The efficacy and safety of aprotinin for hemostasis during intracranial surgery

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Object. The aim of this study was to determine the safety and efficacy of prophylactic high-dose intravenous aprotinin in reducing intraoperative blood loss in the neurosurgical population.

Methods. A randomized, double-blind, placebo-controlled trial was conducted in parallel groups in two regional neurosurgical departments. One hundred patients with a preoperative diagnosis of intracranial meningioma or vestibular schwannoma subsequently confirmed on histological studies were included. All patients were older than 18 years of age, pregnancy had been excluded, there was no history of bleeding diathesis, no previous exposure to aprotinin, and no ingestion of antiplatelet or anticoagulant medications within the 2 weeks preceding surgery. Aprotinin was administered in doses of 30,000 kallikrein-inhibiting units (KIU)/kg body weight on induction of anesthesia and was continued as an infusion of 10,000 KIU/kg/hr until surgery was complete, or for a maximum of 8 hours. Intraoperative blood loss, blood transfusion, the Glasgow Outcome Scale score, and the Index of Independence were measured, and screening for deep vein thrombosis and the Mini-Mental State Examination were performed.

Conclusions. Intraoperative blood loss was reduced from 1014 ml (geometric mean) to 508 ml (p = 0.028). Although this study was not designed to evaluate the need for blood transfusion, 37 U of blood was used in 11 patients in the aprotinin group and 58 U in 13 patients in the placebo group (not significant). There were no significant differences in postoperative thrombotic risk or other outcome measures between treatment groups. Aprotinin therefore can be safely used to reduce intraoperative blood loss in patients who are not receiving anticoagulation therapy.

Key Words • hemostasis • aprotinin • meningioma • vestibular schwannoma • intraoperative bleeding

Recently attention has been focused on the efficacy of aprotinin in reducing intraoperative bleeding. The main hematological action of aprotinin is the inhibition of plasmin, thereby preserving the stable hemostatic plug, maintaining levels of factors V and VIII and von Willebrand factor, and preventing destruction of the glycoprotein receptors on the circulating platelets. With aprotinin, blood loss has been reduced after prostate surgery,31 and cardiac and liver surgery.1,21,27,28,30 Aprotinin has also been used to prevent fibrin coated grafts from leaking.7 Intravenously administered proteinase inhibitors were first used during craniotomy as early as 1963,2 and in 1970 500,000 KIU was used to treat intraoperative hemostatic disorders in neurosurgery.18 Antifibrinolytic agents such as tranexamic acid were investigated in the 1970s as a treatment to reduce the risk of rebleeding after subarachnoid hemorrhage. These studies mostly demonstrated a reduced risk of rebleeding at the expense of a greater risk of delayed ischemic deficit. Studies in which aprotinin and tranexamic acid were combined showed a similar reduction in the rebleeding risk, without an increase in the risk of ischemia;2,4 aprotinin may actually decrease the risk of ischemia.12,18 Topical aprotinin has been used to reduce the risk of rebleeding in brain tumor surgery in a large uncontrolled series.32 There have been no randomized, prospective studies of the use of aprotinin in neurosurgery.

Paradoxically, although it is able to reduce intraoperative bleeding, aprotinin is also a weak anticoagulant. It inhibits the kallikrein-mediated positive feedback loop on factor XII, and the activated clotting time is prolonged.6 In cardiac surgery the effect on the activated clotting time requires the modification of heparin dosing to maintain full heparinization. Nevertheless, surgeons remain skeptical at first about a drug that purportedly can reduce bleeding without increasing the risk of thromboembolism.

Trasylol is the licensed form of aprotinin made by Bayer PLC (Newbury, Berks., UK); this drug is derived from bovine lung tissue. It has been indicated for treatment of patients at high risk of blood loss during and after open heart surgery.

Abbreviations used in this paper: DVT = deep vein thrombosis; GOS = Glasgow Outcome Scale; KIU = kallikrein-inhibiting unit; MMSE = Mini-Mental State Examination; SD = standard deviation; VS = vestibular schwannoma.
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Surgery involving extracorporeal circulation. Trasylol is also indicated in cardiac surgery for the treatment of patients in whom optimal blood conservation is an absolute priority, including Jehovah’s Witnesses, carriers of blood-borne diseases, and those with rare blood types. It is used for life-threatening hemorrhage caused by hyperplasminemia. The drug is generally well tolerated but may cause local thrombophlebitis or a hypersensitivity reaction, particularly after repeated exposure. Severe adverse reactions are rare, such as the report of profound hypotension in a child who underwent surgery for a septal defect.6

This study was designed to measure the effectiveness of aprotinin in reducing blood loss in patients undergoing neurosurgery. To accomplish this, we have studied patients with meningioma, a tumor type in which bleeding problems during surgery are well known. An appropriate sample size was calculated and the primary outcome measure was defined as intraoperative blood loss. We have included a pilot study of surgery for VS in which treatment was more prolonged, thus providing a large cohort of 100 patients for safety analysis.

