

A new formula for blood transfusion volume in the critically ill

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Background: Published formulae, frequently used to predict the volume of transfused red cells required to achieve a desired rise in haemoglobin (Hb) or haematocrit (Hct), do not appear to have been validated in clinical practice.

Aims: To examine the relation between transfusion volume and the resulting rise in Hb and Hct in critically ill children.

Methods: Phase 1: Sample of 50% of children admitted during 1997; 237 of these 495 patients received at least one packed red cell transfusion; 82 children were transfused without confounding factors that could influence the Hb/Hct response to transfusion and were analysed further. Actual rise in Hb concentration or haematocrit was compared to that expected from use of existing formulae. A new formula was developed. **Phase 2:** In 50 children receiving a packed red cell transfusion during 2001, actual rise in Hb concentration was compared to expected rise in Hb with use of the new formula.

Results: Phase 1: Existing formulae performed poorly; median ratio of actual/predicted rise in Hb or Hct ranged from 0.61 to 0.85. Using the regression coefficients new formulae were developed for both Hb and Hct. These formulae were applicable across all age and diagnostic groups. **Phase 2:** Median ratio of actual/predicted rise in Hb improved to 0.95 with use of the new formula.

Conclusions: Existing formulae underestimate the volume of packed red cells required to achieve a target Hb or Hct. Adoption of the new formulae could reduce the number of transfusion episodes in PICU, cutting costs and reducing risk.

Paediatricians are faced with considerable clinical uncertainty when making decisions about blood transfusion.¹ There is a paucity of data on which to base transfusion decisions.² A systematic review of the literature highlighted only three randomised controlled trials of red cell transfusion in children.³ Key unresolved issues include the haemoglobin (Hb) threshold at which a child should receive a blood transfusion and the target Hb that the clinician should aim to achieve. Lack of evidence leads to variation in transfusion practice. A recent survey of paediatric critical care physicians in Canada, using a number of hypothetical clinical scenarios, found wide variation in the physicians' Hb threshold for transfusion from 7 to 13 g/dl.⁴

Once a decision is made to transfuse blood a reliable formula is needed to estimate the volume of blood that must be transfused to achieve a target Hb concentration. Paediatric and haematology textbooks provide a number of formulae, each of which takes account of the child's weight, estimated circulating blood volume, and the Hb concentration or haematocrit of the blood to be transfused.^{5–9} This relation can be summarised as:

$$\text{Volume of packed RBCs to transfuse} = \frac{\text{total blood volume} \times (\text{target Hb} \textit{ minus} \textit{ current Hb})}{\text{Hb of donor unit}}$$

Commonly used formulae vary according to the value that is assumed for total blood volume (TBV) and for the Hb/Hct of each unit of packed cells (table 1). Surprisingly, despite being used in everyday practice for many years, these formulae do not appear to have been validated in clinical practice.

We formed a clinical impression that use of the standard formulae in paediatric intensive care results in a lower than

expected post-transfusion Hb level, sometimes necessitating a further transfusion within a few days. This study was undertaken to test this hypothesis and, if confirmed, to derive a more reliable formula for clinical use.

METHODS

Phase 1

The case notes of all children admitted to the paediatric intensive care unit (PICU) at Birmingham Children's Hospital in 1997 were requested. Data collection continued until a convenience sample of 50% of admissions had been completed. Birmingham Children's Hospital PICU is an 18 bedded multidisciplinary unit admitting children from birth to 16 years of age. Data was extracted from case notes and included age, weight, and diagnostic category. Transfusion episodes were noted and the exact volume of blood transfused was recorded from the daily fluid chart. The Hb and Hct before and after transfusion were noted from haematology laboratory results. The before and after transfusion values for Hb and Hct were those that most closely preceded and followed the transfusion. This was treated as missing data if no result was available for the 24 hours before or following transfusion. Anonymised data were entered into a database for subsequent analysis. Local regional ethic committee approval was not sought as no patient identifiers were recorded and the study was undertaken in 1997 with the purpose of reviewing existing clinical practice.

