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Standardizing blood dose using body surface area and analyzing effect of blood storage on hemoglobin increment in pediatric patients

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Abstract

Introduction: Pediatric patients exhibit a wide variation in weight which results in diverse transfusion practices. This study aims to standardize red blood cell (RBC) doses according to body surface area (BSA) and to analyze the role of RBC storage in post-transfusion hemoglobin levels.

Material and methods: In this original prospective cohort study on hospitalized pediatric patients aged up to 14, we classified patients into transfusion-dependent (n = 31) and non-transfusion-dependent (n = 158). The non-transfusion-dependent group was further classified into ≤10 kg (n = 72) or >10 kg (n = 86) according to body weight (bw). We derived a regression equation between BSA and blood dose in non-transfusion-dependent subjects, and modified the equation by fixing blood dose to 15 mL/kg bw for only BSA based blood dose. We measured pre-transfusion and post-transfusion hemoglobin (Hb) levels, and ascertained effects of blood storage ≤15 days (n = 15) and >15 days (n = 16) on post-transfusion Hb.

Results: Pediatric patients ≤10 kg and >10 kg bw (n = 158); mean ± standard deviation of weight and BSA were 4.5 ± 3.1 kg; 22.9 ± 10.4 kg; 0.26 ± 0.14 m^2; 0.9 ± 0.28) m^2 respectively. The regression equation ≤10 kg and >10 kg bw when adjusted. Blood dose fixed at 15 mL/kg bw adjusted blood dose ≤10 kg; 15 mL/kg bw = −19.12 + 329.69x BSA m^2. The regression equation >10 kg bw: adjusted blood dose >10 kg bw; 15 mL/kg bw = −158.8 + 563.3x BSA (m^2). The adjusted blood dose with BSA did not exceed 20 mL/kg bw. No significant differences were observed in pre and post-transfusion Hb in transfusion-dependent (n = 31) versus non-transfusion-dependent patients (n = 158) due to the RBC storage duration.

Conclusions: RBC blood dose can be standardized by regression equation between standardized RBC dosage and BSA. Post-transfusion Hb is not dependent on days of RBC storage at the blood bank.

Key words: body surface area, regression equation, RBC storage changes, dose banding

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Introduction

Transfusion practices show variations due to the clinical presentation of patients and differing understanding of transfusion benchmarks among clinicians.

The pediatric age group is especially vulnerable to such variations due to a higher oxygen consumption and higher cardiac output to blood volume ratio than the adult population [1]. Premature infants also have higher fetal hemoglobin (HbF) than full-term infants with decreased erythropoietin production [1, 2]. Children differ from adults due to the wide variation in body size (up to 10-fold) for any given age group [3, 4]. Approaches towards standard blood dosing include blood transfusion according to body weight (kg), total blood volume, body surface area (BSA), body mass index (BMI), and dose banding appropriate to the body surface area. These are some of the measures for blood dosing regimen with predictable endpoints [5–8].

New-born children and infants have a higher variation of body weight than older children and adults in anthropometric indices e.g. a greater head circumference than chest circumference at birth and during the first year of life, a big trunk with relatively short legs, and older children displaying variations in weight for height due to undernutrition or wasting [5, 9]. A reference standard dosing regimen which estimates blood dose or RBC distribution volume as a mathematical function of body size for any age or weight category could result in predictive endpoints in transfusion [5, 10, 11]. A significant correlation between regression coefficients is one way to ensure such a relationship between the blood dose to be transfused and the body size, especially in pediatric patients.

A blood transfusion dose of 10 mL/kg body weight (bw) to 20 mL/kg within the pediatric population is acceptable under most guidelines [5, 7]. A standardization of RBC transfusion volume has been attempted, with several formulae based on physiological characteristics such as baseline hemoglobin (Hb), hematocrit of RBC unit, weight etc and their statistical relationships [5, 7, 10, 12]. A regression equation based relationship predicting the Hb (g/dL) levels and volume transfused (ml) according to body size has been attempted to estimate blood dosing [10, 11].

