CASE REPORT

Risk of Heparin-induced Immediate-type Hypersensitivity during Arteriovenous Fistula Placement

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Abstract:
Heparin is commonly used to prevent clotting; however, severe hypersensitivity reactions during vascular access (VA) placement are rarely but occasionally reported. A 49-year-old man experienced a heparin-induced hypersensitivity reaction during VA placement. Severe side effects may occur even while placing the VA; therefore, we reconsidered the routine use of heparin, as the side effects are unpredictable. Physicians should be aware of the risk of heparin-induced hypersensitivity and be ready to effectively manage it during VA placement.

Key words: heparin-induced hypersensitivity, end-stage renal disease, vascular access placement

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Introduction

Heparin is widely used as an anticoagulant. Some nephrologists use heparin in the process of arterio-venous fistula (AVF) placement in order to prevent clotting of arteries during clumping.

Despite its widespread application in daily clinical practice, hypersensitivity reactions to heparin are rare. Furthermore, in contrast to delayed-type hypersensitivity, immediate-type anaphylactic reactions after heparin administration are extremely rare.

We herein report a case of a 49-year-old patient who developed a hypersensitivity reaction after the intravenous administration of heparin during AVF placement. This is a rare report that focuses on a heparin-induced hypersensitivity reaction during AVF placement.

Case Report

A 49-year-old man with end-stage renal disease caused by diabetic nephropathy was admitted to our hospital for AVF surgery prior to starting hemodialysis (HD). His medical history included hypertension and chronic heart failure (CHF). CHF was caused by ischemic cardiomyopathy with hypoperfusion in the inferior-posterior myocardial region proven by pharmacological stress myocardial scintigraphy. Echocardiography revealed a poor left ventricular function with an ejection fraction (EF) of 35% and diffuse hypokinesis (Fig. 1). His family history was unremarkable, and he had no history of allergies. His medication included olmesartan, perindopril, amlodipine, carvedilol, furosemide, iron sulfate, and sennosides. He had never been administered heparin. A physical examination performed at admission showed a height of 1.66 m, a body weight of 77.0 kg, a body mass index of 28.0 kg/m², a temperature of 36.7°C, a pulse of 109 beats/min with regular rhythm, a blood pressure of 121/79 mmHg, an oxygen saturation of 99% (room air), and significant pitting edema of both legs. The findings of the chest, heart, and abdomen were unremarkable. The laboratory examination revealed severe renal dysfunction (Table). Chest radiography performed on admission (Fig. 2A) showed an increased cardio-thoracic ratio without congestion in both lung fields. Electrocardiogram (ECG) showed sinus tachycardia and P mitrale in lead V₁ on admission. Given his low EF, we decided to place the AVF as peripheral as possible in order to avoid acute heart failure after AVF placement. We selected an end-to-side anastomosis between the cephalic vein and the radial artery.

On day 2 after admission, the patient walked into the operating room (OR) with no complaints. On the initial physical examination, his pulse was 80 beats/min with regular
suddenly complained of dyspnea at 10:23 AM. His oxygen saturation was 95% (room air). In the supine position, his oxygen saturation remained 95% (room air); therefore, supplemental oxygen was provided (3 L/min via mask). Monitoring included electrocardiographic lead II, blood pressure, and oxygen saturation. We injected 1% lidocaine into the right forearm for local anesthesia at 9:32 AM, and an anaphylaxis reaction to the heparin and managed him. We injected heparin at 1,500 units (1,000 units per reaction of any type, even after antibiotic prophylaxis, was speculated that the patient’s pulmonary edema was a result of an anaphylaxis reaction to the heparin and managed him in the intensive-care unit (ICU). Methylprednisolone 500 mg and antihistamines (famotidine 10 mg/day and chlorpheniramine 5 mg/day) were administered in the ICU. His respiratory condition improved soon after the administration of these drugs, and the partial pressure of arterial oxygen (PaO$_2$)/fraction of inspiratory oxygen (FiO$_2$) ratio improved from 258.3 to 480. Neither the ECG findings nor the cardiac biomarker levels changed. The findings of a drug-induced lymphocyte stimulation test (DLST) were negative: the simulation index (SI) was 1.2 (reference values: S.I. <1.6, negative test; S.I. 1.6-1.8, false positive test; S.I. >1.8, positive test).

The patient’s respiratory condition recovered well, and he was extubated on day 4 after admission. HD was started with a temporary catheter from day 6 after admission; heparin was replaced with a saline-replenishing catheter and with mesilate nafamostat as an anticoagulant. On day 22, a DLST to heparin showed positive results (S.I. 2.6). Throughout the day, the patient’s dyspnea gradually decreased with good oxygenation maintained (arterial oxygen partial pressure: 248 mmHg). After maintaining this condition, AVF placement was completed at 11:12 AM.

