Introduction of a donor exposure reduction programme for multiple-transfused very-low-birth-weight infants

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Objective. To conduct an audit of the frequency of red cell concentrate transfusions (RCCTs) in infants of different weight categories, the donor exposure rate (DER) in these transfused infants and the volume of blood wasted during each transfusion, and to identify from this baseline information specific categories of infants who would benefit from the introduction of a limited donor exposure programme (LDEP).

Study setting. Neonatal wards and neonatal intensive care unit (NICU), Tygerberg Hospital, Western Cape.

Study design. A prospective descriptive study and comparison with a historic control group.

Subjects. Information on the birth weight, age at the time of each RCCT and number of blood donors to whom an infant was exposed were collected *post factum* for all infants admitted to the neonatal wards and NICU between May 1993 and May 1994. During this time, the red blood cell concentrate was supplied as single paediatric bags (180 ml) transfused within 14 days of donation. An LDEP was introduced in February 1995. With this system, red blood cells were supplied as triple packs: a main unit of 250 ml with three empty satellite packs allowing up to three separate transfusions. These were assigned to a specific infant and were to be transfused within 21 days of donation. A second system where one adult blood bag was divided into two 180 ml bags and assigned to one infant to be transfused within 35 days of donation was also assessed.

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Results. Of the 7 854 infants admitted during the first 12-month audit period, 387 (4.9%) received 977 RCCTs. Of these, 183 (47.3%) received one transfusion, 72 (18.6%) two transfusions, 51 (13.2%) three transfusions, 27 (7.0%) four transfusions and 54 (13.9%) five or more transfusions. Infants (N = 188) with a birth weight below 1 500 g admitted to the NICU were identified as the group with the highest prevalence of RCCTs (68.6%), and it was therefore decided that in the prospective study such infants would qualify for the LDEP. A total of 81 infants was transfused with either the double (N = 47) or the triple bags (N = 34) over a 5-month period. The decrease in the mean DER (± SD) was clinically significant when the triple (1.9 ± 0.8) (P = 0.0001) and the double bags (1.6 ± 0.8) (P = 0.0001) were compared with the previous single-bag system (4.4 ± 3.5). Of concern was the large mean volume of concentrated red cells (118.5 ± 12.5 ml) wasted per transfusion with the single-bag system.

Conclusions. This survey confirmed a high RCCT rate as well as a very high DER in very-low-birth-weight (VLBW) infants treated at a tertiary centre. By assigning a triple or double bag of red cells from one blood donor and extending the storage of blood for small-volume RCCTs in infants from 14 days to 35 days, donor exposure was reduced significantly. We urge the introduction of the multibag blood transfusion system and extended storage period of blood for small-volume RCCT for VLBW infants in South Africa.

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The frequency of red cell concentrate transfusions (RCCTs) to very-low-birth-weight (VLBW) infants is among the highest for any patient group in tertiary hospitals.[1,2] VLBW infants requiring intensive care receive the majority of these blood transfusions.[3] Reasons for this are multifactorial and include blood loss during repeated blood sampling for laboratory studies and consequently replacement transfusions, the necessity to maintain an acceptable oxygen-carrying capacity during ventilation and in infants with bronchopulmonary dysplasia, severe bacterial infection, and anaemia of prematurity.[4,5] The risks associated with multiple RCCTs such as transmission of cytomegalovirus (CMV), hepatitis, HIV and human T-cell leukaemia virus, although infrequent are not trivial and are directly related to the number of donors to which the infants are exposed and indirectly related (as in the case of CMV) to the infant's birth weight or gestational age.[5] Limiting donor exposure by attempting to supply all the red cells for transfusion to a VLBW infant from one donor may reduce the risk of transfusion-transmitted infection.[5] Currently, no blood transfusion service in South Africa has a limited donor exposure programme (LDEP) whereby donor exposure is limited during the multiple blood transfusions administered to VLBW infants. The supply of blood as 'one unit of blood for one infant' results in unnecessary wastage of this scarce commodity. In addition, owing to concerns about high potassium levels in stored blood,[6] only red cells stored for less than 7 days are usually used for small-volume transfusions in infants, a policy that results in greater pressure on the transfusion service's blood stocks.

