EFFECT OF HIGH-DOSE APROTININ (TRASYLOL) ON BLOOD LOSS AND COLLOID USE IN CARDIOPULMONARY BYPASS PATIENTS

TREVOR DOBBINSON, FFARCS; TAJAMMAL BHATII, FFARCS; AHSAN ZAFFRULLAH, FFARCSI

Twenty-six consecutive adult patients subjected to cardiopulmonary bypass surgery were studied for blood loss and colloid use at operation and for the first 48 h thereafter. The first group of 14 patients received no aprotinin and the subsequent 12 patients were given aprotinin 4 mg/kg into a central vein before surgical incision, 4 mg/kg into the pump oxygenator, and 1 mg/kg/h as a continuous infusion till the end of surgery. The patients receiving aprotinin had less blood loss at operation and in the intensive care unit with a mean (± SEM) of 1292 ± 299 mL vs 3072 ± 369 mL (P = 0.009). Overall, they required less colloid infusion with 8.9 ± 1.7 units vs 18.2 ± 2.9 units (P = 0.03). Blood use was also less and the mean was 1.7 ± 0.4 units vs 3.9 ± 0.5 units. There were also significant reductions in platelet and fresh frozen plasma infusions.

CARDIOPULMONARY bypass (CPB) surgery patients tend to bleed after operation. This bleeding is manifested in the operating room postbypass and during the first few hours of postoperative recovery. The bleeding mechanism is obscure and appears to involve several different aspects of disordered hemostasis.1-3 Since platelet function abnormalities are now believed to be focally important, attention has been directed to factors that may "protect" platelets during the body's exposure to the pump-oxygenator system. Several different drugs have been tried with variable success.4-7 Most recent among these is aprotinin which appears, from the reports of Bidstrup et al, to have considerable potential.8 We have now used this drug in approximately 80 patients; and in this paper, we report its use in the first 12 patients for whom we have comparable historical data.

Methods

Twenty-six consecutive patients undergoing CPB surgery were studied for the effects of opera-

From the Department of Anesthesia, King Khalid University Hospital (Drs. Dobbinson and, Bhatti) and Department of Anesthesia, Security Forces Hospital (Dr. Zaffrullah), Riyadh. Address reprint requests and correspondence to Dr. Dobbinson: Department of Anesthesia (41), King Khalid University Hospital, P.O. Box 7805, Riyadh 11472, Saudi Arabia.

nulation in a ratio of 1.5 mg protamine to each 100 IV total dose heparin received. CPB was established with the Shiley S 100A oxygenator reaching hypothermia at 25 to 28°C rectal temperature. During the period of aortic cross clamping, bloodpotassium cardioplegia and sustained topical ice slush gave myocardial protection. The oxygenator prime comprised of 2 L of solution containing Ringer's lactate (1400 mL), 5% dextrose (350 mL), and plasma protein fraction ([PPF], 250 mL, Human USP 5% solution). Additional fluids (Ringer's lactate, PPF, and blood) were added during the procedure in order to achieve a hemoglobin concentration of 70 to 80 g/L at the end of bypass. The operating field was continually observed for clinically important blood loss. Bleeding was secured mainly by surgical packing and diathermy. Continued bleeding, after the intake of protamine, was treated with fresh frozen plasma (FFP) and platelet concentrate infusions when no clot formation could be seen. In those cases where bleeding was heavy and sustained, other hemostatic agents such as epsilon amino caproic acid (EA CA), desmopressin (DDA VP), factor VIII concentrate, and fibrinogen were used. Therapy was also guided by the "clotting profile" (comprised of activated partial thromboplastin time [APIT], prothrombin time [PT], thrombin time [TT], fibrinogen assay, fibrin degradation product [FOP] level, reptilase time, and platelet count) obtained in the operating room or in the intensive care unit. Two mediastinal drains with a 20 mm Hg low pressure continuous suction were placed at operation for postoperative use. These chest tubes were removed when the drainage reached a maximum of 50 mL which had accumulated from the previous 8 h period. Hemodynamic management varied from patient to patient and was dictated by normal standards of practice. Hypotensive patients were nursed supine, but all others received 10° to 20° head-up posture which progressed to 45° Fowler at the time of extubation. Postoperative blood hemoglobin concentration was adjusted to 90 to 100 g/L by use of an appropriate colloid solution. The latter was usually PPF, whole b'lood, or packed cells. Crystalloid solutions were not used as volume expanders. Patients remained intu- . bated and lungs were artificially ventilated only until circulatory stability was achieved. Extubation mainly occurred between 5 to 10 h after operation.

