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Original Articles

Characteristics of Uncontrolled Hemorrhage in Cardiac Surgery

Cody Trowbridge, MPS, CCP; Alfred Stammers, MSA, CCP; Myra Klayman, BA, CCP; Nicholas Brindisi, BS, CCP; Edward Woods, MD

Geisinger Medical Center, Danville, Pennsylvania

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Abstract: Patients with uncontrolled hemorrhage require massive transfusion therapy and consume a large fraction of blood bank resources. Institutional guidelines have been established for treatment, but early identification and prevention in susceptible patients remains challenging. Uncontrolled hemorrhage was defined as meeting institutional guidelines for recombinant FVIIa administration. Patients who received rFVIIa were compared with patients who did not require the therapy but who were operated on during the same time period. After institutional review board approval, demographic, operative, and transfusion data were analyzed from a prospective database. Patients receiving rFVIIa were more likely to undergo multiple procedures (2.6 ± 0.8 vs. 1.8 ± 0.8; $p < .001$); aortic surgery (59% vs. 11%; $p < .005$); have a higher Cleveland Clinic Clinical Severity score (7.8 ± 2.7 vs. 5.5 ± 4.0; $p < .005$); require longer bypass (265 ± 92 min vs. 159 ± 63 min; $p < .001$), cross-clamp (182 ± 68 min vs. 112 ± 56 min; $p < .001$), and circulatory arrest (15 ± 24 min vs. 2 ± 7 min; $p < .05$) times; and require more autotransfusion (2580 ± 1847 mL vs. 690 ± 380 mL; $p < .05$). Uncontrolled hemorrhage is associated with more complex surgery requiring longer bypass times and more autotransfusion. **Keywords:** cardiac surgery, recombinant factor VIIa, hemorrhage. *JECT. 2008; 40:89–93*

Uncontrolled hemorrhage in cardiac surgery is more frequently encountered than in other surgical specialties, and patients who suffer from hemorrhage are 15-fold more likely to die (1). However, it was Karkouti et al. (2) that first established that major blood loss is an independent risk factor for adverse outcomes, instead of simply a marker for the severity of the illness. The distinction is important, because it mandates that we identify, investigate, and bring into clinical practice therapies to reduce this complication. The logical first step is to identify which patients or operative variables will present with the greatest risk for contributing to major blood loss.

Recently, significant interest in using recombinant FVIIa as a rescue therapy for uncontrolled hemorrhage has been shown by a number of peer-reviewed papers, but most trials have been small case series with differential results (3–8). Despite growing investigative interest, rFVIIa is only approved for use in patients with hemophilia A or B with inhibitors to factor VIII or factor IX or in patients with congenital FVII deficiency (9). Other reported uses are off-label and based on limited clinical data.

Furthermore, patients with circulating tissue factor (TF) or predisposing coagulopathy may be at an increased risk for thromboembolic complications with the use of rFVIIa (9). A recent large review in the *Journal of the American Medical Association* found that most thromboembolic events occurred with the off-label use of rFVIIa and often resulted in severe morbidity and mortality. The cautious application of rFVIIa is particularly warranted in cardiac surgery, because myocardial ischemia itself is known to contribute to pro-thrombotic states, and cardiopulmonary bypass (CPB) levels of TF are markedly elevated (10). In the presence of large amounts of shed blood (expected with uncontrolled hemorrhage), tissue factor levels are elevated even further (11). Therefore, extreme caution is

Address correspondence to: Cody C. Trowbridge, MPS, CCP, Geisinger Medical Center, Perfusion Services 20-15, 100 N. Academy Avenue, Danville, PA 17821. E-mail: cctrowbridge@geisinger.edu
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warranted in the decision to use of rFVIIa to arrest uncontrolled hemorrhage.

Despite these cautions, rFVIIa has been used as a compassionate rescue therapy at our institution in >70 cardiac surgery patients. The initial series of 17 patients led to the definition of specific criteria for the administration of rFVIIa, and a subsequent series found that the use of this criteria resulted in the cessation of the hemorrhagic event in 100% of the patients. In an effort to improve safety, criteria are being established to exclude the potential for giving rFVIIa in the presence of disseminated intravascular coagulation by testing for soluble fibrin monomer complexes and antithrombin III levels before administration.