A potential cause of variation of post-transfusion hemogram is the 'age of stored RBC' effect on a patient's Hb on attaining a steady baseline value. Fresh RBCs are no longer considered superior compared to the older (stored) RBCs for transfusion for the overall outcome of hospital stay [13]. An evaluation of whether older units attain comparable baseline Hb concentration 24 hours after transfusion as 'new RBC units' could affect transfusion therapy upon patients [13, 14].

Our observational study had the following aims:

- to standardize RBC dose for transfusion using 'body surface area' (BSA) in pediatric patients, to calculate blood dose acceptable to guidelines of normal homeostasis;
- to compare the effect of RBC storage up to 15 days, and greater than 15 days, on hemoglobin increment (g/dL) 24 hours after blood transfusion in transfusion-dependent and non-transfusion-dependent patients.

Definitions

Pearson correlation coefficient typically measures a linear relationship between two continuous variables.

Linear regression is used to study the linear relationship between a dependent variable y and one or more independent variables x. The linear regression models describe the dependent variable by the equation y = a + + bx; where a (the intercept) and b (the slop) of the regression line are estimated from an underlying relationship between variables y and x (adapted from Schneider et al. Dtsch Arztebl. 2010).

Body surface area: an accurate measurement of body size, usually determined by using the weight and height of a person.

Material and methods

This prospective cohort study involved data of pediatric (age 0–14) subjects admitted at a tertiary level hospital from 1 January to 31 December 2019. We adhered to the STROBE statement for the present study as a research template [15].

Institutional ethical approval of this study was obtained (No: 543/IEC-AIIMSRPR/2018).

We conducted the study according to a planned protocol (flow diagram) set out in Figure 1. We obtained a pre-transfusion sample just before the transfusion, with a follow-up sample 24 hours after transfusion of a non-transfusion-dependent patient. The samples were then tested by routine hemogram in an automated cell counter (Sysmex S100). We conducted this prospective cohort study under the following sub-categories (Figure 1).

Model 1

Weight sub-groups [≤10 kg (n = 72) and >10 kg (n = 86)] in non-bleeding patients for a regression equation evaluating change of blood dose with unit change in BSA.

Model 2

Transfusion-dependent (n = 31) and non-transfusion-dependent patients (n = 152) for comparison of the effect of RBC storage (≤15 days and >15 days) on post-transfusion Hb (g/dL) increment.

