Outcome of invasive procedures for venous thrombosis in Behçet's syndrome: case series and systematic literature review

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ABSTRACT

Objective. *Systemic therapy aimed at suppressing the diffuse inflammation in the vessel wall is the major treatment modality for venous thrombosis in Behçet's syndrome (BS). Endovascular and/or surgical interventions are also used. We here report five patients who were referred to our clinic after having such interventions and also present a literature review to assess the outcome of invasive procedures for venous thrombosis in BS.*

Methods. *Our patients were presented and a literature search for endovascular and/or surgical interventions in PubMed was performed. Recanalisation, reocclusion or other complications were assessed as outcomes.*

Results. *Five BS patients with lower extremity thrombosis were referred to our clinic with post thrombotic syndrome due to incomplete recanalisation or infectious complication after endovascular interventions. Twenty-one articles reporting on 36 patients were found suitable for review.*

There were totally 21 lower extremity venous intervention cases, 14 of which had failure such as complication, reocclusion or incomplete recanalisation. Reocclusions occurred in 10 patients and reinterventions to 8 of them could restore flow only in 4 cases. Ileal infarct and vena cava wall-duodenal perforation were major complications. Invasive procedures of 8 abdominal thrombosis cases resulted with death due to ileus in one patient, and reocclusion in another. Seven of the 12 upper extremity/superior vena cava thrombosis cases resulted with reocclusions.

Conclusion. *Endovascular and surgical interventions seemed to be unsuccessful because of recurrent infectious and vascular complications in 22 (53.6%) of 41 patients with venous thrombosis. The indication of these procedures is controversial. Their economic burden on the healthcare system must be considered.*

Introduction

Behçet's syndrome (BS) is a complex multisystem disorder with an unknown aetiology. It is characterised by recurrent oral and genital ulcers, skin lesions, pathergy reaction and uveitis. It may also involve vascular, musculoskeletal, central nervous and gastrointestinal system (1). BS usually presents in the third decade and is seen equally in both genders. Disease course is more severe among males and mortality may occur during the first 5-10 years from onset (2, 3). Vascular involvement can be seen in up to 40% of patients with BS and is the most common cause of morbidity and mortality. Both veins and arteries may be affected; however, venous disease is more common than arterial disease (75% *vs*. 25%). Lower extremity vein thrombosis (LEVT) is the most frequent manifestation of vascular involvement. It involves mostly superficial, deep femoral, common femoral, popliteal veins and vena saphena magna (2). LEVT in BS has poor recanalisation so it causes severe post thrombotic syndrome (PTS) in 51% of cases (4). PTS is characterised as chronic limb pain, heaviness, oedema and skin changes which can progress to cause leg ulcers, and impaired quality of life (5). Superficial thrombophlebitis, vena cava thrombosis, pulmonary artery aneurysms, pulmonary artery thrombosis, Budd-Chiari syndrome (BCS), peripheral artery aneurysms or occlusion, dural sinus thrombosis and abdominal aortic aneurysms are other vascular manifestations.

Inflammation of the vessel wall has been considered to be responsible for the development of thrombosis in BS rather than any thrombophilic factors (6-8). Also, due to typical sticky nature of thrombi, pulmonary embolism is unexpected. For this reason immunosuppressives (IS) are the mainstay treatment in contrast to deep vein

thrombosis (DVT) due to causes other than BS (9, 10). Anticoagulation (AC) is still controversial and there are no controlled data on antiplatelet or fibrinolytic agents in addition to IS in the management of vascular involvement in BS (11). In DVT due to other causes; acute removal of thrombus material is expected to preserve venous function and prevent PTS (12). For this purpose, pharmacomechanical catheter directed thrombolysis (PCDT) and aspiration, balloon angioplasty, stent or filter insertion are offered as interventional treatment options. The efficacy of these procedures in DVT due to BS is unknown. In this paper, we aimed to describe five BS patients who were referred to our clinic with several complications following multiple vascular interventions and then reviewed all reported BS cases that have undergone surgical or endovascular interventions due to venous involvement of BS.

Materials and methods

In Istanbul University-Cerrahpasa Behçet's Disease Centre we screened the files of the patients with DVT in our archives between 2015 December and 2018 December and included the ones who had vascular intervention. We reported our experience with five BS patients who underwent several invasive interventions due to venous involvement and had several complications.

