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Venous function after pharmacomechanical thrombolysis for extensive iliofemoral deep vein thrombosis

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Background: Chronic venous insufficiency is an important complication following iliofemoral deep venous thrombosis. Early thrombus removal may preserve venous function and prevent this complication. This study represents the largest reported South African series of pharmacomechanical thrombolysis for iliofemoral deep venous thrombosis to date.

Objective: To evaluate the long-term outcome following pharmacomechanical thrombolysis for proximal and extensive deep venous thrombosis in a private, specialist vascular unit.

Methods: All patients who underwent pharmacomechanical thrombolysis for iliofemoral deep venous thrombosis between August 2009 and January 2016 were invited to return for clinical assessment and venous ultrasound. Clinical findings were recorded according to the Villalta score and clinical, etiology, anatomic and pathology (CEAP) classification. The quality of life (QoL) was assessed utilising the VEINES-QoL/Sym questionnaire, providing two scores per patient, one describing the QoL and the other symptom severity (Sym).

Results: Thirty two patients (35 legs) were evaluated. There were 25 females and 7 males, with a mean age of 33.5 years (±14 years). The mean follow-up period was 31 months (range 3 months – 80 months). Results of the CEAP classification were C0 = 24 (75%), C1 = 1 (4%), C2 = 2 (6%), C3 = 2 (6%) and C4 = 3 (9%). Thirty-one (97%) patients had Villalta scores from 0 to 4, indicating no or mild evidence of venous disease. One patient (3%) had a Villalta score of 6, indicating post-thrombotic syndrome. The mean QoL score was 87% (±12) and the mean Sym score was 86% (±14). Twenty-four (75%) patients had no abnormality on ultrasound, with fibrosis the most observed abnormality.

Conclusion: Most patients who had undergone pharmacomechanical thrombolysis for extensive iliofemoral deep venous thrombosis showed few significant clinical signs of chronic venous insufficiency, had excellent function on venous ultrasound and reported excellent QoL.

Introduction

Venous thromboembolism (VTE) is a multifactorial disease that may manifest as deep venous thrombosis (DVT), pulmonary embolism (PE) or both. DVT is a common problem encountered in clinical practice, with the complications ranging from minor to the severe, and even life-threatening.

Subsequent chronic venous insufficiency (CVI) because of post-thrombotic syndrome (PTS) is associated with increased morbidity and poses a significant health care burden.[1] PTS significantly impacts health-related quality of life (QoL) after DVT. It is characterised by a chronic feeling of limb heaviness, swelling, pain, paraesthesia and/or leg ulcers. The incidence of PTS is 30% – 50% with iliofemoral DVT, with leg ulcers developing in 5% – 10% of patients.[1,2]

The use of anticoagulation therapy alone in the treatment of VTE is well established. However, there is increasing evidence favouring active intervention with thrombolysis and/or mechanical thrombus removal in iliofemoral DVT.[3,4,5] Catheter-directed thrombolysis (CDT) significantly improves venous disease-specific QoL and furthermore decreases the economic burden of this disease entity.[1,6,7] Recently presented results from the ATTRACT trial suggests that removing the thrombus reduces early DVT symptoms and reduces the severity of PTS in the subgroup of patients with iliofemoral DVT. An expert panel ascribed this to the different prognosis and natural history of iliofemoral DVT compared with femoropopliteal DVT.[8]

There are multiple clinical scoring systems available to aid in the evaluation of venous diseases. The 'CEAP' classification describes clinical signs (C), etiology (E), anatomic distribution (A) and

the underlying venous pathology based on ultrasound (P).[9] Another scoring system, the Villalta score, specifically assesses the development of PTS.[10]

Many scales exist to evaluate the health-related QoL of patients. The most extensively validated is the VEINES-QoL/Sym questionnaire. This is best utilised to assess the effect of DVT on the QoL, as well as the outcome of treatment.[11]

Methods

This is a cross-sectional study with ethical clearance from the Sefako Makgatho University Research Ethics Committee (SMUREC/M/272/2015:PG). Patients who underwent pharmacomechanical thrombolysis (PMT) for iliofemoral deep venous thrombosis (IFDVT) between August 2009 and January 2016 were invited for a clinical assessment and venous ultrasound study. The clinical examinations were focussed on venous disease-specific findings, utilising the C-class of the CEAP classification (Table 1) and the Villalta score (Table 2).

The venous ultrasound examinations were performed by an independent dedicated vascular technologist, who was blinded to the results of the clinical scoring systems. Normal venous flow was considered as spontaneous, phasic and augmentable without reflux on augmentation manoeuvres. The veins were considered normal if they were compressible without narrowing or fibrosis. When seen, abnormalities were localised to specific venous segments from the popliteal vein distally to the inferior vena cava proximally.[12]

TABLE 1: Clinical parameters of the clinical, etiology, anatomic and pathology classification.

