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RETROPERITONEAL HEMATOMA FOLLOWING ENOXAPARIN TREATMENT IN AN ELDERLY WOMAN

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SUMMARY – Retroperitoneal hematoma may occur as a result of trauma, but also from rupture of arterial aneurysms (aortic or iliac), surgical complications, tumors and anticoagulation therapy. A life threatening retroperitoneal hemorrhage is an infrequent complication of anticoagulation treatment. Enoxaparin is a low-molecular-weight heparin with several advantages over unfractionated heparin. Nevertheless, enoxaparin use is not without risk and severe retroperitoneal bleeding may occur following its use, with a potentially fatal outcome. The case of a 76-year-old woman hospitalized for acute coronary syndrome who developed a large retroperitoneal hematoma on day 5 of enoxaparin therapy is presented. The use of enoxaparin in the acute coronary syndrome as well as in standard thromboprophylaxis has increased over the past decade, which may lead to an increased occurrence of retroperitoneal bleeding in clinical settings. Therefore, physicians should be extremely observant for symptoms and signs of retroperitoneal hemorrhage, and identification of a group of high-risk patients who require close anticoagulation monitoring is mandatory. The treatment of patients with retroperitoneal hematoma should be provided in the intensive care unit setting. Enoxaparin must be discontinued; protamine may be administered depending on the time elapsed from the last enoxaparin dose; fresh frozen plasma and packed red blood cells should be administered if necessary; and surgical intervention may be required if the patient fails to stabilize.

Key words: *Anticoagulants – adverse effects; Enoxaparin – adverse effects; Hematoma – chemically induced; Retroperitoneal space – surgery*

Introduction

Retroperitoneal hematoma often occurs as a result of trauma. Other causes of retroperitoneal hematoma have also been reported, e.g., vascular lesions such as rupture of aortic or iliac aneurysm, complications from surgical procedures, tumors and anticoagulation therapy. A life threatening retroperitoneal hemorrhage is an infrequent complication of anticoagulation medications, and only a few reported cases exist in the world literature of patients with enoxaparin induced spontaneous retroperitoneal bleeding[1].

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The use of enoxaparin in the acute coronary syndrome has increased over the past decade, which is in part due to favorable results from several trials[2-7]. Enoxaparin is a low-molecular-weight heparin (LMWH) and as such it has several advantages over unfractionated heparin (UFH)[8-10]. It has a more predictable anticoagulant response than UFH, and it also has better bioavailability at lower doses than UFH. The anticoagulation monitoring is not necessary in most patients due to the dose-independent clearance mechanism and longer half-life. Furthermore, enoxaparin is more rarely related to major bleeding since it binds less to platelets and inhibits platelet function to a lesser extent. Enoxaparin also has a lower incidence of heparin-induced thrombocytopenia than UFH. Unfortunately, enoxaparin use is not without risk and severe retroperitoneal bleeding has

been reported following its use. We report on a patient who had a major bleeding episode as a probable result of enoxaparin use.

Patient and Methods

A 76-year-old woman was transferred from a smaller hospital on day 9 of admission. The initial cause of hospitalization was chest pain; she had a 5-year history of chest pain on physical activity, when pain would last for approximately 10 minutes, to resolve on sublingual application of nitroglycerine. Several days prior to admission, chest pain started to occur during rest, predominantly at night, expanding to the back, and was accompanied by nausea, sweating and general weakness.

The patient's history included the following: nine years before, the patient had undergone hysterectomy and bilateral adnexectomy, and suffered a mild ischemic stroke several months later; at that time, an incomplete right bundle block was noted on electrocardiography (ECG). Eight years before, she had undergone cholecystectomy. The patient also had chronic atrophic gastritis and a peripyelic cyst of the right kidney. Three years before, mild hyperglycemia and hyperlipidemia were diagnosed, whereas two years before two significant stenoses of the LAD and stenosis of the diagonal artery were verified on coronarography. A family history of hypertension was present in her mother, brother and sister as well in her three sons.

She used several antihypertensive and cardiac drugs, which included combined lisinopril dihydrate and hydrochlorothiazide, atenolol, isosorbide mononitrate (ISMN), acetylsalicylic acid and the antidiabetic repaglinide.

