Heparin monitoring during cardiac surgery. Part 2: calculating the overestimation of heparin by the activated clotting time

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Activated clotting time (ACT) values were converted to heparin concentration, enabling an assessment of the accuracy of the ACT and a quantification of the prolongation imposed by bypass. Blood samples were obtained from 42 adult cardiopulmonary bypass (CPB) patients before and during bypass surgery. Samples were analysed for ACT (HemoTec ACT) and anti-factor Xa (anti-Xa) plasma heparin concentration. The mean heparin concentration calculated before bypass was an accurate reflection of plasma heparin; however, calculated values rose to around 170% of anti-Xa values upon connection to bypass. By adjusting for this rise, for 95% of cases the calculated heparin concentration would vary between 0.60 and 1.65 times anti-Xa values. Without accounting for artificial prolongation or individual sensitivities, the ACT may give values between 0.8 and 3.0 times that indicated by the anti-Xa assay. When both individual heparin sensitivities and the effects of bypass are considered, the ACT may provide a more suitable indication of heparin levels; however, typical use may overestimate heparin up to threefold. Perfusion (2003) 18, 277–281.

Introduction

The Hepcon/HMS system enables the operator to perform an automated in vitro heparin dose–response (HDR) test for each patient, to determine individual heparin sensitivities. The Hepcon HDR cartridge is a modified HemoTec activated clotting time (ACT), with known quantities of heparin added. Obtaining the HDR would also enable the HemoTec ACT to provide an estimation of heparin concentration, similar to the method described by Bull et al.1 Conversion of ACT values into heparin concentration permits direct comparison with anti-factor Xa (anti-Xa) plasma heparin concentration, thus providing data on the accuracy of the ACT. This also enables quantification of the prolongation imposed by bypass on the ACT, which may lead to the use of an adjustment factor to account for this. A simple method of calculating heparin concentration from the ACT may also be used as a cost-effective alternative to repeated Hepcon titrations.

Methods

Forty-two adult patients, 50 years or above, undergoing first-time elective coronary artery bypass grafting (CABG) surgery were enrolled in this study. The details for intraoperative management and blood sampling regime for these patients have previously been supplied.2 Laboratory heparin concentrations were determined using a chromogenic anti-Xa assay, as previously described.2

Calculations

The HDR slope is calculated from the following formula:

\[
\text{Slope (second/U/mL)} = \frac{\text{ACT}_2 - \text{ACT}_1}{[\text{heparin}]}
\]

where [heparin] = the heparin concentration (U/mL) used to achieve the change in clotting time (ACT2 – ACT1).

The Hepcon HDR cartridge obtains duplicate clotting times, using three in vitro heparin concentrations: 0, 1.5 and 2.5 U/mL. The given HDR is the average of two calculated slopes.
Using the HemoTec HDR slope given by the Hepcon, the formula can be rearranged to calculate heparin concentration, using

\[
[\text{heparin}] = \frac{\text{ACT}_2 - \text{ACT}_1}{\text{Slope} \,(\text{second} / \text{U} / \text{mL})}
\]

where \(\text{ACT}_2\) = test ACT, \(\text{ACT}_1\) = baseline ACT and \(\text{Slope}\) = calculated slope from Hepcon/HMS.

If the ACT is an accurate test of heparinization, the calculated heparin (\(\text{Hep}_{\text{calc}}\)) concentration 5 min after heparin administration, before CPB, should approximate the anti-Xa plasma heparin concentration. However, values for \(\text{Hep}_{\text{calc}}\) obtained during bypass would be expected to be higher than anti-Xa heparin concentration due to the effects of haemodilution and hypothermia artificially prolonging the ACT. The effect these factors have on the ACT during bypass, and therefore the \(\text{Hep}_{\text{calc}}\), can be calculated from the difference in \(\text{Hep}_{\text{calc}}\) from anti-Xa heparin at each time point during CPB, using mean results from the entire group. This will give an adjustment factor for the effect of CPB, using

\[
\text{Adjustment} = \frac{\text{Hep}_{\text{calc}}}{\text{anti-Xa}}
\]

From this, a new \(\text{Hep}_{\text{calc}}\) can be generated once the required adjustment factor is known.

\[
\text{Hep}_{\text{calc}} \text{ with adjustment (}\text{Hep}_{\text{calcAdj}}\text{)} = \frac{\text{ACT}_2 - \text{ACT}_1}{\text{Slope} \,(\text{second} / \text{U} / \text{mL})} \times \frac{1}{\text{Adjustment}}
\]

This formula can now be used to calculate heparin concentrations for individual patients from their HemoTec ACT. The adjustment factor can also be applied to the HemoTec ACT, to provide an estimation of the value of the ACT without the effects of haemodilution and hypothermia.