C-class	Clinical signs
0	No visible or palpable signs of venous disease
1	Telangiectasis, reticular veins, malleolar flare
2	Varicose veins
3	Oedema without skin changes
4a	Hyperpigmentation and eczema
4b	Lipodermatosclerosis and atrophie blanche
5	Skin changes with healed ulceration
6	Skin changes with active ulceration

TABLE 2: Villalta scale.

Variable	None	Mild	Moderate	Severe
Symptoms				
Pain	0	1	2	3
Cramps	0	1	2	3
Heaviness	0	1	2	3
Paraesthesia	0	1	2	3
Pruritis	0	1	2	3
Clinical signs				
Pretibial oedema	0	1	2	3
Skin induration	0	1	2	3
Hyperpigmentation	0	1	2	3
Redness	0	1	2	3
Venous ectasia	0	1	2	3
Pain on calf compression	0	1	2	3
Venous ulcer	Absent	-	-	Present

Each participant completed the self-administered VEINES-QoL/Sym questionnaire.[11] This is a 26-item tool used to evaluate a patient's venous disease-specific QoL and symptom severity (Sym). Ten items are symptom related, nine assess limitations to daily activities, one assesses the time of day the symptoms are most intense (used as a descriptor only), one assesses changes over the past year and five cover the psychological impact of venous disease.[13] The results from each participant were converted to 'T-scores', utilising the VEINES-QoL/VEINES-SYM Scoring Manual provided by the original authors who had designed and validated the questionnaire.[13] Two summary scores are generated for each patient, one relating to QoL, the other describing Sym. For reporting and interpretation purposes, these T-scores were converted to percentages, based on hypothetical best-case and worst-case scenarios.

Results

All statistical analyses were undertaken using the SAS programme (SAS Institute Inc., Carey, NC, USA, Release 9.4), running on Microsoft Windows. A total of 46 patients underwent PMT for IFDVT during the period of August 2009 to January 2016. Thirty-two patients were available for follow-up: 25 females and 7 males. The left leg was involved in 24 patients, the right leg in 5 patients while 3 patients had bilateral involvement. In 26 patients, full thrombus clearance was achieved, while 6 patients had partial clearance as shown by post-therapy venography. In 18 patients, there was a residual stenosis in the common iliac vein following thrombolysis; 12 required venous stent placement and 6 patients underwent percutaneous balloon angioplasty (PTA). Two patients had an abnormal inferior vena cava, one being hypoplastic and the other absent.

The distribution of Villalta scores are shown in Figure 1. The distribution of patients according to the C-classes from the CEAP classification is shown in Figure 2. The mean QoL score was 87% (range 75% – 99%) and the mean Sym score was 86% (range 72% – 100%) is shown in Table 3. The mean QoL and Sym percentages are recorded for each Villalta score. The inverse relationship between the QoL/Sym and Villalta scores are illustrated in Figure 3.

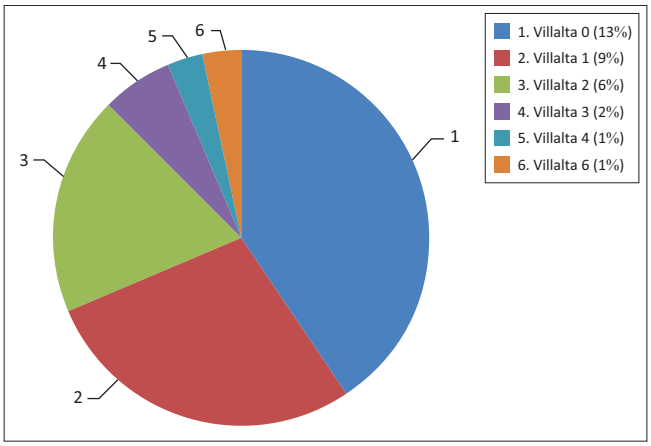

FIGURE 1: Results of the Villalta scores (n).

