

ORIGINAL ARTICLE

Medicine Science 2021;10(4):1452-6

The efficacy of Pharmacomechanical catheter-directed thrombolysis in patients with concomitant deep vein thrombosis and pulmonary embolism: A retrospective analysis of 26 patients

 Emced Khalil*Ordu University, Training and Research Hospital, Ordu, Turkey*

Received 10 September 2021; Accepted 02 October 2021

Available online 24.11.2021 with doi: 10.5455/medscience.2021.09.286

Copyright@Author(s) - Available online at www.medicinescience.org

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.



Abstract

This study aimed to analyze the impact of pharmacomechanical catheter-directed thrombolysis (PCDT) on venous patency, pulmonary artery systolic pressure, O₂ saturation and in-hospital mortality in patients admitted for deep vein thrombosis (DVT) and concomitant pulmonary embolism (PE).

Twenty-six patients presenting with DVT and concomitant non-massive PE were analyzed in a retrospective manner. All subjects underwent PCDT with urokinase. The primary end-point of this study was the difference in pre-and post PCDT sPAP and O₂ saturation. Duplex ultrasonography performed before discharge revealed complete recanalization of the compromised vein in 21 (80%) of the subjects. Duplex ultrasonography performed 3 months after discharge showed restenosis of the compromised vein in only two patients (8%). There was partial recanalization in 5 patients (20%). A significant improvement in SaO₂ was observed following the infusion of urokinase compared to baseline values (94.5±1.1 % vs. 98.6±0.5 %, p<0.001). The presenting sPAP was 48.6±7.9 mmHg and the final sPAP measured before discharge was 28.4±2.7 mmHg (p<0.001). Recurrent PE, major bleeding and mortality was not observed in any of the subjects. Findings of this study including patients with concomitant DVT and non-massive PE has shown that PCDT provides excellent result concerning venous patency, oxygenation and pulmonary hemodynamics in the acute and short-term setting.

Keywords: Venous thromboembolism, pulmonary embolism, catheter-directed thrombolysis, pulmonary artery pressure

Introduction

Acute venous thromboembolism (VTE) is a potentially life-threatening cardiovascular disorder which may lead to significant morbidity and mortality. The term VTE encompasses a spectrum of diseases including deep vein thrombosis (DVT) and its most serious complication, pulmonary embolism (PE). About 50% of the DVTs of the proximal lower extremity veins eventually lead to PE. In the United States, two million individuals are diagnosed with DVT annually and 500,000 to 600,000 of these subjects present with PE [1,2]. It has been reported that VTE is responsible for 100,000 annual deaths and is the third common cause of deaths in United States [3]. Inherited clotting disorders including factor V Leiden, prothrombin gene mutation, antithrombin deficiency, protein

C deficiency, protein S deficiency, and hyperhomocysteinemia, and acquired conditions such as surgery, trauma, prolonged immobility, estrogen use, pregnancy, and presence of venous catheters are predisposing risk factors for the development of VTE [4].

Systemic thrombolysis has been recommended for PE presenting with massive PE or those with hemodynamic compromise [5]. Pharmacomechanical catheter-directed thrombolysis (PCDT) through a multi-sidehole catheter placed into the thrombus has been recently used for the resolution of thrombus located in the pulmonary vasculature. A number of studies have shown the efficacy of PCDT in removing thrombus and reducing the risk of post-thrombotic syndrome [6,7]. However, there is still paucity of evidence concerning the efficacy of PCDT in patients with DVT and concomitant PE.

This study aimed to analyze the impact of PCDT on venous patency, pulmonary artery systolic pressure, O₂ saturation and in-hospital mortality in patients admitted for DVT and concomitant PE.

