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Case Report

Catheter Directed Thrombolysis in Iliofemoral Deep Vein Thrombosis

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Background Iliofemoral deep vein thrombosis (IFDVT) is associated with more severe outflow obstruction which results in more severe DVT symptoms and late clinical sequelae. Despite anticoagulation therapy, IFDVT patients is still at risk to develop postthrombotic syndrome (PTS). Recent studies found that additional catheter-directed thrombolytic therapy may offer advantages in reducing PTS and maintaining venous patency. Several ongoing multi-center randomized controlled trials are expected to evaluate safety and efficacy of CDT in IFDVT patients, and define who will benefit most.

Case Illustration A 59-year-old male was presented with numbness, pain, and movement limitation in the left leg that were preceded by left leg swelling. Peripheral edema was found in both patient's leg but more prominent on the left side. Dupplex sonography revealed extensive soft thrombus from left iliac vein to left tibialis vein. Initial anticoagulation therapy took no effect to the thrombus. Catheter-directed thrombolysis was performed and provided satisfactory symptoms resolution as well as thrombus dissolution.

Summary A case of iliofemoral DVT has been reported. The present therapeutic strategy of anticoagulation therapy has not been proven to prevent PTS. CDT is an effective way in achieving clot lysis in acute thrombosis, and this may help to prevent PTS and subsequent ulceration. The potential benefits of therapy must be weighed carefully against the risk of bleeding. There are several ongoing RCTs that are awaited to help provide evidence on functional outcome after CDT and define who will benefit most.

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Keywords: iliofemoral, deep vein thrombosis,catheter-directed thrombolysis, postthrombotic syndrome, anticoagulation, management

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Laporan Kasus

Catheter Directed Thrombolysis pada Trombosis Vena Dalam Iliofemoral

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Latar Belakang : Trombosis vena dalam iliofemoral berhubungan dengan obstruksi aliran vena berat yang mengakibatkan gejala dan sekuele yang lebih berat. Pasien dengan kondisi ini memiliki risiko tinggi terjadinya sindrom pasca trombosis walaupun sudah mendapat terapi antikoagulan. Studi terkini menunjukkan bahwa terapi trombolisis dengan bantuan kateter memberikan manfaat dalam mengurangi sindrom pasca trombosis dan menjaga patensi vena. Beberapa *randomized controlled trials* besar sedang berjalan dan diharapkan dapat mengevaluasi keamanan dan efikasi tatalaksana ini pada pasien dengan trombosis vena dalam iliofemoral, dan juga menjelaskan siapa saja yang paling mendapat manfaat.

Ilustrasi Kasus : Seorang laki-laki 59 tahun datang dengan keluhan baal, nyeri, dan sulit menggerakan tungkai kiri yang didahului dengan kaki bengkak. Edema perifer ditemukan pada kedua tungkai pasien namun lebih berat pada tungkai kiri. Duplex sonografi menunjukkan trombus yang ekstensif dari vena iliaka hingga tibialis kiri. Terapi antikoagulan saja tidak memberi efek terhadap trombus. Trombolisis dengan bantuan kateter dilakukan dan memberikan perbaikan gejala dan pengurangan trombus yang bermakna.

Kesimpulan : Dilaporkan sebuah kasus trombosis vena dalam iliofemoral. Strategi tatalaksana terkini dengan antikoagulan tidak terbukti dalam hal mencegah sindrom pasca trombosis. Trombolisis dengan bantuan kateter adalah cara yang efektif dalam mencapai lisis bekuan darah pada trombosis akut, dan dapat membantu mencegah kejadian sindrom pasca trombosis. Potensi keuntungan dari terapi ini harus ditimbang baik-baik mengingat risiko perdarahan yang dapat terjadi. Saat ini terdapat beberapa *randomized controlled trials* besar yang sedang berjalan dan diharapkan dapat menyediakan basis bukti atas tatalaksana ini.

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Kata Kunci: iliofemoral, trombosis vena dalam, trombolisis dengan kateter,sindrom pasca trombosis, antikoagulan

Background

Deep vein thrombosis (DVT) is the third most common cardiovascular pathology, after coronary artery disease and stroke. In the United Kingdom, 1 in 1000 people

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develop DVT each year.[1] However, this figure would likely be lower in Asian.[2] Its natural history leads to thrombus extension, pulmonary embolism (PE), post-thrombotic syndrome, reccurent venous thrombosis, and mortality after acute DVT. The primary treatment of DVT is systemic anticoagulation, which reduce the risk of PE, and the extension and recurrence of venous thrombosis.

