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The Effect of Antifibrinolytic Use on Intraoperative Cell Salvage: Results from a National Registry of Surgical Procedures

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Abstract: Intraoperative cell salvage (ICS) is a critical component of any blood management program involving surgery with a high potential for blood loss. The introduction of antifibrinolytics (AF) may reduce blood loss. The purpose of this study was to evaluate the use of AF on ICS in non-cardiac surgical procedures. Following institutional review board approval, 69,935 consecutive case records between January 2016 and September 2019 from a national registry of adult surgical patients were reviewed. Procedure types were stratified into one of nine surgical categories: general (GN, n = 1,525), neurosurgical (NS, n = 479), obstetric (OB, n = 1,563), cervical spine (CS, n = 2,701), lumbar spine (LS, n = 38,383), hip arthroplasty (HA, n = 13,327), knee arthroplasty (KA, n = 596), vascular (VA, n = 9,845), or orthopedic other (OO, n = 1,516). The primary endpoint was the use of AF with the secondary endpoints ICS shed blood volume and volume available for return. The overall use of AF across all surgical procedures increased from 21.4% in 2016 to 25.4% in 2019. The greatest increases were seen in NS (4.4% to 16.2%), LS (13.7% to 23.1%), and HA (55.8% to 61.9%). For several procedure types, there was an initial increase then either a leveling off or a decline in AF use: OB initially increased from 6.2% to 10.8% in 2018, whereas GN (9.4% to 7.2%) and VA surgery declined slightly (9.9% to 5.7%). When comparing patients who did not receive AF with those who did, there were similar volumes of ICS available for return in all groups, except for LS, GN, and VA, where lower volumes were seen in the No-AF groups. The use of AF has increased each year over the 4-year period in most of the surgical categories, but several have declined. There may be a beneficial effect of AF with lower ICS volumes available for return in a few groups. **Keywords:** surgery, antifibrinolytics, intraoperative cell salvage. *J Extra Corpor Technol. 2020;52:182–90*

The use of intraoperative cell salvage (ICS) is widely applied in surgical procedures where the potential for the loss of blood could induce anemia or result in a high likelihood for the transfusion of allogeneic red blood cells (RBCs). Although this modality has been found to be effective in patients undergoing cardiac surgery and received a high level of recommendation (class I, level of evidence A) (1), its benefits in non-cardiac surgeries are less well established. It is generally accepted that the use of ICS should be considered in high-risk surgeries where volumes of blood loss (>1,000 mL) are anticipated (2). How ever this recommendation does not address patient-specific concerns where allogeneic RBC transfusion is not an option. Another issue affecting the decision to the use of ICS is predicting what surgical procedures would have sufficient volume of blood loss to justify a cost–benefit value both for the patient and healthcare provider (3–6).

Although the use of antifibrinolytics (AF) in cardiac surgery as a blood conservation measure has been well established, it is only more recently that they have been applied in non-cardiac surgical settings. The primary category of AF is lysine analogues, and the most commonly used medications are epsilon aminocaproic acid and tranexamic acid (TXA). The mechanism of action of AF is to

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inhibit fibrinolysis by interfering with plasminogen activators and stopping plasmin formation, which stabilizes the polymerized fibrin clot and enhances hemostasis (7). Although there have been reports demonstrating the benefits of AF in non-cardiac settings (8–11), it is generally unknown what the impact of these medications is on a more global scale. Furthermore, there are concerns regarding their safety in off-label applications, and a number of reports have appeared on potentially harmful side effects, especially for an increased risk of seizures, hypotension, cardiac arrhythmias, rhabdomyolysis, thrombosis, and renal dysfunction (12,13). One means of assessing their impact is to study the utilization of ICS in surgical procedures where AF may have been applied. Therefore, the purpose of this study was to review the impact of AF on ICS over the past several years in non-cardiac surgical procedures and the impact on collected volumes of shed blood.

METHODS

Consecutive surgical procedure ICS data from the SpecialtyCare Operative Procedure rEgistry (SCOPE™), between January 2016 and September 2019 at 215 hospitals throughout the United States, were reviewed. The SCOPE was established in 2011 as a national quality control process for systematically collecting intraoperative data from surgical procedures and has been described elsewhere (14,15). It serves a multifunctional purpose focused on quality enhancement and performance improvement. It was designed to achieve the following goals: standardization of electronic data recording of specific perioperative quality indicators, creation of reporting tools including dashboards and written reports, and benchmarking of performance at multiple levels including the clinician, the hospital, and geographical region. The system uses proprietary software application[1] that records demographic and operative data for every procedure. Institutional ethics review board approval[2] was obtained for the use of data from the SCOPE.