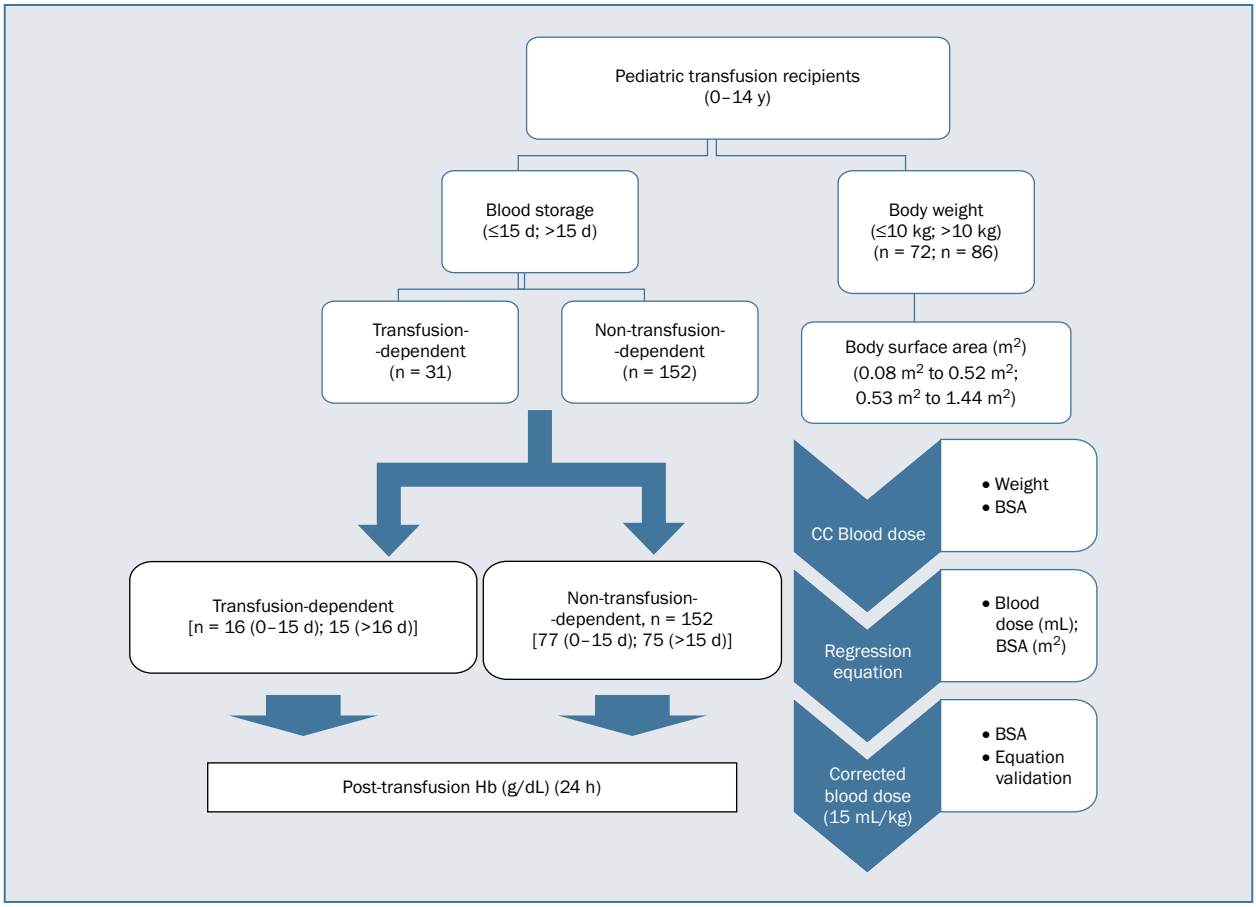

Figure 1. Study design of research

Inclusion criteria

Model 1

Pediatric patients aged 0–14 undergoing transfusion (red cells, whole blood).

Model 2}

Transfusion of whole blood/red blood cell units stored at the blood bank ≤15 days and >15 days to the following sub-group of patients: routine pediatric transfusion recipients considered as non-transfusion-dependent and transfusion-dependent patients [sickle cell disease (SCD); thalassemia major; blood dyscrasias etc. requiring repeated transfusions].

Exclusion criteria

Patients >14 years; surgical patients; emergency transfusions; actively bleeding patients under clinical evaluation; unrefrigerated blood categorized as fresh blood.

The outcome variables were as follows: blood dose calculated from BSA from the regression equation ($y = a + bx$) based upon blood dose and BSA as dependent and independent variables respectively.

An adjusted blood dose was acquired after fixing the blood dose to 15 mL/kg bw which yielded the final regression equation. We validated the adjusted blood dose from BSA by comparing the same with weight-based blood dose (15 mL/kg bw) for a standard blood dose according to BSA.

A statistical comparison of Hb increment after RBC transfusion in the transfusion dependent and non-transfusion dependent paediatric subjects (independent sample T test).

Potential confounders

Variation within regression equation depending on the sample size and patient characteristics. Transfusion variables such as underlying alloimmunization of the patient in the transfusion-dependent group. Ongoing hemolysis, undiagnosed blood loss, sampling errors, patient variables such as dehydration and fluid administration.

Statistical calculations

Model 1

Pre-transfusion and post-transfusion hemogram estimated in two weight categories [(≤10 kg (n = 72) and >10 kg (n = 86)]. The minimum sample size was derived using the correlation coefficient of blood dose to the BSA alpha probability p (<0.05); power (0.8) [16].

