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ORIGINAL ARTICLE

Risk factors for exchange transfusion in neonates with unconjugated hyperbilirubinemia: A tertiary care hospital study.

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ABSTRACT… Objective: To assess the prevalence of exchange transfusion requirement and identify risk factors associated with exchange transfusion in neonates with unconjugated hyperbilirubinemia in a tertiary care hospital. **Study Design:** Comparative Cross-sectional. **Setting:** Department of Neonatology, Holy Family Hospital Rawalpindi. **Period:** January 2022 to December 2022. **Methods:** A total of 136 neonates, from 28 weeks of gestation to 28 days of life after birth, with severe pathological hyperbilirubinemia, unconjugated hyperbilirubinemia and or who had signs of kernicterus were included through non-probability consecutive sampling. Patients were then divided in to two groups based on exchange transfusion received or not. SPSS version 26 was used for data entry and analysis, and descriptive and inferential statistics were applied. **Results:** A total of 136 neonates were recruited, out of which 57% (n=78) were male and 43% (n=58) were female. The average gestational age was 36.6 ± 1.9 weeks. 111 (82%) neonates were term, while 25 (18%) were preterm. The average age of the study population was 6.0±3.3 days, with a mean weight of 2.7 ± 0.7 kg. The average STB level was 20.8 ± 5.5 mg/dl. 64.7% (n=88) required exchange transfusion were belonged to group-A, while 35.3 %(n=48) without exchange transfusion were in group-B. The burden of disease was calculated to be 64.7%. Polycythemia, ABO and Rh incompatibility were identified as significant risk factors for ET ($p<0.05$). **Conclusion:** The burden of disease was 64.7%. Exchange transfusion was required in the majority of neonates with unconjugated hyperbilirubinemia. The identified risk factors for the requirement of exchange transfusion in neonates were polycythemia, ABO and Rh incompatibility.

Key words: Exchange Transfusion, Hyperbilirubinemia, Neonates, Phototherapy, Risk Factors.

INTRODUCTION

Neonatal hyperbilirubinemia persists as a pervasive challenge, constituting the foremost cause of hospital admissions and readmissions among neonates worldwide. Despite concerted efforts to identify neonates at risk of pathological hyperbilirubinemia (HB), this pattern of hospitalization continues unabated.[1] Approximately 60% of term infants experience neonatal hyperbilirubinemia, with most cases representing physiological bilirubin increases that typically resolve within the first week of life. However, when serum total bilirubin (STB) levels surpass 5 mg/dL, visible jaundice may ensue, particularly in preterm infants, where the incidence escalates to 80%.[2] Severe hyperbilirubinemia, defined as a serum total bilirubin (STB) level exceeding 20 mg/dL, is a relatively rare occurrence, affecting less than 2% of term infants. Nevertheless, in neonates, it carries the potential for acute bilirubin encephalopathy or lasting neurological consequences for survivors.[3,4]

Although the precise pathogenesis of neonatal hyperbilirubinemia remains elusive, it is acknowledged to arise from a confluence of perinatal and genetic factors.[5] Various therapeutic interventions, such as phototherapy, exchange transfusion (ET), intravenous immunoglobulins (IVIG), and anti-D administration to Rh-negative mothers, have been employed to manage or prevent severe hyperbilirubinemia. In most instances, prompt detection and the judicious application of intensive phototherapy serve to

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mitigate the necessity for the invasive, painful, and time-consuming ET procedure.[6] Exchange transfusion, involving the replacement of neonatal blood with compatible donor blood at a ratio of 160ml/kg, represents a definitive and efficacious approach to averting kernicterus, particularly when intensive phototherapy proves insufficient in arresting the rapid elevation of bilirubin levels or in cases of acute bilirubin encephalopathy.[7]

ET, however, is not without its challenges, as it entails inherent risks and complications, including vascular incidents, cardiovascular compromise, electrolyte and hematologic imbalances, thrombocytopenia, hyperglycaemia, metabolic acidosis, hypokalaemia, cardiac arrhythmias, volume overload, hypocalcaemia, necrotizing enterocolitis, infection, transient vasospasm, portal vein thrombosis, transfusion-related infections, and the potential need for intubation and mechanical ventilation, which carry additional risks.[3]

