Aprotinin in aortic surgery requiring profound hypothermia and circulatory arrest

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Abstract

Objectives: The use of aprotinin in cardiac surgery to improve haemostasis and reduce blood loss particularly in patient groups at increased risk of bleeding is well established. Previous retrospective studies in profound hypothermic surgery have highlighted concerns that in this circumstance aprotinin may paradoxically cause increased bleeding and intravascular thrombosis. We therefore adopted a modified protocol for administering aprotinin, which was not started until cardiopulmonary bypass had been reinstituted after circulatory arrest. Methods: Between April 1993 and June 1995, 45 patients underwent 46 thoracic aortic procedures which required hypothermic circulatory arrest; 25 of these were emergencies. All of these patients received aprotinin. Results: There were five deaths (10.8%) in hospital. Two patients with preoperative oliguric renal failure required postoperative dialysis, and a further six (13%) developed transient renal dysfunction with complete recovery. Two patients suffered postoperative stroke; one from embolisation of a severely diseased aorta, while the other had signs of an acute evolving stroke before surgery. None of the patients suffered acute Q-wave perioperative myocardial infarction. The mean blood loss was 575 ml in the first 12 h, with a mean postoperative transfusion requirement of 1 U blood. Conclusions: We cannot implicate aprotinin in increased postoperative blood loss, renal dysfunction or mortality when used with hypothermic circulatory arrest according to this protocol. Elucidating the role of aprotinin in hypothermic circulatory arrest requires a randomised prospective study. © 1997 Elsevier Science B.V.

Keywords: Aortic surgery; Aprotinin; Circulatory arrest; Hypothermia

1. Introduction

Aprotinin is used in cardiovascular surgery to improve haemostasis, reducing postoperative blood loss and blood product transfusion requirement [7]. Its efficacy was originally demonstrated in patients undergoing repeat cardiac surgery [15]. Subsequent reports have confirmed particular benefit in groups of patients at increased risk of bleeding, including patients on aspirin [2,12], those with infective endocarditis or renal failure [1] and paediatric cardiac surgical patients [3,4], and its use has been extended to cardiopulmonary transplantation [8] and left ventricular assist device placement [6]. Patients undergoing surgery of the thoracic aorta requiring cardiopulmonary bypass, profound hypothermia and circulatory arrest are at high risk of haemostatic problems. Multiple suture lines in friable or dissected, high-pressure vessels, long cardiopulmonary bypass times, and the effect of hypothermia on the clotting cascade may all predispose to increased bleeding [10]. In these circumstances, aprotinin would intuitively be expected to be an important adjunct to surgical haemostasis. However, there have been reports of higher bleeding rates [21], as well as increased mortality and morbidity [16], and it has been speculated that aprotinin fails to preserve haemostatic function in
profound hypothermia and may initiate a process of disseminated intravascular coagulation and microvascular thrombosis during circulatory arrest [20].

Because of these concerns, we have used a modified aprotinin protocol for surgery requiring profound hypothermic circulatory arrest since 1993. Aprotinin is not administered until cardiopulmonary bypass has been reinstated after the period of circulatory stasis. We describe the protocol used and report our results.

2. Materials and methods

2.1. Patients

This report details 46 consecutive procedures in 45 patients undergoing surgery of the aorta, employing profound hypothermia and circulatory arrest between April 1993 and June 1995. Preoperative risk factors for renal dysfunction and thrombotic events were identified by case note analysis. The perfusion details are given in Fig. 1.

2.2. Cardiopulmonary bypass and hypothermic circulatory arrest

A standard cannulation technique and bypass circuit was used in all cases. Bicaval venous cannulation was employed with arterial return to the right common femoral artery. The circuit was made up from \( \frac{1}{2} \) internal diameter venous tubing, a membrane oxygenator (Compact-flo, Miradola, Italy) and an arterial segment of \( \frac{5}{8} \) tubing. This was primed with a compound sodium lactate solution. A parallel \( \frac{1}{4} \) cannula was connected between the arterial return and the SVC cannula by means of Y connections, primed and clamped at both ends.