Additionally, we did a systematic literature search in PubMed using the following keywords: ("Behçet*" OR "Behcet**" OR "Adamantiades-Behcet") AND ("surgery" OR "surgical" OR "intervention" OR "stent" OR "bypass" OR "filter" OR "percutaneous" OR "angioplasty" OR "thrombectomy" OR "thrombolytic" OR "thrombolysis" OR "graft") AND ("thrombosis" OR "thrombus") from inception up to June 22 of 2019. Papers reporting any vascular or endovascular intervention in BS patients with venous involvement were eligible. The criteria for exclusion were: review papers, arterial or cardiovascular or cerebrovascular interventions, cases with unsatisfactory data and papers in languages other than English. The full texts of papers considered to be eligible were retrieved for further assessment by two independent reviewers (ED, SNE). Disagreements were resolved by senior author (ES). We retrieved the data on demographic features, involved veins, treatment modalities, type of interventions, duration of follow-up and outcome in each included paper. Recanalisation (or patent stent), symptom free clinical follow-up, reocclusion or other complications were assessed as described in papers as outcome parameters.

Informed consent was obtained from each patient. Descriptive statistics were used to describe the findings.

Results

Case 1. A 37-year-old man was diagnosed with BS in 2003 but then lost to follow-up. He had had a DVT extending from inferior vena cava to left popliteal vein. Thrombectomy, thrombolysis, left iliac vein stent and arteriovenous fistula with a graft between superficial femoral artery and common femoral vein had been performed and AC had been prescribed. At the end of one month due to reocclusion; thrombolysis, thrombectomy and graft revision had been redone. Glucocorticoids (GC), azathioprine (AZA) and intravenous (IV) antibiotics had been prescribed.

He was admitted to our clinic with purulent discharge at a surgical site. Right iliac vein thrombosis and collections around vascular structures were found to be consistent with a soft tissue infection. AZA was switched to interferon and IV antibiotics were started. Due to non-resolving infectious complications for 2 months, we referred him to cardiovascular surgery for debridement. Graft excision and debridement resulted in infection control. He is still asymptomatic, continuing interferon 3 days/week and low dose GC with AC for the last 16 months.

Case 2. A 25-year-old man with right femoral DVT had had thrombectomy, balloon angioplasty 18 months before and had used AC for more than a year. He was referred to us due to non-recanalised chronic DVT extending to iliac vein and newly diagnosed with BS. We prescribed interferon and he is asymptomatic at 10th month.

Case 3. A 30-year-old man with BS had had a thrombectomy and thrombolysis because of left iliac, femoral, popliteal vein DVT. After one month from the procedure, under AC therapy, he had ileal infarct and therefore small bowel resection. AZA was started then and continued in our clinic. Fourteen months later, a follow-up imaging revealed partially recanalised flow with chronic thrombosis.

Case 4. A 36-year-old-man had been diagnosed with BS due to left iliac, femoral, popliteal and crural DVTs. He had had thrombectomies and a vena cava filter insertion. AZA, GC and AC had been prescribed. After five months, he was referred to us due to only a partial recanalisation. Complete recanalisation was achieved after one year of infliximab.

Case 5. A 41-year-old woman with BS had had thrombectomy, thrombolysis and AC therapy due to left femoral and popliteal DVT. After 3 months, she was asymptomatic. Control imaging revealed partial recanalisation then complete recanalisation at 3 and 12 months respectively; and AC therapy was stopped.

Systematic literature review

The initial search identified 561 articles (Fig. 1). We excluded 480 after going over the titles or abstracts. After reading full texts of 81 articles, the reasons for the exclusion were: Language other than English (n=5), irrelevant intervention such as arterial, cardiovascular or cerebrovascular involvement or no intervention (n=47), full text not available (n=4) and insufficient data about patients or outcome (n=4). Finally, we included 21 articles reporting 36 cases for the final analysis (Tables I, II).