Study Design

All surgical patients older than 18 years who underwent a procedure where ICS was used were included. National policies and procedures on ICS were established using a best-available evidence approach and distributed to all facilities, which were used to guide the conduct of cell salvage. Only hospitals that were actively performing ICS with surgery from the start of the study time period through the end were included. Patients were excluded from the analysis if they did not have ICS or had missing information on the use of AF, did not have all required quality indicators recorded, or had missing ICS data (Figure 1). All ICS devices were set up and used according to the manufacturer's instructions for use, and the conduct of the cell salvage process was conducted by following national clinical practice guidelines.[3] An attending autotransfusionist (either a perfusionist or an autotransfusion technician) decided what make and model of ICS device to use and selected an appropriate bowl size to match the anticipated blood loss. The decision to use a specific device was made locally by the attending autotransfusionist. A complete list of ICS devices is shown in Appendix 1.

Study Groups

Surgical cases where ICS was used were stratified by procedure type as follows: general (GN), neurosurgery (NS), obstetric (OB), cervical spine (CS), lumbar spine (LS), hip arthroplasty (HA), knee arthroplasty (KA), vascular (VA), or orthopedic other (OO). Groups were established as either receiving intravenous AF or not (No-AF). Further separation was performed based on whether cases were a first operation or a reoperation. Reoperation categorization did not distinguish how many surgical procedures a single patient may have received.

Endpoints

The primary endpoint was the use of AF with the secondary endpoints such as ICS shed blood volume and volume available for return.

Statistical Analysis

Descriptive statistics were calculated as count and percentage for categorical variables, mean and SD for continuous and normally distributed variables, or median and interquartile range (IQR) for heavily skewed continuous variables. Unadjusted group differences were assessed using chi-squared tests, Welch's ANOVA, and the Kruskal–Wallis rank-sum test, respectively (16–18).

RESULTS

From January 2016 through September 2019, a total of 69,935 ICS procedures from 215 hospitals were included in the analysis, with 25.7% of these receiving AF. The overall use of AF increased across all surgical procedures from 21.4% in 2016 to 25.4% in 2019 (Figure 2). The greatest increase occurred from 2017 to 2018 (24.5% to 28.1%), whereas in the most recent years, the use is declining (28.1% to 25.4%). Within procedure types, the most prominent changes in AF use were seen in NS (4.4% to 16.2%), LS (13.7% to 23.1%), and HA (55.8% to 61.9%) (Table 1). For

[1]Case Documentation System, SpecialtyCare, Nashville, TN.
[2]Protocol #012017, ADVARRA Center for IRB Intelligence, 6940 Columbia Gateway Drive, Suite 110, Columbia, MD, 21046.

[3]Clinical Quality Service Manual on Autotransfusion, SpecialtyCare, Brentwood, TN.

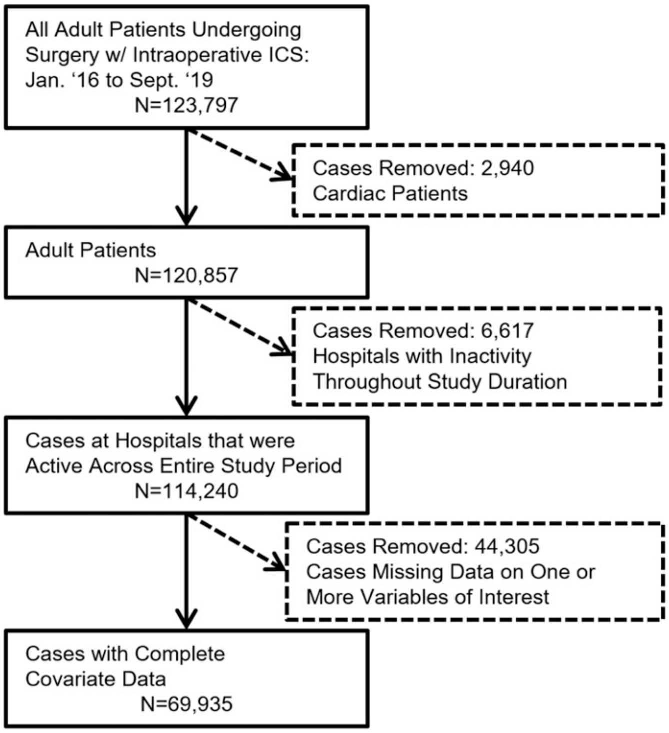

Figure 1. Patient flow diagram outlining recruitment and final enrolment. ICS, intraoperative cell salvage.

several procedure types, there was an initial increase, then either a leveling off or a decline in AF use: OB initially increased from 6.2% to 10.8% in 2018, whereas GN (9.4% to 7.2%) and VA surgery declined slightly (9.9% to 5.7%).

When examining the trends in the use of AF with ICS, there was a steady consistent increase in the use of both modalities from 2016 through 2018, then a 12.6% decline over the most recent year for non-reoperative patients (Figure 3). There was a slightly higher use of AF in reoperations than first-time surgeries (13.3% vs. 12.1%, $p < .001$). For reoperations, there was an initial 32.5% increase in AF use from 2016 through 2017, then a yearly 50% reduction in growth for the last 2 years. When examining the effect of reoperation status within procedure groups, there was a trend toward higher use in NS, CS, KA, and OO, whereas in the remaining groups, there were similar trend lines for non-reoperations and reoperations (Figure 4).

