Variable Anticoagulant Response In Patients Undergoing Cardiopulmonary Bypass With Low AT III Levels

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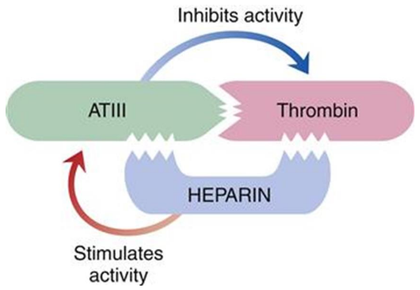
INTRODUCTION

The primary mechanism of action of unfractionated heparin is to enhance the enzymatic activity of antithrombin III (ATIII), potentiating its inhibitory effect on activated factor X (factor Xa) and thrombin. The activated clotting time (ACT) is the most frequently used test to measure heparin activity while on CPB.

A target activated clotting time (ACT) of greater than 400 sec is used to prevent blood clots during cardiopulmonary bypass (CPB). The ACT has been shown to be highly susceptible to variation. Does not correlate well with Anti-Xa measures of heparin activity and heparin concentration, especially during hypothermia and hemodilution. The individual response to a fixed dose of heparin varies, with some patients requiring higher than usual doses to achieve a target ACT, a phenomenon known as heparin resistance. This may be due to ATIII deficiency, AT-independent binding of heparin to plasma proteins, proteins released from platelets and endothelial cells, or more commonly, acquired AT III deficiency.

In both pediatric and adult populations, heparin concentrations decrease upon institution of CPB, while the ACT increases.

We hypothesized that higher doses of heparin alone will be needed in patients undergoing CPB with low AT III to achieve the target ACT necessary for CPB.



METHODS

After obtaining IRB approval, we retrospectively reviewed the charts of adult patients undergoing cardiac procedures that required CPB from 2016 to 2017 at an academic medical center. Data collected included patient demographics, baseline ATIII level, heparin-loading dose, total heparin given during the case, baseline ACT (ACT1) and ACT prior to the initiation of CPB (ACT2). ATIII was divided into two categories: normal (80-120%) and low (<80%). ATIII data sorted into categories (low and normal) was tested for normality and found to be non-parametric. The Mann U Whitney test was used to compare variables and test for significance. Heparin responsiveness of each patient was quantified by using the heparin sensitivity index (HSI) (sec/unit/kg):

$$HSI = \frac{ACT\ after\ Heparin - Baseline\ ACT}{Heparin\ Bolus\ Dose}$$

RESULTS

In all, the charts of 300 patients were reviewed for this study. The patients were a mean age of 61.5 ± 11.5 years with a BMI of 30.2 ± 10.13. Patients' average ACT achieved prior to initiating CPB was 515 ± 136.9 sec (Table 1). There was no statistically significant difference between ACT2 in the low or normal AT III groups (p=0.234). There was also no significant difference in the total heparin loading dose between either ATIII groups (p=0.116). However, the total heparin given (loading plus on-CPB maintenance) was significantly higher in the lower AT III range (45,577 ± 21,214 Units) as compared to the normal group (38,925 ± 13,478 Units) (p=0.016). Heparin sensitivity was not significantly different in either the low or normal range AT III (p=0.154) (Table 2). The was no correlation between the HSI in the low group (r =-0.03), normal group (r = 0.06) or both groups combined (r = 0.07).

Table 1

ATIII Quantiles	Avg Heparin Loading Dose (Units)	Avg ACT_2 (secs)
Low (N=91)	31,720 ± 9948	506 ± 132
Normal (N=207)	29,200 ± 6717	518 ± 139

Table 2

Variable	Compared to ATIII groups
Heparin Loading Dose	p=0.116
Heparin on CPB	p=0.012*
Total Heparin Given	p=0.016*
Heparin Sensitivity Index	p=0.154
ACT to Initiate CPB	p=0.234

DISCUSSION

ACT can be influenced by variables other than ATIII such as hypothermia, hemodilution and low platelet count which are commonly seen during cardiac surgery. Heparin produces its major anticoagulant effect through an AT-dependent mechanism. AT-independent binding of heparin results in a variable anticoagulant response. Garvin et. al found that heparin responses were independent of preoperative plasma AT activity in patients undergoing primary CABG.2

DISCUSSION

Augmentation of ACT values during hemodilution means that larger doses of heparin are required to maintain heparin concentration than would be used to maintain ACT alone. In patients with low AT III, higher doses of heparin were needed to achieve the target bypass ACT and did not require supplementation with fresh frozen plasma or reconstituted ATIII injection. In addition, the amount of heparin required to initiate bypass (ACT 400 sec) was not significantly different regardless of ATIII concentration. However, the total heparin given intraoperatively was significantly higher in patients with low ATIII, meaning more heparin was given while on bypass in order to maintain an adequate ACT. Also the HSI was not significantly different between the two ATIII groups, indicating that the HSI should still be a relevant calculation for heparin response in even low ATIII patients. Measuring heparin concentration has been suggested as a supplemental means to confirm adequate anticoagulation. The known augmentation of ACT values during hemodilution (without concomitant increase in heparin concentration) means that larger doses of heparin are required to maintain heparin concentration than would be used to maintain ACT alone.

CLINICAL IMPLICATIONS

The primary mechanism of action of unfractionated heparin is to enhance the enzymatic activity of antithrombin potentiating its inhibitory effect on activated factor X and thrombin. The individual response to a fixed dose of heparin varies, with some patients requiring higher than usual doses to achieve a target ACT, a phenomenon known as heparin resistance. In patients with low ATIII levels significantly higher total heparin does was given to maintain a target ACT as compared to the normal group (p=0.016). Heparin sensitivity was not significantly different in either the low or normal range AT III (p=0.154). There was no correlation between the HSI and the ATIII levels in both groups. More specific test to measure heparin's effects at the level of thrombin, that overcomes some of the limitations of the standard ACT, less susceptible to artifactual modulation, not altered by hemodilution and hypothermia and which has been shown to correlate better with heparin concentration during CPB has to be considered and be used as a supplement especially in patients with low ATIII levels.

REFERENCES

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