Iliofemoral DVT (IFDVT) is different from other more distal DVT because it is associated with more severe outflow obstruction which results in more severe DVT symptoms and late clinical sequelae.[3] Despite anticoagulation therapy, IFDVT patients is still at risk to develop postthrombotic syndrome (PTS) with a cumulative incidence of PTS of up to 50% 2 years post-DVT.[1 4] There is therefore a great need for improved therapy that can improve long-term functional outcome. Thrombolytic therapy for acute DVT is used as the initial treatment in order to clear the thrombus from the deep venous system. Recent studies found that additional thrombolytic therapy for rapid dissolution of thrombus in acute DVT may offer advantages in reducing PTS and maintaining venous patency. It does not replace anticoagulation for the treatment of these patients, since anticoagulation is important to prevent recurrence, thrombus extension and PE. Catheter-directed thrombolysis (CDT) is the preferred tehcnique since systemic thrombolytic therapy is associated with unacceptably high risk of bleeding.

However, there has not been any strong evidence to support this practice. Several ongoing multi-center randomized controlled trials are expected to evaluate safety and efficacy of CDT in IFDVT patients, and define who will benefit most.

Case Illustration

A 59-year-old male presented to emergency department with numbness, pain, and movement limitation in the left leg since six hours before admission. These complaints were preceded by left leg swelling since ten days before admission. However, there was no bluish discoloration. The patient had a history of dyspneu on exertion for the last 5 months that was worsening since two weeks before admission accompanied by orthopneu and paroxysmal nocturnal dyspneu. The patient had been treated at another hospital for one day but then return home at his own request one day before admission.

The patient was afebrile. Respiratory rate, blood pressure, and pulse were, respectively, 22 breaths/min, 88/56 mmHg, and 93 beats/min. There was raised jugular vein pressure of 5+3 mmHg. The cardiac auscultation revealed normal first and second heart sound with grade 3/6 pansystolic murmur in the apex area. Fine crackles were heard over the patient's lung bases. Liver was palpable two fingers under right costal margin. Peripheral edema was found in both patient's leg but more prominent on the left side.

His hemoglobin level was 10.8 g/dL, his white blood cell was 7,650 cells/mm^3, and his platelet count was 78,000 cells/mm^3. The findings of blood chemistries level were as follow; ureum 99 mg/dL, creatini 1.32 U/L, random blood glucose 157 mg/dL. His serum albumin level was 2.6 g/dL. Electrocardiography (ECG) examination showed sinus rythm with left QRS axis deviation (LAD). There was inverted T wave in V5, V6, I, and aVL. There was also evidence of bifasicular block. A chest x-ray revealed cariothoracic ratio of 68%, normal aortic and pulmonary segment, and flattening of the cardiac waist. There was sign of right pleural effusion. However, there was no sign of congestion nor infiltrate.

Echocardiography examination showed decreased left ventricular (LV) function with ejection fraction (EF) of 18%, decreased right ventricular (RV) function with TAPSE of 0.8 cm, regional wall motion abnormality, moderate to severe mitral regurgitation (MR), and moderate tricuspid regurgitation (TR) with mild pulmonary hypertension. Lower extremity dupplex sonography was performed in this patient. The investigation revealed soft thrombus from left iliac vein to left tibialis vein (**Figure 1A**). In contrast, there was no DVT in the right leg. Arterial flow was normal in both legs.

Patient was then diagnosed as ADHF ec old myocardial infarct, iliofemoral DVT, moderate-severe MR, moderate TR, mild PH, hyponatremia, hypokalemia, hypoalbuminemia. Initial treatment was given which included enoxaparin 2x60 mg SC (LWMH), furosemide 2x20 mg IV, simvastatin 1x20 mg, captopril 3x6,25 mg. Dupplex sonography examination was to be evaluated after three days of LWMH administration to evaluate treatment efficacy.

Despite LWMH treatment for three days, evaluation of the dupplex sonography showed no improvement on the DVT of the left leg. Leg circumference was also measured and showed