Demographic data and total ICS volumes are shown in Table 2. More female patients received AF which also was seen in patients with slightly lower body surface areas (BSA). The AF group had greater volumes of shed blood, volume available for return, and estimated blood loss. An ICS-limited procedure is one where the autotransfusion circuit was modified to contain a cardiotomy reservoir and aspiration set. These were used in situations where the anticipated blood loss was not expected to exceed 400–500 mL which was an estimate of the volume required to process and return one unit of washed cells. There was no difference in the percent of limited procedures between groups. Table 3 shows the use of AF by procedure type and the amount of ICS volume available for return. For all procedure types, the number of No-AF cases was higher than AF cases, except for HA. In all procedure types, the amount of ICS volume available for return was higher in the AF group. When comparing patients who did not receive AF with those who did, there were similar volumes of ICS available for return in all groups, except for LS, GN, and VA, where lower volumes were seen in the No-AF groups (5).

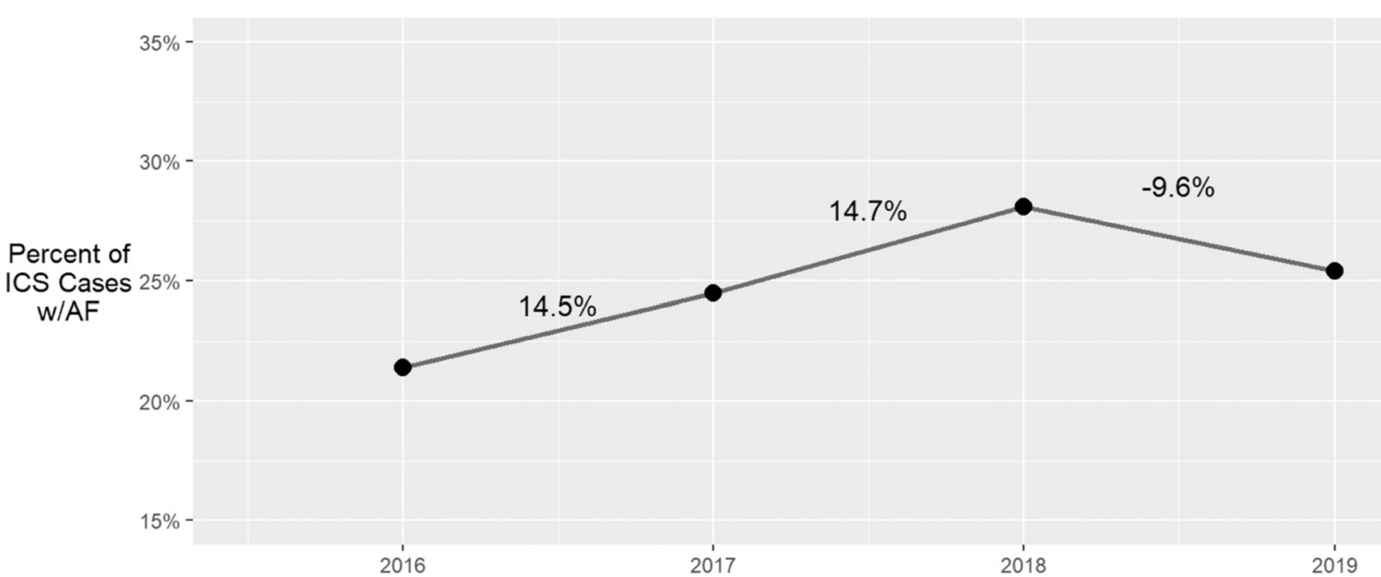

Figure 2. Trend analysis in the use of AF over the study period. The number represents the percent of cases where AF had been used. AF, antifibrinolytic; ICS, intraoperative cell salvage.

Table 1. Change in AF use by procedure type over the study period.

	2016 (%)	2017 (%)	2018 (%)	2019 (%)	% Change 2016–2019
CS	12.4	12.9	17.3	13.0	4.8
GN	9.4	7.10	10.5	7.2	−23.4
Hip	55.8	60.7	63.8	61.9	10.9
Knee	28.6	36.6	32.6	28.8	.7
Lumbar	13.7	17.6	22.1	23.1	68.6
Neurosurgery	4.4	19.2	27.0	16.2	268.2
OB	6.2	8.3	10.8	6.8	9.7
Ortho other	18.4	20.2	27.4	23.0	25.0
VA	9.9	9.1	9.40	5.7	−42.4

The median and interquartile values for both shed blood volume and volume available for return are shown using box plots depicted in Figures 5 and 6. Median values for shed blood greater than 250 mL in the No-AF groups were seen in the procedure types NS, GN, HA, LS, OO, and VA, with all, but the OO group, having higher median values when AF were used.

