The Utility of Preoperative Level of Erythrocytosis in the Prediction of Postoperative Blood Loss and 30-day Mortality in Patients with Tetralogy of Fallot

Abstract

Background: Postoperative major bleeding is a relatively common complication of patients undergoing corrective surgery of tetralogy of Fallot (TOF). Life-threatening blood losses can lead to aggressive transfusions or reoperation. Little is known about the risk factors associated with a bleeding tendency in TOF patients. This study aimed to establish predictive models for postoperative blood loss and mortality in TOF patients. **Methods:** We conducted a retrospective observational study involving patients with TOF who were posted for corrective cardiac surgery in a single hospital between 2010 and 2015. Hospital records including sociodemographic, pre- and intra-operative characteristics were extracted. Postoperative blood loss (within 24 and 48 h) and 30-day mortality were the primary and secondary outcomes, respectively. Multivariate linear and logistic regression models were used to identify determinants of outcomes. **Results:** A total of 60 patients were included in this study. The median age was 1 year (interquartile range = 0.62–5) and the male to female ratio of 1.7:1. Mean postoperative blood loss within 24 h was 283 ± 212 mL. In multivariate linear regression, preoperative hematocrit ($\beta = 6.63$, $P = 0.042$) and duration of intraoperative oxygenator with CPB ($\beta = 5.16$, $P = 0.025$) were significantly correlated with postoperative blood loss within 24 h. After adjusting for sociodemographic, intra- and post-operative characteristics, preoperative hematocrit (odds ratio [OR] = 1.10, 95% confidence interval [CI] = 1.01–1.21), and postoperative red blood cell transfusions (OR = 3.88, 95% CI = 1.16–12.9) showed statistically significant association with 30-day mortality. The area under the receiver operating characteristic curve of the multivariable model was 0.863. **Conclusions:** Preoperative levels of erythrocytosis appear to predict postoperative blood loss and short-term mortality in TOF patients undergoing corrective surgery.

Keywords: *Anesthesia, blood loss, mortality, patient safety, predictors, tetralogy of Fallot*

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Introduction

Tetralogy of Fallot (TOF) is the most common cause of cyanotic congenital disease.[1] This syndrome usually requires surgical interventions early in life to avoid future complications related with cyanosis, chronic hypoxia, and heart failure.[1,2] Since the first operative correction of TOF performed in 1954, there have been multiple advances not only in the operative technique but also the perioperative care.[3] These improvements have resulted in longer survival rates and recovery enhancement, however, TOF patients are still considered a population at high-risk for developing in-hospital morbidities, especially in developing countries where there is lower accessibility to medical advances and mortality is still high.[4]

Postoperative blood loss in TOF patients might be a life-threatening complication.[5]

It is known that blood loss is related with the degree of anatomic and physiologic impairment in patients with TOF,[5] however, it has been difficult to establish a predictive model for postoperative blood loss using simple laboratory test and intraoperative characteristics.[1] We hypothesized that preoperative hematological conditions can be useful to predict postoperative blood loss and it might even be associated with short-term mortality.[6] This study was undertaken to establish predictive models for postoperative blood loss (within the first 24 h) and 30-day mortality in patients undergoing corrective surgery of TOF.

Methods

Patients

Institutional Review Board approved this retrospective observational study and waived the requirement for written

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informed consent because of the nature of the study design. We retrospectively reviewed the medical records (sociodemographic, hospital admission records, preoperative data, intraoperative reports, and evolution in pediatric Intensive Care Unit [ICU]) to collect information of 60 children (pediatric age <15 years) who underwent corrective cardiac surgery to repair TOF malformation in a tertiary institution between 2010 and 2015.

Anesthetic management

Preanesthetic assessment included laboratory studies taken 2 days prior surgery, echocardiogram, and cardiac catheterization. Propofol 1 mg/kg was used for the induction of anesthesia and rocuronium 0.6 mg/kg as a neuromuscular relaxant for endotracheal intubation. In addition, tranexamic acid (in bolus [30 mg/kg] and continuous infusion [10 mg/kg/h]) and desmopressin (0.3 mg/kg) was administered for all patients during surgery. All the surgeries were conducted with similar techniques by the same team of surgeons, anesthesiologist, and perfusionist during the study under standard cardiopulmonary bypass (CPB) techniques. Weaning from CPB was done with the inotropic support of milrinone 50 mcg/kg in all cases as a protocol. Rescue inotropes were added depending on the requirement. A standard electrocardiogram was recorded in all patients preoperatively and then immediately after surgery.