Key risk factors contributing to the need for exchange transfusion encompass Rh incompatibility, ABO incompatibility, prematurity, low birth weight/preterm birth, inadequate feeding, polycythaemia, sepsis, cephalohematoma, early discharge within 24 hours of delivery, suboptimal utilization of phototherapy, suboptimal phototherapy practices or equipment, delayed measurements of total serum bilirubin, G6PD deficiency, and other factors.[2,8,9,10]

Notably, the global rate of ET has been on a decline, owing to factors such as antenatal antibody screening, anti-D administration to Rh-negative mothers, intensive phototherapy, and intravenous immunoglobulins (IVIG).[11] Nonetheless, in many developing countries, the incidence of severe jaundice necessitating subsequent exchange transfusion remains high. A meta-analysis reveals the highest incidence of Severe Jaundice per 10,000 live births in the African region at 667.8, followed by Southeast Asia at 251.3. Consequently, the rate of exchange transfusion remains elevated in these regions, despite declining rates in developed countries.[12]

This study's rationale is twofold: firstly, to ascertain the burden of exchange transfusion within a tertiary care hospital in an underdeveloped country like ours, and secondly, to pinpoint the associated risk factors. By identifying and effectively managing these risk factors in a resource-constrained setting, we aim to reduce the prevalence of this costly, time-intensive, and invasive procedure—exchange transfusion—along with its associated complications.

METHODS

This cross-sectional study was conducted in the neonatology department of Holy Family Hospital Rawalpindi over a period of 1 year from January 2022 to December 2022. All term and preterm neonates, from 28 weeks of gestation to 28 days of life after birth, with severe pathological hyperbilirubinemia, were included in the study. All neonates with unconjugated hyperbilirubinemia who had signs of kernicterus were also included. Neonates who needed ventilatory support, were low birth weight (less than 1000g), less than 28 weeks of gestation, with severe septicaemia and DIC, on ionotropic support or neonates with conjugated hyperbilirubinemia were excluded from the study.

A haemoglobin level of 22g/dl or above and haematocrit of >65% or above were used to label the neonates with polycythemia.[23]

Using the WHO sample size calculator, using a 95% Confidence Interval, the sample size was calculated to be 136.

The patients who met the above inclusion criteria were stratified into two distinct groups: Group A, comprising individuals who underwent exchange transfusion, and Group B, consisting of patients who did not undergo exchange transfusion as part of their treatment regimen.

After getting approval from the ethical review committee, ref no 141/IREF/RMU/2021, all term and preterm neonates who met the inclusion criteria of our study were recruited through a non-probability consecutive sampling technique. Patient's medical records were evaluated, and

the researcher collected data on a pre-designed proforma.

Data was entered and analyzed using SPSS version 26. Mean and standard deviation were calculated for all quantitative variables like age and bilirubin level. Frequency and percentage were calculated for all qualitative variables like gender, number of exchange transfusions, and other risk factors. Effect modifiers like age and gender were controlled by stratification. Post-stratification chi-square tests were applied. P value of less than 0.05 was taken as significant.

RESULTS

A total of 136 neonates were enrolled in our study. The baseline parameters of study subjects including gender, gestational age, birth weight, age at presentation and presence or absence of risk factors is shown in Table-I. The average STB level ranged from 11.4 to 39.8 mg/dl, with a mean of 20.8 ± 5.5 mg/dl. The mean STB in neonates who required exchange transfusion (ET) was 22.7 ± 5.4 mg/dl, compared to 17.3 ± 3.6 mg/dl in neonates who did not need ET (p=<0.05).

Among the 136 neonates included in the study, 88 of them, constituting 64.7%, required exchange transfusion and were categorized under group A, while the remaining 48 neonates (35.3%) were placed in group B. The calculated disease burden was also found to be 64.7%, as illustrated in Figure 1 (rounded off to 65% for diagrammatical representation).

