

## Original Research Article

# Clinical profiles and outcomes of neonates with neonatal hyperbilirubinemia and treated with double volume exchange transfusion: a retrospective study

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### ABSTRACT

**Background:** Double volume exchange transfusion (DVET) for severe unconjugated hyperbilirubinemia has become less common events now days in pediatric practices. But kernicterus is still common in low income country like India. The aim of the study was to determine the clinical profile and outcome in neonates who were treated with DVET.

**Methods:** This was a retrospective study in neonate's  $\geq 34$  weeks of gestation that were treated with DVET for severe neonatal hyperbilirubinemia over a period of four years.

**Results:** In our study, 37 neonates underwent DVET. Male neonates (62.13%) and normal vaginal delivery (NVD) (70.2%) are common. ABO Isoimmunisation was commonest cause (56.75%) of exchange transfusion. The mean TSBR at pre exchange and Post Exchange were  $27.39 \pm 5.99$ mg/dl and  $15.16 \pm 4.00$ mg/dl ( $p < 0.05$ ). Ten neonates (27%) among 37 neonates required twice DVET. Thrombocytopenia 14 (37.83%); Seizure 5 (13.5%) and Hypocalcaemia 3 (8.1%) were common complication noted among total 17 (45.94%) neonates. BIND occurred in 15 neonates (40.5%) at the time of admission and seven (18.9%) neonates had persistent neurological abnormality at discharge. Neonate with BIND had early onset of jaundice ( $44.13 \pm 15.37$  hours vs.  $61.22 \pm 28.23$ hrs,  $p < 0.05$ ), with higher pre exchange TSBR value ( $28.96 \pm 8.5$ mg/dl vs.  $26.22 \pm 3.17$ mg/dl). Neonates admitted with BIND had higher percentage of persistent encephalopathy (40% vs. 4.5%,  $p < 0.05$ ), abnormal tone (33.3% vs. 4.5%,  $p < 0.05$ ), abnormal feeding (33.3% vs. 4.5%,  $p < 0.05$ ) and abnormal posture (26.6% vs. 0%,  $p < 0.05$ ) at discharge as compared to those without BIND. No death occurred in this study population.

**Conclusions:** Early detection and aggressive therapy with DVET can prevent neonates from brain injury.

**Keywords:** Acute bilirubin encephalopathy and phototherapy, Bilirubin induced neurological dysfunction, Double volume exchange transfusion, Kernicterus

### INTRODUCTION

Newborn infants develop some degree of hyperbilirubinemia as a normal transition in physiology. High levels of unbound unconjugated bilirubin can cross the blood brain barrier and because bilirubin induced neurological dysfunction (BIND). Kernicterus and BIND are often used interchangeably although Kernicterus is a

pathological diagnosis and BIND as clinical diagnosis.<sup>1</sup> Kernicterus is a preventable condition. Although BIND are rare in high income countries, it is still more common in low income country.<sup>2</sup> Exchange transfusion (ET) is considered to be the most effective and quickest method to lower the bilirubin level in infants at high risk of BIND.<sup>3</sup> But there is risk of complication related to procedure and metabolic and hematological alteration.<sup>4</sup> A

pilot Kernicterus registry in the United States from 1984 to 2002 showed 97% of babies had been discharged from hospital in less than 72 h after birth.<sup>5</sup> Another pilot USA registry concluded that the increase in the Kernicterus cases was due to inability to identify at-risk infants and to manage them in a timely manner.<sup>6</sup> Both Agency for healthcare research and quality (AHRQ) review and Pilot Kernicterus Registry show that a high number of babies diagnosed with acute bilirubin encephalopathy (ABE) had residual neurological injury.<sup>6,7</sup> Exchange transfusion is also associated with metabolic and hematologic complication.<sup>8</sup> A study from India by Murki et al, reported ABE in 21.8% of 64 neonates with serum bilirubin >18 mg%.<sup>9</sup> A study from India by Mukhopadhyay et al, Showed a long term neurological impairment in most babies with high BIND Score before exchange transfusion in north Indian baby.<sup>10</sup> But there were few studies conducted in the southern part of India.