DISCUSSION

Blood conservation programs have long realized the benefit of using ICS as a modality to reduce allogeneic RBC transfusion during surgical procedures where the risk of blood loss is high (19,20). In addition, the quality of salvaged autologous blood obtained through ICS is higher than that of traditional banked blood which may have deteriorated because of time in storage and loss of RBC deformability (21). Other risks associated with allogeneic RBC transfusion include the risk of transmissible factors associated with disease and result in RBC alloimmunization (22). The use of AF outside of cardiac surgery has grown dramatically over the past decade which was more than likely influenced by the positive results in reducing blood loss and lowering RBC transfusions in cardiac surgical patients (1,7).

Although ICS offers an alternative to allogeneic RBC transfusion, its utility is enhanced in those procedures where the volume of shed blood is relatively high. Although some classifications of surgery have a greater likelihood to experience high-volume surgical bleeding (trauma, cardiac, neurosurgery, and VA), others may experience episodic procedures without a consistent volume loss (19,23). The use of ICS has been shown to be safe and effective in various procedure types where large volumes of blood loss are not routinely expected. These include neurosurgery (24), OB (13,25) spine surgery (5), and various orthopedic procedures (22,26). However, there may be certain situations where the use of this ICS should be considered, despite a low or moderate expected blood loss volumes. In addition, patients who for religious reasons chose not to accept donor blood transfusions or who have various antibodies to elements of blood, or who choose not to receive a transfusion for personal reasons may all benefit from ICS. Nevertheless, the use of ICS is equivocal, and several randomized clinical

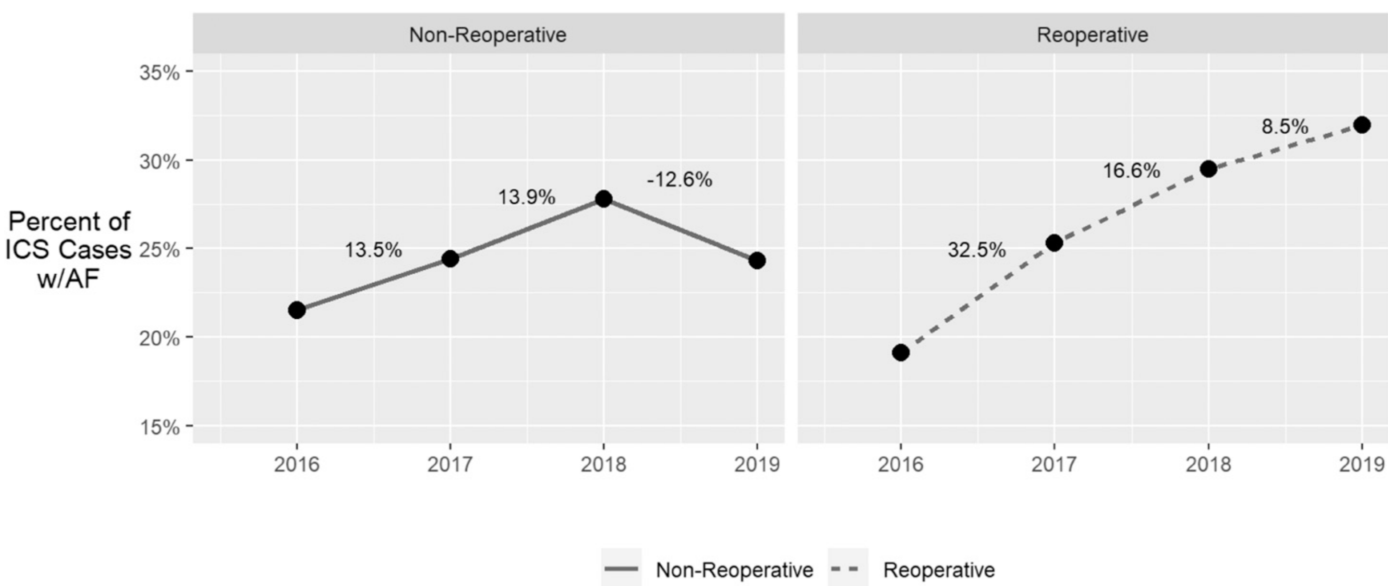

Figure 3. Case distribution of the use of AF and ICS in both first-time operations and in reoperations. The number represents the percent of cases where AF had been used. AF, antifibrinolytic; ICS, intraoperative cell salvage.