A comparison of various risk factors for ET between two groups is shown in Table-II to identify which factors increased the risk of need for ET. Polycythemia, ABO and Rh incompatibility showed a significant increase in need for ET (p value< 0.05), whereas other risk factors like gender, sepsis, cephalohematoma, effective phototherapy, IUGR and age at presentation did not display a significant association with it as shown in Table-II.

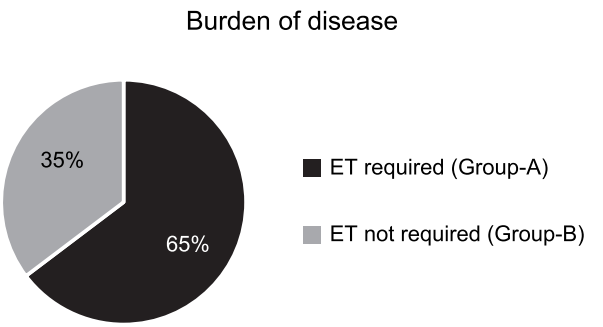

Figure-1. Burden of disease shown by the study population

Study Parameters	Frequency	Percentage (%)
Gender		
Male	78	57.4
Female	58	42.6
Gestational age		
Term	25	18.4
Preterm	111	86.4
Age		
0-24 hours	7	5.1
24-48 hours	5	3.7
48 hours – 7 days	1	0.7
8 – 14 days	92	67.6
15 – 21 days	28	20.6
22 -28 days	3	2.2
Weight		
<1.5 kg	1	0.7
1.5-2 kg	18	13.2
2.1 – 2.5 kg	44	32.4
>2.5 kg	73	53.7
Exchange transfusion		
Performed	88	64.7
Not performed	48	35.3
Risk factors		
Sepsis	31	22.8
Polycythemia	23	16.9
ABO incompatibility	30	22.1
Rh incompatibility	16	11.8
Cephalhematoma	1	0.7
Late presentation	5	3.7
Ineffective phototherapy	4	2.9
Early age (≤7 days)	98	72.1
IUGR	3	2.2

Table-I. Baseline parameters of neonates (N=136)

Risk Factor	% of Neonates Requiring ET(Group-A) n=88	Total no. of cases n=136	P-Value
Gender			
• Male	65.4% (n=51)	78	0.848
• Female	63.8% (n=37)	58	
Gestational Age			
• Term (≥37 wks)	64.9% (n=72)	111	0.935
• Premature (<37 wks)	64% (n=16)	25	
Polycythemia			
• Present	87% (n=20)	23	0.014
• Absent	60.2% (n=68)	113	
ABO Incompatibility			
• Present	80% (n=24)	30	0.047
• Absent	60.4% (n=64)	106	
Rh Incompatibility			
• Present	87.5% (n=14)	16	0.042
• Absent	61.7% (n=74)	120	
Cephalohematoma			
• Present	1 (100%)	1	0.459
• Absent	64.4% (n=87)	135	
Sepsis			
• Present	67.7% (n=21)	31	0.687
• Absent	63.8% (n=67)	105	
Presentation			
• Early	60% (n=3)	5	0.822
• Late	64.9% (n=85)	131	
Phototherapy			
• Effective	63.6% (n=84)	132	1.34
• Ineffective	100% (n=4)	4	
Age			
• ≤ 7 days	69.4% (n=68)	98	0.067
• > 7 days	52.6% (n=20)	38	
IUGR			
• Present	66.7% (n=2)	3	0.943
• Absent	64.7% (n=86)	133	

Table-II. Comparison of risk factors for exchange transfusion treatment (N=136)