Aims and Objectives of this study was to determine the clinical profile, incidence and severity of BIND, complications, and outcomes in the form of mortality or neurological abnormality in neonates who underwent DVET for severe unconjugated hyperbilirubinemia at the time of discharge.

## METHODS

The data were collected from the database hospital record during the period of May 2014 to February 2018 of those neonate admitted and treated in tertiary neonatal care teaching hospital after approval from the institutional ethical committee. All neonates more than equal to 34 completed weeks of gestation who underwent DVET for neonatal hyperbilirubinemia were included in the study. Maternal demography and neonatal characteristic data were collected. Neonatal age, sex, birth weight, blood grouping and Rh typing, age on admission, treatment history at referral hospital and maximum bilirubin, age on exchange transfusion, type of feeding, sibling requiring phototherapy and exchange transfusion, physical examination, gestational age, admission weight, dehydration and weight loss, presence of acute bilirubin encephalopathy, cephalohematoma, total serum bilirubin (TSBR) at admission were collected.

Neonates of less than 34 weeks gestation, Apgar score <5 at 5 min, any stage of hypoxic ischemic encephalopathy, other cause of encephalopathy, sepsis, major congenital malformations, conjugated bilirubin >2 mg%, metabolic disorders, meningitis, DVET other than the cause of neonatal hyperbilirubinemia and missed data or incomplete records were excluded from the study.

BIND was diagnosed in the presence of the following clinical features: Early phase (Stage I): hypotonia, lethargy, high pitched cry, and poor suck; Intermediate phase (Stage II): irritability, opisthotonos, seizures, apnea, oculogyric crisis, hypertonia, and fever; and Advanced phase (Stage III): pronounced opisthotonos,

shrill cry, apnea, seizures, and death. BIND scoring was categorized as mild (1-3), intermediate (4-6) and severe (7-9). The neonates who were referred with a high bilirubin level for exchange transfusion were emergently treated with intensive phototherapy after sending all the relevant investigation from emergency room and arranged for exchange transfusion. Neonates were managed according to the American Academy of Pediatrics, 2004 guidelines. 3Double volume exchange (160ml/kg) transfusion (DVET) was performed with push pull technique from the umbilical vein or by peripheral artery using fresh whole blood within 5 days of collection.

All neonates were investigated for complete blood count, serum bilirubin (direct, indirect, and total by spectrophotometric test using 2, 4-dichloroaniline), blood grouping and Rh typing, reticulocyte count, Coomb's test, G6PD levels, and blood culture. Pre and Post Exchange transfusion serum bilirubin and Hb along with serum sodium, potassium, calcium, urea, and creatinine were documented. Adverse event, duration of exchange and Post Exchange hematological parameter, duration of phototherapy and hospital stay were documented

Neurological examination at the discharge was done with Hammer-Smith short neurological assessment as per unit protocol. Neurological examination finding in the form of alertness, tone, posture, vision and hearing, seizure and antiepileptic medications, feeding method and sleep pattern and hearing assessment at discharge (BAE), MRI and BERA were collected. Outcome in the form of discharge or death were collected.

## Statistical analysis

Results were described using measures of central tendency, mean and standard deviation for continuous data with a normal distribution or median and range for skewed data. Nonparametric test was compared with chi square test and fisher exact test. Categorical variables were described as frequency and percentage. Comparisons between continuous variables were done using paired *t*-tests for data with a normal distribution and Wilcoxon signed rank test was used to compare skewed data. A *p* value <0.05 was considered statistically Significant. Statistical analysis was done using STATA 12 software.

## RESULTS

A total of 54 neonates were treated with DVET during this study period. Seventeen neonates were excluded from our study as five neonates were preterm less than 34 weeks, four neonates with incomplete data, three neonates with birth asphyxia, three neonates with other causes of encephalopathy and two had major congenital malformations. A total of 37neonates were analyzed. Maternal and neonatal demographic data were tabulated

in Table-1. Male neonates were common (62.13%) in this study.

