

Blood Transfusion Reactions in Malaysian Newborn Infants

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Summary

A prospective observational study was carried out over a seven month period in the neonatal intensive care unit (NICU) of a large Malaysian maternity hospital to determine the rate of blood transfusion and the incidence of transfusion reactions in newborn infants. During the study period, the rates of blood transfusion was 6.1% (n=117) of NICU admission or 8.2 per 1,000 live births. The median birth weight of the infants who had received blood transfusion was 1,740 grams (range: 725 - 4,350), and their mean gestational age was 33.6 weeks (sd = 5.1, range = 24-41 weeks). The median age of infants when they first received blood transfusion was 4.0 days (range: 1-27 days). When compared with infants of birth weight between 3,000 and 3,499 grams, infants of birth weight less than 1,500 grams received significantly higher median number of transfusions per infant, ($p < 0.001$). The incidence of transfusion reaction was 2.7% (3/110) of all transfused infants or 1.3% (3/223) of all blood transfusions. Febrile non-hemolytic reaction was the only type of transfusion reaction detected during the study period. This study showed that transfusion reactions in newborn infants were not common.

Key Word: Blood transfusion reactions, Newborn infants

Introduction

Recent advances in neonatal intensive care have resulted in both an increased need for transfusion of blood, and an awareness of the possible adverse consequences of these products in the sick newborn infants. Frequent blood sampling in the sick infants often causes considerable loss of blood volume which requires "top-up" blood transfusion to maximise the oxygen carrying capacity in the infants¹. Newborn infants differ from adults and older children in several aspects with regards to blood transfusion practices. They have smaller blood volumes, difficulties in body temperature regulation, citrate intolerance and an immature immune system^{1,2}. It has been estimated that about 90% of the indications for erythrocyte transfusion in the newborn infants in some neonatal intensive care units (NICUs)

were for replacement of iatrogenic blood loss². A number of complications associated with blood transfusion have been reported in the infants in recent years. These include: volume overload with resultant congestive cardiac failure, especially in preterm infants with persistent ductus arteriosus,¹ transmission of transfusion-related infection,^{2,4} and post-transfusion graft-versus-host disease^{5,6}. Based on Medline search of studies published between 1966 to 1996, it was found that, except for reports on transfusion-related infections, only one study has been reported on other types of blood transfusion reactions in the newborn infants⁷.

The Kuala Lumpur Maternity Hospital was the largest maternity hospital in Malaysia. Its neonatal intensive care unit (NICU) catered only for sick newborn infants

delivered in this hospital. The objectives of this study were to determine: a) the rate of blood transfusion in newborn infants admitted to this NICU and b) the incidence of transfusion reactions following blood transfusion in these infants.

Methods

This was a prospective observational study carried out at the NICU of the Kuala Lumpur Maternity Hospital over a seven-month period, between 1 December 1996 to 30 June 1997. All newborn infants who were born in the hospital during the study period and received packed red cells or whole blood transfusion during their stay in the NICU were included in the study.

Prior to blood transfusion, the following blood tests were carried out on the infants: serum haemoglobin (Hb) level, reticulocyte counts (Retic counts), haematocrit (Hct), serum bilirubin (SB) and renal profiles (RP). Data on the frequency of transfusion and their indications, infants' highest and lowest body temperature, blood pressure, and heart rates during the 24 hours before and after each transfusion were documented. Subsequent Hb, Hct, Retic counts, SB, and RP were repeated on the third, seventh and fourteenth post-transfusion days. When there was evidence of haemolysis, as was suggested by a decrease in Hb levels post-transfusion associated with an increase in reticulocyte count and SB level, the Coomb's test was carried out, and the antibody levels were determined if the Coomb's test was positive. The serial number of the blood bags of the donors, the number of blood transfusion received by each infant from each donor, and signs of transfusion reactions in these infants during and following transfusions were documented. For logistic reasons, we did not include screening for blood transfusion-related infections, such as viral and parasitic infections, in this study. The outcome (whether they survived or died) of all infants who received blood transfusion before discharge was also recorded.