A recent study confirmed the importance of limiting exposure of VLBW infants receiving multiple blood transfusions to as few blood donors as possible and recommended using blood stored for up to 35 days for small-volume RCCTs in infants.[7]

An audit was carried out in the neonatal wards of Tygerberg Hospital in order to determine: (*i*) the frequency of RCCTs in infants of different weight categories; (*ii*) the donor exposure rate (DER) in these transfused infants; and (*iii*) the volume of blood wasted in neonatal transfusions. It was hoped that from this baseline information (historic controls) specific categories of infants would be identified who would benefit from the introduction of an LDEP.

Patients and methods

The neonatal unit at Tygerberg Hospital, the teaching hospital for the University of Stellenbosch, mainly serves patients from the Bellville area who are from a lower socio-economic background (metropolitan). It also serves as the tertiary referral centre for infants from the rural Western Cape up to the Namibian border in the north, Beaufort West in the east and George in the south.

Information on birth weight, age at the time of RCCT and the number of blood donors an infant was exposed to was collected prospectively for all infants admitted to the neonatal wards between May 1993 and May 1994. During this time, the infants received plasma-reduced antibody-negative group O Rh-specific CPDA-1 and Adsol red blood cell concentrates cross-matched against the infant's serum. The red blood cells were supplied as single paediatric bags (180 ml) with undetermined CMV antibody status and transfused within 14 days of donation. In the ward, a 150 ml Buretrol chamber (Baxter) was connected to the blood bag and the prescribed volume of blood was allowed to run into the chamber and also to fill the tubing and filter (170 - 260 micron) of the transfusion set (Baxter). A total of 40 ml of red blood cells was needed to prime the tubing and the filter. The red cells were transfused over a period of 3 - 4 hours using a Danby transfusion pump (Adcock-Ingram).

Once this baseline information was analysed, an LDEP programme was introduced in February 1995. We obtained 55 Fenwal (Baxter Healthcare, UK) quadruple blood collection bags for RCCTs. With this system, CPDA-1 red blood cells are supplied as triple packs: a main unit of 250 ml with three empty satellite packs (40 ml of red cells each) allowing up to three separate transfusions. These were assigned to a specific infant and were to be transfused within 21 days of donation. All the triple bags were used by May 1995, and a second system was assessed from May to July 1995 — one adult blood bag divided into two 180 ml bags containing an Adsol red cell concentrate was assigned to one infant, and was to be transfused within 35 days of donation.

In both multibag systems the CMV antibody status of the blood was unknown and leucocyte depletion filtration was not done.

After compatibility testing (O Rh-specific), the blood was labelled and kept on reserve for that particular infant and

was to be used within 21 or 35 days of donation for the triple- or double-bag system, respectively. Two days before the expiry date for the assigned stored unit of blood (19 or 33 days after donation, respectively), the blood bank reminded the doctor caring for that specific infant of the impending expiry. If no further transfusions were necessary for that specific infant, the blood was issued to another infant. The red cells were transfused over a 3 - 4-hour period through a blood filter (Baxter) using a Danby pump. The volume of red cells transfused ranged between 10 and 15 ml/kg.

Statistical analysis

The nominal and ordinal data are expressed as frequencies and percentages. Mean (± SD) and/or median and interquartile range (IQR) (Q1 - Q3), are given for counted and measured variables. The donor exposure for those infants with birth weights below 1 500 g who received multiple RCCTs with the single-bag method was compared with that for infants who received multiple RCCTs with the double- and triple-bag system, respectively, using the Wilcoxon two-sample test.

Results

Of the 7 854 infants admitted during the first 12-month audit period (historic control group), 387 (4.9%) received 977 RCCTs at a mean age of 12.2 ± 13.8 days. The most transfusions were given to infants with birth weights below 1 000 g (37.6%) and between 1 000 g and 1 500 g (38.7%). The mean volume of red cells transfused was 21 ± 12.2 ml, which resulted in a mean volume of blood wasted of 118.8 ± 12.2 ml per RCCT. The number of admissions, the percentage of infants transfused according to birth weight categories, the mean age at the time of the first RCCT, and the volumes of blood transfused and wasted are shown in Table I.

