Original Research Article

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

ABSTRACT

Objectives: 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), analyse aetiologies for severe hyperbilirubinemia, rates of readmission 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 centre who underwent double volume exchange transfusion for severe neonatal hyperbilirubinemia before and after implementation of the national clinical practice guidelines.
Results: Overall 56 neonates 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 the overall phototherapy rates (*p=0.064*), readmission rate for phototherapy (*p=0.038*) and the number of infants needing exchange transfusion (*p=0.246*). ABO-hemolytic disease of the newborn was the most common aetiology. One infant had delayed presentation of severe hyperbilirubinemia and eventually developed cerebral palsy. The rest of the babies 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

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 [1] (NCPGNJ) 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 the use of 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" vs "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 rates of double volume exchange transfusion for severe neonatal hyperbilirubinemia in infants ≥35 weeks' gestational age in our centre before and after implementation of the National Clinical Practice Guidelines. We hypothesized that the National Clinical Practice Guidelines will improve the process of early identification and prompt management of significant hyperbilirubinemia and reduce the incidence of exchange transfusion. We also analysed the aetiologies of severe hyperbilirubinemia in our population, rates of readmissions for phototherapy and neurodevelopmental outcomes up to 2 years of age.

METHODS

We retrospectively reviewed the medical records of neonates ≥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 centre. 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 analysed anonymously. Ethics approval was not required by the hospital's Institutional Review Board.

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 the NCPGNJ guidelines were implemented. Apart from inborn infants who required phototherapy during the birth hospitalizations, our centre admitted cases referred for phototherapy from polyclinics, Children's Emergency and private paediatricians and these included inborn as well as outborn infants.

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.

RESULTS

Table 1 shows trends of live births, referrals for phototherapy, total number of cases of phototherapy and exchange transfusion during the study period. There was a steady decline in the overall phototherapy rates (*p=0.064*), number of referrals needing readmissions for

phototherapy (*p=0.038*) and the number of infants needing exchange transfusions (*p=0.246*) after implementation of the guidelines.

Table 1. Description of trends of number of live births ≥35 weeks' gestation, referrals for phototherapy, total number of cases of 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	0.064
Total no. of admissions referred for phototherapy (% of live births)	2120 (18.9)	1925 (17.1)	1885 (16.7)	1424 (13.1)	1486 (13.6)	1640 (14.6)	0.01	-0.019 to -0.001	0.038
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)	0.011	-0.033 to 0.011	0.246

During the study period, 56 babies 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.