The following definitions were used during the study. Early haemolytic reaction to blood transfusion was diagnosed when there was no improvement in the infant's serum Hb level or when there was a further decrease in the Hb levels by 3 grams/dl within 3 days after blood transfusion without evidence of blood loss. This might be associated with a positive Coomb's test in

the infants following transfusion. Late haemolytic reaction to blood transfusion was defined as a drop in the Hb levels by 3 grams/dl within 3 to 14 days post-transfusion without evidence of blood loss. This was associated with a positive Coomb's test post-transfusion. An infant was diagnosed to have developed febrile non-haemolytic reaction to transfusion when he/she developed one or more of the following clinical features during blood transfusion: changes in vital signs, development of rhonchi, and/or loss of control of body temperature with resultant body temperature rising more than 37.5 °C during blood transfusion. The fever settled following cessation or completion of transfusion. Graft-versus-host reaction to blood transfusion was diagnosed to be present when an infant developed skin lesions ranging from maculopapular sunburn-like rashes to bullae with sudden rise in serum bilirubin levels within a week following blood transfusion. Tachycardia was diagnosed to be present when the infant's heart rate was more than 160 beats/minute. Fever was defined to be present when the axillary temperature of the infant was more than 37.5 °C.

Statistical analysis

The incidence of blood transfusion was calculated according to the ethnic groups, gender groups and birth weight distribution of infants admitted to the NICU. The frequency of blood transfusion, and the age of the infants when transfusion was first given among the various birth weight and gestational sub-groups were compared. The Chi-square test (or Fisher Exact test when the expected cell was less than 5) was used for analysis of categorical variables. For continuous variables, mean values were calculated when the distribution was normal, and the median values were calculated when the distribution was not normal. Kruskal Wallis test and Mann-Whitney U test were used for comparison of groups whose distribution were not normal. Two-tailed tests were used for all analysis. P values of ≤ 0.05 were considered statistically significant.

Results

During the study period, there were 14,385 deliveries at the Kuala Lumpur Maternity Hospital; 167 (11.6 per

1,000 deliveries) of these were stillbirths and 14,218 (988.4 per 1,000 deliveries) were live births. A total of 1,928 (135.6 per 1,000 live births) infants were admitted to the NICU. Blood transfusion was given to 117 of these infants. Thus, the incidence of blood transfusion in the infants born in this hospital was 6.1% of NICU admission, or 8.2 per 1,000 live births.

Of the 117 infants who received blood transfusion, the records of 7 infants were lost following discharge. The data of these 7 infants were excluded from subsequent analysis. We present here the data of the remaining 110 infants.

The median birth weight of the 110 infants who had received blood transfusion was 1,740 grams (range: 725 - 4,350). Their mean gestational age was 33.6 weeks (sd= 5.1, range= 24-41 weeks). The median age of these infants when they first received blood transfusion was 4.0 days (range: 1-27 days). Table I shows the relationship between the rates of blood transfusion and the ethnic, gender, and birthweight distribution of the infants admitted to the NICU. When compared with infants who did not receive blood transfusion, there was no significant difference in the ethnic distribution in infants who received blood transfusion. However, when compared with infants who did not receive blood

Table I
Rates of blood transfusion according to ethnic, gender and birth weight distribution