*Corresponding Author: Emced Khalil, Ordu University, Training and Research Hospital, Ordu, Turkey, E-mail: emjedkhalil@gmail.com

Materials and Methods

Study population

All patients admitted with DVT in our institute between September 2018 and October 2020 were screened in a retrospective manner. Ethical approval was obtained from the Ordu University Clinical Research Ethics Committee (no: 2021/112). Those with concomitant DVT and pulmonary embolism were included in the final analysis. Patients >75 years and < 18 years, those with known allergy to urokinase, absolute contraindications for thrombolytics, and subjects with symptoms lasting >14 days were excluded. Only patients with concomitant PE and iliofemoral or femoropopliteal DVT were included in this analysis. In addition, patients with hemodynamic instability and those with massive pulmonary embolism on thorax computed tomography were excluded. Written informed consent was obtained from all patients. The study was approved by the local ethics committee and was conducted in accordance with the Helsinki Declaration.

Pulmonary embolism was diagnosed by CT angiography, and DVT was diagnosed by duplex ultrasonography. All subjects underwent transthoracic echocardiography upon admission and prior to discharge. Systolic pulmonary artery pressure (sPAP) was calculated through the peak tricuspid regurgitation velocity using the following formula: $sPAP = 4v^2$ (v = peak tricuspid regurgitation velocity).

Catheter-directed thrombolysis

Following the insertion of an 6F introducer into the contralateral femoral vein with ultrasound guidance, a temporary inferior vena cava (IVC) filter (Reya Venocat, Biolas, Ankara, Turkey) was deployed to the infrarenal segment of the IVC to prevent the further embolization of the clot to the pulmonary venous system. Afterwards, the patient was taken to supine position and another 6F intraducer was inserted into the ipsilateral popliteal vein with ultrasound guidance. A 0.018-inch hydrophilic guidewire (Terumo glidewire, NJ, USA) was used to pass the thrombotic lesion. A catheter with multiple side holes (UniFuse Infusion Catheter; Angiodynamics, Latham, NY, USA) was then advanced over this guidewire. 200 000 IU of urokinase was administered over 15 to 20 minutes from the side-holes of this multi-hole catheter. Percutaneous balloon dilatation and stenting of the iliac vein was reserved for the patient with a >50% residual stenosis of the iliac vein on control venography despite thrombolytic administration. An aspiration maneuver was routinely performed to eliminate the potential thrombotic debris in the femoral and iliac vein (Figure 1). The IVC filter was then removed under fluoroscopic guidance. Following the completion of the procedure a temporary venous catheter was replaced with the intraducer in the popliteal vein and 0.01 mg/kg urokinase infusion was continued over 48 hours. All patients received dose adjusted unfractionated heparin (target aPTT: 2 times of the baseline aPTT) throughout the hospitalization. Temporary caval filter and venous catheter was removed 48 hours after the procedure.

After completion of treatments the patients were discharged with a prescription for coumadin or rivaroxaban and compression stockings. The use of compression stockings was described to each patient. We scheduled regular follow-up studies for a period of one

year for all subjects. If the first year of follow-up is uneventful, the majority of patients are switched to aspirin treatment.

The primary end-point of this study was the difference in pre-and post PCDT sPAP and O_2 saturation. Mortality rate and venous patency at discharge were also analyzed.

Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check, the Shapiro-Wilk test was used. Data are given as mean $\pm$ standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. The paired samples t-test was used for comparison of pre-and post PCDT variables. P values of <0.05 were accepted to be statistically significant.



