Practice Perspectives for Venous Disorders

(Practice Guidelines for Venous Interventions in South Africa)

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Phlebology is a rapidly evolving discipline worldwide, with fundamental and advanced concepts related to venous pathology, pathophysiology, imaging and therapeutic algorithms evolving at a frantic pace. Vascular Surgery, certainly in South Africa, together with its allied vascular disciplines is assuming greater responsibility currently for the comprehensive care of patients with acute and chronic venous disorders. It is absolutely essential then, that some form of guidance is available to inform current understanding of venous disorders and how to appropriately manage these patients.

Advances in venous imaging has contributed enormously to our understanding of venous pathology, both functionally and anatomically. We are just beginning to conceptualize the significant variability in the pattern and distribution of primary varicose veins. We are only beginning to appreciate venous anatomy and anomalies in venous dsiorders. This has resulted in evolving consensus documents attempting to standardise concepts in venous nomenclature, venous imaging and venous pathology.

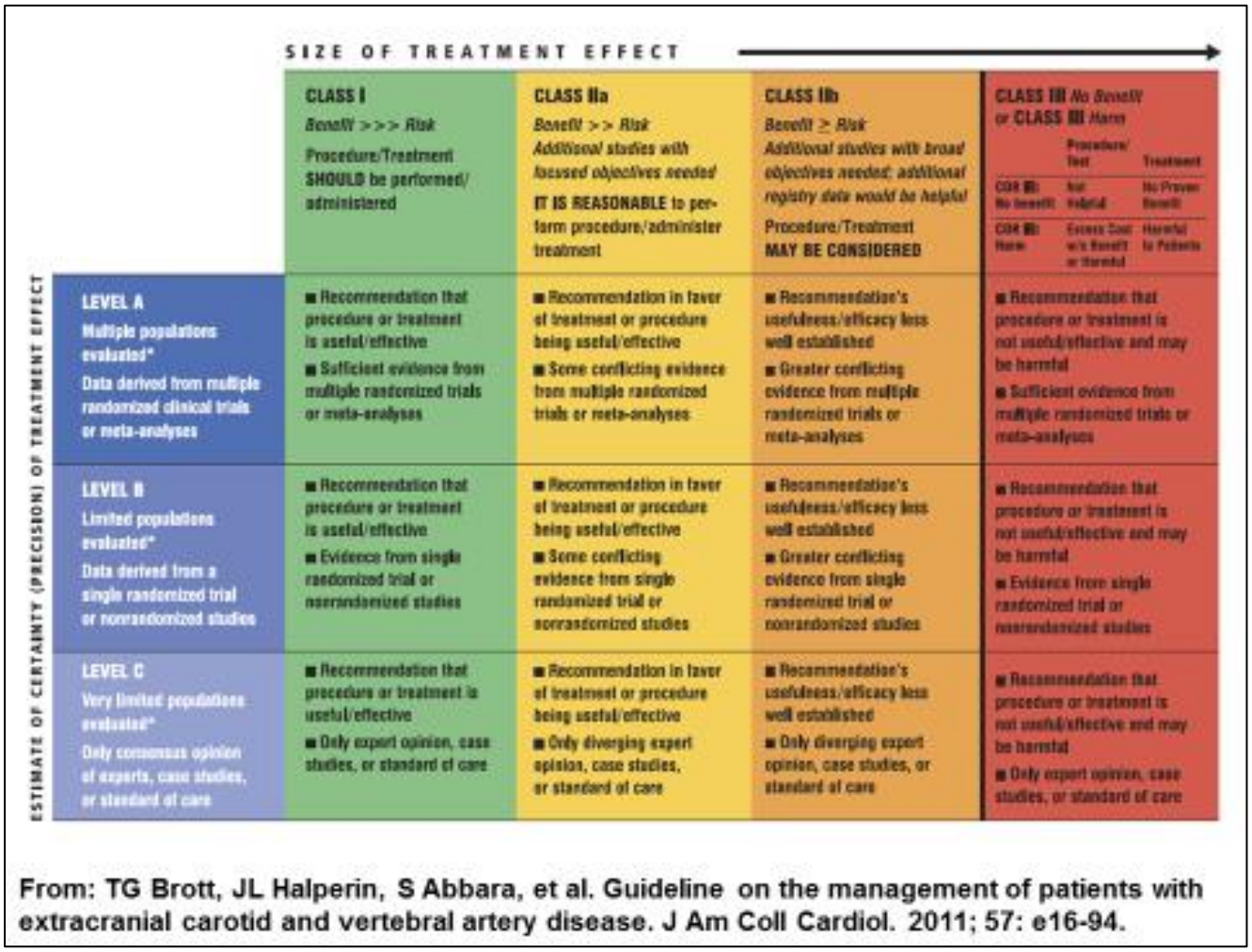
It is only by embracing these advances in the understanding of venous disorders that we will be able to provide a "best-fit" treatment algorithm for an individual patient with a venous disorder. Treatment of venous disorders, acute and chronic, have evolved beyond just surgical options currently. Minimally invasive technologies are not only being developed each year to treat both acute and chronic venous disorders, but the technologies that are currently available already have a proven record of safety and efficacy that is well established. Some of these percutaneous, minimally invasive technologies are currently performing better than surgery in select patients who are suitable for such treatment options.

