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Case Reports

Management of Heparin-Resistant Patients with Benefits? Maximizing Biocompatibility in Cardiopulmonary Bypass: Combining ATryn® Recombinant Antithrombin III and Carmeda® Heparin-Bonded Perfusion Circuits: A Case Series

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Abstract: As many as 25% of our cardiopulmonary bypass (CPB) patients have a diminished heparin response and fail to reach a therapeutic activated clotting time (ACT). We treat a majority of these patients with antithrombin III (ATryn®, recombinant antithrombin III [rhAT], rEVO Biologics). Our current CPB circuit uses Medtronic Carmeda® coating. We observed less postoperative bleeding in a number of patients treated with rhAT. We theorized that adding rhAT would allow patients with diminished heparin response to safely achieve a therapeutic ACT. On the basis of our postoperative bleeding observations, we wondered if using rhAT with a heparin-bonded CPB circuit enhanced its biocompatibility and perhaps improved patient outcomes. Data were collected on 15 patients undergoing CPB who received antithrombin III (AT) replacement therapy for diminished heparin response. We used patient data from 2012, prior to rhAT usage for comparison. All patients achieved therapeutic ACT after rhAT administration. We also observed decreased postoperative atrial fibrillation rates, improved platelet preservation, decreased intensive care unit and ventilator times in patients receiving rhAT compared to rates commonly observed at our center. Heparin-resistant patients can be treated with rhAT to achieve therapeutic ACTs. Our observations suggest that the use of rhAT in conjunction with Carmeda® heparin-bonded circuits may also have a positive benefit on some of the well-established negative clinical consequences of CPB and improve patient outcomes. **Keywords:** atrial fibrillation, cardiopulmonary bypass, anticoagulation, inflammatory response. *JECT. 2015;47:44–47*

In cases requiring cardiopulmonary bypass (CPB), heparin is used to elevate the activated clotting time (ACT) from a baseline of 90–120 seconds to 480 seconds or higher, which allows the patients' blood to contact the foreign surface of the extracorporeal circuit without forming clot. Heparin binds to the serine protease inhibitor antithrombin III (AT), causing a conformational change that results in a 1000-fold increase in AT activity by increasing the binding capacity for certain intrinsic clotting proteins (1,2). AT's anticoagulant properties are through inactivation of thrombin and other serine proteases involved in blood clotting, most notably factor Xa. A small percentage of patients have an AT deficiency, which can lead to a diminished heparin response. Their ACT does not elevate to therapeutic levels required to initiate CPB when given the standard bolus dose of heparin. Heparin resistance observed during CPB is often due to AT deficiency and is observed in 4–26% of cases, depending on the specific definition (3). These patients require replacement of AT, either from fresh frozen plasma transfusions or concentrated AT preparations for injection to restore AT to adequate levels that enable heparin to elevate the ACT over 480 seconds. We currently use a recombinant antithrombin III (rhAT) preparation (ATryn®, rEVO Biologics, Framingham, MA). In our current practice, we follow postoperative bleeding by observing 12-hour chest tube drainage giving an indication of how quickly patients return to normal coagulation status. In a majority of

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patients who require rhAT, we have observed a reduction in postoperative bleeding. In our practice, we also use a Medtronic Carmeda® heparin-bonded CPB circuit (Medtronic, Inc., Minneapolis, MN; Carmeda®, Carmeda AB, Upplands Väsby, Sweden) for all of our CPB patients. Heparin-bonded circuits have been shown to be more biocompatible than non-coated circuits (4). They mimic normal endothelium, having been shown to reduce inflammatory mediators, as well as inhibiting platelet activation and thrombin formation. These benefits have been shown to decrease blood transfusions, decrease ventilator time, and decrease overall length of stay (5). We recently observed reduced postoperative bleeding in patients receiving rhAT and theorized that the combination of rhAT and a heparin-bonded circuit improved the efficacy of our technique. We therefore compared patients treated with rhAT and a heparin-bonded circuit to our Affinity Medical Center (AMC) 2012 database averages, the year before we started using rhAT.