Confounding variables were noted that could be associated with accelerated blood loss or red cell breakdown, as these might lead to a smaller than expected rise in haemoglobin or haematocrit following transfusion. These were: (1) evidence of bleeding; (2) a patient within 24 hours following surgery;

Abbreviations: Hb, haemoglobin; Hct, haematocrit; PICU, paediatric intensive care unit; PRC, packed red cells; TBV, total blood volume

Table 1 Existing formulae for calculating the transfusion volume of packed red cells (PRC)

Formula (reference)	Assumptions	Derivation
$\text{Volume}_{(\text{ml})} = 3 \times \text{delta Hb}_{(\text{g/dl})} \times \text{weight}_{(\text{kg})}^{7,8}$	Donor unit Hb 23 g/dl TBV = 70 ml/kg	$\frac{\text{TBV} \times [\text{desired Hb} - \text{current Hb}]}{\text{Hb of donor unit}} = \frac{70 \times \text{wt} \times \text{delta Hb}}{23}$
$\text{Volume} = 4 \times \text{delta Hb}_{(\text{g/dl})} \times \text{weight}_{(\text{kg})}^6$	Donor unit Hb 23 g/dl TBV = 90 ml/kg	$\frac{\text{TBV} \times [\text{desired Hb} - \text{current Hb}]}{\text{Hb of donor unit}} = \frac{90 \times \text{wt} \times \text{delta Hb}}{23}$
$\text{Volume} = 1 \times \text{delta Hct}_{(\%) } \times \text{weight}_{(\text{kg})}^3$	Donor unit Hct 70% TBV = 70 ml/kg	$\frac{\text{TBV} \times [\text{desired Hct} - \text{current Hct}]}{\text{Hct of donor unit}} = \frac{70 \times \text{wt} \times \text{delta Hct}}{70}$

Hb, haemoglobin; Hct, haematocrit; TBV, total blood volume.

(3) haemolysis; and (4) disseminated intravascular coagulation. In addition other conditions associated with an alteration in circulating blood volume were noted: (1) capillary leak syndrome; (2) renal replacement therapy; and (3) plasma exchange. Patients in whom no confounding variables or conditions were present were identified as a “clean” subgroup for further analysis.

Statistical analysis

Demographic data from the 50% convenience sample were compared with the remainder of 1997 admissions using non-parametric statistics, to provide evidence that the sample group was representative. One way analysis of variance was used to look for differences in transfusion practice across diagnostic groups (pre-transfusion Hb, post-transfusion Hb, post-transfusion Hb *minus* pre-transfusion Hb (delta Hb), and volume of blood transfused). A linear regression analysis of delta Hb and transfusion volume/kg was performed, fitting a straight line with zero intercept. This was repeated for the “clean” subgroup in whom no confounding factors were present. Only the first transfusion episode per admission was used in the analysis. Both the one way analysis of variance and the significance tests of regression analyses of delta Hb for different diagnostic groups make the assumption that these variables have a Normal distribution in the sub-populations concerned. The Shapiro-Wilk test showed that this was satisfactory. Where appropriate absolute p values and/or 95% confidence intervals (CI) are reported. Differences are quoted as statistically significant when $p < 0.05$.

Phase 2

Data were collected prospectively in a second cohort of 50 patients admitted in 2001 to the same PICU. The proposed formula derived from the 1997 cohort was used to calculate the volume of packed red cells to transfuse and the post-transfusion Hb value compared with the expected value. Once again only the first transfusion episode for each patient was included. No confounding factor was present in these patients.

RESULTS

Phase 1

Data were collected from 495 case notes, representing 50% of all admissions in 1997 (n = 989). Demographic variables (age, sex, length of stay, severity of illness, diagnostic categories, mortality rate) were similar in the study group compared to the remainder of 1997 admissions (data not shown). Of the 495 patients, 237 (47.9%) received at least one blood transfusion; 383 transfusions were recorded. The median number of transfusions per patient was 1 (range 1–15), with 89% receiving one or two transfusions. Eighty two patients were transfused without confounding variables and were used for further analysis. All packed red blood cell units were red cells in citrate phosphate dextrose (CPD) solution. The median haematocrit of the packed red blood cell units supplied for the year 1997 was 0.69 (range 0.64–0.72) (personal communication, Birmingham Blood Transfusion Centre).

