Journal of Cardiothoracic and Vascular Anesthesia 000 (2020) 1–7

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Balancing the Blood Component Transfusion Ratio for High- and Ultra High–Dose Cell Salvage Cases

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Objective: To assess the ratio of non-red blood cell to red blood cell components required to avoid coagulopathy when transfusing large amounts of salvaged blood using laboratory test–guided therapy.

Design: Retrospective cohort study.

Setting: Single-center, academic hospital.

Participants: Thoracoabdominal and abdominal open aortic surgery patients.

Measurement and Main Results: Thirty-eight patients in whom at least 1,000 mL of salvaged red blood cells were transfused were identified and divided into the following 2 cohorts: 1,000-to-2,000 mL of salvaged red blood cells (high dose) (n = 20) and >2,000 mL of salvaged red blood cells (ultra-high dose) (n = 18). Compared with the high-dose cohort, the ultra high-dose cohort received ~4 times more salvaged red blood cells (1,240 ± 279 mL *v* 5,550 ± 3,801 mL). With transfusion therapy guided by intraoperative coagulation tests and thromboelastography, the adjusted ratio of non-red blood cell to red blood cell components (plasma + platelets + cryoprecipitate:allogeneic + salvaged red blood cells) was 0.59 ± 0.66 in the high-dose and 0.93 ± 0.27 in the ultra high-dose cohorts. Multiple coagulation parameters were normal and similar between cohorts at the end of surgery, as determined by the mean, median, and 95% confidence intervals.

Conclusions: When transfusing large volumes of salvaged blood, it is important to balance the ratio between non-red blood cell and red blood cell components. Through a laboratory test–guided approach, coagulopathy was not detected when transfusing blood in ratios of approximately 1:2 for patients receiving 1,000-to-2,000 mL of salvaged blood and 1:1 for patients receiving >2,000 mL of salvaged blood.

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Key Words: blood; cell; coagulopathy; ratio; salvage; surgery; vascular

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https://doi.org/10.1053/j.jvca.2020.08.044
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DESPITE the benefits of cell salvage for reducing allogeneic transfusion requirements,[1,2] concerns still exist for the risk of coagulopathy, especially when salvaged red blood cells (RBCs) are given in sufficiently high quantities.[3,4] Salvaged blood, which is washed before reinfusion, is devoid of clotting factors and platelets (PLT), which normally are present in whole blood.[5] When salvaged RBCs are used as the only agent for volume resuscitation, there exists a risk for potentially uncontrolled dilutional coagulopathy and bleeding.[6,7] In such cases, coagulation monitoring and administering additional units of fresh frozen plasma (FFP), PLT, and cryoprecipitate (CRYO) become increasingly important. The optimal transfusion ratio among RBC, PLT, FFP, and CRYO for patients with major surgical bleeding is somewhat controversial and has yet to be studied in elective surgery patients. Much of the research on transfusion ratios has been focused on trauma patients, wherein retrospective studies supported early access to plasma-based components, with a balanced ratio of 1:1:1 for FFP:PLT:RBCs.[8] More recently, however, the prospective randomized 2015 PROPPR trial reported no difference in the primary outcome (all-cause mortality) when patients were transfused in a 1:1:1 compared with 1:1:2 ratio of FFP:PLT:RBCs.[9] In the absence of clear transfusion guidelines for blood component ratios, it remains unclear whether the risk of coagulopathy truly exists when transfusing large volumes of salvaged RBCs.[6]

In order to evaluate the ratio of non-RBC to RBC components needed to avoid coagulopathy when transfusing large amounts of salvaged blood, the authors of the present study performed a retrospective cohort study of major vascular surgery patients treated with laboratory test–guided transfusion therapy. To the authors' knowledge, herein are reported the largest volumes of salvaged blood given to patients in whom coagulation tests also were performed and analyzed. The hypothesis of the present study was that large volumes of salvaged RBCs would not be significantly associated with coagulopathy when delivered with an adequate ratio of non-RBC blood components.

