OBSTETRICS

Single-unit vs multiple-unit transfusion in hemodynamically stable postpartum anemia: a pragmatic randomized controlled trial

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BACKGROUND: The American Academy of Blood Banks recommends single-unit red cell transfusion protocols across medicine to reduce transfusion complications and the use of a scarce resource. There are minimal data regarding single-unit protocols in obstetrics.

OBJECTIVE: We aimed to compare single-unit vs multiple-unit transfusion protocols for treatment of hemodynamically stable postpartum anemia.

STUDY DESIGN: We performed a randomized trial comparing initial transfusion with 1 unit of packed red blood cells (single-unit protocol) to 2 units of packed red blood cells (multiple-unit protocol) from March 2018 to July 2019. Women who required transfusion >6 hours postpartum were approached for consent. Unstable vital signs, hemoglobin level <5 g/dL, hemoglobinopathy, and cardiomyopathy were exclusion criteria for enrollment. Hemoglobin assessment and standardized clinical evaluation were performed 4 to 6 hours posttransfusion; additional packed red blood cells were given if indicated. The primary outcome was total units transfused. Secondary outcomes included length of stay, endometritis, wound separation or infection, venous thromboembolism, and intensive care unit admission within 30 days postpartum. Breastfeeding, depression, maternal attachment, and fatigue scores were assessed at 4 to 9 weeks postpartum. A total of 66 women were required to detect a 20% reduction in units transfused with a single-unit protocol (power=80%; α=0.05).

RESULTS: A total of 66 women were randomized (33 per arm). There were no differences between groups in demographic or clinical characteristics, including delivery mode, blood loss, and randomization hemoglobin levels. The mean number of units transfused was lower in the single-unit protocol than in the multiple-unit protocol (1.2 U vs 2.1 U; $P<.001$). Only 18.2% of women in the single-unit arm required additional packed red blood cells. At posttransfusion assessment, women in the single-unit arm had lower hemoglobin levels (7.8 g/dL vs 8.7 g/dL; $P<.001$), but there were no differences in vital signs or symptoms between groups. There were also no differences in length of stay, 30-day complications, or 4 to 9 week postpartum outcomes.

CONCLUSION: In women with hemodynamically stable postpartum anemia, a single-unit protocol avoided a second unit of packed red blood cells in >80% of women without significant impact on morbidity. Our work supports the use of single-unit initial transfusion in this population.

Key words: breastfeeding, depression, estimated blood loss, fatigue, hemoglobin, maternal attachment, maternal morbidity, packed red blood cells, red cell, transfusion complication

Introduction

Postpartum anemia is a significant public health issue, with rates as high as 27% to 80% across the globe.[1–3] To optimize outcomes and prevent anemia, there are recommendations regarding the management of an acute postpartum hemorrhage, including the use of massive blood transfusion protocols when indicated.[4] Yet, many postpartum women will require transfusion after the acute events of the delivery room, where recommendations are less clear.[5,6] Overtransfusion increases the risk of alloantibody development, infectious disease transmission, and complications such as transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO).[7,8] Undertransfusion in postpartum women may theoretically impact healing, breastfeeding, depression, and the ability to care for the newborn.[8–11] There is a paucity of data on the appropriate management of hemodynamically stable postpartum anemia.

Although there is limited evidence, it is common practice in obstetrics to offer a transfusion of packed red blood cells (pRBCs) to women in the postpartum period with a hemoglobin (Hb) level <7 g/dL (hematocrit <20%) and to symptomatic women with even higher Hb levels.[12] Transfusions were historically initiated with 2 units of pRBCs. However, the most recent recommendation from the American Association of Blood Banks (AABB) for a stable patient is to begin tranfusion with 1 unit and reassess.[13] The American College of Obstetricians and Gynecologists (ACOG), in the newly released 2017 practice bulletin on postpartum hemorrhage, has included the AABB's statement endorsing the use of single-unit transfusions.[14] However, whereas nonobstetric fields have successfully demonstrated that single-unit transfusion protocols can decrease the number of units transfused without increasing morbidity,[15–17] no such trials have been performed in obstetrics.

