**Optimal Heparin Dosing for Cardiopulmonary Bypass**

Optimal heparin dosing for cardiopulmonary bypass has been debated since its estimation via empirical approach was introduced in the 1960s. The initial heparin dose at most centers ranges between 300 IU/kg and 400 IU/kg, with an acceptable activated clotting time (ACT) of at least 400 seconds needed to initiate bypass. During cardiopulmonary bypass, point-of-care ACT monitoring evaluates heparin’s effect on thrombin inactivation. This technique is effective in preventing visible clot formation while on bypass, but many argue that it is at the expense of increased bleeding complications.

Multiple studies have shown that on-pump ACT is greatly affected by 2 factors: hemodilution and hypothermia. Further, ACT is a measurement of whole-blood coagulation and is not a direct endpoint of thrombin suppression. For these reasons, many believe that maintaining a specific heparin concentration would better estimate thrombin suppression. The gold standard for heparin concentration levels is the anti-Xa assay. However, a plasma sample is needed for the anti-Xa assay, making this test difficult to perform in the operative setting. The Hepcon Hemostasis Management System Plus (Hepcon HMS; Medtronic, Minneapolis, MN) offers a whole-blood heparin concentration test. The manufacturer reports that measured heparin concentration, inherent inaccuracy of the device, and machine's accuracy suffers because of the lack of resolution between cartridges. Garvin et al observed poor correlation of the calculated HDR with the measured HDR resolution between cartridges. Garvin et al suggested that the Hepcon HMS offers a theoretical advantage over point-of-care ACT monitoring but failed to show any clinical advantage, especially in healthy patients undergoing routine cardiac surgery.

Errors in Calculating the Heparin Bolus Dose

The Hepcon HMS uses an individualized heparin dose-response curve (HDR) to calculate the patient’s heparin bolus dose to achieve a targeted ACT. An individualized HDR is calculated by mixing the patient’s blood with 0-, 1.5-, and 2.5-U/mL doses of heparin. The Hepcon HMS then calculates a baseline ACT from the control (0 U/mL) and 2 additional ACT values from the heparin doses (1.5 and 2.5 U/mL). The Hepcon HMS uses the 3 ACT values and the patient’s estimated blood volume to determine the heparin bolus dose. Potential errors in this calculation as reported by Garvin et al include inaccurate estimation of the patient’s blood volume, lack of fidelity of the measured heparin concentration, inherent inaccuracy of the device, and differences in the in vivo and ex vivo heparin activity.

A method for estimating blood volumes was described by Allen et al in 1956. Since that time, there has been no evaluation of the blood volume error in patients undergoing cardiac surgery. For this reason, Garvin et al suggested that the severity and nature of cardiac disease may be a substantial source of variation in blood volume estimates and therefore may contribute to the imprecision of point-of-care anticoagulation management instruments. Other potential sources of error are based on the Hepcon HMS assumptions: (1) the volume of distribution of heparin is equivalent to the calculated blood volume, and (2) administered heparin will remain free in the circulation and will not bind to endothelial surfaces or plasma proteins other than those on which heparin anticoagulation activity depends. In other words, the Hepcon HMS measures total heparin and not just antithrombin III-bound functional heparin.

The Hepcon HMS channel resolution is limited to 0.4 U/mL, and the machine’s accuracy suffers because of the lack of resolution between cartridges. Garvin et al observed poor correlation of the calculated HDR with the measured HDR after a heparin bolus; the expected levels differed 51% of the time by >0.3 U/mL, which was more than the sensitivity of 1 channel in the assay. Furthermore, measured levels that differed

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in >2 channels (0.7 U/mL) were observed in 18.5% of samples. In practical terms, the Hepcon HMS did not estimate the prebypass heparin bolus requirement accurately. These authors found that these HDR variations caused 7.4% of patients to miss their ACT goal of 300 seconds and 16.9% of patients to miss their ACT goal of 350 seconds.

Heparin’s mechanism of action at high and low doses is unclear. While low heparin concentrations facilitate thrombin binding to antithrombin, Buyue et al have suggested that heparin’s primary effect in the setting of higher heparin concentrations is the inhibition of prothrombin consumption.9 Further complicating this picture is the role of tissue factor pathway inhibitor (TFPI), which is an endogenous serine protease inhibitor that is found in vivo bound to endothelial cell surfaces, thereby accounting for the difference between in vivo and ex vivo activity. A small amount of TFPI is found in plasma and bound to platelets. TFPI is released with heparin administration and neutralizes factor Xa by forming the TFPI-FXa complex.6 Brodin et al demonstrated significant synergy between antithrombin and TFPI in postheparin plasma, with an almost equal contribution of each to the prolongation of anticoagulation in a laboratory setting.10 These authors concluded that if an endothelial source of TFPI is absent, the Hepcon HMS initial HDR calculation may underestimate the contribution of TFPI to heparin responsiveness. This fact would lead to an overcalculation of the required heparin dose needed to achieve the necessary ACT goal and cause an expectation of a higher postbolus ACT. However, as previously noted, Garvin et al did not achieve their ACT goals in 7.4% to 16.9% of their patients with the Hepcon HMS. Furthermore, Koster et al noted in their study of patients undergoing standard cardiac surgery that both the Hepcon HMS group and the control group had similar soluble fibrin values, suggesting similar anticoagulation activity.11 These authors provided an explanation for these 2 findings: the generation of fibrin, even in the presence of high heparin concentrations, most likely has to be attributed to reduced antithrombin III concentrations or reduced inhibition of clot-bound thrombin.

