Utilization and Effectiveness of Desmopressin Acetate After Cardiac Surgery Supplemented With Point-of-Care Hemostatic Testing: A Propensity-Score–Matched Analysis

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Objectives: **To explore the utilization pattern and hemostatic effectiveness of desmopressin acetate (DDAVP) supplemented with point-of-care (POC) hemostatic testing in contemporary cardiac surgery.**

Design: **Retrospective, observational study.**

Setting: **Single quaternary care university hospital.**

Participants: **The study comprised 2,468 consecutive patients undergoing cardiac surgery—1,237 before and 1,231 after the introduction of POC testing.**

Interventions: **The incidence of DDAVP administration during the year before (2012) and after (2013) the initiation of POC-based viscoelastic (ROTEM; Tem International GmBH, Munich, Germany) and platelet function (Plateletworks; Helena Laboratories, Beaumont, TX) testing was determined. Propensity-score matching was used to examine the association between DDAVP administration and major bleeding during each time period.**

Measurements and Main Results: **DDAVP was administered more than twice as often after POC implementation (41% *v* 20%, $p < 0.001$). Major bleeding was defined based on the universal definition of perioperative bleeding in adult cardiac surgery. Propensity matching identified 224 well-balanced pairs of DDAVP recipients and control patients before and 298 such pairs after the implementation of POC testing. After adjusting for matched data, DDAVP administration was associated with 1.70 (95% confidence interval 1.25-2.32, $p < 0.001$) and 1.51 (95% confidence interval 1.15-1.98, $p = 0.003$) increases in the odds of major bleeding before and after the initiation of POC testing, respectively.**

Conclusions: **Clinicians should be cognizant of the potential for increased use of DDAVP despite limited evidence of benefit in contemporary cardiac anesthesia practice supplemented with POC-based hemostatic testing.**

KEY WORDS: desmopressin acetate, hemostasis, hemorrhage, cardiac surgery, extracorporeal circulation, blood coagulation, point of care testing

EXCESSIVE BLOOD LOSS is a frequent and serious complication of cardiac surgery with cardiopulmonary bypass (CPB). Such bleeding often necessitates the transfusion of blood products and is associated with significant morbidity and mortality.[1–3] Although causes of bleeding are multifactorial, one of the primary etiologies appears to be a coagulopathy due to platelet abnormalities related to the effect of the extracorporeal circuit.[4]

Desmopressin acetate (DDAVP) is a medication that stimulates the release of von Willebrand factor (vWF) and factor VIII from the vascular endothelium, thereby augmenting platelet adhesion and aggregation,[5,6] and is indicated for treatment of bleeding in patients with von Willebrand disease.[7] Over the last 2 decades, multiple studies have assessed its efficacy in cardiac surgery, and meta-analyses of these trials have reported mild reductions in perioperative blood loss after DDAVP administration.[8–11] However, individual study results have been inconsistent,[12,13] and some have suggested that DDAVP may offer hemostatic benefits only to specific subgroups with preoperative aspirin intake,[8,14–16] comorbid uremia,[17,18] and prolonged CPB durations.[8,14,16] In all, sparse evidence to support its efficacy and concerns regarding an increased risk of myocardial infarction[11] have resulted in weak recommendations for the use of DDAVP in cardiac surgery.[19–21]

With improvements in cardiac surgical techniques; increasing availability of novel hemostatic therapies (eg, prothrombin complex concentrates, fibrinogen concentrates, topical sealants); and escalating use of adjunctive point-of-care (POC) hemostatic testing to better guide the management of post-CPB coagulopathy,[22,23] the evaluation of DDAVP treatment in contemporary cardiac anesthesia practice is warranted. In this single-center, retrospective, observational study, propensity matching was used to explore the independent relationship between DDAVP administration and perioperative blood loss in cardiac surgery, both before and after in-center implementation of a POC-based coagulation management algorithm over a 2-year period (2012 to 2013).[22] The study goals were as follows: (1) examine DDAVP utilization patterns and (2) determine whether DDAVP therapy was associated with reduced blood loss—both before and after the implementation of POC-based guidance.

METHODS

Data Sources

After obtaining Research Ethics Board approval, perioperative data on consecutive adult (>18 years) patients undergoing cardiac surgery with CPB from January 1, 2012 to December 31, 2013 were obtained from prospectively collected clinical

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D. Orlov is supported in part by a tuition award from the Department of Anesthesia, University of Toronto. K. Karkouti is supported in part by a merit award from the Department of Anesthesia, University of Toronto.

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1053-0770/2601-0001$36.00/0
http://dx.doi.org/10.1053/j.jvca.2016.11.022

databases. Patient demographics, comorbidities, medications, laboratory results, surgical parameters, details of intraoperative coagulopathy management, POC test results, and postoperative outcomes were abstracted and analyzed. Data integrity was ascertained by full-time research personnel blinded to study specifics. For patients who underwent more than 1 cardiac surgical procedure during the study period, only data from the first procedure were used in the analyses.