Best venous practice should incorporate preferably all of the following aspects:

- The evidence-base for a particular procedure or device must be of the highest quality
- The procedure/s must be cost effective
- The expertise to evaluate patients with venous disorders must be available
- The expertise to perform venous procedures must be available

It is envisaged that these practice guidelines will not only inform venous practice in South Africa, but will also be relevant to informing the venous practice in the rest of Sub-Saharan Africa.

In line with previous practice guidelines developed by the VASSA (Vascular Society of Southern Africa), best venous practice is addressed by the class of recommendation based on the level of the quality of evidence. Recommendations and levels of evidence are based on the model adapted from Brott TG et al.



From: TG Brott, JL Halperin, S Abbara, et al. Guideline on the management of patients with extracranial carotid and vertebral artery disease. J Am Coll Cardiol. 2011; 57: e16-94.

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1. Acute Ilio-femoral Deep Vein Thrombosis: Overview, Medical Treatment and Compression Stockings

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Overview

The prevalence of deep vein thrombosis (DVT) in Africa varies between 2.4% and 9.6% in patients after surgery and between 380 and 448 per 100 000 births per year in pregnant and postpartum women. Tuberculosis was associated with a prevalence of 61.5% in a single study[2].

Iliofemoral deep vein thrombosis (IFDVT) is defined as thrombus involving iliac and/or common femoral veins, with or without extension to the inferior vena cava. It represents one quarter of all cases of DVT and 40% of all proximal DVT's[1]. When the femoral vein is thrombosed, the primary collateral routes of drainage is via the profunda femoris vein (which empties into the common femoral vein). Venous thrombosis above the entry point of the deep femoral vein thus causes more severe outflow obstruction and results in more dramatic initial DVT symptoms and late clinical sequelae.

The natural history of iliofemoral DVT is associated with a higher risk of adverse outcomes relative to femoral popliteal or distal DVT. IFDVT has a 2.4-fold increased risk of recurrent venous thromboembolism (VTE) over 3 months compared with patients with less extensive DVT[4], and is

associated with an increased severity of the post thrombotic syndrome, venous claudication, venous ulcers and impaired quality-of-life[5].

ANTICOAGULATION

Regardless of whether endovascular intervention is warranted, anticoagulation is the mainstay of therapy for patients with lower extremity DVT in order to prevent pulmonary embolus, thrombosis related death and recurrent deep vein thrombosis.

All patients with no contraindications, should be anticoagulated for a finite period following the 1st episode of lower extremity DVT, although some may benefit from indefinite anticoagulation to reduce the risk of recurrent thrombosis[24].

Studies have shown that early ambulation is not associated with progression of DVT or development of pulmonary embolism and should be encouraged[3].

Anticoagulation is the only therapy that has demonstrated a decrease in mortality related to subsequent events, such as fatal pulmonary embolization.

