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Can the Minimum Protamine Dose to Neutralize Heparin at the Completion of Cardiopulmonary Bypass be Significantly Lower than the Conventional Practice?

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Abstract: Systemic anticoagulation with heparin during cardiopulmonary bypass (CPB) should be neutralized by protamine administration to restore normal hemostasis. However, protamine has potentially serious side effects and excessive protamine can cause increased postoperative bleeding. Thus, our goal is to appropriately dose protamine at the completion of CPB to neutralize heparin so that neither residual heparin nor excessive protamine is present. We performed a retrospective study of 216 patients who underwent cardiac surgery to search for a safe minimum protamine dose (PD) when measuring heparin concentration (HC). In addition, we developed a formula to determine PD using total heparin dose (THD) and CPB time without measuring HC. When protamine-to-heparin ratio (P-to-H) is set at 1 mg protamine to 100 international unit (IU) heparin in HMS Plus Hemostasis Management System (HMS), we determined that 75% of the calculated total PD is a safe minimum PD to sufficiently neutralize circulating heparin after CPB. On average, this translates into either .37 mg protamine/100 IU heparin of THD or .54 mg/100 IU of the first heparin bolus. The formula we developed to calculate PD without measuring HC can provide a PD that strongly agrees with the safe minimum PD when measuring HC. The safe minimum PD to neutralize circulating heparin after CPB can be significantly lower than conventional dosing practices. Reduction of PD may decrease the risk of postoperative bleeding and protamine-related adverse events. Based on our data, we decreased P-to-H in HMS to examine whether it is possible to reduce PD further than the safe minimum PD determined in this study. **Keywords:** heparin protamine titration, protamine dose, protamine-to-heparin ratio, cardiopulmonary bypass, anticoagulation. *J Extra Corpor Technol. 2021;53:170–6*

Systemic anticoagulation with heparin during cardiopulmonary bypass (CPB) should be neutralized by protamine administration to restore normal hemostasis at the completion of CPB. However, protamine has been shown to have anticoagulant properties in the absence of heparin and other side effects including anaphylactic response with hypotension, bradycardia, and pulmonary hypertension (1–7).

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In addition, overdosing of protamine has been linked to increased postoperative bleeding (4,8–10), which is supported by increased activated clotting time (ACT) (11,12) and decreased platelet function (11,13–15) with excessive protamine dose (PD). It indicates that optimal PD should be just enough to neutralize circulating heparin at the completion of CPB so that neither residual heparin nor excessive protamine is present after protamine administration and neutralization of heparin.

However, PD strategy has been variable depending on institutions and clinicians. One of the most common strategy is a fixed protamine-to-heparin ratio (P-to-H) with either the first heparin bolus (FHB) or total heparin dose (THD) during CPB, which does not account for heparin metabolism during CPB. Another recent strategy is to use statistical or pharmacokinetic modeling of heparin

metabolism over time into account; a mathematical calculation of PD as a function of baseline and post-heparin ACTs; PD based on measured heparin concentration (HC), which should improve the accuracy of heparin neutralization and reduce PD (5,7,16–21).

At Massachusetts General Hospital (MGH), clinical practice guideline for heparin management is designed to use as minimum heparin as possible to maintain target ACT (tACT) $\geq$ 400 seconds and HC $\geq$ 2.0 international unit (IU)/mL on CPB, which allows for minimal PD to neutralize heparin at the completion of CPB (22). We have used HMS Plus Hemostasis Management System (HMS; Medtronic, Minneapolis, MN) to measure HC and ACT after the heparin bolus and during CPB, and to determine PD necessary to neutralize heparin at the completion of CPB.

Our actual protamine dose (APD) is determined based on HC and other considerations including time between last heparin protamine titration (HPT) and protamine administration. It results in a wide range of APD compared to PD calculated by HMS based on HC with last HPT, which allows us to determine a safe minimum PD to neutralize heparin in this retrospective study. We also developed a statistical formula to calculate PD using THD and CPB time without measuring HC, which agrees strongly with the safe minimum PD determined in this study.

