

CASE REPORTS

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Intraoperative Heparin Flushes and Subsequent Acute Heparin-induced Thrombocytopenia

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HEPARIN-INDUCED thrombocytopenia is one of the most important immune-mediated adverse reactions in clinical medicine because of its paradoxical strong association with thromboembolic complications.¹⁻³ Although most cases of heparin-induced thrombocytopenia occur in patients receiving therapeutic- or prophylactic-dose heparin,⁴ a few cases have been reported in patients receiving ongoing intermittent heparin "flushes" to maintain patency of indwelling intravascular catheters, particularly in intensive care unit patients receiving such heparin for several days.⁵⁻⁸ However, it is unknown whether a very brief, low-dose heparin exposure, such as occurs during intermittent heparin flushing restricted to the intraoperative use of a single intraarterial catheter, could trigger clinically significant immune sensitization to heparin. Potentially, such an event could be important, because if a large dose of heparin was necessary a few days or weeks later, unexpected, life-threatening, acute thrombocytopenia with risk for thrombosis or bleeding could result. We describe two patients in whom such a trivial intraoperative exposure to heparin proved to be the cause for immune sensitization to heparin, resulting in subsequent acute heparin-induced thrombocytopenia, with a fatal outcome in one patient.

Case Report

Case 1

A 55-yr-old woman underwent elective right total knee arthroplasty. There was no history of previous heparin use or previous hospital

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admission. She received routine flushes of unfractionated heparin (estimated total exposure, < 100 units heparin) *via* intraarterial catheter that was used for intraoperative monitoring only. No perioperative or postoperative prophylactic heparin was administered, although the patient was administered graduated-compression, antiembolism stockings. A deep venous thrombosis involving the calf veins was diagnosed by contrast venography on postoperative day 12, and the patient was therefore administered a 5,000-unit bolus of unfractionated heparin. Ten minutes after receiving the heparin bolus, severe dyspnea developed, together with hypertension, tachycardia, diaphoresis, followed by a shaking chill (fig. 1). Pulmonary embolism was suspected clinically (and confirmed by ventilation/perfusion [V/Q] radionuclide lung scanning performed the next day), and heparin was continued, with gradual abatement of the symptoms. The platelet count decreased abruptly and unexpectedly from $402 \times 10^9/l$ (measured shortly before the heparin bolus) to $108 \times 10^9/l$ the next morning (fig. 1). Unfortunately, the diagnosis of heparin-induced thrombocytopenia was not recognized immediately, and heparin was continued, together with overlapping warfarin anticoagulation. On postoperative day 20, acute subdural hematoma complicated by cardiac arrest developed in the patient. At this time the INR was 4.9, the activated partial thromboplastin time was 120 s (attributable to heparin and warfarin therapy), and the platelet count was $38 \times 10^9/l$. The heparin was discontinued because of the intracranial hemorrhage, and heparin-induced thrombocytopenia was suspected when it was observed that the platelet count rapidly recovered to normal. The patient died secondary to irreversible neurologic injury.

A review of the medical records to determine all possible sources of heparin exposure revealed documentation of use of an intraarterial catheter at surgery (anesthetic records). Although the specific use of heparin flushes was not recorded, a discussion with the attending anesthesiologist confirmed that unfractionated heparin was present in the standard pressure-solution setup used at our center for invasive lines (per hospital policy).

Serial plasma samples that were available in this patient were tested for antibodies that cause heparin-induced thrombocytopenia, using two different assays (platelet serotonin release assay,⁹ platelet micro-particle assay¹⁰): results of testing were negative using the preoperative sample and samples available from postoperative days 2 and 4; in contrast, strong positive testing results were shown in the samples available from postoperative days 6, 8, and 10, and on day 20 (fig. 1). Potent platelet activation was triggered by the patient's plasma in the presence of as little as 0.03 units/ml heparin.

Case 2

A 66-yr-old man underwent elective right total knee arthroplasty. There was no history of previous heparin use or previous hospital admission. He received routine flushes of unfractionated heparin (es-

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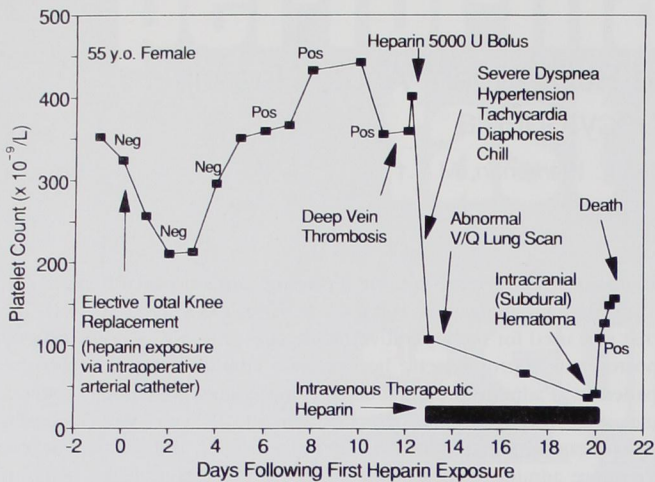