Data Collection
Data were collected prospectively for fluid therapy and blood loss. All colloids used, from the start of anesthesia to the end of the second postoperative day, were recorded according to the type of fluids and the time of administration. Operating room-measured blood loss and postoperative chest tube drainage were also recorded. No attempt was made to account for extraneous blood loss. In general, small and probably similar unaccounted loss occurred in most patients with the exception of those who bled excessively. Measurements were compared by means of the Student's Hest for unpaired data. Postoperative chest tube drainage was not normally distributed and therefore groups were compared by means of Wilcoxon's rank sum test for unpaired data. The frequency of blood use between the groups was compared with the Fisher exact test for small numbers.

Results
There were no significant differences in the physical characteristics of patients studied (Table 1). The mean operating times were similar in both groups. However, the mean postbypass time appeared to be significantly shorter in the Trasylol-treated patients. This group received fewer units of colloid and, in particular, fewer units of red cells, FFP, and platelets which were given postbypass in the operating room (Table 2). In the intensive care unit, 1 Trasylol-treated patient bled heavily and was given 3 units of FFP and 12 units of platelets. Four patients who were not given Trasylol received five units of FFP and two patients received four units of platelets. Although average blood loss appeared to be less at all surgical care stages in the Trasylol patients (Table 3), this finding was not consistent because one patient did bleed excessively and two others had moderately heavy blood loss. There appeared to be a "shift to the left" in the amount of postoperative chest tube drainage in that more patients bled minimally in the Trasylol group and more patients bled excessively in the non-Trasylol group (Figure 1).
nulation in a ratio of 1.5 mg protamine to each 100 IV total dose heparin received. CPB was established with the Shiley S 100A oxygenator reaching hypothermia at 25 to 28°C rectal temperature. During the period of aortic cross clamping, bloodpotassium cardioplegia and sustained topical ice slush gave myocardial protection.

The oxygenator prime comprised of 2 L of solution containing Ringer's lactate (1400 mL), 5% dextrose (350 mL), and plasma protein fraction ([PPF], 250 mL, Human USP 5% solution). Additional fluids (Ringer's lactate, PPF, and blood) were added during the procedure in order to achieve a hemoglobin concentration of 70 to 80 g/L at the end of bypass. The operating field was continually observed for clinically important blood loss. Bleeding was secured mainly by surgical packing and diathermy. Continued bleeding, after the intake of protamine, was treated with fresh frozen plasma (FFP) and platelet concentrate infusions when no clot formation could be seen. In those cases where bleeding was heavy and sustained, other hemostatic agents such as epsilon amino caproic acid (EA CA), desmopressin (DDA VP), factor VIII concentrate, and fibrinogen were used. Therapy was also guided by the "clotting profile" (comprised of activated partial thromboplastin time [AP1T], prothrombin time [PT], thrombin time [TT], fibrinogen assay, fibrin degradation product [FOP] level, reptilase time, and platelet count) obtained in the operating room or in the intensive care unit.

Two mediastinal drains with a 20 mm Hg low pressure continuous suction were placed at operation for postoperative use. These chest tubes were removed when the drainage reached a maximum of 50 mL which had accumulated from the previous 8 h period.

Hemodynamic management varied from patient to patient and was dictated by normal standards of practice. Hypotensive patients were nursed supine, but all others received 10° to 20° head-up posture which progressed to 45° Fowler at the time of extubation. Postoperative blood hemoglobin concentration was adjusted to 90 to 100 g/L by use of an appropriate colloid solution. The latter was usually PPF, whole blood, or packed cells. Crystalloid solutions were not used as volume expanders. Patients remained intubated, bated and lungs were artificially ventilated only until circulatory stability was achieved. Extubation mainly occurred between 5 to 10 h after operation.