METHODS

Patient Population

We reviewed the anesthesia and perfusion records of 313 patients from January 1, 2018 to May 4, 2018, who had cardiac surgery with CPB at MGH. Patients with the following criteria were excluded for accurate analysis: missing or incomplete data and patients with heart transplant, lung transplant, LVAD insertion, and red blood cell transfusion between heparin dose response (HDR) test and FHB or deceased. Ninety-seven patients were excluded, resulting in 216 patients to be analyzed.

Anticoagulation Management

We performed an HDR test in vitro using HMS to determine baseline ACT (bACT), individual slope, and calculated heparin concentration (CHC) to reach tACT before or right after induction of anesthesia. Our HMS is set to use IU of heparin (23,24) and we used porcine heparin sodium (1,000 USP units/mL) from SAGENT Pharmaceuticals (Schaumburg, IL) or FRESENIUS KABI (Lake Zurich, IL). Our tACT on CPB is $\geq$400 seconds and target HC is $\geq$2.0 IU/mL. Our practice at MGH to determine FHB to go on CPB is described in detail elsewhere (22).

Supplemental doses of heparin were administered as necessary to maintain tACT and target HC during CPB. During and after the completion of CPB, volumes in the CPB circuit are transferred to patients as much as possible. To determine PD required to neutralize heparin at the completion of CPB, we measure HC 5–10 minutes after cross clamp comes off. The P-to-H in our HMS was set at 1:1 (1 mg protamine per 100 IU heparin) for calculation of PD. HMS calculates and provides three PDs: patient, pump, and total PDs. Calculated total protamine dose (CTP) is calculated pump dose plus calculated patient protamine dose (CPP).

$$\text{CPP (mg)} = \text{measured HC (IU/mL)} \times \text{Total Blood Volume (TBV, mL)}^{(25)} \times 1\ \text{mg}/100\ \text{IU}$$

$$\text{Pump protamine dose (mg)} = \text{measured HC (IU/mL)} \times \text{Pump Volume (1300 mL)} \times 1\ \text{mg}/100\ \text{IU}$$

$$\text{CTP(mg)} = \text{CPP} + \text{pump protamine dose}$$

Our guideline does not specify whether to use CTP or CPP. It is a discretion among perfusionist, anesthesiologist, and surgeon to determine APD for each patient based on HC and other considerations including time between last HPT and protamine administration. We administer protamine sulfate (10 mg/mL, FRESENIUS KABI, Lake Zurich, IL) by bolus with a test dose (~10 mg) first to observe any adverse reaction, then up to a half dose, remove cannulas, and give the other half dose. Heparin neutralization by protamine was verified by measuring ACT and HC using a red HPT cartridge 3 minutes after the completion of protamine infusion. After we confirm the heparin neutralization, we do not administer any more protamine prophylactically to prevent a controversial heparin rebound (5), which is beyond the scope of this study.

P-to-H is expressed as either milligram of protamine/100 IU heparin or percentage with the following formula throughout this manuscript:

$$\left[(\text{Protamine dose in mg} \times 100)/\text{Heparin in IU}\right] \times 100(\%)$$

Data Analysis

We used Microsoft Office Excel 365 (Microsoft Corporation, Redmond, WA) to perform data input, calculations, histogram, scattered plot, fitted linear regression, Bland-Altman analysis, and other statistical analysis (Correlation coefficient, R; Student's t test, p; bias; limits of agreement, LOA).

RESULTS

Post-protamine ACT per Baseline ACT Shows a Two Tailed Standard Distribution

The average of CPP and CTP from HC using HPT right before the completion of CPB were 152 mg and 187 mg, respectively, for 216 patients. The average of APD was 174 mg, which is 114% of CPP and 93% of CTP. The ratio

of APD to heparin is 46% of the THD and 67% of FHB on average (Table 1A).

