



Clinical Profile and Outcomes of Neonates with Hyperbilirubinemia Undergoing Double Volume Exchange Transfusion- A Single Centre Experience

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Article History

Received on - 2024 Dec 02

Accepted on - 2025 Jan 24

Keywords:

Acute bilirubin encephalopathy; BIND; Double volume exchange transfusion; Jaundice; Kernicterus; Neonatal hyperbilirubinemia; Newborn

Online Access



DOI: <https://doi.org/10.60086/jnps1263>

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Abstract

Introduction: Hyperbilirubinemia is one of the most common conditions observed in neonates. Double Volume Exchange Transfusion (DVET) is the most efficient treatment to rapidly reduce the alarmingly high serum bilirubin levels.

Methods: This was a retrospective descriptive study of babies who underwent DVET for neonatal hyperbilirubinemia over a five year period.

Results: Total 36 babies fulfilling the inclusion criteria were analysed. The mean age of jaundice onset was 41.77 ± 39.79 hours and mean total serum bilirubin (TSB) at admission was 22.54 ± 10.73 mg / dl. Bilirubin induced neurological damage (BIND) was seen in 14 babies at admission. Babies with BIND had significantly higher bilirubin at admission ($p - 0.002$) and significantly late presentation ($p - 0.034$) compared to babies with no BIND. Rh hemolytic disease was the most common etiology (55.56%). Most common complication of DVET was thrombocytopenia followed by hypocalcemia. All babies with no BIND had normal neurological examination at discharge. One baby with BIND had abnormal neurological findings at discharge. There was no mortality.

Conclusion: DVET is a safe and effective therapy for alarmingly high bilirubin. Timely management with DVET can prevent complications of BIND.

Introduction

One of the most frequent disorders that require urgent care is neonatal hyperbilirubinemia. Hyperbilirubinemia is seen in 60% of term neonates and 80% of preterm neonates during the first week of life.¹ The incidence of neonatal hyperbilirubinemia appears to be influenced by various factors, including environmental conditions. In particular, regions with hot and humid climates have reported higher rates of neonatal hyperbilirubinemia.² The "hot season" (March to October) was significantly associated with an increased risk of neonatal hyperbilirubinemia and this association was further supported by the minimum ambient air temperature recorded on the infant's birth date, which showed a significant 3% risk increase for each 1°C increase in ambient temperature.² Due to its tropical environment, Southern India gets humid and hot weather, especially in the summer.

The common modalities of treating neonatal jaundice include phototherapy, IVIg, and double volume exchange transfusion (DVET).³ The fastest and most efficient way to reduce the bilirubin level in newborns who are at high risk of bilirubin induced neurologic dysfunction (BIND) is DVET.⁴ Neonates who develop BIND have shown



to develop high incidence of cerebral palsy, deafness and language problems.³

Studies show that if neonates at risk, receive aggressive treatment can show improved neurological outcome.⁵ This study has been conceptualised to study the clinical profile of neonates with hyperbilirubinemia who underwent DVET in our NICU over a five-year period. It is expected that this research may provide beneficial data regarding early identification of high risk groups of present era and encourage early aggressive management of neonatal hyperbilirubinemia.

Methods

This is a retrospective descriptive study analyzing the etiology and clinical profile of neonates who underwent DVET for neonatal hyperbilirubinemia over a five year period from May 2017 to April 2022. Study was conducted in NNF accredited level III A NICU of our NABH accredited hospital located in Karnataka, India. The research was approved by Regional Ethical Committee. Sample size was calculated to be 33 as per the formula.⁵ All neonates admitted to NICU with severe hyperbilirubinemia who underwent DVET as per the unit policy were enrolled into the study. Lost data, incomplete records and babies who underwent DVET for reasons other than neonatal jaundice were excluded. Data were collected regarding baseline characteristics, risk factors for hyperbilirubinemia, modified BIND score at admission, blood investigations, data related to DVET including procedural complications and early clinical outcome at discharge. For neonates ≥ 35 weeks of gestation, we used AAP practice guidelines (2004) for deciding DVET and for neonates ≤ 34 weeks we used NICE guidelines (1998) for deciding DVET as per the unit policy. Data entry was done using MS Excel and statistical analysis was done using SPSS version 20 for MS windows. Data was expressed as mean, standard deviation, median, inter quartile range, frequency and percentage. Between groups comparison was done using independent t test, Mann Whitney test and chi square test. $P < 0.05$ was considered statistically significant.