The median pre-transfusion Hb for all patients was 10.5 g/dl (IQ range 9.4–12.3), median haematocrit 0.31 (IQ range 0.27–0.36). The median volume of blood transfused was 12.2 ml/kg (IQ range 8.0–16.7). Table 2 shows the performance of existing formulae at predicting the rise in Hb following transfusion. For each patient this was expressed as the ratio of “actual rise in Hb”/“predicted rise in Hb” using the formula. Only data from the 82 “clean” subgroup without confounding variables are shown. The median ratio of actual/predicted rise in Hb was less than 1 for all the formulae tested.

Since the established formulae performed poorly we developed a new formula by performing a regression of “delta Hb_(g/dl)” against “volume transfused_(ml)/weight_(kg)”. Figure 1A shows data for all 237 patients while fig 1B illustrates the relation for the “clean” subgroup without confounding variables. For the whole group (n = 237) the relation between delta Hb_(g/dl) and volume transfused_(ml) was:

$$\text{Delta Hb}_{(\text{g/dl})} = 0.17 \times (\text{volume}_{(\text{ml})}/\text{weight}_{(\text{kg})})$$

95% CI 0.15–0.19; R = 0.58

Table 2 Performance of established formulae in predicting the rise in Hb or Hct following transfusion

Established formula for volume of packed red cells (ml)	Actual/predicted rise median (interquartile range)
$3 \times \text{wt}_{(\text{kg})} \times \text{desired rise in Hb}_{(\text{g/dl})}$	0.64 (0.46–0.78)
$4 \times \text{wt}_{(\text{kg})} \times \text{desired rise in Hb}_{(\text{g/dl})}$	0.85 (0.61–1.04)
$1 \times \text{wt}_{(\text{kg})} \times \text{desired rise in Hct}_{(\%)}$	0.61 (0.46–0.81)

Values shown are median value and interquartile range of individual data for 82 children without confounding variables.

Table 3 Comparison of transfusion variables across diagnostic groups using one way analysis of variance

Diagnostic category	Pre-transfusion Hb (g/dl)*	Post transfusion Hb (g/dl)*	Delta Hb (g/dl)**	Transfusion volume of packed cells (ml/kg)**	Delta Hb/(vol/kg)
Post-cardiac surgery (n=30)	10.7 (10.1 to 11.2)	13.5 (12.8 to 14.1)	2.7 (2.1 to 3.4)	13.7 (11.5 to 15.9)	0.21 (0.17 to 0.25)
Cardiology (n=9)	11.3 (10.3 to 12.3)	13.6 (12.4 to 14.7)	2.3 (1.1 to 3.5)	16.6 (12.2 to 20.9)	0.19 (0.11 to 0.26)
General surgery (n=15)	9.7 (8.9 to 10.5)	14.5 (13.6 to 15.4)	4.8 (3.9 to 5.8)	19.5 (16.4 to 22.7)	0.25 (0.19 to 0.30)
Liver disease (n=6)	8.2 (7.0 to 9.5)	10.1 (8.7 to 11.5)	1.9 (0.4 to 3.4)	10.1 (5.1 to 15.1)	0.20 (0.12 to 0.29)
Other medical (n=21)	9.1 (8.5 to 9.8)	13.2 (12.5 to 14.0)	4.1 (3.3 to 4.9)	18.4 (15.7 to 21.0)	0.22 (0.18 to 0.27)

Data shown are mean and 95% CI for each diagnostic group. Only data from children without confounding variables are included (n=82). A single haematology/oncology case is omitted from the table as the group size is too small. *p<0.001. **p<0.01.

For the “clean” subgroup (n = 82) the relation was:

$$\text{Delta Hb}_{(g/dl)} = 0.21 \times (\text{volume}_{(ml)}/\text{weight}_{(kg)})$$

$$95\% \text{ CI } 0.20\text{--}0.22; R = 0.72$$

This last formula can be rearranged to:

$$\text{Volume of packed cells to transfuse}_{(ml)} =$$

$$4.8 \times \text{weight}_{(kg)} \times \text{desired rise in Hb}_{(g/dl)}$$

Similar regression is shown for haematocrit data (fig 2). For the whole group the relation was:

$$\text{Delta Hct}_{(\%)} = 0.49 \times (\text{volume}_{(ml)}/\text{weight}_{(kg)})$$

