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Severe Bleeding Complication of Low Molecular Weight Heparin in A Dialysis Patient with Deep Venous Thrombosis

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Abstract

Low-molecular-weight heparin (LMWH), a mixture of polysaccharide molecules, is derived from unfractionated heparin (UFH) by physical and/or chemical processes. Using subcutaneous injections of LMWH to treat patients with deep vein thrombosis has several major advantages over the use of conventional intravenous or subcutaneous UFH therapy. For instance, there is no requirement for laboratory monitoring of activated partial thromboplastin time with LMWH. However, in the report we observed a 65-year-old female with end-stage renal disease and found that she, after receiving anti-coagulant treatment with Nadroparin (LMWH), developed bleeding complications. It indicates that the potential bleeding adverse effect of LMWHs should be taken into account when applied to patients with severe renal disease. (J Intern Med Taiwan 2007; 18: 140-145)

Key Words ：Low molecular weight heparin, Hemodialysis, Complication

Introduction

Thromboembolic events are common among patients with end-stage renal disease[1-2]. Congestive heart failure, malignancy, post-operative state, and immobility are strongly associated with thromboembolism and commonly found among patients under regular hemodialysis. In addition, multiple vascular access manipulation poses an additional risk of developing venous thromboembolism, which is unique to the hemodialysis population.

Low-molecular-weight heparin (LMWH) is de-

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rived from unfractionated heparin (UFH) by physical and/or chemical processes. LMWH is a mixture of polysaccharide molecules with a mean molecular weight of 4500 daltons. Using subcutaneous injections of LMWH to treat patients with deep vein thrombosis has several major advantages over the use of conventional intravenous or subcutaneous UFH therapy. First, there are more predictable anticoagulant responses to fixed doses of LMWH and more favorable antithrombosis to hemorrhagic ratios compared with UFH treatment[3-6]. Secondly, there is no requirement for laboratory monitoring of activated partial thromboplastin time with LMWH. Thirdly, the pharmacokinetics of LMWH uptake and clearance also lend themselves to subcutaneous dosing, by which uptake is greater than 90% (compared with less than 30% when UFH is administered subcutaneously). Finally, the low degree of binding to plasma proteins results in a plasma half-life two to four times that of UFH[7]. Although UFH is still the most common anticoagulant used in hemodialysis, LMWH is also considered as a safe alternative with less bleeding complications.

We observed a 65-year-old female with end-stage renal disease, who presented left femoral deep venous thrombosis. After receiving anticoagulant treatment with Nadroparin (LMWH), she developed severe bleeding complications. There is potential risk of hemorrhage when the use of LMWH in patients with impaired renal function. If prescribed, doses should be lowered. Moreover, the use of other antithrombotic drugs should be minimized.

Case Report

A 65-year-old female with end-stage renal disease secondary to hypertension was hospitalized because of uremic symptoms. Her body weight was 61kg at that time. Epoetin beta had been prescribed for one year and the dose was 82 units/kg/wk subcutaneously. Maintenance hemodialysis without any anticoagulant was initiated thrice a week by femoral vein cannulations. The right femoral vein cannulation was complicated by hematoma formation. Hemodialysis was then performed via contralateral left femoral vein.

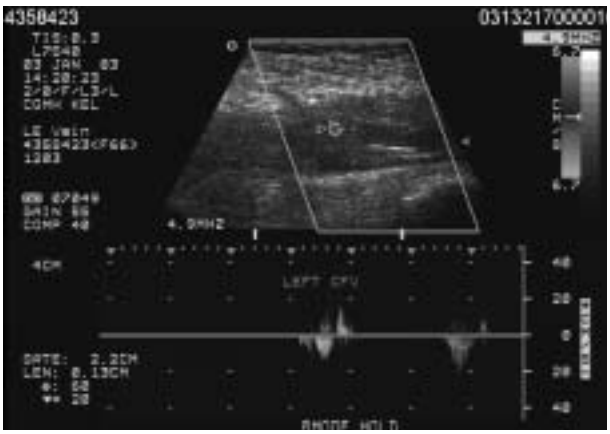

Fig.1.Thrombi in the left femoral vein and the left popliteal vein.

