Options in the treatment of superficial and deep venous disease in patients with Klippel-Trenaunay syndrome

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ABSTRACT

Objective: Klippel-Trenaunay syndrome (KTS) is a congenital mixed mesenchymal malformation syndrome that includes varicose veins, capillary and venous malformations, lymphatic abnormalities, and hypertrophy of various connective tissue elements. The purpose of the present study was to describe the clinical characteristics and outcomes in a subset of patients with KTS in whom venous interventions, including iliofemoral venous stenting, were performed after failure of conservative therapy.

Methods: A single-center retrospective data review of 34 patients with KTS who had undergone interventions for venous disease between January 2000 and December 2020 was performed.

Results: Their mean age was 38.4 ± 17.5 years (range, 12-80 years). No gender predilection was found. Of the 34 patients, 61% had had all three features of the classic triad for KTS. Varicose veins were present in all 34 patients (100%), and 30% had had a history of bleeding varicosities. Most patients (79%) had CEAP (Clinical, Etiology, Anatomy, and Pathophysiology) class ≥C4. Of the 34 patients, 30% had a history of deep vein thrombosis and/or pulmonary embolism. Factor VIII elevation was the most common thrombophilia condition (12%). The venous filling index was elevated at baseline (5.9 ± 5.1 mL/s) and did not normalize despite intervention (3.5 ± 2.3 mL/s; $P = .04$). The superficial venous interventions (n = 35) included endovenous laser therapy; stripping of the great saphenous vein, small saphenous vein, anterior thigh vein, or marginal vein; ultrasound-guided sclerotherapy; and stab avulsion of varicose veins. One coil embolization of a perforator vein was performed. Deep interventions (n = 19) included endovenous stenting (n = 15), popliteal vein release (n = 3), and valvuloplasty (n = 1). The venous clinical severity score had improved from 9.4 ± 4.5 to 6.2 ± 5.6 ($P = .04$). The visual analog scale for pain score had improved from 5.5 ± 2.7 to 2.5 ± 3.3 ($P = .008$). Healing of ulceration was noted in 75% of the patients. Significant improvements in the total pain ($P = .04$) and total psychological ($P = .03$) domains were noted in the 20-item chronic venous disease quality of life questionnaire.

Conclusions: Superficial and deep venous interventions are safe and effective in patients with KTS when conservative therapy has failed. Iliofemoral venous stenting is a newer option that should be considered in the treatment of chronic deep venous obstructive disease in patients with KTS in the appropriate clinical context. An aggressive perioperative deep vein thrombosis prophylaxis protocol should be in place to reduce thromboembolic complications in these patients. (J Vasc Surg Venous Lymphat Disord 2022;10:1343-51.)

Keywords: iliofemoral vein stent; IVUS; Klippel-Trenaunay syndrome; KTS; Varicose veins; Venous leg ulcers

Klippel-Trenaunay syndrome (KTS), or capillary lymphaticovenous malformation, is a congenital mixed mesenchymal malformation syndrome that includes the constellation of the following findings: varicose veins, capillary malformations, venous malformations (VMs), lymphatic malformations, and hypertrophy of various connective tissue elements.[1] The classic triad of KTS includes limb hypertrophy, varicose veins, and port wine stain (nevus flammeus).[2] Rheologically, KTS is categorized as a slow flow combined vascular malformation or a hemolymphatic malformation.[3,4] It can be complicated by venous leg ulcers, cellulitis, superficial thrombophlebitis, deep vein thrombosis (DVT), pulmonary embolism (PE), and bleeding from varicosities.[5,6]

Traditionally, the venous symptoms in those with KTS have been managed with conservative therapies, including compression, elevation, and wound care.[2,7] With the advent of minimally invasive endovascular therapies, these have been used increasingly for patients with KTS. However, the overall experience with these therapies, including iliofemoral venous stenting, for patients with KTS has remained limited.

The purpose of the present study was to describe the clinical characteristics and evaluate the outcomes for a subset of patients with KTS in whom venous interventions, including iliofemoral venous stenting, had been performed.

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Author conflict of interest: S.R. has U.S. patents for intravascular ultrasound diagnostics and an iliac vein stent design. T.S. and C.L. have no conflicts of interest.

Additional material for this article may be found online at www.jvsvenous.org.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X

https://doi.org/10.1016/j.jvsv.2022.04.020

METHODS

Study design and setting. A retrospective data review of consecutive patients with KTS who had undergone interventions for venous disease between January 2000 and December 2020 was undertaken. We performed a single-center study (three surgeons) at a specialty venous clinic at a tertiary care hospital. All the patients provided written informed consent. The institutional review board approved the report of de-identified patient data from the study.