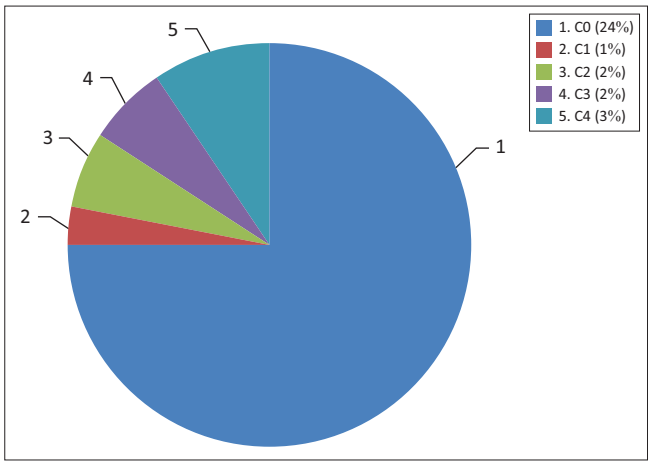

FIGURE 2: Distribution of patients according to clinical findings utilising the clinical, etiology, anatomic and pathology classification (n).

TABLE 3: Mean quality of life and Sym scores.

Parameter	Number	Mean	Std. dev.
QoL%	32	87.16	12.24
Sym%	32	86.34	14.01

QoL%, quality of life; Sym%, symptom severity; Std. dev., standard deviation.

Twenty-four patients (75%) had normal venous function and anatomy on follow-up ultrasound examination. In 8 patients, abnormal findings were recorded: these included stenosis, fibrosis and/or reflux. There was a statistically significant correlation between the presence of abnormal sonar findings and a higher CEAP classification. The lower C-scores had normal sonars, while the higher C-scores were more abnormal (p = 0.070) in Table 4. The same was found with the Villalta scores. Lower Villalta scores were often normal on ultrasound, and the higher Villalta scores were often abnormal (p = 0.007) as shown in Table 5.

Discussion

Venous thromboembolism is commonly encountered in clinical practice with an incidence of 1.0–1.5 per 1000 persons per year and is responsible for more than 100 000 deaths per year in the United States.[1]

PTS develops in 20% – 50% of patients with proximal leg DVT, even when optimal anticoagulation therapy is used.[2] PTS is characterised by symptoms of leg heaviness, pain, swelling, itching and paraesthesia. Open-leg ulcers occur in 5% – 10% of cases with PTS.[2,14] The estimated costs of managing PTS in the US are estimated to be in the order of $1100 in the first year of treatment for mild to moderate PTS, and $5000 for severe PTS with open ulcers. The mean annualised medical cost for patients with PTS is $14 800 higher than for patients that do not have PTS,[1] emphasising the economic burden of the disease.

Persisting thrombus has been linked to venous valve dysfunction and PTS.[2] Standard anticoagulation therapy has been proven efficient in preventing thrombus extension and PE, but does not remove the thrombus from the vein.[15,16]

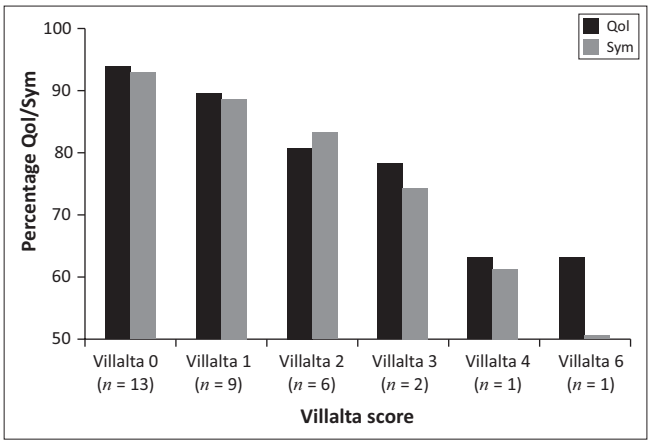

FIGURE 3: Relationship between the Villalta score and the VEINES-QoL/Sym score.

TABLE 4: Clinical, etiology, anatomic and pathology compared with ultrasound.

CEAP	Ultrasound		
	Total (n)	Normal (n)	Abnormal (n)
C0	24	20	4
C1	1	0	1
C2	2	2	0
C3	2	1	1
C4	3	1	2
Total	**32**	**24**	**8**

CEAP, clinical, etiology, anatomic and pathology

TABLE 5: Villalta compared with ultrasound.