Table I. Comparison of statistical parameters. Less than or equal to 10 kg versus greater than 10 kg weight category

Parameter	Less than or equal to 10 kg body weight (n = 72)	Greater than 10 kg body weight (n = 86)
Range weight (kg) and BSA area (m^2)	Weight (0.8 kg to 10.40 kg) BSA (0.08 m^2 to 0.52 m^2)	Weight (11 kg to 50 kg) BSA (0.53 m^2 to 1.44 m^2)
Mean ±SD weight and BSA	Weight 4.5 ±3.1 kg BSA 0.26 ±0.15 m^2	Weight 22.9 ±10.4 kg BSA 0.9 ±0.28 m^2
Mean ±SD pre-transfusion Hb	Pre-transfusion Hb 7.0 ±1.7 g/dL	Pre-transfusion Hb 6.3 ±1.5 g/dL
Blood dose	Blood dose 86.0 ±74.6 mL respectively	Blood dose 243.0 ±86.1 mL
Pearson correlation coefficient (CC) blood dose with weight (kg) and BSA (m^2)	Weight 0.64 BSA 0.68 ($p \leq 0.01$)	Weight 0.47 BSA 0.50 ($p < 0.05$)
Regression coefficient (r^2) blood dose with weight (kg) and BSA (m^2)	0.41 for BSA ($p < 0.05$)	0.25 BSA (m^2) as predictor variable respectively ($p \leq 0.05$)

BSA — body surface area; SD — standard deviation; Hb — hemoglobin

A Pearson correlation coefficient (CC) performed separately for each weight category (≤10 kg and >10 kg) to estimate CC of blood dose (mL) with weight (kg) and BSA (m^2) (Table I).

We performed a linear regression analysis (r^2) for variation in blood dose (mL) administered to patients with a unit change BSA (m^2) in our patient data. Blood dose (y) = b + ax [where y = blood dose (mL), b = constant equal to value of y when x = 0, a is the coefficient of x i.e. the slope of regression line of how much y changes with a unit change in x where x = BSA). To compute a regression equation between blood dose and the BSA, we used 'blood dose' as a 'dependent variable', with BSA (m^2) as an 'independent variable'.

A validation of this modified regression equation was performed on a standard weight/BSA chart.

Two modalities validated the adjusted equation:

- a comparison of 'calculated blood dose' from BSA of a patient (subjects) included in the present study with blood dose calculated as 15 mL/kg bw and 20 mL/kg bw respectively for each weight category (≤10 kg and >10 kg)
- a comparison of weight-based 'calculated blood dose with the corresponding BSA of patient' from data acquired from chemotherapy standardization group 2008 [17].

Model 2

We compared the effect of RBC storage (≤15 days vs. >15 days) on pre-transfusion and post-transfusion Hb g/dL of both multi-transfused (transfusion-dependent) and routinely transfused (non-transfusion-dependent) patients. Two sample T-test on 24 hours Hb levels for the duration of RBC storage (≤15 days vs. >15 days).

A 'independent T testing' of pre-transfusion and post-transfusion Hb (≤15 days, >15 days RBC storage) for both transfusion-dependent and non-transfusion-dependent patients.

A comparison of increment for transfusion-dependent and non-transfusion-dependent patients for the effect of blood storage (RBC storage ≤15 days and >15 days) on the post-transfusion Hb levels (in g/dL) 24 hours after RBC transfusion (independent T test).

We estimated the following parameters for the patients:

- hemogram [(Hb (g/dL); Hct (%)] performed by cell counter (Sysmex, S-100);
- body surface area (monsteller formula) [18].

We estimated missing data for weight/height using an IAP reference chart for the 5+ age-group (gender specific) and Fenton chart for pre-term neonates [4, 19, 20].

Patients lost to follow-up were not included in the present study.