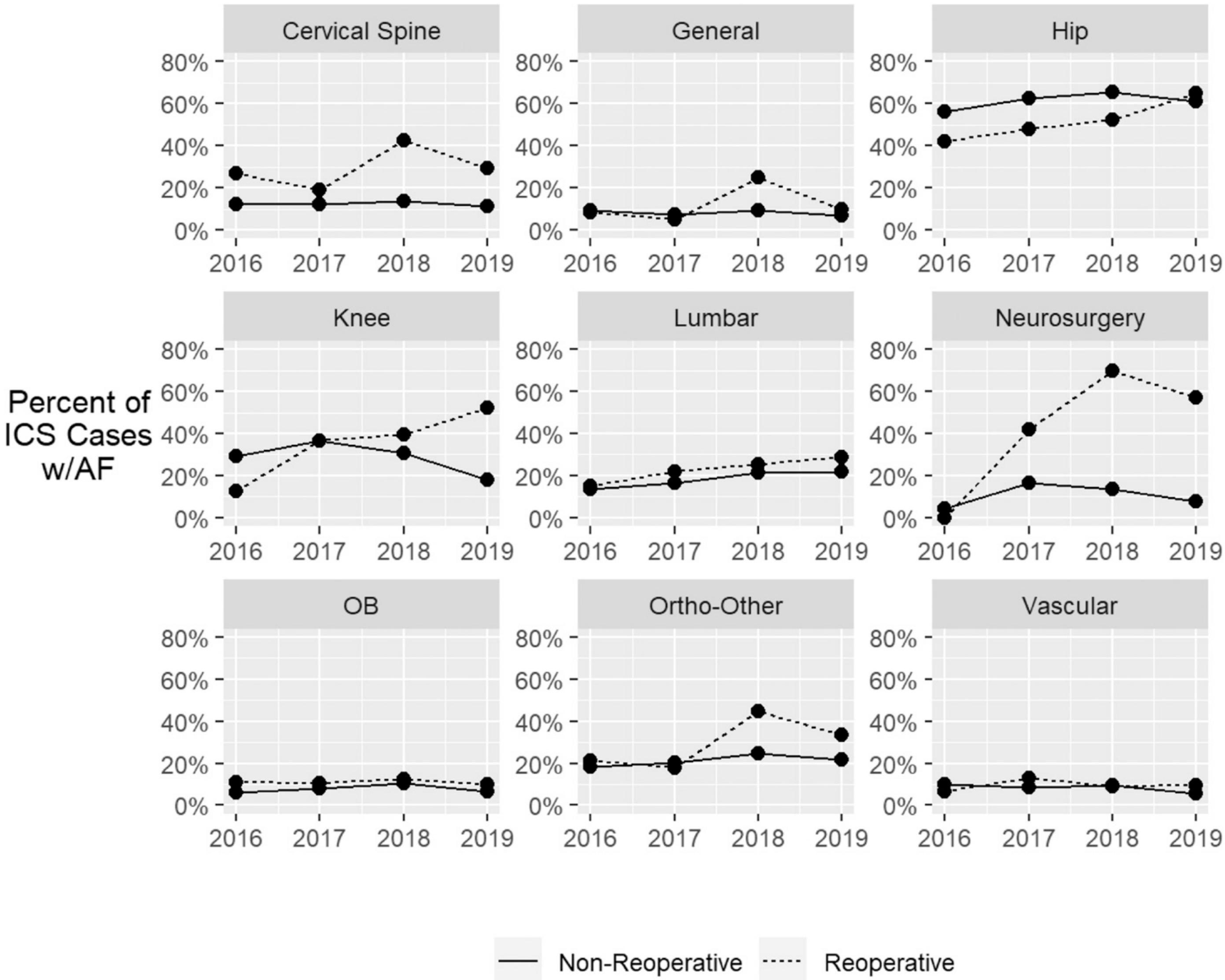

Figure 4. Yearly change in the use of combined AF and ICS use by procedure type and operative state. AF, antifibrinolytic; ICS, intraoperative cell salvage; OB, obstetrics.

trials and meta-analyses have raised concerns about its benefits in reducing RBC transfusions in diverse surgeries, such as abdominal VA (3), total hip or knee arthroplasties (6,27), and pediatric spine surgery (28). Several of the reasons for the failure of ICS to affect outcomes include variation in surgical and anesthetic techniques, lesion complexity, techniques of ICS, or small volumes of blood recovered. Furthermore, it is not inconceivable with the heightened awareness of blood

Table 2. ICS volume available for return by AF use.

	No-AF	AF	*p* Value
Number (count [%])	51,954 (74.3)	17,981 (25.7)	–
Age, years (median [IQR])	63.0 (52.0, 71.0)	63.0 (52.0, 71.0)	<.0001
Gender, female (count [%])	26,338 (50.7)	10,086 (56.1)	<.001
BSA (median [IQR])	1.95 (1.77, 2.14)	1.92 (1.73, 2.12)	<.001
Reoperation (count [%])	6,280 (12.1)	2,383 (13.3)	<.001
ICS limited (count [%])	1,927 (3.7)	671 (3.7)	.908
Shed blood volume (median [IQR])	877.0 (300.0, 1,600.0)	986.0 (550.0, 1,550.0)	<.001
Volume available for return (median [IQR])	124.0 (.0, 250.0)	125.0 (.0, 250.0)	<.001
Estimated blood loss (median [IQR])	300.0 (110.0, 600.0)	300.0 (200.0, 600.0)	<.001

AF, antifibrinolytic; BSA, body surface area; ICS, intraoperative cell salvage; IQR, interquartile range.