Clinical Material and Methods

Aprotinin was administered in a double-blind, placebo-controlled trial in 100 patients who underwent surgery for meningioma or VS.

Sample Size Calculation

Two parallel groups of patients were included in the investigation. In the first group, a study of intracranial meningioma surgery was constructed to test whether the drug is efficacious in reducing intraoperative bleeding. A separate cohort of patients undergoing surgery for VS was included as an exploratory subgroup for which blood loss was likely to be much less but treatment was more prolonged, therefore providing important safety data. According to data from a retrospective analysis of estimated blood loss from 58 consecutive operations for intracranial meningioma, the geometric mean blood loss was 2013 ml with a geometric SD of 1.86 ml. To enable a 40% reduction in blood loss was aprotinin to be detected as statistically significant at the 5% level (with a two-sided test) with 80% power, 50 evaluable patients were required. Because two neurosurgical departments were involved in the enrollment of patients for study, six additional patients were included to compensate for possible center-related effects, making a total of 56 patients.

Patient Population

Patients were entered in the study if intracranial meningioma or a cerebellopontine angle tumor that was likely to be a VS had been diagnosed preoperatively. All patients were older than 18 years of age, had no potential for child bearing, or had negative results on a pregnancy test if female. All patients who had taken aspirin or nonsteroidal antiinflammatory drugs within 2 weeks of surgery were excluded. Because of the increased risk of intraoperative bleeding, heparin or other anticoagulant medications were not given in the perioperative period. Any patient in whom there was a previous exposure to aprotinin or a history of pancreatitis (who therefore might have received aprotinin in the past) were excluded from the study because of the potential risk of anaphylaxis. All patients or their guardians gave informed consent. Patients whose histological findings were not confirmatory were excluded from the evaluation of efficacy but included in the safety analysis.

Treatment Assignments

The study was approved by the local ethics committees at both centers. On entry, patients approved for inclusion were randomly assigned to one of two treatment groups in accordance with a computer-generated randomization schedule. The randomization was double-blind, with code-break cards available for use in an emergency. Aprotinin was supplied by Bayer PLC in preservative-free, 50-ml vials of sterile, pyrogen-free solution, containing 500,000 KIU, made isotonic with 0.9% sodium chloride. The placebo was 50 ml 0.9% sodium chloride only. The vials for each group were identifiable only by the patient study number.

After induction of anesthesia and commencement of invasive blood pressure monitoring, a 5-ml test dose was given slowly; once it was clear that there was no allergic or pseudoallergic reaction the remainder of the loading dose (30,000 KIU/kg) was infused over 15 to 20 minutes. The entire loading dose was administered before the start of surgery. The loading dose was followed by a continuous infusion of 10,000 KIU/kg/hr until the patient was transferred to the intensive care unit. The dose regimen had been devised from a previous pilot study to ensure that plasma-inhibiting levels were achieved throughout the operation. For safety reasons, a time limit of 8 hours of treatment was defined because of potential accumulation of the drug within the renal tubules. Any adverse events were recorded along with their possible relationship with the study drug.

Pretreatment Procedures

Blood samples were obtained before surgery to measure hemoglobin, hematocrit, erythrocytes, white blood cell count, differential, and platelets. Biochemical studies included assessments of sodium, potassium, urea, and creatinine levels. A partial thromboplastin time, prothrombin time, fibrinogen, and resistance to activated protein C were measured. Other preoperative assessments included venous duplex ultrasonography of the legs, neurological status, Index of Independence of activities of daily living,16 and an MMSE score of cognitive and psychomotor function.9

Procedures Performed During Treatment

Blood sampling was performed for hemoglobin or hematocrit and aprotinin concentration at the following times: 10 minutes after administration of the loading dose; immediately before opening the dura (in meningioma) or visualization of tumor (in VS); during resection; and at completion of resection. At Center 1 the serum was separated and saved for measurement of a variety of molecular markers of hemostasis; these results will be reported elsewhere. The intraoperative blood loss was recorded, as was the administration of all blood, platelets, fresh frozen plasma, nonhemic colloids, crystalloids, and other blood products. Central venous pressure was maintained at 5 to 15 mm Hg by using colloid infusion. Blood transfusion was only performed if the hemoglobin concentration fell below 8.5 g/dl or the he-
matocrit below 25%. The following time points were recorded: induction of anesthesia; incision; time of dura opening (meningioma) or time of tumor visualization (VS); beginning of resection; completion of resection; and time of skin closure.