The demographic characteristics of total 41 patients including our patients, were: 25 males, 9 females, while in 7 patients from the systemic review the gender was not given. The mean age was 32.9 (SD±9.4) (range 19–58 years), however ages of 17 patients were not given. Median follow-up period was 18.5 months (IQR 18.5) (10.5, 29) (range 1–60 months), though this information was not provided for 9 cases. Twenty-seven (65.8%) of the

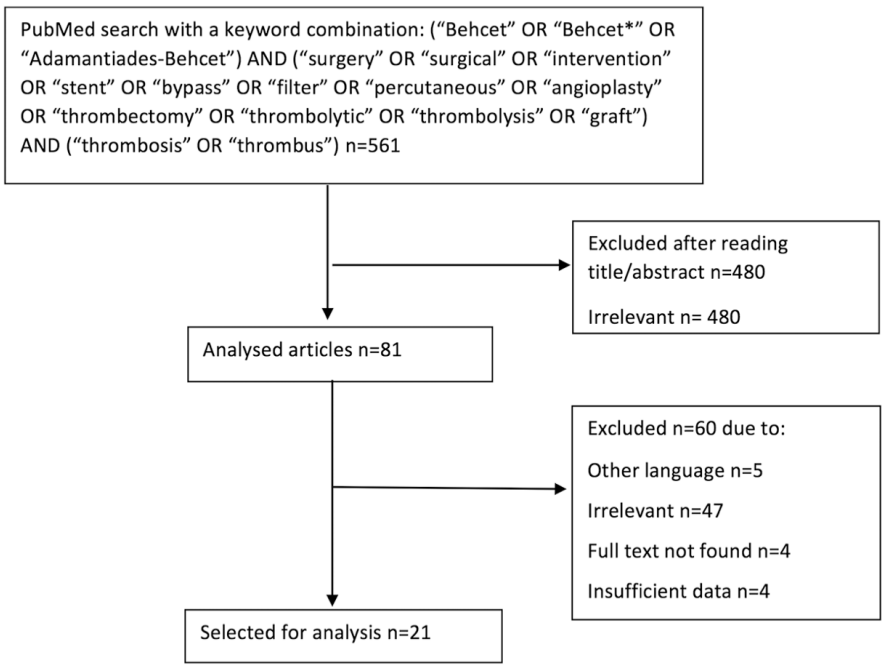

Fig. 1. Flow chart of the study inclusion process.

Table I. Demographic and clinical characteristics of all patients (both published and our cases).

	No. of patients	Mean age (SD), gender	Med. follow-up (month)	Initial IS treatment, n (%)	Acute/chronic
Total	41 (26 centres)	32.9 (SD±9.4) 9 F, 25 M*	18.5 (10.5, 29)	16 (39%)	19 acute 14 chronic*
Lower ext.	21 (15 centres)	31.8 (SD±6.4) 5 F, 12 M*	18 (10.5, 18)	6 (28.5%)	11 acute 5 chronic*
Hepatic/IVC	8 (5 centres)	37 (SD±17.6) 1 F, 5 M*	24 (4.5, 42)	5 (62.5%)	1 acute 5 chronic*
Upper ext./ SVC	12 (10 centres)	37.5 (SD±9.5) 3 F, 8 M*	24 (12, 36)	3 (25%)	7 acute 4 chronic*

*Remaining data was not available; IS: immunosuppressive; ext.: extremities; F: female; M: male; IVC: inferior vena cava; SVC: superior vena cava.

patients had already been diagnosed as BS before the time of intervention; 10 (24.3%) patients had been newly diagnosed with vascular involvement and 4 were diagnosed during complications. Anticoagulants were used in 37 (90.2%), initial IS were used in 16 (39%) patients. IS therapy was not initiated in 15/27 (55.5%) of patients with a known diagnosis of BS.

Lower extremity vein thrombosis

There were 21 LEVT (including iliac vein in 17 and inferior vena cava [IVC] in 6, and not described in 2) cases. In 7 (33.3%) patients target vessels rmained patent after initial intervention after a median follow-up of 24 (IQR: 26) months. Of those 4/7 interventions were performed under IS therapy. In 2 (chronic) cases, the initial interventions had to be discontinued due to inability to enter occluded segment. Reocclusions occurred in 10 patients; 6 patients were in the early postoperative period (ranging 8 days to 1 month). After reintervention of 8/10 of reoccluded cases, blood flow was restored was only in 4 patients, in 15 months (SD ± 10.3); 4 of them remained occluded. In one of the reoccluded cases, IVC filter resulted in perforation of the vessel wall and penetration into the duodenum so the patient had surgical excision of the filter. In another reoccluded patient (our first case) had surgical debridement of complicated abscess. There were 2 cases with partial recanalisation. One had an ileal infarction after 1 month of the procedure and open surgical ileal resection was performed. Overall; 12 (38.7%) of 31 vascular LEVT interventions (3 surgical, 28 endovascular) resulted in favourable results (Table III). Eight of these 12 successful procedures were performed along with IS therapy.