We performed all statistical calculations on SPSS Statistics (version 26.0); independent T-test of the blood dose (derived) and blood dose (15 mL/kg bw; 20 mL/kg bw) on Minitab (trial version) [21]. The calculations for each weight category (≤10 kg and >10 kg) and 'days of storage' on post-transfusion Hb were performed on Minitab (trial version) and Prism 9 for macOS [21, 22].

Results

We reviewed the parameters evaluated under Model 1 (≤10 kg (n = 72) and >10 kg (n = 86) category (Table I)

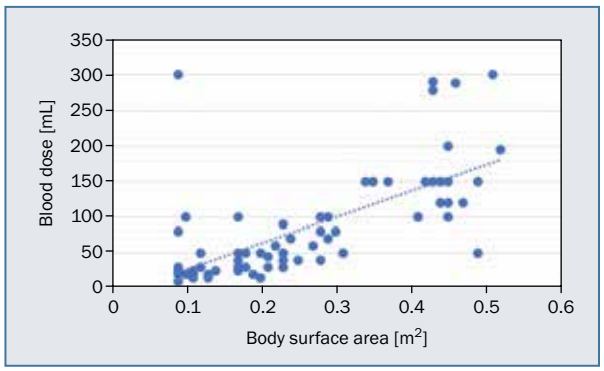

Figure 2. Blood dose to body surface area (BSA) (m^2) unadjusted patient data ≤10 kg body weight

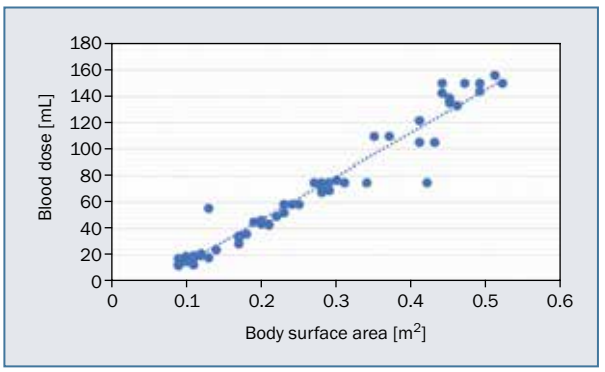

Figure 3. Blood dose to body surface area (BSA) (m^2) adjusted to 15 mL/kg for ≤10 kg body weight

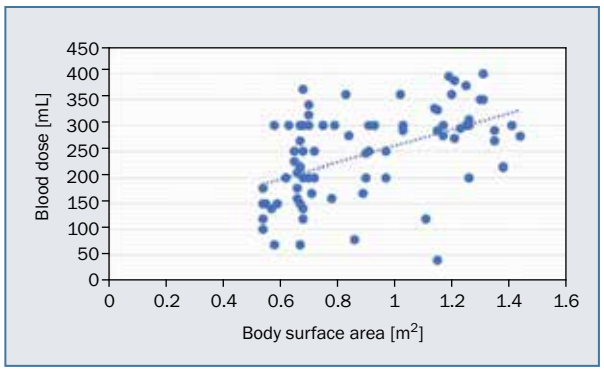

Figure 4. Blood dose to body surface area (BSA) (m^2) unadjusted patient data >10 kg body weight

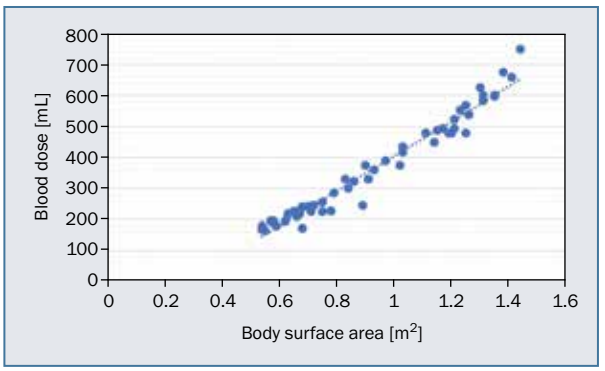

Figure 5. Blood dose to body surface area (BSA) (m^2) adjusted to 15 mL/kg for >10 kg body weight

collected over a 12 month period. CC of blood dose was performed with the weight of the subjects and corresponding BSA under both weight subgroups (Table I).