Fig. 1. Serial platelet counts in a 55-yr-old woman who underwent elective total knee replacement. Before postoperative day 12, the only heparin exposure was intraoperative (flushing of an intraarterial catheter). Nonetheless, the acute onset of dyspnea, hypertension, tachycardia, diaphoresis, and chills occurred 10 min after a 5,000-unit (U) bolus of heparin administered on day 12 for lower-limb deep vein thrombosis. Acute heparin-induced thrombocytopenia was suggested by the abrupt and unexpected decrease in platelet count that worsened during continuing heparin use and that recovered rapidly after discontinuation of heparin. The patient died of intracranial hemorrhage on day 20. The role of the intraoperative heparin exposure in causing immune sensitization to heparin is shown by the heparin-induced thrombocytopenia antibody seroconversion (negative [Neg] testing on days 0, 2, and 4) and positive [Pos] testing on days 6, 8, 10, and 20). V/Q = ventilation perfusion.

timated total exposure, < 100 units) via left radial artery intraarterial catheter that was used for intraoperative monitoring. No perioperative or postoperative prophylactic heparin was administered. Routine antithrombotic surveillance studies (¹²⁵I-fibrinogen scanning, impedance plethysmography) indicated probable deep venous thrombosis of the right lower limb on postoperative day 9, and the patient was administered a 5,000-unit bolus of unfractionated heparin, followed by maintenance-heparin infusion. Ten minutes after administration of the heparin bolus, diaphoresis and severe right thigh pain developed, followed by fever up to 38.4°C. The platelet count decreased abruptly and unexpectedly from $331 \times 10^9/L$ (measured shortly before the heparin bolus) to $167 \times 10^9/L$, 1 h after bolus administration, and $121 \times 10^9/L$, 4 h later, prompting discontinuation of the heparin. The next day, the attending clinician—unaware of the incidental intraoperative heparin exposure—believed that heparin-induced thrombocytopenia was not possible because of the absence of any known previous heparin exposure. Therefore, intravenous heparin infusion (without a subsequent bolus) was restarted; over the next 3 days the platelet count progressively decreased to a nadir of $67 \times 10^9/L$, at which time the diagnosis of heparin-induced thrombocytopenia was reconsidered. The platelet count rapidly recovered to normal after discontinuation of heparin and substitution of alternate anticoagulant therapy (ancrod and warfarin). The patient recovered uneventfully. Laboratory testing results for heparin-induced thrombocytopenia were strongly positive, using the platelet serotonin release assay.⁹

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Discussion

We describe two patients in whom unexpected, immune-mediated, acute heparin-induced thrombocytopenia developed approximately 1.5 weeks after undergoing elective major knee replacement surgery. In both patients, the diagnosis of heparin-induced thrombocytopenia was not apparent immediately. Two reasons were identified for the delay in diagnosis. First, the dramatic clinical symptoms and signs experienced by the patients (including prominent dyspnea in one patient and diaphoresis and fever in the other) are not widely recognized as features of abrupt-onset *in vivo* platelet activation associated with acute heparin-induced thrombocytopenia, although recent reports have described their occurrence.^{1,11,12} Indeed, a recent report of "pseudopulmonary embolism"¹² attributable to acute heparin-induced thrombocytopenia has highlighted the diagnostic dilemma that acute dyspnea can cause when it occurs shortly after heparin bolus use in a patient with acute deep venous thrombosis (case 1). The second reason the clinical recognition of heparin-induced thrombocytopenia was delayed in these two patients was because the attending physicians were not aware that heparin had been administered perioperatively. Indeed, documentation of the use of heparin flushes was not available in the anesthetic records for either patient, although we confirmed that heparin was used as per standard practice in both cases. The absence of previous heparin exposure in either patient and, especially, the demonstration of acute heparin-induced thrombocytopenia antibody seroconversion on day 6 after receiving heparin only via the intraarterial catheter (case 1) clearly shows the causal role of incidental heparin flushes as the explanation for heparin sensitization in both patients; thus, accounting for the subsequent course of events. To our knowledge, documentation of the role of such small intraoperative doses in triggering heparin sensitization has not been published previously. Our observations underscore the potential risk to the patient even for a minor and seemingly trivial exposure to heparin, such as the low doses (estimated at < 100 units) received by both of these patients during intraoperative treatment. Our experience with these two patients prompted a randomized

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clinical trial of heparin *versus* saline for intraoperative flushing of intravascular catheters, currently in progress, to determine the frequency and clinical impact of heparin sensitization resulting from this practice.

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Effects of Sevoflurane on QT Interval in a Patient with Congenital Long QT Syndrome

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THE inhaled anesthetics enflurane, halothane, and isoflurane prolong the electrocardiographic QT interval in healthy patients.¹ In patients with idiopathic long QT syndrome, however, cardiac arrest and death during halothane anesthesia,² absence of QT interval change

during enflurane administration,³ and shortening of QT interval during isoflurane anesthesia⁴ suggest that generalizations from healthy patients to patients with long QT syndromes are unjustified. Similarly, thiopental prolongs QT interval in healthy patients⁵ but had no effect in patients with long QT syndrome.⁶ We recently anesthetized a young woman with idiopathic long QT syndrome. We report the effects of sevoflurane on the QT interval in this patient.

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Key words: Anesthetics; arrhythmias; propofol; polymorphic ventricular tachycardia.

Case Report

A 17-yr-old, otherwise healthy, 49-kg girl presented for extraction of impacted wisdom teeth. She was receiving no medication. Preoperative examination revealed an irregular pulse and electrocardiography (ECG) was ordered. Although the initial ECG was entirely normal, with a QT interval of 362 ms (QT interval corrected for heart rate, QTc of 396 ms), recording was continued. Multifocal premature ventricular extrasystoles, and a 14-beat run of polymorphic ventricular tachycardia