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ORIGINAL ARTICLE

Association of Hematocrit and Red Blood Cell Transfusion with Outcomes in Infants Undergoing Norwood Operation

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Abstract The objective of this study was to investigate the association between red blood cell (RBC) transfusion and hematocrit values with outcomes in infants undergoing Norwood operation. This study included infants ≤2 months of age who underwent Norwood operation with either a modified Blalock–Taussig shunt or a right ventricle-pulmonary artery shunt. Demographics, preoperative, operative, daily laboratory data, and postoperative variables were collected. The primary outcome measures evaluated included mortality, ICU length of stay, length of mechanical ventilation, and days to chest closure. The secondary outcome measures evaluated included lactate levels, estimated glomerular filtration rate, and inotrope score in the first 14 days after heart operation. Cox proportional hazard models were fitted to study the probability of study outcomes as a function of hematocrit values and RBC transfusions after operation. Eighty-nine patients qualified for inclusion. With a median hematocrit of 46 (IQR 44, 49), and a median RBC transfusion of 92 ml/kg (IQR 31, 384) in the first 14 days after operation, 81 (91 %) patients received RBC transfusions. A multivariable analysis adjusted for risk factors, including the age, weight, prematurity, cardiopulmonary bypass and cross-clamp time, and postoperative need for nitric oxide and dialysis, demonstrated no association between hematocrit and RBC transfusion with majority of study outcomes. This single-center study found that higher hematocrit values and increasing RBC transfusions are not associated with improved outcomes in infants undergoing Norwood operation.

Keywords Hematocrit · Infants · Congenital heart disease · Norwood · Blood transfusion

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Introduction

In recent years, red blood cell (RBC) transfusion strategies have stimulated great interest, especially in children undergoing heart surgery. In both adult and pediatric literature, RBC transfusions have been shown to be independently associated with worsening organ dysfunction and mortality [2, 6, 8, 11, 13, 16, 23]. Some of the complications associated with RBC transfusion include infectious risks, transfusion-related acute lung injury, transfusion-related circulatory overload, and hemolytic transfusion reactions [1, 7, 10, 17, 18]. It is proposed that children after heart surgery need higher hematocrit to

enhance oxygen delivery and improve cardiac output [15]. Neonatal age, cyanotic heart disease, and pediatric cardiopulmonary bypass (CPB) circuits are known factors of increased need for transfusion [15].

Despite continuous technical and medical improvements in pediatric cardiac surgery, transfusion remains unavoidable in most operations. Neonates and infants undergoing Norwood operation present a unique challenge for intraoperative and postoperative management. The speculated reasons include complex operative procedure, prolonged CPB time, balancing pulmonary circulation (Q_p) and systemic circulation (Q_s), increased multi-organ dysfunction, delayed sternal closure, prolonged ICU recovery time, and increased risk of mortality. Existing literature on the association between blood transfusion and outcomes after cardiac surgery are limited to heterogeneous patient populations undergoing uncomplicated and complicated repairs [2, 4, 6, 8, 9, 12, 13, 15, 16, 21, 23]. As blood transfusion is a modifiable factor in the postoperative care of children undergoing heart surgery, we sought to explore association of hematocrit and RBC transfusion with outcomes in infants undergoing Norwood operation. We hypothesized that higher hematocrit values and increasing blood transfusions in the first 2 weeks after the Norwood operation are associated with improving outcomes.

Materials and Methods

We performed a single-center retrospective observational study in 15-bed pediatric cardiovascular ICU (CVICU) at Arkansas Children's hospital during the period January 2006–December 2012. The study included all infants <2 months of age who underwent Norwood operation with either a modified Blalock–Taussig shunt (mBTS) or a right ventricle-pulmonary artery (Sano) shunt. Subjects excluded from the study were infants operated upon in outside institutions and subsequently transferred to our institution, infants receiving extracorporeal membrane oxygenation (ECMO) in the postoperative period, infants with 'Do Not Resuscitate' order, and infants receiving orthotopic heart transplant (OHT) for failed Norwood operation prior to hospital discharge. We identified the potential subjects by querying the departmental surgical database and the hospital medical records. The Institutional Review Board of the University of Arkansas Medical Sciences approved the study, and the need for informed consent was waived.