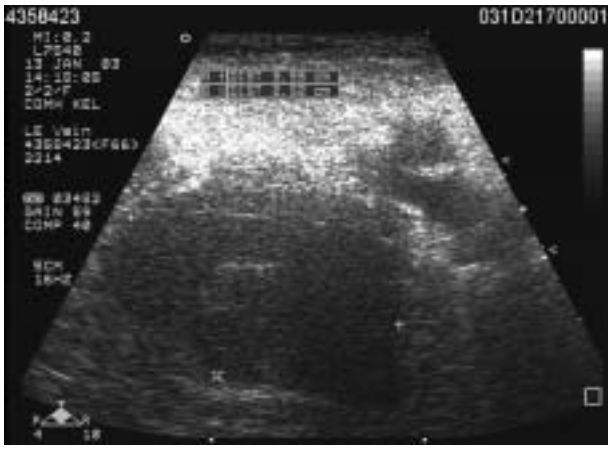

Fig.2.A large hematoma 3.5 × 2.5 cm near the right femoral vein.

On the 4th day of admission, the left lower leg swelling was noted and our instant impression was deep vein thrombosis. Femoral catheter was removed and the right internal jugular vein was used as the vascular access. On the 5th day, the duplex venous study revealed thrombi in the left femoral vein and the left popliteal vein (Fig. 1). To add, mild venous insufficiency, but without hematoma, of the right popliteal vein could also be known from this duplex venous study. Heparinization (UFH) was prescribed (82U/kg loading dose and 10U/kg per hour), but right neck hematoma was noted 2 hours later. The catheter was removed and heparinization was hold immediately.

Cuffed double-lumen (Hickman catheter) was inserted through the left subclavian vein simultaneously. In the meanwhile, the coagulation analyses were: prothrombin time: 11.0/11.2 sec; activated partial thromboplastin time: 25.6/31.4 sec; platelet count: 137 × 1000/mm^3 and albumin: 4.1 g/dL. The 6th day, the patient began to receive anticoagulant treatment with Nadroparin (LMWH) in a single bolus (5700 anti-Xa unit Institut Choay [95 aXaU IC/kg]) to reduce the possible bleeding complications. The left leg DVT was getting better and the dose of Nadroparin was tapered to 64 aXaU IC/kg/12hrs (total 26600 aXaU IC) from the next dose. After 4-day-treatment (8 doses) of Nadroparin, hemodialysis without heparin via Hickman was performed again but severe right thigh pain with inguinal mass was emerged after hemodialysis. A large hematoma developed and at the same time the platelet count was 130 × 1000/mm^3. Subsequent venous duplex scan confirmed a large hematoma 3.5 × 2.5 cm near the right femoral vein (Fig. 2). The Nadroparin was discontinued to reverse the bleeding tendency, but the hematoma kept progressing. The patient received operation for debridement of the right thigh hematoma. No more anticoagulant therapy was prescribed since then. Maintenance hemodialysis was reinitiated via Hickman three times a week. Review her history, there was no liver disease or liver problem noted. Besides, the NSAIDs or anticoagulants were not prescribed before.

Discussion

Although renal failure has conventionally been associated with a bleeding tendency, in recent studies thrombotic events are commonly found among patients with end-stage renal disease[8]. Many dialysis patients have traditional risk factors for thrombosis and pulmonary embolism, including immobilization, intravascular devices, surgical procedures, advanced age, congestive heart failure, hyperhomocysteinemia, and cancer. Lupus nephritis and membranous glomerulonephritis are two kidney diseases associated with thrombosis that leads to end-stage renal disease[9]. On the other hand, non-traditional risk factors associated with uremic patient may increase procoagulant activity, such as endothelial dysfunction, inflammation, and malnutrition. Several end-stage renal disease treatment factors, such as, recombinant erythropoietin administration, dialyzer bioincompatibilty, and calcineurin inhibitor administration may also have prothrombotic effects.