Blood loss is not usually measured in neurosurgical procedures. In operations with high blood loss there is spillage down the drapes and onto the floor. The wound is regularly irrigated with saline and swabs are not routinely counted or weighed. A rigorous standardized technique for wound draping and irrigation use was devised so that blood loss could be measured. The Cranial Incise sheet (Johnson & Johnson Medical, Arlington, TX) is a single drape consisting of a central clear plastic adhesive window that is placed onto the wound area. Surrounding this window is a highly ab-sorbent integral disposable drape for which a gutter can be fashioned to avoid spillage. This absorbent area drains directly into a large collection bag that hangs down and touches the floor, so that when it is full it does not tend to pull off the wound. Small towels could be used under this drape according to the surgeon’s preference, but these remained dry throughout the procedure. At the end of the procedure the irrigation fluid and blood collected in the bag can be aspirated into the suction bottle and the single drape can then be removed and weighed (the dry weight of the sheet was 490 g).

All swabs used were weighed on an electronic scale in increments of grams and the fluid content was calculated by subtraction of the dry weight from the wet weight. Swabs were weighed as soon as they had been used to prevent them from drying out. Cottonoids were not weighed but they were wrung out and their fluid contents aspirated into the suction bottle. Suction of blood and wash was directed into disposable containers; at the end of the procedure all containers were weighed and the dry weight was subtracted to calculate the blood loss. By using the Aquaflow system all wash delivered to the wound was dispensed from 500- or 1000-ml bags under pressure with a pneumatic compression bag. At the end of the procedure all excess wash was aspirated into the suction system. The total volume of wash used was recorded. The wash volume was subtracted from the suction volume, the swab fluid volume, and the drape fluid volume to determine the blood loss, and this was recorded in milliliters. In long procedures in which a large volume of wash was used and blood loss was small, evaporation of wash from the surgical drape resulted in apparently negative blood loss. For long procedures, therefore, the blood loss tended to be underestimated.

Aprotinin Assay

Plasma levels of aprotinin were measured using a sandwich enzyme-linked immunosorbent assay method, with antibodies and standards supplied by Bayer. Briefly, a microtiter plate was coated with monoclonal antiaprotinin antibody to capture aprotinin antigen in the test and standard samples. After washing, the bound aprotinin was detected with a polyclonal antiaprotinin immunoglobulin G antibody and visualized with anti–rabbit immunoglobulin G peroxidase conjugate.

Posttreatment Procedures

Blood was sampled at 2 hours postsurgery for aprotinin concentration and hemoglobin or hematocrit levels, and at 1 and 7 days postoperatively for full blood count and electrolytes. The volume of wound drainage was measured, as was the hematocrit of the drainage fluid. All administration of blood, blood products, nonhemic colloids, and crystalloids transfused postoperatively was recorded up to Day 7. A venous duplex scan was performed between the 3rd and 5th day. Neurological status was recorded between 5 and 7 days and at 3 months, and an Index of Independence of activities of daily living an MMSE were performed at the same intervals. The Glasgow Coma Scale score was recorded at 6, 12, 18, and 24 hours and at 7 days postsurgery; at 7 days postoperatively a motor score was recorded. The GOS score was determined by interview at 3 months.

The patient’s location, for example, neurosurgical ward, home, and so on, was recorded for the 90 days after surgery. Any major or costly workups were recorded, as were the number of visits to the hospital for therapy or to the general practitioner. Whether the patients were back at work or had returned to their previous activities at 3 months was also recorded, and if they were disabled but residing at home, whether a caregiver was needed part or full time.

