

Optimizing Blood Transfusion Practices Through Bundled Intervention Implementation in Patients With Gynecologic Cancer Undergoing Laparotomy

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OBJECTIVE: To examine blood transfusion practices and develop a standardized bundle of interventions to address the high rate of perioperative red blood cell transfusion among patients with ovarian and endometrial cancer.

METHODS: This was a retrospective cohort study. Our primary aim was to determine whether an implemented bundled intervention was associated with a reduction in perioperative red blood cell transfusions among cases of

laparotomy for cancer. Secondary aims included comparing perioperative demographic, surgical, complication, and cost data. Interventions included blood transfusion practice standardization using American Society of Anesthesiologists guidelines, an intraoperative hemostasis checklist, standardized intraoperative fluid status communication, and evidence-based use of tranexamic acid. Prospective data from women undergoing laparotomy for ovarian or endometrial cancer from September 28, 2015, to May 31, 2016, defined the study cohort and were compared with historical controls (September 1, 2014, to September 25, 2015). Outcomes were compared in the full unadjusted cohorts and in propensity-matched cohorts.

RESULTS: In the intervention and historical cohorts, respectively, 89 and 184 women underwent laparotomy for ovarian cancer (n=74 and 152) or advanced endometrial cancer (n=15 and 32). Tranexamic acid was administered in 54 (60.7%) patients. The perioperative transfusion rate was lower for the intervention group compared with historical controls (18.0% [16/89] vs 41.3% [76/184], $P<.001$), a 56.4% reduction. This improvement in the intervention group remained significant after propensity matching (16.2% [13/80] vs 36.2% [29/80], $P=.004$). The hospital readmission rate was also lower for the intervention group compared with historical controls (1.1% [1/89] vs 12.5% [23/184], $P=.002$); however, this improvement did not attain statistical significance after propensity matching (1.2% [1/80] vs 7.5% [6/80], $P=.12$). Cost analysis demonstrated that this intervention was cost-neutral during index hospitalization plus 30-day follow-up.

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AABB, American Association of Blood Banks; ASA, American Society of Anesthesiologists.

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CONCLUSION: Application of a standardized bundle of evidence-based interventions was associated with reduced blood use in our gynecologic oncology practice.

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Prior studies have shown increased rates of perioperative complications such as venous thromboembolism and infection in patients who have received perioperative blood transfusion.^{1–3} Moreover, women with ovarian cancer who receive perioperative blood transfusion after debulking surgery have shorter recurrence-free survival.^{4,5} Following established guidelines, a more conservative approach to transfusion has emerged, allowing for continued patient safety with less use of allogeneic red blood cells.^{6–9}

Along with evidence-based blood transfusion guidelines, interventions such as the antifibrinolytic agent, tranexamic acid, may reduce blood loss. Tranexamic acid has been used in the perioperative setting across several surgical subspecialties and in some specialties is used routinely.^{10–12} Furthermore, a recent randomized, double-blind, placebo-controlled trial demonstrated that preoperative administration of tranexamic acid reduced blood loss and transfusion rates in women with advanced ovarian cancer.¹³

There is a limited number of published studies on blood transfusion reduction interventions specific to surgical gynecologic oncology.^{13–16} When assessing our institution's National Surgical Quality Improvement Program data, we discovered our perioperative blood transfusion rate was double the national average at 10.5% for all gynecologic surgery cases compared with 5.1% nationally for 2013; this rate was disproportionately affected by the high transfusion rate for patients undergoing hysterectomy for malignancy. Our aim was to examine blood transfusion practices and develop a standardized bundle of interventions to address the high rate of perioperative red blood cell transfusion among patients with open ovarian and endometrial cancer at our institution.