Figure 1A. Complete occlusion of right superficial femoral vein

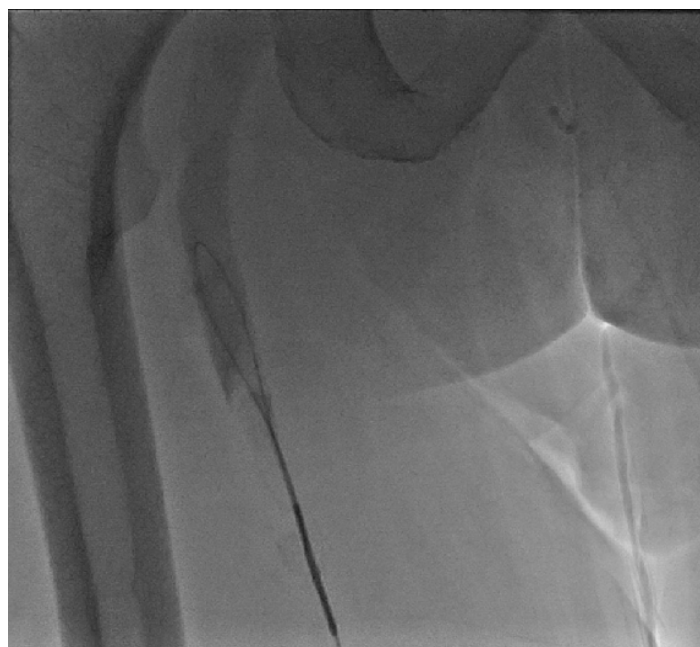


Figure 1B. Pharmacomechanical catheter-directed thrombolysis



Figure. 1C Complete resolution of the thrombus

Results

A total of 26 patients (48% male, mean age: 56 ± 9) were available for the final analysis. Clinical characteristics and demographic features of the study group are given in Table 1. Among our patients, 18 (69%) were acute DVT and the rest were subacute DVT. Eleven (42%) of the subjects had proximal DVT and 11 (42%) had extensive DVT (popliteal, superficial femoral and iliac vein). Duplex ultrasonography performed before discharge revealed complete recanalization of the compromised vein in 21 (80%) of the subjects. Duplex ultrasonography performed 3 months after discharge showed restenosis of the compromised vein in only two patients (8%). There was partial recanalization in 5 patients (20%). A significant improvement in SaO₂ was observed following the infusion of urokinase compared to baseline values (94.5 ± 1.1 % vs. 98.6 ± 0.5 %, p<0.001). The presenting sPAP was 48.6 ± 7.9 mmHg and the final sPAP measured before discharge was 28.4 ± 2.7 mmHg (p<0.001) (Figure 2). At the same time, a decrease in the diameter of the right ventricle was observed in postoperative control thorax CT angiography (Figure 3). Recurrent PE, major bleeding and mortality were not observed in any of the subjects (Table 2)



Figure 2A. Pulmonary artery thrombus (left pulmonary artery diameter appears large

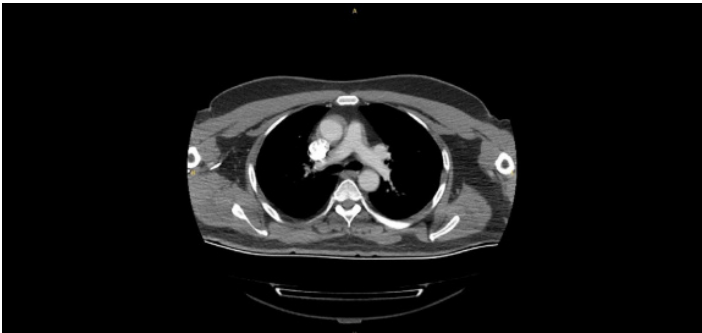


Figure 2B. Resolution of thrombotic material after PDCT (left pulmonary artery diameter returns to normal



Figure 3A. Right ventricular enlargement due to pulmonary embolism



Figure 3B. Right ventricular diameter after PDCT

Table 1. Clinical characteristics of the study group Characteristics	
	n=26
Age, years	56 ± 9
Gender, male	12 (46%)
Proximal DVT, n	11 (42%)
Extensive DVT, n	11 (42%)
Acute DVT, n	18 (69%)
Diabetes, n	6 (23%)
Smoking, n	8 (30%)
Prolonged immobilization, n	8 (30%)
Previous major surgery, n	6 (23%)
Pulmonary thrombus localization	
Right main pulmonayr artery, n	14 (53.8%)
Left main pulmonary artery, n	6 (23%)
Subsegmental , n	6 (23%)

Table 2. Pre and Post-operatif SaO₂ and Spap values

	Baseline	After Treatment	P value
SaO ₂	94.5±1.1	98.6±0.5	<0.001
sPAP	48.6±7.9	28.4 ±2.7	<0.001

Discussion

This study aimed to investigate acute and short-term effects of PCDT on sPAP, SaO₂ and venous patency in patients presenting with DVT and PE. Our findings indicate that PCDT leads to an acute improvement in SaO₂, and sPAP and also restores venous flow in majority of the patients with concomitant DVT and PE. Short-term results of duplex ultrasound reveal that venous patency is maintained in the majority of subjects 3 months after the procedure. These findings indicate that PCDT provides excellent improvement in not only venous patency but also clinical characteristics and hemodynamics of the patients with concomitant DVT and non-massive PE.