Despite optimal anticoagulation, >30% of patients with history of symptomatic DVT will develop symptomatic post thrombotic syndrome (PTS), likely due to chronic venous occlusion, suboptimal collateral development and venous valvular dysfunction.

Initial anticoagulation therapy refers to therapy given immediately after the diagnosis and is typically from 0 to 10 days. Long-term anticoagulant therapy is given for a finite period beyond the initial period, usually 3-6 months and occasionally up to 12 months. Extended anticoagulation refers to therapy given indefinitely.

1. Initiation of Anticoagulation:

There are a number of regimes for initiating anticoagulation, all of which are acceptable[6]:

a. Intravenous Unfractionated Heparin (UFH) at initial bolus of 80 units per kilogram followed by continuous intravenous infusion initially dosed at 18 units/kg/hour with adjustments to target an aPTT ratio range of 1.5 to 2.5 times the control.

b. Low Molecular Weight Heparin (LMWH):
   - Enoxaparin (Clexane) 1 mg/kg s/c twice daily or 1.5 mg/kilogram s/c daily
   - Nadroparin (Fraxiparine) 0.1 ml /10 kg s/c twice daily
   - Dalteparin (Fragmin) 100 anti-Xa U/kg s/c twice daily or 200 U/kg s/c once-daily

c. Fonduparinux (Arixtra)
   - 5mg s/c once daily (<50 kg)
   - 7.5 mg s/c once-daily (50-100 kg)
   - 10 mg s/c once-daily (>100 kg)

d. Direct Factor Xa and Thrombin inhibitors
   - Rivaroxaban (Xarelto) 15 mg orally twice a day (for 3 weeks)
   - Apixaban 10mg orally twice a day (for 1st 7 days) (not available in RSA)
   - Dabigatran (Pradaxa) and Edoxaban require initiation of treatment with a LMWH.

Warfarin is inappropriate as the only initial anticoagulant for the treatment of patients with VTE.

With the exception of patients who are pregnant, have active cancer or have severely impaired renal function (Cr Cl < 30ml/min/kg), the subcutaneous low molecular weight heparin or Fonduparinux or the oral factor Xa inhibitors are preferred over the UFH infusion.

Relative to UHF, LMWH is associated with lower rates of recurrent symptomatic venous thromboembolism (OR 0 .57, 95% CI 0.44-0.75) and major bleeding events (OR 0.50, 95% CI 0.29-0.85)[22]. Data indicates that the direct oral anticoagulants are non-inferior to LMWH/warfarin for the prevention of recurrent VTE (dabigatran HR 1.09 95% CI 0.76-1.57[13], rivaroxaban HR 0.89, 95% CI 0.66-1.19[12]). Rivaroxaban had a significantly reduced rate of major bleeding relative to conventional therapy (HR 0.54, 95% C I 0.37-0.79)[12], whereas dabigatran was similar to that of warfarin (HR 0.73, 95% CI 0.48-1.11)[13]. They also have the advantage of dosing convenience, no need for laboratory monitoring, lack of interactions with food and limited interactions with other medication.

Unfractionated heparin is the preferred initial anticoagulation in patients with severe renal failure or those who may require acute reversal (e.g. undergoing a procedure or high likelihood of bleeding). It is also an alternative to LMWH in patients who may have poor subcutaneous absorption (e.g. severe oedema or obesity) [25]

LMWH is preferred in patients with active malignancy and acute VTE with adequate renal function and a reasonable life expectancy[15]. Vitamin K antagonists are less effective for preventing recurrent VTE (HR for LMWH 0.47 95% CI 0.32-0.71)[23]. LMWH is also preferred for pregnant women.

A recent Cochrane meta-analysis of 29 studies comparing LMWH to intravenous or subcutaneous UFH showed that at 3 months, low molecular weight heparin had fewer thrombotic complications, improved thrombus regression, reduced rate of major haemorrhage and a non-significant reduction in mortality[7].

