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ORIGINAL ARTICLE

Outcome of venous stenting following catheter directed thrombolysis for acute proximal lower limb venous thrombosis: a prospective study with venous Doppler follow-up at 1-year

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Abstract Functional outcome of venous stent placement for the management of acute iliofemoral deep vein thrombosis (DVT) following catheter-directed thrombolysis (CDT), remain undefined. The purpose of this study was to assess immediate and intermediate term outcomes among patients treated with venous stenting following CDT in patients with proximal lower limb DVT. Thirty consecutive patients aged between 20–70 years with proximal lower limb DVT formed the study group. The mean duration of CDT done with streptokinase was 4.5 ± 1.3 days. Patients with residual venous obstruction and/or large clot burden were treated further with venous angioplasty and/or stenting. Primary endpoint was to evaluate the safety, efficacy and patency of venous stenting in the management of incomplete result following CDT. After 12 months, post-thrombotic syndrome (PTS) was assessed clinically using Villalta scale and deep venous patency was assessed through duplex ultrasound. We studied 8 (5 female and 3 male) patients with 9 (3 left and 6 right) limb involvement and 13 stent (4 balloon expandable and 9 self expandable) placement. All patients improved clinically immediately following venous stenting. Technical success was achieved in all patients. One patient developed pulmonary embolism during course of hospital stay. One patient had stent thrombosis and PTS and another patient died due to carcinoma breast during follow-up. Deep venous stenting is an effective mode of treatment in proximal acute lower limb DVT with high late patency rate up to 1-year.

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Introduction

Symptomatic proximal lower limb deep vein thrombosis (DVT) is a challenging situation and merits rapid effective treatment to prevent complications like venous thromboembolism (VTE) and post-thrombotic syndrome (PTS) [1]. In venous thromboembolic disease, catheter-directed thrombolysis (CDT) with or without assisted mechanical thrombolysis is now the established standard of medical care in the treatment of acute and sub-acute proximal DVT [2]. Endovascular management using percutaneous mechanical thrombectomy alone or in combination with pharmacological thrombolytic agents has recently received attention amongst the clinicians as a safe and effective means for the treatment of acute proximal DVT [3]. Although stent implantation is used to treat peripheral arterial obstruction or stenosis worldwide [4], there is little data on the efficacy and long-term patency of stents that are implanted for venous disease and especially in case of acute DVT [5]. This study was performed to evaluate the immediate and intermediate term safety, efficacy and patency of venous stenting in the management of proximal lower limb DVT following CDT.

Materials and methods

Study design

It was a prospective, nonrandomised study conducted between 2011 and 2013 at Sri Jayadeva Institute of

Cardiovascular Sciences and Research, Bangalore, India. The study design was approved by the institute's ethics committee and all patients provided written informed consent.

Patients

All patients with proximal lower limb DVT who met the inclusion criteria were included in this study.

Eligibility criteria

Inclusion criteria

1. Men and women between 20–70 years of age
2. Patients with recent (between 1–8 weeks) lower limb proximal DVT
3. Patients understand the nature of the procedure and provide written informed consent before enrolment in the study.

Exclusion criteria

1. Patients with DVT of more than 8 weeks
2. Patients for whom antiplatelet therapy, anticoagulants, or thrombolytic drugs are contraindicated
3. Recent (<6 weeks) ischemic stroke or cerebral bleeding
4. Patients with recent (<6 weeks) major surgery
5. Severe uncontrolled hypertension (diastolic blood pressure greater than 110 mmHg, systolic blood pressure greater than 200 mmHg)
6. Patients with a history of prior life-threatening reaction to contrast medium
7. Patients with uncorrected bleeding disorders (gastrointestinal ulcer, menorrhagia, liver failure)
8. Patients considered hemodynamically unstable at the onset of the procedure
9. Patients who refuse treatment
10. Hemoglobin <9 mg/dL, INR >1.6 before warfarin is initiated, and platelet count <100000/mL.

Primary endpoint

Primary endpoint of this study was to evaluate the immediate and intermediate-term patency of venous stenting and efficacy in reducing PTS in the management of residual obstruction following CDT in acute proximal lower limb DVT.

Secondary endpoint was to evaluate the technical success, complications and adverse events following proximal deep vein stent implantation.

Adverse and serious adverse events

Adverse events (AE) were defined as any undesirable experience occurring to a participant during the study, whether or not considered related to the investigational drug or intervention. This definition includes events occurring during the hospital stay or until 30 days of follow-up.