Cardiopulmonary bypass was instituted with nonpulsatile flow maintaining a mean arterial pressure of 50–60 mmHg. Alpha stimulants were used intermittently if required. The patient was then cooled gradually to 15°C using a gradient of less than 10°C between the blood and heat exchanger. The heart was protected with cold antegrade crystalloid cardioplegia (St. Thomas’s) and topical cooling. In all but one patient, who presented with a ruptured thoraco-abdominal aneurysm involving the aortic arch, retrograde cerebral perfusion was employed during circulatory arrest. The retrograde perfusion was delivered through the SVC cannula via the parallel arterial line to maintain a left jugular bulb pressure around 25 mmHg, achieving flow rates of 300–700 ml/min as previously described [14].

2.3. Haemostatic protocol

Infusion of aprotinin was started after completion of the period of circulatory arrest with the recommencement of cardiopulmonary bypass. A loading dose of 280 mg was given as a bolus over several minutes into the bypass pump, and then a continuous intravenous infusion of 70 mg/h was started. This was continued until the patient arrived in the intensive care unit after surgery. During rewarming, haemofiltration was commenced and the filtrate replaced with fresh frozen plasma. Prior to discontinuation of bypass, all suture lines were thoroughly checked. Patients were warmed to 37°C and maintained at this temperature for 10 min before coming off bypass to reduce temperature after drop. Once bypass had been discontinued, the anastomoses in the surgical field were tightly packed with gauze swabs and protamine reversal of heparin commenced. When protamine-induced clotting had been identified in the surgical field, the anastomoses were repacked, and platelets, fresh frozen plasma and cryoprecipitate were administered empirically in a pre-emptive attempt to secure total haemostasis. A variable and often prolonged period of inspection and cautery haemostasis was conducted until the wound was judged satisfactory for closure.

3. Results

3.1. Patient population

There were 24 male and 21 female patients with a mean age of 46 years (range 26–83 years). The indications for surgery are shown in Table 1. Of the 46
procedures, 29 were aortic root replacements, with total arch replacement on 10 occasions and hemiarch replacement on eight. The ascending aorta was replaced in 10 cases, three with hemiarch and three with total arch replacement. Isolated aortic arch replacement was performed three times, total thoracic aortic replacement once, and thoraco-abdominal aortic replacement once. On one occasion, hypothermic circulatory arrest was used for repair of an aberrant right subclavian artery aneurysm, and on a further occasion, for ligation of a patent ductus arteriosus with repair of a large sinus of Valsalva aneurysm. Twenty-five (54%) operations were performed as emergencies; 18 patients underwent surgery for acute type A aortic dissections, three patients had surgery for infected aortic grafts and a further two patients had undergone previous cardiothoracic surgery.

Two patients had acute oliguric renal failure on presentation and in a further 11 there was renal dysfunction (serum creatinine > 120 \( \mu \)mol/l) at the time of surgery. Intraoperative contrast for imaging had been given to 20 patients less than 24 h prior to surgery. Hypertension was present in 18 patients, ischaemic heart disease in 12, diabetes in five and peripheral vascular disease in three. One patient had undergone previous nephrectomy for renal cell carcinoma and one patient had chronic lymphatic leukaemia.

### 3.2. Mortality

There were five postoperative deaths, representing a mortality of 10.8%, all in patients undergoing emergency operations.

Patient 1 with mega-aorta syndrome and unstable angina secondary to critical left main stem stenosis underwent replacement of the ascending aorta and aortic arch in conjunction with coronary revascularisation. Postoperatively, the patient had clinical signs of a diffuse brain injury, from which he eventually died. Computerised tomography revealed multiple cerebral infarcts which were confirmed to be embolic at post mortem. At operation, the aneurysmal aortic arch and carotid ostia contained confluent friable atheroma; it is presumed that surgical manipulation of these vessels caused fragmentation and embolisation.

