BIRTH RELATED FACTORS DETERMINING RED BLOOD CELL TRANSFUSION AMONG SICK NEONATES

Mini Chellamma Viswanathan¹, Sajith Vilambil², Kumari Krishnakumariam Chakrapani Usha³

¹Assistant Professor, Department of Transfusion Medicine, Government Medical College, Trivandrum, Kerala, India.

²Associate Professor, Department of Transfusion Medicine, Government Medical College, Thrissur, Kerala, India.

³Professor and HOD, Department of Transfusion Medicine, Sree Mookambika Institute of Medical Sciences, Kanyakumari, Tamilnadu, India.

ABSTRACT

BACKGROUND

Many of the neonates with low birth weight and gestational age require transfusion of red blood cells during their neonatal period. This research is assessing factors and clinical conditions for red blood cell transfusions of low birth weight (LBW) infants. We wanted to identify the birth related determinants of red blood cell transfusion in sick neonates.

METHODS

This was a case control study done in 300 neonates admitted to the Sri Avittom Thirunal Hospital (SATH), Government Medical College, Thiruvananthapuram. Cases were sick neonates who were transfused with red cells. The neonatal demographic and birth characteristics, details of the baby, indication for admission and transfusion, pre and post transfusion haematocrit, treatment given and outcome, complications occurring during delivery and post-natal complications also were analysed. All statistical data were analysed using SPSS software version 16.

RESULTS

On assessment of the age, mean age of the cases and controls were compared and there was no significance. O+ blood group was seen predominantly in the neonates who received transfusion. Mean birth weight was 1.8 ± 0.4 in both groups and there was no significant difference. Mean gestational age was 33.9 ± 2.8 in the case group and 33.5 ± 2.7 in the control group. Statistically significant difference was not there. On comparison, APGAR score was statistically significant. On comparing the diagnosis, the prevalence of congenital pneumonia, Small for Gestational Age (SGA) ($p = 0.002$) and Neonatal Jaundice (NNJ) were found to be significantly higher in the case group. On assessing the intra natal complications, 78.7 % of the mothers in the case group had intra-natal complications compared to 61.3% in the control group. p Value was significant. Caesarean section was significantly more in the case group. p value was significant in caesarean section and cord prolapse. Post-natal complications were significant in this study. The frequency of anaemia and cardiac diseases were significantly higher in the case group compared to the control group. When pre transfusion haematocrit was compared, mean haematocrit in the case group was 27.1 ± 4.4 compared to 54.1 ± 6.3 in the control group. This is statistically significant. On analysis, clinical sepsis was significantly higher in the transfused group.

CONCLUSIONS

After analysis it was found that APGAR score, presence of congenital pneumonia, SGA, neonatal jaundice, intra natal complications, caesarean section, cord prolapse, post-natal complications, frequency of anaemia and cardiac diseases, pre transfusion haematocrit and clinical sepsis were significantly more in the case group.

KEY WORDS

Neonate, Intra Natal, Haemorrhage, Low Birth Weight, Post Natal, Sepsis

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BACKGROUND

Majority of the neonates with low birth weight and gestational age require transfusion of red blood cells during their neonatal period. Most of these transfusions will be administered in the first postnatal month. Many aspects of haematopoiesis are either incompletely developed in preterm infants or are adapted to serve the foetus. This lack of development and/ or adaptation to extra uterine life

diminishes the capacity of the neonate to produce red cells, platelets and neutrophils particularly during the stress of life-threatening illnesses encountered after pre term birth such as sepsis, severe pulmonary dysfunction, necrotising enterocolitis, and immune cytopenias.

The serious medical and surgical problems of preterm birth can be further complicated by phlebotomy losses, bleeding, haemolysis and consumptive coagulopathy. Preterm infants begin life with quantities of blood cells and clotting proteins that are barely adequate. These infants have a diminished ability to increase production adequately to compensate for the haematologic problems they experience. Preterm infants especially those with birth weight less than 1.5 kg and with respiratory distress are given numerous red cell transfusions early in life because of several interacting factors. Neonates delivered before 28 weeks of gestation are born before the bulk of iron transport has occurred from the mother to foetus before the onset of marked erythropoietic activity of foetal marrow.

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Corresponding Author:

Dr. Sajith Vilambil,

Associate Professor,

Department of Transfusion Medicine,

Government Medical College,

Thrissur, Kerala, India.

