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Orıgınal Article

Comparative efficacy of long-term anticoagulation in patients with iliofemoral acute deep vein thrombosis treated with pharmaco-mechanical catheter-directed thrombolysis

Farmakomekanik kateter aracılı tromboliz ile tedavi edilen akut ilyofemoral derin ven trombozlu hastalarda uzun süreli antikoagülasyonun karşılaştırmalı etkinliği

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ABSTRACT

Aim: We aimed to compare the stability of pharmacologic profile, rate of symptomatic recurrent venous thromboembolism, major bleeding and the net clinical benefit on the regimen with vitamin K antagonist (VKA), low molecular weight heparin (LMWH) and direct oral anticoagulant (DOAC) for long-term anticoagulation in patients undergoing pharmaco-mechanical catheter-directed thrombolysis (PMCDT) for the treatment of deep vein thrombosis (DVT).

Material and Methods: During the period from January 2019 until June 2019, data of 112 patients who underwent PMCDT for the treatment of acute iliofemoral DVT in our institution with long-term apixaban (Pfizer, Turkey) medication were prospectively collected (Group 1-DOAC). Data of control groups within January 2017- December 2018 period were collected retrospectively. Control groups consisted of PMCDT patients with extended LMWH (Tinzaparin, Abdi Ibrahim Pharma, Turkey) treatment (Group 2-LMWH; N=119) and with VKA (Coumadin, Eczacibasi Pharma, Turkey) treatment (Group 3- Control; N=111). Results: Patients treated with VKA showed a significant incompliance starting from third month up to one year. Patency rate diminished significantly below 70%. 32% of VKA patients were out of therapeutic range even in the first month leading to 40% at the end of the year. Likert Scale, Villalta/VCCS and VEINES-QOL-Sym scores confirmed the clinical data.

Conclusion: This study highlights the potential role of DOAC as a reasonable alternative to VKAs/LMWH in the long-term anticoagulation strategy for DVT. We await larger clinical trials to support these findings and establish the role of DOAC as the standard of care for patients with DVT.

Keywords: deep vein thrombosis; venous thromboembolism; pharmaco-mechanical catheter-directed thrombolysis; vitamin k antagonists; low molecular weight heparin; direct oral anticoagulants

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Öz

Amaç: Derin ven trombozu (DVT) tedavisi için farmakomekanik kateter aracılı trombliz (FMKAT) yapılan hastalarda; vitamin K antagonistlerini(VKA), düşük molekül ağırlıklı heparini (DMAH) ve direk oral antikoagülan ajanları (DOAK) farmakolojik profilllerinin stabilitesine, semptomatik rekürren venöz tromboembolik, major kanama ve klinik fayda oranlarına göre karşılaştırmayı hedefledik.

Gereç ve Yöntemler: Ocak 2019 ile Haziran 2019 tarihleri arasında kliniğimizde akut iliofemoral DVT tanısı ile FMKAT yapılan ve uzun dönemde apiksaban (Pfizer, Türkiye) tedavisi ile takip edilen 112 hastanın verileri toplandı. (Grup 1- DOAK) Kontrol gruplarının dataları ise Ocak 2017 ile Aralık 2018 tarihleri arasında yine kliniğimizde akut iliofemoral DVT tanısı ile FMKAT yapılan ve uzun dönemde DMAH (Tinzaparin, Abdi Ibrahim İlaç, Türkiye) tedavisi (Group 2-DMAH; N=119) ve VKA(Coumadin, Eczacibasi İlaç, Türkiye) tedavisi (Grup 3- Kontrol N=111) hastalardan toplandı.

Bulgular: VKA tedavisi ile takip edilen hastalarda 3.aydan başlayıp 1 yıla kadar ki takip sürelerinde belirgin oranda tedaviye uyumsuzluk saptandı. Patensi oranları %70'in altındaydı. VKA hastalarının %32'si yıl sonunda terapötik dozlarda değildi. Likert skalaları, Villalta/VCCS ve VEINES-QOL-Sym skorlama sistemlerinin sonuçları klinik sonuçlar ile uyumluydu.

