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Protamine Test Dose: Impact on Activated Clotting Time and Circuit Integrity

Lauren Jansa, CPC, CCP, Courtney Fischer, CPC, CCP, Cyril Serrick, CPC, CCP, and Vivek Rao, MD, PhD

Department of Perfusion, Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network, Toronto, Canada; Department of Anesthesia and Pain Management, Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network, Toronto, Canada; and Division of Cardiovascular Surgery, Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada

ABSTRACT

BACKGROUND Recurrent observation of clot in the cardiopulmonary bypass circuit after the administration of a protamine test dose (PTD) prompted concern over the effects of PTDs on patient activated clotting times (ACTs).

METHODS Data were prospectively collected on 120 patients who had cardiopulmonary bypass while undergoing a variety of cardiac surgical procedures from July to October 2018 at the Toronto General Hospital, Toronto, Canada. ACTs were documented before cardiopulmonary bypass termination, after PTDs, and after protamine full doses. Statistical analysis was completed using a paired *t* test.

RESULTS The average PTD was calculated to be 36 ± 21 mg or 11% ± 7% of the full protamine dose of 367 ± 153 mg. This "test" dose ranged from 1% to 67% of full dose depending on the anesthetist. Post-PTD ACTs were widely variable. On average, there was a 40% ± 25% drop from the last ACT during cardiopulmonary bypass (650 ± 155 seconds) to the ACT after PTD (376 ± 153 seconds) ($P < .0001$). In fact, 81% ± 5% of the patients' post-PTD ACTs were lower than the institutional ACT standard of 480 seconds for safe cardiopulmonary bypass initiation.

CONCLUSIONS Regardless of the PTD, there is no reliable way to predict how a patient's ACT will respond to a PTD. Clot formation is possible and circuit integrity is at risk when pump suction devices are continuously in use during PTD administration. Therefore, the study investigators strongly recommend that the direct recovery of mediastinal shed blood into the pump circuit be discontinued before any amount of protamine is administered to the patient.

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Protamine is the gold standard for heparin reversal after open heart surgery using cardiopulmonary bypass (CPB).[1] The mechanism of action involves an electrostatic bond between the positively charged protamine molecules and the negatively charged heparin molecules.[1] This heparin-protamine interaction can be associated with a substantial decrease in patients' systemic blood pressure, increased pulmonary artery pressure, and an overall decrease in systemic vascular resistance.[1] These secondary responses to protamine administration ultimately result in decreased cardiac output, which puts the patient at risk of postcardiotomy decompensation.[2] Therefore, a protamine test dose (PTD) is routinely administered to examine a patient's hemodynamic response to protamine before full heparin reversal in patients who have undergone CPB.[1] Historically, at our institution (Toronto General Hospital, Toronto, Canada), there has been no standardization to cease the recovery of mediastinal shed blood into the bypass circuit during and after PTD administration because it was believed that such a small dose would not significantly affect patient activated clotting times

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Address correspondence to Dr Rao, Division of Cardiovascular Surgery, 4PMB-457, Toronto General Hospital, 200 Elizabeth St, Toronto, ON, Canada, M5G2C4; email: vivek.rao@uhn.ca.

FIGURE 1 Intraoperative photograph demonstrating clot in the venous reservoir.

(ACTs). Therefore, suction devices draining directly into the CPB circuit have been routinely used during and after PTD and have been discontinued only when the remainder of the protamine dose is administered. This approach has the benefit of blood conservation by ensuring that any shed blood is returned to the patient during the test dose through the CPB arterial line, as well as working under the assumption that the team can recommence CPB urgently if necessary. However, on occasion this practice has been unpredictably associated with the observation of clot in the CPB circuit, thus rendering the circuit unusable (Figure 1). Therefore, the purpose of this study was to investigate the PTD and the impact on patient ACT levels and, ultimately, circuit integrity.