Materials and Methods

Study Design

After Institutional Review Board approval with waived informed consent, 74 consecutive patients undergoing open thoracoabdominal or abdominal aortic aneurysm surgery were identified at the authors' institution between July 2016 and June 2019, of whom 38 patients received at least 1,000 mL of salvaged RBCs. Only adult patients older than 18 years were included. There were no exclusion criteria. Patients were divided into 2 cohorts. Those transfused between 1,000 and 2,000 mL of salvaged RBCs comprised the high-dose (HD) cohort, and those who received >2,000 mL of salvaged RBCs were designated as the ultra high–dose (UHD) cohort. These volumes were selected because they correlate with approximately up to 1 entire blood volume and greater than 1 entire blood volume of estimated blood loss during surgery, respectively. These also represent proposed thresholds at which coagulopathy develops and becomes highly clinically significant, respectively.[9-11]

Vascular surgeons performed all cases, and 1 surgeon in particular did all but 2 of the cases. Eleven cases were staffed by anesthesiologists with vascular/thoracic/transplantation training and the other 27 cases by cardiac anesthesiologists. The cell salvage device used for all cases was the XTRA (LivaNova, London, UK) with a 225-mL centrifuge bowl. The default settings were a fill, wash, and empty rate of 350 mL/min, 450 mL/min, and 450 mL/min, respectively, with a wash volume of 600 mL. A laboratory test–guided targeted transfusion strategy was used with the goal of avoiding coagulopathy.[12] This thromboelastography (TEG)-based algorithm involves initially obtaining a TEG and measuring the international normalized ratio (INR) value, fibrinogen concentration, and PLT counts. The following TEG values were measured: reaction (R) time with and without heparinase, maximum amplitude (MA), alpha angle, and K time. The frequency of additional testing depended on the specifics of each case, and tests were ordered at the discretion of the anesthesiology team based on both the clinical picture and laboratory testing results. Most laboratory tests were performed in a STAT laboratory adjacent to the operating room capable of providing expedited results (10-30 min) for certain tests, including hemoglobin, TEG, and PLT counts. Additional tests not able to be run in the STAT laboratory (eg, fibrinogen) were performed in the CORE laboratory, with a 30- to 60-minute turnaround. Because these tests were used to detect coagulopathy intraoperatively, they were used by the study team as a proxy to determine a patient's coagulation status.[13] Estimated blood loss and all allogeneic RBC, FFP, PLT, and CRYO units administered intraoperatively were recorded. The final intraoperative laboratory test results were used to assess coagulation function at the end of surgery, defined as just before or during wound closure.

Data and Statistical Analysis

Patients in both the HD and UHD cohorts were evaluated separately for baseline characteristics, such as age, sex, comorbidities, and preoperative coagulation tests. In each cohort, the number of blood products received intraoperatively, including RBCs, FFP, PLT, and CRYO, also were assessed. One unit of PLT was defined as a single donor apheresis unit (~250-300 mL), and 1 U of CRYO was defined as 5 pooled single-donor units (~100-120 mL). Given that salvaged RBCs have approximately the same hematocrit as allogeneic (banked) RBCs, for the adjusted ratios, 300 mL of salvaged RBCs was used to define 1 RBC unit. Therefore, for each individual non-RBC product, the unadjusted and adjusted ratios were calculated using the number of units transfused intraoperatively, as follows:

$$\text{Unadjusted Ratios}: \frac{\text{FFP Units}}{\text{Allogeneic RBC Units}}; \frac{\text{PLT Units}}{\text{Allogeneic RBC Units}}; \frac{\text{CRYO Units}}{\text{Allogeneic RBC Units}}$$

$$\text{Adjusted Ratios}: \frac{\text{FFP Units}}{\textit{Allogeneic RBC Units}+ (\textit{mL of Salvaged RBCs}/300)}; \frac{\text{PLT Units}}{\textit{Allogeneic RBC Units}+ (\textit{mL of Salvaged RBCs}/300)}; \frac{\text{CRYO Units}}{\textit{Allogeneic RBC Units}+ (\textit{mL of Salvaged RBCs}/300)}$$

In order to simplify the ratio calculation and because PLT and CRYO each contain a substantial volume of plasma, all non-RBC products were summed to calculate the overall unadjusted and adjusted ratios between non-RBC and RBC blood components. The unadjusted and adjusted non-RBC- to RBC ratios were calculated as follows:

$$\text{Unadjusted Ratio}: \frac{\text{PLT} + \text{FFP} + \text{CRYO Units}}{\text{Allogeneic RBC Units}}$$

$$\text{Adjusted Ratio}: \frac{\text{PLT} + \text{FFP} + \text{CRYO Units}}{\text{Allogeneic RBC Units} + (\text{mL of Salvaged RBCs}/300)}$$

Statistical analyses were performed using JMP, Version 12.1.0 (SAS Institute, Inc, Cary, NC). The Student *t* test, Mann-Whitney *U*, and chi-square tests were used to compare the 2 cohorts, as appropriate, to identify any association between cell salvage volume transfused and coagulation results. The volume of salvaged RBCs also was analyzed as a continuous variable with scatterplots and linear regression, with coagulation test results as the dependent outcome. For all analyses, $p < 0.05$ (2-tailed) was used to define statistical significance.