Once-daily regimes of LMWH are as effective as twice-daily regimes[8]. A recent study demonstrated a decreased risk of major bleeding and risk of death in favour of the once-a-day regime, but at the expense of increased recurrence[9].

Fonduparinux has been shown to be equivalent in efficacy to the LMWH's, and is an alternative to LMWH in patients with heparin induced thrombocytopenia (HIT).

The oral factor Xa and direct thrombin inhibitors are attractive as initial oral anticoagulants because of the quick onset of action. They should not be used in patients with significant renal failure (CrCl <30 ml/min) or in pregnancy. Their use has not been assessed in unstable patient with massive pulmonary embolus or massive ilio-femoral DVT requiring intervention and thus should be used with caution in these cases.

2. Long Term Anticoagulation

Long term anticoagulation is administered beyond the initial few days for a finite period of 3-6 months and for up to 12 months. Options for long term anticoagulation include oral anticoagulants (warfarin, factor Xa inhibitors and direct thrombin inhibitors) and parenteral subcutaneous anticoagulants (LMWH and Fonduparinux).

As a general principle, oral agents are preferable to parenteral agents. In non-pregnant patients without severe renal failure or active malignancy, the direct oral anticoagulants have an advantage over warfarin in that there is no need for laboratory monitoring and there is a lower risk of bleeding. Warfarin has the advantage of lower cost and having an effective immediate antidote.

Warfarin

- Warfarin is the preferred anticoagulant patients in whom the direct thrombin inhibitors are not available, where cost is an issue and in patients with severe renal insufficiency
- warfarin should be started at a dose of 5 mg orally on day 1 of anticoagulation with the LMWH.
- The INR should be measured 2 to 3 days after commencing warfarin and then daily with dose adjustments to achieve a therapeutic range of 2-3
- LMWH should be continued for a minimum of 5 days and for at least 2 days after a therapeutic INR is reached.

The efficacy of warfarin is supported in many trials. The seminal trial in 1960 comparing warfarin to observation resulted in a dramatic reduction in recurrence of pulmonary embolus (0 vs 26%) and showed a mortality benefit[10]. A meta-analysis in 2010 of 13 prospective cohort studies and 56 randomised clinical trials confirmed a very low rate of recurrent VTE and fatal VTE of 3.4 and 0.4% respectively, during the 1st 3 months of warfarin therapy[11].

Direct oral anticoagulants

- Rivaroxaban (Xarelto) can be administered as monotherapy, commencing at 15 mg orally twice daily for 3 weeks and then 20 mg daily.
- Dabigatran (Pradaxa) is commenced after 5 days of LMWH. The dose is 150 mg orally twice a day.

Many of these agents are renally excreted and are thus contraindicated in patients with severe renal insufficiency (CrCl < 30 ml/min). They are not licensed for use in pregnancy.

There is also concern regarding the efficacy and distribution of these agents in obese patients with a body weight of >120 kg or BMI > 40 kg/m^2.

Randomised trials and one meta-analysis have reported the safety and efficacy of these agents for the treatment and prevention of recurrent VTE[12-14]. Most of these trials were performed in stable patients and were designed as non-inferiority trials that compared the new agent with standard anticoagulation and showed comparable safety and efficacy.

Low Molecular Weight Heparin

- LMWH is the preferred agent for those patients in whom the oral agents are not feasible (e.g. patients with no or poor oral intake).
- LMWH is also preferred in patients with active malignancy and in pregnancy.
- LMWH is contraindicated in patients with severe renal insufficiency (CrCl <30 ml/min)

Several randomised trials and meta-analyses have shown that LMWH is at least as effective as warfarin in the prevention of recurrent VTE with a similar rate of major bleeding and mortality[15].

Randomised trials have also suggested that LMWH lowers the frequency of post thrombotic syndrome compared to warfarin[16].

There are no direct comparisons of LMWH with the direct oral anticoagulants.

Fonduparinux

Fonduparinux is an alternative to LMWH in patients with heparin induced thrombocytopenia. It is contraindicated in patients with severe renal dysfunction. The dose should also be reduced by 50% in patients with moderate renal insufficiency (CrCl 30-50 ml/min).