Abdominal thrombosis

There were 8 patients with hepatic vein (HV)/IVC thromboses; 4 of them were chronic and overall 11 interventions were performed (Table III). One chronic BCS patient who had endovascular and surgical treatment, without any medical treatment died due to ileus and multi organ failure at the 5th month of follow-up. Also another chronic BCS patient had reocclusions for 3 times at 5 years follow-up despite multiple interventions, AC and GC therapy. Four patients with IS therapy had successful results during a median follow-up of 24 months. Patent stents were reported in 2 patients only with AC therapy, though follow-up times were not stated.

Upper extremity/superior vena cava (SVC) thrombosis

There were 12 upper extremity/SVC thrombosis cases and overall 18 interventions (Table III). Five patients had favourable results at a median 24 (IQR: 18) months of follow-up. Seven patients (2 chronic and 5 acute thrombosis) were reoccluded; 6 of them were under AC monotherapy. Reintervention in these patients resulted in blood flow with patent stents. IS was initiated in 3/7 reintervention patients. All 12 patients were using AC; 3 of 5 initially successful cases were under IS therapy.

Discussion

In this systematic review, initial endovascular or surgical interventions resulted in unfavourable results in 22 (53.6%) of 41 BS patients with venous thrombosis. Among the cases with favourable outcomes; the follow-up time

Table II. Demographic characteristics, treatments and outcomes of literature cases.

Author, year, reference	Gender, age	Involved veins	Invasive procedure	Medical treatment	Follow-up period	Outcome
Uyaroglu, 2018 (23)	Male, 24	SVC, intracardiac thrombus	Shunt between left brachiocephalic vein and right atrium; under GC, interferon, AC 1 month later balloon angioplasty	GC, Infliximab	3 years	Asymptomatic
Atas, 2018 (24)	Male, 33	Left femoral, common iliac veins	Ultrasound-accelerated catheter-directed thrombolysis	GC, AC, cyclophosphamide, infliximab	2 months	Recanalised
Lakha, 2018 (25)	Male, 19	Left common iliac, common femoral veins	Pharmaco-mechanical thrombolysis and thrombectomy failure; then thrombolysis and stent; reoccluison at 5 months: thrombolytic thrombectomy,second stent	AC, 5 months later AZA, GC	12 months	Asymptomatic
Chassin-Trubert, 2018 (26)	Female, 37	İliofemoral veins	IVC filter; 12 months later thrombosis and IVC wall perforation into duodenum; surgical removal	AC	6 months	Asymptomatic
Thorell, 2015 (27)	Female, 52	Chronic Subclavian veins, left brachiosephalic vein (SVCS) , LEVT	SVC stent	AC, AZA	12 months	Patent stent
Seinturier, 2014 (28)	Female, 30	Right femoral, common iliac vein, Pulmonary parenchyme lesion	Endovascular fibrinolysis, thrombectomy, thrombolysis failure. At 1 year baloon dilatation, stent	AC, GC. After 2 months AZA	30 months	Asymptomatic
Li, 2014 (29)	2 patients, NA	LEVT*	IVC filter	Pulse GC, post op thrombolysis, AC, IVIG, immunosuppressive	24 months	Emboli resolution at 3 months, no relapse
Li, 2014 (29)	2 patients, NA	IVC hepatic vein (BCS)	IVC thrombectomy, HV balloon angioplasty	Immunosuppressive	24 months	Recanalised
Geng, 2013 (30)	Male, 40	Bilateral LEVT, IVC, PAA, left renal vein	IVC filter, PAA coil	AC, GC, Cyclophosphamide	9 months	No relapse
Celik, 2013 (31)	Female, 32	SVC, bilateral jugular, brachiocephalic veins, SVCS	Local thrombolysis	AC, GC, AZA	24 months	Asymptomatic
Jeong, 2013 (32)	Female, 25	IVC, bilateral iliac veins	Thrombectomy, balloon angioplasty	NA	1 month	No relapse
Yu, 2012 (33)	Male, 36	SVC (No thrombosis), SVCS	SVC balloon angioplasty. At first week: SVC stent due to occlusion. 2 months later, excision and bypass due to stent thrombosis	AC, 2 months later GC	12 months	No relapse
Tekbas, 2012 (34)	Male, NA	Chronic bilateral iliofemoral veins, IVC	PTA and stent failure	AC	NA	Reocclusion
Tekbas, 2012 (34)	Male, NA	Chronic bilateral iliofemoral veins, IVC	Failure of first venous access	AC	NA	Occlusion
Tekbas, 2012 (34)	3 patients, Male, NA	Chronic unilateral iliofemoral vein	PTA, stent. At first month: PTA and local thrombolysis due to reocclusion	AC	NA	Reocclusion
Tekbas, 2012 (34)	Male, NA	Chronic bilateral subclavian, brachiosephalic, internal jugular veins, SVC	Failure of right side intervention; left PTA and stent. At first week: PTA due to reocclusion	AC	48 months	Patent stent
Tekbas, 2012 (34)	Male, NA	Chronic bilateral subclavian, brachiosephalic, internal jugular veins, SVC	Bilateral PTA and stent. At 8 months: PTA due to reocclusion	AC	36 months	Patent stent
Tekbas, 2012b(34)	Male, NA	Chronic subclavian vein	PTA	AC	12 months	Patent vein
Tekbas, 2012 (34)	Male, NA	Chronic hepatic IVC stenosis (BCS), Iliofemoral veins	IVC stent, iliofemoral PTA	AC	NA	Patent stent