All but four patients had no residual heparin based on HPT with red cartridges after protamine administration. However, two of those four patients had lower post-protamine ACT (ppACT) than bACT, indicating errors in HPT (data not shown). This suggests that APD based on HPT was sufficient to neutralize heparin in almost all cases and it is likely that free protamine still exists after neutralizing heparin in some cases. The average of ppACT was 112 ± 15 seconds, which is significantly lower than bACT, 132 ± 16 seconds (p, .00). On average, ppACT/bACT was 86 ± 12% (Table 1A) and shows a standard two tail distribution (Table 1B and Figure 1). Even though ACT is not an ideal test to monitor residual heparin or excessive protamine since it can be affected by other factors such as hemodilution, impaired platelet, and/or kidney function, it indicates that ppACT/bACT about 80–90% is a good indicator of proper neutralization of heparin. Thus, we determined to use ppACT/bACT (%) as a reliable indicator to analyze a safe minimum PD in this study.

Table 1. Patient information, protamine doses, ppACT/bACT distribution.

A

	Average	SD
Height (cm)	171.7	10.2
Weight (kg)	84.6	17.0
BMI	28.6	4.9
BSA (m^2)	1.97	.23
Platelets (counts/nL blood)*	221	65
First heparin bolus (FHB, IU)	26,006	7,083
Total heparin dose (THD, IU)	37,928	10,751
First Hep. Conc†	3.5	.9
Last Hep. Conc‡	2.7	.7
Cal. patient protamine dose (CPP, mg)	152	23
Cal. pump protamine dose (mg)	35	9
Cal. total protamine dose (CTP, mg)	187	60
Actual protamine dose (APD, mg)	174	53
APD/THD (%)§	46	10
APD/ FHB) (%)§	67	15
CPB time (min)	134	60
Cross clamp time (min)	96	47
Baseline ACT (bACT, sec)	132	16
Post-protamine ACT (ppACT, sec)	112	15
ppACT/bACT (%)	86	12

B

	# of Patients (%)	Average	SD
52 < ppACT/bACT ≤ 70%	16 (7%)	64%	5
70 < ppACT/bACT ≤ 80%	54 (25%)	77%	3
80 < ppACT/bACT ≤ 90%	78 (36%)	86%	3
90 < ppACT/bACT ≤ 100%	51 (24%)	95%	3
100 < ppACT/bACT ≤ 141%	17 (8%)	111%	12

*From 135 patients.
†Heparin concentration measured by HPT prior to CPB after FHB.
‡Heparin concentration measured by HPT right before CPB completion.
§Protamine:Heparin ratio expressed as %: [(Protamine dose in mg × 100)/ Heparin in IU] × 100.

Smaller Ratio of APD per CTP or CPP was Sufficient to Neutralize Heparin

The averages of APD/CTP and APD/CPP are widely distributed as 74–107% of APD/CTP and 94–142% of APD/CPP (Table 2A, C). However, ppACT/bACT are similar in all groups (83–89% on average) and no statistically significant difference exists in neighboring groups (Table 2A, C) and between any two groups (Table 2B, D). It suggests that 74 of CTP (average of 60–80% group) or 94% of CPP (averages of 71–100% group) are likely enough to neutralize heparin completely in almost all cases. Seventy-four percent of CTP is 138 and 94% of CPP is 143 mg, which is 79% and 82% of APD, respectively. Thus, we can set either approximately 75% of CTP or 95% of CPP as a safe minimum PD to neutralize heparin at the completion of CPB. It will decrease PD without affecting neutralization of heparin. It also decreases probability of excessive protamine, which likely reduce the postoperative bleeding and side effects of protamine.

As CPB Time Decreases, Higher APD/THD Ratio is Required to Neutralize Heparin at the Completion of CPB

Average APD/THD was 46 ± 10% and APD/FHB was 67 ± 15% (Table 1A). However, both had a wide range as 23–79% for APD/THD and 33–109% for APD/FHB. This wide range may reflect the heparin metabolism in part, thus can be correlated to CPB time. We investigated whether APD, THD, FHB, APD/THD, or APD/FHB had any correlation with CPB time and affected ppACT/bACT.