The mean number of RCCTs in the historic control group was 2.5 ± 2.4. One hundred and eighty-three infants (47.3%) received one transfusion, 72 (18.6%) two transfusions, 51 (13.2%) three transfusions, 27 (7.0%) four transfusions, and 54 (13.9%) more than four transfusions. One infant received 21 transfusions. The mean DER in the historic control group equalled the number of RCCTs given to an infant. The mean and median number and the frequency of RCCTs given to the historic control group of infants are shown according to birth weight categories in Table II. Infants with birth weights below 1 500 g (N = 188) admitted to the neonatal intensive care unit (NICU) were identified as the group with the highest frequency of RCCTs (68.6%) as well as the highest mean DER (4.4 ± 3.5) (Table III). It was therefore decided that such infants would qualify for the LDEP in the prospective trial.

Table I. Numbers of infants admitted and transfused over the 12-month period (historic controls) and volumes of red blood cells transfused and wasted

	Birth weight (g)					
	< 1 000	1 000 - 1 499	1 500 - 1 999	2 000 - 2 499	> 2 500	All infants
No. of admissions	85	450	641	1 064	5 641	7 854
No. transfused	32 (37.6%)	174 (38.7%)	84 (13.1%)	39 (3.7%)	58 (1.0%)	387 (4.9%)
Age (d) at first transfusion (mean ± SD)	15.7 ± 15.2	13.7 ± 14.9	12.5 ± 11.5	9.5 ± 14.4	6.6 ± 12.1	12.2 ± 13.8
Volume (ml) transfused (mean ± SD)	14.8 ± 11.7	18.5 ± 9.5	23.9 ± 14.0	26.4 ± 9.2	34.5 ± 12.7	21 ± 12.2
Blood wasted* (mean ± SD)	125.1 ± 11.7	121.3 ± 9.5	116.1 ± 14.0	113.4 ± 9.2	105.6 ± 12.7	118.8 ± 12.2

* Volume of red cells in blood bag (180 ml) minus volume of blood required to prime transfusion set (40 ml) minus red cell volume transfused = volume of blood wasted per transfusion.

Table II. Frequency of red cell concentrate transfusions according to birth weight categories (historic control group)

	Birth weight (g)					
	< 1 000	1 000 - 1 499	1 500 - 1 999	2 000 - 2 499	> 2 500	All infants
No. of infants	32	174	84	39	58	387
No. of transfusions						
Mean ± SD*	3.3 ± 2.2	2.9 ± 3.0	2.4 ± 1.9	1.7 ± 1.3	1.6 ± 1.3	2.5 ± 2.4
Median (Q1 - Q3)	2 (2 - 5)	2 (1 - 4)	1.5 (1 - 3)	1 (1 - 2)	1 (1 - 2)	2 (1 - 3)
Maximum	9	21	11	7	8	21
Percentages of infants with No. of transfusions						
1	21.9	39.1	50.1	64.1	70.7	47.3
2	31.3	21.8	11.9	15.4	13.8	18.6
3	6.3	13.8	19.0	12.8	6.9	13.2
4	6.3	8.6	7.1	2.6	5.2	7.0
> 4	34.2	16.7	11.9	5.1	3.4	13.9

* Mean donor exposure rate equivalent to mean number of RCCTs.

Table III. Control period infants (< 1 500 g) transfused in NICU and the neonatal wards (historic controls)

	NICU	Neonatal ward
No. admitted	188	346
No. transfused	129 (68.6%)	128 (37.0%)
No. of transfusions		
Total	380	228
Mean ± SD	2.9 ± 3.1	1.7 ± 1.1
Donor exposure (> 1) (mean ± SD)	4.4 ± 3.5	2.7 ± 1.1

A total of 81 VLBW infants admitted to the NICU qualified for the LDEP and were transfused with either the double (N = 47) or the triple bags (N = 34) over a 5-month period. Of these, 34 (42%) received a single and 47 (58%) multiple transfusions. The frequency of blood transfusions with the triple and double bags as well as the number of donors they were exposed to are shown in Table IV.