The anesthesiologist noticed a large amount of foamy sputum from the tracheal tube and auscultated tracheal stenosis sounds and wheezes in both lungs. On a laboratory examination, the levels of cardiac biomarkers were not elevated. Chest radiography demonstrated pulmonary edema (Fig. 2B), but electrocardiographic monitoring and ECG showed no changes, and an arterial blood gas analysis revealed no acid-base disturbance or electrolyte imbalance. We speculated that the patient’s pulmonary edema was a result of an anaphylaxis reaction to the heparin and managed him in the intensive-care unit (ICU). Methylprednisolone 500 mg and antihistamines (famotidine 10 mg/day and chlorpheniramine 5 mg/day) were administered in the ICU. His respiratory condition improved soon after the administration of these drugs, and the partial pressure of arterial oxygen (PaO$_2$)/fraction of inspiratory oxygen (FiO$_2$) ratio improved from 258.3 to 480. Neither the ECG findings nor the cardiac biomarker levels changed. The findings of a drug-induced lymphocyte stimulation test (DLST) were negative: the simulation index (SI) was 1.2 (reference values: S.I. <1.6, negative test; S.I. 1.6-1.8, false positive test; S.I. >1.8, positive test).

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rhythm, blood pressure was 150/80 mmHg, and oxygen saturation was 95% (room air). In the supine position, his oxygen saturation remained 95% (room air); therefore, supplemental oxygen was provided (3 L/min via mask). Monitoring included electrocardiographic lead II, blood pressure, and oxygen saturation. We injected 1% lidocaine into the right forearm for local anesthesia at 9:32 AM, and an anaphylaxis reaction to the heparin and managed him. We injected heparin at 1,500 units (1,000 units per reaction of any type, even after antibiotic prophylaxis, was speculated that the patient’s pulmonary edema was a result of an anaphylaxis reaction to the heparin and managed him in the intensive-care unit (ICU). Methylprednisolone 500 mg and antihistamines (famotidine 10 mg/day and chlorpheniramine 5 mg/day) were administered in the ICU. His respiratory condition improved soon after the administration of these drugs, and the partial pressure of arterial oxygen (PaO$_2$)/fraction of inspiratory oxygen (FiO$_2$) ratio improved from 258.3 to 480. Neither the ECG findings nor the cardiac biomarker levels changed. The findings of a drug-induced lymphocyte stimulation test (DLST) were negative: the simulation index (SI) was 1.2 (reference values: S.I. <1.6, negative test; S.I. 1.6-1.8, false positive test; S.I. >1.8, positive test).

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Table. Laboratory Tests on Admission.

| blood tests | value         | continue |
|-------------|---------------|----------|
| WBC         | 6,700 /μL     | AST 16 IU/L |
| neutrophils | 68.3 %        | ALT 12 IU/L  |
| lymphocyte  | 17.8 %        | γGTP 13 IU/L |
| monocyte    | 7.7 %         | ALP 316 IU/L |
| eosinophils | 5.6 %         | T-Bil 0.2 mg/dL |
| basophils   | 0.6 %         | CK 975 IU/L  |
| RBC         | 274×10^4 /μL  | CRP 1.09 mg/dL |
| Hb          | 8.5 g/dL      |           |
| Ht          | 25.5 %        | protein 3+  |
| MCV         | 93.1 fL       | glucose 250 |
| MCH         | 30.9 pg       | gravity 1.016 |
| MCHC        | 33.2 %        | pH 6.5     |
| Plt         | 21.5×10^4 /μL | urobilinogen ± |
| TP          | 6.5 g/dL      | bilirubin - |
| Alb         | 2.9 g/dL      | ket -      |
| BUN         | 53 mg/dL      | WBC 2+     |
| Cr          | 7.4 mg/dL     | nitrate -  |
| eGFR        | 7.1 mL/min/1.73m² | occult blood 2+ |
| UA          | 4.9 mg/dL     | RBC 30-49 /hpf |
| Na          | 140 mEq/L     | WBC 50-99 /hpf |
| K           | 6.2 mEq/L     | epidermal casts 1+ |
| Cl          | 112 mEq/L     | TP 672 mg/dL |
| Ca          | 5.8 mg/dL     | Cr 65.7 mg/dL |
| iP          | 6.6 mg/dL     | venous blood gas |
| LDH         | 289 IU/L      | Value       |
| HCO₃⁻       | 17.6 mmol/L   |            |

Hb: hemoglobin, Ht: hematocrit, Plt: platelet, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cr: serum creatinine, eGFR: estimated glomerular filtration rate, UA: uric acid, LDH: lactic acid dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γGTP: γ-glutamyl transpeptidase, ALP: alkaline phosphatase, T-Bil: total bilirubin, CK: creatine kinase, CRP: C-reactive protein

patient’s hospitalization, we observed no reactions against other allergens. In fact, a DLST performed for cefazolin and lidocaine at the same time as the second test for heparin showed negative results. The patient’s clinical course was uneventful, and he was discharged on day 23 after admission. The patient now attends an outpatient HD clinic without any problems and also avoids heparin.