ADMINISTRATION OF MORE HEPARIN VERSUS ANTITHROMBIN III

In practical terms, the Hepcon HMS solution for an inadequate antithrombin level is the administration of more heparin to overcome the antithrombin deficiency. This gives adequate anticoagulation results but increases the amount of heparin given to the patient. Newsome et al reported that higher heparin concentrations were a cause of heparin rebound in the postoperative period.12 In essence, the Hepcon HMS potentially was increasing the risk for postoperative bleeding through the administration of more heparin to indirectly remedy the antithrombin deficiency when antithrombin administration would solve the problem directly without potential postoperative side effects. Koster et al described the need for a functional point-of-care antithrombin III cartridge so that adequate antithrombin III can be administered in a timely manner if necessary.11

LACK OF PROSPECTIVE STUDY DATA FOR COMPARISON

No prospective, randomized studies have been conducted to determine the superiority of the Hepcon HMS versus ACT monitoring. Most studies involved straightforward cases that did not involve redo operations, deep hypothermic circulatory arrest, or cardiopulmonary bypass lasting >2 hours. The authors argue that the use of the Hepcon HMS is not warranted in the absence of these factors. At the authors’ institution, the bring-back rate for bleeding is <3% (5 patients in 2015), and they do not see clinically significant heparin rebound with their standard ACT/protamine dosing. Given these facts, the authors find it difficult to justify the increased cost of the Hepcon HMS. Their perioperative transfusion rate for primary coronary artery bypass graft (CABG) and valve surgery is extremely low (approximately 14% intraoperatively through the first 24 hours). In the authors’ blood transfusion protocol, if a patient undergoing a primary CABG or valve surgery has a hematocrit >30% with no antibodies, then only a type and screen is ordered. In contrast, no study showing decreased transfusion rates with the Hepcon HMS mentioned a transfusion protocol. The decision to transfuse was left to the discretion of the surgical team, which can lead to a wide transfusion variation and possible bias. Avidan et al13 found that transfusion rates in cardiac surgery were lower with a protocol in place, and the Society of Cardiovascular Anesthesiologists guidelines recommend transfusion protocols for cardiac surgery.14

ALTERNATIVE METHODS FOR DOSAGE GUIDANCE

Alternative models have been used to determine heparin concentration and guide further dosing of heparin and protamine. As mentioned earlier, the Hepcon HMS uses tiered concentrations of heparin mixed with the patient’s blood to determine an HDR curve. Raymond et al used the slope generated from this curve, a baseline ACT, and an adjustment factor to take into account the effects of hemodilution and hypothermia on prolonging ACT to calculate the heparin concentration for a given ACT.15 By taking into account the individual’s heparin sensitivity using the slope and the effects of cardiopulmonary bypass with the adjustment factor, they were able to calculate a heparin concentration that agreed with the anti-Xa heparin concentration. Although the slope generated by the HDR curve was utilized in their calculation, they were able to determine a cost-efficient method to predict the heparin concentration without using multiple Hepcon HMS cartridges throughout the case.

Furthermore, Suárez Cuenca et al have determined a calculation for the dose of protamine using the basal ACT, postinitial heparin ACT, preprotamine ACT, and the initial heparin bolus.8 Using their formula, the authors were able to give a lower dose of protamine compared to their normal practice without any changes in postoperative bleeding. They claim that the formula allows “fast, simple, objective, and functional” calculations to obtain heparin concentration without repeated Hepcon HMS calculations, thereby providing a cost-efficient alternative. When compared to conventional ACT methods for a CABG or a single-valve case with a cardiopulmonary bypass run of <2 hours, the Hepcon HMS costs an
additional $65 per patient or $10,000 per year for the authors’ institution. This number does not include the upfront cost of purchasing the machine. Because of their low perioperative transfusion rates and reoperation rates in this patient population, the authors would not be able realize a cost savings through a reduction in transfusion rates or decreased reoperations.

CONCLUSIONS

An ideal intraoperative laboratory test to assess a patient’s anticoagulation status during cardiopulmonary bypass still does not exist. The Hepcon HMS attempts to alleviate some of the issues of traditional ACT monitoring by calculating an HDR curve based on a patient’s heparin sensitivity. Although this has theoretical benefits, the Hepcon HMS has not been shown to be clinically superior to ACT monitoring. Until a prospective study assesses the clinical benefits of the Hepcon HMS versus ACT monitoring, these benefits do not appear to outweigh the increased cost of using the device, especially in healthy patients undergoing routine cases, such as CABGs and single-valve surgeries.

REFERENCES