E-mail: drsajithmenon@gmail.com

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Age in Days	Case		Control	
	Number	Percent	Number	Percent
1 – 5	127	84.7	133	88.7
6 – 10	19	12.7	17	11.3
>10	4	2.7	0	0.0
Mean $\pm$ SD	3.5 $\pm$ 3		3.3 $\pm$ 1.9	

Table 1. Comparison of Age in Days

t = 0.53, p = 0.599

Sex	Case		Control		χ^2	p
	Number	Percent	Number	Percent		
Male	79	52.7	75	50.0	0.21	0.644
Female	71	47.3	75	50.0		

Table 2. Comparison of Sex

Blood Group	Case		Control		χ^2	p
	Number	%	Number	%		
A +ve	37	24.7	49	32.7	8.01	0.237
A -ve	6	4.0	0	0.0		
B +ve	26	17.3	24	16.0		
B -ve	5	3.3	4	2.7		
AB +ve	6	4.0	5	3.3		
O +ve	59	39.3	58	38.7		
O -ve	11	7.3	10	6.7		

Table 3. Comparison of Blood Group

Group	Mean	SD	N	t	p
Case	1.8	0.4	150	0.06	0.950
Control	1.8	0.4	150		

Table 4. Comparison of Birth Weight

Gestational Age in Weeks	Case		Control	
	Number	Percent	Number	Percent
≤ 30	25	16.7	23	15.3
31 – 35	68	45.3	78	52.0
>35	57	38.0	49	32.7
Mean $\pm$ SD	33.9 $\pm$ 2.8		33.5 $\pm$ 2.7	

Table 5. Comparison of Gestational Age in Weeks

t = 1.21, p = 0.227

5 Minute Apgar Score	Case		Control		χ^2	p
	Number	Percent	Number	Percent		
≤ 5	12	8.0	0	0.0	12.5**	0.000
>5	138	92.0	150	100.0		

Table 6. Comparison of 5 Minutes APGAR Score

**:- Significant at 0.01 level

Diagnosis	Case		Control		χ^2	p
	Number	Percent	Number	Percent		
Preterm	120	80.0	132	88.0	3.57	0.059
Low birth weight	89	59.3	90	60.0	0.01	0.906
Sepsis	22	14.7	15	10.0	1.51	0.219
SGA	55	36.7	31	20.7	9.39**	0.002
Cong. Pneumonia	23	15.3	6	4.0	11.03**	0.001
Meningitis	2	1.3	4	2.7	0.68	0.409
GI bleed	14	9.3	6	4.0	3.43	0.064
Seizures	9	6.0	13	8.7	0.78	0.376
NNJ	23	15.3	5	3.3	12.76**	0.000

Table 7. Comparison of Diagnosis

**:- Significant at 0.01 level.

Intra natal Complications	Case		Control		χ^2	p
	Number	Percent	Number	Percent		
Normal	32	21.3	58	38.7	10.73**	0.001
Abnormal	118	78.7	92	61.3		

Table 8. Comparison of Intra Natal Complications

**:- Significant at 0.01 levels.

Intra Natal Complications		Case		Control		χ^2	p
		Number	Percent	Number	Percent		
CS	No	86	57.3	103	68.7	4.13*	0.042
	Yes	64	42.7	47	31.3		
APH	No	143	95.3	148	98.7	2.86	0.091
	Yes	7	4.7	2	1.3		
Assisted Delivery	No	132	88.0	126	84.0	1	0.318
	Yes	18	12.0	24	16.0		
Haemorrhage	No	131	87.3	134	89.3	0.29	0.590
	Yes	19	12.7	16	10.7		
Cord Prolapse	No	146	97.3	150	100.0	4.05*	0.044
	Yes	4	2.7	0	0.0		
Difficult	No	144	96.0	147	98.0	1.03	0.310

delivery	Yes	6	4.0	3	2.0		
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Table 9. Comparison of Intra Natal Complications

*:- Significant at 0.05 level

Post Natal Complications	Case		Control		χ^2	p
	Number	Percent	Number	Percent		
Normal	45	30.0	73	48.7	10.95**	0.001
Abnormal	105	70.0	77	51.3		