Therefore, we aimed to compare single-unit vs multiple-unit transfusion protocols in hemodynamically stable postpartum anemia. We hypothesized that a single-unit transfusion protocol can reduce the number of units transfused.

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AJOG at a Glance

Why was this study conducted?

The American Academy of Blood Banks recommends single-unit red cell transfusion protocols across medicine to reduce transfusion complications and the use of a scarce resource. There are minimal data regarding single-unit protocols within obstetrics.

Key findings

A single-unit transfusion protocol reduced the mean number of units transfused compared with a multiple-unit transfusion protocol (1.2 U vs 2.1 U; $P<.001$). Only 18.2% of women transfused with a single-unit required additional packed red blood cells (pRBCs). There were no significant differences in secondary outcomes—vital signs or symptoms at postpartum assessment, maternal morbidity, depression, maternal attachment, breastfeeding, or fatigue scores—between groups.

What does this add to what is known?

In women with hemodynamically stable postpartum anemia, a single-unit protocol avoids a second unit of pRBCs in >80% of women without significant impact on morbidity.

Materials and Methods

We performed a randomized controlled trial of hemodynamically stable postpartum women requiring blood transfusion at the Hospital of the University of Pennsylvania from March 2018 to July 2019. This study was approved by the Institutional Review Board at the University of Pennsylvania and was registered on ClinicalTrials.gov (NCT03419780).

Women were approached for inclusion, and written consent was obtained if they met all of the following criteria: aged ≥18 years, determined to require blood transfusion by their primary provider (Hb level either <7 g/dL or >7 g/dL with signs or symptoms of anemia, including but not limited to heart rate 110−129 beats per minute, blood pressure 81−99 mm Hg systolic or 41−59 mm Hg diastolic, fatigue, and/or dizziness), and >6 hours after delivery without a contraindication to transfusion. Women were excluded if they met any of the following criteria: non−English speaking, Hb level <5 g/dL, heart rate of >130 beats per minute, blood pressure <80 mm Hg systolic or <40 mm Hg diastolic, diagnosis of hemoglobinopathy, or left ventricular ejection fraction <35%. Women remained eligible if they had received an acute blood transfusion but were deemed to require additional blood at a later point in their postpartum course.

Women were then randomized to 1 of 2 arms: (1) single-unit protocol (initial transfusion of 1 U pRBCs) or (2) multiple-unit protocol (initial transfusion of 2 U pRBCs). Randomization was done via computer-generated block randomization in a 1:1 scheme. After randomization was performed, the patient and provider were both made aware of arm assignment. In both arms, 4 to 6 hours after initial transfusion, a complete blood count, review of patient symptomatology, and physical examination of the provider were performed. Assessment at this time could include evaluation of volume status and orthostatic vital signs. In accordance with the pragmatic nature of this trial, additional blood could be given if deemed necessary by the clinical provider. Additional blood was given 1 unit at a time until no further blood was deemed necessary per provider discretion.

The primary outcome was number of units transfused per patient after randomization. Secondary outcomes included Hb level at 4 to 6 hours posttransfusion, vital signs and symptomatology at first posttransfusion assessment by provider assessment, Hb level at hospital discharge, use of intravenous iron, and maternal length of stay. Complications, including endometritis, wound infection, venous thromboembolism, intensive care unit admission, and adverse transfusion reaction, were evaluated during the postpartum admission and during any contact or readmission within our health system, both inpatient or outpatient, up to 30 days postpartum. We also evaluated the following secondary outcomes at the postpartum visit (4−9 weeks postpartum):

(1) The Edinburgh Postnatal Depression Scale (EPDS), which is a commonly used screening tool for depression during pregnancy. It is a self-report 10-question scale

FIGURE 1
Study participants

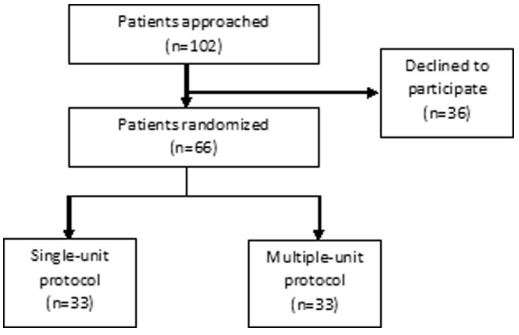

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TABLE 1
Baseline demographics