Results

Table 1: Demographic statistics of the variables

Variable	Number
Age at admission (In hours)	63.72 \pm 54.65
Gestational age (Weeks)	38.47 \pm 1.44
Birth weight (Kg)	3.03 \pm 0.47
Male	21 (58.33%)
LSCS	13 (36.11%)
Outborn	36 (100%)

A total of 39 neonates were treated with DVET for

hyperbilirubinemia during the study period, of which three cases with incomplete data were excluded and 36 cases were analysed. Demographic parameters of the study population are summarised in Table 1.

In the present study, all 36 babies were out born cases with an average age at admission of 63.72 \pm 54.65 hours and mean gestational age at birth being 38 weeks. 58% cases were male babies and 36% cases born by LSCS. Positive DCT was observed in 27 (75%) cases. The etiologies for hyperbilirubinemia has been illustrated in Table 2. Most common etiology was isoimmune hemolytic jaundice secondary to Rh incompatibility (55.56%) followed by ABO incompatibility (13.89%), dehydration and sepsis. The lab parameters of the study population are represented in Table 3. The mean age of jaundice onset was 41.77 \pm 39.79 hours and mean total serum bilirubin (TSB) at admission was 22.54 \pm 10.73 mg / dl. Babies had received 15.22 \pm 12.44 hours of phototherapy prior to DVET and 42.33 \pm 10.44 hours of phototherapy after DVET. Out of 36 neonates, 61% neonates (N = 22) had no neurological symptoms at admission and 39% neonates (N = 14) had BIND at admission as illustrated in Figure 1. Comparison between the BIND and no BIND group has been expressed in Table 4. Both the groups had no statistical difference in terms of gestational age, birth weight, onset of jaundice or gender. Mean TSB at admission was 18.24 \pm 7.58 mg / dl in babies with no BIND and 29.30 \pm 11.69 mg / dl in babies with BIND. The difference was statistically significant (P - 0.002). Mean age at admission was also greater in babies with BIND (87.64 \pm 51.70 hours) as compared to babies with no BIND (48.5 \pm 51.95 hours), with P value 0.034. There was no mortality among study population. Multiple DVET was required in five neonates (Two among no BIND and three among BIND). Neurological examination at discharge was normal for all babies with no BIND and only one baby among 14 cases of BIND had abnormal neurological findings at the time of discharge. This baby had tone abnormalities and feeding difficulties. The complications encountered during the procedure is shown in Table 5. Post DVET, thrombocytopenia was the most common complication followed by hypocalcemia and hyperkalemia.

Table 2: Cause of hyperbilirubinemia

Etiology	N (%)
Rh incompatibility	20 (55.56%)
ABO incompatibility	5 (13.89%)
Dehydration	4 (11.11%)
Sepsis	4 (11.11%)
Minor group incompatibility	2 (5.56%)
G6PD deficiency	1 (2.78%)

Table 3: Lab parameters

Variable	Mean ± SD
Reticulocyte count	9.61 ± 5.91
Onset of jaundice(Hours)	41.77 ± 39.79
Total serum bilirubin at admission	22.54 ± 10.73
Post exchange TSBR	14.51 ± 6.34
Phototherapy before DVET (Hours)	15.22 ± 12.44
Phototherapy After DVET (Hours)	42.33 ± 10.44
Platelet count	93138.88 ± 54127.97
Calcium	8.42 ± 1.01
Potassium	4.98 ± 0.69

