Impact of National Clinical Practice Guidelines on Exchange Transfusion for Severe Neonatal Hyperbilirubinemia in Singapore

ABSTRACT

Aims: To review the incidence of double volume exchange transfusion for severe neonatal hyperbilirubinemia in infants ≥35 weeks' gestational age before and after implementation of National Clinical Practice Guidelines (NCPGNJ), analyze etiologies for severe hyperbilirubinemia, readmission rates for phototherapy and neurodevelopmental outcomes up to 2 years.

Study design: Retrospective study

Place and Duration of Study: KK Women's and Children's Hospital, Singapore, between January 2016 and December 2021.

Methodology: National Clinical Practice Guidelines on Evaluation and Management of Neonatal Jaundice (NCPGNJ) was implemented in January 2019. We retrospectively reviewed the medical records of neonates in our center who underwent double volume exchange transfusion for severe neonatal hyperbilirubinemia before and after implementation of the national clinical practice guidelines.

Results: Overall, 56 infants underwent double volume exchange transfusion for severe

hyperbilirubinemia during the study period. There was a decline in the incidence of exchange transfusion from 107 per 100 000 live births in epoch 1 (2016-2018) to 61 per 100 000 live births in epoch 2 (2019-2021). There was a steady decline in overall phototherapy rates (*p=0.06*), readmission rates for phototherapy (*p=0.04*) and number of neonates needing exchange transfusion (*p=0.25*). ABO-hemolytic disease of the newborn was the most common etiology. One infant had delayed presentation of severe hyperbilirubinemia and eventually developed cerebral palsy. The rest of the infants had normal neurodevelopmental and audiological assessments at follow-up.

Conclusion: The evidence-based National Clinical Practice Guidelines (NCPGNJ) has reduced the incidence of exchange transfusion. It provides a unified framework for all healthcare professionals who manage neonates with hyperbilirubinemia in different healthcare settings.

Keywords: Neonatal jaundice, hyperbilirubinemia, exchange transfusion

1. INTRODUCTION

Neonatal jaundice is a physiological process that affects most newborns. However, some infants may develop severe hyperbilirubinemia. Unbound bilirubin can cross the blood-brain barrier and deposit in the basal ganglia, brainstem nuclei, vestibulo-cochlear nucleus, and cause neurotoxicity. Delayed diagnosis and management can result in acute bilirubin encephalopathy, kernicterus or even death. Double volume exchange transfusion is an established and effective procedure to rapidly eliminate serum bilirubin and reduce the risk of kernicterus in cases of severe hyperbilirubinemia.

The National Clinical Practice Guidelines on Evaluation and Management of Neonatal Jaundice (NCPGNJ) [1] was implemented in all healthcare institutions in Singapore from

January 2019. These guidelines were developed and adapted to local needs based on recommendations from the American Academy of Pediatrics Subcommittee on hyperbilirubinemia [2] and the United Kingdom's National Institute of Clinical Excellence (NICE) guidelines on management of jaundice in newborn infants under 28 days of age [3].

The National Clinical Practice Guidelines (NCPGNJ) introduced transcutaneous bilirubinometry (TcB) as a screening tool for neonatal jaundice along with cut-off readings that would trigger total serum bilirubin measurement. The guidelines also stratified neonates into "normal risk" versus "high-risk" categories, and provided management algorithms for initiating phototherapy, intravenous immunoglobulin or double volume exchange transfusion.

The main objective of this study was to review the incidence of double volume exchange transfusion for severe neonatal hyperbilirubinemia in infants ≥35 weeks' gestational age in our center before and after implementation of the National Clinical Practice Guidelines. We hypothesized that the National Clinical Practice Guidelines will improve earlier identification and prompt management of significant hyperbilirubinemia and reduce the incidence of exchange transfusion. We also analyzed the etiologies of severe hyperbilirubinemia in our population, readmission rates for phototherapy and neurodevelopmental outcomes up to 2 years of age.

2. METHODS

We retrospectively reviewed the medical records of infants ≥35 weeks' gestational age who underwent double volume exchange transfusion for severe hyperbilirubinemia from January 2016 to December 2021 in KK Women's and Children's Hospital (KKH), Singapore's largest tertiary perinatal referral center. Demographic details, risk factors for neonatal hyperbilirubinemia, age on admission, total serum bilirubin levels before and after exchange

transfusion, adverse events related to exchange transfusion, and neurodevelopmental outcomes till 2 years of age were recorded and analyzed anonymously.