THD has a weak/moderate positive correlation (R, .38) with CPB time while APD (R, –.05), FHB (R, –.01), and APD/FHB (R, –.04) do not have any correlation with CPB time. However, APD/THD has a moderately significant negative correlation (R, –.51) with CPB time (Figure 2A). As shown in Table 3A and Figure 2B, when APD/THD ratio became higher, CPB time became gradually shorter with statistically significant difference between neighboring groups except two high-ratio groups with relatively short CPB times. However, ppACT/bACT was similar in all groups, indicating that less APD/THD ratio was sufficient to neutralize heparin as CPB times became longer (Table 3B). In contrast, CPB time was not different with different ratio of APD/FHB (Table 3C). In addition, when smallest ratio (33–50%) was used, ppACT/bACT was significantly higher than neighboring group (51–60%; Table 3C). These data suggest that a fixed ratio of protamine to FHB better be around 55% or higher (average of 51–60%). More importantly, we should be able to predict a PD without measuring HC better by developing a formula using this statistical correlation between APD/THD and CPB time.

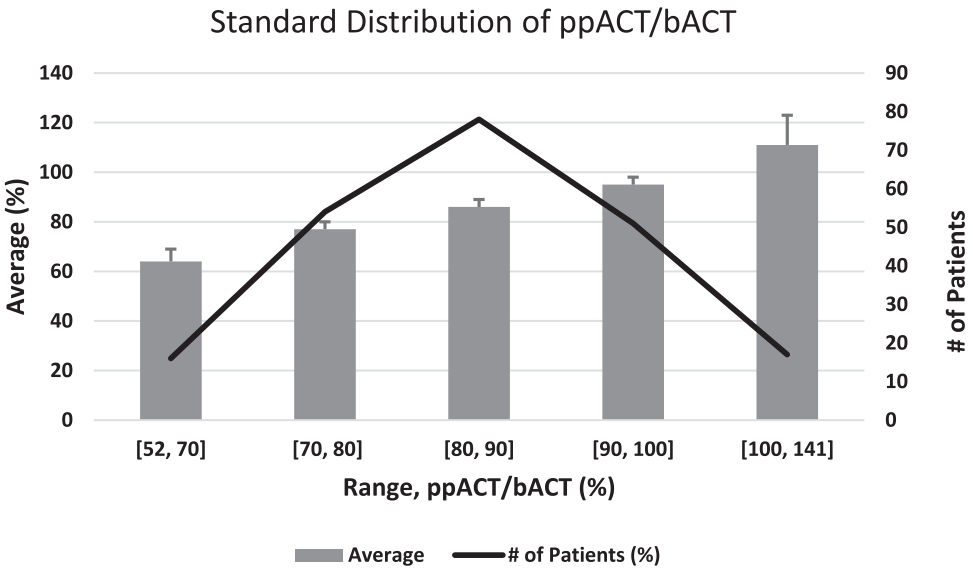

Figure 1. ppACT/bACT shows a standard distribution. ppACT/bACT (%) was calculated from ppACT to bACT of each patient and plotted into a histogram with indicated intervals in a bar graph. On top of each bar, SD is shown. A line graph shows the number of patients in each range. X-axis is the range of ppACT/bACT (%), Y-axis on left is averages of ppACT/bACT (%), and Y-axis on right is the number of patients. It shows a standard two-tail distribution with a peak at 80–90% range. All numbers are also shown in Table 1B with more detail.

Prediction of a Safe Minimum PD Using THD and CPB Time Without Measuring HC

Since 75% of CTP is likely a safe minimum PD from our current analysis, we investigated whether 75% CTP/THD has correlation with CPB time and found that 75% CTP/THD has a moderately significant negative correlation (R, –.50) with CPB time (Figure 3A). With this correlation, we made a formula (CalPD75) to calculate PD using THD and CPB time, which can provide a safe minimum PD without measuring HC. This formula can be applied when CPB time is less than 360 minutes. We do not have enough data beyond 360 minutes to support this formula.

$$\text{CalPD75(mg)} = \left[(-0.07\ \text{(mg/IU/min)} \times \text{CPB time(min)} + 46.4\text{(mg/IU)}) \times \text{Total Heparin (IU)}\right]/10000$$

Table 2. ADP/CTP and ADP/CTP distributions.