Demographics, preoperative, operative, laboratory data, and postoperative variables were collected. Demographic information collected included age (days), weight (kg), gender, underlying genetic abnormality, prematurity (≤36 weeks), and antenatal diagnosis (yes/no). Intraoperative variables collected included CPB time, cross-clamp time, and need for open chest after heart operation. Majority of the patients undergoing Norwood operation at our institution are left electively with open chest. The laboratory indices collected included daily hematocrit, and creatinine and lactate values for the first 14 days after operation. We collected intraoperative and postoperative daily amount of RBC transfusions in milliliters per kilogram (ml/kg) for the first 14 days after heart operation. Our center does not have a protocol for RBC transfusion in children undergoing heart operations for congenital heart disease. However, the most common indications of RBC transfusion in these patients include (1) hematocrit <30 %, (2) continued bleeding, and/or (3) evidence of decreased oxygen-carrying capacity, such as demonstrated by a low mixed venous saturation and/or tachycardia. Bleeding is considered significant if blood loss exceeds 10 or 4 ml/kg/h for three consecutive hours. The other postoperative variables collected in our study included use of nitric oxide and dialysis after heart operation.

The primary outcome measures evaluated included in-hospital mortality, ICU length of stay (LOS), length of mechanical ventilation, and days to chest closure. The secondary outcome measures evaluated included lactate levels, estimated glomerular filtration rate (eGFR), and inotrope score in the first 14 days after heart operation. Both unadjusted and adjusted outcomes were evaluated. Open chest was defined as any patient who arrived in the CVICU without closure of the sternum. Inotrope score was calculated using the equation: Dosages of dopamine + dobutamine (in μg/kg/min) + [Dosages of epinephrine + norepinephrine + isoproterenol (in μg/kg/min)] × 100 + dosages of milrinone (in μg/kg/min) × 15 [14]. eGFR was assessed using modified Schwartz formula [0.413 × height (cm)/serum creatinine (mg/dl)] [20]. Length of ICU stay was calculated from the date of postoperative admission until discharge from ICU. Duration of mechanical ventilation was from the date of postoperative admission until extubation.

Statistical Analysis

Continuous variables are presented as the median (Q1, Q3), where Q1 is the 25th percentile and Q3 is the 75th percentile, whereas categorical variables are presented as numbers and percentages. *P* values were calculated using Chi-square test and/or Fisher's exact test of independence for categorical variables and Wilcoxon rank-sum test for continuous variables. A power analysis demonstrated a sample size of 90 patients to yield at least 80 % power to detect a difference of 10 % in mortality rates between patients with mean blood transfusion levels and patients with blood transfusion one standard deviation above the mean. This is equivalent to detecting an odds ratio in

mortality of 2.67 between the two blood transfusion levels. The above calculation was done assuming blood transfusion levels are normally distributed and a two-sided significance level of 5 %.

Cox proportional hazards models were fitted to study the probability of study outcomes as a function of hematocrit values and RBC transfusions after operation. Variables with a P value of ≤ 0.1 in the univariate analysis were entered into the multiple regression Cox models. Variables with ≥ 20 % missing values were not considered for inclusion into the multivariate models. The following variables were selected for multivariable models: age, weight, prematurity, CPB and cross-clamp time, and postoperative need for nitric oxide and dialysis. It should be noted that both the blood transfusion and hematocrit were used as continuous variables in the multiple regression Cox models to predict study outcomes. The model results were expressed in terms of adjusted odds ratio for categorical variables and hazard ratios for continuous variables, 95 % confidence interval, and P values. Several additional multiple logistic analyses were performed to explore variables left out of the model and to achieve a parsimonious model. The model's goodness of fit was evaluated using the Hosmer–Lemeshow test, and the discrimination of the model was assessed using the area under the receiver operating characteristic curve (ROC). Analyses were performed using STATA/MP, version 11.1 software (Stata® Corp LP, College Station, Texas).

