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Single versus double-unit transfusion: Safety and efficacy for patients with hematologic malignancies

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Abstract

Objectives: Although hemoglobin thresholds for red blood cell (RBC) transfusion have decreased, double-unit RBC transfusion practices persist. We studied the effects switching from predominantly double-unit to single-unit RBC transfusions had on utilization and clinical outcomes for malignant hematology patients.

Methods: Retrospective chart review compared malignant hematology patients before and after implementing single-unit RBC transfusion policy. Hemoglobin threshold was 8.0 g/dL for both groups. RBC utilization metrics included number of RBC units transfused, RBC units transfused per admission, and number of transfusion episodes. Clinical outcomes included length of stay, 30-day mortality, and outpatient RBC transfusion 30-days post-discharge.

Results: Baseline hemoglobin was similar in both groups. The single-unit group was transfused with fewer RBC units per admission (5.1 vs 4.5, $P=0.01$) than the double-unit group, but had more transfusion episodes per admission (4.1 vs 2.7, $P<0.001$). After implementing single-unit policy, a 29% reduction in RBC utilization was observed. Mean hemoglobin at discharge was lower in the single-unit group (8.9 vs 9.5 g/dL, $P=0.005$). No significant differences in length of stay or 30-day mortality were observed.

Conclusion: Transfusing malignant hematology patients with single RBC units is safe and efficacious. Electronic provider order systems facilitating RBC transfusion requests provide excellent adherence to transfusion policy.

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CONFLICT OF INTEREST

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Keywords

Blood; double; erythrocyte; hematology; red blood cell; single; transfusion; unit

1 | INTRODUCTION

Blood transfusion therapy remains critical to patients being treated for a wide spectrum of diseases including hematologic malignancies. However, blood products remain a costly resource that carry a residual risk of infectious disease and are associated with both immunologic and non-immunologic adverse effects.¹ Consequently, efforts continue to limit blood transfusion to those patients who are most likely to derive benefit.

Variability in transfusion practices persists despite high-quality evidence and guidelines that support restrictive red blood cell (RBC) transfusion strategies in diverse patient populations.^{2,3} The interventions used to reduce unnecessary RBC transfusion usually focus on adhering to lower hemoglobin (Hb) thresholds or “triggers” before initiating a transfusion.⁴ Implementation of institution-wide electronic health records (EHR) that provide clinical decision support (CDS) have been used to standardize the use of blood products.⁵ These systems have also been shown to reinforce current recommendations for blood use, reduce blood utilization, and improve safety.

Another strategy that can reduce RBC exposure is to encourage transfusing single-unit, rather than double-unit, RBC transfusions for hemodynamically stable patients who are not bleeding. This clinical scenario describes the situation in which most hematology-oncology patients require RBC transfusion. The concept of single-unit transfusions was first studied in the 1960s. Data were largely retrospective and mainly explored the perioperative period. Single-unit transfusions were associated with higher or normal pre-transfusion Hb levels and hence were deemed unjustified with minimal benefit compared to double-unit transfusions.⁶⁻⁸ These patients receiving single units would likely not have been transfused per current guidelines. Nevertheless, these beliefs heavily influenced transfusion practice toward double-unit transfusion despite the paucity of the supporting data.

There are relatively few studies examining the use of single-unit transfusions in stable patients without bleeding. In 2004, Ma et al found that adopting a single-unit transfusion policy significantly reduced RBC utilization in an orthopedic population, while achieving posttransfusion hemoglobin level targets.⁹ In 2017, another group demonstrated in a large cohort that promoting single-unit transfusions had a greater impact on RBC utilization than simply reducing Hb transfusion thresholds.¹⁰ However, there is less evidence supporting single-unit transfusions in patients with hematologic malignancies. A Swiss group showed that implementing a single-unit transfusion policy reduced the number of red cell units transfused to patients with hematologic malignancies undergoing intensive chemotherapy or hematopoietic stem cell transplantation by 25%.¹¹ More recently, Chantepie et al noted a significant reduction in the number of RBC units transfused among allogeneic hematopoietic stem cell transplant patients when a single-unit transfusion policy was implemented.¹² We altered electronic ordering protocols for patients admitted to our adult Malignant Hematology and Transplantation Service to recommend single-unit transfusions. Prior to