All AEs were monitored from the time of enrolment through the 30-day follow-up visit.

Clinical events which were considered and reported as serious AEs include:

- Death
- Myocardial infarction
- Acute pulmonary embolism
- Stroke
- Endovascular complication requiring surgical intervention-like venous rupture or perforation or dissection.

Clinical events to be considered and reported as minimal AEs include:

- Local complication like bleeding, hematoma, pseudo aneurysm, or arterio-venous fistula.

Written proformas were filled up during inclusion of patients which contained epidemiological information (age, sex, occupation, and place), questionnaires for risk factor evaluation (smoking, drug history, malignancy, co morbid condition, and hyper-coagulable state), and information of the clinical examinations (limb involvement).

Investigations

All patients were investigated with the following tests;

1. Complete hemogram
2. Bleeding time (BT), clotting time (CT), prothrombin time (PT) and activated plasma thromboplastin time (aPTT)
3. Renal function test, Liver function test
4. Work up for hyper-coagulation state
5. Duplex venography/ultrasound abdomen.

Intervention

In our study, popliteal vein and/or femoral vein cannulation under ultrasound guidance was done to access the lesion in the same limb which was affected by DVT. Peripheral angiogram (PAG) was done in this group through popliteal vein approach. At the start of CDT, an intravenous bolus dose of unfractionated heparin (UFH), 5000 U, followed by a continuous intravenous UFH infusion at the rate of 1000 U/h was given through the side port of the sheath [6]. At first, thrombus was manually aspirated by using

Judkin's right guiding catheter (JR 3.0 8F, Cordis) and then CDT was done through multipurpose catheter into the region of the thrombus with Streptokinase (STK) infusion. The STK was continued till satisfactory lysis of the clot was achieved. Two-third of the total doses of STK (1 lacs units/h) was given upfront through the catheter and other one-third of STK was given through the side port of popliteal venous sheath to bath the clot along the catheter. UFH was also infused through the side port of the sheath. Check angiogram was done every 24-h to assess the clot burden and efficacy of treatment. The post lysis thrombus burden was graded by scoring system which divides the grade of thrombolysis as; grade I $\leq$ 50 %; grade II = 50–90 %, and grade III = complete thrombolysis [7]. In those who had partial response to CDT and residual venous obstruction, additional PTA and or stenting of iliac vein was performed. The length of the stent was chosen based on the length of the stenotic lesion on venography, and we chose the stent diameter based on measurements of venous diameter by visual observation. Patients who exhibited inadequate stent expansion were treated with low-pressure balloon dilatation at 2–4 atm.

Oral anticoagulant

Patients received oral warfarin or Nicoumalone for at least 12 months (where predisposing factors were present) or for indefinite period (where predisposing factors were absent), after completion of CDT. The International Normalized Ratio (INR) was maintained within 2–3.

Follow-up

Patients were followed-up during their hospital stay and at monthly intervals till a period of 12 months. After 12 months, patency of the deep venous system was investigated using duplex ultrasound. The venous patency was defined by unidirectional laminar blue color flow (away from the Doppler probe) in the vein with the presence of compressibility while pressed by the Doppler probe and absence of brighter internal echo for thrombus. The venous thrombosis or restenosis was defined as absence of laminar blue color flow, lack of compressibility and presence of thrombus (brighter echo) inside the vein. The PTS was assessed using the Villalta scale, which consists of five patient-rated venous symptoms (pain, cramps, heaviness, paraesthesia, and pruritus) and six clinician-rated physical signs (pretibial oedema, skin induration, hyperpigmentation, pain during calf compression, venous ectasia, and redness). Each is rated on a four-point scale (0-none, 1-mild, 2-moderate, 3-severe). Points were totalled to produce an overall score (range 0–33). Subjects were classified as having PTS if their score was >5 or if a venous ulcer developed in the leg with DVT [8]. The Villalta scale is a reliable, validated, and responsive measure of PTS [9].

Results

Thirty patients with proximal lower limb DVT received CDT and mechanical thromboaspiration. Among these 30 patients, 8 patients had undergone deep venous stenting as they had residual venous obstruction following CDT or assisted CDT (CDT + venous angioplasty). Eight patients were followed up prospectively; data were collected, compiled and analyzed.