Results

Eighty-nine patients qualified for inclusion. During the first 14 days after heart operation, 81 (91 %) patients received RBC transfusions. Median hematocrit for the study population was 46 (IQR 44, 49), and median RBC transfusion was 92 ml/kg (IQR 31, 384) in the first 14 days after heart operation. The median age of patients was 7 days (IQR 5, 10), and median weight of patients was 3.17 kg (IQR 2.9, 3.5). Five (6 %) patients had an underlying genetic abnormality, and ten (11 %) patients were classified as premature ($\leq$36 weeks gestational age) (Table 1). Seventy-three (84 %) patients were admitted to CVICU with open chest. Sixty-four (72 %) of the study patients underwent Norwood operation with Sano shunt. Thirty (35 %) patients needed dialysis after heart operation, and 13 (15 %) patients had positive blood cultures during their postoperative stay (Table 1). Unadjusted primary and secondary outcomes are documented in Table 2.

For univariable analysis, the study population was divided in three groups: Group 1 represented patients with mean transfusion <10th percentile in the first 48 h after heart operation, group 2 represented patients with mean transfusion between 10th and 90th percentile in the first 48 h after cardiac surgery, and group 3 represented patients with mean transfusion >90th percentile in the first 48 h after cardiac surgery. We did not find any relationship between the amount of blood transfused and the hematocrit values in three groups (Table 1). To our surprise, the patients in group 1 had the highest hematocrit (median hematocrit: 46.8 in the first 48 h), compared to patients in group 3 (median hematocrit: 45.2 in the first 48 h, $P < 0.01$). It is possible that the amount of bleeding was highest in patients in group 3, as demonstrated by the highest incidence of need for reoperation for bleeding and highest use of factor VII. There was no difference in unadjusted outcomes for the outcome variables, namely mortality, time to chest closure, length of mechanical ventilation, length of ICU stay, eGFR, lactate, and inotrope score among the three groups. eGFR, lactate, and inotrope score were studied at for three different time periods: 0–2 days, 0–7 days, and 0–14 days.

Adjusted primary outcomes are documented in Table 3. A multivariable analysis adjusted for risk factors, including the age, weight, prematurity, CPB and cross-clamp time, and postoperative need for nitric oxide and dialysis, demonstrated no association between hematocrit and RBC transfusion with mortality, ICU LOS, length of conventional mechanical ventilation (CMV), and days to chest closure. Adjusted secondary outcomes are documented in Table 4. After adjusting for risk factors, inotrope score, and eGFR in the first 14 days after heart operation were not associated with hematocrit and RBC transfusion. However, the lactate levels were significantly elevated for the first 7 days after heart operation with increasing RBC transfusion.

Discussion

In a cohort of 89 patients undergoing Norwood operation at a major university medical center, 91 % of the patients received RBC transfusions after surgery. A major finding of this study is that RBC transfusions were not associated with improving outcomes, ICU LOS, length of conventional mechanical ventilation (CMV), and days to chest closure. Our study also did not demonstrate any association between RBC transfusions and hematocrit values with risk-adjusted outcomes for lactate levels, inotrope score, and eGFR in the first 14 days after heart operation.

RBC transfusions have been associated with increased morbidity and mortality in critically ill children [2, 6, 8, 11, 13, 16, 23]. In a large, multicenter study of 977 critically ill children from 30 PICUs, Bateman et al. [2] demonstrated that transfusion was associated with increased ventilator days, PICU stay, nosocomial infections, and mortality.