A. APD/CTP, distribution

APD/CTP	60–80%	*p*	81–90%	*p*	91–100%	*p*	>100%
# Pt (%)	26 (12%)		54 (25%)		64 (30%)		72 (33%)
Avg	74 ± 6%	.00	86 ± 2%	.00	97 ± 3%	.00	107 ± 9%
ppACT/bACT	89 ± 8%	.23	86 ± 15%	.68	85 ± 12%	.59	86 ± 12%

B. APD/CTP, *p*-value of ppACT/bACT

APD/CTP	60–80%	81–90%	91–100%	>100%
60–80%	N/A	.23	.07	.15
81–90%		N/A	.68	.97
91–100%			N/A	.59
>100%				N/A

C. APD/CPP, distribution

APD/CPP	71–100%	*p*	101–110%	*p*	111–120%	*p*	121–130%	*p*	>130%
# Pt (%)	35 (16%)		40 (19%)		45 (21%)		54 (25%)		42 (19%)
Avg	94 ± 7%	.00	105 ± 3%	.00	116 ± 3%	.00	125 ± 3%	.00	142 ± 14%
ppACT/bACT	87 ± 11%	.93	87 ± 15%	.30	84 ± 11%	.83	85 ± 9%	.51	86 ± 15%

D. APD/CPP, *p*-value of pACT/bACT

APD/CPP	71–100%	101–110%	111–120%	121–130%	>130%
71–100%	N/A	.93	.28	.29	.82
101–110%		N/A	.30	.31	.77
111–120%			N/A	.83	.47
121–130%				N/A	.51
>130%					N/A

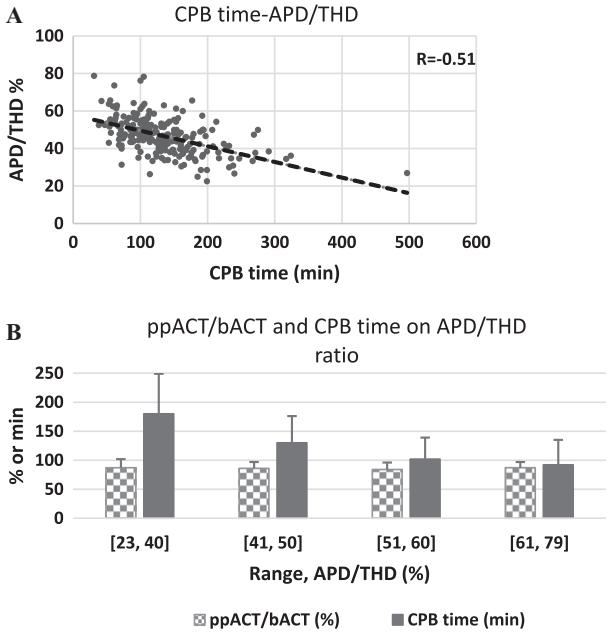

Figure 2. Less APD over THD was sufficient to neutralize heparin as CPB time becomes longer. (A) A XY scattered plot was drawn for CPB time (minutes, X-axis) and APD/THD (%; Y-axis) and data was fitted into a linear regression line, which shows a moderately significant correlation. R value is shown in the upper-right corner. (B) APD/THD (%) was calculated from each patient and plotted into a histogram with indicated intervals in two bar graphs. Checked bars show ppACT/bACT (%) and solid bars show CPB times. On top of each bar, SD is shown. X-axis is the range of APD/THD (%) and Y-axis is % (ppACT/bACT) or minutes (CPB time) in the same scale. All numbers are also shown in Table 3A with more detail.

This formula can calculate PD that is strongly correlated with the 75% CTP (*R*, .81), as shown with linear regression analysis of scattered plot (Figure 3B). Bland-Altman analysis (26,27) of 75% CTP and CalPD75 also show significant agreement with bias of 2 mg and LOA between –49 and 52 mg (Figure 3C), which indicates that this formula can provide a safe minimum PD close to 75% CTP without measuring HC.