Variables	Total No. of NICU Admission n=1928 (%)	No. of Infants Transfused n= 110 (%)	No. of Infants Not Transfused n= 1818 (%)	Odds Ratios of Transfused (95% C.I.)	P values
Ethnic Groups					
Malay	1254 (65.0)	68 (61.8)	1186 (65.2)	Reference	
Chinese	233 (12.1)	16 (14.5)	217 (11.9)	1.3 (0.7, 2.3)	0.4
Indians	272 (14.1)	15 (13.6)	257 (14.1)	1.0 (0.6, 1.9)	1.0
Others	169 (8.8)	11 (10.0)	158 (8.7)	1.2 (0.6, 2.4)	0.6
Males	1118 (58.0)	50 (45.5)	1068 (58.7)	0.6 (0.4, 0.9)	0.006*
Birth weight, g					
< 1000	45 (2.3)	15 (13.6)	30 (1.7)	14.4 (5.7, 36.7)	0.0000*
1000-1499	131 (6.8)	28 (25.5)	103 (5.7)	7.8 (3.7, 17.0)	0.0000*
1500-1999	288 (14.9)	19 (17.3)	269 (14.8)	2.0 (0.9, 4.6)	0.06
2000-2499	269 (14.0)	9 (8.2)	260 (14.3)	1.0 (0.4, 2.5)	1.0
2500-2999	568 (29.5)	13 (11.8)	555 (30.5)	0.7 (0.3, 1.6)	1.0
3000-3499	358 (18.6)	12 (10.9)	346 (19.0)	Reference	
≥3500	269 (14.0)	14 (12.7)	255 (14.0)	1.6 (0.7, 9.7)	0.3

Note: C.I. denotes confidence intervals, * denotes statistical significance.

transfusion, a significantly lower proportion of the infants who were transfused was males. A significantly higher proportion of the infants who received blood transfusion were extremely low birth weight (ELBW) infants of birth weight less than 1,000 grams and VLBW infants (birth weight < 1,500 grams) ($p < 0.05$)

A total of 223 transfusions were given to the 110 infants during the study period. The median number of transfusions received by each infant was 1.5 times (range: 1 - 8). Fifty-five (50.0%) of the infants received one blood transfusion, 29 (26.4%) received two transfusions, 10 (9.1%) received three transfusions, 8 (7.2%) received four transfusions, 3 (2.7%) received five blood transfusions, 3 (2.7%) received six, 1 (0.9%) received seven and 1 (0.9%) received eight transfusions. Table II shows that there was no significant difference in the median age when infants of different birth weight requiring blood transfusion were compared ($p=0.28$), although the smaller infants, especially the VLBW infants, appeared to need transfusion at a later age. However, when compared with infants of birth weight between 3,000 to 3,499 grams, low birth weight (LBW,

birth weight < 2500 grams) infants required significantly larger median number of blood transfusions per infant ($p < 0.05$). Table III shows that, when preterm infants of different gestational age groups were compared with infants of term gestation (between 37 and 41 weeks), the preterm infants of gestation less than 33 weeks received blood transfusions at significantly later age and significantly larger number of transfusions.

There were three main indications for blood transfusion. These were anaemia (74.0%), hypovolaemia (16.1%) and exchange transfusion (9.9%) (Table IV). All, except one, infants with hypovolaemia was treated with packed cell transfusion. The causes of hypovolaemia were: pulmonary haemorrhage ($n= 20$), gastrointestinal bleeding ($n=2$), subaponeurotic haemorrhage ($n=3$), and massive intraventricular haemorrhage ($n=11$). The Hb was measured prior to transfusion in only 175 (78.5%) of the 223 blood transfusions. The mean Hb level of the infants just prior to receiving blood transfusion was 11.6 g/dl ($sd=2.8$), confirming that anaemia was the most common cause of transfusion.

Table II
Age and frequency of blood transfusion according to birth weight distribution

Birth weight in grams	Median Age At First Transfusions days (range)#	No. of Infants Given Transfusions $n = 110$ (%)	No. of Blood Transfusions given $n = 223$ (%)	Median No. of Transfusion per Infant (range)##	p values ###
<1000	5.0 (1-24)	15 (13.6)	44 (19.7)	3 (1-6)	0.004*
1000 - 1499	4.5 (1-27)	28 (25.5)	74 (33.2)	2 (1-8)	0.004*
1500 - 1999	3.0 (2-23)	19 (17.3)	32 (14.3)	1 (1-5)	0.2
2000 - 2499	4.0 (1-11)	9 (8.2)	18 (8.1)	2 (1-4)	0.04*
2500 - 2999	3.0 (1-9)	13 (11.8)	17 (7.6)	1 (1-3)	0.7
3000 - 3499	4.0 (1-22)	12 (10.9)	15 (6.7)	1 (1-2)	Reference
≥ 3500	3.0 (1-9)	14 (12.7)	23 (10.3)	1 (1-5)	0.6