these changes, most patients on these inpatient services were transfused with two RBC units each transfusion episode when the Hb level fell below 8 g/dL. We studied how changes in these ordering protocols affected not only RBC utilization, but also patient outcomes. If we could show single-unit transfusions were both safe and effective, practices could be changed to further promote more judicious blood use in hematology-oncology patients.

2 | PATIENTS AND METHODS

Institutional review board approval was obtained to access patient records within the EHR. All patients were admitted to the adult (≥ 18 years old) malignant hematology ward or the bone marrow transplant unit at West Virginia University Hospital (WVUH). Consecutive patients hospitalized for diagnoses including induction or consolidation chemotherapy, autologous or allogeneic transplant, as well as a wide array of non-hematologic complications of their malignancy or treatment were eligible. Exclusion criteria included patients who were: actively bleeding, required more than 2 RBC units per day, received erythropoietin, actively hemolyzing, pregnant, had end-stage renal disease, or cirrhosis. All patients in this study received leukoreduced and irradiated products, and the study was limited to RBC transfusion.

WVUH does not have a formal patient blood management program; however, the local blood utilization committee has developed criteria for RBC transfusion in collaboration with clinicians including oncologists. Over a 4-week period, nursing administrators and malignant hematology faculty began educating providers working on the bone marrow transplant unit including physicians, mid-level, laboratory, and nursing staff on the use of single-unit transfusions. Educational methods took the format of informational poster boards, mandatory in-service computerized training, newsletter emails, and didactic sections at weekly team meetings. The computerized provider order entry system (CPOE, Epic) for blood transfusion orders was modified on September 1, 2014 to encourage single-unit transfusions (Figure 1). Providers attempting to order RBC transfusions were defaulted to a single-unit order instead of the historical double-unit transfusion. The Hb threshold remained unchanged at less than 8 g/dL. Providers could override the default order at their discretion and order more than 1 RBC unit.

Comparisons were retrospectively made between patients who received RBC transfusions from August 1, 2013 to August 31, 2014 before the CPOE system was modified (double-unit group) and those who were transfused between September 1, 2014 to August 30, 2015 after CPOE changes were implemented (single unit group) as outlined in Figure 2. A transfusion episode was defined as each instance in which either 1 or 2 RBC units were ordered. Primary objectives measured patient safety outcome indicators including median number of days per admission (length of stay), 30-day readmission rate, 30-day mortality, and the need for outpatient transfusion within 30 days of discharge. Thirty-day mortality was calculated from the day of RBC transfusion (day 0). Transfusion-related adverse events, including any complication such as fever or pulmonary edema determined by the physician to be related to the RBC transfusion, were also recorded. Secondary objectives assessed utilization metrics compared between the single- and double-unit groups including overall RBC usage, number

of RBC units transfused per admission, and the number of transfusion episodes per admission.

2.1 | Statistical analysis

Demographic and baseline clinical characteristics were analyzed using descriptive statistics. Categorical data were described using contingency tables, including counts and percentages. Continuously scaled measures were summarized by mean with standard deviation or median with range. Fisher's exact test and Wilcoxon rank sum test were used in the data analysis for categorical variables and continuous variables between two groups, respectively. A generalized linear mixed model (GLMM) was used in the data analysis for repeated measurements. GLMM handles normal and non-normal variables as well as unbalanced designs where the number of repeated measurements varies across individuals. P -values <0.05 were considered significant for all comparisons.

