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Should Standard On-Pump Protamine Dosing Formulas Be Recalculated for Off-Pump Coronary Artery Bypass Grafting?

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ABSTRACT

Background: Since 1994 at the authors' institution, approximately 9000 cardiac surgical procedures were performed using activated clotting time (ACT)-monitored heparin anticoagulation for cardiopulmonary bypass and protamine administration calculated from a standard unchanged formula. This formula incorporates physiologic consequences of bypass pump–induced dilutional coagulopathy, platelet dysfunction, and coagulation/fibrinolytic cascade component activation, and thus may overcorrect in a subset of off-pump coronary artery bypass graft (OPCAB) patients who may in fact manifest a relative perioperative hypercoagulability state. This study evaluated a strategy of decreased protamine dosing in OPCAB.

Methods: Eighty consecutive OPCAB patients who underwent surgery performed by a single surgeon at a single institution over a 12-month period were retrospectively analyzed. Patients underwent a mean of 2.91 ± 0.1 OPCAB grafts with full heparinization and 50% of the calculated protamine dose was administered. ACT, partial thromboplastin times, thoracostomy tube outputs, transfusions, and clinical outcomes were assessed.

Results: Of 80 patients, 76 (95%) returned to baseline ACT values with 50% protamine dosing. All patients demonstrated intraoperative clinical evidence of hemostasis. Mean 8- and 24-hour thoracostomy tube outputs were 424 ± 24 mL and 806 ± 38 mL, respectively. A mean of 1.7 ± 0.2 packed red blood cell transfusions/patient was administered. There were no transfusions of platelets, fresh frozen plasma, or cryoprecipitate; no reexplorations; and no mortalities. Patients were discharged a mean of 4.4 ± 0.1 days postoperatively.

Conclusion: A standard protamine dosing formula adequate for on-pump cardiac surgical procedures significantly overestimates protamine requirements for OPCAB. Patients treated with decreased protamine do not appear to have adverse outcomes.

INTRODUCTION

Surgical myocardial revascularization without the use of cardiopulmonary bypass (CPB) continues to increase in applicability and use. Prospective randomized studies comparing off-pump coronary artery bypass grafting (OPCAB) to standard on-pump coronary artery bypass grafting (CABG) have recently been reported and document equivalent extent of myocardial revascularization together with clinical benefits such as decreased blood loss and transfusion, decreased indices of myocardial injury, and more rapid recovery [Puskas 2003, Ascione 2001]. Short- to mid-term graft patency appears to also be equivalent. However, large-volume OPCAB centers have noted in OPCAB patients postoperative thrombotic events such as deep venous thrombosis and pulmonary embolism, complications occurring only very rarely in standard on-pump cardiac surgical patients. In general, CPB requires high-dose systemic anticoagulation and also produces an obligate dilutional coagulopathy, coagulation and fibrinolytic protein activation, and platelet dysfunction and destruction, yielding a net relative antithrombotic perioperative state. OPCAB patients are not exposed to such CPB pump–induced blood component alterations and hence, to some degree, may encounter a relative hypercoagulability state more typical of general, gynecologic, and urologic surgical patients. However, OPCAB patients undergo systemic anticoagulation. The heparin anticoagulation and protamine reversal techniques that have been routinely used for decades of CPB-facilitated cardiac surgery may form a central feature of the thrombotic/antithrombotic balance amenable to modification in OPCAB. Various permutations are in use in clinical practice yet formal reports systematically evaluating strategies and analyzing clinical outcomes are scarce. This study sought to examine the effect of reduced protamine

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dosage on coagulation indices and perioperative clinical outcomes in OPCAB patients.

MATERIALS AND METHODS

All patients undergoing OPCAB performed by the same surgeon at a single institution during a 12-month period were retrospectively analyzed (n = 80). All patients intended for OPCAB received OPCAB; there were no conversions to on-pump CABG. Mean values are expressed as mean ± standard error of the mean. Sixty-three men and 17 women underwent OPCAB. The mean age was 65.8 ± 1.1 years. The mean left ventricular ejection fraction was 49.2% ± 1.8%. All patients underwent baseline assay of activated clotting time (ACT). All patients then underwent full heparinization with a goal ACT of 400 to 450 seconds determined by surveillance monitoring of ACT measurements every 30 minutes. This approach is identical to that used for on-pump cardiac surgical procedures. Supplemental systemic heparin was administered as needed. A mean of 2.91 ± 0.1 grafts/patient were performed. On completion of myocardial revascularization, the ACT was measured and the protamine dose was calculated with the following formula, which has been successfully used at the authors' institution for approximately 9000 on-pump cardiac surgical procedures during the past 9 years:

0.02 mg/mL × [(ACT – 120)/(ACT – PRT)] × Patient blood volume (mL)

PRT indicates protamine response time, which is an activated clotting time of 2 mL of patient blood mixed with 0.04 mg protamine.

Patient blood volume was derived from standard nomograms.

Instead of receiving the standard dose of protamine obtained from this formula, all patients received 50% of the calculated dose and then underwent assay of the ACT and visual inspection for surgical hemostasis. Additional protamine was administered in the unusual event of persistently elevated ACT and absence of surgical hemostasis. On arrival to the intensive care unit (ICU), patients underwent assay of partial thromboplastin time (PTT), a sensitive indicator of systemic heparinization. Preoperative and postoperative PTT values were statistically compared with a 1-tailed Student *t* test. Thoracostomy tube outputs, transfusions, and clinical outcomes were assessed.