Table 1 Patient characteristics

	All patients ($N = 89$) Median transfusion: 20.0 ml/kg	Group 1 ($N = 26$) Median transfusion: 0 ml/kg	Group 2 ($N = 54$) Median transfusion: 27 ml/kg	Group 3 ($N = 9$) Median transfusion: 215 ml/kg	P value
Age (days)	7 (5,10)	7 (6, 13)	7 (5, 10)	7 (3, 7)	0.45
Weight (kg)	3.2 (2.9, 3.5)	3.1 (2.9, 3.8)	3.2 (2.9, 3.5)	3.0 (2.8, 3.2)	0.32
Male gender	56 (64 %)	18 (69 %)	33 (61 %)	5 (56 %)	0.33
Underlying genetic abnormality	5 (6 %)	2 (8 %)	3 (6 %)	0 (0 %)	0.68
Prematurity (≤36 weeks)	10 (11 %)	2 (8 %)	7 (13 %)	1 (11 %)	0.75
Antenatal diagnosis	50 (56 %)	16 (62 %)	29 (54 %)	5 (56 %)	0.80
CPB time (min)	164 (139, 180)	159 (138, 177)	165 (140, 180)	151 (145, 227)	0.91
Cross-clamp time (min)	46 (33, 58)	45 (32, 54)	48 (35, 61)	37 (31, 42)	0.20
Delayed sternal closure	73 (84 %)	21 (81 %)	43 (80 %)	9 (100 %)	0.15
Sano shunt	64 (72 %)	18 (69 %)	39 (72 %)	7 (78 %)	0.88
Use of nitric oxide	36 (40 %)	12 (50 %)	19 (35 %)	5 (56 %)	0.34
Duration of nitric oxide (days)	6 (4, 8)	5 (4, 9)	7 (4, 9)	4 (3, 5)	0.23
Dialysis	30 (35 %)	4 (15 %)	24 (44 %)	2 (22 %)	0.03
Positive blood cultures	13 (15 %)	4 (15 %)	8 (15 %)	1 (11 %)	0.95
Use of factor VII	12 (13 %)	0 (0 %)	7 (13 %)	5 (55 %)	<0.001
Reoperation for bleeding	8 (9 %)	0 (0 %)	5 (9 %)	3 (33 %)	<0.001
Mean hematocrit					
0–2 days	46.5 (43.3, 49.3)	48.6 (45.9, 52.4)	46.2 (42.3, 47.8)	43.6 (39.7, 46.4)	<0.01
0–7 days	46.3 (44.3, 48.9)	48.4 (46.2, 50.2)	46.0 (44.2, 48.1)	45.0 (41.2, 45.9)	<0.01
0–14 days	46.3 (44.4, 48.3)	46.8 (45.9, 50.1)	45.6 (44.3, 47.9)	45.2 (42.3, 47.1)	0.04

Group 1 represents patients with mean transfusion <10th percentile in the first 48 h after cardiac surgery

Group 2 represents patients with mean transfusion between 10th and 90th percentile in the first 48 h after cardiac surgery

Group 3 represents patients with mean transfusion >90th percentile in the first 48 h after cardiac surgery

CPB cardiopulmonary bypass time, *RBC* red blood cell

On the other hand, the transfusion requirements in pediatric intensive care unit (TRIPICU) randomized trial found a restrictive transfusion strategy (at hemoglobin <7 g/dL) was not inferior to a liberal transfusion strategy (at hemoglobin <9.5 g/dL) [16]. In the cardiac surgery subgroup from this trial, no statistical difference in multiple organ dysfunction, mortality, or LOS was found between the two transfusion threshold groups [23]. However, this study included patients in varied risk categories for cardiac surgery and excluded neonates and patients with cyanotic congenital heart disease [23]. In contrast, our study examines this association in a homogenous population of patients undergoing complex cardiac repair.

It has been demonstrated in existing literature that a restrictive RBC transfusion policy (threshold of hemoglobin 8.0 g/dl) in children undergoing elective repair for non-cyanotic congenital heart defect during the entire perioperative period is associated with a shorter hospital stay [8]. In another study, it was demonstrated that children with single-ventricle physiology do not benefit from liberal transfusion strategy (mean hemoglobin 13.9 ± 0.5 g/dl) after cavopulmonary connection [6]. In another study of 94 pediatric patients undergoing heart transplantation, escalating amounts of RBC transfusions were associated with increased length of ICU stay, inotrope scores, and major adverse events [12]. In another study examining the association between hemoglobin level and transfusion with outcome in neonates after cardiac operations for hypoplastic left heart syndrome (HLHS), neither hemoglobin levels nor transfusions were associated with 2-year mortality or neurodevelopmental outcomes [4]. This study also demonstrated that more transfusions on postoperative days 2–5 were associated with morbidity measured by ventilation days [4]. Although our study is lacking the neurodevelopmental outcomes, our study throws some light on end-organ function as demonstrated by lactate levels, inotrope score, days of mechanical ventilation, and eGFR.