3 | RESULTS

With the exception of number of lines of therapy received, there were no statistically significant differences in the baseline clinical characteristics of the 147 patients (accounting for 201 admissions) in the double-unit (DU) group and the 126 patients (170 admissions) in the single-unit (SU) group eligible for the study (Table 1). This included the oncologic diagnosis, the reason for admission, and the median lines of therapy which were defined as the number of chemotherapy regimens the patient received prior to the admission analyzed. The median lines of therapy received by the double-unit group were 1 (1-6) compared the single unit group which was 1 (1-3) with $P = 0.04$.

The baseline Hb levels at admission were similar between the DU (9.5 g/dL) and the SU (9.7 g/dL) groups (Table 2). Patients in the single-unit group were transfused with less RBC units per admission than those in the double-unit group (5.1 vs 4.5, $P = 0.01$). Based on a generalized linear mixed model (GLMM), the estimated absolute mean difference of RBC transfused between the two groups is 0.83 with 95% CI (0.69, 0.99). However, patients in the single-unit group had a higher number of RBC transfusion episodes per admission than the double-unit group (4.1 vs 2.7, $P < 0.001$) and a lower increment in Hb levels per transfusion episode (0.8 vs 1.6, $P < 0.001$). The mean Hb level at discharge was slightly higher in the DU group (9.5 vs 8.9 g/dL, $P = 0.005$). Overall, total RBC utilization fell by 29% after implementing the single-unit policy (1031 vs 732 units). The number of transfusion episodes performed in accordance with the suggested threshold of Hb <8 increased from 76% to 90% after CPOE modification, which met statistical significance ($P < 0.001$). Despite the differences in discharge Hb levels, there was no increase in the 30-day readmission rates, 30-day mortality, in-hospital deaths, or the need for outpatient RBC transfusion within 30-days of discharge (Table 2). Furthermore, the length of stay was the same for both groups (median = 18 days).

4 | DISCUSSION

Patients admitted to hospitals with hematologic malignancies often develop transient bone marrow failure that requires transfusion support.¹³ Marrow failure may develop when the

primary disease occupies the bone marrow space and impairs hematopoiesis, or when the intense chemotherapy used to treat these cancers suppresses cellular production. Other factors that contribute to the development of hospital-acquired anemia in oncology patients include phlebotomy and hemodilution.¹⁴ These patients rely on transfusion support during the periods when their innate mechanisms are unable to regenerate sufficient blood cells.

Single-unit RBC transfusions were often discouraged when hemoglobin “triggers” were higher than they are today. Restrictive transfusion practices are now commonplace, and randomized trials show that these practices are safe and effective across a wide array of surgical, septic, and cardiac patients. There are less data supporting use of lower Hb thresholds in patients being treated for hematologic malignancies; however, a single-center pilot study of patients with acute leukemia receiving chemotherapy found no significant difference in fatigue, bleeding complications, or neutropenic fever in patients randomized to receive RBC transfusion at either 7 or 8 g/dL thresholds.¹⁵

Single-unit transfusions can provide adequate oxygen delivery and symptom relief for most stable patients, and single units have been promoted by the AABB Choosing Wisely Campaign as the standard transfusion option for non-bleeding patients.¹⁶ A recent study demonstrated the impact that a “Why give two when one will do” campaign had on decreasing RBC utilization at a community hospital.¹⁰ In fact, their study showed that promoting the use of single-unit transfusions as part of a patient blood management program had a greater impact on RBC utilization than a restrictive Hb transfusion threshold.

There are few studies that specifically address RBC dose in hematology patients, and there are no published guidelines for transfusion strategies for this group.¹⁷ One study of a cohort of hematology patients from Switzerland undergoing intensive chemotherapy and stem cell transplant found that RBC use could be reduced by 25% through use of single-unit transfusions without increased patient risk.¹¹ Similarly, we found that switching from a double- to a single-unit practice reduced RBC utilization by 29% without compromising safety and efficacy. Patients admitted after instituting the single-unit policy were exposed to 1 less RBC unit than those admitted when the double-unit practice was standard.