Both transfusion groups had a low to moderate, but significant, correlation coefficient (CC) of transfused blood dose with weight as well as BSA (p <0.05) (Table I, Supplementary Table 1 — see the supplementary file in the on-line version of the article).

BSA of range (0.08–0.52 m^2) for weight ≤10 kg (n = = 72) and (0.53–1.44 m^2) for >10 kg (n = 86) had regression coefficient r^2 = 0.46 and r^2 = 0.26 (p <0.05) (Table I).

The regression equation of blood dose and BSA based upon 'patient data' for weight category of ≤ 10 kg [BSA range (0.08–0.52 m^2)] and >10 kg (0.53–1.44 m^2) was as follows:

- weight sub-groups (≤10 kg bw) blood dose (mL) = = −10.3 + 366.9x BSA (m^2);
- weight sub-groups (>10 kg bw) blood dose (mL) = = 102.3 + 157.9x BSA (m^2).

We then adjusted blood dose to 15 mL/kg/bw for each weight category (≤10 kg and >10 kg) and derived blood dose, which formed the 'adjusted regression equation' with BSA. A scatter plot depicting the relationship of independent and dependent variables can be seen in Figures 2–5:

- adjusted blood dose (≤10 kg); (15 mL/kg bw) = −19.12 + 366.9x BSA (m^2);
- adjusted blood dose (>10 kg bw) (15 mL/kg bw) = = −158.8 + 563.3x BSA (m^2).

We then validated equation from data which compared patient weight (kg) and corresponding BSA (m^2). We then validated this equation from an existing data of 'Chemotherapy standardization group' which compared patient weight (kg) and corresponding BSA (m^2) [17].

The mean blood dose [(≤10 kg; n = 72) and (>10 kg bw; n = 86)] with standard 15 mL/kg bw was 67.4 ±46.5 mL and 342.2 ±157.7 mL respectively comparable to the blood dose (SD) calculated with derived regression equation using the BSA 67.42 ±45.46 m^2 and 342 ±155.1 m^2 (Table II).

This equation was further validated by using data from the data of a chemotherapy standardization group (Supplementary Tables 2A, 2B — see the supplementary file in the on-line version of the article) (≤10 kg and >10 kg) [19].

The blood dosages calculated with 15 ml/kg bw were not statistically different from dosage calculated by the regression equation for BSA (0.08–0.52 m^2) and (0.53– –1.44 m^2) Independent sample T-test (p = 0.91 and 0.53) (Supplementary Tables 3A, 3B — see the supplementary file in the on-line version of the article).

Table II. Comparison of blood dose from weight with body surface area (BSA)

		Blood dose (15 mL/kg bw) (≤10 kg)	Blood dose (20 mL/kg bw) (≤10 kg)	Calculated blood dose (≤10 kg)	Blood dose (15 mL/kg) (>10 kg)	Blood dose (20 mL/kg bw) (>10 kg)	Calculated blood dose (>10 kg)
N	Valid cases	72	72	72	86	86	86
M±ean ±SD		67.4 ±46.5	90.1 ±63.1	67.4 ±45.4	342.2 ±157.7	456.0 ±210	342.0 ±155.1
Minimum; maximum values		12.0; 156.0	16.0; 208.0	10.5; 152.3	165.0; 750.0	220.0; 1000.0	145.2; 750.0

SD — standard deviation

Blood doses calculated with bw (20 mL/kg) for ≤10 kg and >10 kg were significantly different compared to 'calculated dose' from the regression equation with mean [standard deviation (SD) higher in volume (mL) compared to the regression equation for BSA (0.08–0.52 m^2) and (0.53–1.44 m^2)] (independent test; p = 0.05 and 0.006) (Supplementary Tables 2A, 3B — see the supplementary file in the on-line version of the article).