Venous thromboembolism can be briefly described as the partial or total occlusion of venous flow by thrombotic material, and comprises DVT and PE which are potentially lethal [8]. A huge majority of VTE-related deaths result from PE. Pelvic or leg veins are the most frequently responsible veins for DVTs progressing to PE [9]. Dislodgment of the clot from the pelvic or leg veins and its travel to the right heart and pulmonary venous system through the veins lead to PE. Population-based studies have shown that 10% to 30% of the patients with VTE die within the first month of presentation [10]. In addition to the morbidity and mortality resulting from VTE, it also causes a heavy burden on the healthcare system due to increased healthcare costs as a consequence of chronic venous insufficiency and post-thrombotic syndrome as well as pulmonary hypertension and right heart failure [10]. Timely recognition and treatment of the VTE is therefore crucial to prevent acute and chronic complications of DVT and PE. Systemic thrombolysis consisting of intravenous injection of a thrombolytic agent, particularly tissue plasminogen activator (tPA), has been shown to be more effective than heparin at restoring venous patency after DVT [11,12]. However, systemic thrombolysis occasionally prevents the enlargement of the pre-existing clot and protects against new thrombosis. On the other hand, systemic thrombolysis with intravenous tPA carries a 3–6% risk of intracranial hemorrhage in this patient subgroup [13].

The catheter-directed approach, which involves percutaneous introduction of an infusion catheter into the thrombus and prolonged infusion of the thrombolytic agent for at least 24 hours is increasingly utilized in cases of VTE due to better venous patency and reduced complication rates [14-16]. With this method, the thrombolytic agent is delivered only to the exposed surface of the clot with systemic thrombolysis and the vast majority of the thrombolytic agent bypasses the clot through the venous collaterals which form within hours after occlusion. Total dose of the thrombolytic agent and prolonged infusion, in addition to local administration with CDT, are believed to reduce the risk of systemic bleeding while improving the penetration of the lytic agent into the clot [17-19].

Several studies have shown promising results concerning

post-thrombotic syndrome and recurrent VTE with CDT. The randomized prospective CaVenT study has shown that CDT provides a 14.4% absolute risk reduction at 2 years follow-up and 28% absolute risk reduction at 5 years follow-up for post-thrombotic syndrome compared to standard treatment with anticoagulation only [20]. In addition, despite reports showing that the CDT approach is a safe and effective treatment for DVT, some authors have emphasized the importance of access route to ensure success without complications [21]. However, it remains unclear whether CDT improves oxygenation and pulmonary hemodynamics in patients with concomitant acute DVT and PE. Our findings indicate that CDT provides complete recanalization of the venous flow in 80% of the patients with DVT. The rest 20% had partial recanalization. Moreover, a significant improvement was observed in SaO₂ and sPAP in our study population presenting with non-massive PE in addition to the DVT. Major systemic bleeding, mortality and recurrence of the VTE was not observed in any of the study subjects at 3-months follow up.

Conclusion

In conclusion, findings of this study including patients with concomitant DVT and non-massive PE has shown that PCDT provides excellent results in terms of venous patency, oxygenation and pulmonary hemodynamics in the acute and short-term setting. Nevertheless, larger prospective, randomized, and controlled trials are required to clearly address the role of PCDT in this subgroup of patients.

Our study showed that CRP/ALB ratio measured at the postoperative 3. day, together with elevated CRP levels, were independent predictors of major complications after gastrectomy for gastric cancer. Therefore, the easily calculated CRP/ALB ratio may allow estimation of the risk of major complications and can provide valuable information at the postoperative early follow-up period.

Conflict of interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Financial Disclosure

All authors declare no financial support.