Diagnosis of KTS. The causative gene for KTS is believed to be a regional somatic mutation. In the present series, KTS had been diagnosed clinically and radiologically by based on the presence of capillary lymphaticovenous malformations with hypertrophy of skeletal and soft tissue elements.[1] Capillary malformations are the port wine stains seen on clinical examination. The varicosities will be atypical, such as lateral varicose veins. Deep VMs include ectasia, aneurysmal degeneration, external compression, duplication, hypoplasia, and segmental aplasia. Lymphedema is commonly encountered in these patients, and cavernous lymphatic malformations can also occur.[2] Noninvasive imaging studies, including duplex ultrasound, computed tomography, and magnetic resonance imaging (MRI), can be helpful for delineating many features of the syndrome. In addition, ascending venography and lymphoscintigraphy have been used in select patients.[6]

Inclusion criteria. Patients with KTS who had undergone any form of surgical or endovascular treatment for their venous disease after failure of ≥3 to 6 months of conservative therapy were included in the present study. Only patients with ≥6 months of follow-up data were included in our study.

Exclusion criteria. Patients with syndromes other than KTS were excluded. In addition, patients with KTS who only had received conservative management of their disease were excluded. Finally, patients with <6 months of follow-up data were also excluded.

Conservative therapy. A trial of conservative therapy was attempted for all patients for ≥3 to 6 months. Conservative therapy included graduated compression stockings, leg elevation, assisted ambulation, and manual decongestive therapy.[8] Initially, compression garments (ie, elastic or nonelastic), leg elevation, and mobilization were recommended to all the patients. If these had failed to control symptoms, decongestive therapy in the form of either manual lymphatic drainage and/or the use of an intermittent pneumatic lymphatic pump. Local wound care was also considered for patients with ulcers. The outcomes were assessed by measurement of the leg dimensions at each visit. The symptoms were also assessed in detail at each visit to document any improvement or worsening.

ARTICLE HIGHLIGHTS

- **Type of Research:** A single-center, retrospective study
- **Key Findings:** When performed in patients with Klippel-Trenaunay syndrome (KTS), venous intervention, including iliofemoral venous stenting, can result in improvement in the venous clinical severity score, visual pain scale score, and grade of swelling. Elevation in the venous filling index in patients with KTS might be related to the presence of underlying microscopic arteriovenous fistulas or shunts.
- **Take Home Message:** Iliofemoral venous stenting should be considered as a treatment option for patients with KTS in the appropriate clinical context when conservative therapy has failed.

Treatment indications. At our center, the indications for invasive treatment of KTS are in line with those described at the Mayo clinic and Lee et al[4] in their experience.[1,7] The absolute indications included hemorrhage, nonhealing ulcerations, recurrent infections, and acute thromboembolism. The relative indications included pain, swelling, functional impairment, and other complications of chronic venous hypertension that were refractory to conservative therapy. The additional indications considered included location of a lesion in an area with high risk of complications (eg, DVT and PE).[4] All the patients in our sample had had CEAP (Clinical, Etiology, Anatomy, and Pathophysiology) class ≥3. In general, the superficial venous system was treated first. If that had failed to relieve the symptoms, treatment of the deep venous system was considered in the appropriate clinical context.

Data collection. The following data points were recorded: demographic data, clinical presentation, associated findings, CEAP classification, preoperative and postoperative venous clinical severity score (VCSS), and the results of diagnostic imaging studies. The type of surgical or endovascular procedure performed and the subsequent outcomes at follow-up were also recorded. The performance of reintervention was also recorded.

Clinical parameters. Swelling was graded clinically from grade 0 to 4 (grade 0, none; grade 1, pitting but not obvious overall grade 2, ankle edema; grade 3, gross, involving the leg below the knee; grade 4, gross, involving the whole limb). The visual analog scale (VAS) for pain was used to assess pain using a scale of 0 to 10. The VCSS was also recorded.[7]

Thrombophilia panel. Patients with KTS have a propensity for developing venous thromboembolism. The VMs can develop thrombi and phleboliths.[9] The marginal vein is especially predisposed to the development

of venous thromboembolism, which can lead to PE.[4] Patients with KTS and a history of venous thromboembolism and/or the presence of a marginal embryonic vein underwent thrombophilia panel testing. However, this testing could not be obtained for the entire patient cohort because of insurance coverage issues. Most carriers will only cover thrombophilia testing if the patient has a history of chronic embolism and thrombosis. The thrombophilia panel includes testing for the following factors at our center: homocysteine, prothrombin time, international normalized ratio, partial thromboplastin time, dilute Russell viper venom time, thrombin time, protein C, protein S, antithrombin III, prothrombin G20210A mutation, platelet count, factor V gene mutation, factor VIII, factor IX, factor XI, anticardiolipin antibody, β_2-glycoprotein antibodies, and lupus anticoagulant.[10]