Our study adds to the existing literature by providing data assessing single-unit transfusion feasibility for patients with hematology malignancies treated in an inpatient academic setting. It also confirms that transfusion practices can be standardized for these patients by implementing specific transfusion protocols within the EHR that facilitate how practitioners order blood products. The use of as-needed or “PRN” orders for blood transfusion are generally discouraged. Our hematology-oncology service checks routine Hb levels at night and if needed, patients are transfused before morning so that they may undergo chemotherapy and other treatments during the day. The as-needed protocol order for transfusion applies only to stable inpatients.

Compliance with the ordering protocols was very high despite the ability providers had to order additional RBC units if they desired. Willingness to comply with ordering protocols has been demonstrated by others.¹¹ One possible explanation for the readiness to adopt the single-unit strategy is that providers found it easier to rationalize transfusing smaller RBC

volumes (single units) than to lower Hb thresholds for transfusion (such as reduce Hb threshold to 7.0 g/dL).

Although we did not see a decrease in transfusion reactions in the SU group, there are several potential risks of over-transfusion to which patients with hematologic malignancies are particularly susceptible. These are not limited to common allergic and febrile reactions, but also include transfusion-associated volume overload (TACO), which may be exacerbated by the chemotherapy. Iron overload may also be a concern in patients undergoing stem cell transplant. Knowing that multiple transfusions are typically required in the course of these patients, single-unit transfusions may help curtail these risks.

Limitations of this study include its longitudinal design and retrospective nature which did not allow for a true control group. A prospective randomized trial comparing single versus double transfusion in hematology is currently ongoing ([NCT02461264](#)). We recognize the broad array of diagnoses for which our patients were admitted could confound results. Given the limitations of this retrospective study, data necessary to perform a detailed multivariate analysis were unavailable. It is interesting to note that adherence to policy recommended units was higher in the double-unit group compared to the single-unit group (Table 2). However, it must also be noted that with increased education regarding transfusion utilization, a reduction in overall RBC usage may be in part due to improved compliance with the 8 g/dL threshold of transfusion. Furthermore, the double RBC transfusion group was 147 patients, and the single transfusion group was 126. The difference in sizes of the two cohorts may account for a portion of the 29% reduction in RBC units transfused.

Our study did not examine the effects concurrent thrombocytopenia can have on bleeding and worsening anemia in hematology-oncology patients.¹⁸ This study demonstrated a potential disadvantage of single-unit RBC transfusions, namely, the need for more individual transfusion episodes. This issue, which has been addressed for platelet transfusion therapy, is less of a concern in hospitalized patients who do not need to return for another transfusion; reducing RBC exposure and use is considered more important.

However, we did address the durability of the single-unit strategy by comparing the need for outpatient RBC transfusion 30-days after discharge. We found that patients receiving single units did not require outpatient transfusions more frequently than those transfused with double units. Data regarding costs were not included in the scope of this study given the significant variation in cost of transfusion administration between institutions limiting the generalizability of findings. Finally, it is important for future studies to explore quality of life differences in hematology-oncology patients because they are susceptible to debilitating fatigue and this contributes to the hesitation some providers have when ordering 1 or 2 units of RBC's.

The results of our study suggest that single-unit transfusions are safe and effective for patients with hematologic malignancies who are admitted to inpatient services. Our data show that modifying the blood ordering system to promote the use of single units when the patient's Hb is less than 8 g/dL is widely adhered to by ordering providers and such a strategy is feasible for inpatient management. As for most blood utilization efforts, success

depends on physician involvement and their commitment to changing ordering practices.^{19,20} Randomized multi-center trials are required to confirm our results. Ideally, these studies would address different Hb triggers as our study and most others have used an 8 g/dL threshold; it is unclear if outcomes would be the same if a lower Hb threshold was utilized.

