Use of aprotinin in knee replacement surgery

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Summary
We have studied the effect of aprotinin on blood loss and subsequent blood transfusion in 17 patients undergoing knee replacement surgery. Patients receiving aprotinin (total dose 2000000 kallikrein inhibiting units) received fewer units of blood than control patients (P < 0.05), although there was no significant difference in blood loss between the two groups. The study was stopped when one patient in the aprotinin group needed an above-knee amputation because of ischaemia secondary to arteriovenous thrombosis after knee replacement surgery. Although the patient had peripheral vascular disease which could have accounted for the thrombosis, the role of aprotinin under tourniquet conditions is unclear. (Br. J. Anaesth. 1994; 73: 408-410)

Key words

Blood transfusion is associated with a wide range of complications. Various methods may be used to reduce blood loss during surgery, thereby reducing the need for transfusion. Aprotinin is a serine protease inhibitor which has been used extensively to reduce blood loss in patients undergoing cardiac surgery. Experience in its use in other forms of surgery is limited. One study [1] indicated that patients undergoing hip replacement surgery have reduced blood loss and transfusion requirements without an increase in the risk of venous thromboembolic disease (demonstrated by 131I-fibrinogen uptake). We undertook a study to investigate the effect of aprotinin on blood loss and blood transfusion during total knee replacement surgery.

Methods and results
We studied 17 patients undergoing elective total knee replacement. The patients were treated by the same surgical team and anaesthetist. The study was approved by our local Ethics Committee and all patients gave informed consent. No patient had a history of clinical coagulation abnormalities. Four patients in the aprotinin group and five patients in the control group were receiving non-steroidal inflammatory drugs.

Patients were allocated randomly in pairs to one of two groups. Group A received aprotinin 500000 KIU (kallikrein inhibiting units) over 20 min immediately before inflation of the tourniquet. They then received 500000 KIU over the 20 min before deflation of the tourniquet followed by an infusion of 1000000 KIU over the next 2 h. Group B had identical anaesthetic and surgical management, but without aprotinin.

All patients were premedicated with temazepam. Anaesthesia was induced with a dose of propofol sufficient to obtund the eyelash reflex and maintained with enflurane, nitrous oxide and oxygen administered via a circle system through a laryngeal mask. Sciatic and femoral nerve blocks were performed using 0.375% bupivacaine.

All patients received a Kinemax joint prosthesis from the same surgical team under tourniquet control. Two Redivac drains were inserted. Each drain was heparinized to prevent drained blood clotting and remained in situ for 48 h after operation. All patients received low-dose heparin prophylaxis for deep venous thrombosis and diclofenac 100 mg daily per rectum as part of their analgesic regimen, commencing in theatre.

Blood loss was measured during operation by careful weighing of swabs and monitoring of suction losses. Postoperative blood loss was assessed over 48 h by measuring blood in the drain bottles and by a descriptive assessment of blood seepage onto the dressings (minimal, moderate or heavy). All assessments were obtained by a member of staff who was unaware of whether or not the patient had received aprotinin.

The decision whether or not to transfuse was made by the surgical team after operation. They were blinded to the study and their decision was a clinical one, based on a bedside assessment of blood loss into the drains, the preoperative haemoglobin concentration and the patient's condition, especially arterial pressure and heart rate. It was planned originally to enter 40 patients into the study with interim analyses at 20 and 30 patients. The original design of the study involved sequential analysis of the results after 20, 30 and 40 patients. We stopped the study after 17 patients. A patient developed an arteriovenous thrombosis which required the leg to be amputated.

Statistical analysis of blood loss and transfusion requirements was by the Mann-Whitney U test. Statistical analysis of the number of patients transfused was by the Fisher exact test (two-tailed).

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Results of blood loss and units of blood transfused are shown in table 1. Eight patients received aprotinin and nine received no drug. One of the aprotinin patients and six patients in the control group received a blood transfusion after operation (associated probability = 0.073). There were fewer units of blood transfused in patients given the aprotinin regimen (P < 0.05). Blood loss, although lower in the aprotinin group, was not significantly different. Calculations based on the results obtained showed that a further 23 patients would be required to have an 80% chance of detecting a 300-ml difference in blood loss. There was no significant difference in preoperative haematocrit between the two groups. Routine haematocrits were measured in the week after surgery and after blood transfusion, if given. There was no significant difference in final haematocrit between the two groups. The decision to stop the study after 17 patients was taken after careful consideration of the following patient.