Statistical analysis

An exploratory analysis was conducted initially to describe quantitative variables expressed as mean ± standard deviation or median with interquartile range (IQR) according to the normal distribution of data, and qualitative variables presented as absolute and percentage frequency values. Pearson's correlation coefficients were calculated to find a significant relationship between each clinical variable and postoperative blood loss within 24 h (univariate analysis). Univariable analyses (using Chi-square test and Fisher exact test for categorical variables, and Student's *t*-test or the Mann–Whitney U-test for quantitative variables, accordingly) were used to assess comparisons of variables between survivors and nonsurvivors. Multivariable linear regression was conducted using a model that includes only variables that reached statistical significance ($P < 0.05$) in univariable linear regression analysis. Multivariate analysis with logistic regression was used to corroborate independent factors associated with 30-day mortality. The adjusted models included potential confounders such as the age, gender, weight, estimated blood volume, duration of ischemia, duration of intraoperative oxygenator with CPB, and intra- and post-operative transfusions. Statistical significance was defined as a $P < 0.05$. All statistical analysis was performed using Stata version 12.0 (Stata, College Station, Texas, USA).

Results

Patient characteristics

A total of sixty patients were included in this study. The median age was 1 year (IQR = 0.62–5 years), and the male to female ratio was 1.7:1. The median estimate of blood volume of the patients was 681.5 mL (IQR = 560–1191 mL). Mean ICU length of stay was 7.01 ± 6.5 days. Baseline and preoperative patient characteristics are described in Table 1.

Predictors of postoperative blood loss

Mean postoperative blood loss within the first 24 h was 283 ± 212 mL. In univariable linear regressions, preoperative hematocrit ($R^2 = 0.1418$, $P = 0.003$), preoperative platelet count ($R^2 = 0.0773$, $P = 0.042$), duration of intraoperative oxygenator with CPB ($R^2 = 0.1048$, $P = 0.012$), and duration of ischemia ($R^2 = 0.0688$, $P = 0.043$) were significantly correlated with postoperative blood loss. Figure 1 illustrates the correlation between preoperative hematocrit and postoperative blood loss. Preoperative hematocrit remained significantly correlated with postoperative blood loss in multivariable linear regression analysis ($\beta = 6.63$, $P = 0.042$), as well as duration of intraoperative oxygenator with CPB ($\beta = 5.16$, $P = 0.025$). Table 2 shows details of both the univariable and multivariable linear regression analysis. The predictive model of postoperative blood loss was: 6.63* (preoperative hematocrit) − 0.000251* (preoperative platelet count) + 5.16* (duration of intraoperative oxygenator with CPB) − 5.28* (duration of ischemia) − 31.14.

Risk factors of 30-day mortality

Mortality rate at 30 days was 28.3% (17/60). In multivariable logistic regression, preoperative hematocrit (odds ratio [OR] = 1.10, 95% confidence interval [CI] = 1.01–1.21) and postoperative red blood cell transfusions (OR = 3.88, 95% CI = 1.16–12.9) showed
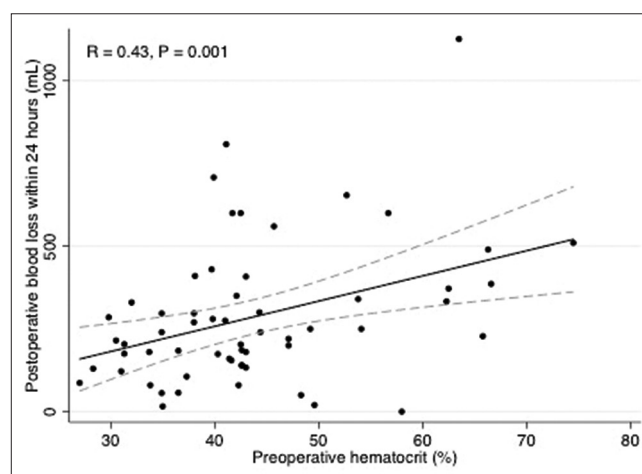

Figure 1: Linear regression illustrating the correlation between preoperative hematocrit and postoperative blood loss within 24 h