Results

Patient Characteristics

There were 20 patients in the HD and 18 patients in the UHD cell salvage cohorts. Basic demographic and clinical characteristics for both cohorts are shown in Table 1. Overall, the HD and UHD cohorts were relatively balanced with respect to age; sex; preoperative coagulation testing; and the presence of various comorbidities, including hypertension, diabetes, congestive heart failure, renal disease, and obesity.

Transfusion Requirements

On average, the UHD cohort received ~4 times more salvaged RBCs (5,550 ± 3,801 mL) than the HD cohort (1,240 ± 279 mL) (Table 2). Salvaged RBC volume ranged between 1,000 and 1,879 mL in the HD cohort and between 2,025 and 15,000 mL in the UHD cohort. As expected, the UHD cohort was transfused a greater number of allogeneic blood component units. For a normal sized adult patient, the median estimated intraoperative blood loss was about one half of an entire blood volume in the HD cohort and slightly more than an entire blood volume in the UHD cohort. The first and last intraoperative hemoglobin levels also are shown in Table 2.

Transfusion Ratios and Coagulation Tests

To assess whether the UHD cell salvage cohort was more likely to experience coagulopathy than the HD cohort, transfusion component ratios and coagulation test results were compared between the 2 groups. When comparing the HD and UHD cohorts, there were no significant differences in the mean unadjusted ratios for FFP, PLT, and CRYO (Table 3). The adjusted ratios were less in the HD than the UHD cohort for FFP and PLT, although no differences were demonstrated between the 2 cohorts with respect to CRYO.

When combining all the non-RBC blood components together, the mean unadjusted ratio of non-RBC to RBC components was similar between the HD and UHD cohorts, but the adjusted ratio for non-RBC to RBC units (including both allogeneic + salvaged RBCs) was lower in the HD than the UHD cohort (0.59 ± 0.66 *v* 0.93 ± 0.27; $p = 0.04$) (see Table 3). These ratios resulted from the laboratory test–based transfusion strategy targeted to avoid coagulopathy and could be described as approximately 1:2 in the HD cohort and 1:1 in the UHD cohort.

In both cohorts, the median values for INR, TEG R time with and without heparinase, TEG alpha angle, TEG K time, TEG MA value, and fibrinogen level were within the normal range as measured at the end of surgery (Table 4). Coagulation test results did not differ significantly between cohorts, except for the PLT count, which was lower in the UHD cohort. However, even the lower 25th percentile of the interquartile range was still more than 50,000, a threshold that has been recommended for patients undergoing surgery or invasive procedures. Furthermore, for the entire study population (both cohorts combined), the mean, standard deviation, median, interquartile range, and 95% confidence interval values for all coagulation tests were within the range associated with adequate hemostatic function (Table 5).

Across the entire range for the volume of salvaged RBCs transfused, coagulation tests did not vary significantly by linear regression (Fig 1). The only test for which the line of best fit slope differed significantly from zero was the PLT count ($p = 0.027$). Only 2 patients, however, had a PLT count <50,000/uL (45,000/uL and 46,000/uL), and the TEG MA (an index of PLT function) was not decreased at higher cell salvage volumes.

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Table 1
Demographic and Clinical Characteristics for Patients in the High-Dose and Ultra High–Dose Cell Salvage Cohorts