Upon admission, the work-up included blood tests, ECG and cardiac ultrasonography. Enoxaparin was included in the treatment (2x60 mg subcutaneously). On day 5 of the hospital course, a drop in blood pressure and anemia were observed (minimal values during the course of illness: red blood cells 3.03, hematocrit 0.280, platelets 93, prothrombin time (PT) international normalized ratio (INR) of 1.06, fibrinogen 6.5. Clinically, the patient complained of abdominal pain, predominantly suprapubically and in the left groin, which irradiated to the left leg. On physical examination, the abdominal wall was hard, painful on palpation of the lower quadrants, especially on the left side. Abdominal CT scan was performed which confirmed a blood collection adjacent to the left psoas and surrounding the left iliac artery, which had a sclerotic wall, and extending towards the femoral region and precoccygeally. The aorta was heavily sclerotic with a slightly wider diameter, but without any signs of aneurysm or rupture. The widest transverse diameter of the hematoma was 8-9 cm. Duplex scan of the lower limb circulation detected numerous atherosclerotic plaques without significant disturbances of the hemodynamics to the foot level. The patient was suspected of having a rupture of the left iliac artery. The patient also had melena, so gastroscopy was performed, which was normal.

Enoxaparin was excluded from the treatment, 3 units of blood were administered, blood glucose levels were corrected, the patient was rehydrated and her condition stabilized. Antibiotics were administered (amoxycillin with clavulanic acid and metronidazole). Moderate acute renal insufficiency (maximal creatinine 448.6 μmol/L) with preserved diuresis was observed.

Control CT scan was performed on day 9 of admission (4 days after the clinical onset of hematoma), which showed no significant changes in comparison with the first CT scan. Transverse diameter of the hematoma was 7-8 cm and longitudinal diameter 15-18 cm. Since the patient remained clinically stable and could be transported to a facility with vascular surgery, she was transferred to our hospital.

Urgent Multislice CT angiography (MSCT angiography) was performed upon admission using standard, maximum intensity projection (MIP) and volume rendering (VRT) protocols. Heavy atherosclerotic changes

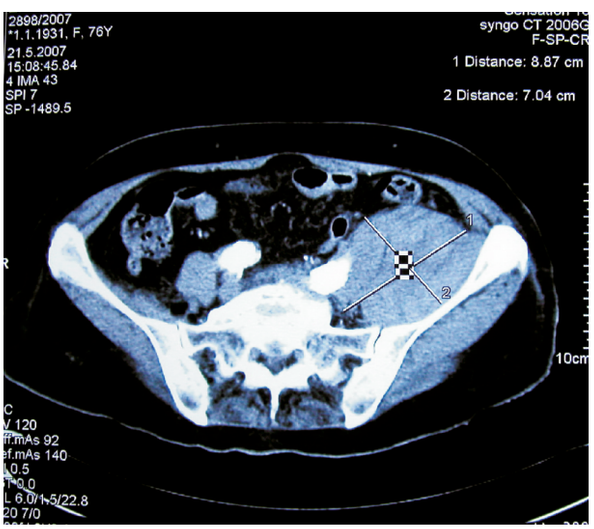

Fig. 1. CT scan of lower abdomen/pelvis: visible left sided retroperitoneal hematoma 8.8x7 cm in transverse diameter.

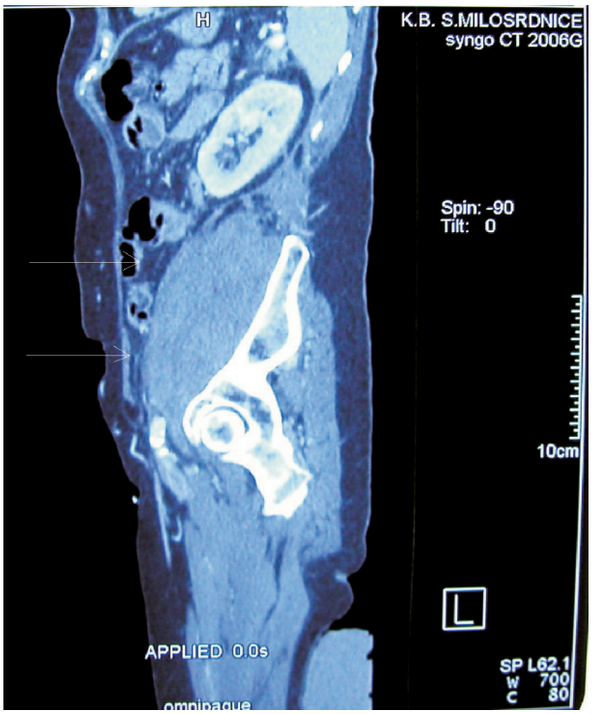

Fig. 2. Sagittal CT scan showing expansion of the retroperitoneal hematoma to the left inguinal region.

