Our Treatment Outcomes in Patients with Acute Deep Vein Thrombosis Associated with Congenital Inferior Vena Cava Agenesis

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ABSTRACT

Introduction: In this study, we present the treatment outcomes of patients with acute deep venous thrombosis (DVT) associated with congenital agenesis of the inferior vena cava (IVCA).

Patients and Methods: In this retrospective study, the clinical findings and follow-up data of patients who were scheduled for an interventional procedure due to acute DVT in 2019-2021 and who were found to have IVCA in venography were analyzed retrospectively.

Results: A total of 11 patients with acute DVT associated with IVCA were identified during the study period. Eight of the patients (72.7%) were male. The mean age of the patients was 25.5 ± 6.5 years (16-36 years). Five of the patients were followed up with conservative medical treatment. Endovascular procedure was performed in six patients. At the end of the first year, moderate post-thrombotic syndrome was found in 1 patient and mild post-thrombotic syndrome was detected in 2 patients. Patients who received only medical treatment had a significantly higher Villalta score at the end of the first year than patients who received endovascular treatment (6.6 ± 4.1 and 2.1 ± 1.9, p= 0.04).

Conclusion: Congenital IVCA is a rare diagnosis that should be kept in mind in young patients with deep venous thrombosis. In these patients, endovascular approach may be effective to prevent postthrombotic syndrome.

Key Words: Deep vein thrombosis; inferior vena cava agenesis; thrombolysis.

Konjenital İnferior Vena Kava Agenezisine Bağlı Akut Derin Ven Trombozu Olan Hastalarda Tedavi Sonuçlarımız

ÖZ

Giriş: Bu çalışmada, konjenital vena kava inferior agenezisi (İVKA) ile ilişkili akut derin ven trombozu (DVT) nedeniyle tedavisi yapılmış hastaların sonuçları sunulmuştur.

Hastalar ve Yöntem: Bu retrospektif çalışmada 2019-2021 yıllarında akut DVT nedeniyle girişimsel işlem planlanan ve venografide İVKA tespit edilmiş hastaların klinik bulguları ve takip verileri incelenmiştir.

Bulgular: Çalışma süresi boyunca toplam 11 İVKA ilişkili akut DVT hastası tespit edilmiştir. Hastaların 8 (%72.7)'i erkekti. Hastaların ortalama yaşı 25.5 ± 6.5 yıl (16-36 yıl) idi. Hastaların beşi konservatif medikal tedavi ile takip edilmiştir. Altı hastaya endovasküler işlem uygulanmıştır. İlk yılın sonunda hastaların birinde orta şiddette posttrombotik sendrom, ikisinde hafif seviyede posttrombotik sendrom saptanmıştır. Sadece medikal tedavi alan hastaların Villalta skoru ilk yılın sonunda endovasküler tedavi uygulanan hastalara göre anlamlı olarak daha yüksek bulunmuştur (6.6 ± 4.1 ve 2.1 ± 1.9, p= 0.04).

Sonuç: Genç DVT hastalarında konjenital vena kava inferior agenezi akılda tutulması gereken nadir bir tanıdır. Bu hastalarda endovasküler yaklaşım posttrombotik sendromdan korunmak için etkili olabilir.

Anahtar Kelimeler: Derin ven trombozu; inferior vena kava agenezisi; tromboliz.

INTRODUCTION

Deep venous thrombosis (DVT) is a multifactorial disease, involving interactions between acquired or inherited predispositions. The estimated incidence of overall venous thromboembolism (VTE) ranges from 104 to 183 per 100.000 person-year[1,2]. Obesity, hospitalization for surgery, acute illness, immobilization, active cancer, trauma and immobility are well-known risk factors of DVT. Potential complications of DVT are pulmonary embolism and post-thrombotic syndrome (PTS)[3].

Venous thromboembolism is predominantly a disease of older age[3]. Inferior vena cava agenesis (IVCA) a rare congenital anomaly is characterized by absence or interruptions

Cite this article as: *Erdem H, Selçuk E. Our treatment outcomes in patients with acute deep vein thrombosis associated with congenital inferior vena cava agenesis. Koşuyolu Heart J 2021;24(Suppl 1):S53-S57.*

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Submitted: 28.06.2021
Accepted: 01.08.2021
Available Online Date: 25.08.2021

of inferior vena cava. IVCA is detected in approximately 5% of predominantly young patients with DVT[4]. The diagnosis of DVT associated with IVCA is generally considered an exceptional case. The first reason for this is the rarity of the disease, and another reason is that it is underdiagnosed in standard imaging methods. Only case reports or limited series are available in the current literature about the management of this clinical condition. The knowledge about the optimal treatment strategy is still vague. In this study, we present the results of patients we treated for DVT associated with IVCA.