MATERIALS AND METHODS

We collected data on the 15 patients who received rhAT. All patients undergoing CPB at our institution were placed on CPB using a custom Medtronic Carmeda® BioActive Surface circuit. The circuit contained the following components: Biopump BP-80X for both arterial return and kinetic-assisted venous drainage, Carmeda® Affinity NT oxygenator, Affinity CB353 20 μ arterial filter, MVR 1600 venous bag, Intersept CB1351 filtered cardiotomy reservoir, and Carmeda® Myotherm XP cardioplegia delivery system. Each patient received a heparin bolus (porcine intestinal mucosa) of 350 U/kg prior to CPB. ACT was measured using Medtronic ACT Plus (Medtronics Corp). If the first ACT was below 480 seconds, the patient was then bolused with an additional 150 U/kg of heparin and the ACT was repeated. These 15 patients failed to reach an ACT of 480 seconds after an additional heparin bolus and received 500 U of rhAT (ATryn®) and were placed on CPB. Platelet count and function were determined via Plateletworks® ADP kit (Helena Laboratories, Beaumont, TX). Outcomes were compared between rhAT-treated patients and the AMC 2012 database according to whether the patient received coronary artery bypass graft (CABG) or valve surgery. The following variables were compared: ventilator time, intensive care unit (ICU) time, platelet preservation, new onset postoperative atrial fibrillation (POAF), transfusion rates for all blood products, and 12-hour chest tube output. Ten CABG patients received rhAT and five valve patients received rhAT. There were 133 CABG and 31 valve patients in the AMC 2012 database that we used to compare. A two-sample *t* test in Minitab 16 Statistical software was used to calculate the data's statistical significance. Institutional review board ruled our study exempt from their approval as it is a retrospective chart review with no patient identifiable information collected.

RESULTS

The 15 study patients had an average post-heparin ACT of 418 seconds. The average ACT increased to 444 seconds following the second heparin bolus. The average ACT increased to 593 seconds following rhAT bolus, with all 15 patients having an ACT of >480 seconds (Table 1). There were 10 patients in the rhAT CABG group that were compared to 133 AMC 2012 CABG patients. There were 5 patients in the rhAT valve group that were compared to 31 AMC 2012 valve patients. Patient average age was 63.9 years for rhAT CABG vs. 66.3 years for AMC 2012 CABG and 53.4 years for rhAT valve vs. 66.7 years for AMC 2012 valve. The rhAT CABG patients were 80% male vs. 59% male AMC 2012 CABG. The rhAT valve patients were 40% male vs. 61% male AMC 2012 valve. Average CPB time was 103 minutes for rhAT CABG vs. 106 minutes for AMC 2012 CABG and 155 minutes for rhAT valves vs. 146 minutes for AMC 2012 valves. Platelet preservation, POAF rates, and ventilator time were improved in the patients receiving rhAT compared to our AMC 2012 group. Ventilator time was significantly lower in the rhAT group compared to our AMC 2012 group: 6.2 vs. 13 hours for valve ($p = .03$) and 8.3 vs. 11.9 hours for CABG ($p = .05$; Table 2). ICU time trended lower for valve ($p = .10$) and CABG ($p = .20$; Table 3). Transfusion rates of all blood products were lower in the rhAT valve patients (40% rhAT vs. 72% for AMC 2012); however, transfusion rates did not show a significant change in the patients undergoing CABG procedures. Platelet counts were 84% and 80% of baseline in CABG and valve cases vs. an average percent

Table 1. ACT response for rhAT group.

Average ACT Post 350 U/kg Bolus, Seconds	Average ACT Post Extra 150 U/kg Bolus, Seconds	Average ACT Post 500 U rhAT Bolus, Seconds
418	444	593

ACT, activated clotting time; rhAT, recombinant antithrombin III.

Table 2. Ventilator time (hours).

	N	Mean	SD	SE	*p*-Value
Valves					
2012 Averages	31	13.0	15.60	2.8	
rhAT	5	6.18	2.22	.99	.03
CABG					
2012 Averages	133	11.9	18.5	1.6	
rhAT	10	8.29	2.81	.89	.05

CABG, coronary artery bypass graft; rhAT, recombinant antithrombin III.

Table 3. ICU time (hours).

