Case Report

# Retroperitoneal hematoma due to spontaneous lumbar artery rupture during fondaparinux treatment. Case report and review of the literature

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**Abstract.** We present the case of a 78 year-old man who developed a spontaneous rupture of the lumbar artery leading to a retroperitoneal hematoma while receiving fondaparinux therapy after a total hip replacement. A selective angiographic embolization stopped the bleeding. Fondaparinux was discontinuated and the patient presented a complete resolution of his medical status. Spontaneous hematomas has been well described during low molecular weight heparin (LMWH) treatment, expecially in elderly patients, but there are no previous reports of hematomas induced by fondaparinux. We reviewed the literature to identify the possible risk-factors of bleeding. Our review shows that even if many works suggest that fondaparinux is a safe and effective alternative to LMWH in the prevention of venous thromboembolism following major orthopaedic surgery, it should carefully be used in elderly people and patients with renal disfunction. (www.actabiomedica.it)

**Key words:** Fondaparinux, bleeding, hematoma, total hip arthroplasty, lumbar artery rupture

## Introduction

Fondaparinux is replacing low-molecular-weight heparins (LMWHs) in anticoagulation therapy because of its advantages and efficacy that is largely documented in many studies (1-6).

Fondaparinux is the first of a class of selective antithrombin-dependent factor Xa inhibitors, it does not interact with plasma proteins other than antithrombin, leading to a predictable pharmacokinetics, which renders monitoring and dose adjustment unnecessary. It reduces the relative risk of deep vein thrombosis (DVT) by 91% in patients undergoing total hip replacement, and by 79.5% after total knee replacement (7). Compared with enoxaparin, the pentasaccharide decreases the incidence of DVT with a relative risk reduction of 50.6% ($p<0.001$) (8). This superior efficacy leads to an overall 1% increase in the rate of major bleeding, when compared with enoxaparin (9).

Spontaneous hematomas, not related to trauma, surgery or puncture, are a rare clinical entity and several causes have been identified, including underlying vascular lesions, acquired and congenital coagulopathies, antithromboembolic treatments and small undetectable occult tumors (10-12). Many studies are present in the literature on the association between LMWHs and hematomas (13-17), but there are no previous studies reporting this complication with the synthetic pentasaccharide. This case is the first report of a patient developing severe spontaneous hematoma while he was in treatment with fondaparinux.

Additionally, we reviewed the literature to detect other risk factors that are correlated to this type of bleeding.

**Case report**

A total hip replacement was performed in a 78 year-old male.

He had undergone a left simple nephrectomy five years earlier. He was not diabetic, and did not have a bleeding disorder or coagulopathies. He was not taking any antiplatelet drugs. Laboratory values at admission were normal, including serum creatinine (0.9 mg/dl). He was treated with 2.5 mg/day of fondaparinux started 6 hours post surgery.

His hospital stay was complicated by episodes of hypotension, which were treated with a transfusion of packed red blood cells. He developed a subfascial hematoma at the surgical site and the wound stopped bleeding in a few days after the operation. However the patient's condition continued to worsen. The defining event occurred in day 9, when the patient became acutely hypotensive, with a blood pressure of 90/55 mm Hg and a pulse rate of 110 bpm. His hemoglobin decreased from 9.1 g/dL to 6,6 g/dL. Fondaparinux was discontinued. An urgent CT scan of the abdomen and pelvis revealed a large right retroperitoneal hematoma with extravasation of intravascular contrast material (Fig. 1) and a right gluteus maximus hematoma (Fig. 2). Angiography was rapidly perfor-