$$95\% \text{ CI } 0.44\text{--}0.54; R = 0.54$$

For the “clean” subgroup the relation was:

$$\text{Delta Hct}_{(\%)} = 0.63 \times (\text{volume}_{(ml)}/\text{weight}_{(kg)})$$

$$95\% \text{ CI } 0.58\text{--}0.68; R = 0.71$$

Again this last formula can be rearranged to:

$$\text{Volume of packed cells to transfuse}_{(ml)} =$$

$$1.6 \times \text{weight}_{(kg)} \times \text{desired rise in Hct}_{(\%)}$$

The 10th and 90th centile limits for post-transfusion Hb equate to ± 1.7 g/dl relative to the mean. Hence for a target post-transfusion Hb concentration of 13.0 g/dl there would be an 80% chance that using the new formula the final Hb concentration would lie between 11.3 and 14.7 g/dl. The 10th and 90th centile limits for haematocrit equate to $\pm 5\%$ relative to the mean value. Therefore if a post-transfusion haematocrit of 35% is the target there would be an 80% chance that using the new formula the final haematocrit would lie between 30% and 40%.

To investigate the influence of age the regression lines for “delta Hb_(g/dl)” on “volume transfused_(ml)/weight_(kg)” were calculated for three age groups and were found to be very similar; age <1 month (regression coefficient 0.20), 1–12 months (0.22), and >1 year (0.20). Similarly we investigated the influence of diagnostic group and found that the regression coefficient was remarkably consistent (table 3).

We identified evidence suggesting that transfusion practice was influenced by diagnosis. Diagnostic group differences were found in pre-transfusion Hb level, delta Hb, post-transfusion Hb level, and the volume of transfusion (table 3). However the ratio “delta Hb_(g/dl)/transfusion volume_(ml)” did not differ, indicating that differences in delta Hb between diagnostic groups were attributable to differences in the volumes of blood transfused.

Phase 2

After introduction of the new formula the median ratio of actual/predicted rise in Hb improved to 0.95 (IQ range 0.70–1.07). There was a small median difference between the predicted rise in Hb against actual rise in Hb of -0.24 g/dl (range -2.52 to 1.95) ($p = 0.02$, Wilcoxon signed rank test). The regression equation coefficient of this cohort resulted in a value of 4.87 as the best fit value for use in the formula, very close to the original value of 4.80. The mean (SD) volume of packed cells administered was 18.6 (6.0) ml/kg.

DISCUSSION

We believe that this study has important policy and health economic implications. Transfusions are estimated to account for 1% of total hospital costs.¹⁰ Since currently used formulae underestimate the volume needed to produce a desired rise in Hb, many patients are under transfused. Hence they may need to be transfused again, exposing the patient to additional risk and increasing costs. Alternatively the patient is left with a suboptimal Hb. The financial implications are especially relevant to paediatric practice since only part of a unit of blood will usually be transfused and the remainder of the unit discarded.

Recently published transfusion guidelines for neonates and older children from the British Committee for Standards in Haematology Transfusion Task Force contain surprisingly little about how to calculate transfusion volume.¹¹ The only formula referred to in these guidelines is the formula that performed least well in this study ($3 \times \text{wt} \times \text{delta Hb}$).

A new formula is proposed that has been validated in a second cohort of children. The formula appears valid across the paediatric age range and across children from different diagnostic groups and with differing pre-transfusion Hb values. The formula is appropriate for supplied red cell units with a median haematocrit of $\sim 70\%$ (Hb ~ 23 g/dl). It may be thought mnemonically more convenient to round 4.8 in the new formula up to 5.0 and the numerical consequences of this should be slight. For this data, the median magnitude of difference (positive or negative) between the actual change in Hb and the change predicted by the formula would be increased to 8.9% by using the value 5.0 compared with a median absolute difference of 7.5% when using 4.8.