Specific details of the tumor and the patients’ outcome were also gathered prospectively for the two groups. In the meningioma group the following data were collected: the widest diameter of the tumor on the enhanced preoperative scan; the classification according to site of tumor origin (convexity, sphenoid ridge, olfactory groove, and so on); sinus involvement, whether radiologically or surgically confirmed or both; excision, whether total, subtotal, or none; intracranial hematoma, whether asymptomatic on neuroimaging studies, symptomatic, or evacuated; wound hematoma, whether bruising, frank hematoma, or evacuated; and wound infection.

In the group with VSs the following specific data were recorded: tumor size; wound infection; posterior fossa hematoma, whether asymptomatic on neuroimaging studies, symptomatic, or evacuated; and wound hematoma whether bruising, frank hematoma, or evacuated.

Thromboembolic Risk

Pharmacological manipulation of coagulation to reduce bleeding can only be undertaken if there is no increased risk of venous thromboembolism or other problems related to hypercoagulability. Resistance to activated protein C has been shown to be associated with an increased risk of thrombosis, and was measured with an activated partial thromboplastin time–based assay (Chromogenix, Milan, Italy).

In all patients studied, duplex ultrasonography was used to screen for thrombosis in the deep leg veins. A protocol has been developed in Southampton that has been shown to have 99% accuracy for above-knee lesions and 89% for below-knee lesions compared with contrast venography. The advantages of this test being available at the bedside in the neurosurgical patients outweigh the increased sensitivity of isotope fibrinogen scanning. Patency and reflux were both checked.

Statistical Methods

The primary efficacy parameter, intraoperative blood loss, was found to be approximately normally distributed
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Results

Description of Data

Patients were enrolled and evaluated in identical ways at both centers, and recruiting continued until sufficient numbers of patients were entered in the meningioma group. From the meningioma group, four patients were excluded because results of histological examination did not confirm a meningioma, one suffered a cardiac arrest on induction of anesthesia and did not receive the study drug and was completely excluded from analysis, and in one the blood loss measurements were inaccurately recorded. From the VS group, one patient was excluded because of an urticarial reaction, in one the excision was abandoned, in one an aneurysm was found, and in two the operation exceeded 11 hours. A total of 100 patients was enrolled for safety analysis, and 56 patients with meningiomas who completed the study were used for efficacy analysis (Table 1).

Demographic Data

In comparing the demographic data between the two groups (aprotinin and placebo), the height of the patients was evenly matched. In the meningioma group the patients who received a placebo weighed slightly more and the female/male ratio was higher with treatment; 40 of the 56 patients in the study were female, highlighting the preponderance of meningioma in the female population. For the group with VSs, the patients were more commonly male and hence tended to be taller and heavier than those subjects in the meningioma group (Table 1).

Accuracy of Blood Loss Measurement

By measuring the difference between the pre- and postoperative (at Days 5–7) hemoglobin concentrations and estimating the amount of hemoglobin each patient received by blood transfusion—assuming that 1 U of blood raises the hemoglobin level by 1 g/dl—the hemoglobin loss was calculated. Simple regression analysis of hemoglobin loss compared with blood loss (Fig. 1) shows the relationship

![Fig. 1. Scatterplot showing hemoglobin loss and blood loss according to tumor group. Simple regression with 95% confidence limits showing the different points for patients entered from the two centers. Y = 347.366 × 189.473; r² = 0.638; p = 0.0001. Circles designate meningiomas, squares, acoustic nerve tumors, and triangles, excluded patients.](image-url)
between the two. Most of the higher blood loss values (≥ 2000 ml) followed meningioma surgery.

Factors That May Affect Blood Loss

The age of the patient is important in the assessment of thrombotic risk, not only because of changes in the blood vessels themselves, but also because coagulation factors change with age. Factors VII and VIII and fibrinogen increase and antithrombin and bleeding time decrease with age. No relationship between age and blood loss was found in this study; there was no difference in blood loss between male and female patients, and height and weight had no relationship to the amount of blood loss.

The tumor position had an effect on the amount of blood lost: patients with anterior skull base tumors had a median blood loss of 1136 ml, those with parasagittal tumors lost 1660 ml, with convexity lesions it was 859 ml, those with intraventricular tumors lost 834 ml, and those with lesions in the posterior fossa lost 322 ml. In the one suprasellar meningioma, which was included in the anterior skull base category, the patient lost more than 5 L of blood.

Involvement of the dural venous sinuses makes it more difficult in any meningioma operation to achieve a complete excision while maintaining a reasonable blood loss. When there was no involvement of the sinus the median blood loss was 639 ml; when the sinus was involved the median blood loss doubled to 1239 ml (p = 0.013, Wilcoxon signed-rank test). When tumor size was accounted for, however, the effect of sinus involvement on blood loss diminished.