PATIENTS and METHODS

This single-center retrospective study included all patients who presented with proximal DVT and detected IVCA on venography between 06/2019 and 06/2021 at a high-volume venous thrombosis center (> 50/per year endovascular procedures for acute venous thrombosis). Demographic data, clinical presentation, family history, possible predisposing factors, treatment protocols, recurrent thrombotic episodes, PTS rates were investigated. The Institutional Ethical Committee of Bezmialem Vakif University approved the study protocol (Decision No: 2021/298, Date: 08.07.2021). Preoperative informed consent was obtained from all patients who underwent interventions. The study was conducted conformed to the principles of the Declaration of Helsinki after institutional approval.

All patients with IVCA were identified by venography while undergoing an endovascular procedure for extensive deep vein thrombosis. Initial venography was performed in the contralateral femoral vein (during inferior vena cava filter insertion) in all patients. In patients with IVCA drainage points were determined by performing selective venography on well-developed collateral veins. In these patients, the treatment protocol (conservative or interventional) was decided together with the operator and the patient (the patient's family for under 18-year-old patients) according to the patient's clinical condition. Ipsilateral venography was not performed in patients who were scheduled for conservative medical treatment. Then, ultrasound-guided 8 French sheath placement was performed through an ipsilateral popliteal vein in the prone position for patients who were decided for catheter-directed therapy (CDT). The most proximal level of the thrombosed vein was reached with a hydrophilic wire and support catheter. Then, selective venography was performed to evaluate the ipsilateral iliac vein anatomy and inferior vena cava structure. Depending on the patient's clinical condition and availability of proper device pharmacomechanical thrombectomy (PMT) or ultrasound accelerated thrombolysis (EKOS Corporation, Bothell, WA, USA) were preferred by the operator.

Patients referred to conservative medical therapy were treated with low molecular weight heparin (LMWH) for the first few days, leg elevation, and adequate hydration. Patients were hospitalized for several days depending on the status of their leg symptoms due to excessive thrombus burden.

PMT and percutaneous aspiration were performed in patients with severe leg swelling and pain who were targeted for rapid thrombus removal. The MantisCURVE Rotational, Directional Pharmacomechanical Thrombectomy Catheter (Invamed, Ankara, Turkey) and Dovi Aspiration Thrombectomy Catheter (Invamed, Ankara, Turkey) were used for PMT. An inferior vena cava filter was not used in any patient because it was anatomically inappropriate. In the first session, recanalization was aimed in the proximal venous structures in the ipsilateral extremity until the outflow veins of a suitable diameter for thrombectomy. Ultrasound-enhanced thrombolysis (10-20 mg alteplase for 12 hours) was applied to the patients in the EKOS group through a multihole infusion catheter. According to the operator's decision, after 12 hours, it was decided whether to extend the thrombolytic infusion by performing venography again, , according to the clinical condition of the patients. The patients were followed up with oral warfarin (INR target 2.5-3) after LMWH for the first few days. Outpatient follow-up of all patients was performed primarily by the clinicians of the study center. The presence of PTS was determined by Villalta score (0-4: Absent; 5-9: Mild PTS; 10-14: Moderate PTS; ≥ 15, or presence of venous ulcer: Severe PTS)[5].

Statistical Analysis

Categorical variables were presented as counts and frequencies; continuous variables as mean (Standard deviation, SD) or median (minimum-maximum) as appropriate. The Chi-square test or Fisher's exact test was used for comparison between categorical variables. Student t-test or Mann Whitney U test was used to compare continuous variables. A two-tailed p-value of 0.05 was considered statistically significant. SPSS version 23.0 (SPSS, Chicago, IL) was used for all statistical analyses.

RESULTS

Inferior vena cava agenesis was detected in 11 of 114 patients (9.6%) who underwent interventional procedure for acute proximal deep vein thrombosis during the study period. Eight of the patients (72.7%) were male. The mean age of the patients was 25.5 ± 6.5 years (range 16-36 years). None of the patients had a prior history of DVT or a family history of VTE. Six of the patients had acute deep vein thrombosis located on the left leg and five of them on the right leg. Table 1 summarizes the demographic and clinical characteristics of the study patients.