A 78-yr-old man was entered into the study. He had severe knee derangement and pain, which greatly limited his mobility, and a mild degree of angina. He was allocated to receive aprotinin and underwent a surgically difficult knee replacement, with a tourniquet time of 80 min. After deflation of the tourniquet it was noted that initial perfusion of the leg was poor, although this had improved after 30 min. During the following 10 days perfusion of his leg was variable and he underwent angiography which showed complete occlusion of the superficial femoral artery with very poor downstream flow. Management of the patient was discussed with the vascular surgeons who felt that the occlusion was huge with no possibility of a bypass procedure. Thrombolytics were discussed but were thought not worth using with such an extensive occlusion. He underwent an above-knee amputation. Pathology showed severe peripheral vascular disease with a calcified, atheromatous popliteal artery. There was a 4-cm long organized thrombus in the centre. Widespread arteriovenous thrombosis was present in the specimen sent.

**Comment**

Transfusion of autologous blood is associated with many complications and measures which reduce transfusion requirements in surgical patients without added risk are desirable. Aprotinin, a serine protease inhibitor, is currently used extensively in cardiac surgery to reduce blood loss, particularly in patients undergoing repeat surgery. This has been shown to be effective in several studies [2, 3] although the exact mechanism is unclear.

A study of 120 patients undergoing total hip replacement [1] showed a significantly lower incidence of blood loss, transfusion requirements and haematoma in patients given aprotinin compared with control.

Our study failed to show a significant difference in blood loss between the two groups. If we had been able to complete the full study of 40 patients as proposed, and the observed trends continued, a significant difference might have been revealed. The reason for the difference in clinical assessment of transfusion requirements between the two groups is interesting. The requirement for blood transfusion does not lie on a linear scale, but rather begins at a "trigger point" at which the clinician feels that blood is needed to improve the patient's clinical status. This point may be determined by a strict transfusion procedure or may be the result of the clinician's interpretation of a variety of factors. In the postoperative period this "transfusion trigger" is often governed by haematocrit or continuing blood loss from the operation site [4]. It may be that the blood loss in knee replacement surgery lies on or above this trigger point and a moderate reduction in blood loss produces a dramatic decrease in blood transfused. Although our study did not show a significant difference in blood loss, the drain losses were less in the aprotinin group (median loss 663 ml) than the control group (median loss 960 ml) and this may have resulted in a better general haemodynamic state.

In patients with severe peripheral vascular disease, total knee replacement is performed reluctantly and usually without tourniquet control. In the clinical case described above, the patient's peripheral vascular disease was masked by the severe limitation of mobility resulting from his arthritic knee. This prevented claudication pain from occurring. Aprotinin has been used previously in patients with peripheral vascular disease. In a series of 10 patients undergoing reconstructive surgery for sarto–iliac occlusive disease there were no thrombotic complications [5].

It was not possible to determine if aprotinin contributed to the vascular occlusion. Thrombosis accompanying aprotinin therapy has been reported to the Committee on Safety of Medicines on two occasions since 1974 and although there have been occasional anecdotal reports of graft occlusion in CABG patients receiving aprotinin, the current opinion is that aprotinin does not increase the risk of thrombosis [6]. One report [7] documented three cases of thrombi formation on pulmonary artery catheters in patients receiving high-dose aprotinin. The authors believed that thrombus formation on pulmonary artery catheters was facilitated by high-dose aprotinin and speculated that preserved or enhanced platelet adhesion may lead to early activation of the coagulation cascade. On the other
hand, aprotinin has been shown to have an anti-platelet action which would theoretically decrease the risk of thrombosis [8]. Two further studies in patients undergoing hip replacement surgery have found no increase in the risk of venous thrombosis [9] and a decrease in venous thrombosis [10] in patients receiving aprotinin. However, previous studies have not used aprotinin during tourniquet controlled surgery. It could be that circulatory stasis provides a different set of conditions for the effects of aprotinin.

The results from this curtailed study indicated that aprotinin appears to reduce blood transfusion requirements in patients undergoing total knee replacement. The authors’ opinion is that the patient’s peripheral vascular disease was sufficient to account for his ischaemic leg. However, it is not possible to determine if aprotinin was a contributing factor. Given the current level of knowledge on aprotinin we would recommend caution in its use in surgical patients with peripheral vascular disease where surgery is to be performed under tourniquet control.

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References