was significantly greater in patients preoperatively treated with 5000 rad. In our global experience, no technical or clinical problems occurred in patients subjected to a preoperative dose of 30 Gy. After these last two failures, whenever reduction of the tumor size is needed to facilitate the procedure, we recommend that a preoperative radiation dose of no greater than 30 Gy be used.

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Topical use of aprotinin in cardiac surgery

To the Editor:

We read with great interest the letters concerning the topical effect of aprotinin by Edmunds¹ and by Tabuchi, de Haan, and van Oeveren.²

We³ demonstrated the efficacy of topical aprotinin (1 million KIU) in the pericardial cavity in reducing postoperative blood loss in patients undergoing cardiac operations.³ O'Regan and associates⁴ recently reported that topical application of aprotinin in the pericardial cavity significantly reduced the postoperative blood loss after cardiac operations. The mechanism by which aprotinin exerts its effect topically differs from its systemic effect, wherein the mechanism of action is conservation of platelet function and inhibition of fibrinolysis.

de Haan and associates⁵ reported an increased activity of tissue-plasminogen activator from the pericardium and proposed a fibrinolysis-related bleeding tendency after cardiopulmonary bypass. Of equal interest is a recent report by Tabuchi and associates,⁶ who demonstrated enormous activation of fibrinolysis on the surgical wound during cardiopulmonary bypass. Tabuchi, de Haan, and van Oeveren² have recently reported a tremendous increase of fibrin degradation products in the blood of the surgical wound compared with systemic blood. Low-dose systemic aprotinin reduced fibrin degradation products in wound blood by half compared with that in a control group (17,900 ± 6,800 ng/ml versus 38,200 ± 9,300 ng/ml).

The results of these studies,^{2,5,6} combined with the results of Tatar,³ and O'Regan,⁴ and their colleagues, suggest that a local fibrinolytic state persists after closure of the thoracic cavity and contributes to the postoperative blood loss. Topical aprotinin seems to exert an antifibrinolytic action by which it stabilizes fibrin sealing of the surgical wound.

Systemic absorption and effect of the topically applied aprotinin is a concern. The plasma aprotinin levels were measured in eight patients in our original study, and aprotinin could not be detected in any. However, this was a small number from which to reach a conclusion. Therefore we measured systemic drug concentrations in 30 of 150 patients in whom we used aprotinin topically (1 million KIU) in the pericardial cavity immediately after our original study at the GATA Department of Cardiovascular Surgery. Systemic aprotinin levels were determined by means of the sandwich-enzyme-linked immunosorbent assay technique at the first hour after the chest tubes were unclamped. Aprotinin could not be detected in any patient's blood. The exposure time to topical aprotinin was 11.4 minutes on average. Although aprotinin is a small molecule (about 7000 daltons), short exposure time and low topical dose limit systemic absorption. Our data once again confirm that the drug remains restricted to the pericardial space and the effect is completely due to topical action.

Although aprotinin has been reported as safe in earlier studies, a number of adverse reactions including renal impairment, graft occlusion, anaphylaxis after reuse, and disseminated intravascular coagulation after profound hypothermic bypass have begun to accumulate with increasing systemic use of aprotinin. The topical use of aprotinin will completely abolish most of the complications and eliminate the need for prophylactic use. We have used topical aprotinin extensively since 1991 with no adverse actions or intolerance. Another important consideration is treatment cost, which may be reduced by approximately 80% with the topical use of the drug.

We agree that "nothing is ever simple in the enzymatic stew of coagulation"¹ but believe that a simple approach to the problems sometimes brings better solutions. In our opinion, topical use of aprotinin will be established as a therapeutic option to reduce postoperative blood loss. It can at least be combined with systemic use to reduce the high intravenous doses. We also emphasize that careful surgical hemostasis is the key in reducing postoperative blood loss and that pharmacologic agents should be used not as an alternative but a supplement to surgical hemostasis.

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