Severe or extreme hyperbilirubinemia was defined as total serum bilirubin (TSB) level above the threshold for exchange transfusion [1].

Epoch 1 (2016-2018) and Epoch 2 (2019-2021) refer to the periods before and after implementation of the NCPGNJ guidelines. Apart from inborn infants who required phototherapy during the birth hospitalization, our center also admitted cases referred for phototherapy from polyclinics, Children's Emergency and private paediatricians and these included both inborn and outborn infants.

3. STATISTICAL ANALYSIS

Descriptive statistics are presented as mean ± standard deviation for continuous data, frequency, and percentage for categorical data. Statistical analysis of the trends of live births, referrals for phototherapy, total number of cases of phototherapy and exchange transfusion was performed using linear regression. *P values* less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS.

4. RESULTS

Table 1 shows the trends of total number of live births ≥35 week' gestation, total number of cases of phototherapy, total number of referrals for phototherapy and number of cases of exchange transfusion during the study period. There was a steady decline in the overall phototherapy rates (*p=0.06*), number of referrals needing admission for phototherapy

(*p=0.04*) and number of infants needing exchange transfusions (*p=0.25*) after implementation of the national clinical practice guidelines.

Table 1. Description of trends of number of live births ≥35 weeks' gestation, total number of cases of phototherapy, referrals for phototherapy and number of cases of exchange transfusion

	Epoch 1			Epoch 2			% decrease per year	95% confidence interval (CI) (%)	*P value*
	2016	**2017**	**2018**	**2019**	**2020**	**2021**			
Total no of live births ≥35 weeks' gestation	11225	11241	11263	10907	10918	11216			
Total no. of cases of phototherapy (% of live births)	6251 (55.6)	7566 (67.3)	7125 (63.3)	5981 (54.8)	4145 (38)	4403 (39.3)	5	-10 to 0.5	0.06
Total no. of admissions referred	2120 (18.9)	1925 (17.1)	1885 (16.7)	1424 (13.1)	1486 (13.6)	1640 (14.6)	0.01	-0.02 to -0.001	0.04

for phototherapy (% of live births)									
No of cases of double volume exchange transfusion (% of total no. of cases of phototherapy)	11 (0.18)	10 (0.13)	15 (0.21)	9 (0.15)	6 (0.14)	5 (0.11)	0.01	-0.03 to 0.01	0.25

During the study period, 56 infants received exchange transfusion, epoch 1 (36) and epoch 2 (20). There were no differences in baseline characteristics of the infants between the two epochs. The incidence of exchange transfusion declined after implementation of the neonatal jaundice guidelines (NCPGNJ) (Figure 1).

Figure 1. Incidence of double volume exchange transfusions per 100000 live births