Table 10. Comparison of Post Natal Complications in Different Groups

**:- Significant at 0.01 level

Post Natal Complications		Case		Control		χ^2	P
		Number	Percent	Number	Percent		
Post-partum haemorrhage	No	137	91.3	134	89.3	0.34	0.558
	Yes	13	8.7	16	10.7		
Anaemia	No	107	71.3	134	89.3	15.38**	0.000
	Yes	43	28.7	16	10.7		
Diabetes Mellitus	No	134	89.3	134	89.3	0	1.000
	Yes	16	10.7	16	10.7		
Hypertension	No	126	84.0	135	90.0	2.39	0.122
	Yes	24	16.0	15	10.0		
Cardiac diseases	No	150	100.0	141	94.0	9.28**	0.002
	Yes	0	0.0	9	6.0		
Puerperal sepsis	No	148	98.7	148	98.7	0	1.000
	Yes	2	1.3	2	1.3		
Lactation failure	No	143	95.3	147	98.0	1.66	0.198
	Yes	7	4.7	3	2.0		

Group	Mean	SD	N	t	p
Case	27.1	4.4	150	43.17**	0.000
Control	54.1	6.3	150		

Table 12. Comparison of Pre-Transfusion Haematocrit

**:- Significant at 0.01 level

Clinical Sepsis	Case		Control		χ^2	p
	Number	Percent	Number	Percent		
Yes	83	55.3	40	26.7	25.48**	0.000
No	67	44.7	110	73.3		

Table 13. Comparison of Clinical Sepsis

Odds = 3.41 (2.10 – 5.53)

Several diseases during neonatal period require repeated blood sampling leading to iatrogenic anaemia. Preterm infants are unable to mount an effective erythropoietin response.

An important reason for the lower haemoglobin values of preterm infant than those of term infants is that preterm infants have a relatively diminished erythropoietin plasma level in response to anaemia. The major physiological impact of anaemia of prematurity is decreased oxygen delivery to the tissues which result in compensatory responses like increase in heart rate, cardiac output and cerebral blood flow, poor growth, decrease in activity etc. Low RBC mass contributes to tachypnoea, dyspnoea, apnoea, tachycardia, bradycardia, feeding difficulties and lethargy and these problems can be alleviated by PRC transfusions. Since red blood cell transfusion remains the primary treatment of anaemia in the neonatal period, the basis of PRC transfusion is discussed in this review.

We reasoned that assessing risk factors and clinical conditions before the first transfusion will improve our ability to estimate the need for red blood cell (RBC) transfusions of low birth weight (LBW) infants. Such estimation can identify infants who require more number of RBC transfusions. Minimising the number of units of RBC transfusion will decrease donor exposure. Risk based estimation of blood usage can identify those infants who are likely to require only one/more transfusion. This helps to identify unnecessary transfusions also.

METHODS

This was a case control study done in 300 neonates. Sample population were newborn babies with gestational age less than 37 weeks and/or birth weight less than 2500 grams admitted to the Neonatal Intensive Care Unit (NICU) of Sri Avittom Thirunal Hospital (SATH), Government Medical College Thiruvananthapuram. SATH has a level III NICU caring for both in-born and out-born infants.

Study was done for a period of one and a half years in the Department of Transfusion Medicine, Government Medical College Thiruvananthapuram.

Cases were sick neonates admitted to the NICU who were transfused with packed red cells at least once during their hospital stay. Controls are sick neonates who did not receive packed cells. Infants with chromosomal abnormalities, congenital heart disease, other life-threatening congenital abnormalities, death within first 24 hours were excluded from the study.

Case records of sick neonates admitted in NICU of SATH for a period of one and a half years were studied. The neonatal demographic and birth characteristics known to be associated with anaemia of prematurity were recorded. The details of the baby such as age, sex, birth weight, gestational age, blood group, 5 minutes APGAR score, indication for admission in NICU, diagnosis, indication for packed red cell (PRC) transfusion, pre transfusion haematocrit, post transfusion haematocrit, presence of clinical sepsis, type of antibiotics given and outcome of the baby were recorded. Complications occurring during delivery like cord prolapse, assisted delivery, difficult delivery, haemorrhage or caesarean section etc. were recorded. Post-natal complications were also considered which included puerperal sepsis and lactation failure.

Ethics

The study was approved by the human ethical and research committee, Government Medical College Thiruvananthapuram. The parents of the study subjects were counselled about the nature of the study. A written consent was obtained from the parents of the newborns included in the study.

Statistics

All statistical data were analysed using SPSS software version 16. Continuous variables were expressed as mean $\pm$ standard deviation. And qualitative data expressed as percentage. Independent t test was used for comparing quantitative data between two groups. Categorical variables were compared using χ^2 test. The predictive variables were calculated by univariate analysis.

RESULTS

Our study was a case control study done in 300 neonates admitted in the NICU of Sri Avittom Thirunal Hospital, Government Medical College, Thiruvananthapuram. Study subjects were divided into cases (n=150) and controls (n=150). Birth related details of both groups were studied and analysed.