	High-Dose Cell Salvage (n = 20)	Ultra High–Dose Cell Salvage (n = 18)	p Value
Age, y (mean [SD])	65 ± 14	66 ± 15	0.75
Sex, n (% male)	15 (75.0)	12 (66.7)	0.57
ASA classification ≥3, n (%)	19 (95.0)	18 (100.0)	1.00
TAAA/AAA, (n)	4/16	11/7	0.02
Preoperative INR, median (IQR)	1.0 (1-1.1)	1.1 (1-1.1)	0.98
Preoperative PTT, median (IQR)	24 (23.2-25.4)	24.2 (23.1-26.1)	0.85
Preoperative platelet count (× 1,000/uL), median (IQR)	199 (135-265)	193 (138-241)	0.52
Heparin (U), median (IQR)	10,500 (7,250-13,875)	14,000 (9,250-17,875)	0.15
Protamine (mg), median (IQR)	70 (50-127.5)	150 (70-200)	0.02
Surgical duration (min), median (IQR)	305 (278-464)	484 (376-625)	0.0017
Comorbidities, median (IQR)*			
Hypertension, n (%)	3 (15.0)	3 (16.7)	1.00
Diabetes, n (%)	2 (10.0)	2 (11.1)	1.00
Congestive heart failure, n (%)	3 (15.0)	3 (16.7)	1.00
Pulmonary disease, n (%)	10 (50.0)	3 (16.7)	0.04
Renal disease, n (%)	5 (25.0)	3 (16.7)	0.70
Coagulopathy, n (%)	1 (5.0)	5 (27.8)	0.05
Obesity, n (%)	7 (35.0)	5 (27.8)	0.23

Abbreviations: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; Hb, hemoglobin; INR, international normalized ratio; IQR, interquartile range; PTT, partial thromboplastin time; SD, standard deviation; TAAA, thoracoabdominal aortic aneurysm.
* By International Classification of Diseases-Tenth Revision.

Table 2
Transfusion Data for Patients in the High-Dose and Ultra High–Dose Cell Salvage Cohorts

	High-Dose Cell Salvage (n = 20)	Ultra High–Dose Cell Salvage (n = 18)	p Value
Salvaged RBCs transfused (mL), mean ± SD	1,240 ± 279	5,550 ± 3,801	0.0002
Salvaged RBCs transfused (mL), median (IQR)	1,143 (1,000-1,500)	4,253 (2,638-7,310)	< 0.0001
Salvaged RBCs transfused (mL), range	1,000-1,879	2,025-15,000	–
RBC units (allogeneic), mean ± SD	1.3 ± 3.0	11.0 ± 10.5	0.0011
FFP (U), mean ± SD	3.2 ± 4.4	25.3 ± 20.1	0.0002
PLT (U), mean ± SD	0.5 ± 1.0	3.9 ± 2.6	< 0.0001
CRYO (U), mean ± SD	0.3 ± 1.0	1.1 ± 1.3	0.040
Estimated blood loss (mL), mean ± SD	2,500 (2,000-3,000)	6,400 (4,000-8,750)	0.002
First intraoperative Hb (g/dL), mean ± SD	11.7 ± 1.4	11.2 ± 2.3	0.47
Last intraoperative Hb (g/dL), mean ± SD	8.7 ± 1.1	8.6 ± 0.7	0.75

Abbreviations: CRYO, cryoprecipitate; FFP, fresh frozen plasma; Hb, hemoglobin; IQR, interquartile range; PLT, platelets; RBC, red blood cell; SD, standard deviation.

Table 3
Transfusion Ratios for Patients in the High-Dose and Ultra High–Dose Cell Salvage Cohorts

	High-Dose Cell Salvage (n = 20)	Ultra High–Dose Cell Salvage (n = 18)	p Value
Unadjusted FFP:RBC ratio, mean ± SD*	2.80 ± 2.37	3.05 ± 2.13	0.83
Unadjusted PLT:RBC ratio, mean ± SD*	0.27 ± 0.23	0.57 ± 0.68	0.14
Unadjusted CRYO:RBC ratio, mean ± SD*	0.03 ± 0.06	0.08 ± 0.09	0.13
Adjusted FFP:RBC ratio, mean ± SD	0.51 ± 0.62	0.79 ± 0.27	0.04
Adjusted PLT:RBC ratio, mean ± SD	0.07 ± 0.14	0.14 ± 0.04	0.03
Adjusted CRYO:RBC ratio, mean ± SD	0.06 ± 0.24	0.03 ± 0.04	0.71
Unadjusted non-RBC:RBC ratio, mean ± SD*,†	3.08 ± 2.40	3.61 ± 2.77	0.66
Adjusted non-RBC:RBC ratio, mean ± SD‡	0.59 ± 0.66	0.93 ± 0.27	0.04

Abbreviations: CRYO, cryoprecipitate FFP, plasma; PLT, platelets; RBC, red blood cell; SD, standard deviation.
* Sixteen patients excluded for a denominator of 0 U allogeneic RBCs (14 in the high-dose and 2 in the ultra high–dose cohorts).
† Unadjusted non-RBC:RBC ratio = FFP + PLT + CRYO:allogeneic-only RBCs.
‡ Adjusted non-RBC:RBC ratio = FFP + PLT + CRYO:allogeneic + salvaged RBCs.