Baseline demographic profile

The mean age of study patients was 42.1 $\pm$ 10.8 years and male:female ratio was 3:5. Mean duration of symptoms at presentation was 15.7 $\pm$ 18.8 days. The mean duration of CDT done with streptokinase was 4.5 $\pm$ 1.3 days. Among the risk factors, 3 patients had diabetes mellitus and 2 patients had obesity/dyslipidemia. Malignancy, bed ridden due to trauma, post-partum period, uterine fibroid and smoking was seen in one case each. In these 8 patients, there was involvement of 9 limbs and right lower limb was involved in 6 cases and May–Thurner syndrome with left lower limb involvement was seen in 3 cases. One patient had bilateral lower limb involvement. Only one patient received inferior vena caval (IVC) implantation before venous stenting. Organized thrombus was the reason behind in right-sided venous obstruction, whereas iliac artery compression was the reason behind the left sided venous obstruction. All patients received CDT and mechanical manual thromboaspiration (Table 1). Grade III (complete) lysis was achieved in 10 (33 %) and Grade II (50–90 %) lysis in 20 (67 %) of patients. Patients with significant residual lesion in Grade II lysis following catheter-directed thrombolysis underwent percutaneous transluminal angioplasty alone (12/20) or venous stenting (8/20).

Procedural details of venous stent implantation

Among these 8 patients, 9 limbs and 13 lesions were treated with venous stent implantation. Five patients received single stent, two patients received 2 stents and one patient received 4 stents implantation. The patient who received 4 stents, 2 overlapping stents was deployed in common iliac vein and inferior vena cava junction due to clot protrusion. One stent was deployed in the common femoral and superficial femoral vein and another stent was delivered in the popliteal vein as she had extensive lower limb DVT. The stent deployed in the popliteal vein had restenosis during follow-up. Ten stents

Table 1 Baseline patient characteristics

Case no.	Age (years)	Sex	Risk factors	Duration (days)	Location of DVT	Stenotic lesion	Cause	CDT	IVCF
1	40	M	Trauma	15	CIV, EIV, CFV, SFV	Right CIV, EIV, CFV	OT	Yes	No
2	33	F	Post partum, obese	5	CIV, EIV, CFV, SFV, PV	Right CIV and EIV	OT	Yes	No
3	31	M	Obese, smoking	10	CIV, EIV, CFV	Left CIV and EIV	IC	Yes	No
4	37	M	Splenectomy	60	B/L CIV, EIV, IVC	Bilateral CIV and EIV	OT	Yes	Yes
5	40	F	DM, breast carcinoma	7	CIV, EIV, CFV	Left CIV and EIV	IC	Yes	No
6	39	F	Uterine fibroid	10	CIV, EIV, CFV	Right CIV and EIV	OT	Yes	No
7	55	F	DM	15	CIV, EIV, CFV	Right CIV and EIV	OT	Yes	No
8	62	F	DM, HTN	4	CIV, EIV, CFV, SFV, PV	Right CIV, EIV, CFV, SFV, PV	OT	Yes	No

DM diabetes mellitus, *HTN* hypertension, *CIV* common iliac vein, *EIV* external iliac vein, *CFV* common femoral vein, *SFV* superficial femoral vein, *PV* popliteal vein, *OT* organized thrombus, *IC* iliac artery compression, *CDT* catheter directed thrombolysis, *IVCF* inferior vena caval filter

Table 2 Procedural details of stent and implantation

Case no.	Stent	Diameter (mm)	Length (mm)	Pre dilatation	Post dilatation	Thrombolytic therapy after stenting
1	SMART	6	120	Yes	No	No
2	Wall stent	8	40	Yes	Yes	No
3	Wall stent	8	40	Yes	Yes	No
4 (i)	Wall stent	8	60	Yes	Yes	No
4 (ii)	Wall stent	8	60			
5	SMART	6	120	Yes	No	No
6	SMART	6	120	Yes	Yes	No
7 (i)	Wall stent	8	40	Yes	Yes	No
7 (ii)	Wall stent	8	40			
8 (i)	Wall stent	8	40	Yes	Yes	No
8 (ii)	Wall stent	8	40			
8 (iii)	Wall stent	6	40			
8 (iv)	SMART	6	120			