One final calculation of heparin concentration was derived from the ACT: this time neither individual heparin sensitivities nor adjustment for bypass effects were used in the equation. The aim of this calculation was to estimate the level of agreement between ACT and plasma heparin concentration through typical use of the ACT, without obtaining a prior dose–response. The ACT was converted to heparin concentration using the mean dose–response slope derived from the entire patient group, rather than the slope generated for each patient.

**Statistics**

Agreement between the methods for determining heparin concentration was assessed using the technique described by Bland and Altman. The application of this method has previously been described.

**Results**

*Heparin calculations from HemoTec ACT*

The results are shown in Figure 1. Values are expressed as mean ± SD. The \(\text{Hep}_{\text{calc}}\) level 5 min after heparin bolus was \(4.4 \pm 1.42\) U/mL, then rose to \(4.7 \pm 1.62\) U/mL 20 min into bypass before falling to \(3.8 \pm 1.16\) U/mL at the end. In comparison, the values for anti-Xa heparin over the same time period fell from an initial value of \(4.0 \pm 0.70\) U/mL to \(2.7 \pm 0.38\) U/mL by 20 min into bypass, dropping to \(2.3 \pm 0.46\) U/mL at the end of bypass. A weak correlation exists between the two measures (\(r = 0.39\)). The values for \(\text{Hep}_{\text{calc}}\) at each time point were expressed as a fraction of anti-Xa heparin to assess the effect of bypass on the results (Figure 2). From this, the adjustment factor for CPB was 1.7 during the hypothermic stage and 1.6 after rewarming. No adjustment was used for the sample obtained before CPB. These adjustment factors were used to calculate \(\text{Hep}_{\text{calcAdj}}\).

*Comparison of \(\text{Hep}_{\text{calcAdj}}\) with anti-Xa heparin concentration*

Results for \(\text{Hep}_{\text{calcAdj}}\) were \(4.4 \pm 1.42\) U/mL at the 5 min sample, then a fall to \(2.8 \pm 0.95\) U/mL by 20 min

**Figure 1** Time course of mean values for heparin concentration by the anti-Xa assay and values calculated from the ACT. Time points are: A) 5 min after heparin administration, before connection to bypass; B) 20 min after initiation of bypass; C) 40 min on bypass; D) 60 min on bypass; E) immediately prior to disconnection of bypass, before protamine administration.
on CPB, until a final value of $2.4 \pm 0.73$ U/mL at the end of bypass (Figure 1). For combined results, the values for Hep\textsubscript{calcAdj} correlate well with anti-Xa heparin concentration ($r = 0.75$). Mean results for the two determinations of heparin concentration were anti-Xa heparin $2.8 \pm 0.8$ U/mL, Hep\textsubscript{calcAdj} $2.9 \pm 1.3$ U/mL, indicating a bias of only 0.1 U/mL for the Hep\textsubscript{calcAdj}. The limits of agreement calculated around this bias were $\pm 1.71$ U/mL, shown in Figure 3. The range of differences between the two measures appeared to increase with magnitude. In addition, the difference between measures was shown to correlate with magnitude ($r = 0.60; p < 0.001$). Therefore, log transformation was also used to determine the limits of agreement. The range for the logged data was $-0.220$ to $-0.218$, with the antilog of these limits indicating that, for 95% of cases, the Hep\textsubscript{calcAdj} would be between 0.60 and 1.65 times the value of anti-Xa heparin.

**Use of adjustment factor for ACT**

The adjustment factor that was previously derived for the calculations of Hep\textsubscript{calcAdj} was applied...
directly to the ACT, providing a value for heparin effect without the prolongation associated with CPB. This adjusted ACT value (ACT_{Adj}) is strongly associated with plasma heparin levels (Figure 4; r = 0.71).

**ACT calculations not accounting for heparin sensitivity/effects of bypass**

The mean HDR slope for the patient population was 85.5 seconds/U/mL. When this value was used in the calculation for each patient, the mean heparin concentration derived was 4.3 ± 1.42 U/mL, indicating a bias of 1.5 U/mL with limits of agreement for the difference ± 2.8 U/mL. Log transformation revealed that the ACT value converted to heparin concentration may vary from 0.8 to 3.0 times the plasma heparin concentration. These limits are shown in the scatter plot of original data (Figure 5).

**Discussion**

The vast majority of cardiac centres rely on the ACT for intraoperative monitoring of heparin anticoagulation, despite its poor relationship with plasma heparin concentration. There are two main factors known to confound the ACT result during bypass: a range of individual sensitivities to heparin across the patient population, and artificial prolongation during bypass by factors such as haemodilution and hypothermia.