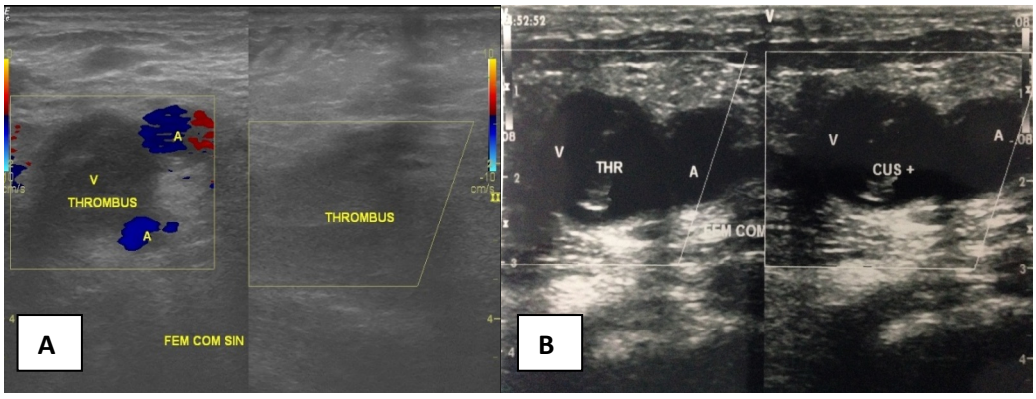

Figure 1. A.) Femoral dupplex sonography before CDT showed thrombus in left common femoral artery. B.) Femoral dupplex sonography after CDT showed thrombus dissolution.

enlargement of the left leg compared to the right leg. Catheter directed thrombolysis was then planned in order to obtain a better result.

On the fifth day of hospitalization, the symptoms had not subsided yet. CDT was prepared. CDT was then performed in the cathlab by an ultrasound-guided popliteal vein puncture approach. Venography showed soft thrombus from left popliteal vein to left iliac vein. Thrombusuction was performed in the left iliofemoral vein followed by alteplase administration through the catheter at a dose of 0,5 mg/hour. The catheter was left in place so the thrombolytic agent could be infused over the following 24 hours. LWMH was temporarily replaced with unfractionated heparin (UFH) at a dose of 100 unit/hour.

Venography evaluation was performed the following day. Thrombus was still visible on the examination, but venous flow had improved. Administration of alteplase (through the sheath) and UFH were continued for one more day. The symptoms, however, had significantly improved and the swelling on the left leg had reduced. On the following day, alteplase and UFH were discontinued and replace with enoxaparin 2x60 mg SC overlapping with oral warfarin. Dupplex sonography evaluation showed partial DVT in left common femoral vein (**Figure 1B**) while DVT in left external iliac vein, popliteal vein, and posterior tibial vein had disappeared. The patient was still hospitalized for the following week while the treatment was being optimized and the patient started mobilization. On the eighteenth day patient was discharged.

Discussion

Iliofemoral Deep Vein Thrombosis

Lower extremity DVT is typically divided into proximal DVT (highest thrombus extent in the popliteal vein or proximally), which carries an increased risk of symptomatic PE, and distal DVT (isolated calf vein thrombosis). However, it is suspected that proximal DVT patients with the most extensive thrombus burden may be at higher risk for poor clinical outcomes than those with less extensive, but still proximal, DVT.[3]

Iliofemoral DVT refers to complete or partial thrombosis of any part of the iliac vein or the common femoral vein, with or without involvement of other lower extremity veins or the IVC. When the femoral vein is thrombosed, the primary collateral route by which blood leaves the extremity is by drainage into the deep (profunda) femoral vein (which empties into the common femoral vein). As a result, venous thrombosis above the entry point of the deep femoral vein (ie, thrombosis in or above the common femoral vein) causes more severe outflow obstruction, which often results in more dramatic initial DVT symptoms and late clinical sequelae.

In a prospective study, patients with IFDVT had a 2.4-fold increased risk of recurrent VTE over 3 months of follow-up compared with patients with less extensive DVT.[5] In a prospective, multicenter, cohort study, patients with DVT involving the common femoral vein or iliac vein had significantly increased severity

of the postthrombotic syndrome (PTS) over 2 years of follow-up (P<0.001).[6]

IFDVT patients should receive initial anticoagulant therapy for the prevention of pulmonary embolism (PE) and recurrent DVT. American Heart Association (AHA) in its 2011 Scientific Statement recommeds intravenous UFH *(Class I; Level of Evidence A)*, UFH by subcutanous injection *(Class I; Level of Evidence B)*, an LMWH *(Class I; Level of Evidence A)*, or fondaparinux *(Class I; Level of Evidence A)* to be given to patients with IFDVT in the absence of suspected or proven heparininduced thrombocytopenia.

This patient had suffered from IFDVT with soft thrombus extending from left iliac vein to left tibialis vein. He therefore had a 2.4-fold increased risk of recurrent VTE over the next 3 months compared with patients with less extensive DVT. He also carried a significantly increased severity of the PTS over the next 2 years, while severe PTS leads to such a poor quality of life. LWMH which was given in this patient as an initial treatment was in line with AHA recommendation *(Class I; Level of Evidence A)*. However, despite initial anticoagulation, there had not been any improvement in symptoms nor femoral dupplex sonography evaluation.