As expected, there was a relationship between tumor size and blood loss (p = 0.025). There was no difference in the sizes of the tumors in each study group: 4.3 ± 1.7 cm in the aprotinin group and 4.6 ± 1.3 cm in the control group (mean ± SD).

Effect of Aprotinin

For patients with meningiomas, the mean volume infused was 579 ml (range 340–975 ml) in the aprotinin group and 615 ml (range 350–990 ml) in the placebo group. For VSs the mean volume was 862 ml (range 600–1173 ml) in the aprotinin group and 784 ml (range 454–1080 ml) in the placebo group.

Blood Loss. In the efficacy study, blood loss was significantly reduced in the aprotinin group (Table 2), from 1014 to 508 ml (50% reduction; geometric mean based on least-squares mean of log transformed data). Blood losses were much smaller in the group with VSs, and aprotinin was not shown to reduce bleeding. The difference between centers was not statistically significant.

Blood Transfusion. A 41% reduction in blood transfusions was also achieved in the aprotinin group. In this group, 11 patients received 37 U of blood (range 2–8, mean 1.28 U), whereas in the control group, 13 patients received 58 U of blood (range 1–12, mean 2.15 U). There was no statistically significant difference between treatment groups in the proportion of patients receiving transfusions or in the

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<td>1014 ± 1.27</td>
<td>240 ± 1.28</td>
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* Geom = geometric; LSM = least-squares mean; SE = standard error.
† Significant at a probability level of 0.05.
‡ Not significant.
amount of blood transfused. The median number of donors to whom the patient was exposed due to transfusion was zero in the aprotinin group and one in the placebo group.

**Serum Levels of Aprotinin.** Assays of aprotinin were performed 10 minutes after loading, at the start of resection, during resection, at completion of resection, and 2 hours postsurgery (Fig. 2). Plasmin-inhibiting levels (> 100 KIU/ml) were achieved throughout surgery and in many cases for 2 hours after surgery. Kallikrein-inhibiting levels (> 200 KIU/ml) were achieved in only a minority of patients. The aprotinin levels did not correlate with blood loss.

**Effect of Aprotinin on Surgical Outcome**

**Duration of Surgery.** The total surgical time was reduced from 308 to 281 minutes, a difference that was not statistically significant (p = 0.65). Most of that reduction occurred during the excision of the tumor.

**Resection of Tumor.** Less blood loss may lead to a clearer operative view, and the likelihood of the surgeon achieving a total removal may be increased. No evidence was found in this study that aprotinin reduced the rate of subtotal excision. The median blood loss was slightly higher for subtotal excisions, but the difference was not significant (p = 0.48, Wilcoxon signed-rank test).

**Postoperative Outcome.** There was no significant difference in the outcome at 7 days or in GOS scores measured prospectively at the 3-month follow-up review. The one death was in an elderly patient who suffered a stroke in a geriatric unit just before the 3-month follow up. The outcomes of tumor-specific issues are shown in Table 3.

**Results of MMSE.** At 5 days postoperatively the patients in the aprotinin group had significantly improved scores on the MMSE, despite having less mobility. At 3 months there was no difference between the two treatment groups. Because repeated applications of the MMSE may result in a slight improvement in performance, the improvement we saw cannot be attributed to any benefit of tumor removal. Results of the preoperative examination for intracranial meningioma were worse in the aprotinin group. For patients with VSs, the MMSE score varied within normal limits.

**Index of Independence.** No significant differences were found in the improvement of the index at the 5-day or 3-month assessment (Table 3). This test compared the pa-
Hemostasis requires three basic elements: 1) an adequate number of functioning platelets; 2) a supply of clotting factors; and 3) control of the natural anticoagulant mechanisms at the site of hemorrhage. Bleeding starts to become prolonged when the platelet count falls below 100,000/µL, and the most common cause of platelet dysfunction is the administration of aspirin or nonsteroidal antiinflammatory drugs. In a previous study we found that 45% of patients with a postoperative hematoma had received drugs altering the platelet function in the preoperative period.