MATERIALS AND METHODS

This was a retrospective cohort study. We implemented a bundled intervention with the primary goal of reducing perioperative red blood cell transfusions among cases of laparotomy for cancer. Secondary aims included comparing intraoperative and postoperative outcomes, and 30-day costs of care, between the intervention cohort and a historical cohort of similar patients. Women aged 18 years or older, diagnosed with presumed or biopsy-proven ovarian,

fallopian tube, primary peritoneal, or stage III or IV or recurrent endometrial cancer undergoing surgical treatment by laparotomy between September 28, 2015, and May 31, 2016, were included in the intervention cohort. A historical cohort of women meeting the same inclusion criteria who underwent surgical treatment using laparotomy were identified from September 1, 2014, to September 25, 2015. Patients receiving neoadjuvant chemotherapy were excluded from analysis. Surgical site infection reduction and enhanced recovery algorithms were the standard of care for all patients who underwent surgery in both the intervention and historical cohorts.^{17,18}

Initial quality improvement measures leading to standardization of blood use practices were deemed not to be research by the Mayo Clinic institutional review board. Institutional review board approval was obtained for retrospective cohort comparison of the postimplementation cohort with the historical cohort. Only the medical records of patients who had previously signed a standard Minnesota Research Authorization form allowing the use of their electronic health record for research were reviewed and included in this study.

A multidisciplinary team consisting of gynecologic oncology surgeons, anesthesia providers, blood management specialists, and nursing staff collaborated on the initial quality improvement project to create an evidence-based blood management intervention bundle. Bundled blood transfusion reduction interventions were developed based on quality improvement methods such as intraoperative and postoperative cause-mapping and swim lanes, retrospective data analysis, and evidence-based chart review of patients diagnosed with presumed or biopsy-proven ovarian, fallopian tube, primary peritoneal, or advanced endometrial cancer undergoing surgical treatment through laparotomy.

The final intervention bundle included standardization of blood transfusion practices according to the American Association of Blood Banks, American Society of Anesthesiologists, an intraoperative hemostasis checklist, enhanced intraoperative fluid status communication, and evidence-based use of tranexamic acid^{7,9,13} (Boxes 1 and 2). Tranexamic acid was dosed according to Lundin et al¹³ at 15 mg/kg intravenously within 30 minutes of incision in accordance with the randomized controlled trial of tranexamic acid in patients with ovarian cancer. A hemostasis checklist was developed to ensure all surgical sites were hemostatic before closure (Fig. 1). Communication checkpoints, which consisted of nurse-initiated



Site	Hemostatic			Intervention if not hemostatic
	Yes	No	N/A	
Right:				
Cardinal pedicle				
Pelvic lymph nodes				
IP pedicle				
Peritoneal biopsy sites				
Common lymph nodes				
Para aortic lymph nodes				
Left:				
Cardinal pedicle				
Pelvic lymph nodes				
IP pedicle				
Peritoneal biopsy sites				
Common lymph nodes				
Para aortic lymph nodes				
Vaginal Cuff				
Bladder/Peritoneum				
Sacrum				
Sigmoid colon				
Colon resection/reanastomosis				
Small bowel resection/reanastomosis				
Mesenteric biopsies				
Omentum				
Splenic flexure				
Hepatic flexure				
Liver				
Spleen				
Right diaphragm				
Left diaphragm				

Figure 1. Intraoperative hemostasis checklist included in the intervention bundle. N/A, not applicable; IP, infundibulopelvic.

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communication to verbalize the point in the procedure and patient status with each 500 mL of fluid collected in a suction canister, were developed to increase awareness of fluid and patient status for all individuals in the operating room. In hemodynamically stable patients, transfusion was guided by hemoglobin level and one unit of packed red blood cells at a time was the standardized transfusion practice.

Pertinent data on demographics, medical history, surgical characteristics, and outcomes were abstracted from the medical records by the first author and entered into a Research Electronic Data Capture web-based application designed for this specific study.

Current tobacco use was defined as use within 3 months of the surgical date, length of stay was calculated using the day of surgery as day 0, perioperative red blood cell transfusion was defined as intraoperative if administered after surgical incision and before discharge from the postanesthesia care unit, and postoperative if administered after discharge from the postanesthesia care unit through 48 hours postoperatively.