Sonuç: Bu çalışma DOAK'ların DVT hastalarında tedavi için DMAH ve VKA'lara uygun bir seçenek olduğunu gösterdi. DOAK tedavisinin DVT hastalarında standart bir tedavi olarak tercih edilebilmesi için bizim elde ettiğimiz sonuçları destekleyecek geniş kapsamlı klinik çalışmaların sonuçları beklenmektedir.

Anahtar kelimeler: derin ven trombozu; venöz tromboembolizm; farmakomekanik katater araçılı tromboliz; vitamin k antagonistleri; düşük molekül ağırlıklı heparin; direk oral antikoagülanlar

Introduction

Venous thromboembolism (VTE), which comprises deep venous thrombosis (DVT) and pulmonary embolism (PE), is a significant cause of morbidity and mortality worldwide.

Standard treatment of VTE, using low-molecular-weight heparin (LMWH) overlapped with vitamin K antagonists (VKAs), is effective but requires frequent laboratory monitoring and has the potential for multiple drug and dietary interactions. In recent years, novel treatment strategies with direct oral anticoagulants (DOACs) have been increasing in popularity and availability [1,2].

Post-thrombotic syndrome (PTS) is a chronic complication of DVT, which develops in 20% to 50% of patients. PTS arises from a combination of venous outflow obstruction, venous hypertension, valvular incompetence, and secondary calf muscle pump dysfunction leading to ambulatory venous hypertension. PTS results in substantially increased healthcare costs and significantly impaired quality of life. Little is known about effects of different anticoagulants on PTS development [3].

Several studies have shown that average patients spend more than 20 % of their time below the therapeutic range during treatment with VKA. It is confirmed that the therapeutic intensity of VKA treatment is an essential determinant for development of PTS since the time spent beneath the therapeutic range is associated with PTS development [4-6]. Furthermore, a systematic review found a significantly lower rate of PTS in patients treated with LMWH alone compared to patient treated with LMWH followed by VKA [7].

DOACs approved for treatment of VTE have a stable pharmacological profile and thereby could overcome the disadvantages of VKA. However, the risk of PTS in DVT patients treated with DOACs is unknown [8].

Pharmaco-mechanical catheter-directed thrombolysis (PMCDT) refers to mechanical thrombus disruption concomitant with fibrinolytic therapy, offering a lower dosage of thrombolytic agent, a shorter procedure and an improvement in outcomes. PMCDT is an alternative option for treatment of DVT and decreasing the incidence of PTS. The patients who are most likely to benefit have iliofemoral DVT, symptoms for <14 days, good functional status, life expectancy of >1 year, and a low risk of bleeding. More rapid thrombus resolution is associated with the improved valvular function [9-10].

Long-term treatment is preconized in a significant proportion of the patients with VTE. However, limited direct/indirect comparisons are available to appropriately weight the benefit/risk ratio of the diverse treatments available.

We aimed to compare the stability of pharmacologic profile,

rate of symptomatic recurrent VTE, major bleeding (MB) and the net clinical benefit on VKA, LMWH and DOAC for extended anticoagulation. We chose patients undergoing PMCDT for treatment of DVT, since it is verified to clean all thrombus load by angiography/ultrasound at the end of the procedure and start comparison of three pharmacologic regimens in totally cleaned DVT confirmed at baseline.

Material and Methods

The study was approved by Clinical Research Ethics Committee of Numune Training & Research Hospital, Ankara- Turkey (25.04.2018/1917). Patient informed consent forms were collected in all cases.

Study Design and Patient Selection

During the period from January 2019 until June 2019, data of 112 patients who underwent PMCDT for the treatment of acute iliofemoral DVT in our institution with long-term apixaban (Eliquis, Pfizer, Turkey) medication were prospectively collected (Group 1-DOAC). Data of control groups within January 2017-December 2018 period were collected retrospectively. Control groups consisted of PMCDT patients with extended LMWH (Tinzaparin-Innohep, Abdi Ibrahim Pharma, Turkey) treatment (Group 2-LMWH; N=119) and with VKA (Warfarin-Coumadin, Eczacibasi Pharma, Turkey) treatment (Group 3- Control; N=111).