Model 2: a comparison of blood storage period (≤15 days and >15 days) in 'transfusion dependent group'(n = 31); we did not observe a significantly different value of pre-transfusion Hb 5.7 ±2.1 g/dL and 5.5 ±1.7 g/dwith (p = 0.75); post-transfusion Hb 8.4 ±2.1 g/dL and 9.1 ±2.2 g/dL (p = = 0.29) and Hb increment 2.7 ±1.5 and 2.3 ±1.4 (p = 0.51) (2 sample T test) (Table III).

Non-transfusion-dependent group (n = 158) did not have significant difference: pre-transfusion Hb 6.6 ±1.5 g/ /dL and 6.6 ±1.7 g/dL (p = 0.94); post-transfusion Hb 9.2 ±1.9 g/dL and 9.0 ±2.2 g/dL (p = 0.68) and Hb increment 2.5 ±1.4 and 2.4 ±2.0 respectively. (Two-tailed independent T test (p >0.61) (Table III).

Transfusion-dependent and non-transfusion-dependent patients had significant differences in the pre-transfusion Hb (≤15 days and >15 days) (p = 0.016) with no statistical difference in post-transfusion Hb (p = 0.08). The Hb increments when compared for transfusion dependent and non-transfusion dependent were non-significantly different (p = 0.89; Table III).

Table III. Effect of red blood cell (RBC) storage on transfusion subgroup

Parameter	Less than or equal to 15 days RBC storage	Greater than 15 days RBC storage
Mean ±SD storage duration [days] RBC*	9.2 ± 3.6 (n = 79)	26.4 ± 6.4 (n = 79)
Mean ±SD pre-transfusion Hb [g/dl]*	6.6 ± 1.5	6.6 ± 1. 7
Mean ±SD post-transfusion Hb [g/dl]*	9.2 ± 1.9	9.0 ± 2.2
Mean ±SD Hb increment [g/dl]*	2.5 ± 1.4	2.4 ± 2.0
Mean ±SD storage duration [days] RBC#	8.8 ± 3.4 (n = 16)	26.4 ± 6.3 (n = 15)
Mean ±SD pre-transfusion Hb [g/dl]#	5.7 ± 2.1	5.5 ± 1.7
Mean ±SD post-transfusion Hb [g/dl]#	8.4 ± 2.0	9.1 ± 2.2
Mean ±SD Hb increment [g/dl]#	2.7 ± 1.5	2.4 ± 1.4

*Dependent (n = 158); #transfusion-dependent (TD) (n = 31); SD — standard deviation; Hb — hemoglobin

Discussion

Pediatric patients where the blood transfusion is in small aliquots targeting Hb show variation depending on physical parameters such as age, BSA, and blood dosage [2, 10, 23]. An objective of transfusion recommendations corresponding to BSA is to achieve the desired clinical response among patients with minimal allogeneic transfusions and transfusion associated side-effects [23–25].

The reasons for choosing non-bleeding, non-transfusion-dependent subjects to estimate blood dose equation were as follows: 1) blood is mostly administered to pediatric patients as per body weight, and not in units as in adults; and 2) non-bleeding patients are less likely to have post-transfusion Hb increment impacted by ongoing blood loss or hemodilution because of volume replacement.

The storage duration of RBC also does not adversely affect survival during the hospital stay [27, 28]. We assessed pre-transfusion Hb and 24 hours post-transfusion Hb as a function of 'days of storage' *ex vivo* and subsequent RBC survival. Post-transfusion Hb was chosen to assess days of storage effect because Hb assessment is generally performed to ascertain steady state response following RBC transfusions [13, 28].