However, the identification of early markers of uncontrolled hemorrhage and more punctual and accepted interventions may preclude the need for rescue therapy. Such a strategy is more attractive than resorting to an expensive, off-label pharmaceutical of questionable safety. The purpose of this study was to characterize the demographic and operative parameters of the patients who suffered uncontrolled hemorrhage and necessitated rescue therapy in the form of rFVIIa.

MATERIALS AND METHODS

After institutional review board approval, data on 204 patients were prospectively collected. Patients suffering from uncontrolled hemorrhage were defined as those patients who met institutional guidelines for the administration of rFVIIa (rFVIIa, $n = 17$) and were compared with those who did not meet this criteria (No rFVIIa, $n = 187$). All patients received similar pre-operative, operative, and post-operative care.

A univariate comparison of the groups was conducted that compared demographic, procedure, operative, volume administration, and transfusion data. All data were loaded onto Microsoft Excel and analyzed with SAS (version 8.0; SAS, Cary, NC). Parametric data were analyzed using two-sample t tests, and non-parametric data were compared using χ^2 tests for independence with or without Yates's correction, and Fisher exact test, as appropriate.

Transfusion decisions were based on an institutional algorithm. Packed red blood cells (RBCs) were transfused for hemocrits <22% for patients ≤65 years old and 24% for patients >65 years old. If non-surgical bleeding occurred, other blood products were used. Fresh frozen plasma (FFP) was transfused when the thromboelastograph (TEG) R-time was >16 minutes or 12–16 minutes with a fibrinogen level <100 mg/dL. Platelets (Plt) were transfused if the TEG maximum amplitude (MA) was <49 mm or if the platelet count was <100,000. Cryoprecipitate (CRYO) was transfused if the R-time was >16 minutes, and the fibrinogen level was <100 mg/dL. Uncontrolled hemorrhage occurred when the criteria for rFVIIa administration was met, which included non-surgical bleeding despite a platelet count >100,000, a fibrinogen level >100 mg/dL, a TEG R-time <12 minutes, a TEG MA >49 mm, and a TEG LY30 of ≥8%.

Anesthesia Management

Patients received 0.5–5.0 mg of midazolam in the preoperative care unit, followed by the placement of two 16-gauge intravenous lines. After arriving in the operative suite, a radial or brachial arterial line was placed, followed by a continuous cardiac output pulmonary artery catheter (Baxter), inserted through an internal jugular introducer. Induction was accomplished by 5.0–10.0 mg midazolam, 0.5–1.0 mg Fentanyl, and 7.0–10.0 mg of pancuronium (cisatracurium or vecuronium were occasionally used instead of Pavulon to maintain a heart rate <100 bpm).

Before CPB, formal anesthesia guidelines were in place to keep fluid administration <1200 mL. Blood pressures were maintained with either Neo-Synephrine and ephedrine or epinephrine infusion through the central line. Fentanyl (as needed), Ativan (2 mg), and Versed (5–10 mg) were given before initiation of CPB at the discretion of the anesthesia staff. In addition, 1 g of cefazolin was given <60 minutes before skin incision, followed by repeat 1-g doses every 4 hours until closure.

Amicar or aprotinin was used on all cases, with selection based on surgeon preference. If Amicar was used, 5 g was infused before CPB. If aprotinin was used, a 1-mL test dose was given, followed by 2,000,000 KIU infused over 30 minutes, which was followed by a 1,000,000-KIU/h drip continued through intensive care unit (ICU) arrival.

CPB Management

The CPB circuit consisted of a an oxygenator with integrated arterial line filter and cardiotomy reservoir (Synthesis; Cobe Cardiovascular, Arvada, CO), $SmART_x$-coated tubing (Cobe Cardiovascular, Allen, TX), Myocardial Protection System (MPS; Quest), in-line blood gas monitoring (CDI 500; Terumo Cardiovascular, Ann Arbor, MI), and centrifugal pump (Revolution; Cobe Cardiovascular). The circuit was primed with 1400 mL of PlasmaLyteA, 35 mEq $NaHCO_3$, 5000 IU heparin, and 25 g mannitol.