Note: # Kruskal-Wallis test: $p=0.28$; ## Kruskal-Wallis test: $p=0.001$; ### p values based on Mann-Whitney U tests; * denotes statistical significance.

Table III
Age and frequency of blood transfusion according to gestation distribution

Gestation in weeks	Median Age At First Transfusions		No. of Infants Given Transfusions n = 110 (%)	No. of Blood Transfusions given n = 223 (%)	Median No. of Transfusion per Infant	
	days (range)#	p values ###			(range)##	p values ###
≤ 28	6 (1-22)	0.02*	25 (22.7)	74 (33.1)	2 (1-7)	0.000*
29 - 32	5 (2-27)	0.007*	28 (25.5)	55 (24.7)	2 (1-4)	0.008*
33 - 36	4 (1-21)	0.07	17 (15.5)	35 (15.7)	2 (1-8)	0.08
37 - 41	3 (1-22)	Reference	40 (36.4)	59 (26.5)	1 (1-5)	Reference

Note: # Kruskal-Wallis test: $p=0.02$; ## Kruskal-Wallis test: $p=0.001$; ### p values based on Mann-Whitney's U tests; * denotes statistical significance.

Table IV
Relationship between indications for transfusion and types of blood used

Indications for Blood Transfusion	Packed Red Cells n = 200 (%)	Whole Blood n = 23 (%)	Total n = 223 (%)
Anaemia	165 (82.5)	0 (0)	165 (74.0)
Hypovolemia	35 (17.5)	1 (4.3)	36 (16.1)
Exchange Transfusion	0 (0.0)	22 (95.7)	22 (9.9)

Table IV also shows that packed red cells were used for majority (200/223 or 89.7%) of the blood transfusions. Whole blood was used in only 10.3% (23/223) of the transfusions and was used primarily for exchange transfusion. Eighty-nine (80.9%) infants received only packed red cell transfusion, seventeen (15.5%) infants received only whole blood transfusion and four (3.6%) infants received both packed red cell and whole blood. Of the 89 infants who received only packed red cell transfusions, 55 (61.8%) received more than one transfusion. A single transfusion was given to all, except one, of the 17 infants who were transfused with only whole blood. For the 4 infants who were transfused

with both packed cells and whole blood, the number of blood transfusion received ranged between 2 to 4 times.

The blood used for the 223 blood transfusions came from 140 blood donors. As mentioned above, 55 (50%) of the 110 infants received more than one blood transfusion. However, only 12 (21.8%) of these 55 infants received blood from the same donors during repeated transfusions. No infant, who required more than 2 blood transfusions, received all the blood from a single donor. On the other hand, the blood from 87 (62.1%) of the 140 blood donors was used in single transfusions, while the blood from the remaining 53

(37.9%) donors was used in multiple transfusions of different recipient infants. The median number of blood donors per infant who received blood transfusion was 1.0 (range: 1 - 8). All, except two, of the blood donors were of blood group O Rhesus positive. None of the donor's blood was irradiated or filtered before being used for transfusion.

Eighty-four (76.4%) infants survived to go home. There was no significant difference between the age of first transfusion between infants who survived or died before discharge [median age of survivors at first transfusion: 4 (range 1-27) days; median age of non-survivors at first transfusion: 4 (range 1-22) days, $p=0.7$]. The survivors received significantly less number of blood transfusion than the non-survivors [median number of blood transfusion per survivor: 1 (range 1-8); median number of blood transfusion per non-survivor: 2 (range 1-7); $p=0.01$]. The median age of the survivors at discharge was significantly older [27 (range 3-99) days] than the non-survivors [14 (range 1-88) days] ($p=0.009$).