Demographics	Single-unit protocol (n=33)	Multiple-unit protocol (n=33)	*P*-value
Age[a]	29 (6)	29 (6)	1.00
Race			.39
Black	26 (78.8)	24 (72.7)	
White	4 (12.1)	7 (21.2)	
Asian	3 (9.1)	1 (3.0)	
Other	0	1 (3.0)	
Ethnicity			1.00
Non-Hispanic	32 (97.0)	32 (97.0)	
Hispanic	1 (3.0)	1 (3.0)	
BMI at initial prenatal visit[a]	27.3 (6.9)	27.0 (6.7)	.86
Nulliparous	12 (36.4)	14 (42.4)	.80
Twin gestation	4 (12.1)	4 (12.1)	1.00
Placental abnormalities	1 (3.0)	4 (12.1)	.36
Gestational diabetes	1 (3.0)	3 (9.1)	.61
Pregestational diabetes	1 (3.0)	1 (3.0)	1.00
Chronic hypertension	2 (6.1)	1 (3.0)	1.00
History of venous thromboembolism	0	1(3.0)	1.00
Maternal cardiac disease	1 (3.0)	1 (3.0)	1.00
Hypothyroidism	1 (3.0)	3 (9.1)	.61
Fibroids	1 (3.0)	1 (3.0)	1.00
Hemoglobin, g/dL[a]			
Initial prenatal	11.0 (1.7)	11.1 (1.4)	.91
Third trimester	10.4 (1.5)	10.3 (1.2)	.76
Antepartum intravenous iron sucrose administered	5 (15.2)	4 (12.1)	1.00
Antepartum red blood cell blood transfusion	1 (3.0)	0	1.00

Data are presented as number (percentage) unless noted otherwise.

BMI, body mass index.

[a] Presented as mean (standard deviation).

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on affective and cognitive features of depression in the 7 days preceding delivery; each item is scored on a 4-point scale of 0 to 3, with a total score of 30. Higher scores indicate increased depressive symptomatology.[18,19]

(2) The Maternal Attachment Inventory (MAI), which measures maternal affectionate attachment. It is a self-report, 26-item instrument; each item is scored from 1 (almost never) to 4 (almost always), with a possible range of scores from 26 to 104. Higher scores indicate higher maternal attachment to the infant.[20]

(3) The Multidimensional Fatigue Index (MFI), which measures 5 dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. Although not specifically designed for the postpartum period, the MFI has high feasibility, reliability, and validity in chronically anemic and postpartum women and has been used in multiple randomized controlled trials related to postpartum anemia. It is a self-report, 20-item instrument; each item is scored on a 5-point scale indicating to what extent the statement applies to the mother. Scores range from 20 to 100. Higher scores indicate a higher degree of fatigue.[21–23]

The mothers were enquired about breastfeeding at this visit as, "Are you feeding your baby with any breastmilk?"

To determine our sample size, we analyzed baseline data at our institution from 2013 to 2015, when most providers were using multiple-unit transfusion protocols. Women transfused for hemodynamically stable postpartum anemia received an average of 1.9 U, with a standard deviation of 0.3 U.[24] Thus, we determined that we would require 33 women per arm to have >80% power to demonstrate a 20% reduction in mean units transfused, from 1.9 to 1.5 U per patient with a standard deviation of 0.5 U, using a 2-sided α of 0.05. This would result in a decrease of 38 U for every 100 women transfused, which was felt to be clinically significant.

Fisher exact tests and chi-square tests were used for categorical variables and *t* tests or Wilcoxon rank sum tests were used for continuous variables, where appropriate. Analysis was performed as intention-to-treat. Statistical analyses were performed with Stata 15 (StataCorp, College Station, TX) and statistical significance was set at $P<.05$.

Results

From March 2018 to June 2019, a total of 102 eligible women were approached, of whom 66 (64.7%) provided written informed consent and underwent randomization. A total of 33 women were randomized to the single-unit protocol and 33 to the multiple-unit protocol (Figure 1).

