.6%) female infants, 39 (73%) birth weight < 2500 g, 36 (67%) infants with a history of cesarean section, and 38 (71%) preterm infants but there are not statistically significant.

Conclusion: Post phototherapy rebound hyperbilirubinemia should be considered in the onset of jaundice < 3 days.

Keywords: *Phototherapy, Neonatal hyperbilirubinemia, Rebound hyperbilirubinemia*

Introduction

Hyperbilirubinemia in neonates is a common condition. Approximately 60-70% of term neonates and 80% of preterm neonates develop jaundice in the first week of life. Most of the hyperbilirubinemia is physiological and does not require special therapy, but there are some conditions where after phototherapy the hyperbilirubinemia recurs. Rebound hyperbilirubinemia after stopping phototherapy is a rare phenomenon.[1,2] Some authors define it as a post-phototherapy bilirubin level that requires reinstitution of phototherapy according to AAP guidelines.[3] The detection of rebound hyperbilirubinemia after stopping phototherapy is a common practice that prolongs hospital stay and increases laboratory costs.

In the previous study, recurrent hyperbilirubinemia occurred in 24.9% of the neonates who were the study subjects, the majority causes are hemolytic disease (71%) (ABO incompatibility 54.8%, Rhesus 4.8%, other etiologies unknown 16.9%). From previous studies, it was found that low birth weight increased

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the risk of recurrent hyperbilirubinemia by 3.5x and the male gender increased the risk by 1.6x. Other risk factors include gestational age, mode of delivery, birth weight based on gestational age, pregnancy more than once, and the onset of jaundice.[4] Phototherapy is widely recognized as a relatively safe and effective method for the treatment of neonatal hyperbilirubinemia.

Bilirubin levels often increase after discontinuation of phototherapy. The factors causing the elevated bilirubin levels after stopping phototherapy have been investigated in several previous studies with different risk factors. This research has not been carried out in Dr. Soetomo hospital so that this study is the beginning to find risk factors for recurrent hyperbilirubinemia babies so that it can find prevention and prognosis for babies with the disease.

Material and Methods

Study Population

A case-control study was conducted on hyperbilirubinemia infants (age 0-28 days) in Dr. Soetomo General Hospital, Surabaya. Subjects were chosen using the total sampling technique and were included in the study if they met the following inclusion criteria: hyperbilirubinemia which had phototherapy. Exclusion criteria in this study include multiple congenital anomalies, sepsis, and direct hyperbilirubinemia. The control of this study is an infant with hyperbilirubinemia but does not have rebound hyperbilirubinemia.

Phototherapy is using blue light (minimum intensity of phototherapy light 10-12mW/cm^2/nm) with an effective surface area of 60x30 cm and a distance of the light from the baby of 40 cm for 1-2 x 24 hours.

Hyperbilirubinemia is defined as a condition in which bilirubin levels increase with normal values depending on gestational age or birth weight and postnatal age (in hours) and clinically requires phototherapy or exchange transfusion.[5]

Rebound hyperbilirubinemia is defined as post-phototherapy bilirubin level requiring reinstitution of phototherapy according to AAP (American Academy of Pediatrics) guidelines (Bansal et al., 2010).[3]

Data of sex, the onset of jaundice, birth weight, gestational age, and mode of delivery from all infants that met the criteria of rebound hyperbilirubinemia were recorded from the medical records. Birth weight is grouped by ³ 2500 gram < 2500 gram; onset of jaundice is grouped by and ³ 3 days and < 3 days old; mode of delivery is grouped by vaginal delivery and caesarean section; gestational age is grouped by term and preterm infant.

Statistical Analysis

The data were analyzed using Microsoft Excel 2019 and using IBM SPSS Statistic Version 21.0. A descriptive analysis was used to present the correlation. A Chi-square test was used to seek the bivariate correlation of rebound hyperbilirubinemia and risk factors.

Variables that have correlations were analyzed further by analysis of variance to define any influences between variables. A value of $p < 0.05$ was considered to be significant.

Ethics

This study was conducted after obtaining ethical approval from the Health Research Ethics Committee of Dr. Soetomo General Hospital, Surabaya. Before conducting the research, the procedure was fully explained to the parents. The study was conducted only after informed consent was signed by the parents/ guardians. The confidentiality of the research subjects was maintained in this study.