On assessment of the age in days of the transfused neonates, 84.7% were in the age group of 1-5 days, 12.7% were in the age group of 6-10 days and 2.7 % were in the age group of more than 10 days. Mean age of the cases and

controls were compared using independent t tests. There was no significant difference between case and control groups.

On analysis of the sex, 52.7% of the transfused group was males and 47.3% was females. The control group had equal distribution of males and females. There was no significant difference between the two groups in this study.

While blood groups were analysed, O+ Blood group was seen predominantly in the neonates who received transfusion. In the total number of study subjects O+ blood group had the highest frequency followed in order by A+, B+, O-, AB+ and B-. Neonates with AB - blood group were lacking in the study group. Analysis did not show any statistical significance.

Birth weights of case and control groups were compared by independent t test. Mean birth weight was 1.8 ± 0.4 in both groups. There was no significant difference between the two groups. On analysing the gestational age of the neonates in weeks, 16.7 % of the case group and 15.3% of the control group belonged to <30 weeks. Mean gestational age was 33.9 ± 2.8 in the case group and 33.5 ± 2.7 in the control group. Statistically significant difference was not found between the two groups. On assessment, neonates with ≤ 5 minutes APGAR score was 8% in the case group compared to 0% in the control group. This observation was statistically significant. (P value =0.000)

80% were pre term (PT) infants and 59.3% were low birth weight (LBW) infants in the case group. 9.3% of neonates had gastro intestinal bleed, 6% had seizures and 1.3% had meningitis. On comparing the diagnosis, the prevalence of congenital pneumonia, (p=0.001) Small for Gestational Age (SGA) (P=0.002) and Neonatal Jaundice (NNJ) (P=0.000) were found to be significantly higher in the case group. In the control group, 88% were PT infants, 60% LBW and 20.7% small for gestational age (SGA). 10% of the control group had sepsis, 2.7% had meningitis. 8.7% had seizures 4% had GI bleed and 3.3% had neonatal jaundice.

On assessing the intra natal complications, 78.7 % of the mothers in the case group had intra natal complications compared to 61.3% in the control group. p value was significant. On assessment of intra natal complications in case group, caesarean section done in 42.7%, ante partum haemorrhage in 4.7%, assisted delivery in 12%, haemorrhage in 12.7%, cord prolapse in 2.7%, difficult delivery in 4%. The control group revealed caesarean section in 31.3%, ante partum haemorrhage in 1.3%, assisted delivery in 16%, haemorrhage in 10.7% and difficult delivery in 2%. Caesarean section was significantly more in the case group. p value was significant in caesarean section and cord prolapse.

Post-natal complications were significant in this study and p value was 0.001. On assessment of post-natal complications of the case group, 28.7% had anaemia, 16% had hypertension, 10.7% had diabetes, 8.7% had postpartum haemorrhage, 4.7% had lactation failure and 1.3% had puerperal sepsis. In the control group 10.7 % had anaemia, 10% had hypertension, 10.7% had diabetes, 10.7% had postpartum haemorrhage, 2% had lactation failure and 1.3% had puerperal sepsis. The frequency of anaemia and cardiac diseases were significantly higher in the case group compared to the control group. P value was found to be 0.000 and 0.002 respectively.

When pre transfusion haematocrit was compared mean haematocrit in the case group was 27.1 ± 4.4 compared to

54.1 ± 6.3 in the control group. This is statistically significant, and the p value was 0.000.

On analysis, clinical sepsis was detected in 55.3% of the case group and only in 26.7% of the control group. Clinical sepsis was significantly higher in the transfused group with p value 0.000. When outcome was analysed, no deaths reported in the case and control groups.

DISCUSSION

In our study, neonates who had received transfusions were included in the case group and those who had not received transfusions were included in the control group. Our study compared the demographic characteristics and variables which are known to be associated with transfusion of packed red cells in neonates.