Investigative studies. All the patients had undergone duplex ultrasound with contrast-enhanced venography. For select patients, evaluation of chronic iliofemoral venous obstruction was performed using either computed tomography venography or magnetic resonance venography, when it became available. Lymphoscintigraphy was performed for select patients. Of these tests, duplex ultrasound should be the initial diagnostic study for all patients because it is noninvasive, inexpensive, and easily available. VMs will usually demonstrate monophasic flow.[11] Duplex ultrasound can provide, not only excellent B-mode images of various anatomic abnormalities such as hypoplasia, venous compression, ectasia, and aneurysms, but also crucial hemodynamic information such as segmental pressure to rule out other conditions such as high-flow arteriovenous malformations (AVMs). Valvular incompetence of the superficial and deep systems can also be assessed using duplex ultrasound. The use of ascending venography can provide vital information about the patency of the deep system and can also help with operative planning for patients with KTS by providing information about how the VM and deep system communicate with each other. Computed tomography venography can provide visualization of the extent of the malformation; however, but it might not be able to consistently differentiate AVMs from VMs, especially if the computed tomography has not been well timed.[12] Dynamic contrast-enhanced MRI provides excellent resolution of the soft tissue components and VMs that might not be readily apparent by physical examination alone.[7] VMs will be visualized as high T2-weighted signals on MRI.[11]

Procedural details. Deep venous procedures were usually performed with the patient under general anesthesia. All the patients at our center received preoperative DVT prophylaxis with low-molecular-weight heparin (excluding sclerotherapy) in accordance with our routine protocol. Postoperatively, select patients received additional anticoagulation therapy. Overall, interventions were performed on the superficial venous system, deep venous system, or perforator veins. Generally, interventions were performed in a stepwise or staged manner, and they were individualized to the specific patient. Superficial venous procedures were generally performed first. If the symptoms were not relieved, the deep venous system was then addressed. Superficial venous procedures included ultrasound-guided sclerotherapy, endovenous laser therapy (EVLT), high ligation and division of veins with or without stripping, and avulsion of varicose veins (stab phlebectomy). To reduce blood loss during excision of varicose veins and VMs, an Esmarch bandage and thigh tourniquet were used.

The deep venous interventions included valvuloplasty, popliteal vein release, and iliofemoral venous stenting. Closed external venous valve repair (transcommissural valvuloplasty) was performed in one patient to treat a nonhealing ulcer and deep venous reflux. The site of the repair was the proximal femoral vein and profunda vein and was approached through a single incision. After meticulous adventitial dissection, thin valve attachment lines were seen. Transluminal resuspension sutures were then placed. The technique for the repair has been previously described in detail.[13] The ulcer had healed within 3 months postoperatively. In addition, the patient's pain and swelling had both improved after the surgery. Popliteal vein release surgery was performed via a medial incision in three patients to treat severe pain and swelling that had not been responsive to conservative therapy and for whom other causes of chronic venous insufficiency had been excluded. These patients had evidence of popliteal entrapment on plantar flexion maneuver during ascending venography, with supportive evidence from popliteal vein pressure measurements across the entrapped popliteal venous segment. In all three patients, the entrapment had resulted from anomalies of the medial head of the gastrocnemius muscle. The technique for the procedure has been previously described in detail.[14] Finally, iliofemoral venous stenting was considered for patients who had remained symptomatic despite conservative therapy. For these patients, other causes of chronic venous insufficiency had been treated or excluded and they had had radiographic evidence of chronic iliofemoral venous obstruction. In general, these were patients with secondary complications of chronic venous hypertension.

Intravascular ultrasound (IVUS), which is more sensitive than venography,[15] was used to guide iliofemoral venous stenting by providing landing zones for the stents and stent sizing. Wallstents (Boston Scientific, Marlborough, MA) were used for stenting, with the addition of Z-stents (Cook Medical, Inc, Bloomington, IN) used cranially at the iliocaval confluence if additional radial force was required. In the appropriate clinical context, venous

stenosis was treated if the cross-sectional area or diameter was smaller than the following measurements on IVUS: common iliac, external iliac and common femoral vein segments: 16 mm (area, 200 mm^2), 14 mm (area, 150 mm^2), and 12 mm (area, 125 mm^2) diameters, respectively.[10] For iliofemoral venous stenting, any reinterventions performed were also recorded. Reinterventions were performed for residual or recurrent symptoms in these patients and included repeat angioplasty and caudal or cranial stent extension.[16,17] The perforator vein interventions included coil embolization of the perforator vein.

Follow-up surveillance. All the patients were followed up in the clinic initially at 3 to 6 weeks after the procedure and at 3- to 6-month intervals thereafter. The most recent documented follow-up data were used for the purposes of statistical analysis. At each follow-up visit, we assessed the following parameters: VCSS, VAS for pain score, grade of swelling (GOS), healing of ulcers, and quality of life measures. Any complications resulting from the intervention were noted. In addition, compliance to compression therapy was recorded and reinforced. If any superficial intervention were performed (eg, EVLT of a superficial vein), it has been our protocol to obtain an ultrasound to document closure of the treated vein at 3 to 6 weeks after the procedure. If any deep system intervention was performed, the follow-up protocol was individualized according to the procedure performed. Thus, for patients who had undergone valvuloplasty and popliteal vein release, air plethysmography testing was repeated after the procedure during follow-up to document any changes. For patients who had undergone iliofemoral venous stenting, ultrasound of the stented venous segment was obtained at every follow-up visit to detect stent malfunction early if it had occurred. Additional tools, not used in the present study, that can be used to measure the outcomes and monitor these patients with KTS also include water displacement volumetry and bioimpedance.