DISCUSSION

One of our major goals in anticoagulation management in CPB is using minimum amount of protamine at the completion of CPB. To achieve this, our guideline encourages to maintain low level of HC (if it is ≥2.0 IU/mL and ACT ≥ 400 seconds) during CPB regardless of initial CHC determined with HDR, which decreases the amount of heparin usage and PD at the completion of CPB (22). Since it is the discretion of the perfusionist, anesthesiologist, and surgeon to determine APD, we used a wide range of PD (60–146% of CTP or 71–192% of CPP, also see Table 2A, C). This wide range of APD made it possible to search for the safe minimum PD. Our analysis clearly indicates that PD recommended by HMS is likely over-prescribed and it should be sufficient to use about either 75% of CTP or 95% CPP when P-to-H in HMS was set at 1 mg protamine/100 IU heparin.

This suggests that residual free protamine likely exists after neutralizing circulating heparin completely in most

Table 3. CPB time negatively correlates with APD/THD but not with APD/FHB.

A. APD/THD							
APD/THD	23–40%	*p*	41–50%	*p*	51–60%	*p*	61–79%
# Pt (%)	57 (26%)		95 (44%)		47 (22%)		17 (8%)
Avg	35 ± 4%		46 ± 3%		55 ± 2%		67 ± 6%
ppACT/bACT	87 ± 15%	.39	86 ± 11%	.36	84 ± 12%	.40	87 ± 10%
CPB time	180 ± 69	.00	130 ± 46	.00	102 ± 37	.38	92 ± 43

B. APD/THD, *p*-value of ppACT/bACT				
APD/THD	23–40%	41–50%	51–60%	61–79%
23–40%	N/A	.39	.17	.82
41–50%		N/A	.36	.74
51–60%			N/A	.40
61–79%				N/A

C. APD/FHB								
APD/FHB	33–50%	*p*	51–60%	*p*	61–70%	*p*	71–80%	*p*	81–109%
# Pt (%)	37 (17%)		41 (19%)		53 (25%)		52 (24%)		33 (15%)
Avg	45 ± 5%		56 ± 3%		65 ± 3%		75 ± 3%		92 ± 6%
ppACT/bACT	93 ± 15%	.005	85 ± 10%	.12	88 ± 9%	.02	83 ± 10%	.13	79 ± 15%
CPB time	142 ± 52	.41	132 ± 58	.34	145 ± 71	.04	120 ± 52	.44	130 ± 58