	N	Mean	SD	SE	*p*-Value
Valves					
2012 Averages	31	49.4	58.7	10	
rhAT	5	29.0	13.3	509	.10
CABG					
2012 Averages	133	50.2	73.2	6.3	
rhAT	10	37.0	24.5	7.7	.20

CABG, coronary artery bypass graft; rhAT, recombinant antithrombin III.

Table 4. Improved platelet preservation with rhAT.

	Percentage of Platelets Preserved
2012 Averages	74
rhAT CABG	84
rhAT Valves	80

CABG, coronary artery bypass graft; rhAT, recombinant antithrombin III.

Table 5. New-onset postoperative atrial fibrillation.

	Percentage of Patients with POAF
Valve	
2012 Averages	37.5
rhAT	20
CABG	
2012 Averages	26
rhAT	0

CABG, coronary artery bypass graft; POAF, post-operative atrial fibrillation; rhAT, recombinant antithrombin III.

Table 6. Twelve-hour chest tube output (mL).

	Blood Loss, mL
2012 Averages	348
rhAT CABG	320
rhAT Valves	150

CABG, coronary artery bypass graft; rhAT, recombinant antithrombin III.

of platelet preservation for AMC 2012 of 74% (Table 4). Remarkably, no CABG patients receiving ATryn® developed POAF, whereas only one of the five valve patients developed POAF. In contrast, the AMC 2012 data revealed that 26% of patients undergoing isolated CABG procedures and 37.5% of valve patients developed POAF (Table 5). Twelve-hour chest tube output was also lower in the rhAT patients (Table 6). No adverse events, such as stroke or re-operation for bleeding, were seen in the 15 rhAT patients.

DISCUSSION

AT is a serine protease inhibitor that plays a key role in controlling blood coagulation and inflammation (6). In the past, we primarily used AT to supplement anticoagulation through its thrombin inhibition activity, which is increased 1000 fold when bound to heparin (2,7). In our practice, 26% of our patients require a second dose of heparin to achieve adequate anticoagulation (ACT > 480 seconds). Many of these patients also required rhAT supplementation to achieve therapeutic ACTs. The use of rhAT is still considered "off label" for this indication; however, our results indicate it is safe and effective. Because of our recent experience and literature suggesting that the AT inhibits the inflammatory response and low AT levels postoperatively are associated with poor outcomes (8), we have taken a more aggressive approach with rhAT administration.

The most striking secondary observation was the markedly reduced rate of POAF observed in patients who received rhAT. No CABG patients and only one valve patient developed POAF. Atrial fibrillation is the most common irregular heart rhythm observed after CPB. The incidence of POAF is approximately 30% after CABG surgery, 40% after valve surgery, and as high as 50% after combined procedures (8). POAF is associated with an increased risk of mortality and morbidity, including stroke, in patients undergoing cardiac surgery and is one of the most common complications of such surgery. Developing POAF can impact hospital length of stay and thus the cost of hospitalization. One study shows evidence that inflammation plays an important role in the pathogenesis of POAF (9). The heart–lung bypass machine is characterized by a systemic inflammatory response. It is possible, therefore, that rhAT's anti-inflammatory effects explain the decreased rate of POAF we observed. Positive anti-inflammatory effects may also explain the lower ventilator and ICU times observed in the rhAT group.

Our observation's limitations include the small sample size and retrospective design. Patient age was lower in the rhAT group that may have affected outcomes. Also, we did not measure AT levels or biomarkers of inflammation. Also, dosing of rhAT was not based on patient weight, so smaller patients may have added benefit. The use of Carmeda® and its anti-inflammatory properties may limit the differences between the two groups. Nevertheless, these results provide ample cause to investigate rhAT and Carmeda® circuits in a larger, prospective study.

CONCLUSION

It is safe and effective to use rhAT on patients with diminished heparin response. Also, our observations suggest that the use of a combination of Carmeda® heparin-bonded circuits and rhAT when compared to institutional averages was generally associated with a lower rate POAF, better platelet preservation, decreased ventilator and ICU times, lower 12-hour chest tube output, lower post-protamine

ACT and lower rates of transfusion in valve patients, and no adverse reactions in our small cohort of patients. These results suggest that the use of rhAT in conjunction with improved coagulation management may have a positive benefit on some of the well-established negative clinical consequences of CPB and improve patient outcomes. We believe a larger prospective study would be beneficial.

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