Febrile reaction (axillary temperature $> 38.0^{\circ}\text{C}$) during transfusion was observed in three (2.7%) infants. Two of them were term infants with birth weight of more than 3,000 grams and one was an ELBW infant of birth weight 790 grams. The reaction occurred during the first transfusion in both the term infants (at age of 4 days and 22 days, respectively), and at the age of 23 days during the second transfusion of the ELBW infant. There was no clinical or laboratory evidence of hemolysis. Their fever resolved following completion of blood transfusion, and they remained well. One of them (a term infant) died subsequently at the age of 36 days due to unrelated causes while the other two infants were discharged home subsequently. No infant developed evidence of delayed transfusion reactions or graft-versus-host disease. Thus the incidence of transfusion reaction was 2.7 % of all transfused infants or 1.3% of all blood transfusions, and was of the febrile non-haemolytic type.

Discussion

When compared with blood transfusion rates of 8 to 12 transfusions per infant reported in other NICUs,^{1,2,8} the

transfusion rate in the NICU of the Kuala Lumpur Maternity Hospital, at 2.9 transfusions per VLBW infant, and 1.3 per normal birth weight infant, was not high. However, similar to the findings of other NICUs, we found that the transfusion rates were highest among the VLBW and premature infants below 33 weeks gestation. The reasons for the greater number of blood transfusion in VLBW or preterm infants were usually one of the following: a) generally being more ill initially, they required more blood sampling with resultant iatrogenic anaemia, and b) subsequently, as their condition became stable, their rapid growth gave rise to anaemia of prematurity which, when severe, required blood transfusion. These tiny infants were usually discharged home after they had attained sufficient weight gain of about 1.7 kg. When compared with larger infants, their hospital stay were, therefore, much longer. This largely explained why the smaller infants required more blood transfusion and often at a later age when compared with the larger infants.

This study revealed a number of disturbing findings. These include: a) the use of large number of different donors for infants who required multiple blood transfusions, and b) the use of packed red cells, instead of other volume expanders, for treatment of hypovolaemia. Both these practices predisposed the infants to the hazards of transfusion-related infections. Studies done elsewhere showed that the rate of transfusion-associated infections, although not always directly proportional to the frequency of donor exposure, increased when multiple transfusions were given.^{9,10} Because of logistic reasons, we did not include detection of transfusion-related infections in this study and were not able to determine the incidence of these complications. The blood used for transfusion in our NICU during the study period was not filtered prior to transfusion. In view of the prevalence of hepatitis, malaria and HIV infection in this part of the world, the dangers of acquiring transfusion-related infections in these newborn infants requiring repeated transfusions in our NICU must not be taken lightly. Greater efforts should, therefore, be made to reduce the number of donors for each of the infants who require blood transfusion in this NICU. Education of the medical staff in the judicious use of blood products should be intensified and regularly repeated.

The most common indication for blood transfusion in

the sick newborn infants in this NICU was anaemia. Perhaps greater efforts should be made to minimise this condition, by reducing unnecessary frequent blood sampling. Recent studies have reported the effectiveness of early use of recombinant human erythropoietin for the prevention of anaemia in the preterm infants^{11,12}. However, in view of the high cost of erythropoietin, studies should be carried out in Malaysia to determine the cost-benefit of using this new modality of treatment.

Our study showed that the incidence of febrile transfusion reaction was low, and there was no incidence of haemolytic transfusion reaction nor graft-versus-host

disease following blood transfusion in these newborn infants, although the blood used in this NICU was not irradiated or filtered. This low incidence could possibly be explained by the low immune response mounted by the immature immune system of these infants. However, the long-term effects of these blood products on the immune system of these infants were not certain at this juncture.

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