With a sample size of 89 patients in the intervention cohort and an estimated 180 patients in the historical cohort, the study had 93% power to detect a 30% decrease in the primary outcome, perioperative

Box 1. Intervention Bundle for Blood Transfusion Reduction

1. Standardization of blood transfusion practices according to vetted institutional guidelines, including those from the AABB and ASA^{7,9}
2. Intraoperative hemostasis checklist performed before closure
3. Standardized intraoperative fluid status communication at every 500 mL of fluid in the suction canister
4. Evidence-based use of tranexamic acid (15 mg/kg within 30 minutes of incision)¹³

Box 2. Blood Transfusion Guidelines^{7,9}

1. Active bleeding with cardiovascular instability
2. Hemoglobin 7 g/dL or less
3. Hemoglobin 8 g/dL or less in a patient who has stable coronary artery disease, evidence of end-organ ischemia, acute brain injury, or symptoms thought to be related to anemia (hypotension unresponsive to fluid resuscitation, unexplained tachycardia unresponsive to fluid resuscitation, cardiac chest pain, congestive heart failure)
4. Hemoglobin ranging from 8–10 g/dL in a patient who has evidence of acute coronary syndrome



red blood cell transfusion rate (ie, 40% vs 20%), based on a two-sided χ^2 test with type I error level of 0.05. A sequential statistical stopping rule was established to ensure the safety of tranexamic acid use in the intervention cohort with respect to venous thromboembolism events within 30 days after surgery. The stopping rule was calculated using the sequential probability ratio test with a type I error of 5% and 85% power, assuming a 30-day venous thromboembolism rate of 3% and a maximum tolerated rate of 10%. The stopping rule stipulated that use of the bundled intervention would be stopped if three patients experienced a venous thromboembolism among the first 18 patients, or four among the first 31 patients, or five among the first 44 patients, and so on.

To account for potential differences in the study groups from observed confounders, propensity score matching was used, which enables construction of intervention and control cohorts that are similar in terms of their baseline clinical and other characteristics.¹⁹ Logistic regression that models the propensity (probability) of receiving the intervention was used to estimate the propensity scores. Potential confounders included in the logistic model were patient residency location (local, regional, national, international), age, tobacco use, clinical diagnosis, cancer stage, insurance status, body mass index, and count of Elixhauser comorbidities.²⁰ Intervention and historical controls were matched on the propensity scores using nearest neighbor one-to-one matching without replacement. In both the full unadjusted cohort and the propensity-matched cohorts, comparisons of surgical and postoperative outcomes between the two groups were evaluated using the χ^2 or Fisher exact test for nominal variables and the two-sample *t* test or Wilcoxon rank-sum test for continuous variables.

Cost analyses were performed on the propensity-matched cohorts using standardized cost data from the Mayo Clinic Cost Data Warehouse.²¹ This database applies a standardized costing method using a bottom-up costing approach, which allows costs each of the billed services. Costs of hospital services are valued by multiplying billed charges by department-level cost-to-charge ratios as determined by the Medicare cost reports. Professional services are valued using the Medicare Fee Schedules. All costs were inflated to 2016 U.S. dollars using the Gross Domestic Product Implicit Price Deflator.²² Cost outcomes included the index hospitalization plus 30-day postdischarge. To account for the skewness found in the cost data, we used generalized linear modeling with the γ distribution to compare costs between the historical and intervention cohorts; the model was also adjusted for

confounders with residual imbalance, which propensity score matching could not adjust.²³ For analyzing the 30-day postdischarge follow-up costs, two-part modeling was used to account for potential patients incurring zero costs in the follow-up period. The first part of this analysis used logistic regression to model the probability of having positive costs; the second part used the generalized linear model described previously. Statistical differences in costs of the two study cohorts were determined using 95% CIs of the difference in mean costs. Propensity score matching and all statistical analyses on cost outcomes were performed in Stata 14.0.

RESULTS

We compared 89 women in the intervention cohort (September 28, 2015–May 31, 2016) with a historical cohort of 184 women (September 1, 2014–September 25, 2015). There was no difference in demographic variables among those in the intervention cohort and the historical cohort (Table 1; all *P* values >.05). In the intervention and historical cohorts, respectively, 89 and 184 women underwent laparotomy for ovarian cancer (n=74 and 152) or advanced endometrial cancer (n=15 and 32). Propensity matching resulted in 80 intervention patients being matched to 80 historical controls. Standardized differences indicate that the measured patient and clinical characteristics between the intervention and control cohorts were all well balanced after propensity matching with standardized differences less than the recommended threshold of 0.10 for all of the characteristics except the Elixhauser comorbidity count and regional residency (Table 1). Tranexamic acid was administered in 54 (60.7%) patients in the intervention group; only one patient developed a venous thromboembolism; therefore, the statistical stopping rule for venous thromboembolism was not reached.