RESULTS

Mean baseline ACT was 139 ± 3 seconds. Initial mean heparinized ACT was 440 ± 9 seconds, and prior to protamine dosing, mean ACT was 384 ± 7 seconds. After protamine administration, mean ACT was 125 ± 2 seconds. ACT normalization was achieved with 50% protamine dosing in 76/80 patients; 4 patients required an additional 25% dose. Prior to sternotomy closure, all patients demonstrated intraoperative clinical evidence of hemostasis. On arrival in the ICU, mean PTT was 49.2 ± 3.4 seconds, statistically higher than the preoperative mean PTT of 36.1 ± 2.8 seconds ($P < .01$).

Mean 8-hour chest tube output was 424 ± 24 mL, and mean 24-hour output was 806 ± 38 mL, values consistent with published results. Mean peripheral red blood cell transfusion volume was 1.7 ± 0.2 units/patient. There were no transfusions of platelets, fresh frozen plasma, or cryoprecipitate, no reexplorations, and no mortalities. One patient developed a nonocclusive, below-knee deep venous thrombosis. Patients were discharged a mean 4.4 ± 0.1 days postoperatively.

DISCUSSION

Cardiac surgical procedures using CPB have traditionally entailed the use of heparin anticoagulation and protamine reversal. Heparin complexes with the endogenous plasma protein anti–thrombin III (AT III). The interaction of heparin with AT III potentiates the inhibition of coagulation factors of both the intrinsic and common pathways of the coagulation cascade. Therapeutic levels of heparin are ensured using global tests of coagulation such as whole blood clotting time, ACT, or activated PTT. Postbypass, heparin is reversed by the tight binding of protamine sulfate to heparin, thereby neutralizing the anticoagulation properties of heparin [Porsche 1999].

The currently used protamine-dosing algorithms are based on the cardiac surgical population subjected to CPB, with its inherently altered blood component function. The CPB circuit induces a multifactorial postoperative coagulopathy resulting from (*a*) hemodilution, (*b*) activation of factor XIIa, kallikrein, tissue factor, and fibrinolytic systems, and (*c*) consumption of platelets and coagulation factors [Despotis 1999, 2001]. Statistically significant decreases in the concentration of factors involved in both the coagulation and fibrinolytic pathways result from priming dilution by the CPB circuit [Chan 1997]. Intraoperative surface contact activation of the fibrinolytic, coagulation, and plasma kallikrein-kinin system has been observed [Saatvedt 1995, Grossman 1996, Hunt 1998]. In a comparison of cardiac and thoracic surgical patients, increased levels of thrombin–AT III complexes, decreased levels of AT III, increased d-dimer levels, decreased plasminogen and alpha-2 antiplasmin levels, and increased tissue plasminogen activator levels were observed in the cardiac surgical population, suggesting activation of coagulation and fibrinolysis by CPB [Hunt 1998]. Perhaps the greatest effect of CPB on blood component function exists at the platelet level. Platelets are destroyed as a result of shear stress and consumption by the CPB circuit [Slaughter 2001]. Both platelet contractile force and platelet aggregation have been shown to be reduced by CPB and are more pronounced with increasing duration of bypass [Ray 1994, Greilich 2002].

OPCAB patients, on the other hand, are not exposed to the multifaceted, deleterious effects of CPB on blood components. Typical alterations in d-dimer, plasminogen, and platelet counts are not observed in OPCAB patients [Casati 2001]. Postoperative thromboelastogram indices, fibrinogen levels, and international normalized ratios in OPCAB patients demonstrate statistically diminished coagulopathy [Puskas 2003]. OPCAB patients may in fact manifest a procoagulant state similar to the general surgical population [Mariani 1995, Levy 2003, Quigley 2003]. Eliminating CPB subjects the OPCAB population to the same activation of hemo-

static and cytokine-mediated inflammatory mechanisms seen in the general surgical population [Levy 2003]. Thromboelastographic measurements suggest a hypercoagulability state, reflective of increased fibrinogen and platelet activity, in the OPCAB population up to 3 days postoperatively [Quigley 2003]. This state of relative hypercoagulability has also been reflected in elevated levels of prothrombin factors 1 and 2 and endothelial activation as evidenced by elevated levels of von Willebrand factor for the first 24 hours post-OPCAB [Mariani 1999].

Multiple strategies to address this observed state are in clinical practice and revolve much around the earlier use of antiplatelet therapy and the use of the more potent antiplatelet agent clopidogrel. Current protamine dosing approaches may in fact reinforce a procoagulant state in the OPCAB population, thereby increasing the risk of thrombotic events, including bypass graft thrombosis. Alteration of traditional heparin and protamine administration techniques is also in active practice but has not been extensively studied [Gatti 2002]. An overly antithrombotic state, as seen with unreversed heparinization, may subject patients to significant risks of bleeding, transfusion, tamponade, and reexploration. This combination of factors clearly presents a clinical challenge in balancing pro- and antithrombotic factors.

This study examined an intermediate approach of administering 50% of the standard calculated dose of protamine. In 95% of the patients, this dose was sufficient to return the measured ACT to baseline levels and provide visual surgical hemostasis, yet as manifested by the postoperative PTT, the patients were still slightly anticoagulated. Postoperative bleeding and transfusion requirements were low and consistent with published OPCAB results. No patients required fresh frozen plasma, platelets, or cryoprecipitate and none required reexploration. With the exception of a nonocclusive, below-knee deep venous thrombosis, no patients experienced perioperative thrombotic events. The data suggest that a standard protamine dosing approach adequate for on-pump cardiac surgical procedures may significantly overestimate the protamine dose required in OPCAB. These preliminary data also suggest that a 50% reduction in protamine administration safely reverses heparin anticoagulation to an appropriate level and that clinical outcomes appear to be satisfactory. Further examination with increased patient numbers and longitudinal evaluation are warranted.

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