Maintenance of normal hemostasis results from an interaction of various mechanisms, including platelet adherence, vessel wall contraction, platelet aggregation, and fibrin clot formation. The development of thrombosis requires an imbalance between procoagulant and anticoagulant forces. In uremia this balance is altered because of reduced platelet adhesion[10-11] and impaired platelet aggregation[12]. Altered platelet function plays an important role in the hemorrhagic complications of these patients. The receptor defect of glycoprotein GPIb (the receptor for von Willebrand factor) on the surface of uremic platelets and a negative correlation between serum creatinine and the expression of glycoprotein GPIb were found. The defect was not corrected by hemodialysis and/or peritoneal dialysis[13]. Patients who have end-stage renal disease have a bleeding tendency manifesting by a prolonged bleeding time thought to be secondary to platelet dysfunction[3-4]. The simultaneously bleeding and thromboembolic tendency presents a clinical challenge in the care of dialysis patients. Deep venous thrombosis has been treated with a short course of intravenous UFH followed by oral anticoagulants for at least 3 months[14-15]. The development of LMWH renders the clinician a possible therapy with less bleeding complications.

Comparing with LMWH, UFHs readily bind themselves to histidine-rich glycoprotein, polymeric vitronectin, platelet factor IV, multimers of vWF, fibronectin, macrophages, and endothelial cells. Besides, UFHs perform unpredictable anticoagulant

activity due to the wide patient variability in plasma concentrations of these heparin-binding proteins[16]. Therefore, the anticoagulant response to UFHs necessitates frequent hemostatic monitoring. Recent studies have shown that initial treatment with LMWHs is equally or more effective and safer than UFHs[17].

LMWHs produce a more predictable anticoagulant response than UFH, reflecting their better bioavailability (greater than 90%), longer half-life, and dose-independent clearance. The plasma half-life of LMWHs is two to four times as long as that of UFHs, ranging from two to four hours after intravenous injection and from three to six hours after subcutaneous injection[16,17]. Because LMWHs bind less to macrophages and endothelium, the renal and hepatic clearance is slower and results in a longer plasma half-life. The inhibitory activity of LMWHs against factor Xa persists longer than their inhibitory activity against thrombin, reflecting the more rapid clearance of longer heparin chains. The improved bioavailability and longer half-life of LMWHs allow them to be dosed conveniently once or twice daily.

The lower incidence of bleeding in patients treated with LMWHs results from its reduced binding to platelets, endothelium, and high-molecular-weight forms of vWFs[18-19]. On the other hand, unlike UFHs, LMWHs do not increase microvascular permeability[20]. LMWHs are now frequently used as the initial treatment for most patients with deep venous thrombosis[21]. The use of LMWHs, which does not require monitoring or dose finding, has largely replaced UFHs for the initial management of thromboembolism.

The first bleeding episode in the right femoral cannulation site of this case happened at the beginning of hemodialysis, may result from iatrogenic cause and the bleeding tendency of the end-stage renal disease patient. The second episode, right neck hematoma formation, occurred 2 hours after UFH administration. We shifted to LMWH treatment the next day to decrease the bleeding complication of UFH. However, the right femoral cannulation site bleeding appeared 4 days after LMWH treatment. The right femoral vein had received cannulation 10 days ago. This suggested that LMWHs could increased the risk of hemorrhage with decreasing renal function.

Patients with impaired renal function who receive multiple doses of LMWHs have higher anti-Xa levels, reduced drug clearances, and prolonged drug half-life. Nadroparin had potential accumulation of its anticoagulant effect with creatinine clearances as high as 50 ml/min[22]. Additionally, most available LMWHs are not predictably safe to use at standard doses in patients with reduced GFRs, including those on dialysis[23]. The frequency of bleeding in patients with renal insufficicency is different from those who with normal renal function.

In summary, the predisposing factors for deep venous thrombosis are commonly noted in the population. LMWHs are claimed to be safer than UFHs. Due to the potential bleeding tendency, LMWHs should be used cautiously on patients with end-stage renal disease.

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低分子量肝素治療血液透析病人深部靜脈栓塞造成嚴重出血之併發症

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摘 要

低分子量肝素 (Low-molecular-weight heparin) 是一種黏液多醣體，衍生自傳統肝素 (Unfractionated heparin)，在治療深部靜脈栓塞方面比傳統肝素有較多優點，例如可安全使用而毋須實驗室之監測。我們記錄一個65歲血液透析女性病人，因爲深部靜脈栓塞而使用低分子量肝素來治療，而造成嚴重出血的併發症。