MATERIAL AND METHODS

Data were prospectively collected from 120 patients undergoing CPB during a variety of procedures at Toronto General Hospital from July to October 2018. The only criterion for patient inclusion in the study was that the patient was undergoing open heart surgery with CPB using heparin as the anticoagulant agent and protamine as the reversal agent. There were no exclusion criteria. Our Institutional Review Board waived the requirement to obtain any informed consent for this study because this was an observational study with no deviations from standard clinical practice. The CPB circuit used a Balance Biosurface (Medtronic, Minneapolis, MN) disposable pack with Cortiva-coated Fusion oxygenator, operated on the Sorin S3 (LivaNova, London, UK) heart-lung machine. Cardioplegia was delivered using the Quest Medical MPS System (Quest Medical, Allen, TX). The heparin loading dose was recorded along with any additional heparin given during CPB. The heparin loading dose ranged from 300 to 400 IU/kg. In every case, the CPB prime contains a standard dosing of 5000 IU heparin. Additional heparin during CPB was administered if the ACT approached or dropped to less than 480 seconds.[2] Additional heparin administration for ACT values approaching 480 seconds was based on nominal ACT value and anticipated time remaining on CPB. ACT values were measured before heparinization, after heparinization, every 15 to 30 minutes during CPB, before and after the PTD, and after the full protamine dose. After discontinuation of CPB, observation of hemodynamic stability, and an acceptable transesophageal echocardiogram, a PTD was given by the

TABLE 1 Breakdown of Operations Included in the Study and the Number of Patients Within Each Case Type

Case Type	No. of Patients
CABG	48
Aortic valve replacement	17
Valve replacement and CABG	10
Bentall	5
Heart transplantation	2
Hemiarch or valve-sparing root replacement	5
Mitral valve replacement	9
Myectomy	3
>1 valve replacement	8
Pulmonary thrombectomy	5
Redo congenital operations	7
Redo valve(s) replacement	1

CABG, coronary artery bypass grafting.

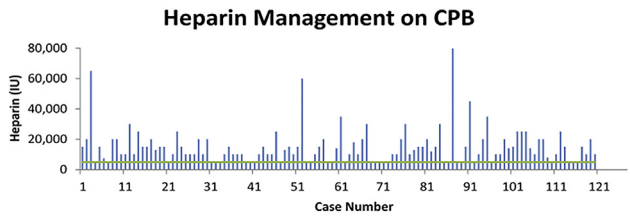

FIGURE 2 Heparin management during cardiopulmonary bypass (CPB). The green line represents our institutional standard of 5000 IU of heparin in the cardiopulmonary bypass circuit prime.

anesthesiologist. No formal protocol existed for the PTD, but the typical practice was to administer a bolus of 20 to 50 mg of protamine intravenously, administered peripherally or centrally. If no reaction was observed, the full reversal dose of protamine (1.0 mg of protamine per 100 IU of initial heparin dose) was administered over a various time interval. Additional 25- to 50-mg increments of protamine were administered if the ACT did not fall within 10% of baseline.

Statistical analysis was completed with Microsoft Excel software (Microsoft, Redmond, WA), using a paired *t* test for continuous variables and the Fisher exact test for categoric variables.

RESULTS

Table 1 describes the types of operations included in this study for all 120 patients. Coronary artery bypass graft procedures comprised the greatest number of cases, accounting for 40% (n = 48) of the study patients, followed by isolated aortic valve replacements at 14% (n = 17) of patients. There was a total of 67 health care professionals involved in this study, including surgeons, perfusionists, and anesthesiologists.

There were no operative deaths, and no patient experienced an adverse reaction to protamine. Individual heparin requirements are summarized in Figure 2. On average, the heparin loading dose was approximately 41,000 ± 12,000 IU, and an additional 15,000 ± 12,000 IU was given during CPB. A total of 75% of the patient population had a repeat dose at some point during the CPB run. The mean CPB time was 113 minutes, whereas the mean cross-clamp time was 84 minutes.