Duration of treatment

The duration of anticoagulation needs to be individualised according to the presence or absence of provoking events and risk factors, the risk for recurrence and the risk of bleeding and also needs to be tailored to individual patient preferences and values.

- Patients with 1st episode of venous thromboembolism (provoked or unprovoked) should receive anticoagulation for a minimum of 3 months
- 3 months anticoagulation is adequate for patients with a provoked episode of VTE with transient risk factors which are no longer present, or those in whom the risk of bleeding is considered to be high.
- In select populations, anticoagulation is extended to 6-12 months (e.g. phlegmasia cerulea dolens or a persisting but reversible risk factor), providing the risk of bleeding is low. The benefits of this is unproven, however.

A number of randomised trials and meta-analyses provide evidence that support anticoagulation for a minimum of 3 months[15]. Without adequate anticoagulation, the risk of recurrent VTE is highest in the 1st 3 months following the initial event. Decreasing anticoagulation to 4-6 weeks is associated with an increased risk of recurrence.

In patients with average risk, data from randomised trials a meta-analysis do not support extending treatment beyond 3 months[15,17].

The detection of residual thrombosis after 3 months on duplex ultrasound has also been used to guide length of therapy. A study using flexible duration based on ultrasound versus a fixed duration of 3 months has shown a reduction in recurrent VTE (12 versus 17%)[18], but this has not been ratified in a larger randomised controlled trial.

Extended anticoagulation

The rationale for indefinite anticoagulation in patients with an unprovoked proximal DVT is based upon the high estimated lifetime risk of recurrent VTE. This needs to be balanced against the potential risk of bleeding.

The estimated risk of recurrence following stopping anticoagulation[15,19,20]:

- 1st unprovoked VTE: 10% at 1 year and 30% at 5 years (approximately 5% per year after the 1st year).
- 2nd unprovoked VT: 15% for the 1st year; 7.5% / yr. thereafter
- 1st VT provoked by surgery: 1% for the 1st year; 0.5% / year thereafter
- 1st VT provoked by non—surgical factor: 5% for the 1st year; 2.5%/year thereafter

Additional risk factors need to be assessed. These include:

a. active malignancy
b. anti-phospholipid syndrome
c. inherited thrombophilia: high-risk thrombophilia's include protein S, protein C, antithrombin III deficiency, homozygous factor V Leiden and homozygous prothrombin gene mutations
d. male gender
e. D-dimer: an elevated d-dimer may be valuable in selecting those at high risk of recurrence, but a negative d-dimer does not identify those at low risk. D-dimer have a low specificity and the timing of measurement is uncertain.
f. Residual vein obstruction: there are conflicting data regarding the ability of residual vein obstruction on imaging to reliably predict recurrence
g. post thrombotic syndrome (PTS): patients with PTS are at increased risk of VTE recurrence

Full anticoagulation is associated with a >90% reduction in the rate of recurrence compared with low intensity anticoagulant regimens (60% reduction) and aspirin (30% reduction). This benefit outweighs the risk of bleeding in low (0 .8%) or intermediate risk (1.6%) patients.

COMPRESSION STOCKINGS

The rationale for the use of compression stockings in a patient with a proximal deep vein thrombosis is to prevent the post thrombotic syndrome (PTS). It is also useful in the symptomatic management of swelling secondary to the obstruction to the main venous drainage, but has no role in the treatment of proximal deep vein thrombosis.

Some guidelines advocate the use of class II stockings for up to a period of 2 years to prevent PTS[15].

Evidence regarding the role of elastic graduated compression stockings for the prevention of PTS is conflicting with smaller trials suggesting benefit and one large randomised trial reporting no benefit. The methodology in many of the trials was flawed.