Patient 2 was transferred to the unit ventilated with pulmonary oedema and cardiogenic shock, having been unsuccessfully treated for 2 weeks at another hospital for prosthetic aortic valve endocarditis. He had undergone aortic root and hemiarch replacement with a valved conduit for a chronic dissecting aneurysm 9 months previously. The infected graft was replaced with a homograft aortic root and an additional segment of homograft aorta. Whilst cardiovascular recovery was satisfactory, throughout the postoperative period this patient had signs of ongoing sepsis that failed to respond to antimicrobial therapy. The patient had previously undergone nephrectomy for renal cell carcinoma, had renal dysfunction with a preoperative serum creatinine of 450 \( \mu \)mol/l and was oliguric on admission. Renal failure complicated the persisting sepsis, haemodialysis was started but the patient died on the 28th day post surgery. There was no evidence at post mortem examination of infarction or intravascular thrombosis in any of the organs.

Patient 3 died 5 days after replacement of the ascending aorta and aortic arch, following acute type A aortic dissection, from a ruptured (non-dissected) infrarenal aortic aneurysm. Post mortem examination confirmed the cause of death. There was no histological evidence of other organ pathology or intravascular thrombosis.

Patient 4 presented with rupture of a chronic type A aortic dissection into the left hemithorax. The dissection extended into the infradiaphragmatic aorta and severe aortic regurgitation was also present. Preoperatively he had developed a right-sided hemiparesis and oliguric renal failure. The patient underwent replacement of the aortic root, aortic arch and descending thoracic aorta. Postoperatively, his hemiparesis progressed to hemiplegia and he became anuric. Despite haemodialysis, he died from renal failure on the 32nd postoperative day.

Patient 5 with chronic lymphatic leukaemia and renal dysfunction presented with an acute type A dissection. The ascending aorta was replaced with a supracoronary graft. Cardiac recovery was satisfactory but a high-output, low-resistance state developed immediately following operation and rapidly progressed to death from multi-organ failure.

### 3.3. Renal function

There were two patients who required dialysis postoperatively, both of whom were oliguric preoperatively. One patient (mortality patient 2) had undergone previous nephrectomy, and was septic and oliguric with a creatinine of 450 \( \mu \)mol/l. The second patient (mortality patient 4) had oliguric renal failure associated with a leaking chronic type A aortic dissection extending into the abdominal aorta. Both of these patients died in hospital and their details are given above in the mortal-
Fig. 2. Mean pre- and postoperative serum creatinine levels + S.D. in surviving patients.

ity section. Postoperative renal failure and dialysis requirement were attributable to their preoperative state. Six patients (13%) suffered from a transient increase ( > 1.5% of the baseline value) in serum creatinine which did not require further treatment and resolved spontaneously. The mean serum creatinine level of the survivors on discharge was 122.7 μmol/l, which was not significantly higher than the preoperative mean of 115.7 μmol/l (see Fig. 2).

3.4. Myocardial infarction

No patient in this series suffered from acute Q-wave perioperative myocardial infarction. Isoenzyme analyses were not performed.

3.5. Blood product transfusion and bleeding

The intraoperative and postoperative transfusion data are given in Figs. 3 and 4. The mean intraoperative number of units (U) of blood transfused was 2 U, and a further 1 U in the first 12 h after surgery. At 12 h, the mean chest drainage was 575 ml (range 140–3160). Three patients were re-opened for excessive postoperative blood loss and in each case a technical cause was identified.

3.6. Other complications

Two patients suffered stroke. One patient suffered atheromatous embolisation from a severely diseased aortic arch, and the other had an acute hemiparesis on admission which progressed to hemiplegia. The details of these two patients who both died in hospital are given in the mortality section above.

4. Discussion

The coagulation defects caused by cardiopulmonary bypass are multifactorial in origin, though the primary cause is the contact of the blood with the artificial surface of the extracorporeal circuit [13,19]. There is a continuous process of fibrin formation and fibrinolysis throughout cardiopulmonary bypass and, if bypass is prolonged, a consumptive coagulopathy may arise. In addition, cardiopulmonary bypass causes platelet dysfunction as well as reducing the platelet count [11]. Aprotinin protects platelet adherent function from the harmful effects of cardiopulmonary bypass and is also a powerful antifibrinolytic agent [17,18].