Statistical analysis. Statistical analysis was performed using a commercially available statistics program (Prism, Irvine, CA). A χ^2 test or t test was used for analysis, as appropriate. $P < .05$ was considered to indicate statistical significance.

RESULTS

Demographics. Data from 34 patients with KTS, involving 34 limbs, were analyzed for the purpose of the present study (Table I). Their mean age was 38.4 ± 17.5 years (range, 12-80 years). No gender predilection was found. Only 61% of the patients had had all three features of the classic triad for KTS. Varicose veins were present in all 34 patients (100%), and 30% had had a history of bleeding varicosities. Most patients (79%) had CEAP class ≥C4. The most frequent symptom was pain (100%). All 34 patients had involvement of the lower limb in the present study.

Table I. Demographics and other details of patients with Klippel-Trenaunay syndrome (KTS)

Parameter	Mean ± SD or No. (%)
Age, years (range)	38.4 ± 17.5 (12-80)
Male gender	17 (51.5)
Varicose veins	33 (100)
Limb hypertrophy	17 (51.5)
CM (port wine stain)	30 (91)
Complete triad	20 (60.6)
Pain	33 (100)
Edema	32 (97)
Superficial thrombophlebitis	11 (33.3)
DVT	10 (29)
PE	3 (9.1)
Thrombophilia conditions	
Factor VIII elevation	4 (12.1)
Antithrombin III deficiency	3 (9.1)
Protein C deficiency	1 (3)
Protein S deficiency	1 (3)
Prothrombin gene mutation	1 (3)
History of bleeding varicosities	10 (30.3)
Lymphedema	13 (39.4)
CEAP	
C3	7 (21.2)
C4	19 (57.6)
C5	3 (9.1)
C6	4 (12.1)
Limb laterality	
Right	12 (35.3)
Left	22 (64.7)

CEAP, Clinical, Etiology, Anatomy, and Pathophysiology; *CM*, capillary malformation; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism; *SD*, standard deviation.

The VMs encountered in our patient population are summarized in Supplementary Table I (online only). The most common VMs included lower extremity intramuscular VMs (n = 12; 35.3%), deep venous incompetence (n = 11; 32.3%), lateral marginal vein (n = 10; 29.4%), and iliac vein hypoplasia (n = 10; 29.4%). Many patients had had more than one VM (Supplementary Figs 1 and 2, online only).

Thrombophilia conditions and venous thromboembolism. Of the 34 patients, 33% had a history of superficial thrombophlebitis and 29% a history of DVT and/or pulmonary embolism (PE; Table I). Of these 34 patients, 4 had had DVT in the calf veins, 2 in the femoropopliteal veins, and 4 in the lateral marginal vein. Two patients with lateral marginal vein thrombosis and one patient with femoral vein DVT had developed PE. Factor VIII

Table II. Preoperative contrast-enhanced lower extremity phlebography findings in patients with Klippel-Trenaunay syndrome (KTS)

Finding	Patients, No. (%)
Lateral marginal vein	10 (29.4)
Incompetent GSV	8 (24.2)
Incompetent perforator veins	6 (18.2)
Incompetent SSV	5 (15.2)
Incompetent popliteal vein	4 (12.1)
Popliteal entrapment	3 (9.1)
Dilated SSV	2 (6.1)
Duplicated SSV	1 (3)
Narrowing of CFV	6 (17.6)
Hypoplastic hypogastric vein	1 (3)
Narrowing of popliteal vein	5 (14.7)

CFV, Common femoral vein; *GSV,* great saphenous vein; *SSV,* small saphenous vein.

elevation was the most common thrombophilia condition (12%), followed by antithrombin III deficiency (9%; Table I).

Contrast phlebography and lymphoscintigraphic findings. The most common phlebographic findings (Table II) included a lateral marginal vein (29.4%), incompetent great saphenous vein (24%), incompetent perforator vein (18%), and incompetent small saphenous vein (15%). Dermal backflow (61%) and collateral lymphatic channels (54%) were the most common lymphoscintigraphic findings (Table III).

Interventions. A total of 34 patients with KTS had undergone venous interventions on 34 limbs (Supplementary Fig 3, online only). These included 35 superficial interventions, 19 deep interventions, and 1 perforator vein intervention. Superficial venous interventions (n = 35) included EVLT or stripping of the great saphenous vein, small saphenous vein, anterior thigh vein, or marginal vein; ultrasound-guided sclerotherapy; and stab avulsion of varicose veins. Of the five extremities treated for a marginal vein, four were in the lateral marginal vein and one in the medial vein. One coil embolization of a perforator vein was performed. Deep interventions (n = 19) included endovenous stenting, popliteal vein release, and valvuloplasty. Reinterventions (n = 4) were required for 4 of 15 patients (27%) in whom stenting had been performed. The reinterventions were distal stent extension (n = 2) and repeat angioplasty for in-stent restenosis (n = 2). One inferior vena cava filter had been placed in the present study in a patient who had developed postoperative DVT or PE after valvuloplasty.