Analysis of neonatal data of case group showed that 84% belonged to the age group 1-5 days, 12.7% to the age group of 6-10 days and only 4 % to the age group of more than 10 days. The mean age at which transfusions were given was 3.5 ± 3 days. According to a multicenter study in 8 NICUs of Brazilian Neonatal Research Network, the number of transfusions was higher during the first 28 days of life compared to that after 28 days of life. The number of transfusions was less after 28 days till discharge.¹

In our study, male to female ratio was similar in the case and control groups. Blood group analysis showed that the percentage of O+ group was more in the transfused group, but statistical significance was not observed. Comparison of the birth weight did not show any significant differences between the case and control groups. This finding correlated with the study by David A Paul et al. Analysis revealed that the mean gestational age of the neonates who received transfusion was 33.9 ± 2.8 days. We could not prove any definite association between low gestational age and transfusion requirements. Brown M.S et al postulated that the best predictor of blood transfusion was gestational age less than 30 weeks.² Jorge Fabres and Gay Wehrli had similar findings where the median gestational age was 26 weeks.³ In a study to find out the risk factors for transfusion, Zuppa et al could prove that the gestational age is an important factor in deciding RBC transfusion in neonates.⁴ Five minutes APGAR score was a significant factor in deciding the transfusions to the neonates in our study. 8% of our case group had APGAR ≤5 while such a low APGAR score was not found in the control group. Various observational studies and randomized controlled trials are in favour of this observation.⁵⁻⁷ We compared the diagnosis of the transfused and non-transfused group. This revealed that the frequency of congenital pneumonia (15.3 %) and neonatal jaundice (8.3%) were significantly higher in the transfused group. Another significant observation in our study was the lower pre transfusion haematocrit value in the transfused group (27.1 ± 4.4). This finding correlated with a study by Rachana Singh et al where they postulated that a low pre transfusion haematocrit associated with a higher number of RBC transfusions.⁸ Gomella in his study revealed that severe anaemia with haematocrit less than 25% was a definite indication for RBC transfusion.⁹⁻¹⁰

Clinical sepsis was found to be significantly higher in the transfused group. Sepsis was present in 55.3% of neonates in the case group compared to 26.7% in the control group. Other studies also point to such a situation.⁵ The clinical

variables assessed in the infant's early hospital course may be used to predict the number of transfusions to be given, interventional strategies and counseling of parents.

Horbar et al opined that presence of anaemia, cardiac disease, severe critical illness, multiple organ dysfunction syndrome are the most significant determinants of red cell transfusions.¹¹

Bishara N, Ohlis R.K and co-workers noted that Extremely Low Birth Weight (ELBW) infants develop anaemia of prematurity due to frequent blood draws as part of their care in NICUs.¹¹ Kasat K, Hendricks and co-workers conducted a study at Cohen Child Medical Centre New York and postulated that tachycardia was the most sensitive predictor of benefit from PRC transfusions.¹² Strauss R.G. Mock DM considered circulating red cell volume/mass as a decisive factor for transfusion rather than haemoglobin or haematocrit.

On comparing the postnatal complications of the case and control groups, the frequency of maternal anaemia was found to be 28.7% and 10.7% respectively. This is significantly higher in the case group.

Fabres et al. found that 85 % of preterm received red blood cell transfusion and it was associated with birth weight, gestational age, age at first transfusion.¹³ Mimica et al. found that number of transfusions was associated with birth weight.¹⁴

In a study by Amelia et al it was found out that the following factors were associated with indications for transfusions: lower gestational age, higher SNAPPE II score, presence of apnoea, pulmonary haemorrhage, clinical sepsis, moderate/severe intraventricular haemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, umbilical catheter use, parenteral nutrition, prolonged hospital stay. Same study narrates that premature newborns who received RBC transfusions during hospital stay had a 3.8- fold greater chance of developing enterocolitis and a 64 % greater chance of also having a diagnosis of grade III to IV haemorrhage in comparison to those who did not receive transfusions. However, it was not possible to establish the temporal relationship between the transfusions and these complications. These variables were closely interrelated and, to some extent, reflect the morbidities and procedures often described for very-low-birth-weight newborns. (Amelia)¹⁵

In a retrospective study of premature infants with peri-intraventricular haemorrhage, progression of disease was found after RBC transfusions. The factors associated with the progression were gestational age and transfusion.¹⁶ In a meta-analysis that included Mohamed and Shah found an association between RBC transfusion and the occurrence of necrotizing enterocolitis.¹⁷ Del Vecchio et al. found an association between the reduction of transfusion rates and a lower incidence of bronchopulmonary dysplasia, retinopathy of prematurity and necrotizing enterocolitis.

CONCLUSIONS

After analysis it was found that APGAR score, presence of congenital pneumonia, SGA, neonatal jaundice, intra-natal complications, caesarean section, cord prolapse, post-natal complications, frequency of anaemia and cardiac diseases, pre-transfusion haematocrit and clinical sepsis were significantly more in the case group.

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