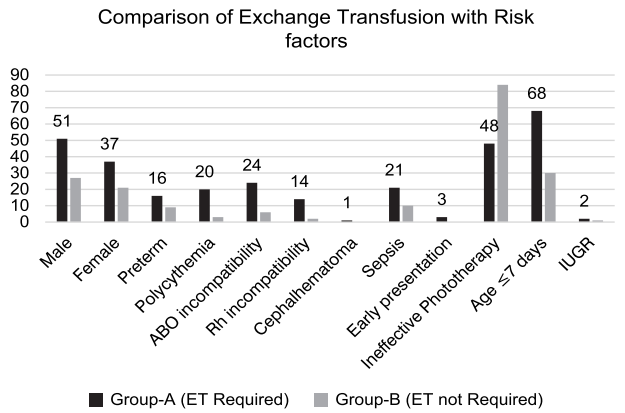

Figure-2. Comparison of exchange transfusion requirement with neonatal risk factors

DISCUSSION

The findings of the present study have highlighted the substantial disease burden, with 64.7% of neonates suffering from unconjugated hyperbilirubinemia necessitating exchange transfusion (ET). The most critical risk factors identified included ABO incompatibility, polycythaemia, and Rh incompatibility, all of which yielded statistically significant results ($p < 0.05$).[13,14,15] While prematurity has traditionally been established as a risk factor for an increased need for exchange transfusion, our study did not find a significant difference between term and preterm infants concerning the requirement for ET.

In preterm infants, several factors come into play, including immature liver enzymes and difficulties in handling the breakdown of red blood cells due to polycythaemia. It is worth noting that early detection of hyperbilirubinemia in preterm infants is of paramount importance, given their heightened susceptibility to developing kernicterus at lower bilirubin levels compared to term neonates.[16] The literature also presents variations in the efficacy of prophylactic phototherapy within six hours of life versus therapeutic phototherapy in preterm neonates.[17]

In contrast to some studies suggesting a higher risk of severe hyperbilirubinemia in males, our study revealed an unexpected trend where more female infants exhibited elevated bilirubin levels necessitating exchange transfusion. This deviation may be attributed to factors such as the diagnosis of G6PD deficiency in male neonates, as observed in a study from Peshawar.[18]

Effective utilization of phototherapy has been shown to reduce the need for exchange transfusion, a procedure fraught with numerous complications, including hypocalcaemia and hypoglycaemia. Advanced phototherapy machines, such as fiber-optic devices, are being explored as more effective alternatives to conventional phototherapy.[20]

Sepsis was also examined as a potential risk factor for ET in our study. Due to the unavailability of blood culture results, we relied on clinical signs and elevated CRP values to identify neonates with suspected sepsis. Interestingly, no statistically significant difference was observed between neonates with sepsis and those without in relation to undergoing ET.

It is important to emphasize that the risk factors highlighted in our study align with universally accepted factors responsible for severe hyperbilirubinemia leading to the invasive procedure of exchange transfusion.

In light of the resource limitations in our country and the scarcity of well-equipped neonatal facilities, it becomes imperative to strategize for the reduction of the need for exchange transfusion. The primary focus should be on mitigating preventable risk factors such as prematurity, ABO and Rh incompatibility, and sepsis. Guidelines are readily available for the implementation of preventive measures, including antenatal and postnatal anti-D administration in Rh-positive mothers giving birth to Rh-negative infants. Modalities like IVIG and anti-D administration have also demonstrated potential in raising the threshold for exchange transfusion.[15,21]

The data gleaned from our neonatal unit regarding exchange transfusion underscores not only the strain on available resources but also the demand for well-trained healthcare personnel. It is imperative to devise guidelines and strategies tailored to the unique circumstances of local neonatal units, taking into account the insights garnered from our study. Additionally, this study should serve as an impetus for young researchers to contribute more data on neonatal jaundice, including its burden, previously unexplored risk factors, recent advancements, and randomized trials as avenues for innovation.[22]

CONCLUSION

The burden of disease was 64.7%. Exchange transfusion was required in the majority of neonates with unconjugated hyperbilirubinemia. The identified risk factors for the requirement of exchange transfusion in neonates were polycythemia, ABO and Rh incompatibility.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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3	Sughra Zulfiqar	Data analysis and paper writing.	
4	Tehreem Fatima	Article writing & composition.	
5	Ayesha Afzal	Literature search.	