Author, year, reference	Gender, age	Involved veins	Invasive procedure	Medical treatment	Follow-up period	Outcome
Tekbas, 2012(34)	Male, NA	Chronic infrahepatic, suprahepatic IVC (BCS)	IVC stent	AC	NA	Patent stent
Vandergheynst, 2008 (35)	Male, 38	SVC (No thrombosis), SVCS	SVC angioplasty	AC, GC, AZA	36 months	Asymptomatic
Han, 2004 (36)	Male, 45	Hepatic vein, IVC (BCS)	IVC baloon angioplasty, stent	AC, GC, AZA	NA	Patent stent
Kuniyoshi, 2002 (37)	Male, 24	Chronic IVC (BCS)	PTA failure for 3 times, 11 months later: resection, thrombectomy, IVC graft	AC, GC	5 years	HV IVC reocclusion, resection, HV-right atrium graft bypass
Kuniyoshi, 2002 (37)	Female, 58	Chronic HV, IVC (BCS)	At 6 months: resection, thrombectomy	None	5 months	Ileus, MOF, exitus
Uthman, 2001 (38)	Male, 27	Right subclavian vein	Local thrombolysis, balloon angioplasty. At first month: balloon dilatation and stent due to reocclusion	AC	6 months	No relapse
Ko,2001 (39)	Female, 24	SVC, left internal jugular, external jugular, subclavian vein	Thrombectomy. Reocclusion at first month	AC, GC after 1 month	6 months	No relapse
Radke, 2001 (40)	Female, 29	Right iliofemoral, IVC, right renal veins	IVC filter, but excised 8 days later due to persistent occlusion	AC, Cyclosporin	12 months	Asymptomatic
Kroger,1997 (41)	Male, 27	SVC, brachiocephalic, subclavian, right internal jugular vein	Thrombolysis. reocclusion after 2 weeks	AC, GC	NA	VCSS
Sağdıç, 1996 (42)	NA	Iliofemoral vein*	IVC filter	AC	28 months	No emboli
Sağdıç, 1996 (42)	NA	Left iliac vein, saphenous thrombophelibitis	Bypass graft and AV fistula,	AC	31 months	Reocclusion and post thrombotic syndrome
Sağdıç, 1996 (42)	NA	SVC	Right innominate vein- right atrium bypass graft	AC	24 months	Collaterals
Bismuth, 1990 (43)	Male, 21	HV, IVC, BCS, intracardiac thrombus*	Mesoatrial shunt graft	AC, GC	4 months	Patent graft

*Pulmonary thrombosis accompanies
IVC: inferior vena cava; SFA: superficial femoral vein; CFV: common femoral vein; AC: anticoagulant; GC: glucocorticoid; AZA: azathioprine; SVC: superior vena cava; SVCS: superior vena cava syndrome; HV: hepatic vein; BCS: Budd Chiari syndrome; PTA: percutaneous transluminal angioplasty; NA: not available; PAA: pulmonary artery aneurysm; LEVT: lower extremity vein thrombosis.

was not available in 3 patients and was only one month in 1 patient, so their final outcomes were ill-defined. In LEVT interventions, 4 of 7 procedures which were reported to be successful initially were IVC filter insertions. The main outcome in these patient reports had been considered as prevention of pulmonary emboli, rather than recanalisation of the involved vein. However it is to be noted that emboli are rare in BS in any event (13).