A number of factors may help to explain the lower than expected Hb rise associated with use of existing formulae. Once removed from the body, red blood cells undergo a progressive loss of viability that leads to a decline in post-transfusion survival.¹² The age of blood is important; the 24 hour post-transfusion survival index of preserved blood is $>90\%$ if blood is transfused within a week of collection but may fall below 80% if transfused later in its shelf life.¹³ Older red cells and those with defects in the cell membrane, the so-called storage lesions, will be taken up and destroyed by the child’s reticuloendothelial system soon after transfusion.¹⁴

Another potential source of error relates to the values for total blood volume that were used in the derivation of the existing formulae. Total blood volume can be extrapolated

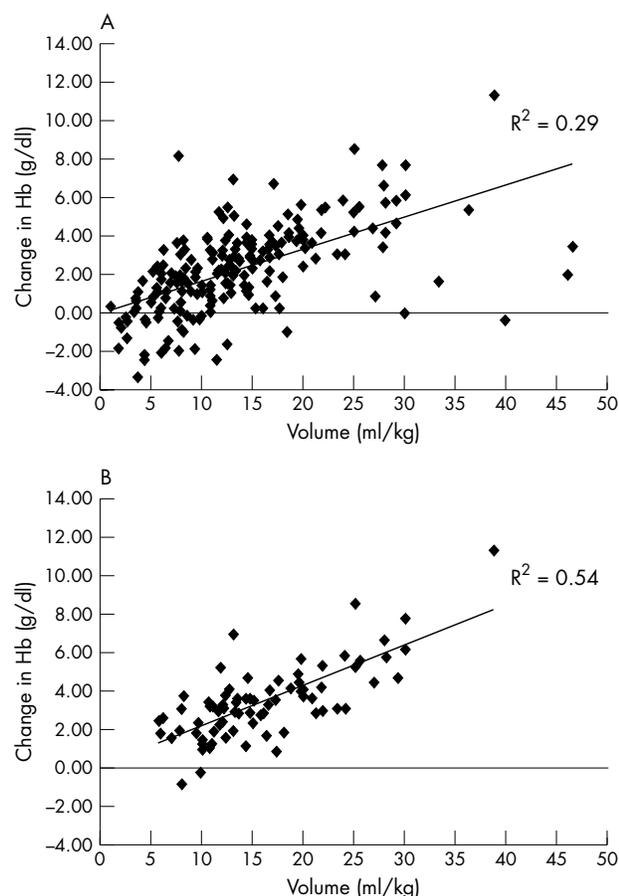


Figure 1 (A) Individual data for transfusion volume relative to weight (ml/kg) against the change in haemoglobin (Hb) concentration following transfusion ($n = 237$). (B) Individual data in those children without confounding factors that could influence the Hb response to transfusion ($n = 82$).

from direct measurement of either plasma volume or red cell mass. It is widely stated in medical textbooks that a neonate has a circulating blood volume of 80–90 ml/kg while a teenager has a circulating blood volume around 70 ml/kg.^{5–9} However the supporting literature is surprisingly sparse and predominantly based on studies of red cell mass.^{15–17} By comparison, estimates based on measurement of plasma volume suggest a relatively stable total blood volume across the paediatric age range¹⁵ and more recent studies in pre-term and term neonates have documented a mean blood volume close to 70 ml/kg.^{18, 19} The findings of the current study would be consistent with a stable blood volume/weight relation across the paediatric age range, since the regression coefficient in the formula was remarkably consistent across age groups.

It is clear from figs 1 and 2 that there is considerable scatter around the regression line, indicating that the rise in Hb or Hct is only partially explained by the volume of blood transfused. In adult medicine transfusion practice is equally imprecise. Based on theoretical assumptions transfusion of one unit of packed red blood cells to a 70 kg adult should raise the Hb concentration by 1 g/dl or haematocrit by 3%. In practice the rise in haematocrit can vary from 2–9%.⁷

In this study we found evidence to suggest that clinicians take account of diagnosis when deciding on the threshold for transfusion and the optimum target Hb. Textbooks of paediatrics, paediatric critical care, and paediatric haematology recommend a wide range of threshold haemoglobin