Postthrombotic Syndrome

PTS is a relatively common and highly significant sequel of DVT. Eighty percent of symptomatic DVTs are above the knee (proximal), with a cumulative incidence of PTS of up to 50% 2 years post-DVT.[1,4] Severe PTS is reported in 50% of cases, and leg ulceration is present in up to 10% of patients.[1] These conditions have been a major factor impairing quality of life 2 years after an acute DVT.

PTS is caused by chronic venous hypertension secondary to venous reflux, venous obstruction, and valvular dysfunction. This manifests clinically as a heaviness, pain, edema, and venous claudication with skin damage. At the most severe form, PTS is associated with venous ulceration. Recurrent DVT is among the most powerful predictors and associated with an up to sixfold greater risk of PTS.[4] Recent research has shown that severe PTS leads to such a poor quality of life that it is comparable to experiencing angina, cancer, or congestive heart failure.[1]

Catheter-directed Thrombolysis

Catheter-directed thrombolysis (CDT) refers to the infusion of a thrombolytic agent directly into the venous thrombus via a multiple–side-hole catheter with the use of imaging guidance. In a 473 patient prospective multicenter registry, the use of urokinase CDT resulted in successful fibrinolysis in 88% of patients with acute IFDVT. CDT was more often successful in patients with recent (≤10 to 14 days) onset of symptoms.[3]

The use of endovascular thrombolysis as an adjunct to anticoagulant therapy is reasonable for patients with acute IFDVT associated with limb-threatening circulatory compromise, rapid thrombus extension despite anticoagulation, or symptomatic deterioration despite anticoagulation. The use of CDT or PCDT (along with anticoagulation) to achieve more rapid relief of presenting DVT symptoms and to prevent PTS can be considered as a first-line treatment in carefully selected patients with acute IFDVT. The potential benefits of therapy must be weighed carefully against the risk of bleeding since there are no published long-term outcome data from a multicenter RCT. Patient selection should be based on a careful assessment of the severity of DVT symptoms, comorbidities, life expectancy, and patient preferences for an aggressive treatment approach. In most IFDVT patients whose onset of DVT symptoms was >21 days before presentation or who are at high risk for bleeding complications, this approach should not be used *(Class III; Level of Evidence B)*. [3]

Patient presented with onset of symptoms <21 days. Initial anticoagulation treatment had been given but had not shown to be effective, making CDT reasonable in this patient. CDT was expected to acheive better recanalization in thrombosed vein, and therefore gave a better symptoms resolution and reduced risk of late clinical sequelae. Despite risk of bleeding, the possible benefit is considered to outweigh this risk.

CDT vs Anticoagulant Alone

Despite the lack of conclusive evidence, some data support the argument that DVT treated with anticoagulation alone results in a high risk of PTS 5-10 years later. Active removal of the thrombus with surgery or catheter-directed lysis clears the thrombus relatively quickly and improves preservation of valvular function while reducing the incidence and severity of PTS.

In a small (n=35) RCT, Elsharawy et al[7] reported that streptokinase CDT plus anticoagulation yielded a higher rate of normal physiological venous function (72%

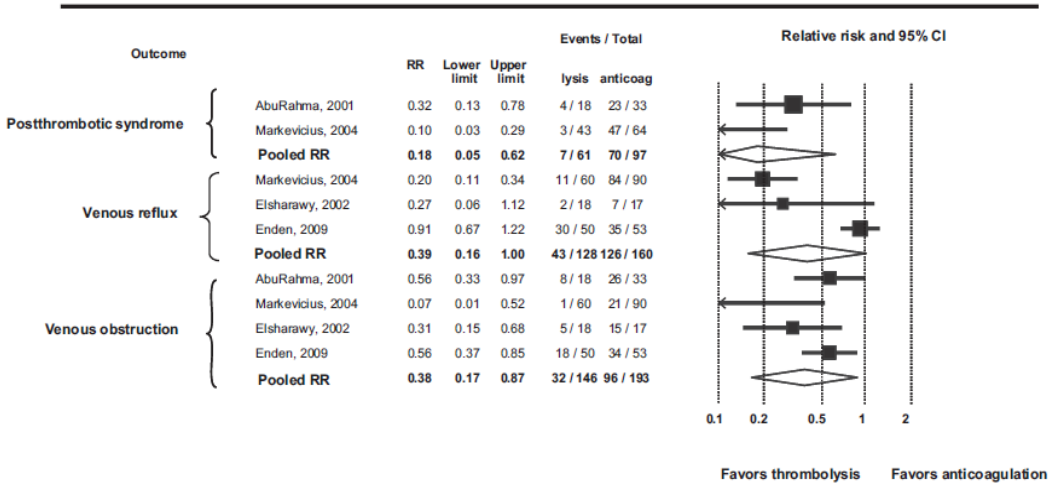

Figure 2. Meta-analysis of pharmacologic CDT vs systemic anticoagulation.[9]