Bull et al. described the use of a heparin dose–response curve to account for individual heparin sensitivities, from which the dose required to achieve a desired clotting time can be calculated. This curve was also used to calculate heparin concentration from ACT determinations, and to predict the dose of protamine required for heparin neutralization. While the method of Bull and associates accounts for individual heparin sensitivities, it does not account for the loss of relationship between ACT and heparin concentration upon connection to bypass. Thus, heparin levels are overestimated, which may predispose to subclinical coagulation. In addition, ACT-based protocols for protamine dosing would result in excessive delivery of this drug. Mean protamine doses based on the ACT have been shown to be 67% higher than doses based on plasma heparin concentrations and twice as high as the dose actually needed for complete heparin neutralization. This may increase the risk of postoperative bleeding due to inhibition of platelet function and clot structure formation by the excess protamine.

In this study, the heparin concentration was calculated from the HemoTec ACT, using the heparin dose–response curve generated preoperatively by the Hepcon instrument. The Hep_{calc} value obtained was a fair reflection of anti-Xa plasma heparin concentration 5 min after heparin administration, before connection to bypass. However, upon initiation of CPB, the values for Hep_{calc} rose to around 170% of anti-Xa heparin concentration. This rise in value of Hep_{calc} is a reflection of the effects of bypass on the HemoTec ACT, namely haemodilution and hypothermia. At the end of CPB, when the patients are rewarmed, the Hep_{calc} was at 160% of anti-Xa heparin. These comparisons were used to provide a value for the effects of bypass on the ACT. After adjusting the calculations by 1.7 during the hypothermic stage, and 1.6 after rewarming, the value for Hep_{calc Adj} was obtained. The relationship between the calculated heparin concentration and plasma anti-Xa heparin was considerably improved by accounting for artificial prolongation during bypass: Hep_{calc} (r = 0.39), Hep_{calc Adj} (r = 0.75). The measure of agreement indicates that the adjusted heparin concentration obtained from the ACT may vary between 0.60 and 1.65 times, or from 40% below to 65% above anti-Xa heparin concentration.

It can be seen from the difference plot in Figure 3 that there is a trend in the bias between measurements. Analysis shows the difference between measurements is strongly positively correlated to magnitude, such that, as the magnitude of measurements for heparin concentration increases, the Hep_{calc Adj} gives increasingly higher values in comparison with anti-Xa heparin concentration. It could be argued that the variable effects of bypass on the ACT, and the artificial nature of the adjustment factor, clouds the results for calculated heparin. Therefore, we analysed separately the Hep_{calc} from the sample taken after heparin bolus, before connection to bypass. Again, there was a strong positive relationship between difference and magnitude (r = 0.71; p < 0.001). Together, these results show that, as the magnitude of heparin measurements increases, ACT-based measures, even without the effects of haemodilution and hypothermia, become increasingly variable compared with anti-Xa heparin, but this variability will tend to increasingly overestimate heparin levels. When this tendency of the ACT to progressively overestimate is combined with the known prolongation by factors, such as haemodilution and hypothermia, it can be seen that the ACT is a poor indicator of intraoperative heparin, particularly at high concentrations. This is further highlighted by the following comparisons. Most centres do not establish individual heparin sensitivities with a dose–response curve, simply recording a baseline ACT then one or more test ACT
determinations to measure heparin effect. In further analyses, the ACT results in this series were converted to heparin concentration using the mean HDR value for the group, not correcting for haemodilution/hypothermia (Figure 5). This is the best approximation of what the agreement between ACT and plasma heparin would be with common usage of this instrument. From these calculations, it was found that the ACT would give values from 0.8 to 3.0 times the value for anti-Xa heparin. Thus, at a heparin concentration of 3 U/mL measured by the anti-Xa assay, the ACT may give values corresponding up to 9 U/mL, and would easily indicate adequate anticoagulation below critical levels of heparin concentration (<2 U/mL).

In conclusion, we have provided a value for the prolongation of ACT during bypass by factors including haemodilution and hypothermia. By accounting for both individual heparin sensitivities and the effects of bypass, the ACT-based measure of heparin concentration agrees moderately well with anti-Xa heparin concentration. However, not only does ACT dramatically increase during bypass by factors other than heparin, the ACT will also tend to overestimate as the concentration of plasma heparin increases. This is because as increased inaccuracy occurs, the ACT is more likely to continue counting rather than stop counting too early. With typical use of the ACT, the user may obtain values up to three times appropriate for the plasma heparin concentration. Potential consequences of this overestimation include the possibility of inadequate intraoperative anticoagulation by heparin, and vastly excessive delivery of protamine, resulting in increased postoperative bleeding.

Acknowledgements

This work was funded by The Prince Charles Hospital Foundation, Grant FRC 0398-02; and an ARC Spirit Grant for Biostatistical Support, Grant C10024120.

References

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