of the aortic wall without signs of aneurysm or rupture were found. The iliac arteries had normal diameters and significant atherosclerotic changes, with no signs of aneurysm. On axial multiplanar reconstruction (MPR) slices a retroperitoneal hematoma was verified in the vicinity of the left iliac bone, being of 9x7 cm transversely (Fig. 1) and 11 cm craniocaudally (Fig. 2), partially adjacent to the left external iliac artery. No extralumination of the contrast was found (Figs. 3 and 4), not even during the venous or delayed phase.

Complete laboratory work-up was ordered, and only mild elevation of white blood cells ($11.9x10^9$/L), bilirubin (26 µmol/L), creatinine (175 µmol/L), blood glucose level (12.2 µmol/L) and ALT (81 U/L 37 ^{0}C), and a mild decrease in RBC ($3.66x10^{12}$/L) and Hb (117 g/L) were found.

As the patient remained hemodynamically stable with no major complaints, no ongoing extralumination or aneurysms were found, and there were no signs of abdominal compartment or other pathologic conditions intra-abdominally, there were no indications for emergency surgery. Two days later, she was transferred back to the local hospital for further conservative treatment. On follow up she remained hemodynamically stable and in good condition.

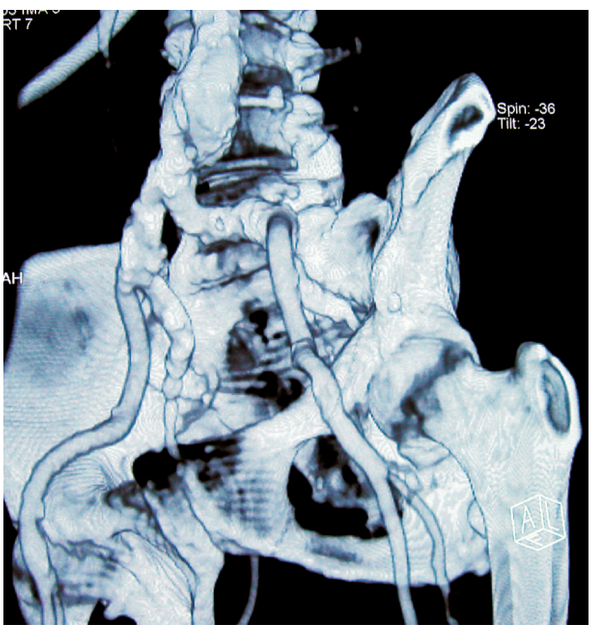

Fig. 3. 3D reconstruction of the aorta, iliac and femoral arteries. There is no evidence of aneurysms or signs of rupture or extralumination.

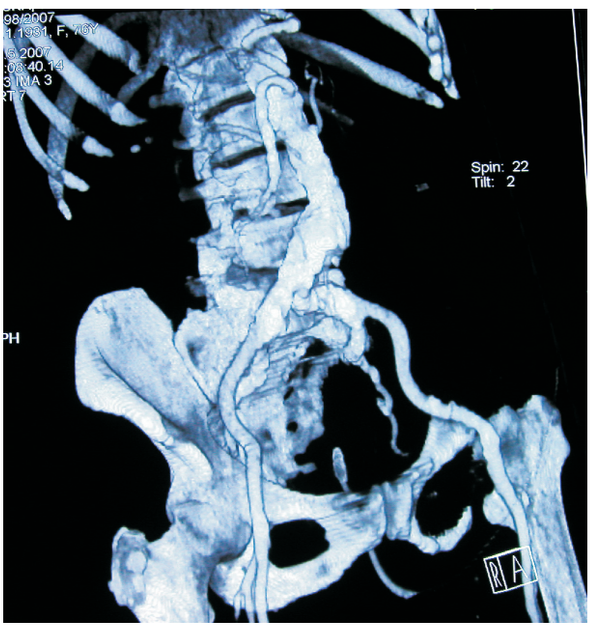

Fig. 4. 3D reconstruction of the aorta, iliac and femoral arteries. Parts of the left side of pelvic bones are removed for precise visualization of the vessels.