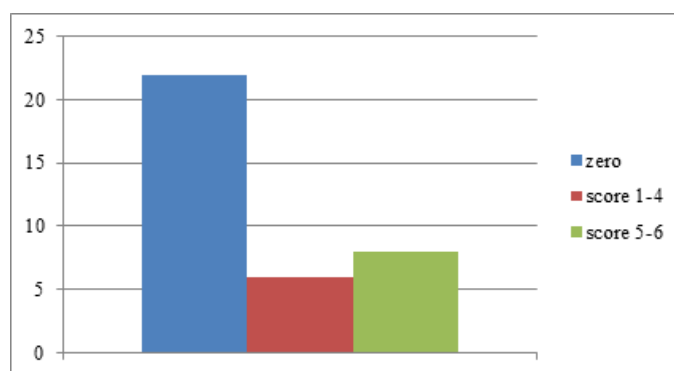


Figure 1: Modified BIND score at admission

Table 4: Comparison between BIND and no BIND group

Variables	Non-BIND (22)	BIND (14)	P value
	Mean ± SD		
Age at admission (In hours)	48.5 ± 51.95	87.64 ± 51.70	0.034
Gestational age (Weeks)	38.13 ± 1.55	39.00 ± 1.10	0.080
Birth weight (Kg)	2.98 ± 0.47	3.11 ± 0.48	0.447
Onset of jaundice (Hours)	33.23 ± 39.91	56.23 ± 36.57	0.099
NVD	11 (50%)	12 (85%)	0.030
Male	13 (59%)	8 (57%)	0.908
Blood group incompatibility	20 (90%)	9 (64%)	0.125
Multiple exchanges	2 (9%)	3 (21%)	0.583
Encephalopathy at admission	0	14 (100%)	< 0.001
Abnormal tone at discharge	0	1 (7%)	0.024
Feeding difficulty at discharge	0	1 (7%)	0.024
DCT (Positive)	19 (86%)	5 (35%)	0.005
Phototherapy before DVET (Hours)	12.91 ± 14.48	18.86 ± 7.38	0.165
Phototherapy after DVET	40.18 ± 8.59	45.71 ± 12.42	0.123
TSB at admission	18.24 ± 7.58	29.30 ± 11.69	0.002
Post Exchange TSB	11.90 ± 4.36	18.62 ± 6.90	0.004
Recticulocyte count	10.70 ± 5.68	7.77 ± 6.05	0.160
Calcium	8.22 ± 1.03	8.74 ± .923	0.135
Potassium	4.81 ± .724	5.25 ± 0.561	0.603
Hospital stay	4.45 ± 1.68	4.86 ± 1.70	0.491

Table 5: Complications of DVET

Variable	Number (%)
Thrombocytopenia	32 (88.89)
Hypocalcemia	21 (58.33)
Hyperkalemia	13 (36.11)
Sepsis	3 (8.33)
Necrotizing enterocolitis	1 (2.78)
Cardiac arrhythmia	0 (0)

Discussion

DVET is an effective method of treating severe neonatal hyperbilirubinemia and thus helps in preventing kernicterus. The purpose of this research was to identify the clinical profile and early clinical outcome of those neonates with severe neonatal hyperbilirubinemia who underwent DVET in NICU, and also to correlate the data with neurodevelopment at various ages.

In our study, a total of 36 neonates (N = 36) who met the inclusion criteria as per methodology were enrolled. All these 36 neonates were outborn and referred to us for management. Our study reported no deaths similar to an Indian study done in the past.⁵ A Bangladeshi research had shown that in BIND, there had been 18.2% (N = 4) deaths as reported by Rasul et al.⁶ Another research from the developed world by Manning et al had noted that the mortality rate is less than 5%.⁷

All cases in our study were outborn, which could be because of timely screening of inborn babies and early initiation of treatment with phototherapy for the inborn babies. This may have prevented the inborn babies to go into higher level of hyperbilirubinemia. The mean age of onset of jaundice in our study was 41.77 ± 39.79 hours. However, another Indian study by Pradhan JB et al reported the mean age of onset of jaundice as 54.29 ± 25.08 hours.⁵

Upon comparison, the mean age of onset of jaundice in neonates with BIND was 56.23 ± 36.57 hours and in neonates with no BIND was 33.23 ± 39.91 hours (p -0.099), which was not statistically significant.