Table 1: Clinical characteristics of the patients included in the study

Variable	Total (*n*=60)	Survivors (*n*=43)	Nonsurvivors (*n*=17)	*P*
Sociodemographic characteristics				
Age (years), median (IQR)	1 (0.62-5)	1 (0.66-5.16)	1 (0.58-3)	0.289
Male, *n* (%)	38 (63.3)	26 (60.5)	12 (70.6)	0.463
Weight (kg), median (IQR)	8.8 (7-15.4)	10 (7.3-18)	7.2 (5.9-10)	0.032
Estimated blood volume (mL), median (IQR)	681.5 (560-1191)	800 (584-1275)	576 (472-800)	0.029
Drugs, *n* (%)				
Beta-blockers	13 (21.7)	8 (18.6)	5 (29.4)	0.360
Diuretics	10 (16.7)	6 (13.9)	4 (23.5)	0.370
Anticonvulsants	5 (8.3)	3 (6.9)	2 (11.7)	0.545
Aspirin	5 (8.3)	3 (6.98)	2 (11.7)	0.545
Preoperative characteristics (mean±SD)				
Hemoglobin (mg/dL)	14.2±3.7	13.6±3.9	15.7±2.9	0.061
Hematocrit (%)	43.7±10.7	42.1±10.9	47.7±9.4	0.068
Platelet count (1/mL)	283,333±124,522	287,759±109,781	271,800±160,597	0.677
PT (s)	12.3±2.5	12.0±1.8	12.9±3.8	0.218
PTT (s)	31.1±5.9	31.3±5.7	30.4±6.8	0.630
Creatinine (mg)	0.35±0.13	0.36±0.14	0.32±0.12	0.350
Intraoperative parameters (mean±SD)				
Duration of extracorporeal bomb (min)	107.7±44.4	98.5±34.1	131.2±58.3	0.009
Bypass time (min)	84.7±38.0	78.0±31.4	101.6±48.2	0.029
Activated clotting time (s)	130.4±18.6	126.9±12.9	139.3±27.2	0.027
Temperature (°C)	33.9±0.9	33.8±0.9	33.8±0.8	0.717
Transfusions (units), median (IQR)				
Red blood cells	1.5 (1-2)	1.5 (1-2)	2 (1-2)	0.735
Fresh frozen plasma	1 (0-2)	1 (0-1)	1 (1-2)	0.019
Platelets	1 (1-1)	1 (0-1)	1 (1-2)	0.001
Cryoprecipitate	0 (0-1)	0	0 (0-4)	0.015
Postoperative parameters (mean±SD)				
Platelet count (mL^{-1})	188,872±80,137	189,536±83,219	186,928±73,219	0.917
PT (s)	15.4±3.4	15.3±3.6	15.6±2.6	0.758
PTT (s)	47.9±22.0	43.7±9.9	58.7±36.6	0.019
Outcomes				
Postoperative bleeding within 24 h (mL)	234 (143-361)	200 (130-350)	275 (220-372)	0.153
ICU length of stay (days)	5 (3-8)	6 (5-8)	2 (1-3)	0.001

IQR: Interquartile range, ICU: Intensive Care Unit, SD: Standard deviation, PT: Prothrombin time, PTT: Partial thromboplastin time

Table 2: Univariable and multivariable linear regression model for prediction of postoperative blood loss

Variable	Univariate analysis		Multivariate linear regression (*n*=53)*		
	R²	*P*	Coefficient	95% CI	*P*
Age	0.0489	0.089			
Gender		0.147			
Weight	0.0260	0.218			
Estimated blood volume	0.0273	0.207			
Hematocrit	0.1468	0.003	6.63	0.24-13.0	0.042
Platelet count	0.0773	0.042	−0.000251	−0.000738-0.0002365	0.306
PT	0.0173	0.338			
PTT	0.0152	0.375			
Duration of extracorporeal membrane	0.1048	0.012	5.16	0.67-9.66	0.025
Duration of ischemia	0.0688	0.043	−5.28	−10.6-0.06	0.053
Activated clotting time	0.0135	0.402			
Temperature	0.0000	0.975			
Intercept			−31.14	−377.75-315.5	0.857

*Pearson *R*=0.51, *P*=0.006. PT: Prothrombin time, PTT: Partial thromboplastin time, CI: Confidence interval

statistically significantly association with 30-day mortality. The area under the receiver operating characteristic curve of the model was 0.8627 [Figure 2]. Table 3 shows the results of the multivariable logistic regression model.

Discussion

Our results showed a significantly positive correlation between preoperative hematocrit and postoperative blood loss, and also a significant association between preoperative hematocrit and 30-day mortality. Our data suggest that preoperative level of erythrocytosis in TOF patients undergoing corrective cardiac surgery might give valuable information to estimate postoperative blood loss and predict the risk of death. We found a predictive model that could be of value before surgery to detect patients at high-risk to develop significant postoperative blood loss to decrease subsequent morbidities such as infections, blood transfusions, hypoxic encephalopathy, or death.

