Carotid surgery presents unique challenges in the management of coagulation because of the requirement for both a fully anticoagulated state for cardiopulmonary bypass (CPB) and a return-to-normal hemostasis at its conclusion. The activated clotting time (ACT) is employed most commonly to assess anticoagulation and ensure adequate heparin and protamine dosing. Despite the routine use of ACT, many studies have demonstrated a lack of correlation between plasma heparin levels and ACT during CPB. Conditions during CPB, such as hemodilution, hypothermia, platelet activation, and coagulopathy also are known to cause falsely elevated ACT readings. For these reasons, relying on the ACT alone may lead to inadequate anticoagulation.

The Hepcon Hemostasis Management System (Hepcon HMS; Medtronic, Minneapolis, MN) works differently from the ACT because it estimates the free plasma heparin level from a whole-blood sample. First, the heparin dose-response (HDR) test is done to determine the patient’s individual response to heparin. The HDR cartridge consists of 6 chambers: 2 contain no heparin and provide the baseline ACT, 2 have 1.5 u/mL of heparin, and the last 2 have 2.5 u/mL of heparin. From a syringe of unheparinized patient blood, the machine adds 0.4 mL to each chamber and measures the clotting time. The results are plotted, and the slope of the graph is used to calculate the dose of heparin required to reach a target ACT (typically 400-480 seconds). During bypass, the patient’s heparin concentration easily can be determined using the heparin assay cartridge (HPT), along with the dose of additional heparin needed to maintain the target heparin concentration. Results of this assay also include the dose of protamine necessary to neutralize the circulating heparin. After protamine is administered, the heparin assay and ACT can be run again to confirm that there is zero circulating heparin and that the ACT has returned to baseline. By using the Hepcon HMS, heparin and protamine dosing are individualized based on each patient’s responsiveness to heparin, eliminating the need for empiric weight-based dosing.

In determining which technology is superior, it is important to ask the following questions: Which therapy more accurately determines the plasma heparin concentration during CPB? Which therapy allows the most appropriate dosing of protamine? What is the clinical impact of each therapy with regard to bleeding and transfusion?

The Hepcon HMS should be used instead of traditional activated clotting time (ACT) to dose heparin and protamine for cardiac surgery requiring cardiopulmonary bypass.

Kelly Ural, MD, and Christopher Owen, MD

Pro: The Hepcon HMS should be used instead of traditional activated clotting time (ACT) to dose heparin and protamine for cardiac surgery requiring cardiopulmonary bypass.

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Section Editor

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ACCURATELY MEASURING PLASMA HEPARIN CONCENTRATION AND ITS CLINICAL IMPLICATIONS

As blood comes into contact with the nonendothelial surfaces of the CPB machine, the inflammatory response is stimulated. As a result, platelets and coagulation factors are consumed. Systemic heparinization during CPB prevents clotting of the bypass machine and attenuates this hemostatic activation by decreasing excessive generation of thrombin and plasmin. Adequate heparinization ensures preservation of coagulation factors and decreases thrombin-mediated consumption and activation of platelets. As such, it is important that a high enough heparin concentration is maintained and accurately measured. Plasma anti-Xa generally is considered the “gold standard” for measuring plasma heparin concentration; however, this assay is not available as a point-of-care test and thus is not practical in the operating room environment. Instead, point-of-care ACT monitoring most commonly is used. Although kaolin ACT values may correlate well with anti-Xa heparin concentration in the pre-bypass period, these levels have been proven to have poor correlation during CPB. These falsely elevated ACT values often are due to depletion of coagulation factors, and not necessarily the result of adequate heparinization.

Heparin levels determined by the Hepcon HMS, however, have been shown to correlate well with anti-Xa plasma levels, even during CPB. This correlation is best demonstrated in a study by Raymond et al in which plasma heparin concentrations, as determined by Hepcon and ACT, were compared to the anti-Xa assay. Their results showed that after the initial bolus of heparin, anti-Xa plasma heparin levels decreased with each interval measurement. Likewise, the Hepcon HMS values
similarly decreased; however, the ACT levels (using both the celite-based Hemochron and the kaolin-based HemoTec tests) did not detect a drop in heparin. The authors concluded that the Hepcon HMS provided a rapid assessment of heparin concentration that correlated well with anti-Xa assays which could lead to improved patient outcomes compared to protocols that rely on ACT alone.