Table 4
Coagulation Tests for Patients in the High-Dose and Ultra High–Dose Cell Salvage Cohorts

	High-Dose Cell Salvage (n = 20)	Ultra High–Dose Cell Salvage (n = 18)	p Value
End surgery INR, median (IQR)	1.25 (1.1-1.3)	1.15 (1.1-1.2)	0.49
End surgery TEG R time with heparinase (s), median (IQR)	5.2 (4-6.8)	4.7 (3.6-5.8)	0.59
End surgery TEG R time without heparinase (s), median (IQR)	4.8 (3.8-55.7)	4.6 (3.5-7.5)	0.45
End surgery TEG MA (mm), median (IQR)	59.6 (52.8-64.1)	56.6 (54.6-60.9)	0.49
End surgery TEG alpha angle, median (IQR)	65.9 (62.3-70.6)	68.5 (60.6-71.0)	0.80
End surgery TEG K time (s), median (IQR)	1.8 (1.2-2.1)	1.7 (1.4-2.1)	0.86
End surgery fibrinogen (mg/dL), median (IQR)	217 (140-246)	208 (169-256)	0.87
End surgery platelet count (x 1,000/uL), median (IQR)	112 (81-147)	74 (62-109)	0.045

NOTE. All laboratory values were measured at the end of the surgical procedures.
Abbreviations: INR, international normalized ratio; IQR, interquartile range; MA, maximum amplitude; R, reaction; TEG, thromboelastography.

Table 5
Coagulation Tests for All Patients (Both High-Dose and Ultra High–Dose Cohorts Combined)

	Median (IQR) (n = 38)	Mean ± SD (n = 38)	(95% CI) (n = 38)
End surgery INR	1.2 (1.1-1.3)	1.2 ± 0.2	(1.1-1.3)
End surgery TEG R time with heparinase (s)	4.8 (3.8-5.8)	5.5 ± 3.0	(4.4-6.7)
End surgery TEG R time without heparinase (s)	4.8 (3.7-9.0)	14.7 ± 22	(6.3-23.1)
End surgery TEG MA value (mm)	56.8 (54.4-61.1)	56.9 ± 6.4	(54.5-59.4)
End surgery TEG alpha angle	66.3 (61.5-70.8)	63.9 ± 11.2	(59.6-68.1)
End surgery TEG K time (s)	1.7 (1.4-2.1)	1.9 ± 0.9	(1.6-2.2)
End surgery fibrinogen (mg/dL)	209 (166-247)	208 ± 64	(183-233)
End surgery platelet count (× 1,000/uL)	91 (67-113)	97 ± 37	(84-111)

NOTE. All laboratory values were measured at the end of the surgical procedures.
Abbreviations: CI, confidence interval; INR, international normalized ratio; IQR, interquartile range; MA, maximum amplitude; R, reaction; TEG, thromboelastography,