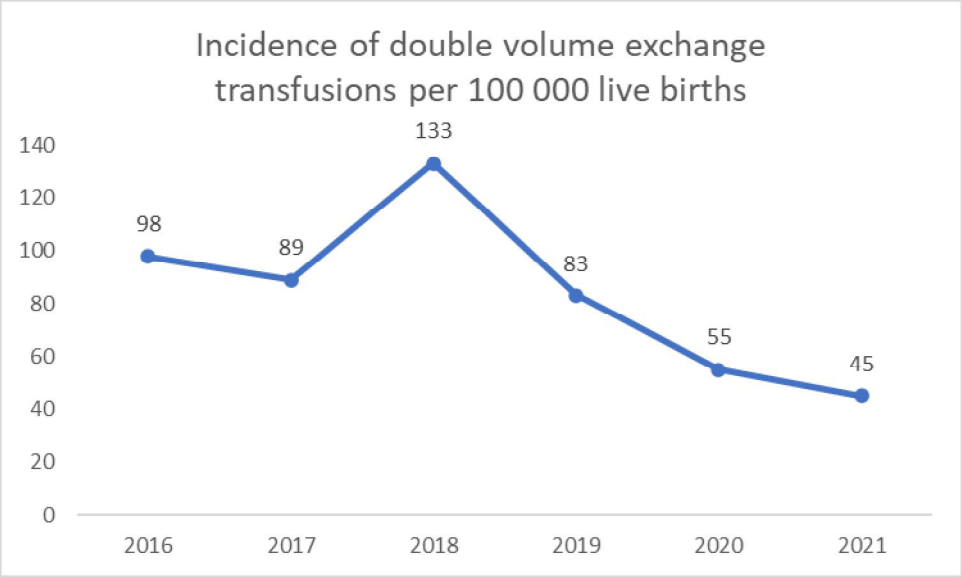

Table 2 shows the distribution of aetiologies responsible for severe hyperbilirubinemia in our cohort. 20 (35.7%) neonates had 2 or more risk factors for severe hyperbilirubinemia. Severe anti-B hyperbilirubinemia was found to be three times more common than anti-A hyperbilirubinemia with higher median antibody titres 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)

Analysis also revealed that neonates with severe hyperbilirubinemia requiring exchange transfusion presented earlier after introduction of the guidelines. In Epoch 1, neonates presented at <24 hours after birth or presented late at >120 hours old. In Epoch 2, neonates presented at <24 hours after birth or between 72-120 hours of life. Overall, the mean peak total serum bilirubin before exchange transfusion was 425±89µmol/L, which got reduced by 56±39% following the procedure. Thrombocytopenia, hypocalcaemia and mild metabolic acidosis were the most common adverse events of exchange transfusion, which resolved spontaneously. The average duration of hospitalization was 3-4 days.

In our centre, we follow-up neonates 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 centre 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 babies in our cohort were not found to have neurodevelopmental delay.

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 jaundice guidelines have been adapted to local needs and provide a unified framework for all healthcare professionals who manage neonates with hyperbilirubinemia in different healthcare settings [1].

In Singapore, G6PD deficiency used to be the commonest cause of severe hyperbilirubinemia resulting in neurodevelopmental disability and mortality in 1950-60s [4]. After the introduction of the mass Newborn Screening Programme in 1965 [5,6], acute bilirubin encephalopathy (ABE) due to this disorder has been virtually eliminated since 1990s and the spectrum of aetiology of severe 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 aetiology 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 baby 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 the rate of readmissions due to jaundice and a non-significant reduction in the rates of exchange transfusions after implementation of the guidelines; the other reason could be the smaller sample size of our cohort. The guidelines have been clinically significant in reducing the need for exchange transfusion at our centre. We used to manage an average of two cases of severe hyperbilirubinemia requiring exchange transfusion every month prior to the guidelines and this has been reduced substantially by about 50% after implementation of the guidelines.

We described one neonate who presented late at day 5 of life with severe hyperbilirubinemia and 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 neonates in our study had a mean peak total serum bilirubin (TSB) of 421 ± 88umol/L before exchange transfusion. Yilmaz Y et al found that their cohort of babies were at risk of moderate-to-severe neurological impairment if TSB > 24mg/dL (410umol/L) [7]. Similarly, Yu et al. found that unfavourable neurological outcomes slightly more than doubled if TSB were more than 425umol/L [8]. Though our study showed normal neurodevelopmental outcomes 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.

Hearing assessment was performed using otoacoustic emissions (OAE) in our centre and none of the babies had hearing impairment at follow-up assessments. Severe hyperbilirubinemia >393 µmol/L has been found to predict auditory neuropathy spectrum disorders with 100% sensitivity and 93% specificity [9], with affected children at increased risk of speech and language delay. Early assessment with automated auditory brainstem

response (AABR) has been recommended, however, because the results of OAE does not diagnose pre-cochlear pathology [10,11].

No previous study has described the local incidence of ET. In Southeast Asia, the incidence of exchange transfusion was estimated to be 1071 per 100,000 live births whereas 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 [12]. 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. Large prospective population-based studies would be useful to delineate the longer-term impact of the neonatal jaundice 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 centre 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.

4. CONCLUSION

Our study has shown that the National Clinical Practice Guidelines on Evaluation and Management of Neonatal Jaundice reduces the incidence of double volume exchange transfusion. It provides a systematic framework for timely management of neonates 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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