The mean DER decreased significantly after the introduction of the triple (1.9 ± 0.8) (P = 0.0001) and double bags (1.6 ± 0.8) (P = 0.0001) compared with the previous single-bag system (4.4 ± 3.5). The changes in donor exposure after the introduction of the LDEP are shown in Table V. The 47 infants who received multiple transfusions with the multibag system were exposed to 91 donors; the 22 who were transfused by triple bag were exposed to 43 donors (mean 1.9 ± 0.8; median 2.0, Q1 - Q3 1 - 3) and the 25 who were transfused by the double bags were exposed to 48 donors (1.6 ± 0.8; median 1, Q1 - Q3 1 - 2).

Discussion

Our study confirmed the indirect relationship between birth weight and RCCT prevalence: the lower the birth weight, the higher the transfusion prevalence.[3] This study also confirmed that the highest prevalence of RCCTs occurred in infants with birth weights below 1 500 g who were treated in the NICU.[3] Strauss[8] reported a RCCT prevalence of 94% and 78% for infants treated in an NICU and who had birth weights below 1 000 g and 1 500 g respectively. This is very similar to the prevalences of RCCT of 86.9% and 68.6% for infants with corresponding birth weights admitted to the NICU in the present study.

Our survey also revealed an indirect relationship between birth weight and age at the time of the first RCCT. The larger infants (birth weights > 2 000 g) received their first RCCTs within the 1st week of life, while most of the smaller infants received their first RCCTs after the age of 1 week. The majority of the larger infants (70%) required only one RCCT. This difference in the time of administration of the first RCCT is probably related to the different causes for low

Table IV. Frequency of RCCTs in infants (< 1 500 g) admitted to the NICU receiving either triple or double bags

	No. of transfusions						
	1	2	3	4	5	> 5	Total
Triple bags							
No. transfused	12	6	5	3	1	7	34
No. of bags available	36	24*	18*	18	6	63	165
Bags used	33%	50%	88%	67%	83%	76%	63%
Bags not used for assigned infant	67%	50%	12%	33%	17%	24%	37%
No. of donors exposed to							
1	100%	67%	80%	0	0	0	58.5%
2		33%*	20%*	100%	100%	0	20.6%
3						100%	20.6%
Double bags							
No. transfused	22	14	3	4	2	2	47
No. of bags available	44	28	12	12	12	12	120
Bags used	50%	100%	75%	100%	83%	100%	77.5%
Bags not used for assigned infant	50%†	0	25%†	0	17%†	0	22.5%†
No. of donors exposed to							
1	100%	100%	0	0	0	0	78.2%
2		0	100%	100%	0	0	13.0%
3		0	0	0	100%	100%	8.8%

* 2 and 1 infants, respectively, required another red cell transfusion after expiry of the first unit of red cell concentrate.
† Some bags were issued to other infants.

Table V. Donor exposure of infants (< 1 500 g) admitted to the NICU who had multiple RCCTs (percentages within bag type)

	No. of donors								
	1	2	3	4	5	6	7	8	> 8
Before 1995 — single bag (N = 79)	0	36.7%	21.5%	10.1%	10.1%	5.1%	5.1%	5.1%	6.3%
Feb. - July 1995									
Triple bag (N = 22)	36.4%	31.8%	31.8%	0	0	0	0	0	0
Double bag (N = 24)	58.3%	25.1%	16.6%	0	0	0			
Triple and double bags (N = 46)	47.8%	128.3%	23.9%	0	0	0	0	0	0

haemoglobin levels in infants of different weight categories. Smaller infants usually become anaemic because of frequent blood sampling during the first weeks of life, as well as the late onset of so-called 'anaemia of prematurity'.[1,9]

The transfusion policy for neonates in operation at our institution before 1995, viz. 'one infant per unit of red cell concentrate', resulted in a very high DER as well as significant wastage of blood. The overall mean DER for the historic control group of infants equalled the mean number of RCCTs administered to the infants, because none of the infants received more than one blood transfusion from any one donor. One infant in our study was exposed to 21 different donors. The DER for this specific infant was probably much higher, since the number of platelet, serum or plasma transfusions was not recorded in this study.