Baseline demographics were similar between groups (Table 1). In addition,

TABLE 2
Admission and randomization clinical characteristics

	Single-unit protocol (n=33)	Multiple-unit protocol (n=33)	*P*-value
Characteristics: admission and delivery			
Hb level at admission, g/dL[a]	10.4 (1.5)	10.6 (1.3)	.71
Labor induction	14 (42.4)	12 (36.4)	.80
Peripartum magnesium level	3 (9.1)	4 (12.1)	1.00
Gestational age[b]	37 (36–39)	39 (36–40)	.63
Mode of delivery			1.00
Spontaneous vaginal delivery	8 (24.2)	9 (27.2)	
Operative vaginal delivery	2 (6.1)	1 (3.0)	
Cesarean delivery	23 (69.7)	23 (69.7)	
Order of cesarean delivery			.09
Primary	13 (56.5)	15 (65.2)	
Repeat ×1	3 (13.0)	7 (30.4)	
Repeat ×2	4 (17.4)	0	
Repeat ×3 or greater	3 (13.0)	1 (4.4)	
Surgical complications[c]	6 (26.1)	6 (26.1)	1.00
Third or fourth degree laceration	2 (20.0)	0	.47
Estimated blood loss[b]	1000 (800–1500)	1000 (800–1200)	.46
Placental abruption	3 (9.1)	3 (9.1)	1.00
Acute blood transfusion before randomization	3 (9.1)	2 (6.1)	1.00
Characteristics: randomization examination			
Hb level at randomization, g/dL[a]	6.8 (0.6)	7.0 (0.6)	.24
Heart rate[a]	96 (12.0)	92 (14.0)	.22
Systolic blood pressure[a]	116 (13.0)	117 (19.0)	.76
Diastolic blood pressure[a]	66 (11.0)	66 (13.0)	.93
Lightheadedness/dizziness/fatigue	24 (72.7)	29 (87.9)	.22

Data are presented as number (percentage) unless noted otherwise.

Hb, hemoglobin.

[a] Mean (standard deviation); [b] Median (interquartile range); [c] Defined as ≥1 of the following: bladder injury, bowel injury, uterine artery laceration, or extension of the uterine incision.

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mode of delivery, visually estimated blood loss, and characteristics at time of randomization were similar among groups (Table 2). Mean Hb level at randomization was also similar in the single-unit and multiple-unit protocol arms (6.8 g/dL and 7.0 g/dL, respectively; *P*=.24).

All women received their initial randomized assignment without any crossover. At the 4 to 6 hour posttransfusion assessment (Table 3), mean Hb level was lower in the single-unit arm (7.8 g/dL vs 8.7 g/dL, *P*<.001). However, there was no difference in vital signs or report of anemia symptoms (lightheadedness, dizziness, or fatigue) between groups.

For our primary outcome, the mean total number of units transfused postrandomization was lower in the single-unit protocol than in the multiple-unit protocol (1.2 U vs 2.1 U; *P*<.001) (Table 4). Only 6 women (18.2%) in the single-unit arm were determined to require further transfusion by their clinical provider. Figure 2 depicts the total number of units transfused per arm.

Women in the single-unit arm were more likely to receive intravenous iron sucrose after their initial transfusion (45.5% vs 21.2%; *P*=.04) (Table 4). There was no difference between groups in maternal length of stay. Other secondary outcomes including endometritis, wound infection, venous thromboembolism, and intensive care unit admission through 30 days postpartum, were not significantly different between groups.

Notably, 29 (87.9%) women in the single-unit arm and 27 (81.8%) women in the multiple-unit arm presented for follow-up 4 to 9 weeks postpartum. At this time point, there were no significant differences between groups in breastfeeding rates overall, breastfeeding rates among those who intended to breastfeed at delivery, EPDS, MAI, or MFI scores (Table 5).

Comment

Principal findings

In this study, no additional blood was required beyond the initial 1 U transfusion for >80% of the women randomized to a single-unit blood transfusion protocol. Women in the single-unit arm had similar outcomes in terms of 30-day morbidity and postpartum outcomes, including breastfeeding rates, depression, mother–infant bonding, and fatigue scores.