Discussion

Literature review revealed that apparently the first reported case of a patient with an acute coronary syndrome who died due to enoxaparin-induced retroperitoneal hematoma was that by Chan-Tack from the University of Missouri in Columbia[1]. Numerous journal articles and case reports deal with heparin-induced retroperitoneal hemorrhage[11-28], but only a few deal with enoxaparin specifically.

Enoxaparin is a LMWH that possesses several advantages over UFH[8-10]. It has a more predictable anticoagulant response than UFH due to the higher ratio of anti-factor Xa-anti-factor IIa activity and better bioavailability at lower doses than UFH because it binds less to the endothelium. Anticoagulation monitoring is not necessary in most patients due to the dose-independent clearance mechanism and longer half-life; only high-risk patients require anticoagulation monitoring. Furthermore, enoxaparin is more rarely related to major bleeding since it binds less to platelets and inhibits platelet function to a lesser extent. Enoxaparin also has a lower incidence of heparin-induced thrombocytopenia than UFH. The easy, subcutaneous route of administration is also important. Unfortunately, despite numerous benefits, enoxaparin use is not without risk and severe retroperitoneal bleeding has been reported following its use, some of which had fatal outcome.

Cohen *et al.*[2], in their ESSENCE study, showed that enoxaparin was more effective than IV unfractionated heparin in reducing the incidence of death, myocardial infarction or recurrent angina in patients with unstable angina or NQWMI. Only minor hemorrhage (injection-site ecchymosis) was more common with enoxaparin and the benefit was maintained at one-year follow up. Among 1,578 patients receiving enoxaparin and aspirin for the management of acute coronary syndromes, 17 (1%) cases of major bleeding episodes were reported, which included intraocular, retroperitoneal and intracranial hemorrhage, hemoglobin decrease by at least 30 g/L, and transfusion requirement of 2 units or more of blood products.

It is recommendable that physicians be extremely observant for the symptoms and signs that suggest retroperitoneal hemorrhage; these include hypotension, hemoglobin decrease, abdominal distention, increasing bruising, peritoneal signs, flank pain, hip pain, signs of intracranial hemorrhage (neurologic deficits, nausea, vomiting, headache, mental status changes), and signs of intraocular hemorrhage (visual changes, nausea, vomiting, photophobia, pain, headache). Enoxaparin should be used very cautiously in elderly patients and in patients with renal insufficiency (creatinine clearance <30mL/min) because of the risk of delayed clearance. A subgroup of high-risk patients require close monitoring, including those with bleeding diatheses, thrombocytopenia, uncontrolled hypertension, or recent gastrointestinal bleeding. In these patients, the activity of enoxaparin should be monitored by anti-factor Xa assay. Since enoxaparin is highly active against factor Xa, anti-factor Xa values that are within the determined therapeutic range are consistent with adequate drug efficacy and safety. Anti-factor Xa values that are elevated above the determined therapeutic range should alert clinicians to the potential for bleeding complications.

The treatment of patients with retroperitoneal hematoma following enoxaparin should be provided at an intensive care unit. The treatment and supportive care are multifactorial and include several steps: discontinuation of enoxaparin; administration of protamine to neutralize the anticoagulant effects of enoxaparin; the protamine dose depends upon the time elapsed since the last enoxaparin dose (1 mg of protamine *per* 1 mg of enoxaparin if <8 h, 0.5 mg of protamine *per* 1 mg of enoxaparin for 8-12 h, and no protamine if more than 12 h have passed since the last administered enoxaparin dose). Fresh frozen plasma and packed red blood cells should be administered, and hemoglobin and coagulation studies monitored serially. If these measures fail to stabilize the patient, surgical intervention may be needed. Some of these retroperitoneal hematomas may lead to abdominal compartment syndrome and only prompt surgical approach with exploration and evacuation of the hematoma may offer patient stabilization. Furthermore, the hematoma may, due to its location, compress surrounding structures and organs leading to various symptoms, which may also require surgery for resolution.