Autotransfusion was used with every case (CATS; Terumo Cardiovascular). A ratio of 1 part anticoagulant (30 IU heparin/mL 0.9% NS) to 10 parts collected blood was used and was washed with 0.9% NaCl solution on the "Quality Wash" program.

Autologous priming was attempted on all patients. During CPB, arterial pressure was maintained between 60 and 90 mmHg, cardiac index was maintained >1.8 L/min/m^2, and blood gases were managed with alpha-stat physiology (pHa, 7.35–7.45; $PaCO_2$, 35–45 mmHg; PaO_2, 150–250

mmHg). Patients were cooled to a temperature specified by surgeon preference and surgical procedure, with temperature control according to institutional policy (gradients <6°C, maximum arterial temperature <37°C, rewarming rate <0.5°C/min). Vacuum-assisted venous drainage was only used when needed and never exceeded –40 mmHg. Volume replacement during CPB was accomplished with PlasmaLyteA, with 12.5 g of albumin added per liter crystalloid solution, or 5% albumin added to achieve [Albumin] >3.5 g/dL or colloid oncotic pressure (COP) >14 mmHg.

Induction of cardioplegic arrest was accomplished with 1000–1500 mL of cold (4°C) 4 blood:1 crystalloid. The MPS was set to deliver 20 mEq/L KCl and 15 mEq/L of $NaHCO_3$, with the crystalloid component consisting of 1 L 0.9% saline with 12.5 g mannitol. Subsequent doses were given at 15- to 20-minute intervals and consisted of cold (4°C) blood with 10–16 mEq/L KCl (adjusted to ensure electrical quiescence and avoid hyperkalemia). Antegrade cardioplegia was delivered at a system pressure of 100–150 mmHg, and retrograde cardioplegia was delivered to a coronary sinus pressure of 30–40 mmHg. Antegrade vs. retrograde delivery was based on surgeon preference and surgical procedure. Before removal of the cross-clamp, warm blood (37°C) was delivered for 5 minutes, with additional [KCl] of 8 mEq for the first minute, 4 mEq for the second minute, and 0 mEq for the remaining 3 minutes.

If Amicar was used, 5 g of Amicar was added to the pump prime, the patient was anticoagulated with a loading dose of 300 IU/kg of heparin, and additional heparin was given during CPB to maintain an activated clotting time (ACT) > 480 seconds (ACTII; Medtronic, Minneapolis, MN) If aprotinin was used, 2,000,000 KIU of aprotinin was added to the pump prime, the patient was anticoagulated with 400 IU/kg of heparin, and additional heparin was given during CPB to maintain ACT > 600 seconds. After termination of CPB and patient stability was assured, heparin was reversed with 0.6 mg of protamine per 100 IU heparin administered.

RESULTS

Patients who had uncontrolled hemorrhage were at a higher pre-operative risk than those that did not according to the Cleveland Clinic Clinical Severity (CCCS) score (5.5 ± 4.0 vs. 7.8 ± 2.7; $p = .003$), but the groups were otherwise similar in pre-operative demographics (Table 1) (12). Uncontrolled hemorrhage patients were also more likely to have aortic surgery (59% vs. 12%; $p < .0001$) and undergo multiple procedures (2.6 ± 0.8 vs. 1.8 ± 0.8; $p < .0001$; Table 1).

The groups were similar in operative hematocrit, pre-CPB volume administration and transfusion, and CPB non-blood product volume administration (Tables 2–4).

Table 1. Demographic and procedure variables.