Results

Although several other medical disciplines have examined the impact of single-unit transfusion protocols, our study addresses the safety of such a protocol in the postpartum population. In addition, previous studies were often performed as retrospective or prospective cohort studies, with significant room for biases affecting decision-making around transfusion.[15,16] Our study removes at least the initial decision of number of units to transfuse from the hands of the provider through a

TABLE 3
Data at 4 to 6 hours posttransfusion assessment

	Single-unit protocol (n=33)	Multiple-unit protocol (n=33)	*P*-value
Posttransfusion Hb level, g/dL[a]	7.8 (0.7)	8.7 (0.9)	<.001
Heart rate, (beats per min)[a]	90 (13.0)	85 (12.0)	.08
Systolic BP (mm Hg)[a]	123 (13.0)	121 (18.0)	.66
Diastolic BP (mm Hg)[a]	72 (9.0)	71 (12.0)	.73
Lightheadedness/dizziness/fatigue[b]	7 (21.2)	6 (18.8)	1.00

BP, blood pressure; *Hb*, hemoglobin.

[a] Presented as mean (standard deviation); [b] Presented as number (percentage).

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randomized trial, decreasing the impact of bias.

Clinical implications

AABB, supported by ACOG, recommends the use of single-unit blood transfusion protocols to reduce transfusion complications such as alloantibody development, TRALI, and TACO. Furthermore, blood is a scarce resource.[13,14] In obstetrics, we must also consider the implication of product transfusion and possible isoimmunization on future pregnancies. However, traditional obstetrical practice is to administer a higher quantity of blood products because of the theoretical concern regarding postpartum healing, fatigue, depression, newborn care, and breastfeeding. In a qualitative study performed in Australia, despite similar guidelines promoting single-unit protocols, 54% of obstetricians still reported they would initiate any postpartum transfusion with 2 units of pRBCs, citing concern for perceived utility.[25] Our data support the adoption of AABB's recommendations into obstetrics to decrease the number of units transfused without increasing morbidity for postpartum women with hemodynamically stable anemia.

TABLE 4
Primary and secondary outcomes up to 30 days postpartum

	Single-unit protocol (n=33)	Multiple-unit protocol (n=33)	*P*-value
Primary outcome: total units transfused[a]	1.2 (0.5)	2.1 (0.4)	<.001
Secondary outcomes			
Last Hb level before discharge, g/dL[a]	8.2 (0.7)	8.9 (0.8)	.003
Postpartum use of intravenous iron	15 (45.5)	7 (21.2)	.04
Maternal length of stay[b]	3.1 (2.5–3.8)	3.4 (2.4–4.1)	.79
Endometritis[c]	0	2 (6.1)	.49
Wound separation or infection[c]	2 (6.1)	1 (3.0)	1.00
Venous thromboembolism[c]	0	1 (3.0)	1.00
Intensive care unit admission[c]	1 (3.0)	1 (3.0)	1.00
Adverse transfusion reactions[c]	0	0	NA
Readmissions within 30 days[c]	1 (3.0)	2 (6.1)	1.00

Hb, hemoglobin; *NA*, not applicable.

[a] Presented as mean (standard deviation); [b] Presented as median (interquartile range); [c] Presented as number (percentage).