Table III. Lower extremity lymphoscintigraphic findings (n = 13) in patients with Klippel-Trenaunay syndrome (KTS) and lymphedema

Finding[a]	Patients, No. (%)
Delayed transit time	6 (46.2)
Dermal backflow	8 (61.5)
Presence of collateral vessels	7 (53.8)
Decreased number of lymph nodes visualized	5 (38.5)
Visualization of popliteal lymph nodes	3 (23.1)
Absence of lymphatic activity	2 (15.4)

[a]Some patients had had more than one finding.

Air plethysmography parameters. The following parameters demonstrated a trend toward improvement after intervention (Table IV): venous volume, ejection volume, ejection fraction, recovery time, and venous filling index (VFI_{90}). For the VFI_{90}, the association between the pre- and postoperative values was significant ($P = .04$).

Clinical parameters. The mean preprocedural VCSS was 9.4 ± 4.5. Trends toward improvement were seen in the following clinical parameters after intervention (Table V): VCSS, VAS for pain score, and GOS. For the VCSS and VAS for pain score, these associations were significant ($P = .04$ and $P = .008$, respectively).

Clinical effects of stenting. A subset analysis of the 15 patients who had received stents was also performed (Table VI). The mean preprocedural VCSS was 10.3 ± 5.1 which had improved to 6.25 ± 6 after stenting ($P = .03$). In addition, the VAS for pain score and GOS had improved significantly (Table VI).

Ulcer healing. Four patients (12%) had had ulcers. In two patients, the ulceration had healed after iliofemoral venous stenting. In one additional patient, the ulcer healed after valvuloplasty. In one patient, a large venous ulceration had not healed despite iliofemoral venous stenting and diligent wound care.

Complications. The procedures were associated with minimal morbidity and no mortality. The procedural complications included access site hematomas (n = 2), superficial thrombophlebitis (n = 1), and DVT/PE (n = 1). The DVT/PE was femoropopliteal in location and had occurred after valvuloplasty. An inferior vena cava filter was placed in this patient as a protective strategy against further embolic episodes.

Anticoagulation therapy. Long-term anticoagulation therapy was continued for 15 patients. The indications for long-term anticoagulation therapy included pulmonary embolism in three, recurrent DVT in five, DVT in the presence of thrombophilia in seven, and a lateral marginal vein associated with a history of DVT/PE that could not be excised in five. Some patients had more than one

Table IV. Air plethysmography parameters in patients with Klippel-Trenaunay syndrome (KTS)

APG parameter (normal)	Preoperatively	Postoperatively	*P* value
VV, mL	197 ± 116	212 ± 156	.74
EV, mL	80 ± 51	92 ± 67	.56
EF, % (>50%)	49 ± 24	54 ± 20	63
RT, seconds	12.8 ± 8.7	13.9 ± 5.9	.71
RVF (<50%)	42.7 ± 27.3	45.4 ± 28.3	.79
VFI_{90}, mL/s (2.2 mL/s)	5.9 ± 5.1	3.5 ± 2.3	**.04**

APG, air plethysmography; *EF*, ejection fraction; *EV*, ejection volume; *RT*, recovery time; *RVF*, residual volume fraction; VFI_{90}, venous filling index *VV*, venous volume.
Data presented as mean ± standard deviation.
Boldface *P* values represent statistical significance.

indication. The agents used for anticoagulation therapy included warfarin, apixaban, and rivaroxaban.

Quality of life questionnaire. The associations between the pre- and postintervention values were significant for the pain ($P = .04$) and psychological ($P = .03$) domains of the 20-item chronic venous disease quality of life questionnaire (Supplementary Table II, online only).

Follow-up. The mean follow-up duration was 77.5 ± 69.9 months (range, 8-224 months).

DISCUSSION

Clinical features. In the present study, 61% patients had had all three features of the classic triad for KTS. All patients had had varicose veins. Pain was the most frequent symptom (100%). These findings are similar to those from previous studies in which all patients had been noted to have varicose veins and pain was the most frequent symptom.[1,18] All three features of the classic KTS triad were present in only 55% of the patients.[1]

Venous thromboembolism in patients with KTS. In the present study, 29% of patients with KTS had had a history of DVT or PE. This is similar to previous studies in which ≤39% of the patients with KTS in a cohort had experienced thromboembolic complications.[19] Patients with KTS have a risk of recurrent DVT.[20,21] In one study,

Table V. Clinical parameters in patients with Klippel-Trenaunay syndrome (KTS) who had undergone venous interventions

	Score		
Parameter	Before intervention	After intervention	*P* value
VCSS	9.4 ± 4.5	6.2 ± 5.6	**.04**
VAS score	5.5 ± 2.7	2.5 ± 3.3	**.008**
GOS	2.5 ± 1.4	1.9 ± 1.6	.15

GOS, Grade of swelling; *VAS*, visual analog scale (for pain); *VCSS*, venous clinical severity score.
Data presented as mean ± standard deviation.
Boldface *P* values represent statistical significance.