Initial venograms revealed that suprarenal IVCA in two patients (Figure 1) and infrarenal IVCA in nine patients (Figure 2). Conservative medical treatment was applied to 5 of the patients. The median length of stay of patients with only medical treatment was 4 days (range 2-8 days). PMT was performed in 4 patients. The median hospital stay of these patients was 2 days

Table 1. General characteristics of patients with deep vein thrombosis associated with congenital inferior vena cava agenesis

Patient	Age (years)	Gender	Previous signs/ symptoms	Predisposing factor	Leg Side	Duration of symptoms	Treatment	Recurrent DVT	Villalta score at first year	Follow-up (months)
1	16	Male	Leg swelling	None	Left	1 day	Medical	16 months after discharge	3	21
2	21	Female	None	Oral contraceptive, smoking	Right	2 days	Medical	None	12	20
3	21	Male	None	None	Right	5 days	Medical	None	8	14
4	24	Male	None	None	Right	4 days	PMT	None	1	17
5	30	Male	None	None	Left	7 days	Medical	None	2	16
6	17	Male	Leg swelling	Smoking	Left	10 days	PMT	None	2	15
7	32	Male	Leg swelling	Knee trauma	Left	2 days	Medical	None	8	13
8	26	Female	Varicose veins in legs	Oral contraceptive	Left	3 days	EKOS	12 months after	1	14
9	36	Female	Enlargement of abdominal veins	Smoking	Right	4 days	PMT	None	6	12
10	32	Male	Enlargement of abdominal veins	Immobilization	Right	1 day	EKOS	None	2	14
11	26	Male	None	Smoking	Left	2 days	PMT	None	1	12

DVT: Deep vein thrombosis, PMT: Pharmacomechanical thrombectomy, EKOS: EkoSonic endovascular system.

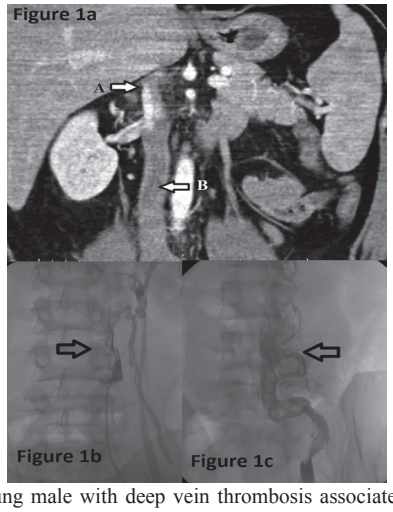

Figure 1. Young male with deep vein thrombosis associated with suprarenal inferior vena cava agenesis. a) Computed tomography reveals that interruption of inferior vena cava at suprarenal level (arrow A) and thrombosed inferior vena cava (arrow B). b) Initial venogram indicated that thrombosed infrarenal inferior vena cava and large lumbar veins (arrow). c) Partial recanalization after EKOS (arrow).

(range 1-4 days). EKOS was used in 2 patients with suprarenal IVCA (3 and 6 days of hospitalization).

The mean follow-up period of the patients was 15.2 ± 3 months (range 12-21 months). In a patient who received conservative medical treatment, deep vein thrombosis developed in the contralateral extremity at the 16th month after discharge. In a patient who underwent EKOS, recurrent deep vein thrombosis developed in the same leg 12 months after discharge.The INR levels of both of these patients are subtherapeutic. Because of their mild symptoms, they were treated with medical anticoagulant therapy (LMWH for ten days followed by edoxaban for prolonged anticoagulation).

All patients were examined for PTS at the end of the first year. The mean Villalta score of pateints was 4.2 ± 3.7 (range 1-12). Mild PTS developed in 2, moderate PTS in 1 of the patients who received only medical treatment, and mild PTS developed in 1 patient who underwent pharmacomechanical thrombectomy. Patients who received only medical treatment had a significantly

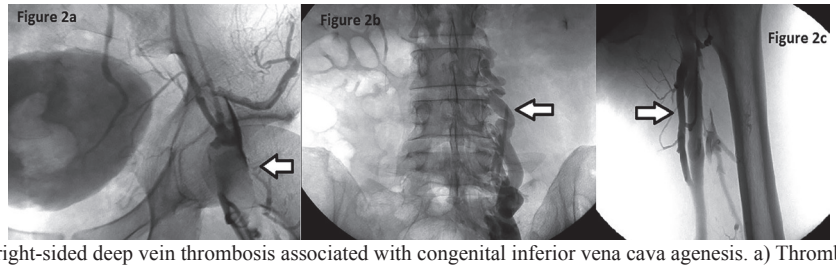

Figure 2. Young male with right-sided deep vein thrombosis associated with congenital inferior vena cava agenesis. a) Thrombosed right common femoral vein, prone position (arrow). b) Venogram from left groin clearly reveals inferior vena cava agenesis, supine position (arrow). c) Right extremity venogram from popliteal vein after pharmacological thrombolysis and aspiration, prone position (arrow).

higher Villalta score at the end of the first year than patients who underwent CDTs (6.6 ± 4.1 vs. 2.1 ± 1.9, p= 0.04). No patients experienced pulmonary embolism during the study period.