Conclusion

The clinical finding of a retroperitoneal hematoma must always lead to thorough evaluation of the patient and search for the etiology. Some causes require an emergency surgical procedure to localize and control the source of bleeding, such as some trauma or vascular patients. If no other evident causes of retroperitoneal bleeding are found in a patient on anticoagulation therapy, it must be suspected that the anticoagulation agent

has caused the bleed. Heparin and LMWH, either alone or in combination with anti-aggregation medications, may lead to severe retroperitoneal bleeding with a potentially fatal outcome. In these settings, the decision on the surgery is sometimes difficult and must be done with extreme caution. If the patient fails to stabilize with conservative treatment in intensive care unit settings, which includes discontinuation of anticoagulation medication, its neutralization if indicated, fresh frozen plasma, packed red blood cells, etc., surgical intervention may be required to evacuate the hematoma and, if possible, to locate the source of bleeding.

References

1. CHAN-TACK KM. Fatal spontaneous retroperitoneal hematoma secondary to enoxaparin. South Med J 2003;96:58-60.
2. COHEN M, DEMERS C, GURFINKEL EP *et al*. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease: Efficacy and safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. N Engl J Med 1997;337:447-52.
3. GURFINKEL EP, MANOS EJ, MEJAIL RI *et al*. Low molecular weight heparin *versus* regular heparin or aspirin in the treatment of unstable angina and silent ischemia. J Am Coll Cardiol 1995;26:313-8.
4. Thrombolysis in Myocardial Infarction (TIMI) IIA Trial Investigators. Dose-ranging trial of enoxaparin for unstable angina: results of TIMI IIA: The Thrombolysis in Myocardial Infarction (TIMI) IIA Trial Investigators. J Am Coll Cardiol 1997;29:1474-82.
5. ANTMAN EM, McCABE CH, GURFINKEL EP *et al*. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) IIB trial. Circulation 1999;100:1593-601.
6. ANTMAN EM, COHEN M, RADLEY D *et al*. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI IIB-ESSENCE meta-analysis. Circulation 1999;100:1602-8.
7. NOBLE S, SPENCER CM. Enoxaparin: a review of its clinical potential in the management of coronary artery disease. Drugs 1998;56:259-72.
8. HIRSH J, LEVINE MN. Low molecular weight heparin. Blood 1992;79:1-17.
9. FRYDMAN A. Low-molecular-weight heparins: an overview of their pharmacodynamics, pharmacokinetics and metabolism in humans. Haemostasis 1996;26 (Suppl 2):24-38.
10. WEITZ JI. Low-molecular-weight heparins. N Engl J Med 1997;337:688-98.
11. IVASCU FA, JANCZYK RJ, BAIR HA, BENDICK PJ, HOWELLS GA. Spontaneous retroperitoneal hemorrhage. Am J Surg 2005;189:345-7.
12. DABNEY A, BASTANI B. Enoxaparin-associated severe retroperitoneal bleeding and abdominal compartment syndrome: a report of two cases. Intensive Care Med 2001;27:1954-7.
13. SHERER DM, DAYAL AK, SCHWARTZ BM, OREN R, ABULAFIA O. Extensive spontaneous retroperitoneal hemorrhage: an unusual complication of heparin anticoagulation during pregnancy. J Maternal Fetal Med 1999;8:196-9.
14. Di ROSA C, VENORA S, MONTEROSSO N, La SPADA NM, VIOLA S. Retroperitoneal hematoma during heparin therapy. Comments on 3 cases. Minerva Chir 1997;52:493-7.
15. KATZ R, ADMON D, PODE D. Life-threatening retroperitoneal hematoma caused by anticoagulant therapy for myocardial infarction after SWL. J Endourol 1997;11:23-5.
16. FERNANDEZ RUIZ M, FERNANDEZ FERNANDEZ A, LASIERRA CIRUJEDA J, VILADES JUAN E, SANCHEZ BEORLEGUI J, POU SANTONJA G. Spontaneous retroperitoneal hemorrhage induced by anticoagulation treatment. Actas Urol Esp 1994;18:136-40.
17. BRUGGER HP, PIROVINO M. Frequency of severe abdominal wall hemorrhage with subcutaneous anticoagulation using calcium-heparin. Schweiz Med Wochenschr 1989;119:16-8.
18. MOSKOVITZ B, BRANER B, ENGEL A, KLEINHAUS U, LEVIN DR. Multifocal bleeding due to anticoagulant therapy. Urol Int 1988;43:53-5.
19. HOLM HA, ABILDGAARD U, KALVENES S. Heparin assays and bleeding complications in treatment of deep venous thrombosis with particular reference to retroperitoneal bleeding. Thromb Haemost 1985;53:278-81.
20. WILLBANKS OL, WILLBANKS SE. Femoral neuropathy due to retroperitoneal bleeding. A red herring in medicine complicates anticoagulant therapy and influences the Russian Communist Revolution (Crown Prince Alexis, Rasputin). Am J Surg 1983;145:193-8.
21. CISTERNINO SJ, NEIMAN HL, MALAVE SR Jr. Diagnosis of retroperitoneal hemorrhage by serial computed tomography. J Comput Assist Tomogr 1979;3:686-8.
22. WALLACH HW, OREN ME. Sciatic nerve compression during anticoagulation therapy. Computerized tomography aids in diagnosis. Arch Neurol 1979;36:448.
23. EMERY S, OCHOA J. Lumbar plexus neuropathy resulting from retroperitoneal hemorrhage. Muscle Nerve 1978;1:330-4.
24. BHASIN HK, DANA CL. Spontaneous retroperitoneal hemorrhage in chronically hemodialyzed patients. Nephron 1978;22:322-7.