**Table 1: Demographic details of the study neonates.**

Variables	Number of neonates (%)
Male	23 ( 62.13 )
NVD	26 (70.2)
Exclusive Breast feeding	37 (100)
Birth weight (gm)*	2858.919±392.5896
Admission weight (gm)*	2700.135±372.14
<b>Diagnosis</b>	
ABO	21 (56.75)
Rh	9 (24.73)
Others	7 (18.9)
Gestational age (week)*	38.62162±1.163122
Age on admission(Hours)*	54.2973±25.08747
Weight loss>10%	7(18.9)
Hypernatremic dehydration	5 (13.5)
Readmission after discharge	10(27)
<b>Treatment at referral</b>	
DVET	1 (2.7)
PT>24Hrs	13 (35.13)
No treatment	7 (18.9)

\*Mean (SD); PT-phototherapy; NVD-normal vaginal delivery.

Normal vaginal delivery (NVD) was common mode of delivery in 26 (70.2%) mothers. ABO incompatibility was commonest cause of severe jaundice with 21 (56.75%) neonates followed by Rh incompatibility in 9 (24.3%) and other etiology in 7 (18.9%) neonates.

The neonatal hyperbilirubinemia characteristics were tabulated in Table 2.

**Table 2: Characteristics of pre and post exchange neonates.**

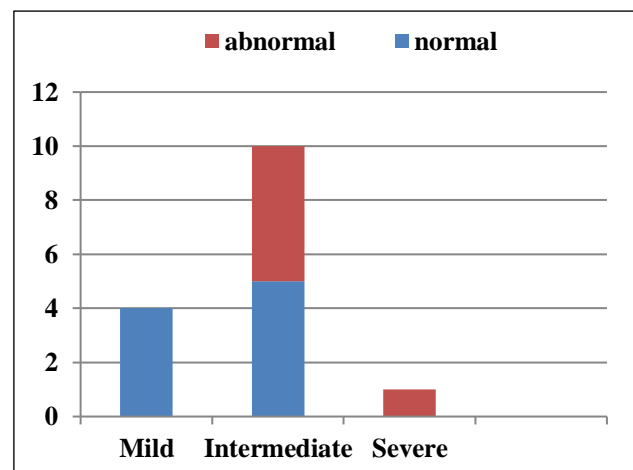
Variables	Number (%)
Onset of jaundice( Hours)*	54.29 ±25.08
Max TSBR(mg/dl) at referral hospital *	24.11± 5.77
Age at exchange( Hours)*	97.62±47.08
Pre exchange TSBR ( mg/dl)*	27.39±5.99
Post exchange TSBR(mg/dl)*	15.16±4.00
Duration of exchange (Hours)*	1.93±0.44
Post exchange rebound TSBR( mg/dl)*	17.21±5.78
Duration of phototherapy (days)*	2.83±0.76
Duration of hospital stay ( days)*	6.48±5.47
Exchange related complications	17 (45.94%)
Thrombocytopenia	14 (37.83)
Seizure	5 (13.5)
Hypocalcaemia	3 (8.1)

\*Mean (SD).

The mean age of onset of jaundice and mean age at exchange transfusion were 54.29±25.08 and

97.62±47.085 respectively. The mean total serum bilirubin value at referral hospital was 24.11±5.7. The mean TSBR at pre exchange and Post Exchange were 27.39±5.99 and 15.16±4.00 (p<0.05) respectively. Total 47 DVET were done in 37 neonates among which 10 (27%) baby required twice DVET. The average duration of phototherapy was 2.83±0.76hrs and average duration of hospital stay was 6.48±5.47 days. Adverse effect related to exchange transfusion were noted in 17 (45.94%) neonates. Thrombocytopenia 14 (37.83%), Seizure 5 (13.5%) and Hypocalcaemia 3 (8.1%) are common complication noted in this study.