Table VI. Clinical parameters of patients with Klippel-Trenaunay syndrome (KTS) who had undergone iliofemoral venous stenting (n = 15)

	Score		
Parameter	Before intervention	After intervention	*P* value
VCSS	10.3 ± 5.1	6.25 ± 6	**.03**
VAS score	6.3 ± 1.8	2.1 ± 2.9	**.02**
GOS	3.1 ± 1	1.6 ± 1.3	**.02**

GOS, Grade of swelling; *VAS*, visual analog scale (for pain); *VCSS*, venous clinical severity score.
Data presented as mean ± standard deviation.
Boldface *P* values represent statistical significance.

patients with KTS demonstrated higher levels of D-dimer, plasmin-antiplasmin complexes, and alterations in protein C and S levels compared with healthy controls.[19] Additionally, localized intravascular coagulopathy (LIC), leading to consumption of certain coagulation factors and blood stagnation within abnormally developed, enlarged blood vessels, could contribute to a greater incidence of venous thromboembolism in patients with KTS.[19] This LIC includes a slight reduction in platelets (100,000-150,000/mm^3), a normal prothrombin time and adjusted partial thromboplastin time, low fibrinogen levels (150-200 mg/dL), and elevated D-dimer levels. D-dimer can be used to differentiate a slow-flow disorder such as KTS vs a high-flow disorder such as Parkes-Weber syndrome. LIC can often result in localized pain, which can be treated by heparin.[9] The marginal vein, a common VM component that is frequently valveless, is often the major culprit for the development of DVT and PE in patients with KTS. We had an aggressive perioperative DVT prophylaxis plan of care in place that included the preoperative use of enoxaparin, early ambulation (same day as that of the procedure), and the use of the PlexiPulse System and compression stockings. One patient had experienced DVT/PE after valvuloplasty, and one patient had experienced superficial thrombophlebitis. In patients with KTS, anticoagulation therapy should be considered for cases of acute thromboembolism or thrombophlebitis and also for patients considered at a greater risk of venous thromboembolism (eg, surgery, trauma, pregnancy). Additionally, patients with a lateral marginal vein should have received anticoagulation therapy during the procedure.[11]

Treatment of marginal veins. Several principles should be remembered when treating the marginal vein. Such veins should be treated expeditiously when encountered in childhood in association with venous stasis and a limb length discrepancy. The deep venous system should be investigated to determine its patency before treatment of a marginal vein is undertaken. If the deep system is patent or hypoplastic, the marginal vein can

be treated. In contrast, if the deep venous system is absent, the marginal vein will be an important venous outflow and should not be treated.[4] A lateral embryonic vein can be treated using invagination stripping, an endovenous laser, or radiofrequency ablation and stab phlebectomy.[12]

Interventions. The treatment of KTS is primarily conservative and nonoperative.[1,2,7] The first step in conservative therapy is to instruct patients on the use of compression wraps or stockings (20-40 mm Hg), elevation, and ambulation. Also, the importance of properly fitted compression should be emphasized to all patients.[7] Medications that can be helpful include aspirin (for pain and swelling associated with VMs), antibiotics (for cellulitis), and anticoagulation (for DVT/PE). Nonoperative management also includes meticulous wound care for patients with ulcers. Additionally, patients should be instructed on personal hygiene.[7] All these elements of conservative therapy should be emphasized to patients at every clinic visit.

Intervention was undertaken in the case of failure of ≥3 to 6 months of conservative therapy. The presence of a deep venous system was confirmed in all patients using contrast venography before any superficial intervention was performed.[1] The goal of treatment was not to alleviate all symptoms completely. Rather, treatment was undertaken with the understanding that improvement in the more severe symptoms would improve the patient's quality of life.[1] Therefore, treatment should be tailored to each individual patient and should be performed in a staged or stepwise manner.[22] Small interventions can be highly effective in treating patients with KTS, because these patients will be longitudinally followed up by venous specialists in the long term. Ultrasound-guided sclerotherapy and stab avulsions of varicose veins were the most common superficial venous procedures, and iliofemoral venous stenting was the most common deep venous procedure. Endovenous laser ablation was the technique used for ablation of superficial incompetent veins. Stripping was performed either traditionally or in cases in which the vein was too close to the skin and in which no effective heat sink could be provided in the limb for the endovenous laser.[6]

Stenting. Iliofemoral venous stenting was performed in 15 patients (45%). It was performed for patients with persistent symptoms despite treatment of superficial venous disease and evidence of deep system abnormality on radiographic imaging. It was found to be safe and effective. These patients showed improvement in their VCSS, VAS for pain score, and GOS after stenting. Two patients had developed access site hematomas but did not require any further intervention. In other special patient populations, stenting has also been shown to be effective and safe.[8,23-26] The beneficial outcomes for patients with KTS in our study were similar to those from our previous experiences with other patient populations. The findings from our report support the role of this minimally invasive technique in the appropriate clinical context for these patients. KTS patients are known to have deep system abnormalities such as segmental absence or hypoplasia, which can result in chronic venous outflow obstruction. During the past several decades, the importance of recognizing and treating chronic deep obstructive venous disease has been well established.