The use of propensity score matching addressed treatment selection bias. Patients were matched by propensity score for age, gender, BMI, and Wells score to have 75 patients in each group.

Inclusion criteria included acute presentation (<14 days), phlegmasia cerulea dolens, extensive proximal DVT + femoropopliteal DVT, life-expactancy > 1 year and low risk of bleeding. Exclusion criteria consisted of low life expectancy (terminally ill patients), renal failure (GFR < 60 mL/min), contraindication to anticoagulation or tPA, isolated femoro-popliteal DVT, subacute (14-28 days) or chronic (>28 days) DVT, severe dyspnea or severe acute medical illness precluding safe procedure, asymptomatic DVT, active gastrointestinal bleeding, stenosis needing stent, success rate <90%, in-hospital recurrent event and malignancy.

All patients were symptomatic upon admission and after calculating the Wells score [11], venous duplex ultrasonography was performed for initial diagnosis. The extent of the thrombus and the calculation of the Marder score [12] was evaluated and calculated by initial contrast venography.

Technique (PMCDT)

All procedures were performed under local anesthesia in single-session in the angio-suite and all vascular interventions were performed under doppler ultrasound guidance. A retrievable thrombolysis catheter with VCI filter (TPSTM, Thrombolysis Catheter, 50 cm, 30 mm filter diameter, 8F, Invamed, Ankara, Turkey) was placed caudal to the renal vein origins via contralateral common femoral vein. Then an ipsilateral retrograde approach via popliteal vein or posterior tibial vein was accessed, and a 7F introducer sheath was inserted.

Percutaneous mechanical thrombectomy device (MantisTM 7F, 90 cm, Invamed, Ankara, Turkey) was inserted, activated and advanced in an antegrade fashion. In every 3- to 5- minute, PMCDT was temporarily deactivated and withdrawn. The macerated thrombus materials and residual thrombolytic agents were suctioned by the help of an automatic aspiration system (Dovi aspiration thrombectomy device, 8F, 90 cm, Invamed, Ankara, Turkey) that was advanced over a 0.035-inch guidewire. A suitable multiple-side-hole infusion catheter (ViperTM, Invamed, Ankara-Turkey) was placed within the thrombosed vessel with the aid of fluoroscopy. The mixture of tissue plasminogen activator

(rtPA, Actilyse, Boehringer Ingelheim, Germany) and saline (1:10) was infused into the residual thrombus.

Before start, ascending venography was obtained to examine the extent and location of the thrombus and to calculate the Marder score. The mixture of rtPA and saline administered in every 5- to 10 cm interval through the device's side injection port as rotational thrombolysis and rtPA delivery were used simultaneously.

Based on venography, the remaining residual stenosis of less than 10% was considered as successful recanalization. When post-treatment venography revealed any underlying stenotic lesion of the affected vessels, balloon angioplasty (PTA) was performed via a 10–12 mm–diameter balloon to ensure adequate flow.(n=24) Thrombus removal, patency of the iliofemoral vein, and thrombi in the filter were confirmed by venography assessment.

Patients were transferred to the inpatient service post-procedurally. For all cases, ViperTM catheter was left in the lumen and 10-15 mg rtPA mixture with saline was administered as continuous infusion to eliminate residual thrombus load or thrombus remnants behind the venous valves (40 mg maximum dose). During catheter directed thrombolysis, routine monitoring of plasma fibrinogen (FIB) concentration, activated partial thromboplastin time and platelet count were performed. When the FIB level was 1.0 to 1.5 g/L, the rate of drug administration was slowed down; when the FIB was <1.0 g/L, thrombolysis was temporarily paused. TPSTMcatheter was retrieved in every patient on postprocedural 2nd day after

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a venographic evaluation of the filter whether any thrombus caught inside. Hospital stay time, Marder score, the immediate procedural success rate were recorded.