We identified immune haemolytic jaundice as a significant factor contributing to neonatal hyperbilirubinemia necessitating DVET. Immune haemolytic jaundice was seen in 75% neonates (N = 27). Rh incompatibility was the main aetiology for severe hyperbilirubinemia in the present study, which was seen in 55.56% neonates (N = 20) followed by ABO blood group incompatibility which was seen in 13.89% neonates (N = 5). This finding is in contrast to another research by Malla et al. In this report, the etiology of severe hyperbilirubinemia was

immune hydrolysis only in 23%.⁸ Dehydration and sepsis were seen in 11.11% neonates (N = 4) respectively. These findings are in congruence with the findings presented by Bujandric et al.⁹

Alarming, 38.8% (N = 14) of the 36 neonates studied BIND at admission. The severity of BIND varied, with 61.11% (N = 22) showing no BIND, 16.67% (N = 6) exhibiting mild BIND, and 22.22% (N = 8) displaying moderate BIND. Multivariate analysis revealed that neonates with BIND had significantly higher bilirubin levels at admission (P = 0.002) and presented later (P = 0.034) compared to those without BIND. In a study published by Mostafa G et al, BIND was observed in three neonates at admission and resolved in all of them at discharge.¹⁰ In another study, BIND was far less common in babies with hyperbilirubinemia. Evidence of bilirubin encephalopathy was present in 12.9% of the neonates (N = 14) in a prospective study done in Europe by Manning et al.⁷ In a study done in northern California by Newman et al, the neurologic examination of 17% of the neonates (N = 14) with hyperbilirubinemia revealed no kernicterus cases. Normal early clinical outcome at discharge was observed in 35 babies. Only one baby among 14 babies with abnormal neurological findings with an abnormal tone and feeding difficulties. This further consolidates the norm that early and aggressive management of hyperbilirubinemia should be encouraged to prevent neurological damage.¹¹ Abnormal CNS findings at the time of discharge were seen in 18.9% of the neonates (N = 7) in the study done by Pradhan JB et al.⁵ In 2018, a prospective cohort study was conducted on 34 babies by A Kumar et al in Bihar, India. In this research, all babies were followed up on until the age of 12 months old. At the six months mark, four out of 34 cases had gross motor and fine motor delays, while two babies had language delay and three had social-emotional delays. Out of the 32 cases that were still being followed up on after a year, four cases had developmental milestone delays.¹² Similarly, another prospective study done by Malla et al demonstrated that 29 (6%) babies from total 481 cases of unconjugated hyperbilirubinemia required DVET. In this study, 44.8% of patients with exaggerated physiological jaundice and 55.2% of patients with pathological jaundice required DVET. There were no mortalities and none of them had kernicterus.⁸ In 2017, results from an observational study done by Singla et al showed that Rh and ABO incompatibility were risk factors in 14 (28% and 28.5%, respectively) of the all babies requiring DVET. Ten (20%) newborns had neurological abnormalities and BIND symptoms. Additionally, a strong correlation between risk factors and neurotoxicity was found. All infants with neurological abnormalities were small for gestational age and none were (P = 0.05) appropriate for gestational age.¹³

Many of the above studies suggest that if risk factors can be identified at the earliest, performing DVET can help prevent

BIND and overall neurological outcome can be improved.

We have to acknowledge the limitations of our study. Firstly, the major limitation of this present study is the retrospective nature of the design. Secondly, this study may not reflect general population of this area as all cases were outborn, referred from various referral hospitals from different areas. Thirdly, multiple etiologies for severe neonatal hyperbilirubinemia in a single subject were not ascertained. And lastly, although the present research covers early neurological sequelae, long term outcome and developmental assessment has not been conducted.

Conclusions

The commonest etiology for DVET was isoimmune incompatibility. Even though significant portion of cases of hyperbilirubinemia who required DVET had severely high levels of bilirubin, it was quite reassuring that majority of the babies had no neurological consequences. The complications of DVET are generally mild. DVET is safe and effective modality of management of hyperbilirubinemia and prevention of BIND.

Conflict of Interest: None

Funding Source: None

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