Clinical Practice and Setting

The study was conducted at a quaternary care academic hospital that performs more than 1,400 cardiac procedures annually. The case mix included a combination of first-time or repeat (redo) aortocoronary bypass or valve repair/replacements, septal myectomies, complex congenital repairs, insertion of mechanical assist devices, and heart transplantation. Perioperative blood management strategies included hematology consultation for known or suspected coagulation disorders; timely cessation of antiplatelet and anticoagulant medications; universal administration of an antifibrinolytic agent (tranexamic acid, >20 mg/kg dose); retrograde autologous priming of the CPB circuit; perioperative cell salvage; adequate heparin reversal guided by activated clotting time measurements; maintenance of normothermia after separation from CPB; selective use of topical sealants; and rescue use of recombinant activated factor VII for refractory bleeding.[24] Chest tube outputs were monitored hourly for up to 24 hours after intensive care unit admission (or until removal if removed within 24 hours) with a low threshold for reexploration in the context of ongoing hemorrhage.

Point-of-Care Transfusion Algorithm

In January 2013, a POC-based transfusion algorithm using viscoelastic (rotational thromboelastometry [ROTEM]; Tem International GmBH, Munich, Germany) and platelet function (Plateletworks; Helena Laboratories, Beaumont, TX) assays was implemented in an effort to rapidly assess factor deficiencies and platelet dysfunction while facilitating timely, targeted, transfusion therapy (Fig 1). Details and outcomes of the POC algorithm have been described previously.[22,25] Its main parameters of interest included the 10-minute clot strength (amplitude) after assessment of the extrinsic (A10-EXTEM) and fibrin-generating (A10-FIBTEM) pathways of hemostasis and the clotting time after assessment of the extrinsic hemostatic pathway (CT-EXTEM)—all measured after rewarming (temperature $\geq$36ºC) before discontinuation of CPB. Platelet function was assessed by subtracting nonaggregated platelets (after exposure to collagen agonist) from the overall platelet count[26] and provided additional insight into the functional platelet reserve.

Blood products were administered in accordance with clinical guidelines and institutional protocols.[20,27] Both before and after the implementation of the algorithm, red blood cells were administered at approximate hemoglobin levels of 7 g/dL during CPB, 8 g/dL after CPB, and 9 g/dL in bleeding patients or those with unstable conditions. Before the algorithm, indications for platelet transfusion (1 pool) included a platelet count of less than 50×10^9/L or ongoing bleeding after reversal of heparin with counts of less than 80×10^9/L. After initiation of the POC algorithm, ongoing blood loss with a functional platelet count less than 75×10^9/L or a combination of A10-EXTEM <35 mm and A10-FIBTEM >8 mm (reflecting platelet-related reduction in clot strength in the absence of hypofibrinogenemia) became triggers for administration of platelet concentrates. Cryoprecipitate (or fibrinogen concentrate) and plasma (or prothrombin complex concentrate) subsequently were administered in a stepwise manner according to previously described thresholds.[22,25]

In cases of massive bleeding before the implementation of the algorithm, blood products were transfused based on clinical judgement and conventional coagulation tests (complete blood count, international normalized ratio of prothrombin time, activated partial thromboplastin time, and fibrinogen concentration). According to the algorithm, the initial management of massive post-CPB bleeding primarily was based on a combination of clinical judgement and POC results given the prolonged turnaround time of conventional testing. In all cases, results of POC testing were available to clinicians immediately after separation from CPB before heparin reversal, thereby influencing initial decisions for the management of bleeding.

DDAVP Administration

DDAVP administration both before and after the implementation of the algorithm was based solely on the clinical judgement of the attending anesthesiologists. The POC algorithm did not specify DDAVP usage (see Fig 1). Similarly, institutional guidance for its administration also was unavailable before POC implementation. Typical indications for DDAVP before the algorithm included recent preoperative use of antiplatelet agents, preoperative thrombocytopenia, uremia, prolonged CPB duration, severe aortic stenosis, and clinical suspicion of platelet dysfunction in the context of ongoing blood loss. After the algorithm, similar indications were applied in addition to POC-based evidence of platelet dysfunction at rewarming.

The typical dose of DDAVP was 0.3 μg/kg administered over 10-to-15 minutes after separation from CPB and reversal of heparin. The actual dose and timing of administration were abstracted from electronic anesthetic records during both study periods.

Dependent Variable

The primary outcome was the severity of perioperative blood loss as defined by the universal definition of perioperative bleeding (UDPB) in adult cardiac surgery.[28] Specifically, delayed sternal closure, quantification of postoperative chest tube drainage and blood product transfusions, administration of recombinant activated factor VII, and postoperative re-exploration were used to classify patients into the following 5 classes of perioperative blood loss: 0, insignificant; 1, mild; 2, moderate; 3, severe; or 4, massive, as defined using the UDPB (Appendix 1). In accordance with the UDPB derivation, cases of conflicting classification based on the various subcomponents (eg, <600 mL chest tube output/12 h and 1 pool of platelets administered perioperatively) were subjected to the worst definition (eg, class 2 in aforementioned example).