	No FVII ($n = 187$) (Mean ± SD or Percentage)	FVII ($n = 17$) (Mean ± SD or Percentage)	p
Demographics			
Age (yr)	66.5 ± 11.3	69.6 ± 8.9	NS*
Weight (kg)	81.7 ± 18.0	87.6 ± 16.5	NS*
Height (cm)	166.8 ± 12.2	172.6 ± 10.2	NS*
BSA (m^2)	1.93 ± 0.25	2.03 ± 0.24	NS*
BMI (kg/m^2)	29.5 ± 7.1	29.2 ± 3.3	NS*
Percent female	43%	29%	NS
CCCS score	5.5 ± 4.0	7.8 ± 2.7	.003*
Procedure			
3 valve	6%	35%	.0003†
2 valves	27%	47%	NS†
1 valve	71%	53%	NS†
CAB?	40%	41%	NS†
CAB only?	3%	0%	NS‡
Aortic	12%	59%	<.0001†
Conversion	4%	0%	NS‡
Salvage	2%	0%	NS‡
Other	24%	18%	NS†
No. of procedures	1.8 ± 0.8	2.6 ± 0.8	<.0001*
3 or more	16%	47%	.005†
1	40%	0%	.002†
2	44%	53%	NS†
3	13% ± 25	29% ± 5	NS*
4	2%	18%	.002
5	1%	0%	NS‡
Redo?	21%	18%	NS†
Minimally invasive?	19%	0%	.046†

*Two-tailed t test.
†χ^2 test.
‡Fisher exact test.
BSA, body surface area; BMI, body mass index; CAB, coronary artery bypass; NS, not significant.

Table 2. Operative variables.

Operative Variables	No FVII ($n = 187$) (Percent or Mean ± SD)	FVII ($n = 17$) (Percent or Mean ± SD)	p
IABP			
Pre-operative	5%	12%	NS*
Intra-operative	4%	6%	NS†
Post-operative	1%	6%	NS†
Drugs			
Aprotinin?	67%	88%	NS*
rFVIIa?	0%	100%	<.0001*
ATIII?	0%	29%	<.0001*
Hematocrit			
Postinduction	34.3 ± 4.8	34.9 ± 4.7	NS‡
First CPB	25.1 ± 4.5	26.1 ± 3.8	NS‡
Last CPB	25.8 ± 3.8	27.1 ± 3.7	NS‡
Cell saver			
Pre-CPB	37 ± 116	128 ± 196	NS‡
CPB	64 ± 170	339 ± 433	.019‡
Post-CPB	690 ± 380	2580 ± 1848	.001‡
Total CS	773 ± 490	3046 ± 2104	<.0001‡

*χ^2 test.
†Fisher exact test.
‡Two-tailed t test.
IABP, intra-aortic; CS, cell saver; NS, not significant.

However, uncontrolled hemorrhage patients received more autotransfusion during CPB (339 ± 443 mL vs. 64 ±

Table 3. Pre-CPB variables.

Pre-CPB Variables	No FVII (n = 187) (Percentage or Mean ± SD)	FVII (n = 17) (Percentage or Mean ± SD)	p
Albumin	237.2 ± 409.7	670.6 ± 966.2	NS*
Crystalloid	1505.5 ± 731.7	1511.8 ± 883.8	NS*
RBCs (units)	0.1 ± 0.5	0.7 ± 2.4	NS*
RBCs (Y/N)	5%	12%	NS†
Urine	365 ± 296	341 ± 182	NS*

*Two-tailed t test.
†χ^2 test.
RBC, red blood cells; NS, not significant.

Table 4. CPB variables.

CPB Variables	No FVII (n = 187) (Percentage or Mean ± SD)	FVII (n = 17) (Percentage or Mean ± SD)	p
AP Taken	952 ± 384	958 ± 515	NS*
AP Given	433 ± 418	368 ± 388	NS*
Crystalloid	434 ± 648	827 ± 1049	NS*
Albumin	551 ± 449	765 ± 504	NS*
RBCs (PRIME)	0.1 ± 0.5	0.2 ± 0.6	NS*
RBC prime (Y/N)	7%	18%	.007†
RBCs	0.6 ± 1.1	2.6 ± 2.9	.012*
RBCs (Y/N)	29%	65%	.006†
FFP	0.1 ± 0.5	1.8 ± 2.6	.016*
FFP (Y/N)	2%	41%	<.0001†
Other	251 ± 324	270 ± 211	NS*
Urine	610 ± 444	736 ± 861	NS*
Ultrafiltration	211 ± 632	589.7 ± 1086.2	NS*
Ultrafiltration (Y/N)	16%	35%	.046†
CPB time	160 ± 63	265 ± 92	.000*
XC time	113 ± 56	182 ± 68	.001*
Circ arrest	1.5 ± 7.0	15.2 ± 24.0	.032*
DHCA (Y/N)	6%	41%	<.0001†

*Two-tailed t test.
†χ^2 test.
AP, autologous prime; XC, cross clump; DHCA, deep hypothermic circulatory arrest; NS, not significant.

