homologous blood transfusions.[6] In our opinion, it is better policy to initially employ, along with blood-sparing surgical techniques, the full spectrum of conventional methods of blood conservation (preoperative autologous blood donation, isovolemic hemodilution, perioperative blood salvage) in an attempt to avoid homologous blood transfusion.

5. A particularly undesirable effect of aprotinin is immunologic sensitization. The patient receiving aprotinin today for a total hip arthroplasty may be your patient tomorrow! For example, a cardiac surgical patient in our department suffered a fatal analphylactic shock after infusion of aprotinin. Unknown to this patient, she had received aprotinin during a tonsillectomy some months earlier. The risk of anaphylactoid reactions after previous exposure to aprotinin, though not necessarily fatal, is quoted as 0.5% by the manufacturer. In the literature, figures range between 1% and 9.1%[7] for such a reaction. By contrast, the incidence of hepatitis C after blood transfusion is less than 1:3.000, the risk of HIV infection is quoted as 1:225,000 to 1:1 million, and the total mortality of transfusion-transmitted infections is given as 1: 260,000.[8,9] Thus, on a critical risk-benefit basis, we seriously doubt the justification of aprotinin administration in total hip arthroplasty. We would challenge the postulated reduction in perioperative blood loss as a reasonable indication for aprotinin, as long as

- valid numbers are missing, which would prove the necessity for aprotinin with respect to its overall risk
- inexpensive, simple, and reliable screening tests for aprotinin sensitization are not available
- there is no reliable prophylaxis against severe anaphylactoid reactions after aprotinin exposure

The proposed red mark "aprotinin used" in the discharge letter of patients having been exposed to aprotinin[10] would appear to be of only limited value. Avoid having to use such warning in the first place!

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In Reply:—We agree that perioperative blood loss associated with total hip arthroplasty depends on the surgical technique and the experience of the surgeon. In our study, Moore's posterolateral approach with osteotomy of the greater trochanter was used in all patients. The prosthetic materials were either cemented or noncemented with cancellous screws used to secure the acetabular component. Cemented prostheses were distributed equally between the two groups [7 in the aprotinin (A) group, 10 in the placebo (P) group]. No significant difference in total bleeding was noted between the cemented and noncemented prostheses in both groups. However, in group P, early postoperative blood loss (during the first 5 h postoperatively) was significantly greater in the case of cement-free prosthesis as compared with cemented prosthesis (525 ± 247 ml *vs.* 330 ± 119 ml, $P < 0.05$). In group A, blood loss associated with noncemented prostheses was significantly greater as compared to cemented prostheses during the postoperative period between 5 and 24 h (322 ± 161 ml *vs.* 147 ± 94 ml, $P < 0.05$). A multiple regression statistical analysis demonstrates that, intraoperatively, only treatment

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significantly affects bleeding. Postoperatively, treatment and type of prosthesis are significant determinants of blood loss. Whereas the effect of treatment is predominant during the first 5 h postoperatively as long as aprotinin is circulating (aprotinin half-life ±150 min), thereafter the benefit of cemented prosthesis on bleeding becomes more apparent. These data suggest that cemented prostheses tend to reduce slightly postoperative blood loss. Therefore, if the type of prosthesis used is considered to have influenced our data, the actual difference between the two groups would have been slightly greater. Finally, blood predonation was carried out in 17 patients of group P and 14 patients of group A and cannot therefore account for the differences in blood loss observed between the two groups.

Wollinsky *et al.*[1] reported that postoperative blood loss was significantly reduced in the aprotinin group, mainly during the first 6 h after surgery. In our study, a significant reduction in intraoperative bleeding was observed ($P < 0.05$). Furthermore, like in Wollinsky *et al.'s* study, blood loss during the first 5 h postoperatively was significantly reduced in the group A ($P < 0.001$). Although external bleeding was similar in the two groups between 5 and 24 h after surgery, hematocrit was significantly greater in group A than in group P despite a significant reduction in blood transfusion and similar transfusion protocol. This suggests that occult undrained blood loss also might have been reduced in the group A. Furthermore, transfusion requirements also were decreased in group A intra- and postoperatively. In these two studies, aprotinin infusion was interrupted at the end of the surgical procedure. Plasma half-life of aprotinin is approximately 150 min.[2,3] Although pharmacologic effect of a drug may last much longer than its half-life, it is reasonable to expect aprotinin pharmacologic effect to last for 4–8 h after the interruption of the aprotinin infusion. The correlation between the observed decreased postoperative blood loss and the expected pharmacologic profile of aprotinin suggests that this effect is due to aprotinin pharmacologic actions.

We reported perioperative blood loss similar to other studies.[1,4] We are aware that perioperative blood loss may be further decreased in our institution. Since this study, our anesthetic technique has been changed considerably. We now routinely use epidural anesthesia or femoral nerve block for this procedure. We completed another study last year in patients undergoing total hip replacement under regional anesthesia.[5] Without aprotinin, intraoperative blood loss was about 400 ml in this latter study, which was much less than in the aprotinin group of our first study. In case of less perioperative blood loss, the potential benefits of aprotinin are probably also less.

We agree with Kasper *et al.* that all conventional methods of blood salvage should be used to avoid homologous blood transfusion. When perioperative bleeding is low, preoperative autologous blood donation is sufficient. However, predonation is not possible in all patients or may be insufficient. We never stated that aprotinin should be used routinely in all patients undergoing hip arthroplasty. Actually, we now restrict the use of aprotinin to difficult cases such as repeat surgery, in patients with coagulapathies that contraindicate regional anesthesia, and when autologous blood was not donated before surgery. In these cases, we believe aprotinin to be helpful in reducing transfusion requirements. In our study, three patients in group P did not donate blood preoperatively; all required homologous blood transfusion. Four patients in this group who had only predonated 2 units of autologous blood received homologous blood. In group A, two of the six patients who had no autologous blood available did not require blood transfusion, whereas the only unit of autologous blood predonated by two patients was sufficient to avoid homologous transfusion. We nevertheless have further encouraged and extended our predonation program for orthopedic surgery.

The risk of anaphylactoid reactions after previous exposure to aprotinin is an important issue that needs to be further investigated. The current incidence of anaphylactoid reaction should be assessed and reconsidered because of the routine use of high-dose aprotinin in cardiac surgery and liver transplantation in many institutions. Furthermore, several patients who had cardiac surgery with aprotinin are likely to undergo a second cardiac surgical procedure that will be potentially more hemorhagic and perhaps require a second administration of aprotinin. The benefits of aprotinin, therefore, must be balanced against the risks when the use of aprotinin is discussed. However, we think that aprotinin should not be prohibited because of the potential risk of anaphylactoid reaction.

In conclusion, our study demonstrates that aprotinin allows significant reduction of perioperative blood loss and transfusion requirements. We are convinced that the observed effect is due to a pharmacologic action of aprotinin. Our study suggests that the blood-sparing effect of aprotinin is not restricted to surgery potentially leading to coagulation disorders or to patients with coagulopathy. We do not recommend the routine use of aprotinin for total hip arthroplasty. Rather, aprotinin should be considered as a supplement to other blood-sparing techniques and used when conventional techniques are not possible or are inadequate.

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