

ANESTHESIOLOGY

■ Efficacy and Safety of Recombinant Activated Coagulation Factor Evaluated during Partial Hepatectomy. Lodge *et al.* (page 269)

To evaluate both the efficacy and safety of recombinant coagulation factor used in hepatic resection patients, Lodge *et al.* monitored patients randomized to receive either placebo or different doses of recombinant activated coagulation factor VIIa for 7 days after their partial hepatectomy procedures.

A total of 204 noncirrhotic adult patients scheduled to undergo partial hepatectomy due to liver cancer/metastases and/or benign tumors were recruited for this trial. A total of 13 hospitals in France, Spain, Germany, and the United Kingdom participated. On the day of surgery, patients received an injection of either 20 or 80 $\mu\text{g}/\text{kg}$ of recombinant coagulation factor or a placebo injection, depending on randomization assignments. The trial drug was administered as a slow intravenous injection 5 min before skin incision to ensure sufficient amounts of recombinant factor VIIa in the liver circulation during surgery. If surgery was projected to last more than 6 h, a second identical dose was given 5 h after first skin incision. The primary endpoint was whether or not patients required red blood cell transfusion during surgery or the 48-h postoperative period. The investigators also recorded total blood loss during surgery, any changes in hematocrit, requirements for transfused red blood cells or fresh frozen plasma, and total surgery time. Adverse events, such as bleeding complications, were also assessed.

The mean red blood cell requirements for those patients receiving transfusions were 1024 ml with placebo, 1354 ml with 20 $\mu\text{g}/\text{kg}$ doses of the recombinant factor, and 1036 ml with 80 $\mu\text{g}/\text{kg}$ doses of the study drug. Prothrombin time was significantly shortened with the recombinant factor VIIa dosing. Although there were no major safety issues associated with the study drug, it produced no statistically significant overall effect with respect to reducing the need for perioperative blood cell transfusions. The authors encourage further investigation to generate treatment modalities that can induce a primary hemostatic effect for patients undergoing hepatic resection, a procedure associated with significant intraoperative blood loss.

■ Can Recombinant Human Antithrombin Restore Heparin Responsiveness in Resistant Coronary Artery Bypass Graft Patients? Avidan *et al.* (page 276)

Heparin resistance, defined as failure to achieve the desired activated clotting time after administration of a standard heparin dose, has been found in 4%–13% of cardiac surgery patients. Infusion of fresh frozen plasma is the standard intervention to restore heparin responsiveness, but carries risk of complications ranging from viral infection to allergic reactions. Avidan *et al.* designed a placebo-controlled, double-blind study to assess the efficacy of administering recombinant human antithrombin to improve heparin responsiveness in patients scheduled to undergo elective cardiac surgery involving cardiopulmonary bypass. Patients enrolled in the study met inclusion criteria for heparin resistance: (1) activated clotting time less than 480 s after intravenous administration of 400 U/kg of heparin and (2) either a baseline heparin dose–response slope of 80 s or less using a heparin dose–response cartridge, or receipt of intravenous heparin before surgery regardless of the heparin dose–response slope.

One group of patients received a single bolus of 75 U/kg of recombinant human antithrombin, and the other group received a single bolus of normal saline placebo. If the activated clotting time remained less than 480 s, this was defined as treatment failure for purposes of the study, and 2 units of fresh frozen plasma were then infused. Patients were monitored for adverse events from time of study drug administration until 4 weeks postsurgery.

Of the 296 patients consented for the study, 54 were found to be heparin resistant. Of these, 27 were assigned to receive recombinant human antithrombin and 27 the saline placebo. The study revealed that 19% of the patients receiving the study drug required fresh frozen plasma, whereas 81% of placebo-treated patients received fresh frozen plasma. Patients in the placebo group also required higher heparin doses for anticoagulation. There was no increase in serious adverse events after administration of recombinant human antithrombin, although there was increased blood loss for 12 h postoperatively, with a trend toward increased 24-h bleeding in the study drug group. So although the antithrombin restored heparin responsiveness in the majority of patients in this study, clinicians should be aware of the risk of heparin rebound-induced bleeding when pa-

tients receive this agent. The authors recommend use of point-of-care tests to detect heparin rebound, and additional study of this phenomenon.