The cumulative incidence of recurrence in any deep vein thrombosis (patients with risk factors are included) is about 18% in 2 years (14). On the other hand, the relapsing nature and incomplete recanalisation of venous thrombosis due to BS is more pronounced even under IS therapy. In our prospective study in LEVT of BS, patients had a 37% relapse rate in one-year of follow-up (15). Vascular inflammation in BS, especially in LEVT, is diffuse and involves extensive segments which may explain why it is less susceptible to mechanical removal.

The failure of these procedures in BS might also be related to the pathergy reaction. Pathergy usually describes a skin inflammation in which trauma leads to the development of a pustule and is a rather specific diagnostic test in BS. This phenomenon may be also seen in sites other than skin and have been reported after dental procedures, injections or venipuncture. For this reason, vascular surgery is recommended in only patients with peripheral arterial aneurysms along with IS therapy. Vascular incision is supposed to trigger an inflammatory response as in pathergy, such as reocclusion or vena cava wall perforation in the same localisation in these cases. There are reports of aneurysm development at anastomosis or angiography catheter puncture sites which are attributed to pathergy reaction and also more frequent occlusions of arterial grafts because of endothelial dysfunction (16). A retrospective study

Table III. Outcome of all patients from the literature and our case series.

	No. of patients	No. of patients with unfavourable outcome	No. of interventions
Total	41	22 (53.6%) failure	60 procedures*
Lower ext.	21	2 occlusions,10 reocclusions, 2 partial recanalisation	31 procedures (3 surgical, 28 endovascular) 12 favourable: 8/12 with IS
Hepatic/IVC	8	1 reocclusion, 1 death	11 procedures (2 surgical, 9 endovascular) 6 favourable: 4/6 with IS
Upper ext./ SVC	12	7 reocclusions	18 procedures (2 surgical, 16 endovascular) 11 favourable: 6/11 with IS

*Some patients have more than one intervention; ext.: extremities; IS: immunosuppressive; IVC: inferior vena cava; SVC: superior vena cava.

showed that, postoperative complications occurred more frequently after surgeries that were performed in patients with positive pathergy test and after vascular surgeries than after non-vascular surgeries in BS (17). Also surgeries that were followed by GC and IS agents showed a significantly lower postoperative complication rate (17).

Not only in BS but in any proximal LEVT, the PTS develops within 2 years in approximately half of the patients (18, 19). PCDT is the delivery of a thrombolytic drug into the thrombus with concomitant thrombus aspiration or maceration (thrombectomy). The objective of this procedure is to diminish the thrombosis burden by means of low-dose thrombolysis and mechanical therapy, thereby reducing the risk of the PTS while minimising the risk of bleeding. There are 2 large randomised controlled trials which examine the efficacy of this procedure on PTS and venous patency in ordinary acute LEVT patients. Vedantham *et al*. assessed the outcome of PCDT in 692 patients with acute proximal DVT due to any cause (20). The addition of PCDT to AC monotherapy did not result in a lower risk of the post-thrombotic syndrome (47% *vs*. 48%) or recurrent venous thromboembolism (12% *vs*. 8%) over the 24-month follow-up period. However, PTS was reported to be milder in PCDT group.

In the CaVenT study; the absolute risk reduction of PTS by additional catheter-directed thrombolysis was 14% and 28% in 24 months and at 5-years of follow-up respectively (21, 22). Also recurrent thromboembolism was 11% *vs*. 18% at 2 years and 15% *vs*. 18% at 5 years of follow-up, in the intervention and control groups, respectively. In this series and literature, it was also the preferred procedure in 10/21 patients with LEVT. BS cases had less recanalisation and more recurrence than the procedures in ordinary LEVT cases.

Our study has some limitations. First, there were no well-defined standard outcomes because of the difference of the thrombus localisation and the type of procedures. Second, our systematic review consisted of only published papers in PubMed; so cases in meetings or abstract books or other sources of databases were ignored. Third, there is the possibility that some unsuccessful interventions were never reported. Finally, the short follow-up times in some cases limit a proper assessment of outcomes.

In conclusion, the interventions reported do not seem to reduce the chronic disease course of BS. Furthermore, they frequently result in infectious or veno-occlusive complications. IS still seems to be the only evidence-based therapeutic option in venous involvement. The repeated hospitalisations and the fiscal burden associated with the interventions need also to be considered.

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