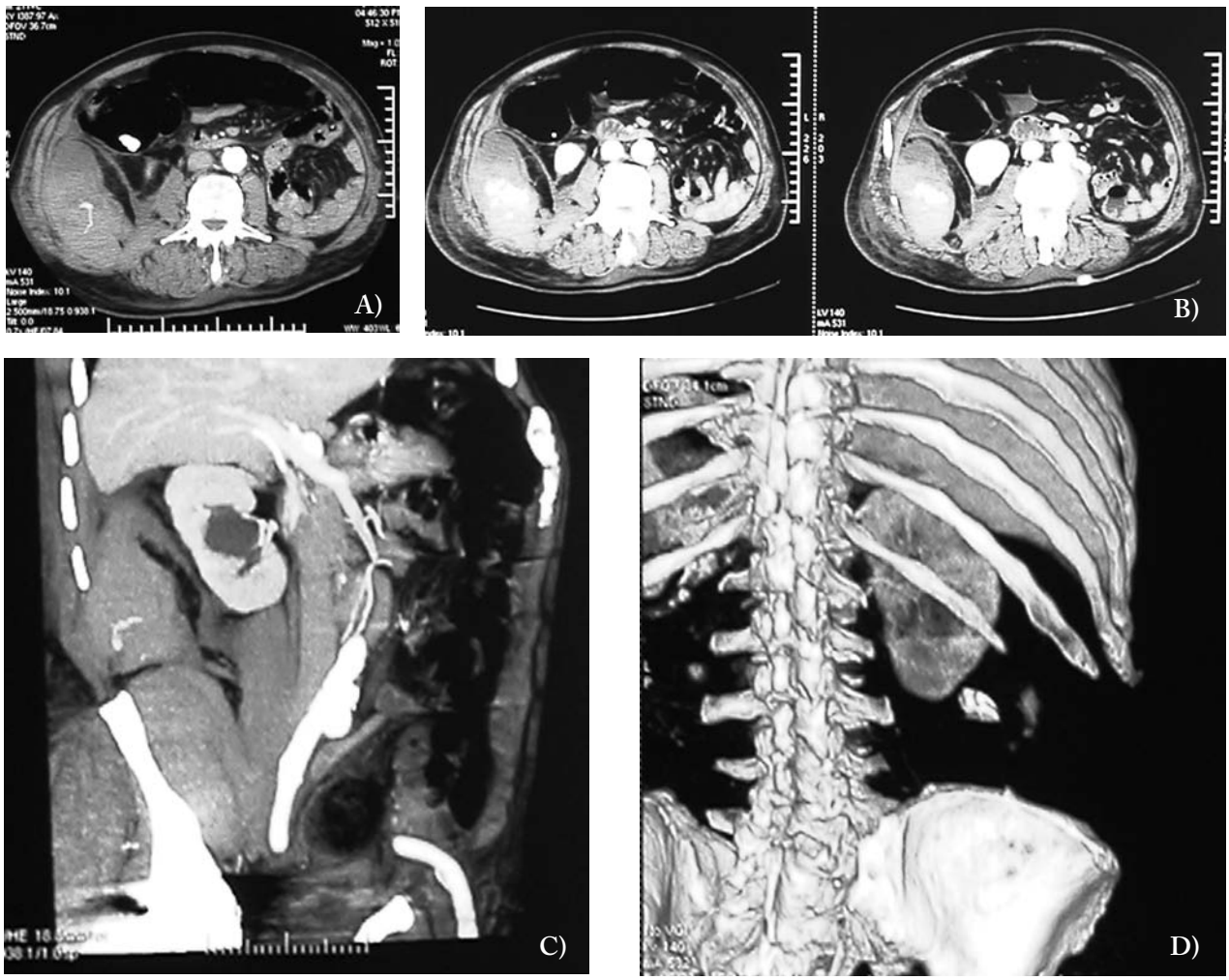


**Figure 1**. Computed tomographic scan of the abdomen. A) large, right-side retroperitoneal hematoma, in the perirenal space; B) displacing anteriorly the right kidney; C; Sagittal view; D: 3D reconstruction. The extravasation of intravenous contrast material (arrow), suggests active bleeding

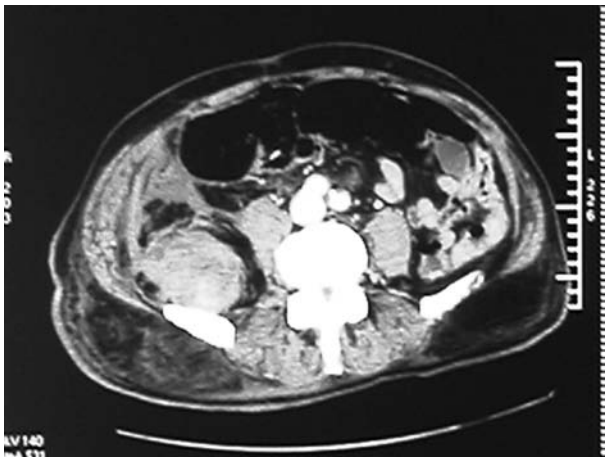

**Figure 2**. CT: a right gluteus maximus hematoma

med which showed extravasation from a right lumbar artery. The bleeding was controlled with a selective angiographic embolisation, and the patient was admitted to the intensive care unit. His medical status improved in few days and he was discharged on postoperative day 29 with no further complaints. The patient remained sympton-free after 13 months; Ct scan, MR and angiographic controls were repeated with no evidence of tumors or alteration of the vascular supply of the kidney.

## Discussion

Fondaparinux has been shown to be more effective than LMWH in the prevention of venous thromboembolic events after major orthopaedic surgery, and is also safe during extended prophylaxis (18, 19).