The last ACT for each patient on CPB is depicted in Figure 3. The average ACT before discontinuing CPB was 650 ± 155 seconds (median, 604 seconds). Six patients had an ACT of less than 480 seconds.

The PTD given to each patient is summarized in Figure 4. The average PTD was 36 ± 21 mg (with a median of 30 mg), accounting for 11% ± 7% of the full protamine dose of 349 ± 72 mg. This "test" dose ranged from 1% to 67% of full dose depending on the anesthetist. However, the majority of patients received a PTD between 4% and 18% of the full dose.

The response of the ACT to the PTD is shown in Figure 5. The change from the last ACT during CPB is displayed in Figure 6. On average, there was a 40% ± 25% drop from the last ACT during CPB (650 ± 155 seconds) to the ACT after the PTD (377 ± 153 seconds; $P < .0001$). In fact, 81% of the patients' ACTs after PTD fell to less than our institutional ACT standard of 480 seconds for CPB initiation, and 54% had an ACT less than 400 seconds, indicating that the circuit integrity may have been compromised.

The post-PTD ACTs were widely variable. The percent decrease from last ACT during CPB to ACT after PTD was calculated for each patient and plotted against the percentage of PTD given with respect to the full dose (Figure 7). There was no correlation between the amount of protamine given and the corresponding effect on ACT. In fact, the ACT response to the PTD was highly unpredictable. Table 2 displays the widely variable ACT decrease after PTDs in our patients. The ACT differential ranged from no change in ACT to 100% ACT normalization back to baseline. A small cohort of patients (5% of the study population) experienced increased ACT values after the PTD.

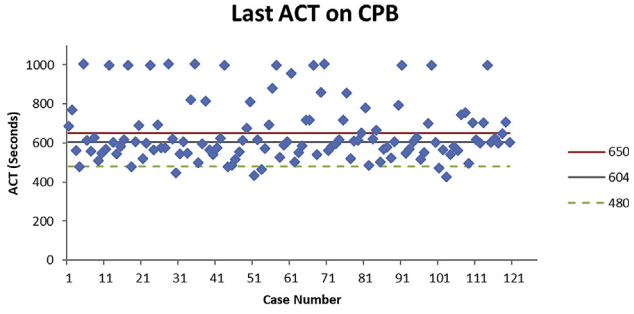

FIGURE 3 Scatterplot demonstrating the last measured activated clotting time (ACT) while the patient was still supported by cardiopulmonary bypass (CPB).

COMMENT

The results of our study conclude that regardless of the protamine dose given during the PTD, there is no reliable way to predict how a patient's ACT will respond. Therefore, the potential exists for even a small dose of protamine to result in a dramatic normalization of coagulation that renders the CPB circuit at risk for thrombosis if mediastinal shed blood continues to be recovered directly into the venous reservoir.

Giving a PTD to ensure that the patient does not become hemodynamically unstable after weaning from CPB is common practice in cardiac surgery. Despite recommendations in the American Society for Extracorporeal Technology Standards and Guidelines for Perfusion Practice that cardiotomy suction be discontinued at

the onset of protamine administration to avoid clotting within the CPB circuit, it is still common practice that cardiotomy suction remains active until at least a PTD is administered.[3] This study is in direct support of these guidelines and shows that this practice is dangerous because of the unpredictable drop in ACT after a PTD. This study documents that only 17% of the patients studied had an acceptable ACT value (greater than or equal to 480 seconds) to reinitiate CPB safely after the PTD. Therefore, 83% of the study patients' CPB circuits were considered unsafe to use in the event of CPB reinitiation given the severe risk of a breach in circuit integrity.