BIND developed in 15 (40.5%) neonates at the time of admission. Among the neonates who developed BIND at admission, 10 (66.7%) had BIND with intermediate category and one neonate with severe category (Table-3). Among the 21 ABO incompatibility neonates, 7 (33.3%) had BIND whereas among nine Rh incompatibility neonate 5neonates (55.5%) and among seven of other etiology group 3 (42.8%) had BIND. In comparison, the neonates who developed BIND (n=15) to those without BIND(n=22), both the group were comparable with respect to gestation (p=0.345),birth weight(p=0.612),age on admission (p=0.53), DCT positivity (p=0.408) and neonates with significant weight loss (p=0.408). However those neonates with BIND had early onset of jaundice (44.13±15.37 hours vs. 61.22±28.23hrs, p<0.05), treated with phototherapy more than 24hrs before referral (40% vs. 31.8%, p<0.05) with higher preexchange TSBR value (28.96±8.5mg/dl vs. 26.22±3.17mg/dl, p=0.18). Among all the 37 neonates who had undergone DVET, none of the baby died in this study. Seven (18.9%) neonates had neurological abnormality documented at discharge from hospital.



**Figure 1: Neurological abnormality among BIND neonates at discharge.**

Those neonates who had admitted with BIND (n=15) when compared to the non-BIND group (n=22) had higher percentage of neonatal neurological abnormalities in the form of persistent encephalopathy (40% vs. 4.5%,p<0.05), abnormal tone (33.3% vs. 4.5%,p<0.05),

abnormal feeding (33.3% vs. 4.5%,  $p < 0.05$ ), abnormal posture (26.6% vs. 0%,  $p < 0.05$ ) and seizure requiring maintenance antiepileptic (20% vs. 0%,  $p < 0.05$ ) at the time of discharge (Table-3). In subgroup analysis among neonates admitted with BIND, all 4(100%) neonates with

mild BIND score (1-3) were neurologically normal at discharge (Figure-1). Five neonates (50%) among the 10 neonates in intermediate BIND score (4-6) and one (100%) in the severe BIND score (7-9) were neurologically abnormal at discharge.

**Table 3: Risk factors and neurological abnormalities among BIND and non-BIND neonates.**

Variables	BIND (n=15) (%)	No BIND (n=22) (%)	p-value
Gestational age (weeks)*	38.4±0.98	38.77±1.26	0.345
Birth weight (gms)*	2899.33±369.79	2831.36±431.62	0.612
NVD	10(66.67)	16 (72.72)	0.723
Male	9(60)	11 (50)	0.738
Onset of NNH (Hours) *	44.13±15.37	61.22±28.23	<0.05
Admission age (Hours)*	87.86±38.40	98.04±53.92	0.53
PT >24hrs before DVET	6(40)	7 (31.8)	<0.05
Pre exchange TSBR(mg/dl)*	28.96±8.5	26.22±3.17	0.18
<b>Diagnosis</b>			
Rh	5 (33.33)	4(18.18)	
ABO	7 (46.67)	14(63.64)	
Others	3 (20)	3(13.64)	
Positive DCT	4 (26.67)	3(13.64)	0.408
Significant weight loss	4 (26.67)	3(13.64)	0.408
Multiple exchanges	6 (40)	4(18.18)	0.258
Abnormal CNS finding at discharge	6 (40)	1(4.5)	<0.05
Encephalopathy	6 (40)	1(4.5)	< 0.05
Abnormal tone	4 (26.6)	0	<0.05
Feeding difficulty	5 (33.3)	1(4.5)	<0.05
Abnormal posture	4 (26.6)	0	<0.05
Seizure	4 (26.6)	0	<0.05
Abnormal sleep pattern	3 (20)	0	<0.05

## DISCUSSION

The objective of these study was to determine clinical profile and the neonatal outcome with severe hyperbilirubinemia who underwent DVET in more than equal to 34 weeks of gestation. During the study period, 862 neonates admitted for neonatal hyperbilirubinemia and 534 babies were treated with phototherapy. Only 54 newborns were treated with DVET with a decreasing trend in DVET over last 3 years. The decreasing trend of DVET therapy seen in last 3 years could be because of pre-discharge assignment of hyperbilirubinemia in most health facilities, late discharge, awareness about the proper management of neonatal jaundice, and availability of well-functioning intensive phototherapy units. Male neonate was predominant with 23(62.13%) of this study. Normal vaginal delivery was common mode of delivery with 26(70.2%) delivered by NVD. The finding was similar to the finding from India by Murki et al, and Manning et al, ABO incompatibility was most common cause of severe jaundice with 21 (56.75%) neonates followed by Rh incompatibility in 9 (24.3%).<sup>9,11</sup> This finding was similarly reported in Iranian population with