A classification of underweight or overweight pediatric population requires age and sex-based standardization with a reference population under evaluation. BSA band based blood dosing or weight to BSA conversion, especially

in infants and children, needs further validation by clinical trials to establish safety in this context [5, 8, 10]. BSA based dosing has been documented to show discrepancies in adults and very young children [23, 29, 30]. In the present study, with adjusted equation based on 'BSA', a more streamlined correlation of blood dose and BSA with higher regression co-efficient was observed for both weight categories (≤10 kg and >10 kg) (Supplementary Table 1 — see the supplementary file in the on-line version of the article). (Figures 2–5).

This equation may show some variation within different representative populations, which however is unlikely to affect significantly the accuracy of calculating blood dose according to the BSA of the patient.

The regression equation calculated with 15 mL/kg bw reference values, and the calculated blood dose from the corresponding BSA did not exceed 20 mL/kg body weight (Supplementary Tables 2A, 2B — see the supplementary file the in the on-line version of the article).

Blood transfusion among patients with cardiac failure and children with malnourishment when transfused according to the BSA (m^2) and Hb (g/dL) threshold is likely to prevent over-transfusions and related adverse side-effects.

The blood transfusion-related to BSA can be standardized according to bands of BSA receiving a similar dosing regimen [8]. This measure could prevent erratic transfusion to a patient, especially pre-term and newborns, since there is considerable heterogeneity in the blood volume and BSA formula in this age group [3, 23]. A regression equation that accommodates such borderline cases with clinical trial-based validation of BSA based dosing from a large representative population size should be the next step for BSA based blood transfusion dosing.

A comparison of fresh versus old RBC (≤15 days and >15 days) for post-transfusion hemogram values among the pediatric population is another step towards attainment of a predictable post-transfusion Hb (g/dL) as an endpoint parameter. A single RBC unit for transfusion of newborns decreases potential donor exposure and chances of infection transmission and immune transfusion reactions.

We evaluated transfusion-dependent and non-transfusion-dependent populations separately to evaluate the effect of RBC storage-based lesions and test the similarity of post-transfusion hemogram after RBC transfusion among diverse test subjects. The blood transfusion in the present study attained similar endpoints (post-transfusion Hb and Hb increment) irrespective of patient type or RBC storage duration. The importance of more such studies to evaluate 'a steady-state hemogram' or other standardized parameters such as 'tissue oxygenation' should be a baseline to assess effect of storage duration upon the efficacy of RBC transfusion [31, 32].

This study had a small number of test subjects with limited standardization related to critical confounding variables such as known alloimmunization status, especially in transfusion-dependent patients; a high or low responder to transfusion demarcation might have been more evident in a larger sample size [10]. Post-transfusion hemogram parameters might have modified the effect of storage due to underlying clinical diagnosis. Missing data of weight and height obtained from the growth chart could have overlooked the physiological variations due to malnutrition or growth retardation, though it is unlikely to be significant. Previous recommendations of transfusing a patient from BSA advise caution in infants under six months and up to 12 months with a combination of weight and BSA for calculating the infusion dose [23].

This present study attempts to standardize endpoints of transfusion among the pediatric population; however, our study's findings should be replicated further in a clinical trial setting before incorporating them into routine patient use.

Conclusions

Blood dose according to the BSA is an appropriate substitute for weight-only based dosing for blood transfusion. However, clinicians utilizing any transfusion regimen with BSA must validate the equation in a clinical trial setting. The duration of blood storage does not affect the post-transfusion Hb in transfusion-dependent or non-transfusion-dependent patients.

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Conflict of interest

This work was accepted as an abstract for oral presentation at the annual conference of the ISBT 2020 and was published as an abstract of the conference Supplement.

Data and material available upon request.

Authors' contributions

SS — concept, research and ethical approval, first author, corresponding author, statistical calculations, interpretation and conclusions; SJ — scientific suggestions for manuscript, co-investigator in study, patient coordination; MP — patient coordination and data collection; AS — calculations, sample size, effect of blood storage duration on post-transfusion Hb (g/dL) levels; AG — availability of departmental resources, mentoring

Ethical approval

No 543/IEC-AIIMSRPR/2018.

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