Before this trial, conventional wisdom predicted that the PTD would not have a significant effect on the ACT because, on average, only 10% of the full protamine dosage is administered during the "test" dose. However, this was proven to be incorrect. After careful analysis of the ACT response, we determined that it was not predictable either on the basis of the amount of the PTD or as a ratio of the PTD to the full protamine dose (Figures 6 and 7). In contrast, this study has proven the opposite. We found that the PTD caused a significant drop in ACT in most patients that can potentially compromise safety if reinitiation of CPB is required urgently. This finding has clinical implications. First, an ACT should be determined after the PTD if there is a potential need to resume CPB. If CPB is needed urgently, before measuring ACT, an additional bolus of heparin should be given to ensure a therapeutic ACT.

Despite a written institutional protocol for the administration of a PTD equal to 10% of the full dose, there is a high degree of variation in anesthesiologists' practice when it actually comes to administering the "test" dose of protamine. The median PTD was 30 mg, which translated to 10% of the full protamine dose. The majority of the PTDs fell between 4% and 18% of the full dose. However, this percentage varied from 1% to 67% depending on the discretion of the anesthesiologist. There were 3 major outliers included in these data points representing a PTD percentage of 25% (100 mg), 33% (100 mg), and 67% (200 mg) of the full dose. If these 3 outliers are excluded from our sample size, the revised average PTD is 10% of the full dosage, ranging from 4 to 60 mg protamine. This observation supports complete standardization along with improved communication among all members of the cardiac team. We recommend that instead of a verbal recognition that the "test dose is given," communication should entail the actual dosage administered in milligrams, along with the percentage of the expected full dose.

Stammers and Mejak[4] reported the incidence of clot or thrombus present during CPB to be approximately 20%. These data were derived on the basis of 671,290 cases over the reporting period of July 1996 to June 1998.[4] It is not reported when the clot was formed, but 1 explanation could be related to retrieval of mediastinal shed blood after PTD administration. We were unable to find previous studies that directly evaluated the effect of PTD on clot formation following cardiac surgery.

We did see 6 patients experience an increase in ACT after PTD. One possible explanation for this phenomenon may be that the ACT samples were taken prematurely, before the protamine had a chance to circulate fully and bind heparin. Another potential reason for this anomaly is that additional heparin was administered by the

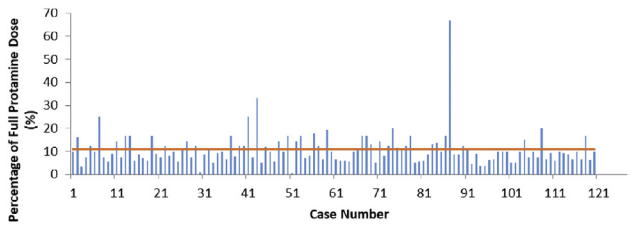

FIGURE 4 The protamine test dose depicted as the percentage of the final full protamine dose. The red line indicates the mean across all patients (11% ± 7%).

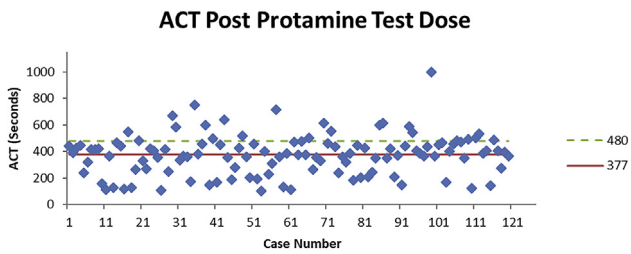

FIGURE 5 The measured activated clotting time (ACT) after the administration of the protamine test dose. The hashed line at 480 seconds represents our institutional threshold for instituting cardiopulmonary bypass. The red line represents the average activated clotting time after a protamine test dose (377 ± 153 seconds).

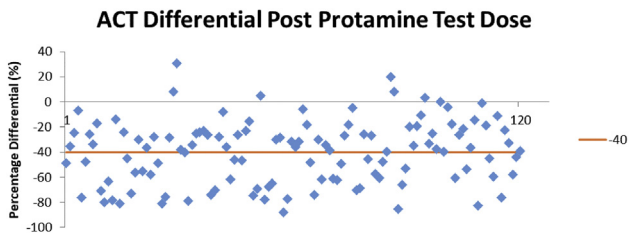

FIGURE 6 The percentage drop in measured activated clotting time (ACT) from before to after administration of the protamine test dose. The red line represents the average drop in activated clotting time (−40% ± 25%).