versus 12%, *P*<0.001) and less valvular reflux (11% versus 41%, *P*=0.04) at 6 months than anticoagulation alone. In an open-label multicenter RCT of 118 IFDVT patients, Enden et al[8] found that alteplase CDT plus anticoagulation resulted in better 6-month iliofemoral vein segment patency (64% versus 36%, *P*=0.004), less functional venous obstruction (20% versus 49%, *P*=0.004), and no difference in femoropopliteal venous reflux (60% versus 66%, *P*=0.53) compared with anticoagulant alone. In this study, in which alteplase infusions of 0.01 mg . kg^{-1} . h^{-1} were used, CDT plus anticoagulation was associated with major bleeding in 2.0% (major bleeding occurred in 1.7% of patients treated with anticoagulant alone).

In a prospective single-centre clinical series of 101 acute IFVT patients treated with CDT, Baekgaard et al[10] found that open veins without reflux were achieved in 82% of the affected lower extremities after 6 years without any mortality, or new PE and only a few cases of new DVT. For patients strictly following the protocol, the result was 86%.

In a meta-analysis (Figure 2) comparing efficay of pharmacologic CDT to systemic anticoagulation in acute IFDVT patients, Casey et al[9] found that pharmacologic CDT was associated with statistically significant reduction in the risk of PTS (RR, 0.19; 95% CI, 0.07-0.48; I^2 = 64%) and venous obstruction (RR, 0.38; 95% CI, 0.18-0.37; I^2 = 46%), and a trend for reduction in the risk of venous reflux (RR, 0.39; 95% CI, 0.16-1.00; I^2 = 92%). On the other hand, data regarding patient-important outcomes such as death, PE, recurrence of DVT, hospitalization, and disability, were inconclusive.

Percutaneous Mechanical, and Pharmacomechanical Thrombolysis

The adjunctive use of mechanical thecniques is has became the standard for catheter-based management of extensive venous thrombosis. Percutaneous mechanical thrombectomy (PMT) refers to the use of a catheter-based device that contributes to thrombus removal via mechanical thrombus fragmentation or aspiration. There is no evidence that any device is effective as a stand-alone therapy for DVT, and use of some devices without additional thrombolytic agent administration may be associated with symptomatic PE. However, some studies suggest that pharmacomechanical CDT (PCDT, or the combined use of CDT and PMT), provides comparable clot-removal efficacy as drug only CDT but with major (40% to 50%) reductions in the needed thrombolytic drug dose, infusion time, and hospital resource use. However, there are no strong prospective studies to validate this finding, and there may be risks associated with greater mechanical manipulation of the thrombus and vein. If PCDT fails, surgical thrombectomy is a valid alternative, primarily in acute IFDVT. No PCDT studies have systematically evaluated recurrent DVT and PTS.[3]

Use of Other Satndard DVT Treatments in Patients Undergoing CDT or PCDT

Before and after CDT or PCDT, therapeutic-level anticoagulation should be used with similar dosing, treatment duration, and monitoring as for IFDVT patients who are not undergoing thrombolysis. During CDT infusions, reduced-dose UFH may be safer than therapeutic-level UFH. However, during single-session PCDT or stand-alone PMT, both of which involve greater mechanical manipulation, it may be reasonable to use therapeutic-level UFH. LMWH has also been used along with PCDT, but there are no studies to support this practice.

Thrombosuction was performed in this patient followed by alteplase infusion for up to 2 days. During alteplase infusion, LWMH was changed with reduced-dose UFH (100 unit/hour) to minimize the risk of bleeding. After finishing alteplase infusion, UFH was changed again to therapeutic level LWMH of 2x60 mg and continued for several days before overlapped with oral anticoagulation. Despite lack of strong evidence regarding this practice, it had been shown to be effective in this patient.

Summary

A case of iliofemoral DVT has been reported. The present therapeutic strategy of anticoagulation therapy has not been proven to prevent PTS, primarily in acute IFDVT. CDT is an effective way in achieving clot lysis in acute IFDVT, and this may help to prevent PTS and subsequent ulceration. The potential benefits of therapy must be weighed carefully against the risk of bleeding. Several ongoing multi-center randomized controlled trials are expected to provide information about safety and efficacy of CDT in IFDVT patients, and define who will benefit most.

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