Result and Discussion

A total of 118 infants in neonatal inpatient installation of Dr. Soetomo hospital with hyperbilirubinemia requiring phototherapy were involved in this study. The base characteristics of this study are described in table 1. Correlation of sex, onset of jaundice, mode of delivery, birth weight, and gestational age with rebound hyperbilirubinemia described in table 2

Table 1. Characteristics of subjects

Variables	n(%)
Rebound hyperbilirubinemia	
yes	53(44.90)
no	65(55.10)
Sex	
male	54(45.80)
female	64(54.20)
Birth weight	
³ 2500 gram	39(33.10)
<2500 gram	79(66.90)
Onset of Jaundice	
< 3 days	10(8.40)
³ 3 days	108(91.60)
Mode of delivery	
vaginal delivery	32(27.10)
caesarean section	86(72.90)
Gestational age	
term	42(35.60)
preterm	76(64.40)

Table 2. Correlation of sex, onset of jaundice, mode of delivery, birth weight, and gestational age with rebound hyperbilirubinemia

Variable	Rebound hyperbilirubinemia		p	OR	CI
	yes	no			
Sex			0.71	0,84	0,40-1,74
male	23	31			
female	30	34			
Onset of jaundice			<0.05*	2,51	1,99-3,16
< 3 days	10	0			
³3 days	43	65			
Mode of delivery			0.21	1,72	0.75-3,93
Vaginal delivery	17	14			
Caesarean section	36	51			
Birth weight			0.08	0.08	0.92-4.55
³ 2500g	14	25			
< 2500g	39	40			
Gestational age			0.17	0.21	0.75-3.93
term	15	27			
pre-term	38	38			

*p-value statistically significant

In this study, 53 infants (44.9%) were found with rebound hyperbilirubinemia. Female babies are more than male babies. Hyperbilirubinemia was more found in cases of infants with birth weight <2500g. The onset of hyperbilirubinemia occurs mostly at <3 days of life. Most cases of hyperbilirubinemia occurred in infants caesarean section delivery. In addition, the most cases of hyperbilirubinemia were also found in infants with pre-term infant.

Female infants with rebound hyperbilirubinemia are more than male infants. The results of this study are different from previous studies with 9% of female babies compared to 12.9% of male infants who experience recurrent hyperbilirubinemia.[6] The cause of the differences in this study is that it does not exclude the possibility of hemolytic diseases such as ABO incompatibility, Rhesus, Coomb test, G6PD, sepsis, type of nutrition, and other risk factors so that there is a possibility that female patients are included in the study sample that will affect the study results.

Onset of jaundice in infants with rebound hyperbilirubinemia was found to be significantly different in infants with yellow onset <3 days with a risk of 2.5 times compared to ³ 3 days. The highest incidence of jaundice was observed on the second to fourth day after birth. Among all infants with the onset of jaundice within 72 hours after birth, 13.8% showed hyperbilirubinemia after cessation of phototherapy.[6] Contributing factors to the development of physiological hyperbilirubinemia in the neonate include increased bilirubin load due to relative polycythemia, shortened erythrocyte life span (80 days compared to 120 days of adults), immature hepatic absorption and conjugation processes, and increased enterohepatic circulation.[7] This study does not record the nutrition of the baby so that this result can be biased.

Mode of delivery by caesarean section also showed more results in infants with rebound hyperbilirubinemia (30.50%) compared to normal delivery (14.40%), but in this study, it was not statistically significant. In another study after discontinuation of phototherapy, rebound hyperbilirubinemia was found in 13.3% of neonates born via cesarean section, but no statistically significant association was found ($p = 0.520$).[6] In this study, the data on infants with cesarean delivery were not recorded with the indication.

Low birth weight babies and preterm infants are not statistically significant in this study. In another previous study, birth weight <2000gram was found to be a significant risk for recurrent hyperbilirubinemia ($p < 0.001$).[6] Similar results were also found by Kaplan M et al.[8] The difference in this result can be caused by the other risk factor like ABO, Rhesus, G6PD were not excluded in this study. Premature babies have immature hormonal and enzyme responses, and hyperbilirubinemia is caused by the liver maturity factor, where the baby's liver function is not fully mature to process erythrocytes so that indirect bilirubin conjugation is not perfect either.

Jaundice can be aggravated by polycythemia, hemolysis, and infection because hyperbilirubinemia can cause a jaundiced kern, so the baby's skin color must be monitored frequently.[9] The three best predictors for recurrent hyperbilirubinemia were gestational age of the infant, age at initiation of phototherapy, and total serum bilirubin.[10]

Conclusion

Jaundice in infants with rebound hyperbilirubinemia was higher in subjects with onset of jaundice < 3 days. There was no correlation of sex, mode of delivery, birth weight, and gestational age with rebound hyperbilirubinemia in infants in this study. Factors affecting rebound hyperbilirubinemia such as ABO, Rhesus, G6PD, and Coomb's test should be investigated at the time of sample selection.

Acknowledgment: The author thanks to Dr. Soetomo general hospital-Universitas Airlangga, Surabaya, Indonesia for the medical record collection.

Ethical Clearance: We obtained an approval of whole project from Ethical Committee Review Board of Dr. Soetomo General Hospital Surabaya.

Source of Funding - Self

Conflict of Interest - Nil

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