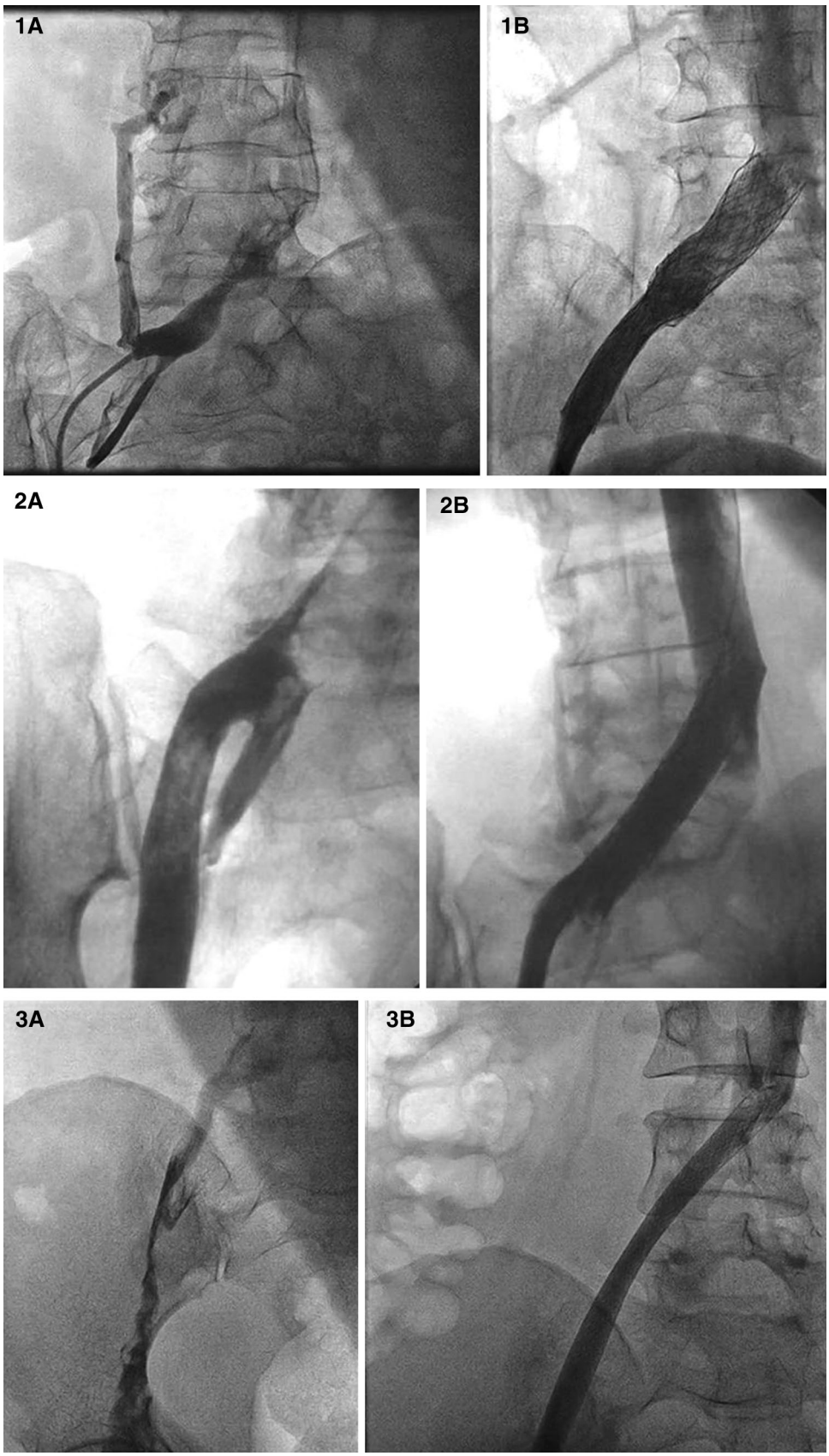
were implanted in the right-sided proximal lower limb vein and 3 stents were implanted in left-sided proximal lower limb vein. Self expandable Wallstents (Boston Scientific) were implanted into 9 lesions and balloon expandable SMART stents (Cordis, Bridgewater, NJ, USA) were implanted in 4 lesions. One patient had bilateral common iliac vein stent implantation. The mean stent diameter was 7.4 ± 1.0 mm, and the mean stent length was 67.7 ± 37.0 mm. All the patients underwent balloon venoplasty to induce venous dilatation prior to stent implantation. In addition, we performed balloon venoplasty for post-stent implantation dilatation in 6 patients. None of these patients received additional thrombolytic therapy for residual thrombi (Table 2).

