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Aprotinin therapy and blood conservation: extending the indications

Blood conservation is now acknowledged as a priority in all forms of major surgery. Professional and public awareness of the risks associated with the use of homologous blood or blood product transfusions have risen sharply in recent years. Two different but complementary approaches to blood conservation have emerged: autotransfusion and the use of pharmacological agents to reduce peroperative bleeding.

The pharmacological approach is conceptually more attractive because it aims at prevention, or at least reduction, of the primary bleeding. Until recently, however, the drugs that had been used (including epsilon aminocaproic acid, prostacyclin, desmopressin and dipyridamole)[1–3] failed to exhibit significant or consistent efficacy and made little or no impact on blood transfusion requirements, particularly in high-risk patients. The serendipitous discovery of the blood-sparing role of high-dose aprotinin (Trasylol; Bayer, Newbury, UK) in patients undergoing cardiac surgery[4] has changed this. For the first time, a pharmacological agent has been truly effective in reducing peroperative bleeding and the need for blood and blood product transfusion. This high degree of efficacy has been demonstrated not only in routine primary cases but also in repeat operations, in patients with coagulation disorders and in those with active sepsis from uncontrolled infective endocarditis. The results from initial single-centre reports have been confirmed in large multicentre studies[5]. Clinical use of aprotinin is now widespread in cardiac surgical practice in several European countries and prelicensing studies in North America will soon be completed.

The question to be considered now is obvious: 'Is aprotinin therapy similarly effective in reducing blood loss in other types of major surgery?' It cannot be assumed that efficacy will be similar because cardiac surgery is a unique surgical scenario related to the obligatory use of cardiopulmonary bypass. Cardiopulmonary bypass is associated with a complicated pathophysiology that includes several significant haematological and haemostatic side-effects not considered to be features of non-cardiac procedures. In addition to mandatory systemic heparinization, the contact activation process (where the patient's circulating blood passes over the artificial surfaces of the extracorporeal circuit) induces a series of haematological reactions including both fibrinolysis and kallikrein and complement activation[6]. Disturbances in platelet function and reductions in platelet surface receptor populations are also described during bypass. Although the precise mode of action of aprotinin therapy in cardiac surgery remains unclear, many believe that the inhibition of increased fibrinolysis (a known effect of a serine protease inhibitor such as aprotinin) is the principal mode of action. If this is so, then aprotinin therapy in non-cardiac procedures might be expected to reduce peroperative bleeding only if increased fibrinolysis were a feature of such surgery. These possibilities are obviously intriguing and require proper study. Urological surgery for example, with its associated urokinase-producing epithelium, seems a logical area to investigate.

In fact, despite the lack of such scientific evidence, there are already empirical data showing that aprotinin therapy does have a similar efficacy in reducing bleeding in non-cardiac procedures. A preliminary report from Thompson *et al.*[7] has described significant reductions in blood loss both during and after aortoiliac surgery. From studies of hepatic surgery, Mallett *et al.*[8] reported similar efficacy in reducing blood loss, particularly during the anhepatic phase of liver transplantation. This particular finding is interesting because the anhepatic phase is associated with a hyperfibrinolytic state. For pulmonary surgery, Cooper[9] recently reported significant reductions in peroperative blood loss and transfusion requirements in patients undergoing bilateral lung transplantation for cystic fibrosis. There are also anecdotal reports of the use of aprotinin therapy in surgery for arteriovenous malformations.

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Such preliminary clinical data suggest that aprotinin therapy will be shown to be effective in reducing bleeding in non-cardiac procedures and that it will have a significant role in blood conservation in surgery in general. At this point, however, a word of caution is necessary. Before aprotinin is grasped eagerly as the answer to bleeding problems in all surgical procedures, the same degree of thought must go into dosage levels, and the same care must be exercised in carrying out prospective placebo-controlled trials as in the initial cardiac surgery studies. Only then will the very real potential for extending the indications of this powerful drug be fully and safely realized.

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