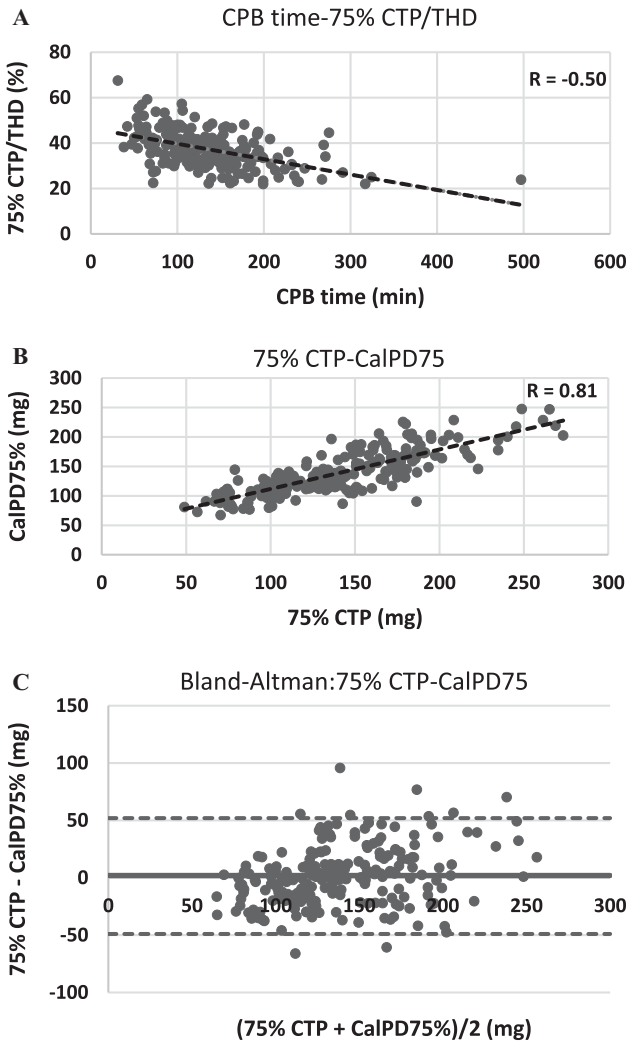

Figure 3. PD calculated with CalPD75 using THD and CPB time without measuring HC strongly agrees with the safe minimum PD. (A) A XY scattered plot was drawn for CPB time (X-axis) and 75% CTP/THD (%; Y-axis) and data was fitted into a linear regression line, which shows a moderately significant correlation. R value is shown in the upper right corner. (B) A XY scattered plot was drawn for 75% CTP (X-axis) and CalPD75 (Y-axis) and data was fitted into a linear regression line, which shows a strongly significant correlation. R value is shown in the upper right corner. (C) Bland-Altman analysis of 75% CTP and CalPD75 shows a strong agreement with bias of 2 mg (solid line) and LOA of 52 and −49 mg (dashed lines). X-axis is the average of 75% CTP and CalPD75. Y-axis is the difference between 75%CTP and CalPD75.

cases. There can be several possible reasons. First, HC determined by HPT is not linear but discrete and heparin can be further metabolized during the time between last HPT and actual protamine given. Second, total blood volume is over-estimated in certain population of patient (28), leading to over-prescription of protamine. Our study also strongly suggests that P-to-H at 1 mg protamine/100 IU heparin is likely an over-estimation. Based on this study, we changed P-to-H in our HMS to .9mg protamine/100 IU heparin for 5 months without any complication, then further reduced to .8 mg protamine/100 IU heparin currently. It will require a future study to demonstrate that this change of P-to-H results in further reduction of PD without compromising heparin neutralization and hemostasis.

We also developed a formula (CalPD75) to predict PD without measuring HC, which shows significant agreement with the safe minimum PD (75% of CTP) determined in this study (Figure 3). It indicates that less PD is sufficient with longer CPB time when the same THD was used. Even though this formula is simple and only dependent on CPB time and THD, CPB time implies the heparin metabolism and THD includes body size indirectly. In addition, this formula would provide a significant advantage over a simple fixed ratio to use optimal amount of protamine and decrease APD on average.

Our current P-to-H is 46% of THD and 67% of FHB on average (Table 1A), which is already significantly lower than the conventional fixed ratio of 80–100% of FHB (5,18) or 60–80% of THD (21). In addition, this study indicates that it can go down safely to 37% of THD (when 75% of CTP is sufficient) and 54% of FHB (when 95% of CPP is sufficient) on average. Recently, the reduction of PD has been observed with formulas using statistical or pharmacokinetic modeling (19,20). Hällgren et al. (20) decreased APD from 426 to 261 mg on average with a shorter intrinsic clotting time and stronger clot firmness using a statistical modeling. Meesters et al. (19) achieved 55% reduction in APD (from 416 to 186 mg on average) with a shorter intrinsic clotting time by using a pharmacokinetic modeling. Our current APD is 174 mg (Table 1) and this study indicates that it can safely go down to 140 mg on average (when 75% of CTP is sufficient). Overall, these studies indicate that a safe minimum PD to neutralize heparin at the completion of CPB can be significantly lower than the conventional practice.

Limitations

While it was suitable to use ppACT/bACT as a reliable indicator of heparin neutralization in this study, it has been shown that different ACT devices have different ratio of ppACT/bACT on the same population of patients (29,30). Thus, heparin neutralization based on ppACT/bACT should be carefully interpreted depending on the ACT device. In addition, we do not use a thromboelastography device, which could provide characteristics of clot formation such as clotting time and clot firmness (4,18) and possibly could have given more insight into this study.

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