In a study of 528 limbs, iliac venous stenting resulted in improvements in pain, swelling, and quality of life. In the same study, reflux parameters did not worsen after stenting and did not require additional corrective procedures such as valvuloplasty.[27] This was also confirmed in a recent study.[28] Iliofemoral stenting for patients with KTS might be sufficient alone for symptom improvement without the need for correction of coexisting deep reflux and has been identified as an area of future research. Long-term follow-up of patients with KTS is important, because adjunctive therapy or reintervention could be needed.[2] Thus, recurrent or residual symptoms after stent placement should be investigated using noninvasive imaging modalities such as duplex ultrasound and IVUS should be performed if a strong suspicion exists of stent malfunction.[16]

Air plethysmography parameters. The baseline ejection fraction (normal >50%) in patients with KTS was 49% ± 24%, which had improved to 54% ± 20% after intervention. Although impaired calf pump function has been noted in some patients with KTS, volumetric studies have not consistently demonstrated this compared with controls.[19] The VFI_{90} (normal, ≤2.2 mL/s; ie, the proportion of 90% of the venous volume divided by the time required to accomplish 90% venous filling), is an important air plethysmography parameter.[29,30] In patients with KTS, this parameter was noted to be elevated at baseline (5.9 ± 5.1 mL/s). Although intervention had significantly improved the VFI_{90} (3.5 ± 2.3 mL/s; $P = .04$), it still had not normalized it. One possible explanation for the elevated VFI_{90} in the patients with KTS is the presence of microscopic arteriovenous fistulas.[3,6] These fistulas, although mostly clinically nonfunctioning,[3] can result in increased venous pooling or an increased venous volume and likely contributed to the abnormal VFI_{90} despite the correction of superficial venous reflux. In contrast to KTS, high-flow AVMs will be seen in those with Parkes-Weber syndrome.[7]

Improvement in clinical parameters. Venous interventions, including minimally invasive endovenous procedures, produced improvement in the VCSS, swelling and pain in those with KTS. These improvements were

similar to those previously reported for patients with KTS who had undergone invasive surgical treatment.[1] Fewer perioperative complications were noted in our patient cohort compared with previously reported open surgical experiences.[1] This had likely resulted from the increased usage of endovenous procedures in our cohort, which are minimally invasive.

Improvements in quality of life. The treatment of KTS involves addressing, not only the physical, but also the psychological and social, aspects of the disease.[4] Anxiety and depression are common for patients with KTS.[31] The psychosocial aspects of the disease can affect the patient's self-esteem and social interactions.[32] Using the 20-item chronic venous disease quality of life questionnaire, we demonstrated significant improvements in the pain and psychological domains among patients with KTS after intervention. In addition, trends toward improvements in the physical, social, and global domains were also noted, although the associations were not statistically significant.

In-stent restenosis. Two patients (2 of 15; 13%) had required reintervention for in-stent restenosis. This was similar to our experience with patients without KTS for whom reintervention for in-stent restenosis was required for <20% patients.[16]

Limitations in measuring outcomes of patients with KTS. Certain limitations in the measurement of interventional outcomes among patients with KTS must be acknowledged. First, treatment was usually performed in a staged and graduated "step-up" manner; hence the same patient could have required both superficial and deep venous intervention performed sequentially. Therefore, it can be difficult to exclusively gauge the exact response of each treatment modality. Second, most interventions will not completely resolve the symptoms in patients with KTS, although they will certainly improve these patients' quality of life. Hence, the need for additional procedures will arise during the lifetime of the patient. Also, sometimes, complete excision of the lesions will not be possible and is not a realistic treatment goal. Third, KTS is, overall, a rare disease, and most current experiences have been limited to small case series without clearly defined outcome measurement protocols. Most patients will be treated conservatively; hence, the operative experience has been even smaller and more selective. Fourth, it has been recommended that the treatment plan for each patient should be individualized and tailored according to their symptoms and presentation. One size does not fit all. Finally, biases will be inadvertently introduced owing to the retrospective nature of the research and the treatment options chosen at the discretion of the treating venous specialists.[1]

CONCLUSIONS

The results of the present study have shown that superficial and deep venous interventions are safe and effective for patients with KTS when conservative therapy has failed. Iliofemoral venous stenting is a newer option that should be considered for the treatment of chronic deep venous disease in patients with KTS in the appropriate clinical context. An aggressive perioperative DVT prophylaxis protocol should be in place to reduce the incidence of thrombotic complications in these patients.

AUTHOR CONTRIBUTIONS

Conception and design: TS, SR
Analysis and interpretation: TS, CL, SR
Data collection: CL
Writing the article: TS, CL, SR
Critical revision of the article: TS, CL, SR
Final approval of the article: TS, CL, SR
Statistical analysis: TS, CL
Obtained funding: Not applicable
Overall responsibility: TS

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Submitted Dec 23, 2021; accepted Apr 26, 2022.