Table 2 Unadjusted inhospital outcomes

	All Patients ($N = 89$) Median transfusion: 20.0 ml/kg	Group 1 ($N = 26$) Median transfusion: 0 ml/kg	Group 2 ($N = 54$) Median transfusion: 27 ml/kg	Group 3 ($N = 9$) Median transfusion: 215 ml/kg	*P* value
Mortality	17 (19 %)	3 (12 %)	7 (13 %)	7 (78 %)	<0.01
Time to chest closure (days)	5 (4, 11)	5 (4, 7)	5 (4, 11)	15 (5, 36)	0.82
Length of mechanical ventilation (days)	12 (7, 23)	14 (8, 20)	13 (9, 23)	13 (5, 54)	0.96
Length of ICU stay (days)	30 (19, 56)	36 (20, 66)	30 (21, 47)	22 (5, 69)	0.49
eGFR					
0–2 days	37.0 (28.5, 46.2)	39.0 (26.5, 50.7)	36.1 (29.1, 41.8)	39.0 (35.3, 41.0)	0.83
0–7 days	42.2 (34.4, 59.4)	47.4 (33.7, 61.1)	42.4 (35.4, 59.0)	39.6 (34.9, 42.64)	0.45
0–14 days	49.9 (42.7, 67.6)	50.9 (43.7, 70.7)	49.9 (43.4, 68.2)	42.6 (35.3, 55.0)	0.39
Lactate					
0–2 days	2.7 (2.0, 3.5)	2.3 (1.8, 3.2)	2.7 (2.2, 3.4)	4.7 (3.6, 5.4)	<0.01
0–7 days	1.9 (1.6, 2.5)	1.7 (1.3, 2.1)	1.9 (1.6, 2.4)	2.9 (2.9, 5.5)	<0.01
0–14 days	1.7 (1.4, 2.3)	1.5 (1.3, 2.0)	1.7 (1.4, 2.2)	2.7 (2.1, 5.5)	<0.01
Inotrope score					
0–2 days	18.0 (14.4, 22.1)	15.0 (12.0, 20.5)	18.5 (15.5, 22.5)	16.5 (15.0, 19.0)	0.11
0–7 days	14.4 (11.8, 17.5)	13.3 (9.8, 18.2)	14.5 (12.6, 17.5)	13.6 (13.3, 16.8)	0.52
0–14 days	11.9 (9.3, 14.4)	11.4 (7.2, 15.2)	11.1 (9.6, 14.0)	12.5 (12.3, 15.1)	0.41

Group 1 represents patients with mean transfusion <10th percentile in the first 48 h after cardiac surgery

Group 2 represents patients with mean transfusion between 10th and 90th percentile in the first 48 h after cardiac surgery

Group 3 represents patients mean transfusion >90th percentile in the first 48 h after cardiac surgery

ICU intensive care unit, *eGFR* estimated glomerular filtration rate

Table 3 Adjusted inhospital primary outcomes

	Mortality		ICU LOS		Length of CMV		Days to chest closure	
	Odds ratio (95 % CI)	*P* value	Hazard ratio (95 % CI)	*P* value	Hazard ratio (95 % CI)	*P* value	Hazard ratio (95 % CI)	*P* value
Effect of first 48-h hematocrit	1.15 (0.85–1.55)	0.38	0.95 (0.89–1.02)	0.19	1.01 (0.94–1.08)	0.80	0.98 (0.91–1.04)	0.47
Effect of first 7-day hematocrit	1.08 (0.62–1.88)	0.79	0.99 (0.89–1.10)	0.88	1.06 (0.96–1.18)	0.27	1.04 (0.94–1.16)	0.43
Effect of first 14-day hematocrit	1.08 (0.64–1.82)	0.78	0.97 (0.86–1.10)	0.69	1.05 (0.92–1.20)	0.48	1.04 (0.91–1.19)	0.57
Effect of first 48-h RBC transfusion	1.02 (1.00–1.05)	0.06	1.00 (0.99–1.00)	0.48	1.00 (0.99–1.00)	0.60	1.00 (0.99–1.00)	0.32
Effect of first 7 days of RBC transfusion	1.03 (1.00–1.06)	0.07	0.99 (0.99–1.00)	0.11	1.00 (0.99–1.00)	0.25	0.99 (0.99–1.00)	0.06
Effect of first 14 days of RBC transfusion	1.01 (0.99–1.03)	0.23	1.00 (0.99–1.00)	0.10	1.00 (0.99–1.00)	0.20	1.00 (0.99–1.00)	0.06

CI confidence interval, *ICU* intensive care unit, *LOS* length of stay, *CMV* conventional mechanical ventilation, *RBC* red blood cell