Medical Therapy

Patients were started administration of tinzaparin (subcutaneously once daily at a fixed dose, determined according to three weight categories: 45–49 kg (5000 IU); 50–70 kg (7500 IU); 71–100 kg (10,000 IU) as soon as they were hospitalized [13].

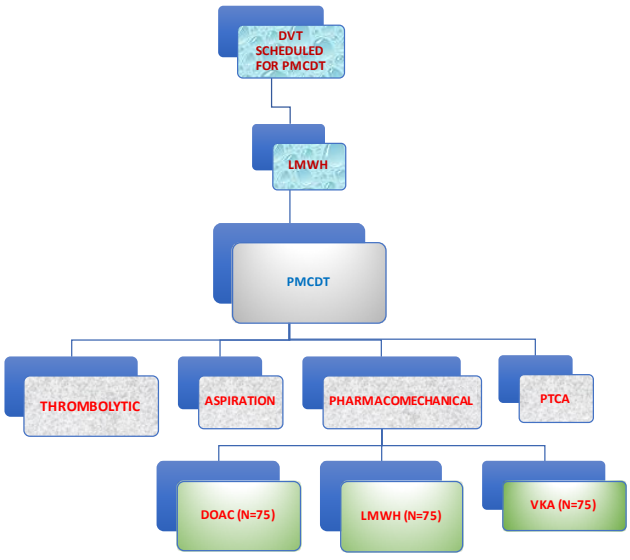
At the end of the procedure, patients received one of the three regimens before discharge.

Group 1: apixaban 2x5 mg (Therapeutic dose range- Anti-Xa Activity: 1.0-2.0 U/mL)

Group 2: Tinzaparin, single daily injection (dosing with respect to body weight) (Therapeutic dose range- Anti-Xa Activity: 1.0-2.0 U/mL)

Group 3: VKA (Therapeutic dose range- international normalized ratio-INR: 2-3)

All patients used thigh-high elastic compression stockings, providing from 30 to 40 mmHg of pressure, for 6 months. Patient flow chart is represented in Fig 1



Follow-up and Outcome Assessments

All patients were evaluated before discharge and were scheduled to return for ambulatory follow-up visits at 1, 3, 6 and 12 months after the procedure except for an emergency. At these visits, physical examination, doppler ultrasonography, INR (VKA patients) and anti-Xa (LMWH and DOAC patients) levels were performed.

Definitions of major and minor complications, anatomical success, early and late re-thrombosis, recurrent DVT, anatomical patency were evaluated within the scope of Reporting Standards for Endovascular Treatment of Lower Extremity Deep Vein Thrombosis [14].

Early symptom relief, was evaluated by assessing leg swelling using standardized leg circumference measurement through 10 cm below the tibial tuberosity of the index leg and leg pain using a 7-point Likert Scale which both instruments were previously reported as effective and inexpensive to document changes in limb symptomatology [14].

PTS was assessed by the Villalta Scale [15] that classifies PTS as absent (score 0–4), mild (score 5–9), moderate (score 10–14), or severe PTS (score ≥15, or presence of ulcer) and VCSS which grades the severity of PTS as absent (score 0- 3), mild to moderate (score 4-7), and severe (score > 8) [16]. Villalta and VCSS scores were calculated at 6th, and 12th -month controls.

To grade the severity of chronic venous disease and its impact on QOL, Venous Insufficiency Epidemiological and Economic Study Quality of Life measure (VEINES-QOL) evaluation were performed at 12th -month control [17].

Statistical analysis

All statistical analyses were conducted using SPSS 18.0 software (version 18.0; SPSS, Chicago, Illinois). Continuous data were reported as means +standard deviation, and the significant difference was verified using student t test. Categoric variables were expressed as frequency and percentages. Nominal data including clinical characteristics and predisposing factors were reported as the number of subjects and were analyzed using Wilcoxon-Mann-Whitney test. Venous patency and re-occlusion rates during follow-up were demonstrated by Kaplan-Meier analysis. Statistical significance was defined a P value of <0.05.

Results

Baseline evaluation of patients on hospitalization is summarized in Table 1.