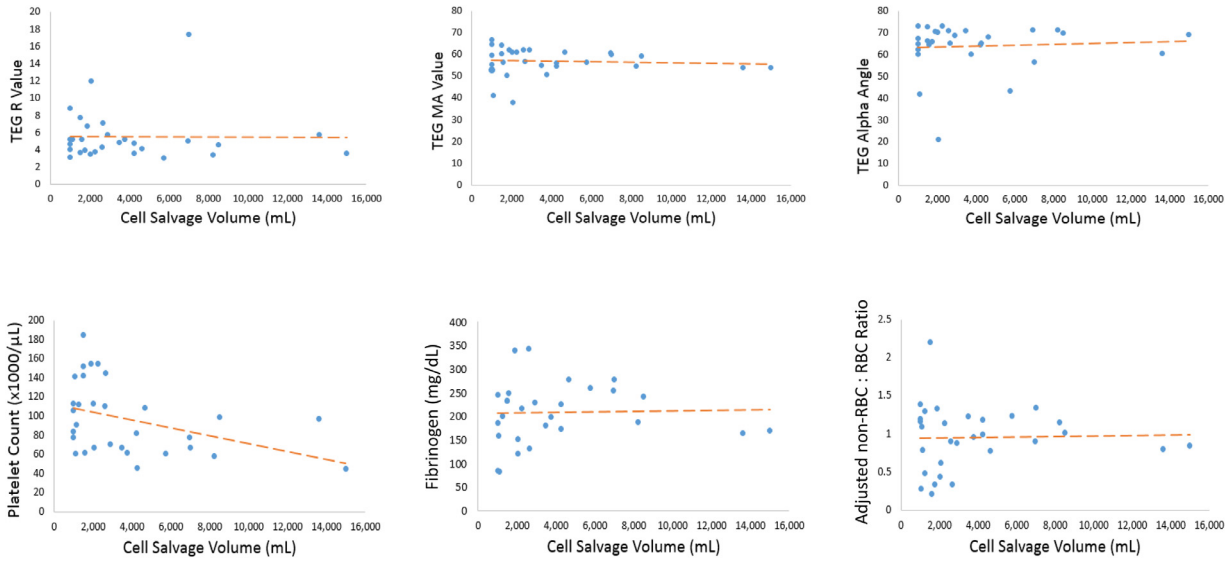

Fig 1. Scatterplots with linear regressions for cell salvage volume transfused (x-axis) and coagulation parameters measured at the end of surgery (y-axis). The line of fit slope was not different from zero for any parameter except for platelet count, for which higher cell salvage volumes were associated with a lower platelet count (p = 0.027). Only 2 patients, however, had a platelet count of less than 50,000/uL, and the thromboelastogram maximum amplitude value (an index of platelet function) was not decreased at higher cell salvage volumes. These findings indicate that high- or ultra high–doses of salvaged blood, when delivered in an appropriate ratio with non-red blood cell components, are unlikely to result in coagulopathy. Adjusted ratio = (FFP + PLTS + CRYO:allogeneic + salvaged RBC). CRYO, cryoprecipitate; FFP, plasma; MA, maximum amplitude; PLT, platelets; R, reaction; RBC, red blood cell; TEG, thromboelastogram.

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Discussion

The primary findings of the present study indicated that patients transfused up to 2,000 mL of salvaged RBCs with a non-RBC to RBC ratio of approximately 1:2 or >2,000 mL of salvaged blood, with a ratio of approximately 1:1, did not show signs of coagulopathy. Because the HD and UHD cohorts had similar coagulation test results at the end of surgery, there did not appear to be a dose-related risk of coagulopathy with this therapeutic approach. Furthermore, the present study's findings supported the use of laboratory test–based targeted transfusion therapy to guide the administration of non-RBC components (FFP, PLT, and CRYO) in patients receiving large volumes of salvaged RBCs.

The present study was unique in reporting multiple coagulation parameters along with blood component transfusion ratios after large volumes of salvaged blood were given. Previous reports by DeBois et al.,[14] in thoracoabdominal aortic surgery patients, described volumes of salvaged blood similar to that in the present study's UHD cohort. In their study, 5,750 mL was the mean volume transfused; however, roughly one half this volume (2,600 mL) was heparinized shed blood from the surgical field that was directly reinfused without washing. Although they described pH, electrolytes, and ionized calcium results, no coagulation tests were reported. Among obstetric hemorrhage patients, Zeng et al.[15] described 7 patients who received a median of 2,400 mL of salvaged blood (about half the amount in the present study's UHD cohort), with relatively normal postoperative coagulation tests, but no data were included on transfusion ratios. Huang et al.[16] reported a median salvaged blood volume of 1,500 mL in patients hemorrhaging from ectopic pregnancy (about one- third the amount in the present study's UHD cohort), with no clinically significant changes in coagulation test results and no data on transfusion ratios. Healy et al.,[17] in major vascular surgery patients, described much smaller salvaged blood volumes in the range of 400-to-700 mL. These investigators recommended that coagulation factors be replaced with FFP and PLT but did not give any specific ratio nor any coagulation test results.