Oxygen delivery is determined by cardiac output, oxygen saturation, and hemoglobin concentration. Theoretically, higher hemoglobin concentration may be needed to augment oxygen delivery in patients with cyanotic heart disease, particularly in the immediate postoperative period when myocardial dysfunction and low cardiac output are common. However, transfused blood may not efficiently deliver oxygen to the microcirculation despite raising the measured

Table 4 Adjusted inhospital secondary outcomes

	Lactate[a]		Inotrope score[a]		eGFR[a]	
	Hazard ratio (95 % CI)	*P* value	Hazard ratio (95 % CI)	*P* value	Hazard ratio (95 % CI)	*P* value
Effect of first 48-h hematocrit	1.02 (0.95–1.10)	0.63	1.04 (0.97–1.13)	0.25	0.97 (0.91–1.04)	0.44
Effect of first 7-day hematocrit	1.10 (0.99–1.21)	0.07	1.06 (0.95–1.18)	0.31	0.97 (0.87–1.10)	0.67
Effect of first 14-day hematocrit	1.10 (0.98–1.23)	0.11	1.08 (0.93–1.25)	0.32	0.89 (0.76–1.04)	0.14
Effect of first 48-h RBC transfusion	0.99 (0.98–1.00)	0.01	1.00 (0.99–1.00)	0.60	1.00 (0.99–1.00)	0.27
Effect of first 7 days of RBC transfusion	0.99 (0.99–1.00)	0.03	1.00 (0.99–1.00)	0.63	0.99 (0.99–1.00)	0.34
Effect of first 14 days of RBC transfusion	1.00 (0.99–1.00)	0.21	1.00 (0.99–1.00)	0.48	1.00 (0.99–1.00)	0.11

CI confidence interval, *eGFR* estimated glomerular filtration rate, *RBC* red blood cell

[a] Represents values in the first 14 days

hemoglobin concentration [10]. This may be due to decreased RBC deformability, increased hemoglobin affinity for oxygen, decreased RBC-dependent vasoregulatory function, or other effects of the storage lesion [3, 5, 19, 22].

Our study has several limitations. This single-center study generated results may be unique to our institution and not be generalizable to all centers. The retrospective nature of the study renders it susceptible to study design flaws and bias. The number of study patients is small, which limits our capability to precisely identify the association of RBC transfusion and hematocrit values with inhospital outcomes. All cofounding risk factors shown in previous studies to be associated with worsening outcomes were included in our multivariable analysis; however, there may be other variables affecting the outcome that were not included. It is possible that physiologic perturbations that may be seen during blood loss can also serve as potential risk factors in affecting outcomes. Our institution lacks a transfusion protocol. Decision to transfuse blood is based on clinical grounds and attending's preference. In the absence of such a protocol, we cannot completely exclude any bias that may have led to excessive transfusions in these patients. Our study also lacked data on transfusion of other blood products such as platelets, fresh frozen plasma, and cryoprecipitate. The number of donors donating data for our study patients is also missing from our study.

We could not find any association between amount of blood transfused and hematocrit values as our study lacked data on the amount of blood loss. Our study also lacked data on hemodynamic monitoring (such as central venous pressures, heart rate, blood pressures, cerebral oximetry), as well as data on the chest tube output. However, our study had data on indirect markers of bleeding like use of factor VII as well as need of reoperation for bleeding. Our unit has no well-defined protocol for ICU and hospital discharge. In the absence of such a protocol, we may have overestimated or underestimated the ICU and hospital LOS. Our study also lacked data on the indication of need for nitric oxide, Q_p/Q_s, and hypoxia. According to our knowledge, there was no change in our clinical practice during the study period. However, it is possible there have been some unknown changes in the practice that could not have been teased out due to retrospective nature of this study. Due to all these shortcomings, we recommend that this association should be rigorously evaluated in future, prospective, multicenter trials. However, this study has prompted our institution to develop a transfusion protocol for patients undergoing Norwood operation.

Conclusions

This single-center study found that higher hematocrit values and increasing RBC transfusions are not associated with improved outcomes in infants undergoing Norwood operation. Due to limitations of a single-center, observational study design, these results can only be considered hypothesis generating and suggest the need for future, multicenter, randomized controlled trials in varied surgical populations.

Conflict of interest None.

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