Early peri-procedural data is listed in Table 2.

Table 1: Baseline characteristic of patients upon admission

	Group 1 (DOAC) (N=75)	Group 2 (LMWH) (N=75)	Group 3 (VKA) (N=75)
Age	57.1±15	52.6±15	50.4±15
Gender (F/M)	44/31	40/35	39/36
BMI (kg/m2)	29.2±8	30.4±10	28.7±9
Wells Score*	5.7±1.5	5.5±1.5	5.8±1.5
Duration of Symptoms (day)	6.4±2	7.3±3	5.9±2
Likert Score >5 #	48	52	57

F/M: female/male BMI: Body mass index
*:Wells Clinical DVT model: A score of 3 or higher indicates a high risk of DVT
#: Leg pain severity measured by Likert Scale

Table 2: Early peri-procedural data

	Group 1 (DOAC) (N=75)		Group 2 (LMWH) (N=75)		Group 3 (VKA) (N=75)	
Procedure Duration (min)	56.8±22		59.6±25		60.2±25	
Post-procedural full patency (%)	94.7±5		92.5±5		97.4±5	
Marder Score (Before/After)	11.4±3	2.3±1	13.6±4	2.5±1	10.9±3	2.1±1
Hospital Stay (day)	2.4±1.1		2.5±1.2		2.0±1.2	

No complications occurred in terms of pulmonary embolism or bleeding during early period. Minor bleeding as subcutaneous hemorrhage at the access site was observed in 2, 3 and 2 patients in Groups 1,2 and 3 respectively.

Follow-up data of patients is documented in Table 3. 4 patients in DOAC group were excluded for not being able to complete 12- month data.

Discussion

The use of VKAs like warfarin is recommended by guidelines in the medical treatment of VTE. However, it is limited by the need for frequent monitoring of INR, drug interactions, drug-food interactions, prior bridging with inpatient parenteral anticoagulation before commencing, as well as the risk of bleeding with its use [18]. Conversely, DOAC does not require regular INR testing and dose adjustments, while still remaining effective and safe in the treatment of VTE, with comparable rates of clinically significant bleeding and mortality [6]. While anticoagulation probably plays an important role, evidence-based data is scarce and optimal anticoagulation treatment of DVT to prevent PTS development is still unknown. In treatment with VKAs, sub-therapeutic anticoagulation in the first few weeks is associated with a higher incidence of PTS development. Analysis of long-term LMWH treatment alone showed a lower incidence of PTS compared to standard treatment with warfarin.9 Together with the observation that the severity of symptoms and signs four weeks after acute DVT is associated with subsequent PTS development, these findings suggest optimal anticoagulation treatment in the first weeks after acute DVT is crucial in preventing the development of PTS later in the course of the disease [19].

Sub-therapeutic anticoagulation might maintain thrombin production, thus promoting coagulation, reducing natural clot lysis and causing venous wall damage, which could lead to PTS development in the long-term. Therefore, DOAC, with their rapid onset and stable pharmacokinetics, could lower the incidence of PTS in comparison to warfarin [20-21].

We designed this study comparing three different regimens after PMCDT, in which patients were completely (>90%) cleaned from the existing thrombi load verified by ultrasonography and venography and continued a thorough follow-up to one year.

As demonstrated in Table 3, our patients treated with VKA showed a significant incompliance starting from third month up to one year. It is known that patients treated with VKA and monitored in a community setting have a lower adherence than patients in a trial setting. Considering that reduced treatment burden and regimen complexity are associated with better compliance, DOAC patients might have a better adherence in clinical practice and thereby contributing to better long-term clinical outcomes like PTS, especially in settings where INR control is suboptimal [22-23].