A stable hemostatic plug is achieved by the conversion of fibrinogen into the insoluble fibrin polymer. A prothrombinase complex is constructed on the surface of the aggregated platelets. The brain has a copious supply of tissue factor (thromboplastin), which forms the most potent trigger of coagulation. The brain generally has only low levels of fibrinolytic activity apart from the pituitary gland, whereas the meninges have a high fibrinolytic activity. Some brain tumors, particularly meningioma, have a high content of plasminogen activators, which we have shown can be reversed by aprotinin. The circulating plasminogen is activated at the surface of a stabilized hemostatic plug by tissue plasminogen activator. The resulting plasmin destroys the fibrin polymer.

Fibrinolysis has a diurnal variation, and is increased by exercise, mental stress, and surgery under the influence of the hypothalamic–pituitary axis. The brain generally has only low levels of fibrinolytic activity apart from the pituitary gland, whereas the meninges have a high fibrinolytic activity. Some brain tumors, particularly meningioma, have a high content of plasminogen activators, to such an extent that some patients may exhibit pathological enhancement of systemic fibrinolytic activity even before surgery has begun. Severe bleeding during surgery and disseminated intravascular coagulation may be triggered by overstimulation of fibrinolysis, which we have shown can be reversed by aprotinin.

In this study we excluded all patients who had taken drugs that modify platelet activity and all patients with a history of bleeding. Aprotinin was used in a dosage regimen that maintained plasmin inhibition throughout the surgery and achieved a 46% reduction in blood loss. Blood transfusion, duration of surgery, and postoperative hematoma were not significantly reduced by aprotinin. Reducing blood loss did not improve the outcome of surgery and treatment did not translate into a pharmacoeconomic benefit. One patient of the 100 studied had an urticarial reaction to aprotinin. There was no significant difference between treatment groups in the risk of developing a postoperative thrombotic event. In patients undergoing cardiac surgery patients there has been concern about graft patency after aprotinin use; this concern has not been supported by a randomized trial. This study is the first randomized trial to include prospective assessment of thrombotic risk—the trend is that aprotinin reduces the risk of DVT. Previous studies in orthopedic surgery have demonstrated a possible benefit of using aprotinin as prophylaxis against thromboembolism, particularly when the agent is combined with heparin.

Aprotinin has been shown to be an effective agent in reducing blood loss associated with both primary and revision coronary bypass surgery, septic endocarditis during cardiac surgery, and cardiac transplantation, as well as blood loss in pediatric patients with congenital heart disease, and in major reconstructive vascular surgery. Most of these studies found a 40 to 50% reduction in blood loss and these operations were all performed concomitantly with full heparinization. During cardiac bypass the activation by the circuit
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leads to a rapid consumption of platelets, release of platelet granule contents, and an increased bleeding time. Plasmin can greatly modify platelet function by hydrolyzing the glycoprotein Ib receptor, important in von Willebrand factor–mediated adhesion and aggregation. Aprotinin administration can block this effect of plasmin and preserve platelet function.

In our study the consumption of platelets and modification of their receptors is not such an issue, yet we report a reduction in blood loss similar to that found in the cardiac studies. The role of fibrinolysis in bleeding during neurosurgery may be more important than platelet dysfunction. The dose used in this study was selected after a pilot study had been conducted, and was shown to achieve a consistent inhibition of plasmin.

Conclusions

The risks of surgical and postoperative bleeding in cranial surgery are so great that effective methods of hemorrhage control are required. We do not believe that a 46% reduction in blood loss justifies the routine use of aprotinin for meningioma surgery, particularly because treatment sensitizes the patient and may preclude further use of the drug. Most neurosurgery can be performed without the need for blood transfusion; we used a transfusion threshold of 8.5 g/dl in this study without any problems. The use of aprotinin to avoid homologous transfusion cannot be justified on economic grounds. In countries in which the blood supply is not as safe as in the UK, reducing donor exposure may be more of an issue. Its prophylactic use is likely to be more effective, but aprotinin can be used to resolve a bleeding crisis. We therefore recommend aprotinin use in selected patients who must undergo meningioma surgery for skull base or parasagittal tumors; in those who have taken aspirin or nonsteroidal antiinflammatory drugs within 2 weeks of surgery and whose operation cannot be delayed for a suitable period; in patients who need surgery and have a history of bleeding; and in Jehovah’s Witnesses. Aprotinin could be considered for pediatric patients with large tumors, but this study does not include patients in that age group.

Dedication

We dedicate this work to our colleague Professor Fausto Iannotti, who died before this paper could be published. He was an inspirational teacher, neurosurgeon, scientist, and friend to so many, whom we deeply miss.

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