Immediate and late follow-up following venous stent implantation

All patients had immediate clinical improvement following venous stent implantation. Immediate stent patency was assessed with Doppler venography and all of them had patent stent at the time of discharge and the average Villalta scale immediately following venous stenting was 2.5 ± 1. Hence, the stent patency rate at the time of discharge was 100 % (Figs. 1a, b, 2a, b, 3a, b). No major vascular complications occurred during stent implantation. One patient exhibited features of serious AE due to acute pulmonary thromboembolism during the hospital stay. Other complications like major bleeding, stent fracturing, stent migration or minimal AE was also not observed in this study. We administered warfarin-based anticoagulation therapy to all patients. One patient developed stent thrombosis and PTS during follow-up period. One patient died due to breast carcinoma during follow-up period. Hence, late stent patency was seen in 88 % of stented patients (Table 3).

Discussion

Early thrombus debulking by CDT and/or mechanical thromboaspiration is currently standard of care in the



Figs. 1–3 **a** Post CDT residual venous obstruction of right sided proximal lower limb deep vein and **b** post venous stenting result of the corresponding vein

Table 3 Early and late follow-up data

Case no.	Immediate occlusion	Occlusion during follow-up	Diagnostic method	Warfarin therapy	Recurrence of VTE	Prognosis	PTS
1	Nil	Patent	Venous Doppler	Continued	Nil	Good	Nil
2	Nil	Patent	Venous Doppler	Continued	Nil	Good	Nil
3	Nil	Patent	Venous Doppler	Continued	Nil	Good	Nil
4	Nil	Patent	Venous Doppler	Continued	Nil	Good	Nil
5	Nil	Not examined	Not done	Continued	Nil	Died due to breast carcinoma	
6	Nil	Patent	Venous Doppler	Continued	Nil	Good	Nil
7	Nil	Patent	Venous Doppler	Continued	Nil	Good	Nil
8	Nil	Occluded	Venous Doppler	Continued	Nil		Yes

VTE venous thromboembolism, *PTS* post thrombotic syndrome

management of proximal DVT. CDT and mechanical thromboaspiration has showed promising results, rapid removal of clot burden and decreased incidence of PTS and VTE [1]. About 25–82 % of patients with ilio-femoral DVT treated with anticoagulants alone suffered from the PTS [8]. CDT therapy has been studied recently and has been shown to be safe and effective in achieving early, intermediate and long-term venous patency [10]. The ipsilateral popliteal venous approach is preferred because it is often difficult to penetrate an occluded superior ilio-femoral vein from the internal jugular vein or the contra-lateral common femoral vein, and venous valves may prevent safe catheterisation [11]. We used streptokinase (STK) as per the previous study which demonstrated the efficacy of continuous infusion of STK for CDT [11]. As our patients were mostly belonging from lower socio-economic status and cost of STK is 3 times lesser than urokinase so STK was used for this purpose. In the present study, patients with partial clot lysis and residual venous obstruction were further treated with PTA and/or proximal lower limb venous stenting. There are only few previous studies where venous stenting was done following CDT in acute proximal lower limb DVT and most of them showed acute patency rate of 90–100 % and medium or long-term patency rate also 80–100 % [5, 12–16]. We also had similar patency rate in our studies with early patency rate of 100 % and late patency rate at 1-year of 88 %. Most of the previous studies [12–16] except one [5] used venous Doppler scan to diagnose stent patency and we also had similar protocol in our study. In our study, only one patient had IVC filter implantation compare to the latest study where IVC filter implantation was done in all cases prior to venous stenting [5]. All previous studies had demonstrated the efficacy of venous angioplasty in May–Thurner syndrome [12–14]. In our study, we have demonstrated the outcome of venous stenting more in right-sided lower limb DVT than in May–Thurner syndrome. Though the late patency was similar to previous studies but the major concern in our study was acute pulmonary embolism in one case compared to previous study [5] where no pulmonary embolism was seen. This could be due to aggressive thrombus removal and less use of IVC filter prior to CDT and venous stenting. There was no incidence of stent fracture, embolization or migration seen during follow-up period.

Limitation of this study

It was a single center prospective study, so sample size in our study was small. We used STK infusion for CDT which was not used in most studies. We included patients till 8 weeks from onset of DVT rather than 3 weeks in most previous studies.

Conclusion

For patients with residual venous obstruction and partial clot lysis despite CDT, venous angioplasty with stenting is an effective therapy and increases the acute venous patency rate both in May–Thurner and non May–Thurner syndrome. This venous patency was maintained during follow-up over 1-year. Further randomized control trials are required to assess the safety and efficacy of venous stenting in acute proximal lower limb DVT cases who had partial lysis following CDT.

Disclosure and conflict of interest None.

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