Discussion

This case confirmed two important clinical issues. First, heparin may cause severe hypersensitivity reactions during vascular access (VA) placement. Delayed reactions to subcutaneously injected heparin are commonly seen, and the work-up includes patch tests and intradermal tests. In contrast, to our knowledge, immediate-type hypersensitivity reactions to systemically administered heparin are very rare. Anaphylaxis to heparin has been linked to allergies to porcine products (1). Several cases of immediate-type reactions after intravenously injected heparin were eventually confirmed to be non-allergic anaphylaxis due to contaminants (2). Among the contaminants, oversulfated chondroitin sulfate (OSCS) can directly activate the contact system and induce the in vitro generation of Cα and Cα anaphylatoxins. Furthermore, OSCS activates kallikrein in vivo and can induce a profound hypotensive response in pigs, thus providing a potential biologic link between the contaminant and the anaphylactoid reactions seen in affected patients. The finding that hypotension did not develop in all animals treated with OSCS-contaminated heparin, even at a relatively high dose, is consistent with the observation that most patients who received contaminated heparin did not experience adverse events (2). Consequently, many physicians remain unaware of anaphylaxis to heparin (3).

Regarding the probability of hypersensitivity to heparin, some may contest that the present patient more likely experienced heart failure exacerbation than an allergic reaction. Indeed, his risk of acute heart failure was high due to the presence of several cardiovascular risk factors, such as CHF, chronic kidney disease, diabetes mellitus, and hypertension. However, the following three reasons exclude this possibility: First, acute heart failure typically develops due to acute coronary syndrome or arrhythmia with a sudden onset; the cardiopulmonary surveillance in this patient did not show any abnormalities. Second, dyspnea was exacerbated shortly after heparin administration. The time course between the
heparin injection and dyspnea onset therefore prompted us to suspect an allergic reaction. Furthermore, a CDC report on acute allergic-type reactions among patients undergoing hemodialysis (4) supports this condition as a probable allergic-type reaction. Finally, the patient’s respiratory condition recovered soon after the methylprednisolone administration. If he had suffered from heart failure, his respiratory condition would not have improved soon after steroid administration. The rationale for our administering steroid therapy was based on its anti-inflammatory effect, and a previous study reported the use of steroid medications for the management of allergic reactions (5). In addition, the possibility of stress cardiomyopathy was excluded because of his ventricular wall motion.

The second important clinical issue of note is that physicians should avoid the routine use of heparin, as hypersensitivity to heparin cannot be predicted and we cannot anticipate which patients may develop shock. In addition, confirming heparin-induced allergic hypersensitivity is difficult. If a DLST is performed soon after the onset of anaphylaxis, then the number of false negative results has been reported to increase (6). Therefore, we cannot deny any possible allergic reaction to heparin using the currently available tests. In this case, we first obtained negative result for heparin on a DLST, but verified the allergic reaction later. However, we did not identify any association between immediate-type hypersensitivity and a positive result of DLST at the second exam, even though heparin would likely affect the patient either prior to admission or after the start of intravenous injection. The allergological work-ups of immediate-type hypersensitivity reactions to heparin rely on skin prick and intradermal heparin testing, with readings after 15 to 20 minutes (7). However, since this test represents delayed reactions to subcutaneously injected heparin, we theoretically cannot evaluate immediate hypersensitivity reactions to systemically administered heparin. While the basophil activation test (BAT) has been proposed as a complementary method for the in vitro diagnosis of heparin allergy (8), researchers with experience in the field of heparin allergy repeatedly failed to detect heparin sensitization by BAT (7). As a result, no test able to prove allergic reactions to heparin is currently available. Therefore, it is important to understand the basis for these clinical events and to predict future occurrences.

In conclusion, heparin injection can cause a severe allergic hypersensitivity reaction during VA placement, and physicians should reconsider the routine use of heparin because it is impossible to anticipate which patients will develop hypersensitivity to heparin. Physicians should consider the risk of heparin-induced hypersensitivity and be ready to effectively manage it during VA placement, especially in outpatient settings.

The authors state that they have no Conflict of Interest (COI).

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