49.2% of the infants who had exchange transfusion.<sup>12</sup> Among 37 neonates who underwent DVET, 10(27.2%) neonates required twice DVET to decrease the bilirubin value and this finding was comparable with 35% reported in Brazil.<sup>13</sup> There was no mortality in our study whereas mortality reported high in Mala et al, and a study from Bangladesh.<sup>14,15</sup> The mortality was less than five percent in the developed country as reported by Manning et al.<sup>11</sup> Among the 37 neonates enrolled in our study, 15 (40.5%) had BIND on admission. The occurrence of BIND was much less in other studies from the west. Johnson et al and Manning et al, Newman et al, reported that out of 140 newborns with bilirubin level >25 mg/dl, none had kernicterus, but 14 had questionable or abnormal neurological examination.<sup>6,11,16</sup> This difference may be because neonates of Asian origin are more susceptible for developing BIND.<sup>9</sup> A study from India by Murki et al, reported ABE in 21.8% of 64 neonates with serum bilirubin >18 mg%.<sup>9</sup> In these study the early age at clinical diagnosis (44.13±15.37hrs) and late referral in baby who received phototherapy for more than 24 hours at referral hospital (40%) were more associated with ABE. The reason could be those neonates developed



early clinical jaundice might have high rate of rise in bilirubin level and unable to treat aggressively with intensive phototherapy. In our study Coomb's test positivity were comparable in neonates with BIND and non-BIND group ( $p = 0.408$ ). This was also observed by F. Ebbesen and a Canadian study.<sup>17</sup> All the baby were exclusive breast fed in both group unlike the findings of Murki et al. who reported low breastfeeding with BIND.<sup>9</sup> In these study, the mean age at admission of neonates with BIND and without BIND was similar between 87 to 98hours (4-5 days) and the male to female ratio 2:1 in BIND group as compared to 1:1 in non-BIND neonates which is similar to the finding by Murki et al, The neurological assessment at the time of discharge , we found that seven (18.9%) neonates had neurological abnormality documented.<sup>9</sup> Six neonates out of 15 (40%) who had admitted with BIND had higher percentage of neonatal neurological morbidity in the form of persistent encephalopathy in 6(40%)neonates, abnormal tone in 5 (33.3% ),abnormal feeding in 5 (40%) neonates, abnormal posture in 4 (26.6%) neonates and sleep pattern in 3 (20%). Only one neonate out of 22 (4.54%) neonate who had no features of BIND at admission had abnormal neurological assessment at discharge. In subgroup analysis among neonates admitted with BIND, all 4 (100%) neonates with mild BIND score (1-3) were neurologically normal at discharge. Five neonates (50%) among the 10 neonates in intermediate BIND score (4-6) and one (100%) in the severe BIND score (7-9) are neurologically abnormal at discharge.

There are few limitations of this retrospective study. First, like most retrospective study the available information was limited to what was considered necessary or attainable at the point of care. Second neurological assessment was not done by a single pediatrician at the time of discharge which might lead to inter observer variation. As our unit as out born referral unit the treatment details at referral hospital are retrospectively collected from the physician or parents. The study population was small. Follow up of this neonate would have given more information for their neurological progression. The strength of the study is that those neonates with mild and intermediate phase of BIND had good outcome with emergent management and without any mortality.

## CONCLUSION

It was reassuring that 95.5% of the neonates with hyperbilirubinemia but no BIND on admission responded well when managed with DVET. Early diagnosis, effective treatment and prompt referral by healthcare personnel with regards to severe hyperbilirubinemia will prevent neurological impairment.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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