Surgery on the thoracic aorta may require profound hypothermic bypass and circulatory arrest; such patients are at increased risk of bleeding because of long bypass times and the effect of low temperature on the clotting system [10]. If these patients have a dissection or systemic infection, the risk of post bypass coagulopathy is yet higher. There have, however, been reports of paradoxical bleeding [21], increased renal dysfunction, myocardial infarction and death [16] with aprotinin administration to patients undergoing profound hypothermic circulatory arrest. Aprotinin is known to inhibit the protein C system and tissue plasminogen activator [5] both of which may be important in preventing intravascular coagulation during low flow states or circulatory stasis. This is the proposed mechanism of the adverse effects reported and was supported by post mortem findings [16].
Although improved haemostasis and reduced blood transfusion in patients undergoing cardiac operations and receiving aprotinin is widely accepted, Westaby et al. [21] have questioned this when used with profound hypothermia and circulatory arrest. Of 80 patients in this study, 53 received aprotinin. Six of those in the aprotinin group required re-opening but none in the non-protamine group. Blood loss in the first 24 h was presented year by year and in the aprotinin group, mean blood loss was in the range 1255–2026 ml, compared with a mean range of 483–1246 ml in patients who did not have aprotinin. The aim of the haemostatic protocol that we used was to prevent intravascular coagulation during circulatory arrest and to then obtain the haemostatic benefit of aprotinin in conjunction with platelets, fresh frozen plasma and cryoprecipitate. Aprotinin loading and infusion were not started until bypass was re instituted after the period of circulatory arrest. Once rewarming had been started, haemofiltration was commenced and the filtrate replaced with fresh frozen plasma transfused into the cardiopulmonary bypass circuit. Platelets and cryoprecipitate were transfused after weaning the patient from bypass and protamine administration to effect secure haemostasis. Three patients required re-opening and in each case a bleeding source was located. None of these three patients had evidence of coagulopathy. Postoperatively, there was minimal blood loss and blood product transfusion, which reflects the length of time taken to secure surgical haemostasis.

The mortality in this series was 10.8%. In the series reported by Westaby et al. [21] the hospital mortality in the aprotinin group was 9.4% (5/53) and 18.5% (5/27) in the non-protamine group, with an overall mortality of 12.5% (10/80). Although there is a trend towards lower mortality in the aprotinin group (despite the apparent increased bleeding problem), this is not statistically significant. Sundt et al. [16] reports a mortality of 35% (7/20) in their aprotinin group and 5% (1/20) in a matched population. Five of the patients who died in this series underwent post mortem examination and platelet–fibrin thrombi were found in multiple organs in four. We were not able to attribute any of our five deaths to the use of aprotinin. We would concede that in the cases of patients 4 and 5, post mortem data is not available, but neither of these deaths were unexplained. In the three post mortem examinations that were carried out, there was no evidence of intravascular platelet–fibrin thrombi.

We did not observe the high level of renal dysfunction reported by Sundt et al. [16] (65% postoperative renal dysfunction and 25% haemodialysis requirement). Two of our patients (4.4%) required postoperative haemodialysis. Both had preoperative oliguria and multiple risk factors, and dialysis would have been required regardless of surgery. A transient increase in serum creatinine (more than 1.5 times the preoperative level) was observed in a further six (13%) patients and there was no significant difference between preoperative and discharge mean levels (see Fig. 2). This degree of transient renal dysfunction does not differ from other cases requiring prolonged cardiopulmonary bypass without hypothermic arrest [9]. No patients in this series developed myocardial infarction, and although stroke occurred in two, aprotinin-induced microvascular thrombosis could not easily be implicated as a causal agent.

Our data does not conflict with that previously published on the use of aprotinin with profound hypothermic circulatory arrest [16,21]. The aprotinin protocol that we adopted was an attempt to avoid the adverse effects that had been observed by others and has been successful in that regard. Although we are mindful of previously expressed concerns, we cannot implicate aprotinin in an increase in postoperative blood loss, renal failure or death. We would, however, concede that we have not shown that aprotinin confers any haemostatic benefit. In conclusion, it appears that the action of aprotinin in hypothermic circulatory arrest is not fully understood and a prospective randomised trial, rather than retrospective anecdote, is required to properly assess its role.

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References