Table 3. ICS volume available for return by AF use and procedure type.

	No-AF	AF	*p* Value
Number (count %)	51,954 (74.3)	17,981 (25.7)	–
GN			
median (IQR)	233.0 (.0, 675.0)	250.0 (.0, 750.0)	<.001
count (%)	1,388	137	–
Neurosurgery			
median (IQR)	137.5 (.0, 290.0)	200 (125.0, 375.0)	<.001
count (%)	392	87	–
OB			
median (IQR)	.0 (.0, 225.0)	.0 (.0, 233.8)	<.001
count (%)	1,417	146	–
CS			
median (IQR)	.0 (.0, 125.0)	.0 (.0, 140.0)	<.001
count (%)	2,250	451	–
Hip arthroplasty			
median (IQR)	121.0 (.0, 225.0)	125.0 (.0, 230.0)	<.001
count (%)	5,074	8,253	–
Knee arthroplasty			
median (IQR)	.0 (.0, 125.0)	.0 (.0, 125.0)	<.001
count (%)	394	202	–
Lumbar spine			
median (IQR)	117.0 (.0, 225.0)	125.0 (.0, 250.0)	<.001
count (%)	30,888	7,495	–
Ortho other			
median (IQR)	118.0 (.0, 235.5)	125.0 (.0, 225.0)	<.001
count (%)	1,167	349	–
VA			
median (IQR)	185.0 (.0, 468.3)	225.0 (.0, 550.0)	<.001
count (%)	8,984	861	–

AF, antifibrinolytic; IQR, interquartile range; OB, obstetrics; Ortho, orthopedics.

transfusion and the publication of restrictive transfusion articles that the increased awareness may alter a clinician's, or patient's, desire to transfuse.

Clearly, the use of ICS may confer its highest benefits in patients who are undergoing high-risk procedures or who are most likely to demonstrate compromised hemostasis, putting them at increased risk for hemorrhage (25). As is true in all interventions in health care, the utilization of ICS must take into consideration cost–benefit relationships in assessing appropriate application. Because cost is always critically considered in assessing value-driven interventions, a modified version of ICS termed limited occurs when only a partial circuit is used (cardiotomy reservoir and aspiration assembly). The use of the limited ICS process provides a level of security in situations where unanticipated increased blood loss is encountered. Without such a system, the period where the best utility of the ICS intervention would be realized would be compromised by the time necessary to mobilize resources and personnel. Therefore, the best option would be to use an alternative means of blood conservation which is a primary reason for the use of AF agents.

The primary category of AF is lysine analogues, with TXA being the most prominent. The mechanism of action of TXA is to inhibit fibrinolysis by blocking the activation of plasminogen-inhibiting plasmin formation, which stabilizes the polymerized fibrin clot and enhances hemostasis (7). Most of the non-cardiac surgery AF research has focused on TXA which has been shown not only to reduce blood loss and lower allogeneic RBC transfusions (8,9,11) but also to possess anti-inflammatory properties and mitigate postoperative pain (29). Although there does not appear to be a prothrombotic effect of TXA (10), there are reports of increased seizure activity when used (12).

The present study was undertaken to determine if the use of AF has affected the distribution of ICS in non-cardiac surgical procedures. We used a national registry of data collected from more than 200 hospitals throughout the United States. Participation in the registry is mandatory, and more than 50 variables are collected on each procedure, with a required completion of mandatory fields necessary before successful submission of the case to a quality improvement database. A sampling of case records for each clinician is undertaken on a quarterly basis to validate the ICS process and to assess the accuracy of the data. Although the data are primarily used for reporting and performance improvement, it also have been incorporated for prospective research (14,15). It became clear that the trend in utilization for ICS was changing over the past several years with 21,811 procedures in 2016 and 20,811 in 2019, representing a 5% decline over that time (unpublished). Although it impossible to delineate the exact reasons for this change, we hypothesized that the use of AF may be influencing the decision to use ICS.

We examined the effect of combining ICS and AF and compared the outcomes of shed blood and volume available for return in an observational manner. Because no effort was made to normalize the study groups through propensity analysis, the results need to be reviewed with caution. Oremus (30) and associates undertook a study in patients undergoing total hip or KA randomizing TXA or a placebo and reinfusing postoperative shed blood while applying a restrictive transfusion protocol. They found that the use of TXA resulted in a reduction in postoperative blood loss by over 60% and that the need for a system to collect and reinfuse postoperative shed blood unnecessary. Although we saw a decline in the combined use of ICS with AF during the most recent year of study, this was not the situation in reoperations. Although it is not unexpected that there would be a decline in the use of ICS when AF are administered, the fact that reoperations did not show this trend may reflect the clinicians' unwillingness to not have an autotransfusion system available.