Villalta	Ultrasound		
	Total (n)	Normal (n)	Abnormal (n)
0	13	12	1
1	9	8	1
2	6	2	4
3	2	0	2
4	1	1	0
6	1	1	0
Total	**32**	**24**	**8**

Active interventions focus on thrombus removal, with concurrent anticoagulant use. Recently presented data have shown that early thrombus removal preserves venous function and limits the severity of PTS in patients with iliofemoral DVT, but has not shown added benefit in femoropopliteal DVT.[8] All our patients had iliac vein involvement with thrombus extending into the inferior vena cava in 12 patients (38%). Surgical venous thrombectomy with anticoagulation proved effective in preventing venous reflux and PTS, but is invasive and requires a temporary arterio-venous fistula to enhance venous outflow.[17] Systemic thrombolysis is effective in lysing the thrombus and maintaining venous patency with 43% of patients progressing to PTS, versus 64% for standard anticoagulation. The limitation is more bleeding complications, at 10% versus 8% compared to standard anticoagulation.[18]

Catheter-directed thrombolysis allows localised administration of thrombolytics directly into the thrombus. It is effective in restoring venous patency and comparable to systemic thrombolysis in preventing PTS, with a lower rate of bleeding

complications. The relative-risk reduction in PTS with CDT is 26%.[6,19]

Pharmacomechanical thrombolysis utilises catheter-directed administration of a fibrinolytic agent directly into the thrombus, concomitant with a catheter-based device to macerate the thrombus. This speeds up thrombus clearance and decreases the amount of fibrinolytic required. The safety, efficacy and cost-effectiveness are currently being evaluated.[20] In our study, patients received PMT with Actilyse® (alteplase, recombinant tissue plasminogen activator; Boehringer Ingelheim Pty) infused via an AngioJet™ (Peripheral Thrombectomy System; Boston Scientific) catheter.

Thrombus clearance was reported according to the grading system reported by Mewissen et al.[21] Twenty-six patients had complete lysis (100%) and six patients had partial lysis (50% – 99%). There was no statistically significant difference in outcomes between patients that had partial clearance versus full clearance. Underlying structural abnormalities have been reported in a significant number of patients with extensive iliofemoral DVT.[19] In this series, there were 18 patients with residual stenosis after successful thrombolysis and was managed by stent placement in 12 patients and percutaneous angioplasty (PTA) in 6 patients.

Clinical findings defined according to the C-class of the CEAP classification and the Villalta scores showed that the majority of patients had no signs of chronic venous disease. The Villalta score is a disease score specific for PTS. Points are given for five symptoms (pain, cramps, heaviness, paraesthesia and pruritus) and six clinical signs (pretibial oedema, skin induration, hyperpigmentation, redness, venous ectasia and pain on calf compression). Points are given for each of these 11 descriptors according to severity, ranging from 0 for not present to 3 for severe. Furthermore, if a venous ulcer was present, the severity of the condition was classified as severe, regardless of the presence or absence of other signs or symptoms. The patient was diagnosed as having PTS if the Villalta score was ≥ 5 or if a venous ulcer was present. A score of 5–9 signifies mild disease, 10–14 moderate disease and ≥ 15 severe disease.[22] Only four patients had objective findings of chronic venous disease with skin pigmentation, venous eczema or lipodermatosclerosis, placing them in the C4 category. We, however, did not differentiate between C4a and C4b. Only one patient had PTS with a Villalta score of 6.

The VEINES-QoL/Sym questionnaire addresses venous disease-specific QoL. The questionnaire was well received by the patients and easily completed. The processed data produce two T-scores per patient, which by themselves do not contribute to understanding the patient's QoL as there are no reference scales that define a good versus a bad outcome. This is a limitation of the VEINES-QoL/Sym questionnaire. For the interpretive purposes of this study, the T-scores were converted to percentages, based on hypothetical worst-case and best-case scenarios. This generated two percentages, QoL% and Sym% which were easier to use. Our patients reported a good QoL with minimal symptoms because of CVI (Table 3). Higher QoL scores reflect better QoL and higher Sym scores represent fewer symptoms.

There was no statistically significant correlation between the VEINES, C-classification and Villalta scores, although the trend was that low Villalta scores (absence of PTS) had better QoL and fewer symptoms. Most patients with normal venous function and anatomy on venous ultrasound also had low C- and Villalta scores.

The limitations of this study are the small sample size with no control arm receiving systemic anticoagulation alone. This limits the ability to generalise the findings.

Conclusion

Patients with IFDVT who had successful thrombus removal with PMT showed few significant residual signs of chronic venous disease, had excellent venous function on venous ultrasound and had excellent QoL. PMT is not indicated for all patients with above the knee DVT given the added invasiveness, cost and potential for complications. PMT must however, be considered when thrombus extends into the iliac veins because of the increased severity of PTS symptoms in these patients.

Acknowledgements

Competing interests

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

Authors' contributions

W.G. was responsible for patient scheduling and clinical evaluation, collecting and processing of data, preparing and editing the manuscript, and online submission for publication. A.R.D.D. was the co-supervisor. J.V.M. was the treating clinician and main supervisor who provided the topic and was involved in clinical evaluation, processing of data and review and editing of the manuscript.

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