In the randomized studies performed on the use of fondaparinux vs LMWH (20-23), the primary safety outcome of major bleeding was defined as a composite of fatal bleeding, bleeding into a critical organ (retroperitoneal, intracranial, intra-spinal, or into other critical organs), bleeding that led to repeat surgery, and overt bleeding with a bleeding index of 2 or higher.The differences regarding major bleeding episodes, observed in these four studies were mainly due to an increased incidence of overt bleeding with a bleeding index of ≥2. In patients receiving their first fondaparinux injection ≥6 hours after surgical closure, the incidence of major bleeding episodes was similar to that seen with enoxaparin (24). None of the 3616 patients treated with fondaparinux showed bleeding into a critical organ. Bleeding into a critical organ was registered in only one of the 3621 patients treated with enoxaparin (21). Even though the incidence of these complications was very low in these studies, several major bleeding complications have been reported in patients treated with LMWH in literature. Retroperitoneal hematoma is the most frequently reported and has the worst prognosis (13, 14, 25, 26) with and high mortality (13.3%) (27). It is often correlated to kidney diseases (11, 12, 28) and is also considered a severe urological complication of anticoagulant therapy (29). One of the causes implicated in retroperitoneal hematoma is the spontaneous rupture of the lumbar artery even if it seems rare and only a few cases have been reported. In 1983 Stewart JR et al (30) reported a case that was correlated to a rupture of a post-traumatic pseudoaneurysm. Chronic renal failure can increase the tendency of bleeding with various mechanisms such as decreased activity of platelet factor III, abnormalities of platelet aggregation and adhesiveness, high uraemia levels or direct injury to the vascular intimal layer. All these modifications can lead to a spontaneous rupture of arteries as reported by Halak et al. (31). Kalinowski and Trerotolo reported a case in which a spontaneous bleeding from a lumbar artery occured in a patient under anticoagulation therapy and emphasized the correlation of this group of patients with spontaneous hemorrage (32). Schuster et al also reported a spontaneous artery rupture during anticoagulant therapy (33).

Vayá et al (34) reported 9 cases of spontaneous hematoma during enoxaparin therapy. Only three patients were taking LMWH at a prophylactic dosage, the other ones received treatment doses (60-80 mg twice a day), and four of them also took aspirin. A certain degree of chronic renal insufficiency was present in 6 of them. Martel et al (27) reported their experience of 15 retroperitoneal hematomas and emphazised that both advanced age and an impaired renal function are well-known risk factors for hemorrhages. Age greater than 70 years has been shown to be associated with a clinically important increased risk of major bleeding due to age-related changes in the

pharmacodynamic and pharmacokinetic properties of heparin (35). Elderly patients, despite a normal serum creatinine value, can have a significantly reduced creatinine clearance (CrCl), that lead to an increase of anti-Xa activity and consequently to an increased risk of bleeding.

Like LMWHs fondaparinux is also excreted in the urine with a correlation between clearance of fondaparinux and creatinine (24).

Fondaparinux binds completely to AT-III, catalysing the inhibition of factor Xa, following this interaction, fondaparinux is released unchanged and is subsequently able to bind to other AT molecules. This binding protects the small pentasaccharide from rapid elimination [half-life ($t_{1/2}$) of 17 h], enabling once-daily administration. Thus in elderly volunteers, who had a mean CrCl which was approximately half of that of young volunteers (60 mL/min vs 132 mL/min), the clearance of fondaparinux was prolonged, with an increased mean terminal elimination half-life ($t_{1/2}$,) of 21 hours. In elderly patients with a moderate reduction of CrCl (30-50 mL/min) even with normal serum creatinine values, the $t_{1/2}$ was 29 hours, which meant the drug was effective for up to 58 hours, leading to an increased risk of bleeding.

In the cases of severe bleeding it is possible to reverse the anticoagulant effect of fondaparinux, with the administration of recombinant factor VIIa (rFVIIa) (2). Huvers et al. (36) reported a good result with a single dose of rFVII in combination with tranexamic acid in controlling a severe post-operative bleeding after a single dose of fondaparinux in a 79 year-old patient with reduced renal clearance. The possibility of neutralizing the effect of fondaparinux is particularly important in patients with impaired renal function that may develop severe bleeding. The same possibility is not yet established for LMWHs. Although protamine sulfate appears to block LMWH-induced bleedings in laboratory animals, this is not the case in humans (37-39).

To our knowledge, this is the first case report of a retroperitoneal hematoma developed in the absence of any precipitating event while the patient was receiving fondaparinux therapy. The results of this case, together with our review of the literature, demonstrate that even if many works state that fondaparinux is a safe medication, with few side effects (40), it should be used with caution in patients of advanced age, especially if they have an impaired renal function. In these high-risk patients not only serum creatinine, but also creatinine clearance should be monitored. Therefore, it would be desirable to carry out clinical trials to know the adequate doses for decreasing clinically significant bleeding in these patients without impairing therapeutic results.

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