170 mL; p = .019) and after CPB (3046 ± 2104 mL vs. 773 ± 490 mL; p < .0001) and received more transfusions during and after CPB (Tables 2–5).

DISCUSSION

Dial et al. (13) reported that hemodilution and surgical blood loss are major contributors to transfusion requirements during cardiac surgery. Consistent with these results, patients in this trial required more autotransfusion, beginning during bypass and extending into the post-bypass period. Furthermore, Koster et al. (14) recently reported improved preservation of hemostasis with the avoidance of cardiotomy suction, through passive venting of the heart and minimizing suction return. In this study, shed blood was primarily returned to the CPB circuit, and larger autotransfusion volumes corresponded to much larger cardiotomy suction use. Although proponents of complete avoidance of cardiotomy exist, the technique is limited in application because of the inability to accommodate even moderate levels of blood loss or venting requirements. Central to preserving adequate hemostasis is limiting surgical blood loss. Although autotransfusion and cardiotomy suction provide useful mechanisms for reducing the requirement for allogeneic RBC transfusion, the use of both have the strong potential to reduce hemostatic potential. With autotransfusion, all blood components except RBCs are lost to the effluent, potentially contributing to both dilutional coagulopathy and decreased plasma protein and colloid oncotic pressure. Thus, excessive surgical blood loss, compensated with autotransfusion, may result in higher non-RBC transfusion requirements, excessive extravascular water accumulation, and resultant increases in end organ dysfunction.

Table 5. Post-CPB variables.

Post-CPB Variables	No FVII (n = 187) (Mean ± SD or Percentage)	FVII (n = 17) (Mean ± SD or Percentage)	p
Crystalloid	547 ± 549	1124 ± 956	.025*
Colloid	113 ± 278	259 ± 344	NS*
RBCs	0.6 ± 1.2	5.4 ± 3.5	<.0001*
RBCs (Y/N)	28% ± 52	100%	<.0001†
FFP	0.6 ± 1.6	8.6 ± 5.5	<.0001*
FFP (Y/N)	12%	94%	<.0001†
CRYO	0.5 ± 2.2	11.4 ± 9.4	.000*
CRYO (Y/N)	7%	82%	<.0001†
Plt	0.6 ± 2.2	6.5 ± 8.7	.013*
Plt (Y/N)	14%	94%	<.0001†

*Two-tailed t test.
†χ^2 test.
NS, not significant.

The management of shed blood during cardiac surgery will continue to receive a great deal of attention, primarily because none of the perfusionist-driven strategies are attractive. The only strategy that is definitively superior is the early identification and cessation of surgical blood loss at the field. Blood allowed to pool in the pleural and pericardial spaces will accumulate supraphysiologic levels of deleterious biological mediators and necessitates further hemodilution to replace the temporarily "lost" volume. Earlier return is an improvement, but the blood will still be exposed to exposed tissue, additional artificial surfaces, negative pressures, and large air–blood interfaces.

Limiting these exposures should be a primary goal of the entire team, requiring time and attention in all facets of care. From this trial, it seems that it is more difficult (and thus would consume more time) to limit shed surgical blood when the operative course includes more than three procedures or aortic surgery.

Because of the power and observational design of this study, it is not possible to determine whether the differences between non-hemorrhage patients and uncontrolled hemorrhage patients predicted the condition, contributed to the condition, or were a result of the condition. All that

can be stated is that patients in the uncontrolled hemorrhage group more frequently required multiple procedures (≥3) and/or aortic surgery; required more autotransfusion, longer bypass times, and more hypothermic circulatory arrest; and required more transfusions. Given these characteristics, efforts to preserve hemostatic potential should be studied further in this patient population.

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