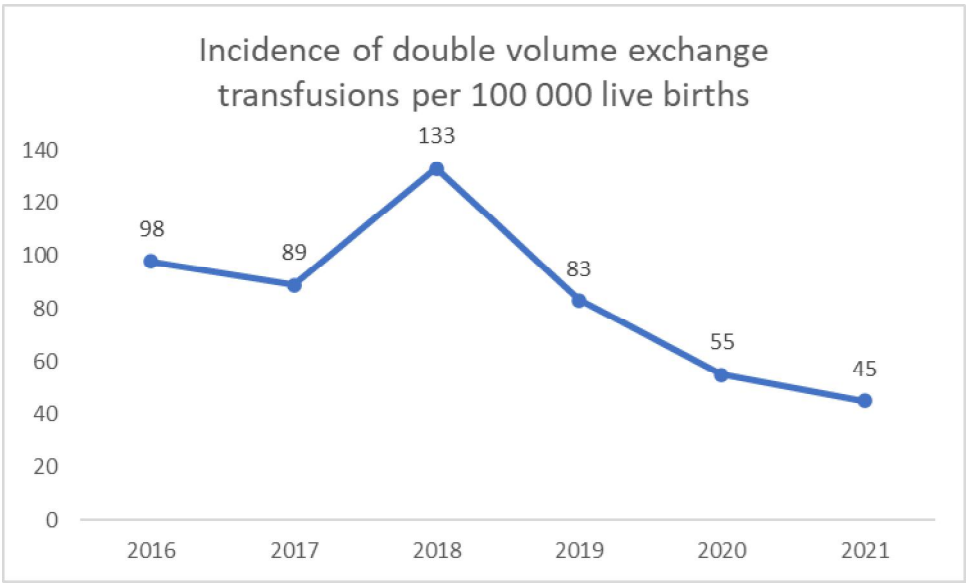

Table 2 shows the distribution of etiologies responsible for severe hyperbilirubinemia in our cohort. 20 (35.7%) neonates had 2 or more risk factors for severe hyperbilirubinemia. Severe anti-B hyperbilirubinemia was found to be three times more common than anti-A hyperbilirubinemia with higher median antibody titers and was more likely to have a positive direct Coomb's test (DCT). This suggests that O-B alloimmunization induces more active hemolysis in our population.

Table 2. Aetiology of severe hyperbilirubinemia

Aetiology of severe hyperbilirubinemia	**Number (%)**
ABO hemolytic disease of the newborn	24 (42.9)
Rhesus hemolytic disease of the newborn	3 (5.4)
G6PD deficiency	1 (1.8)
Cephalohematoma	6 (10.7)
Urinary tract infection	5 (8.9)

Inadequate breastfeeds resulting in excessive weight loss > 10%	8 (14.3)
Unidentifiable risk factors	9 (16.1)

Infants with severe hyperbilirubinemia requiring exchange transfusion were referred to our center earlier after introduction of the national clinical practice guidelines. In Epoch 1, infants presented to us at less than 24 hours after birth or were referred to us at more than 120 hours old. In Epoch 2, infants presented at less than 24 hours after birth or were referred between 72 to 120 hours of life. Overall, the mean peak total serum bilirubin before exchange transfusion was 425±89μmol/L, which was reduced by 56±39% following double volume exchange transfusion. Thrombocytopenia, hypocalcemia and mild metabolic acidosis were the most common adverse events of exchange transfusion, which resolved spontaneously. The average duration of hospitalization was 3 to 4 days.

In our center, we follow-up infants who have undergone exchange transfusion for severe hyperbilirubinemia with an audiological assessment at 3-months of age and perform neurodevelopmental assessments at periodic intervals until 2 years of age. One outborn full-term infant who was managed in a private hospital was admitted at our center with extreme hyperbilirubinemia (791 μmol/L) on day 5 of life. He had features of acute bilirubin encephalopathy which failed to improve with exchange transfusion, and he subsequently developed dystonic cerebral palsy with sensorineural hearing loss. The rest of the 55 infants in our cohort were not found to have neurodevelopmental delay.

5. DISCUSSION

Before the NCPGNJ guidelines were available, healthcare institutions in Singapore used different bilirubin thresholds for initiating phototherapy or considering exchange transfusion. The evidence-based neonatal jaundice guidelines have been adapted to local needs and provides a unified framework for all healthcare professionals who manage newborns with hyperbilirubinemia in different healthcare settings [1].

In Singapore, glucose-6-phosphate dehydrogenase (G6PD) deficiency was the commonest cause of severe hyperbilirubinemia resulting in neurodevelopmental disability and mortality in the 1950-60s [4]. After introduction of the mass Newborn Screening Program for G6PD deficiency in 1965 [5,6], acute bilirubin encephalopathy (ABE) due to this disorder has been virtually eliminated since the 1990s and the spectrum of etiology of severe neonatal jaundice has changed. In addition, with the availability of anti-D immunoglobulin, ABO-hemolytic disease of the newborn has taken over Rhesus-hemolytic disease of the newborn to become the most common etiology of severe neonatal hyperbilirubinemia in many parts of the world, including Singapore.

The NCPGNJ guidelines has allowed us to intervene early with phototherapy and if the infant was to develop severe hyperbilirubinemia, prompt measures such as double blue or intense phototherapy were taken to reduce the bilirubin levels. This is a major reason for the significant reduction in readmissions due to jaundice and a non-significant reduction in the rates of exchange transfusion. The guidelines have been clinically significant in reducing the need for exchange transfusion at our center. We used to manage an average of two cases of severe hyperbilirubinemia requiring exchange transfusion every month prior to the guidelines and this has reduced substantially by about 50% after the guidelines were implemented.