In the present study, we created nine distinct operative procedure categories. These were grouped according to the nomenclature created in the quality improvement database used within our system and served as the basis for registry analysis. The median values for both shed blood and volume available for return were similar, regardless of whether or not AF were used. Interestingly, the use of AF

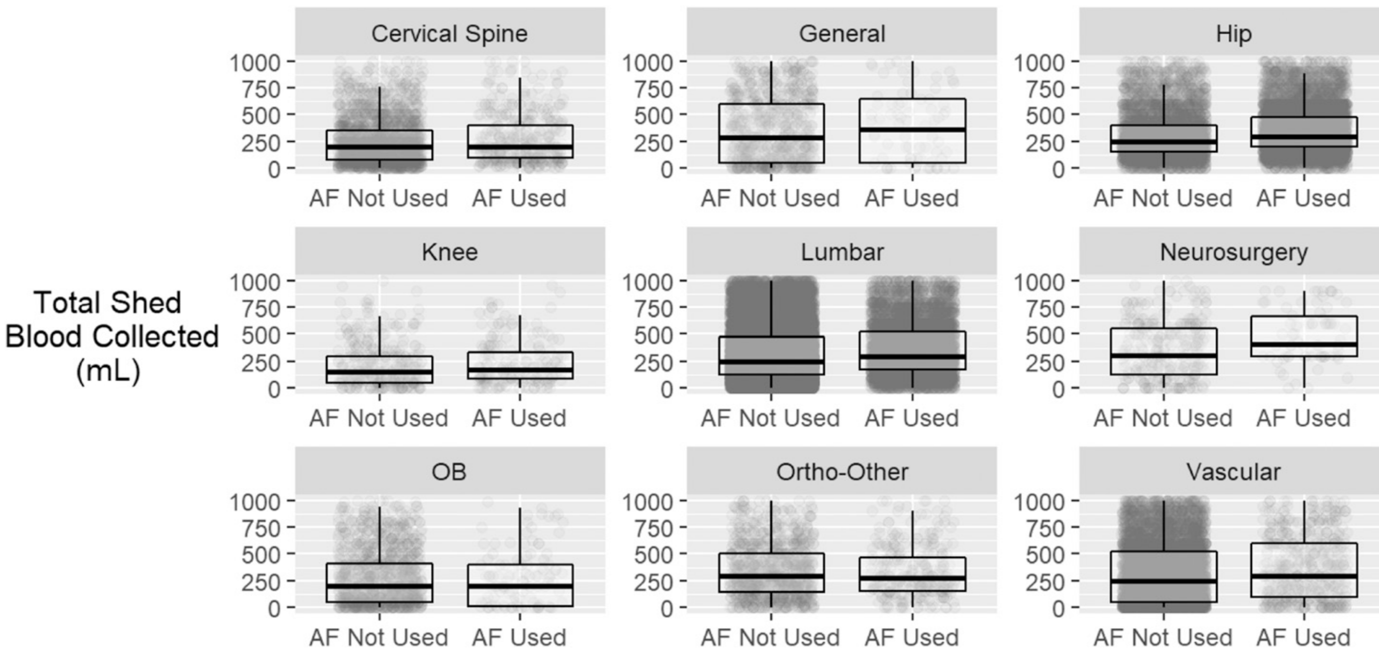

Figure 5. Use of AF and the resultant median and interquartile distribution of shed blood collected. AF, antifibrinolytic; OB, obstetrics.

did not seem to reduce the amount of shed blood nor reduce the amount of volume available for return. This is in contrast to what most have reported when AF are used in non-cardiac surgical procedures. The reasons for this discrepancy are not at first evident but more than likely reflect the non-randomized model of this study and the heterogeneity of the patient populations. However, the present study uses real data from a diverse group of hospitals and surgeons practicing throughout the Unites States and may reflect the actual practice outcomes seen when global assessments of clinical performance are made.