The rate of perioperative blood transfusion was 41.3% (76/184, 95% CI 34.2–48.4%) in the historical cohort compared with 18.0% (16/89, 95% CI 10.0–26.0%) in the intervention cohort, a 56.4% transfusion reduction (*P*<.001; Table 2). This improvement in the intervention cohort remained significant after propensity matching (36.2% [29/80] vs 16.2% [13/80], *P*=.004; Table 2). This reduction was driven mostly by the decreased rate of intraoperative blood transfusion of 35% in the historical cohort compared with 15% in the intervention cohort after propensity matching (*P*=.004; Table 2). There was no difference in postoperative transfusion rates (Table 2).

The transfusion rate among women with ovarian cancer was 40.8% (62/152, 95% CI 33.0–48.6%) in the



Table 1. Comparison of Baseline Characteristics Between the Historical and Intervention Cohorts

Characteristic	Full Unadjusted Cohorts			Propensity-Matched Cohorts		
	Historical (n=184)	Intervention (n=89)	Standardized Difference*	Historical (n=80)	Intervention (n=80)	Standardized Difference*
Age at surgery (y)	62.4±12.4	64.0±11.6	0.132	64.0±13.1	64.4±12.0	0.030
BMI (kg/m ²)	28.7±7.7	29.2±7.9	0.064	28.8±8.4	29.6±7.8	0.098
Elixhauser comorbidity count	2.3±1.7	2.2±1.7	0.030	2.2±1.8	2.4±1.6	0.11
Current tobacco use	13 (7.1)	12 (13.5)	0.213	9 (11.3)	7 (8.8)	0.083
Diagnosis						
Ovarian cancer	152 (82.6)	74 (83.1)	0.014	64 (80.0)	66 (82.5)	0.064
Endometrial cancer	32 (17.4)	15 (16.9)		16 (20.0)	14 (17.5)	
Stage						
I–II	31 (16.8)	15 (16.9)	0.000	15 (18.8)	14 (17.5)	0.032
III–IV	107 (58.2)	46 (51.7)	0.130	40 (50.0)	40 (50.0)	0.000
Recurrent	46 (25.0)	28 (31.5)	0.144	25 (31.3)	26 (32.5)	0.027
Residency [†]						
Local	24 (13.2)	13 (15.3)	0.060	10 (12.5)	12 (15.0)	0.070
Regional	70 (38.5)	35 (41.2)	0.060	37 (46.3)	33 (41.3)	0.100
National	84 (70.6)	35 (41.2)	0.100	31 (38.8)	33 (41.3)	0.050
International [‡]	4 (2.2)	2 (2.4)	0.010	2 (2.5)	2 (2.5)	0.000
Insurance status [‡]						
Government	87 (47.8)	43 (50.6)	0.060	45 (56.3)	43 (53.8)	0.050
Private	94 (51.7)	41 (48.2)	0.070	34 (42.5)	36 (45.0)	0.050
Self-pay	1 (0.6)	1 (1.2)	0.070	1 (1.3)	1 (1.3)	0.000

BMI, body mass index.

Data are mean±SD or n (%) unless otherwise specified.

* Covariate imbalance between the historical and intervention groups was assessed by evaluating the standardized difference for each baseline covariate separately in the full unadjusted cohorts and in the propensity-matched cohorts. The standardized difference for a continuous covariate is defined as the absolute difference in surgical group means divided by an estimate of the pooled SD. The derivation is similar for nominal covariates. A standardized difference less than 0.10 is considered by some authors to denote negligible covariate imbalance between groups.

† Data available for 182 of 184 in the historical cohort and 85 of 89 in the intervention cohort.

historical cohort compared with 16.2% (12/74, 95% CI 7.8–24.6%) in the intervention cohort, a 60.3% transfusion reduction ($P<.001$). After propensity score matching, the difference in transfusion rate remained significantly reduced in the intervention cohort (36.5% vs 15.4%, $P=.014$). In contrast, the reduction in transfusion rate for the smaller group of women with endometrial cancer did not reach statistical significance (26.7% [4/15, 95% CI 4.3–49.1%] vs 43.8% [14/32, 95% CI 26.6–60.9%, $P=.26$] in the full unadjusted cohorts).