REFERENCES

1. Vamvakas Eleftherios C, Blajchman MorrisA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood*. 2009;113(15):3406–3417. [PubMed: 19188662]
2. Holst LB, Petersen MW, Haase N, et al. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomized trials with meta-analysis and trial sequential analysis. *BMJ*. 2015;350:h1354. [PubMed: 25805204]
3. Hoeg RT, Leinoe EB, Andersen P, et al. Measuring the impact of a restrictive transfusion guideline in patients with acute myeloid leukemia. *Vox sang*. 2013;105(1):81–84. [PubMed: 23368963]
4. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev*. 2012;18(4):CD002042.
5. Butler CE, Noel S, Hibbs SP, et al. Implementation of a clinical decision support system improves compliance with restrictive transfusion policies in hematology patients. *Transfusion*. 2015;55(8):1964–1971. [PubMed: 25906831]
6. Reece RL, Beckett RS. Epidemiology of single-unit transfusion. A one-year experience in a community hospital. *JAMA*. 1966;195(10):801–816. [PubMed: 12608160]
7. Crispen JF. The single-unit transfusion. A continuing problem. *Pa Med*. 1966;69(1):44–48.
8. Graham-Stewart CW. A clinical survey of blood-transfusion. *Lancet (London, England)*. 1960;2(7147):421–424.
9. Ma M, Eckert K, Ralley F, Chin-Yee I. A retrospective study evaluating single-unit red blood cell transfusions in reducing allogeneic blood exposure. *Transfus Med (Oxford, England)*. 2005;15(4):307–312.
10. Yang WW, Thakkar RN, Gehrie EA, et al. Single-unit transfusions and hemoglobin trigger: relative impact on red cell utilization. *Transfusion*. 2017;57(5):1163–1170. [PubMed: 28164305]
11. Berger MD, Gerber B, Arn K, et al. Significant reduction of red blood cell transfusion requirements by changing from a double-unit to a single-unit transfusion policy in patients receiving intensive chemotherapy or stem cell transplantation. *Haematologica*. 2012;97(1):116–122. [PubMed: 21933858]
12. Chantepie SP, Mear JP, Parienti JJ, et al. Blood transfusion in hematologic intensive care unit. *Transfusion*. 2017; 57(2): 296–3417. [PubMed: 27861958]
13. Dawson MA, Avery S, McQuilten ZK, et al. Blood transfusion requirements for patients undergoing chemotherapy for acute myeloid leukemia how much is enough? *Haematologica*. 2007;92(7):996–997. [PubMed: 17606456]
14. Makam AN, Nguyen OK, Clark C, et al. Incidence, predictors, and outcomes of hospital-acquired anemia. *J Hosp Med*. 2017;5:317–322.
15. DeZern AE, Williams K, Zahurak M, et al. Red blood cell transfusion triggers in acute leukemia: a randomized pilot study. *Transfusion*. 2016;56(7):1750–1757. [PubMed: 27198129]
16. Callum JL, Waters JH, Shaz, et al. The AABB recommendations for the *Choosing Wisely* campaign of the American Board of Internal Medicine. *Transfusion*. 2014;54:2344–2352. [PubMed: 25100209]
17. Gu Y, Estcourt LJ, Doree C, et al. Comparison of a restrictive versus liberal red cell transfusion policy for patients with myelodysplasia, aplastic anemia, and other congenital bone marrow failure disorders. *Cochrane Database Syst Rev*. 2015;5(10):CD011577.
18. Savage W Implementing a blood utilization program to optimize transfusion practice. Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program. Hematology Am Soc Hematol Educ Program. 2015; 2015: 444–447. [PubMed: 26637756]

19. Shander A, Hofmann A, Ozawa S, et al. Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion*. 2010;50(4):753–765. [PubMed: 20003061]
20. Oliver JC, Griffin RL, Hannon T, et al. The success of our patient blood management program depended on an institution-wide change in transfusion practices. *Transfusion*. 2014;54(10 Pt 2): 2617–2624. [PubMed: 24410741]

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PRN TRANSFUSION OF 1 UNIT PACKED RBC'S FOR HEMOGLOBIN LESS THAN 8G/DL

Priority: Routine

Frequency: PRN

For: Occurrences

Starting: 5/23/2017 Today Tomorrow At: 1406 Show Additional Options

Starting: Today 1406 Until Specified

There are no scheduled times based on the current order parameters.