Our results extend the results of three prior studies with similar findings. The first and second studies were limited to a univariable analysis comparing hemoglobin

Figure 2: Receiving operating characteristics curve for predicting mortality using multivariable logistic regression model

Table 3: Risk factors of 30-day mortality in adjusted models

Variable	Multivariate linear regression (*n*=59)		
	OR	95% CI	P
Age	1.22	0.71-2.09	0.469
Gender	1.20	0.21-6.85	0.836
Weight	2.19	0.32-15.0	0.424
Estimated blood volume	0.99	0.96-1.01	0.315
Hematocrit	1.10	1.01-1.21	0.039
Duration of extracorporeal oxygenation	1.06	0.99-1.13	0.080
Duration of ischemia	0.94	0.88-1.01	0.113
Intraoperative transfusions	1.33	0.29-6.09	0.710
Postoperative transfusions	3.88	1.16-12.9	0.028

OR: Odds ratio, CI: Confidence interval

values between survivors and nonsurvivors in TOF patients and demonstrated a cutoff of 18 mg per cent.[7,8] The third well-done study demonstrated an independent association between preoperative hematocrit and long-term mortality (at 1 year and 36 years of follow-up), however, the authors did not include preoperative hematocrit in the multivariable analysis for short-term mortality and also they did not consider other outcomes such postoperative blood loss.[3,9] Only the study by Zhao *et al.* could not find any association between preoperative hematocrit and outcome, however, the authors thought that this disagreement was because of lower mean hematocrit (49%).[10] Despite the mean hematocrit in this study was lower (43.7 ± 10.7) as compared to the previous studies, our results demonstrate that preoperative hematocrit is still an independent factor associated with postoperative blood loss and 30-day mortality. This may suggest that preoperative hematocrit can be used to grade the severity of TOF. Such grading would provide a basis for valid appraisal of surgical mortality rates among otherwise comparable series of cases.

Secondary erythrocytosis usually occurs in cyanotic syndromes such as TOF to compensate the hypoxemia.[5] In this study, the average of the preoperative hematocrit was lower as compared to other values reported in previous studies.[3,6-8,10]

Preoperative hematocrit has the potential to alter platelet function and this may explain the correlation between preoperative hematocrit and postoperative blood loss shown in this study.[11] Jensen *et al.* showed that patients with cyanotic congenital heart diseases are hypocoagulable mainly due to impaired fibrinogen function, which is negatively affected by elevated hematocrit.[12]

The strengths of this study rely on the consistency of our results and the robustness of the statistical analysis. However, there are several important limitations of this study. First, the small sample size predisposes to wide CIs and limits the inclusion of potentially important confounding variables in our analysis. We did use propensity score adjustment, but a larger sample size would allow for more precise estimates. Nonetheless, the findings of this study are provocative in showing an association between preoperative hematocrit and short-term mortality. Second, we could not extract other potential confounders such as ventricular function, the right ventricle/left ventricle pressures ratio, Aristotle score, New York Heart Association score, surgical experience, duration of surgery, and other hemodynamic parameters that have shown to influence long-term survival.[3] Third, the multivariable analysis for hematocrit as an independent factor associated with postoperative blood loss showed a marginal *P* value, so this result should be interpreted with caution as there could be limitations regarding clinical significance. Further studies are needed to confirm this association as well as to validate the predictive model of postoperative blood loss we proposed.
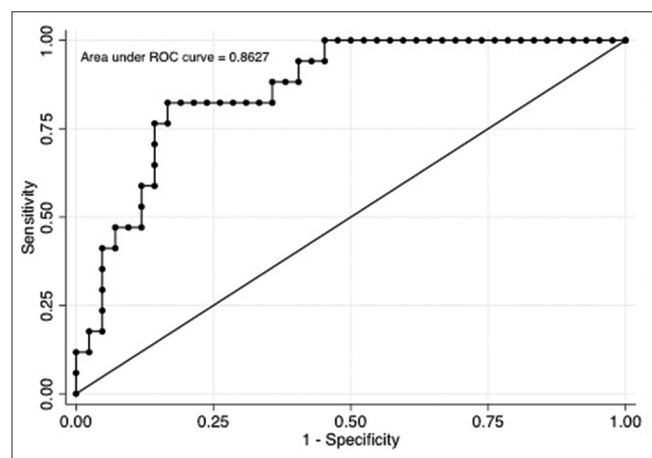
Conclusion

In summary, our data would appear to support the association between preoperative polycythemia and short-term mortality. This study indicates that the preoperative hematocrit value may be used as a reliable index of the operative risk in patients subjected to corrective cardiac surgery of TOF.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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