When comparing surgical variables, in addition to the reduced blood transfusion rates, there was a statistically significant reduction in median estimated blood loss from 500 to 300 mL ($P=.009$) and mean operative time from 279.3 to 241.7 minutes ($P=.01$) in the historical and intervention cohorts, respectively (Table 2). This improvement in the intervention cohort remained significant after propensity matching (Table 2).

When comparing postoperative complications between the historical and intervention cohorts,

there was a significant reduction in hospital readmission rates in the intervention cohort (12.5% [23/184] vs 1.1% [1/89], $P=.002$); however, this reduction did not attain statistical significance after propensity matching (7.5% [6/80] vs 1.2% [1/80], $P=.12$). There were no other significant differences in postoperative complication variables between the two groups (Table 2).

Cost analysis data in the propensity-matched cohorts showed no difference in overall costs, defined as index hospitalization with 30-day follow-up, between the historical and intervention cohorts (Table 3). Total mean cost was \$30,168.94 in the historical cohort and \$32,737.39 in the intervention cohort (95% CI for difference in means $-\$1,361$ to $\$6,498$, $P=.2$).

DISCUSSION

In this investigation, we demonstrate that implementation of standardized blood transfusion practices, an



Table 2. Comparison of Intraoperative and Postoperative Outcomes Between the Historical and Intervention Cohorts

Outcome	Full Unadjusted Cohorts			Propensity-Matched Cohorts		
	Historical (n=184)	Intervention (n=89)	P*	Historical (n=80)	Intervention (n=80)	P*
Transfusion rate						
Intraoperative	70 (38.0)	14 (15.7)	<.001	28 (35.0)	12 (15.0)	.004
Postoperative	16 (8.7)	4 (4.5)	.21	3 (3.8)	3 (3.8)	1.00
Perioperative	76 (41.3)	16 (18.0)	<.001	29 (36.2)	13 (16.2)	.004
EBL (mL)	500 (250–800)	300 (200–600)	.009	450 (250–750)	300 (200–500)	.021
Operative time (min)	279.3±118.6	241.7±105.6	.01	264.6±116.4	234.4±105.9	.09
Length of stay (d)	4 (3–6)	4 (3–6)	.87	4 (3–6)	4 (3–6)	.66
Postoperative complications within 30 d						
Venous thromboembolism	3 (1.6)	1 (1.1)	1.00	1 (1.2)	1 (1.2)	1.00
Readmission	23 (12.5)	1 (1.1)	.002	6 (7.5)	1 (1.2)	.12
Reoperation	8 (4.3)	0	.057	2 (2.5)	0	.50
Infection						
Pulmonary	6 (3.3)	2 (2.2)	1.00	3 (3.8)	1 (1.2)	.62
Sepsis	8 (4.3)	0	.057	1 (1.2)	0	1.00
Wound or pelvic abscess	11 (6.0)	4 (4.5)	.78	2 (2.5)	4 (5.0)	.68
Unplanned ICU admittance	6 (3.3)	0	.18	3 (3.8)	0	.25
Other [†]	3 (1.6)	0	.55	1 (1.2)	0	1.00

EBL, estimated blood loss; ICU, intensive care unit.

Data are n (%), median (interquartile range), or mean±SD unless otherwise specified.

* Comparisons between groups were evaluated using the χ^2 or Fisher exact test for nominal variables, the two-sample *t* test for operative time, and the Wilcoxon rank-sum test for estimated blood loss and length of stay.