We described one infant who was referred to us on day 5 of life with severe hyperbilirubinemia. He had signs of acute bilirubin encephalopathy and subsequently developed dystonic cerebral palsy and sensorineural hearing loss. The delay in presentation could be due to lack of awareness, inadequate parental knowledge, early discharge with no follow-up, failure to recognize risk factors for hyperbilirubinemia and/or delay in checking bilirubin levels. We continue to educate and encourage all our clinicians to follow the recommendations of the National Clinical Practice Guidelines so that we can prevent undesired morbidities of severe hyperbilirubinemia.

The infants in our study had a mean peak total serum bilirubin (TSB) of 421 ± 88umol/L before exchange transfusion. Yilmaz et al found that their cohort of infants were at risk of moderate-to-severe neurological impairment if TSB was more than 24mg/dL (410umol/L) [7]. Tsao et al reported two to three times increased risk of cerebral palsy, hearing impairment and developmental delay on long-term follow-up of infants with severe hyperbilirubinemia [8]. Similarly, Yu et al. found that unfavorable neurological outcomes slightly more than doubled if TSB was more than 425umol/L [9]. Though our study showed normal neurodevelopmental outcomes in our cohort at 2-year follow-up, the longer-term effects of severe hyperbilirubinemia on later developmental outcomes and school performance in our population are not clear.

The auditory system is particularly susceptible to bilirubin neurotoxicity in a dose-dependent manner. The reported incidence of auditory neuropathy spectrum disorder (ANSD) in severe hyperbilirubinemia varies widely in the literature from 9% to 73% [10,11]. Severe hyperbilirubinemia >393 μmol/L has been described to predict auditory neuropathy spectrum disorders with 100% sensitivity and 93% specificity [12], with affected children at increased risk of speech and language delay. Hearing assessment was performed using otoacoustic emissions (OAE) in our center but none of our infants were found to have hearing

impairment at follow-up assessment. Early assessment with automated auditory brainstem response (AABR) has been recommended, however, because the results of OAE does not diagnose pre-cochlear pathology [13,14].

No previous study has described the local incidence of exchange transfusion for severe hyperbilirubinemia. In Southeast Asia, the incidence of exchange transfusion has been estimated to be 1071 per 100,000 live births. Lower rates of exchange transfusion have been reported in America and Europe, the respective rates being 3.8 and 3.5 per 100,000 live births [15]. In our cohort, the estimated incidence of exchange transfusion in epoch 1 was 107 per 100,000 live births and it decreased to 61 per 100,000 live births in epoch 2. Larger prospective population-based studies would be useful to delineate the longer-term impact of the NCPGNJ guidelines on exchange transfusion for severe hyperbilirubinemia and neurodevelopmental sequelae.

The main strength of our study included identification of all infants who underwent double volume exchange transfusion. Limitations of our study include its retrospective nature and single center data. The data were based on the medical records and assessments performed by many different clinicians. Some patients in this study are still undergoing neurodevelopmental follow-up.

6. CONCLUSION

Our study showed that the National Clinical Practice Guidelines on Evaluation and Management of Neonatal Jaundice has reduced the incidence of double volume exchange transfusion. It provides a systematic framework for timely management of newborns with significant hyperbilirubinemia in our population. A multi-pronged approach of universal pre-discharge bilirubin screening, targeted advice for caregivers based on individual risk factors,

follow-up, and prompt initiation of phototherapy at recommended bilirubin threshold levels, will prevent the need for exchange transfusion and the morbidities associated with severe hyperbilirubinemia.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

Emeritus Professor Rajadurai VS designed the study. Dr CJ Jeyanthi designed the proforma for data collection. Dr WD Ng collected and analysed the data and wrote the final manuscript. All authors read and approved the final manuscript.

ETHICAL APPROVAL

Ethics approval was waived by the hospital's Institutional Review Board. Written informed consent from patients was not required as the authors audited changes in management practices locally before and after implementation of the National Clinical Practice Guidelines (NCPGNJ).

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