25. STOREN EJ. Bilateral iliacus haematoma with femoral nerve palsy complicating anticoagulant therapy. Acta Chir Scand1978;144:181-3.
26. BRAUTBAR N, MENZ CL, WINSTON MA, SHINANBERGER JH. Retroperitoneal bleeding hemodialysis patients. A cause for morbidity and mortality. JAMA 1978;239:1530-1.
27. MANT MJ, O'BRIEN BD, THONG KL, HAMMOND GW, BIRTWHISTLE RV, GRACE MG. Haemorrhagic complications of heparin therapy. Lancet 1977; 1(8022): 1133-5.
28. CHIU WS. The syndrome of retroperitoneal hemorrhage and lumbar plexus neuropathy during anticoagulant therapy. South Med J 1976;69:595-9.

Sažetak

RETROPERITONEALNI HEMATOM UZROKOVAN ENOKSAPARINOM

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Retroperitonealni hematom može nastati uslijed traume, no također može nastati kao posljedica rupture aneurizme aorte ili zdjelične arterije, tumora ili antikoagulantne terapije. Retroperitonealno krvarenje opasno za život rijetka je komplikacija antikoagulantne terapije. Enoksaparin je heparin niske molekularne težine koji ima nekoliko prednosti u odnosu na nefrakcionirani heparin. Ipak, upotreba enoksaparina nije bez rizika te može dovesti do potencijalno smrtonosnog masivnog retroperitonealnog krvarenja. Prikazan je slučaj 76 godina stare bolesnice hospitalizirane zbog akutnog koronarnog sindroma, kod koje se razvio velik retroperitonealni hematom 5. dana terapije enoksaparinom. Upotreba enoksaparina u akutnom koronarnom sindromu, kao i u standardnoj tromboprofilaksi porasla je u zadnjem desetljeću, što može dovesti do povećane učestalosti retroperitonealnog krvarenja u kliničkom okruženju. Ova činjenica zahtijeva da liječnici budu krajnje oprezni i spremni na traženje simptoma i znakova retroperitonealnog krvarenja, te valja identificati skupine bolesnika s povišenim rizikom kod kojih je neophodno pažljivo praćenje antikoagulantne terapije. Liječenje bolesnika s retroperitonealnim hematomom mora se odvijati u jedinici intenzivnog liječenja. Enoksaparin se mora isključiti iz terapije, protamin se ordinira ovisno o vremenu proteklom od zadnje doze enoksaparina, svježe smrznuta plazma i koncentrat eritrocita se daju prema potrebi, a kirurško liječenje je potrebno kod bolesnika koji se ne stabiliziraju uz konzervativno liječenje.

Ključne riječi: *Antikoagulanti – štetni učinci; Enoksaparin – štetni učinci; Hematom – kemijski izazvan; Retroperitonealni prostor – kirurgija*