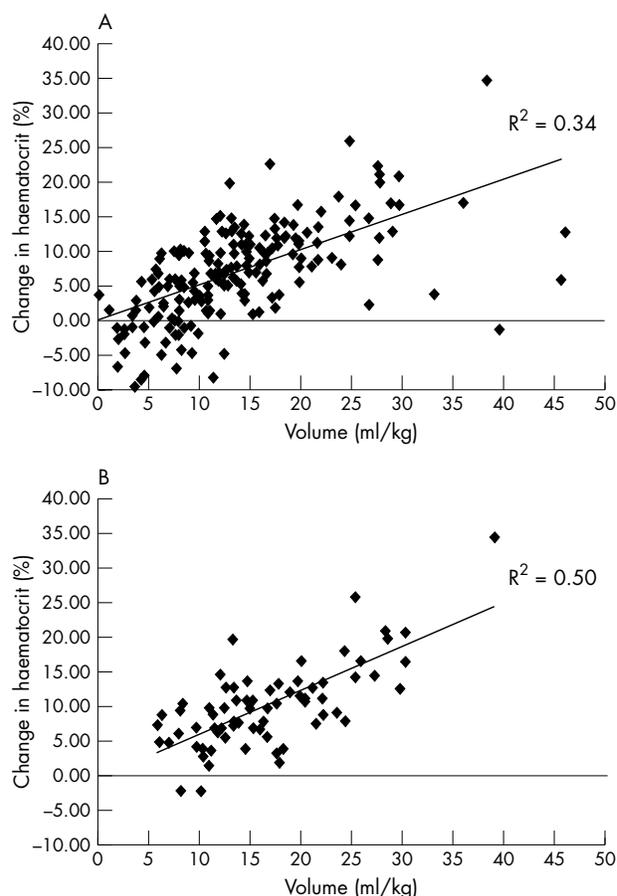


Figure 2 (A) Individual data for transfusion volume relative to weight (ml/kg) against the change in haematocrit (Hct) following transfusion ($n = 237$). (B) Individual data in those children without confounding factors that could influence the Hct response to transfusion ($n = 82$).

concentrations for red cell transfusion.^{5–9, 20–23} Previous surveys have alluded to huge variations in clinician practice, with an Hb trigger for transfusion varying from 7.0 to 13.0 g/dl for the same clinical scenario.⁴ In our study 48% of children received at least one transfusion compared to only 15% of children in a study undertaken in a Canadian PICU.²⁴ There is an urgent need for rigorous randomised controlled trials of paediatric transfusion practice to investigate these areas further. A randomised controlled trial in adult critical care units has established that it is safe to adopt a “restrictive” policy for blood transfusion whereby a transfusion is given only when Hb falls below 7.0 g/dl.²⁵

It is worth acknowledging some of the limitations of this study. The initial data collection phase was retrospective, using a review of medical records. However, the data for the second cohort of children were collected prospectively. The timing of the post-transfusion Hb sample was not standardised. In most cases the Hb value was taken from the morning sample the day after the transfusion episode. In no case was the interval between the end of the transfusion and the Hb sample less than 4 hours or greater than 16 hours. No account was taken of the volume of blood sampled from the child between the end of the transfusion and the post-transfusion sample. However, if this was an important factor we would have expected this to result in a different formula coefficient for small children in whom the sampled volume would be greater relative to their circulating blood volume.

The study population were children in an intensive care unit rather than children on a paediatric ward. By selecting a

What is already known on this topic

- A number of formulae exist to estimate the volume of packed red cells that should be transfused to achieve a target Hb concentration or Hct
- Despite being used for many years the formulae do not appear to have been validated in clinical practice

subgroup of “stable” children in whom there were no confounding factors we aimed to produce a formula applicable to any child requiring a blood transfusion. Further study is needed to establish whether these findings can be extrapolated to children receiving a transfusion outside the intensive care environment. In addition, no pre-term neonates were included and this group will require further study.

In summary, existing formulae that are used in everyday practice to estimate red cell transfusion volume result in a lower than expected post-transfusion Hb value in PICU patients. We believe this to be the first study questioning the formulae used by many clinicians for prescribing red cell transfusions. A new formula is proposed that appears to be valid across different age and diagnostic groups. Adoption of the new formula could reduce the number of transfusion episodes, cutting costs and reducing risk.

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What this study adds

- Existing formulae underestimate the volume of packed red cells required to achieve a target Hb or Hct
- A new formula is proposed that has been validated in a second group of children and can be used in children of all ages
- Adoption of the formula should reduce the number of transfusion episodes in the PICU, cutting costs and reducing risk

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