DISCUSSION

In this study, we presented our about patient with DVT associated with IVCA which are probably underdiagnosed in daily practice. In our series, DVT associated with IVCA was usually detected in young adults. Our early experience indicates that endovascular approaches may be promising for prevention of PTS for these patients.

Inferior vena cava agenesis is a very rare developmental anomaly of vascular system. The estimated prevalence of IVCA in the general population is approximately 1%[6]. It has been reported that this rate rises to 5% in young adults presenting with DVT[4]. In our series, this rate was 9.7 percent. This high rate is probably due to the fact that the study patients were predominantly young and were referred for the interventional procedure due to proximal DVT. These findings also persisted in our study. Lambert M et al. reported that they did not encounter any case of pulmonary embolism in their series include 10 patients with IVCA and DVT[7]. The authors suggested that the possible mechanism for the low incidence of pulmonary embolism in this patient group may be filtering of the clot in the lower extremity before it enters the pulmonary circulation through the azygos and hemiazygos systems[7]. It should be noted that the literature data is very limited to make epidemiological inferences about the real incidence of this disease in the population and its relationship with pulmonary embolism.

The major challenge in the management of this patient group is the determination of the optimal treatment method. There is no study in the literature comparing treatment methods for DVT associated with IVCA. It seems to be unfeaseble to conduct a randomized study due to the rarity of this disease and the difficulty of standardization due to variety of anatomical structures. Most of the cases in the literature were treated with conservative medical treatment[4,6-8]. Standard medical treatment includes bridging with vitamin K antagonists or factor Xa inhibitors after LMWH for the first few days. Prolonged oral anticoagulant therapy is recommended as an expert opinion in patients with DVT associated with IVCA. Recurrent thrombosis episodes nearly one year after treatment have been reported in the literature. Therefore, the precise time of discontinuation of treatment is still uncertain[8]. In these patients, we changed the treatment with a direct oral anticoagulant (edoxaban). We previously presented a patient with DVT associated with IVCA, which was not included in this series, and we followed up uneventfully this patient with rivaroxaban[9].

Oral anticoagulant therapy was not stopped in any of our patients during the study period. Despite this, we detected recurrent thrombosis episodes in two of our patients with subtherapeutic INR levels. Possibly, inadequate recanalization of trombosis due to impared venous outflow, ongoing mechanical venous stasis and endothelial damage cause an increased risk of thrombosis in these patients compared to DVT patients with standard anatomy. Additionally, a previous study suggested that hereditary thrombophilias may be more common in patients with DVT associated with IVCA than in the normal population[10]. The major benefit of catheter-based therapies is the rapid elimination and/or removal of the thrombus, resulting in early resolution of symptoms and a reduction in the long-term rate of PTS. There is no robust consensus on the absolute effectiveness of CDTs for treatment of acute DVT. Current guidelines indicate that percutaneous thrombolysis may be reasonable in young patients with proximal DVT[11]. There are several promising reports about the effectiveness of CDTs in patients with IVC related DVT[12-15].

The major challenge of CDTs in this patient group is to determine the optimal venous outflow in thrombosed venous structures without inferior vena cava. The catheter should be placed as proximal as possible to the iliac vein or major collateral veins (usually ascending paravertebral veins, azygos, or hemiazygous veins) to reestablishadequate recanalized venous wash out.

Often, venograms after the first thrombolytic attempt reveal that the main venous outflow tract. The primary goal of CDTs for pateints with DVT associated with IVCA was not to eliminated the thrombus completely, but to reduce the clot burden. Percutaneous recanalization of DVT associated with IVCA is not straightforward procedure. For this reason determination of individualized approach based on each patient's anatomy is quite important for this patient group.

In conclusion, DVT associated with IVCA is a rare and complex clinical condition. DVT associated with IVCA should be kept in mind in young men with unprovoked DVT. Further studies are required to evaluate the long-term outcome of CDT and medical therapies. In our preliminary experience, CDTs may be effective in reducing the rate of PTS for these patients. These findings need confirmation in larger patient series.

Ethics Committee Approval: The Institutional Ethical Committee of Bezmialem Vakif University approved the study protocol (Decision No: 2021/298, Date: 08.07.2021).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - HE, ES; Analysis/Interpretation - HE, ES; Data Collection - ES; Writing - HE, ES; Critical Revision - HE, ES; Statistical Analysis - HE, ES; Overall Responsibility - HE, ES; Final Approval - All of authors.

Conflict of Interest: The authors have no conflicts of interest to declare

Financial Disclosure: The authors declared that this study has received no financial support.

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