In light of these studies, it is evident that transfusion ratios have not been studied extensively in patients receiving large volumes of salvaged blood. Even though the present study emphasized the importance of transfusing non-RBC blood components in such cases to avoid coagulopathy, the authors cannot comment on the ideal specific ratios of each individual non-RBC blood component (FFP, PLT, CRYO). Very few patients received PLT, especially in the HD cohort, making it challenging to extrapolate and draw conclusions on individual transfusion ratios. In addition, the study's small sample size and the presence of plasma in each unit of PLT and CRYO would confound any transfusion ratios described. Therefore, given the retrospective nature of this study, the authors cannot support the superiority of a given transfusion ratio over another nor can they comment on the optimal ratio required to avoid coagulopathy in large cell savage cases. However, what the present study did offer is support for the safety and efficacy of high- (1,000-2,000 mL) and ultra high– (>2,000 mL) dose cell savage when using laboratory test–guided transfusion therapy to determine how many non-RBC blood components to transfuse. What this means in the practical sense is that when ordering blood products during these cases, extra non-RBC components need to be prepared, with the specific component based on the clinical picture and laboratory test–guided therapy. This concept is supported by the 4- to 5-fold difference seen between the unadjusted and adjusted ratios described. Even though the typical ratio for FFP:PLT:RBC in massive transfusion protocols is 1:1:1, in cases in which large volumes of cell salvage are used, a different ratio may be required. The authors' blood bank allows them to alter the massive transfusion protocol to obtain additional units of non-RBC components for cases that use cell salvage.

The present study's findings when cell salvage volume was analyzed as a continuous variable (see Fig 1), showed that even over the entire dose range for salvaged RBCs, there were no significant changes in multiple coagulation parameters. One exception was the PLT count, which was lower at the end of surgery in patients receiving greater amounts of salvaged blood. However, with only 2 patients having PLT counts <50,000/uL and the TEG MA values not varying according to cell salvage volume, it is unlikely that coagulopathy as a result of thrombocytopenia was a clinically significant problem.

Previous publications on the topic of cell salvage during cardiac surgery have expressed concern regarding residual heparin as a possible cause of coagulopathies after autotransfusion.[18] Three patients in the current study did have significantly elevated TEG R times (without heparinase), suggesting the need for more heparin reversal (eg, protamine). However, the other patients in the cohort showed little difference between their R times with or without heparinase. The most likely reason for this finding is that vascular surgery patients routinely are given moderate doses of intravenous heparin during surgery, which often requires protamine "reversal" near the end of the case. It is important to note that because a laboratory test–guided transfusion strategy was used, the present study may not have been able to fully assess the effect of residual heparin as a cause of coagulopathy. That being said, previous studies have demonstrated minimal amounts of residual heparin in washed blood (the salvaged blood given back to the patient), with concentrations ranging from 0.03-to-0.3 U/mL.[19-21] With such low concentrations reported in the literature, the authors believe it is unlikely that residual heparin is a cause for significant concern when using cell salvage.

There were several limitations to the present study that should be acknowledged. First, its retrospective nature meant that the authors were not able to dictate the parameters for treatment before surgery so there may have been variation in blood administration practices. In addition, higher versus lower transfusion ratios were not compared so the authors can comment only on the ratios described. If the authors were to compare those receiving higher or lower ratios within their cohorts, the comparison would be confounded by differences in the amount of blood lost and the amount of salvaged blood transfused; therefore, the authors did not report such an analysis. There also was no assigned control group receiving only

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allogeneic products because the focus of this study was not to assess the superiority of cell salvage over traditional allogeneic transfusions. Moreover, the use of a targeted algorithm guided by TEG and conventional laboratory tests, such as INR, PLT count, and fibrinogen levels, likely had a direct influence on the transfusion ratio results. Because the algorithm addresses when to transfuse certain non-RBC products based on bleeding and abnormal laboratory results, it is possible that the algorithm naturally produced a non-RBC:RBC ratio of 1:1. However, this bias likely would only be present in the UHD cohort because patients in the HD cohort were less likely to be actively bleeding, as evidenced by the 10-fold fewer allogeneic RBC units transfused. Therefore, the algorithm likely played less of a role in the transfusion strategies for these HD patients. Finally, the results may have limited generalizability because all procedures were performed at a single institution and the focus on patients receiving >1,000 mL of salvaged blood resulted in a relatively small sample size. Perhaps future studies should include multiple centers to recruit more subjects.

Conclusion

In summary, salvaged blood given in quantities that exceed even an entire blood volume may not result in coagulopathy when an appropriate amount of non-RBC blood components are transfused to maintain a balanced ratio. The findings in the present study may be valuable in guiding transfusion practices in high- blood-loss procedures in which greater amounts of FFP, PLT, and CRYO should be prepared and transfused, according to the total amount of RBCs transfused (salvaged + allogeneic). This "rebalanced" transfusion ratio requires planning and adjustment because the typical massive transfusion protocol ratio will result in too many RBC units. Furthermore, the optimal use of salvaged blood in major vascular cases results in substantially reduced blood utilization and overall costs,[22] especially when multiple units can be spared.[23] Cell salvage, even in large quantities, appears to be safe and effective if given properly and should be considered as a patient blood management method to provide high-value care.