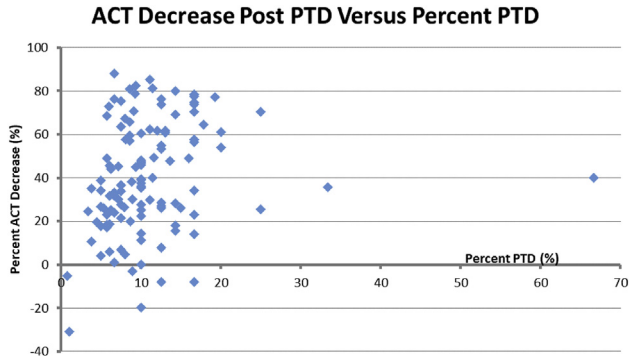

FIGURE 7 The drop in measured activated clotting time (ACT) from before to after administration of the protamine test dose (PTD) displayed as the proportional drop in activated clotting time after full protamine administration. The drop in activated clotting time after the protamine test dose was extremely variable.

TABLE 2 The Relative Decrease in Activated Clotting Time After the Protamine Test Dose

Decrease in Activated Clotting Time, %	Percentage of Study Population, % (n/N)[a]
0-20	16 (19/120)
21-40	36 (43/120)
41-60	17 (20/120)
61-80	22 (27/120)
81-100	4 (5/120)

[a]The remaining 5% (6 of 120 patients) experienced an activated clotting time percent increase, yielding a post–protamine test dose activated clotting time longer than the last activated clotting time during cardiopulmonary bypass.

perfusionist after the last ACT during CPB was taken, meaning that the true last ACT during CPB would have been greater than what was documented. Additionally, it is understood that the ACT test is not always an accurate measure of clotting time; however, it is the only perioperative test available to measure blood clotting time.

When considering the limitations of this study, one must acknowledge that the design was purely observational. However, the main focus of this study was to capture clinically relative and real-time data that represented our "daily" cardiac surgery management. Therefore, the only criterion for patient selection was that the patient was undergoing open heart surgery using CPB. All operation types, surgeons, anesthesiologists, and perfusionists were included in this study. We view this lack of specific inclusion criteria to be a strength of this study because it strengthens generalizability. Although standardizing the PTD to 10% of the full dose would provide consistency with respect to study results, such tight control was not practiced at our institution during this study. However, this study demonstrates that even a consistent 10% PTD would still result in an unpredictable response in ACT.

One future study to examine the effect of PTD on ACT and circuit integrity would be first to calculate how much protamine is needed to reverse heparin by using a device such as the Hemostatic Management System (Medtronic, Minneapolis, MN). This information, in turn, could be used to calculate and observe how a smaller PTD would affect the ACT. However, as seen in this study, the ACT response to even a small protamine dose is unpredictable.

In conclusion, this study was initiated to investigate a concerning observation of clot in the venous reservoir after the PTD. It was an original assumption that a PTD would be too small to have any meaningful clinical impact These data confirm that an individual ACT response to any dose of protamine is unpredictable. This research has prompted a universal shift in practice within our center by discontinuing the use of any direct recovery of mediastinal shed blood into the pump circuit after administration of protamine.

Regardless of the PTD, CPB circuit integrity is at risk during and after the test dose administration. It is strongly recommended that adherence to the American Society for Extracorporeal Technology Standards and Guidelines for Perfusion Practice be enforced.[3] In doing so, any shed heparinized patient blood that is partially reversed by protamine will be excluded from the CPB circuit , thus decreasing the risk of disrupting circuit integrity. This practice will increase patient safety and reduce complications associated with a compromised CPB circuit in the event that emergency initiation of CPB is required.

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