Limitations

The present study has limitations. This study was conducted using a national registry of data collected in a prospective, but non-randomized, manner. Registry data

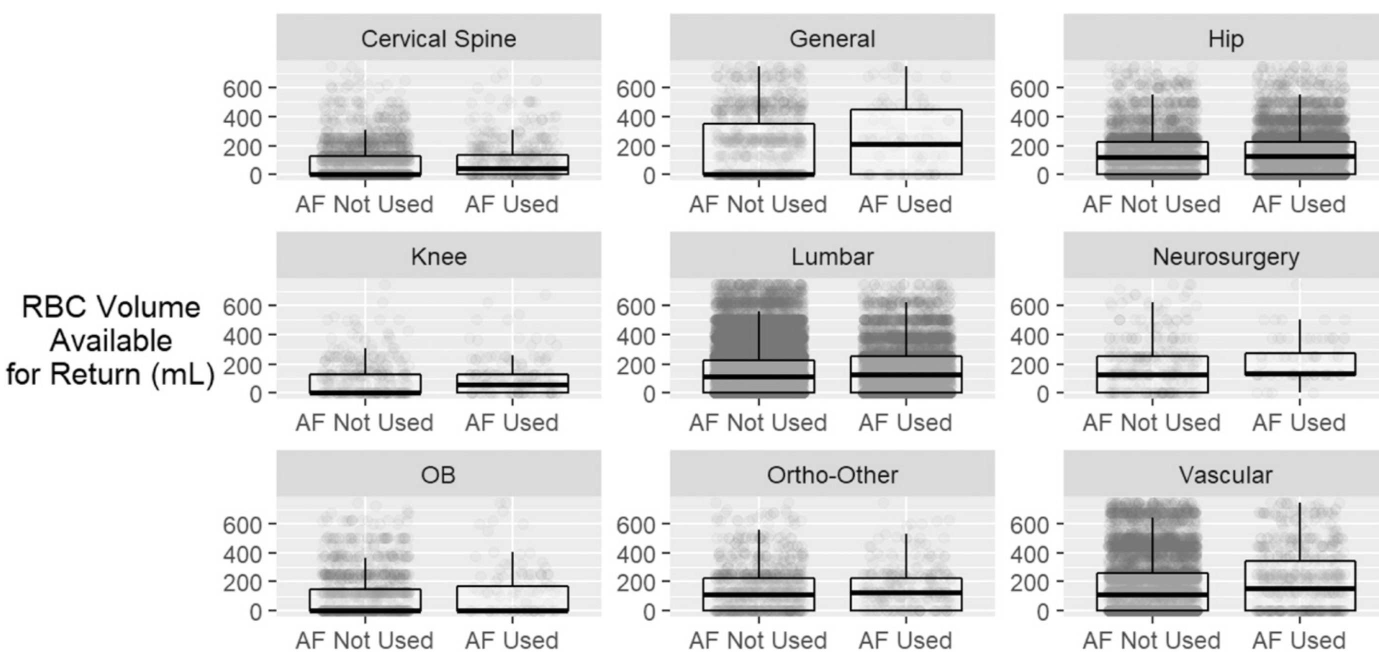

Figure 6. Use of AF and the resultant median and interquartile distribution of ICS red blood cell volume available for return. AF, antifibrinolytic.

do not permit the investigation of certain factors that may be pertinent in determining effects not found with limited variable analysis. We chose to limit the study to specific procedure groups instead of all operations, which may have masked certain procedures where the use of AF had more profound effects on ICS. We did not make any attempt to identify the intravenous dosing regimens for AF, which are known to be variable, nor did we discern the utilization of topical AF. Because of such we cannot rule out, some of these differences may have been procedure specific, related to bleeding or other surgical conditions. Transfusion guidelines were not standardized across and within individual hospitals, so the administration of RBC may have been biased by clinical decisions. The retrospective study design is subject to limitations of inherent selection bias, and the reported results are limited to describe observed associations between the implementation of the described protocol and the improved patient outcomes and do not demonstrate a direct cause and effect relationship. All results are limited to short-term intraoperative outcomes, and intermediate or long-term follow-up data were not available. This was not a longitudinal study, so the effect of postoperative blood management cannot be accounted for in these analyses. And finally, there exists a potential for the miscoding of data, which, despite steps for validation, must be considered in any secondary analysis of registry data.

CONCLUSIONS

We have shown that using data from a national registry on ICS, there is a positive linear trend to the increased use of AF in non-cardiac surgical patients. Although this increase has occurred in most of the surgical procedure categories, several have declined. Although there may be a beneficial effect of AF with lower ICS volumes available for return in a few procedure types, this was not universally found for all. Therefore, the omission of ICS when AF are administered should be carefully considered, and further research in these practice techniques is needed.

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Appendix 1. Distribution of ICS device used in study.

Cell Salvage Device (Make and Model)	Number
1. Fresenius CATS™, Terumo Cardiovascular, Ann Arbor, MI	11,783
2. Haemonetics Cell Saver V™, Haemonetics Corporation, Braintree, MA	20,664
3. Haemonetics Elite™, Haemonetics Corporation, Braintree, MA.	17,028
4. LivaNova BRAT 2™, LivaNova, Arvada, CO.	1,297
5. LivaNova Electra™, LivaNova, Arvada, CO	87
6. LivaNova XTRA™, LivaNova, Arvada, CO	14,238
7. Medtronic Autolog™, Medtronic, Minneapolis, MN	1,769
8. Unknown	3,069

ICS, interaoperative cell salvage.