**IMPORTANCE OF ADEQUATE PROTAMINE DOSING**

Adequate neutralization of heparin by protamine at the conclusion of CPB is necessary to prevent ongoing bleeding after bypass. Although protamine is an effective means of reversing heparin, adverse events, including hypotension, pulmonary edema, and anaphylaxis, occur. Administering an optimal dose of protamine can help to minimize these events. The simplest dosing strategy is to empirically base the protamine dose on either the patient’s weight or on a ratio of the amount of heparin given. In an attempt to refine protamine dosing, point-of-care testing can be used to estimate the circulating heparin at the time of reversal by using in vitro protamine titration. One benefit of the Hepcon HMS is its ability to calculate the amount of circulating heparin at the end of bypass and give the exact dose of protamine necessary to neutralize the heparin. Targeted dosing can prevent excessive protamine administration and reduce protamine-induced platelet dysfunction. After protamine is given, another test can be run to ensure no circulating heparin is present.

Hashimoto et al showed a statistically significant reduction in the amount of protamine administered when a Hepcon HMS titration protocol was followed compared to conventional dosing. They also saw more negative effects of protamine (ie, significant drops in blood pressure and an ACT that did not return to baseline) in the conventional group. Noui et al also demonstrated a significant reduction in heparin/protamine ratios when the Hepcon HMS was used. Despotis et al have shown that the protamine/heparin ratio is one of the main factors influencing postoperative bleeding. In a study by Shigeta et al, reduced protamine resulted in decreased platelet activation and significantly increased the recovery of platelet function. These examples illustrate the clinical benefit the Hepcon HMS provides by accurately determining the minimum dose of protamine necessary for heparin reversal.

**HEPCON HMS MAY LEAD TO LESS BLEEDING AND TRANSFUSION**

It has been proposed that maintaining a higher heparin concentration while on bypass will prevent thrombin activation and lead to less bleeding postoperatively. Wang et al performed a meta-analysis to determine if protamine titration using the Hepcon HMS was associated with less bleeding after CPB. They reviewed 4 randomized controlled trials involving a total of 507 patients. The majority of these patients underwent coronary artery bypass graft procedures. Heparin was administered to maintain an ACT of 400 to 480 seconds. In the study arm, protamine dosing was determined using the Hepcon HMS. Postoperative blood loss was lower in the study group (625-839 mL) compared with the control group (765-995 mL) in all 4 studies. Fewer units of packed red blood cells were given in the study group (0.2-1.8 units) compared with the control group (0.3-2.7 units). The authors concluded that titrated heparin and protamine dosing was more effective than standard dosing for reducing postoperative bleeding.

One of the studies included in this meta-analysis was a large study of 254 cardiac surgical patients by Despotis et al. Patients in the intervention group were given an initial dose of heparin based on the HDR assay, and protamine dosing was based on the residual heparin concentration reported by the Hepcon HMS. The patients in the intervention group had significantly less mediastinal chest tube drainage in the first 4 hours postoperatively (p = 0.05) and received fewer platelet, plasma, and cryoprecipitate units than the control group despite receiving larger overall doses of heparin per kilogram. In addition, fewer of the intervention patients received blood transfusions compared with the control group (17% vs 33%; p = 0.005). The authors proposed that this benefit was likely because the ACT-based protocols led to underdosing of heparin, which does not adequately suppress thrombin generation during CPB. Inadequate heparinization leads to a consumptive state, particularly in patients with prolonged CPB times (ie, > 2 hours). They also suggested that lower protamine doses associated with use of the Hepcon HMS led to less protamine-induced platelet inhibition and therefore less bleeding.

Koster et al compared heparin management using the Hepcon HMS with an ACT regimen to determine the effect on the activation of the inflammatory system during CPB. They found significant reductions in thrombin generation, fibrinolysis, and neutrophil activation in the Hepcon HMS group after bypass. Although the outcome did not reach statistical significance, there were also reductions in blood loss and transfusion in the Hepcon HMS group. The authors postulated that maintaining higher heparin concentrations (as is customary with Hepcon) may ensure more effective inhibition of thrombin generation.

**CONCLUSIONS**

In conclusion, multiple studies support the use of the Hepcon HMS and consider it superior to ACT for optimizing plasma heparin concentration, decreasing coagulation factor consumption, and decreasing postoperative bleeding. The Hepcon HMS is also capable of aiding accurate protamine titration, thereby decreasing overall dose, minimizing negative effects, and preserving platelet function. Combined, these characteristics create a subsequent reduction in blood product transfusion and may improve patient outcomes.

**REFERENCES**