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12/8/69672

Individualized patient heparinization and protamine reversal

To the Editor:

We read with interest the article titled "The Impact of Heparin Concentration and Activated Clotting Time Monitoring on Blood Conservation" by Despotis and associates¹ in the July 1995 issue of the JOURNAL. This article examined an alternative anticoagulation management system (Hepcon HMS; Medtronic Hemotec, Englewood, Colo.) and blood conservation in adult cardiac surgical patients, highlighting once more the need for surgeons and anesthesiologists to reexamine their anticoagulation practices, which have remained largely unchanged for some two decades.

The suggestion that it may be possible (and seemingly appropriate) to administer doses of heparin according to an individual patient's preoperative blood response to heparin (and to subsequently maintain this level on bypass) may go some way toward eliminating "best fit" empirical protocols of heparin administration from the surgical arena. The fact that this dosage tailoring may be achieved without the need for increased administration of protamine, with its recognised "heparin-protamine complex" morbid sequelae, provides greater impetus for this alternative regimen to be formally examined. This study also confirms previous work² from our unit with the Hepcon device, which suggested that empirical protamine administration protocols often result in excessive administration.

There is clearly a need to remain vigilant when one is confronted with the postoperative patient who is actively bleeding after increased heparin administration because heparin rebound may be a concern. Furthermore, a more thorough investigation of the determinants and markers of consumptive coagulopathy needs to be performed. We would be interested to learn whether the authors believe it is possible in the presence of heparin to draw firm conclusions regarding coagulation factor consumption solely on the basis of routine activated partial thromboplastin time and prothrombin time times. Perhaps less equivocal markers, such as fibrinopeptide A, thrombin-antithrombin complexes, or prothrombin fragment 1.2, may assist in confirming this event.

Attempts to delineate purely heparin concentration-dependent postoperative sequelae from those of heparin-protamine complexes are currently under consideration within our unit, as are additional studies assessing the contribution of heparin-bonded cardiopulmonary bypass circuitry to the anticoagulation-neutralization equation.

The contribution of Despotis and associates¹ is therefore timely and welcomed by our group.

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12/8/69749

Reply to the Editor:

We support Martin and colleagues' recommendation that clinicians reexamine the anticoagulation protocols at their institutions. This contention is supported not only by our study¹ but also by the recent study of Jobes and coworkers.² In response to the question regarding the role of heparin as a cause of bleeding, we agree that residual heparin may be a potential cause of excessive bleeding after cardiopulmonary bypass and should be evaluated with a sensitive assay (we used the heparinase activated clotting time). We do not believe that heparin was the cause of bleeding in the control group (C) however, because these patients actually received much less heparin than did patients in our intervention group (I). In patients with demonstrated excessive intraoperative bleeding ($n = 101$), our laboratory-based thrombin time assay, which is exquisitely sensitive to heparin (measurements prolonged to >120 seconds with heparin concentrations of 0.1 U/ml), did not demonstrate significant amounts of residual heparin in either group after arrival at the intensive care unit ($C 24 \pm 15$, $I 27 \pm 23$ seconds, $p = 0.40$). The greater prolongations in whole blood prothrombin time and activated partial thromboplastin time assays therefore almost certainly reflected greater reductions in coagulation factors in the control group.

We recently explored this issue further in a subgroup of patients at high risk for excessive blood loss after extracorporeal circulation ($n = 31$).³ This study demonstrated that consumable coagulation factors V, VIII, and fibrinogen were preserved in patients in the intervention group in the setting of normal thrombin time results ($C 22 \pm 5$, $I 20 \pm 4$ seconds, $p = 0.11$). In addition, maintenance of higher heparin concentrations in our intervention group resulted in reduced activation of coagulation and fibrinolysis, as demonstrated by lower fibrinopeptide A levels ($p = 0.0002$), lower D-dimer ($p = 0.03$) levels, and a trend toward lower prothrombin fragment 1.2 ($p = 0.06$) levels in specimens obtained before discontinuation of cardiopulmonary bypass.³ This confirms previous published data indicating that fibrinopeptide A levels are indirectly related to heparin concentration.^{4,5} Although the potential role of optimized protamine doses on reduced blood product use was not fully addressed, our data provide