Original Article

High Dose Thrombin Time versus the Activated Clotting Time during Cardiopulmonary Bypass

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ABSTRACT

In this study we compared the High Dose Thrombin Time (HiTT) with the Activated Clotting Time (ACT) during cardiopulmonary bypass (CPB) in non-aprotinin treated patients. On the advice of the HiTT test manufacturer each institution should perform comparative ACT/HiTT assays in the cardiac surgery population. In previous tests our target ACT value of 480 seconds corresponds with a mean HiTT value of 190 seconds.

Our results showed that after heparinization (300–400 IU/kg body weight) 8 out of 20 patients did not reach the target ACT of 480 seconds, while the HiTT results in those 8 patients were higher than our target time of 190 seconds. Four heparin pretreated patients who received 400 IU/kg heparin, had relatively low ACT values (467 ± 14 sec.) and high HiTT values (324 ± 47 sec.). Before and during CPB there was a poor correlation between the HiTT and ACT ($r = 0.38$).

The results of this study show that for the individual patient the target HiTT of 190 seconds is no guarantee for reaching an adequate ACT of 480 seconds. Although the HiTT may be a very useful assay for monitoring heparin effects during CPB, the determination of the target time can be a point of discussion. In contrast of the advice of the manufacturer we therefore suggest that comparative ACT/HiTT assay should be done in every individual patient to determine a safe target HiTT time, instead of the whole group of patients.

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INTRODUCTION

The Activated Clotting Time (ACT) has been popularized for monitoring the anticoagulant effects of heparin during Cardiopulmonary Bypass (CPB) (1,2). There are several circumstances other than heparin which may affect the ACT during CPB, such as hemodilution, hypothermia and the use of antifibrinolytic drugs (3–7).

The High dose Thrombin Time (HiTT) is a modified Thrombin Time test (TT) which reflects functional heparin levels and actual anti-coagulation status (1,2,8,9). The HiTT is similar to the common TT as it is neither affected by antifibrinolytic drugs nor by hypothermia, hemodilution, minor decreases in fibrinogen and accumulation of fibrin degradation products (1,7). The heparin/antithrombin III (AT III) complex in the sample prolongs the HiTT test through the neutralization of the thrombin reagent in the test tube. The rate of clot formation is directly related to the functional circulating heparin concentration (2). The manufacturer[a] advises that the HiTT target time of anticoagulation is best determined by each institution in terms of comparative ACT/HiTT assays in the cardiac surgery population. Once the HiTT target time has been established, the HiTT value can be used for anticoagulation measurement.

Due to the use of the serine protease inhibitor drug aprotinin the HiTT assay was introduced in our institution. At that time comparative ACT/HiTT assays were performed and consequently the HiTT value of 190 seconds corresponding with the target ACT of 480 seconds was established (10). In several studies the HiTT was compared with the ACT in the presence of aprotinin, the overall conclusion was that the HiTT is a more useful assay for monitoring heparin during CPB than the ACT (2,8–10). In this clinical study we compared the HiTT with the ACT during CPB in non-aprotinin treated patients.

MATERIALS AND METHODS

The population included 20 adult patients undergoing elective coronary bypass grafting, valve replacement, valve repair and closure of an atrial septal defect. Patients were excluded when aprotinin was used or when they had coagulation disturbances, due to AT III deficiency or platelet dysfunction. The extracorporeal circuit consisted of a CVR venous reservoir[b] with a Cobe Duo oxygenator[c] or a BMR collapsible venous reservoir[d] with Spiral Gold oxygenator[d] and an Affinity arterial blood filter[b] with a roller or Biomedicus centrifugal pump[e]. As prime solution Gelofusine, Mannitol, Human Albumin 20% and NaHCO3 8.4% was used. Porcine heparin[f] 5000 IU/ml was added to obtain a final concentration of 4.2 IU/ml priming. Heparin was given to the patient at a rate of 300 IU/kg body weight in an initial dose to achieve a target ACT of 480 seconds. Four patients were heparin pretreated and received 400 IU/kg heparin. If the ACT was < 480 seconds an additional bolus of 50 IU/kg heparin was given. The ACT was performed with the Hemotec Automated Coagulation Timer[e] with kaolin cartridges. The HiTT was performed with the Hemochron 8000[a] coagulation monitor. All coagulation instruments were frequently tested to assure that they had no drift from their calibrated settings. The CLOTtrac HR Abnormal Coagulation Control[e] was used to confirm the performance of the Hemotec coagulation monitor. The Hemochron Electronic System Verification Tubes[a] were used to perform a quantitative electronic system verification of the Hemochron coagulation monitor.

Blood samples were drawn at predetermined intervals: 5 min. after heparinization; 5, 30, 60, 90, 120 min. and at the end of CPB. Statistical analysis between the ACT and HiTT values was performed by Pearson's analysis of correlation. Data are expressed as the mean ± standard deviation of the mean.

a International Technidyne Corp., Edison, NJ
b Avecor, Minneapolis, MN
c Cobe, Denver, CO
d Baxter, Irvine, CA
e Medtronic, Minneapolis, MN
f Leo Pharmaceutical Products, Weesp, NL

RESULTS

From the population of 20 patients, 8 were female. The mean age of the patients was 64.5 years (± 14.4) with a mean weight of 74.8 Kg (± 12.9) and a mean height of 169.6 cm (± 12.2).