Ethical approval

Ethical approval was obtained from the Ordu University Clinical Research Ethics Committee (no: 2021/112).

References

- Giordano NJ, Jansson PS, Young MN, et al. Epidemiology, Pathophysiology, Stratification, and Natural History of Pulmonary Embolism. *Tech Vasc Interv Radiol.* 2017;20:135-40.
- Anderson Jr FA, Zayaruzny M, Heit JA, et al. Estimated annual numbers of US acute-care hospital patients at risk for venous thromboembolism. *Am J Hematol.* 2007;82:777-82.
- Smith SB, Geske JB, Kathuria P, et al. Analysis of national trends in admissions for pulmonary embolism. *Chest.* 2016;150:35-45.
- Crous-Bou M, Harrington LB, Kabrhel C. Environmental and Genetic Risk Factors Associated with Venous Thromboembolism. *Semin Thromb Hemost.* 2016;42:808-20.
- Tritschler T, Kraaijpoel N, Le Gal G, et al. Venous thromboembolism: advances in diagnosis and treatment. *JAMA.* 2018;320:1583-94.
- Comerota AJ, Grewal N, Martinez JT, et al. Postthrombotic morbidity

- correlates with residual thrombus following catheter-directed thrombolysis for iliofemoral deep vein thrombosis. *J Vasc Surg.* 2012;55:768-73.
7. Baekgaard N, Broholm R, Just S, Jet al. Long-term results using catheter-directed thrombolysis in 103 lower limbs with acute iliofemoral venous thrombosis. *Eur J Vasc Endovasc Surg.* 2010;39:112-7.
 8. Schulman S, Ageno W, Konstantinides SV. Venous thromboembolism: Past, present and future. *Thromb Haemost.* 2017;117:1219-29.
 9. Battinelli EM, Murphy DL, Connors JM. Venous thromboembolism overview. *Hematol Oncol Clin North Am.* 2012;26:345-67, ix.
 10. Beckman MG, Hooper WC, Critchley SE, et al. Venous thromboembolism: a public health concern. *Am J Prev Med.* 2010;38:S495-501.
 11. Forster A, Wells P. Tissue plasminogen activator for the treatment of deep venous thrombosis of the lower extremity: a systematic review. *Chest.* 2001;119:572-9.
 12. Turpie AG, Levine MN, Hirsh J, et al. Tissue plasminogen activator (rt-PA) vs heparin in deep vein thrombosis. Results of a randomized trial. *Chest.* 1990;97:172-5.
 13. Miller DJ, Simpson JR, Silver B. Safety of thrombolysis in acute ischemic stroke: a review of complications, risk factors, and newer technologies. *Neurohospitalist.* 2011;1:138-47.
 14. Chiarello MA, Sista AK. Catheter-Directed Thrombolysis for Submassive Pulmonary Embolism. *Semin Intervent Radiol.* 2018;35:122-8.
 15. Güneş Y, Sincer I, Erdal E. Catheter-directed intra-arterial thrombolysis for lower extremity arterial occlusions. *Anatol J Cardiol.* 2019;22:54-9.
 16. Avgerinos ED, Saadeddin Z, Abou Ali AN, et al. A meta-analysis of outcomes of catheter-directed thrombolysis for high- and intermediate-risk pulmonary embolism. *J Vasc Surg Venous Lymphat Disord.* 2018;6:530-40.
 17. Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis. *Cochrane Database Syst Rev.* 2014:Cd002783.
 18. Kucher N, Boekstegers P, Müller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation.* 2014;129:479-86.
 19. Avgerinos ED, Chaer RA. The ATTRACT iveness of catheter-directed thrombolysis. *J Vasc Surg Venous Lymphat Disord.* 2018;6:303.
 20. Enden T, Haig Y, Kløw NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet.* 2012;379:31-8.
 21. Baran Ç, Çakıcı M, Özçınar E, et al. Comparison of different venous accesses through catheter-directed thrombolysis procedures in patients with acute deep vein thrombosis. *Turk J Vasc Surg.* 2017;26:080-4.