Additional material for this article may be found online at www.jvsvenous.org.

Supplementary Table I (online only). Venous malformations encountered in patients with Klippel-Trenaunay syndrome (KTS)

Venous malformation[a]	Patients, No. (%)
IM VM	12 (35.3)
Deep venous incompetence	11 (32.3)
Iliac vein hypoplasia	10 (29.4)
Lateral marginal vein/vein of Servelle	10 (29.4)
Hypoplastic femoral vein	6 (17.6)
Hypoplastic popliteal vein	5 (14.7)
Extrinsic compression of iliac vein	5 (14.7)
Osseous VM	3 (8.8)
Medial embryonic vein	3 (8.8)
Atretic deep system	2 (5.9)
Persistent sciatic vein	2 (5.9)
Cavernous malformation of fingers	2 (5.9)
Hypoplastic hypogastric vein	1 (2.9)

IM, Intramuscular; *VM,* venous malformation.
[a]Some patients had had more than one finding.

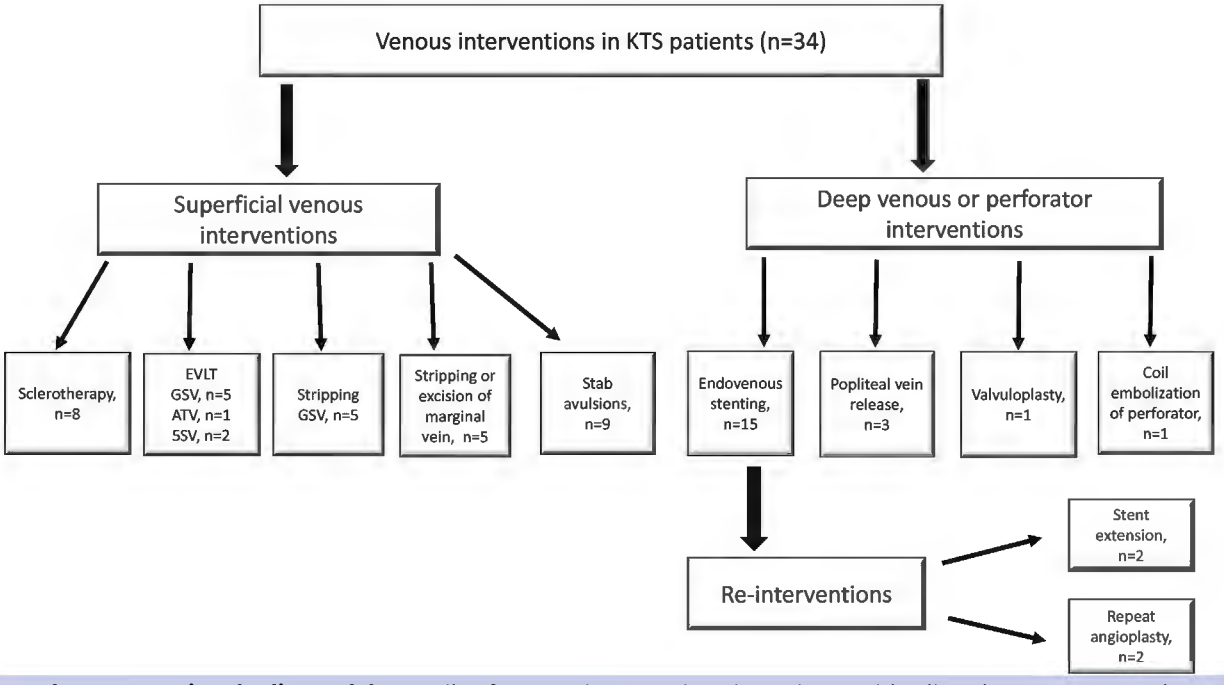
Supplementary Table II (online only). Chronic venous disease quality of life questionnaire scores for patients with Klippel-Trenaunay syndrome (KTS)

	Score		
Domain	Before intervention	After intervention	*P* value
Total pain	69 ± 19.5	37 ± 24.9	**.04**
Total physical	57 ± 35.8	40 ± 28.1	.17
Total social	57.4 ± 22	48.8 ± 31.9	.55
Total psychological	73.2 ± 25.2	54.8 ± 15.9	**.03**
Total global	61 ± 29	36.2 ± 26	.05

Data presented as mean ± standard deviation.
Boldface *P* values represent statistical significance.

Supplementary Fig 1 (online only). Magnetic resonance imaging (MRI) of lower extremity demonstrating lobulated, serpiginous lesions throughout the intramuscular compartment, with involvement of the subcutaneous tissue also present.

Supplementary Fig 2 (online only). Ascending venogram showing extensive superficial varicosity formation and minimal opacification of the deep system.



Supplementary Fig 3 (online only). Details of venous interventions in patients with Klippel-Trenaunay syndrome (*KTS*). Several patients had undergone more than one intervention.