■ Linking Protamine Response to Coronary Artery Bypass Surgery Outcomes. Welsby *et al.* (page 308)

Administration of protamine sulfate is standard therapy for reversing heparin anticoagulation during coronary artery bypass graft surgery, but can cause reactions ranging from minor hemodynamic instability to fatal cardiovascular collapse. Risk factors for protamine reaction are present in 39% of coronary artery bypass graft surgical patients. To assess the extent to which hemodynamic responses to protamine are associated with outcome, Welsby *et al.* undertook a retrospective analysis of 6,921 consecutive patients undergoing primary elective coronary artery bypass graft from 1993–2000 at their institution.

The team used automated record keeping data and quality assurance databases to identify patients' reactions to protamine administration. Using multiple logistic regression models and adjusting for risk factors, the team attempted to find linear associations between patients' outcomes and degree/duration integrals of systemic hypotension (< 100 mmHg) and pulmonary hypertension (> 30 mmHg) in the 30 min after protamine administration.

Overall mortality was 2%, and greater hemodynamic responses were associated with increased mortality, by an odds ratio of 1.28 for systemic hypotension and 1.27 for pulmonary hypertension. Even after accounting for comorbidities and procedure complexity, systemic hypotension and pulmonary hypertension in the 30 min after protamine administration were independently associated with in-hospital mortality. Future randomized trials will be necessary to differentiate causality in the relationship found in this retrospective study. Studies are also needed to identify therapeutic strategies to reduce hemodynamic perturbations and improve patient outcomes after coronary artery bypass graft surgery.

■ Case Reports of Bronchospasm after Administration of Cyclooxygenase-2 Inhibitors. Looney *et al.* (page 473)

Although some studies have proposed that use of highly selective cyclooxygenase-2 (COX-2) inhibitors may be safe

in asthmatic patients, Looney *et al.* report in this issue two cases of life-threatening bronchospasm after administration of parecoxib, a parenteral COX-2 inhibitor.

The first case was a 26-yr-old woman with a history of well-controlled mild asthma who was admitted for arthroscopy of the left knee. After induction with fentanyl and propofol, anesthesia was maintained with sevoflurane. Within 10 min of administering 40 mg parecoxib sodium, toward the end of surgery, the patient's saturation levels fell and peak airway pressures rose acutely. The situation deteriorated further after intubation, and the patient became bradycardic, requiring one dose of 0.6 mg atropine and a brief period of chest compressions. Salbutamol was administered *via* a metered dose inhaler through the endotracheal tube. The patient's saturations recovered to 98%, and she was extubated. In the postanesthesia care unit, her bronchospasm resolved within 30 min, and she was discharged the following day.

The other case was that of a 70-yr-old man who had undergone urgent laparotomy for large bowel obstruction. The patient had a history of ischemic heart disease and a prior coronary artery bypass graft, in addition to diabetes mellitus and presence of mild bilateral wheezing. The day after surgery, the patient was given an intramuscular injection of 40 mg parecoxib sodium for breakthrough pain and developed dyspnea, wheezing, and hypoxia. His condition required reintubation and transfer back to the intensive care unit. After 3 days of treatment with nebulized bronchodilators and intravenous steroids, he made a full recovery.

Theoretically, highly specific COX-2 inhibitors, known as *coxibs*, are well tolerated and can be safely used in patients with asthma. In both cases described in this report, life-threatening bronchospasm occurred within a short period of the administration of parenteral parecoxib. The young female patient confirmed that she had formerly taken oral COX-2 inhibitors without ill effects, whereas the older male patient indicated he had avoided nonsteroidal antiinflammatory drugs since he was on warfarin. Based on these cases, the authors warn that parenteral COX-2 inhibitors should be used with extreme caution in patients with any history of bronchospasm who have not been previously desensitized to the drugs' bronchoconstrictor effects. Further studies using parenteral doses of COX-2 inhibitors on larger numbers of patients with nonsteroidal antiinflammatory drug-sensitive respiratory disease would be necessary to verify the safety of these drugs in this patient population.

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