If Patient hemoglobin is: LESS THAN 8 G/DL LESS THAN (specify in comments)

Comments (F6): As needed nurse may place secondary orders for type and cross, crossmatch additional units and/or nurse transfusion order. May use transfusion order set.

Accept Cancel

FIGURE 1.
Screen used by providers to order RBC transfusion [Colour figure can be viewed at wileyonlinelibrary.com]

FIGURE 2.

Study Design. Abbreviations: PBM–patient blood management program [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1

Baseline clinical characteristics of double- and single-unit RBC transfusion groups

Characteristic	Double unit	Single unit	P-value
Patients	147	126	NA
Age, years	55 (± 15.8)	53 (± 14.6)	0.19
Male	89 (61)	65 (52)	0.14
Oncologic diagnosis (%)			
Acute myeloid leukemia	59 (40)	50 (40)	0.70
Acute lymphocytic leukemia	12 (8)	5 (4)	
Lymphoma	54 (37)	50 (40)	
Myelodysplastic syndrome	13 (9)	11 (9)	
Other hematologic malignancy	9 (6)	9 (7)	
Lines of therapy	1 (1-6)	1 (1-3)	0.04
Total admissions	201	170	
Reason for admission (%)			
Induction chemotherapy	77 (38)	52 (31)	0.13
Consolidation chemotherapy	5 (2)	6 (4)	
Autologous transplant	16 (8)	14 (8)	
Allogeneic transplant	28 (14)	27 (16)	
Neutropenic fever	48 (24)	35 (21)	
Renal/Electrolyte abnormality	7 (3)	4 (2)	
Other ^a	20 (10)	32 (19)	

NA, not applicable.

^aOther admission reasons: Seizure, nausea, delirium, pancreatitis, fracture, syncope, idiopathic pneumonia syndrome, small bowel obstruction, vaso-occlusive disease, sinus venous thrombosis, headache, anemia

TABLE 2

Utilization and clinical outcomes for double- and single-unit RBC transfusion groups

	Double unit	Single unit	<i>P</i> -values
Transfusion characteristics			
Baseline Hb (g/dL) at admission	9.5 ($\pm$ 1.7)	9.7 ($\pm$ 2.1)	0.45
Total no. RBC units transfused	1031	732	NA
RBC units transfused per admission	5.1 ($\pm$ 4.2)	4.5 ($\pm$ 4.4)	0.01
Total no. of transfusion episodes	549	614	NA
Episodes with Hb <8 g/dL pre-transfusion	407 (76)	603 (90)	<0.001
Transfusion episodes per admission	2.7 ($\pm$ 2.2)	4.1 ($\pm$ 4.0)	<0.001
Hb (g/dL) increment per transfusion episode	1.6 ($\pm$ 0.9)	0.8 ($\pm$ 0.8)	<0.001
Hb (g/dL) at discharge	9.5 ($\pm$ 1.0)	8.9 ($\pm$ 1.0)	0.005
Adherence to policy recommended units	995 (97)	667 (91)	
Patient outcomes			
Length of stay in days	18 (1-73)	18 (1-63)	0.95
30-day readmissions	70 (35)	64 (38)	0.57
Median days to readmission	13 (6)	16 (9)	
In-hospital death	9 (6)	6 (5)	
30-day mortality	16 (11)	10 (8)	0.41
Transfusion-related adverse events	4 (2)	5 (3)	0.74
Outpatient transfusions within 30-days of discharge	52 (26)	43 (25)	0.90

Hb, Hemoglobin; NA, not applicable; RBC, red blood cells.