The mean DER was 4.3 ± 3.5 for the historic control VLBW infants admitted to the NICU who received multiple RCCTs. This is much lower than the mean DER of 8 (range 2 - 18) for a group of similar infants reported by Sacher *et al.*,[10] but is similar to the mean DER of 4.9 (SD 3.5, range 1 - 18) in VLBW infants reported by Wood *et al.*[7]

The reduction in mean DER during the LDEP in the present study was very similar to the results obtained by Wood *et al.*[7] after they increased the period of storage of blood from 5 to 35 days for their multibag system for RCCTs in VLBW infants. Wood *et al.*[7] reported a reduction in mean DER from 4.9 ± 3.5 to a mean of 2.0 ± 0.9. Our initial decision to extend storage of blood to 21 days for the triple bags resulted in 3 infants who required blood after the 21-day expiry date being exposed to another donor. By extending the duration of blood storage to 35 days, donor exposure could have been limited even more.

The decision to limit blood storage to 21 days during use of the triple bag system was adopted for the sake of caution. Previous concerns that it is dangerous to transfuse red blood cells stored for more than 7 days because of high potassium levels have proved to be unfounded.[1,3] The plasma potassium levels in stored blood may be as high as 50 mmol/l after 42 days of storage.[1,3] Since most of the potassium-containing plasma is removed during preparation of the red cell concentrate, transfusion of 10 - 15 ml/kg of red cells (haematocrit 80% and serum potassium level 50 mmol/l) will result in transfusion of only 0.1 - 0.3 mmol potassium per kilogram over a 3 - 4-hour period.[1,3] Concerns about the low 2.3 diphosphoglycerate (2.3-DPG) levels in stored blood are also unfounded, since 2.3-DPG is regenerated within hours of transfusion.[1,2] With the current use of Adsol as storage medium, blood can safely be stored for 35 - 42 days and still be used for small-volume (10 - 15 ml/kg) transfusions in neonates.[7,11]

There is, however, some concern about micro-aggregate formation, which increases with storage.[7,12] It also seems that granulocytes are involved in the micro-aggregate formation and that leucocyte depletion through a leucocyte depletion filter may reduce micro-aggregate formation.[7,13]

Although reduction in donor exposure was the primary aim of this study, we became acutely aware of the large volumes of red blood cells that are wasted because of the relatively large volume (180 ml) of the bags in which red blood cells are supplied to infants. Wastage of blood was reduced with the multibag system by issuing unused blood to another infant before the expiry date.

It must be stressed that at present the most effective way of reducing donor exposure is to decrease the need for RCCTs in VLBW infants. This can be accomplished by limiting iatrogenic blood loss during frequent blood sampling, because so-called "bleeding into the laboratory" remains one of the most important reasons for multiple top-up transfusions in VLBW infants admitted to an NICU.[1] Obstetricians should be convinced about the important role delayed cord clamping at the delivery of VLBW infants may play in reducing blood transfusions. Kinmond *et al.*[14] showed that holding infants delivered at between 27 and 33 weeks' gestation 20 cm below the introitus for 30 seconds before clamping the cord reduced the median volume of red cell transfusions significantly.

The exact role of recombinant erythropoietin (rHuEPO) in reducing the need for RCCTs in VLBW infants has not been determined.[4,15] Until more results from multicentre studies on the benefits of rHuEPO in VLBW infants become available, it should be regarded as an investigational drug.[1]

In conclusion, our survey confirmed the high prevalence of RCCT as well as a very high DER in VLBW infants treated at a tertiary centre. By assigning a triple or double bag of red cells from one blood donor and extending the storage of blood for small-volume RCCTs in infants to 35 days, donor exposure was dramatically reduced.

The survival rate for VLBW infants in South Africa continues to improve,[16] and with RCCTs forming an integral part of their management we urge the introduction of the multibag system for RCCTs for VLBW infants in this country. Not only will the DER be decreased but wastage of blood, which is becoming a very scarce commodity, will be reduced.

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