Patency rate diminished significantly below 70%. Major

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Table 3: Long-term follow-up of patient groups

	GROUP 1 -DOAC (N=71)				GROUP 2- LMWH (N=75)				GROUP 3-VKA (N=75)			
	1st Month	3rd Month	6th Month	12th Month	1st Month	3rd Month	6th Month	12th Month	1st Month	3rd Month	6th Month	12th Month
RECURRENCE (N)	2	3	2	3	3	4	3	4	3	5	5	4
DRUG-RELATED INCOMPLIANCE (N)	0	4*	1**	6*	6	7	9	7	2	11	10	11
MINOR BLEEDING (N)	0	5	5*	6*	2	6	9	9	5	10	14	13
MAJOR BLEEDING (N)	0	1	5	4*	3	3	7	6	2	4	8	8
INR OUT OF THERAPEUTIC RANGE (N)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	24	10	13	29
ANTI-Xa OUT OF THERAPEUTIC RANGE (N)	2	3	3	5	1	4	4	8	N/A	N/A	N/A	N/A
PATENCY RATE (%)	90±5	88±5	83±5	80.5±5*	91±5	82±5	77±5	70±4	94±5	80±5	73±4	68±4
REHOSPITALIZATION (N)	0	0	1	1*	0	0	2	1*	4	2	2	5
LIKERT SCALEμ	1.81 ± 0.1	2.1 ± 0.1	2.9 ± 0.12	3.2 ± 0.1	1.9 ± 0.1	3.2 ± 0.1	4.9 ± 0.2	5.2 ± 0.3μ	1.77 ± 0.1	3.7 ± 0.1	5.3 ± 0.3μ	6.8 ± 0.5μ
VILLALTA SCORE#			4.1 + 4	5.8 + 4			10.1 + 5	14.8 + 6			12.4 + 5	16.8 + 6#
VCCS>			3.6 + 1.7	5.8 + 4			7.88 + 3	9.3 + 4>			8.94 + 4>	10.5 + 5>
VEINES-QOL-Sym SCOREδ				61 + 10**				41 + 10δ				38 + 8δ

*: statistically significant vs control (Group 3)
**: statistically significant vs Group 2 and control (Group 3)
N/A: not applicable
μ: Leg pain severity measured by Likert Scale (>5 significant)
#: Villalta Score (>15, significant: Severe Post-thrombotic syndrome)
>: VCCS (>8, significant: Severe Post-thrombotic syndrome)
δ: VEINES-QOL-Sym (Venous Disease Specific- Quality of Life)

bleeding episodes were prominent in the late post-procedural period leading to more significant hospitalization.

32% of VKA patients were out of therapeutic range even in the first month leading to 40% at the end of the year. During the Einstein DVT trial, enoxaparin/VKA patients were 21 % of the time below the therapeutic range (INR 2–3) and more than 90 % of the patients in both rivaroxaban and enoxaparin/ VKA-treated patient had a compliance rate of 80 %.

Likert Scale and Villalta/VCCS scores confirmed the clinical data. VEINES-QOL-Sym score was significantly better in DOAC group with respect to VKA in 6th and 12th month controls and LMWH in 12th month controls, demonstrating better quality of life.

Our study has also some limitations. The main limitation of the study was the retrospective nature of the study which we tried to balance with propensity score matching.

The majority of PMCDT procedures in studies including our study were performed via popliteal approach. This approach has a possibility to leave a burden of residual occlusive thrombus in the popliteal vein, thereby leading to a possible increment in symptoms of PTS. We could have designed another group studying posterior tibial access to compare. Residual thrombus load and the patency of outflow veins were evaluated by venography in our study. But we know that, assessment of the patency of iliofemoral veins should be based on IVUS rather than venograms alone, because even small amounts of thrombus may enhance inflammatory reaction and thereby cause recurrent DVT and/or PTS. Due to reimbursement criteria in our country, we could not use IVUS in our study.

Conclusion

Our study highlights the potential role of DOAC as a reasonable alternative to VKAs/LMWH in the long-term anticoagulation strategy for DVT. DOAC appears to be similar in efficacy, and may potentially result in fewer major bleeding events, rehospitalization, better compliance and stability in therapeutic range leading to better quality of life. This is one of the first reports comparing three popular regimens in the setting of PMCDT. We await larger clinical trials to support these findings and establish the role of DOAC as the standard of care for patients with VTE.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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