Five minutes after heparinization 8 out of 20 patients failed to reach the target ACT of 480 seconds, while the results of the HiTT in those 8 patients ranged between 191 and 380 seconds (Table 1). Four heparin pretreated patients who received 400 IU/kg heparin, had relatively low ACT values (467 ± 14 sec.) and high HiTT values (324 ± 47 sec.) (Table 2).

Five minutes after heparinization the correlation between ACT and HiTT was 0.15 (Table 3). During CPB there was a poor and often a negative correlation between ACT and HiTT. The overall correlation between the ACT and HiTT was 0.38.

Five minutes on CPB a strong elevation of the mean value of the HiTT (346 ± 138 sec.) was measured across the whole group (Table 3).

DISCUSSION

The correlation of 0.998 between the ACT and the HiTT according to the manufacturer package inserts (Table 4) was not reproducible in this study. The tests performed by Hemochron were done in vitro with the Hemochron celite ACT, on the other hand our tests were done in vivo with the Hemotec kaolin ACT. Kaolin has been suggested as an alternative to celite (11). Kaolin, similar to celite, activates the intrinsic pathway via factor XII (9). Several studies found no statistically significant differences between kaolin and celite ACT (9,12,13). Bull (14) suggests that the linear relationship between celite ACT and heparin concentration is disrupted if

Table 1: ACT and HiTT values 5 min. after heparinization at T1

Patient	ACT	HiTT
1	597	230
2	480	265
3	999	296
4	429	297
5	999	332
6	536	285
7	591	246
8	480	288
9	467	380
10	400	215
11	444	289
12	426	235
13	444	288
14	488	267
15	642	151
16	488	226
17	400	191
18	467	358
19	557	252
20	616	264

Table 2: Mean ACT and HiTT values 5 min. after heparinization (400 IU/kg BW) in 4 heparin pretreated patients

Sample Time	ACT Mean ± S.D.	HiTT Mean ± S.D.
T1.	467 ± 14	324 ± 47

values exceed 500 to 600 seconds. Despotis' (15) data demonstrate an excellent correlation between kaolin ACT values greater than 500 seconds and heparin concentration. Wang (1) reported an excellent linear correlation between the ACT and HiTT in vitro, but similar to the study of Tuner (2) the linear relationship was lost during in vivo study. The results of a poor correlation between ACT and HiTT most likely suggest that the HiTT remains unaffected by hypothermia and hemodilution and that the HiTT is a more useful assay for monitoring heparin during CPB than the ACT.

In our study 8 out of 20 patients did not reach the target ACT of 480 seconds after heparinization while the HiTT results of these 8 patients range between 191 to 380 seconds. The amount of heparin required to achieve the target ACT time is variable depending upon patient heparin sensitivity. If the patient has low heparin sensitivity it will be necessary to give additional heparin to achieve a target ACT of 480 seconds, which sometimes increase the HiTT far beyond the target of 190 seconds. Heparin pretreated patients had relative low ACT values (467 ± 14 sec.) in spite of the initial dose of 400 IU/kg heparin, but high HiTT values (324 ± 47 sec.). According to Gravlee (3) heparin pretreated patients need a higher than normal heparin

Table 3: Mean ACT and HiTT values and Correlation

Sample Time	ACT Mean ± S.D.	HiTT Mean ± S.D.	Correlation ACT/HiTT
T1. 5 min. after heparinization	547 ± 166	269 ± 52	0.15
T2. 5 min. CPB	847 ± 158	346 ± 138	−0.31
T3. 30 min. CPB	881 ± 111	259 ± 59	0.02
T4. 60 min. CPB	754 ± 167	255 ± 48	−0.19
T5. 90 min. CPB	812 ± 192	266 ± 56	−0.51
T6. 120 min. CPB	665 ± 128	226 ± 42	−0.83
T7. End CPB	733 ± 176	245 ± 44	0.06

Table 4: HiTT package insert; relationship between heparin level, ACT value (Hemochron celite) and HiTT in porcine heparin adult cardiac surgery patients

Heparin Units/ml	ACT Seconds	HiTT Seconds
0	120	35
1.5	240	98
1.58	264	108
2	289	118
2.25	313	128
2.5	337	138
2.75	362	148
3	386	158
3.25	410	168
3.5	410	178
3.75	459	188
4	483	198
4.25	507	208
4.5	532	218
4.75	556	228
5	580	238
5.5	629	258
6	677	278
6.5	726	297
7	774	317

dose to induce sufficient anticoagulation for safe conduct of CPB, due to decreased AT III levels. The heparin pretreated patients in this study showed that more heparin is translated in high heparin/AT III complex levels, but high levels of functional heparin do not always result in adequate ACT times. Perhaps other mechanisms are responsible for the fact that heparin pretreated patients need more heparin instead of decreased AT III levels. It is important to recognize that the ACT identifies abnormalities in the intrinsic pathway as well as in the final common pathway of coagulation, whereas the HiTT reflects only the final common pathway.

The results show that for the individual patient the target HiTT of 190 seconds is no guarantee for reaching an adequate

ACT of 480 seconds. Although the HiTT may be a very useful assay for monitoring heparin effects during CPB, the determination of the target time can be a point of discussion. In contrast of the advice of the manufacturer the preliminary suggestion will be to do a comparative ACT/HiTT assay in every individual patient to determine a safe target HiTT time.

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