Acknowledgments

The authors would like to acknowledge both financial and project management support from The Johns Hopkins Health System Armstrong Institute for Patient Safety and Quality, Baltimore, MD.

References

1 Carless PA, Henry DA, Moxey AJ, et al. Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2010;4:CD001888.
2 Sikorski RA, Rizkalla NA, Yang WW, et al. Autologous blood salvage in the era of patient blood management. Vox Sang 2017;112:499–510.
3 Rollins K, Trim N, Luddington R, et al. Coagulopathy associated with massive cell salvage transfusion following aortic surgery. Perfusion 2012;27:30–3.
4 Rudra P, Basak S. Coagulopathy during intraoperative cell salvage in a patient with major obstetric haemorrhage. Br J Anaesth 2011;106:280–1.
5 Adam EH, Funke M, Zacharowski K, et al. Impact of intraoperative cell salvage on blood coagulation factor concentrations in patients undergoing cardiac surgery. Anesth Analg 2020;130:1389–95.
6 Paparella D, Whitlock R. Safety of salvaged blood and risk of coagulopathy in cardiac surgery. Semin Thromb Hemost 2016;42:166–71.
7 Ashworth A, Klein AA. Cell salvage as part of a blood conservation strategy in anaesthesia. Br J Anaesth 2010;105:401–6.
8 Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008;248:447–58.
9 Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: The PROPPR randomized clinical trial. JAMA 2015;313:471–82.
10 Dzik WS, Ziman A, Cohen C, et al. Survival after ultramassive transfusion: A review of 1360 cases. Transfusion 2016;56:558–63.
11 Waters JH. Role of the massive transfusion protocol in the management of haemorrhagic shock. Br J Anaesth 2014;113:ii3–8.
12 Hensley NB, Cho BC, Visagie M, et al. How do I audit intraoperative blood component utilization in cardiac surgery? Transfusion 2019;59:3058–64.
13 American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management. Anesthesiology 2015;122:241–75.
14 DeBois WJ, Girardi LN, Lawrence S, et al. Perfusion method for thoracoabdominal aneurysm repair using the open distal technique. Perfusion 2000;15:231–6.
15 Zeng K, Huang W, Yu C, et al. How about "The effect of intraoperative cell salvage on allogeneic blood transfusion for patients with placenta accreta"?: An observational study. Medicine (Baltimore) 2018;97:e10942.
16 Huang J, Qin D, Gu C, et al. Autologous and nonautologous blood transfusion in patients with ruptured ectopic pregnancy and severe blood loss. Biomed Res Int 2017;2017:1–9.
17 Healy CF, Doyle M, Egan B, et al. Transfusion requirements and outcomes in patients undergoing abdominal aortic surgery using intra-operative cell salvage. Ir J Med Sci 2007;176:33–6.
18 Shen S, Zhang J, Wang W, et al. Impact of intra-operative cell salvage on blood coagulation in high-bleeding-risk patients undergoing cardiac surgery with cardiopulmonary bypass: A prospective randomized and controlled trial. J Transl Med 2016;14:228.
19 Paravicini D, Schmitz-Huebner U, Stinnesbeck B. [Heparin elimination in intraoperative autotransfusion with the haemonetics cell saver]. Infusionsther Klin Ernahr 1983;10:19–21.
20 Sistino JJ, Owitz D, Mongero LB. Heparin washout in the pediatric cell saver bowl. J Extra Corpor Technol 1992;24:94–6.
21 Vieira SD, da Cunha Vieira Perini F, de Sousa LCB, et al. Autologous blood salvage in cardiac surgery: Clinical evaluation, efficacy and levels of residual heparin. Hematol Transfus Cell Ther 2019;S2531-1379(19)30161-0. https://doi.org/10.1016/j.htct.2019.08.005; Online ahead of print.
22 Frank SM. Who benefits from red blood cell salvage?—Utility and value of intraoperative autologous transfusion. Transfusion 2011;51:2058–60.
23 Waters JH, Dyga RM, Waters JFR, et al. The volume of returned red blood cells in a large blood salvage program: Where does it all go? Transfusion 2011;51:2126–32.