Data Collection

Data were collected prospectively for fluid therapy and blood loss. All colloids used, from the start of anesthesia to the end of the second post-operative day, were recorded according to the type of fluids and the time of administration. Operating room-measured blood loss and postoperative chest tube drainage were also recorded. No attempt was made to account for extraneous blood loss. In general, small and probably similar unaccounted loss occurred in most patients with the exception of those who bled excessively.

Measurements were compared by means of the Student's Hest for unpaired data. Postoperative chest tube drainage was not normally distributed and therefore groups were compared by means of Wilcoxon's rank sum test for unpaired data. The frequency of blood use between the groups was compared with the Fisher exact test for small numbers.

Results

There were no significant differences in the physical characteristics of patients studied (Table 1). The mean operating times were similar in both groups. However, the mean postbypass time appeared to be significantly shorter in the Trasylol-treated patients. This group received fewer units of colloid and, in particular, fewer units of red cells, FFP, and platelets which were given postbypass in the operating room (Table 2). In the intensive care unit, 1 Trasylol-treated patient bled heavily and was given 3 units of FFP and 12 units of platelets. Four patients who were not given Trasylol received five units of FFP and two patients received four units of platelets.

Although average blood loss appeared to be less at all surgical care stages in the Trasylol patients (Table 3), this finding was not consistent because one patient did bleed excessively and two others had moderately heavy blood loss. There appeared to be a "shift to the left" in the amount of postoperative chest tube drainage in that more patients bled minimally in the Trasylol group and more patients bled excessively in the non-Trasylol group (Figure 1).
APROTININ IN CPB

Although we considered employing a controlled clinical trial at the outset, the initial results were so dramatically impressive that none of the surgical team members was prepared to stop using aprotinin thereafter; thus, the inevitable weakness in the study design was accepted. Since we had already begun investigating aspects of hemostasis in our patients when aprotinin was introduced, we decided to continue data collection with subsequent review of the results.

Surgeons generally state that cardiac surgery patients in the Middle East bleed more than others, but we are aware of only one report that seems to confirm this.10 The patients whom we operated on appear to bleed excessively after surgery, even when CPB time is brief. However, due to the wide range of reported perioperative blood loss, our data are similar to data found in studies which have been conducted in the West. 11-14 We have been unable to define this bleeding tendency clearly; patients who have a benign course and small postoperative chest tube drainage have near normal clotting profiles while those who bleed heavily have disorders in a variety of clotting tests.

The way in which aprotinin prevents bleeding in patients exposed to CPB is not well defined. Previous studies have shown that both dose and time of administration are important.8,15 Thus, 20,000 KIU (kallikrein inactivator units) was shown to reduce fibrinolysis but not blood loss; whereas 400,000 KID reduced blood loss by 21 % and much larger doses (5,000,000 KID) reduced it by more than 80%. In order to be effective, aprotinin must be given at the start of bypass. The drug is not useful if it is given in the postbypass period, and it is probable that prebypass use is not essential. Our data suggest that a small saving may be made by giving the drug before sternotomy. A recent study, reported by Wildevuur et al, employed a dose of 2,000,000 KID in the CPB prime, and this appeared to reduce blood loss as much as the higher dosages.16 Therefore, while the dose response relationship has not been unequivocally established, the total dose required may be only 25% to 30% of that used in our study. This has some importance when one considers the cost of aprotinin (approximately SR40 per 100,000 KID).