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Research implications

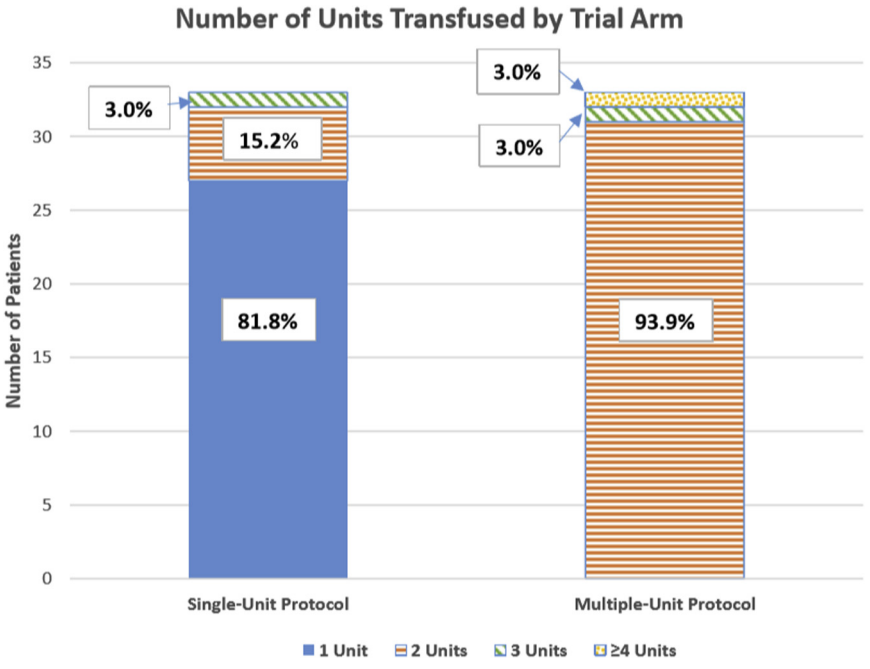
This small randomized trial provides initial data supporting the use of single-unit transfusion for hemodynamically stable postpartum anemia. Further work should be done to implement single-unit protocols as the standard of care at a national level. Future research should focus on both clinical and implementation outcomes, such as healthcare cost, provider and patient acceptability, and adoption into practice.

Strengths and limitations

There are several strengths to our work. This study was performed as a randomized controlled trial, removing provider bias from the initial decision for single-unit or multiple-unit transfusion. In addition, we were able to assess many of the variables that reflect commonly cited reasons for providing multiple units to obstetrical patients, such as wound outcomes, postpartum fatigue, depression, and breastfeeding, with no differences between groups.

There are also several limitations. The decision to proceed with transfusion for any given patient depended on the provider. As strict cutoffs for anemia severity were not employed as enrollment criteria, our population may have included patients for whom another provider may not have thought transfusion was necessary, which could have biased our results. In addition, the decision to give additional product after the posttransfusion assessment also depended on the provider. As providers were not blinded to study assignment, observer bias could have influenced the decision-making process at this time point. Yet, the lack of stringent criteria regarding initial or subsequent transfusion adds a pragmatic aspect to this study, increasing its generalizability. Finally, our small sample size was not powered to detect differences in some of our less common secondary outcomes

FIGURE 2
Number of units transfused by trial arm



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such as wound infection and readmission. In addition, more women in the single-unit arm received intravenous iron sucrose postpartum, which may have impacted postpartum outcomes. However, it is reassuring that no large differences were noted between the groups.

Conclusion

A second unit of pRBCs can be avoided in most postpartum women requiring hemodynamically stable transfusion without significant impact on short-term or postdischarge morbidity. Our work supports single-unit initial transfusion in this population. Large-scale use of single-unit transfusion protocols has the potential to reduce healthcare cost, conserve a scarce resource, and prevent rare but deadly transfusion reactions. ■

TABLE 5
Secondary outcomes at 4 to 9 weeks postpartum visit

Secondary outcomes	Single-unit protocol	Multiple-unit protocol	*P*-value
Presented for postpartum visit[a]	29/33 (87.9)	27/33 (81.8)	.73
Breastfeeding (any) overall[a]	16/29 (55.2)	15/27 (55.6)	.89
Breastfeeding (any) if intended to breastfeed at delivery	16/26 (61.5)	14/22 (63.6)	1.00
Edinburgh Postnatal Depression Scale[b,c]	4 (1—11)	5.5 (2—8)	.34
Maternal Attachment Inventory[b,d]	104 (102—104)	104 (102—104)	.55
Multidimensional Fatigue Inventory[b,e]	44 (34—55)	53 (38—70)	.13

[a] Presented as number (percentage); [b] Presented as Median (interquartile range); [c] Higher scores indicate increased depressive symptoms; [d] Higher scores indicate higher rates of maternal-infant attachment; [e] Higher scores indicate greater fatigue.

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