[†] Three patients in the historical cohort had a postoperative anastomosis leak (n=1), postoperative perforation and anastomosis leak (n=1), and a small bowel obstruction (n=1), respectively.

intraoperative hemostasis checklist, enhanced intraoperative fluid status communication, and evidence-based use of tranexamic acid was associated with reduced blood loss and red blood cell transfusion rates for patients undergoing laparotomy for ovarian or advanced endometrial cancer. This reduction is clinically important given that perioperative blood transfusion carries well-described risks and negative outcomes.^{16,24} Although a bundled approach focused on reducing blood transfusion in patients with gynecologic cancer has not been previously reported, our findings are consistent with those published in previous studies showing the efficacy of tranexamic acid and standardized blood transfusion guidelines.^{7,13}

Table 3. Comparison of Total Costs During Index Hospitalization Plus 30-Day Follow-up Between Propensity-Matched Historical and Intervention Cohorts

	Mean	95% CI	P
Historical	\$30,168.94	\$27,693.93–32,643.95	
Intervention	\$32,737.39	\$29,473.72–36,001.07	
Difference	\$2,568.45	–\$1,361.27 to 6,498.17	.200

Prior studies have shown increased rates of perioperative complications and shorter recurrence-free survival for patients with ovarian cancer who received perioperative blood transfusions, whereas decreasing rates of red blood cell transfusion had a positive effect on perioperative outcomes.^{1,2,4,25} Similarly, our reduction in blood transfusion was associated with a significant decrease in postoperative hospital readmission rates and a trend toward decreased reoperation rates and sepsis in the intervention group.^{1,2,26} Additionally, the intervention had no effect on overall costs and was associated with a reduction in readmission rates.

One particular element of the bundle, tranexamic acid, deserves additional discussion. Tranexamic acid has been well studied and is currently used to aid in the reduction of blood loss and transfusion in orthopedic, urologic, trauma, and other surgical specialties.^{10–12} Prior studies in the population of patients with gynecologic cancer have shown similar success in transfusion practices with tranexamic acid. In 2006, Celebi et al¹⁵ compared tranexamic acid with colloid, crystalloid, and ϵ -aminocaproic acid in patients undergoing laparotomy for cervical cancer in a prospective,



double-blind randomized trial. Women who received 10 mg/kg tranexamic acid had statistically significant reductions in blood loss as high as 33.3%. More recently, Lundin et al¹³ published the results of a randomized, double-blind, placebo-controlled trial, which demonstrated that a single dose of preoperative tranexamic acid at 15 mg/kg intravenously significantly reduced both blood loss and blood transfusion rates in women undergoing surgery for advanced-stage ovarian cancer. Preoperative administration of tranexamic acid did not result in an increase in adverse events, including venous thromboembolism, in our study. Prior studies support the safety of tranexamic acid among women appropriately triaged and screened for contraindications to the medication.²⁷

Limitations include the retrospective nature of historical data collection with the usual biases of observational, single-institution research. Of note, however, our bundled intervention cohort variables were prospectively collected, which aids in reducing overall bias and adds consistency to postintervention data collection; propensity score matching was performed to reduce confounding. Another potential limitation is that a separate quality improvement effort to reduce anastomotic leaks was underway at our institution between July 2013 and January 2016. Because this interval overlaps with our intervention bundle for approximately 3 months, the potential exists for a confounding effect and this could have contributed to the reduced complication rates.²⁸ In contrast, enhanced recovery and surgical site infection reduction initiatives had already been standardized in our division for both the historical and intervention timeframes, making these initiatives an unlikely source of confounding.^{17,18} Although bundled interventions are clinically effective, it is not possible to discern whether one measure of the bundle is more efficacious, because all measures were implemented simultaneously. Similarly, our findings include data from both patients with ovarian cancer and those with endometrial cancer, and our study was not powered to provide results on these diagnoses individually. Although all surgeons at our institution agreed with the use of tranexamic acid, in certain scenarios, its use was deemed unnecessary such as low likelihood of proceeding with debulking; therefore, tranexamic acid was not administered to all patients as a result of the health care provider's preference or contraindication. Finally, because this study was found to be cost-neutral, it is possible that other factors in the 30-day postdischarge timeframe negated any cost savings in the intervention group.

We found that application of a standardized bundle of evidence-based interventions was associated with reduced blood use and estimated blood loss in patients undergoing laparotomy for ovarian cancer and advanced or recurrent endometrial cancer. This is clinically important, because reducing blood loss and blood transfusions should translate to reduced risks of the short- and long-term untoward outcomes associated with transfusion. The transfusion reduction bundle can be used by other institutions to standardize blood transfusion practices and reduce blood loss and transfusion rates.

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