The levels of dosages may also influence the mechanism of action. Aprotinin, a naturally occurring basic proteinase inhibitor, acts principally by forming reversible complexes with trypsin, plasmin, tissue, and plasma kallikrein. These enzymes play a major role in the activation of the coagulation cascade and modulation of the fibrinolytic system. In low concentrations, aprotinin inhibits plasmin activity completely. At intermediate concentrations, platelet adherence and aggregation are reduced while at high concentrations, kallikrein generation is inhibited.7 However, just what relevance these known actions of aprotinin have to the time course of hemostatic derangement caused by CPB is not clear. Detailed understanding of these defects is also limited, consequently, it is not surprising that only a tentative concept of aprotinin's hemostatic effects has been formulated. Van Oeveren et al5 propose the following:

1. Contact at the onset of CPB between patient blood and extracorporeal equipment surfaces initiates release of proteolytic enzymes.
2. Intrinsic coagulation pathway activation via contact factor (XIa), kallikrein generation, and plasminogen activation.
3. Plasmin is formed in the fluid phase. This is responsible for enhanced fibrinolysis and is possibly the main factor causing platelet function deterioration. It may do this by removal of platelet von Willebrand receptor for adheresiveness and removal of fibrinogen subsequent to exposure of fibrinogen receptors in the aggregation process.
4. Platelet function is impaired as evidenced by increased adheresiveness, aggregation, and thromboxane B2 release. Platelet numbers also decrease but it is this deterioration in platelet function that is central to the hemostatic derangements of CPB.

Aprotinin blocks the formation of plasmin and kallikrein in the fluid phase, thereby, inhibiting coagulation factor activation, fibrinolysis, and platelet function impairment during the early part of CPB. It appears that these actions do not inhibit platelet responses at sites of vascular endothelial injury since the drug reduces both bleeding time and blood loss after reversal of heparinization. Evidence from FDP levels suggests that fibrinolysis is inhibited while the blood level of aprotinin is high during CPB and appears in the postbypass period as blood aprotinin level is reduced. The role of the tissue plasminogen activator (t-PA) is not clear, although it is also
inhibited early during CPB and it rises when a high level of aprotinin is maintained. The top A level is then sustained postbypass when the level drops in untreated patients. The high t-P A level in aprotinin-treated patients suggests that there is a potential for uncontrolled fibrinolysis during the postbypass period. This should be kept in mind if bleeding reappears in these patients; therapy with EACA should then be considered. Fibrinolysis is regarded by many to be a minor aspect of the hemostatic defect caused by CPB and attention is now being directed to platelet dysfunction. However, in the foregoing description, Van Oeveren et al combine these two concepts together by postulating that the observed fibrinolytic activity, although small, may have great significance for the platelet lesion.

The recent reports of high-dose aprotinin are highly encouraging because the drug appears to be effective in the majority of patients. Other drugs, thus far studied, have been found either only partially effective or effective but with severe side effects. Our data indicate that not all patients respond to aprotinin, and this may become more apparent with wider use. It is premature to suggest that the drug be used routinely in CPB patients. Aprotinin is said to be safe to use with few side effects. Hypersensitivity reactions and anaphylaxis which have occurred in less than 0.1 % of treated patients are potentially hazardous and may be seen as limiting factors to routine use. In this respect, preservative-free aprotinin is now available from the manufacturer and may be safer to use. None of the drugs which are currently used at the onset of CPB is likely to cause anaphylaxis. However, where aprotinin is to be used in the CPB prime but not before bypass, this possibility must be considered if severe or protracted hypotension occurs.

Several aspects of management in our patients appeared to be favorably influenced by aprotinin. The time devoted to post bypass hemostasis was reduced and there was greater confidence shown by the surgical team to close the chest without the need for FFP or platelet infusions. In addition, hemodynamic stabilization postbypass was more quickly achieved and required less continual volume infusions to maintain stable cardiac preload pressures. The postoperative time to reach acceptable levels of blood drainage for chest tube removal was also less than for patients who were not given aprotinin.

In conclusion, aprotinin appears to be a useful addition to CPB management in programs where nonsurgical postbypass bleeding is excessive. The potential saving of blood and blood products is sufficiently relevant and important that further trials of the drug should be undertaken. A balanced view in relation to cost and benefit will only come with wider use of the drug.

Acknowledgment

The authors wish to thank Professor A.M.A. Gader and Mrs. Farah Chatila, Department of Physiology and Dr. E.A. Bamgboye, Department of Community Medicine, King Khalid University Hospital, Riyadh, for their advice and cooperation during preparation of the statistical aspects of this study.

References