RECOMMENDATIONS:

1. All patients with ilio-femoral deep vein thrombosis require immediate anticoagulation unless there are contraindications. **(Class I / Level A)**
2. Patients with acute DVT who are fully anticoagulated, haemodynamically stable and whose symptoms (pain, swelling) are under control should have early ambulation rather than bed rest **(Class IIa / Level C)**

Initial Anticoagulation

3. An unfractionated heparin infusion, LMWH, Fonduparinux or Rivaroxaban are appropriate agents for the initiation of anticoagulation. **(Class I / Level A)**
4. Unfractionated heparin infusion and Fonduparinux are preferred for patients in renal failure. **(Class 1/ Level A)**

Long-Term Anticoagulation

5. Patient should be anticoagulated for a minimum of 3 months rather than for shorter periods, regardless of whether the event was provoked or not. **(Class I / Level A)**

6. Patients with a provoked VTE who have persistent but reversible risk factors should have extended anticoagulation for a finite period after the risk factor is resolved. **(Class IIa / Level C)**
7. LMWH is the long-term anticoagulant therapy of choice in patients who are pregnant **(Class IIa / Level B)** or have active malignancy **(Class I / Level A).** Dose adjustment is essential in these patients who have chronic kidney disease **(Class 2a / Level B)**

Indefinite Anticoagulation

8. Patients with a 1st episode of unprovoked proximal DVT or recurrent DVT in whom the risk of bleeding is low to moderate should have indefinite anticoagulation **(Class I / Level A)**
9. Indefinite anticoagulation is not advised for patients with a provoked episode of VTE with major transient risk factors or who have a high bleeding risk **(Class I / Level B)**
10. Full intensity anticoagulation is recommended for indefinite anticoagulation rather than low-dose regimens. A lower dose of Rivaroxaban may be considered here. **(Class IIa / Level B)**

Graduated Elastic Compression Stockings

11. Elastic graduated compression stockings should be recommended for use to patients with acute ilio-femoral DVT for the prevention of the post thrombotic syndrome **(Class IIb / Level B)**

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2. Acute iliofemoral deep vein thrombosis: Rationale for thrombus removal strategies

NG Naidoo

Introduction

Oral anticoagulation is currently the standard of care for an acute deep vein thrombosis (DVT). These pharmaceutical agents, including vitamin K antagonists and the direct oral anticoagulants (DOACs), are safe and effective in preventing progression of DVT and pulmonary embolism. However oral anticoagulants are not optimally effective in the prevention of the more chronic complications such as the post-thrombotic syndrome (PTS) or post-DVT syndrome. Recurrent DVTs may occur in patients treated with only oral anti-coagulants, especially unprovoked DVTs. They are not designed to eliminate thrombus (this function is performed by the body`s own fibrinolytic system).

It is well known that infra-popliteal DVTs generally have a benign outcome (> 80% spontaneous resolution). It is also well described that isolated femoro-popliteal disease is generally well tolerated. Axial transformation of the profunda femoris vein, in the absence of venous outflow obstruction, has been reported to mitigate against the development of severe PTS. Despite optimum oral anticoagulation, only 20% of IFDVTs will recanalize completely[1], translating into variable degrees of severity of thrombotic venous outflow obstruction or secondary pelvic vein entrapments. Such incomplete resolution of IFDVTs have been associated with the more severe versions of the post-thrombotic syndrome, including leg swelling, skin changes and leg ulceration. The "open vein" hypothesis, predicts that thrombus removal strategies for acute IFDVT will reduce the incidence, or alternatively reduce the clinical severity, of the PTS. These thrombus removal strategies have been described as essential for the preservation of valves, luminal patency and the elimination of reflux and/or occlusive venous disease.

There is a lack of a universally acceptable anatomical description of the extent of the acute DVT. Deep vein thrombosis has been generally described historically as distal DVT (calf vein thrombosis; infra-popliteal vein thrombosis) or proximal DVT (involving the popliteal and proximal deep veins). A proximal DVT may assume variable anatomical distribution or extent that may confound clinical outcomes: Isolated popliteal vein thrombosis; Isolated femoral vein thrombosis; Isolated femoro-popliteal vein thrombosis; Isolated IFDVT; Extended IFDVT (IFDVT with ipsilateral femoro-popliteal DVT; IFDVT with ipsilateral femoro-popliteal and infra-popliteal DVT; Bilateral IFDVTs with or without associated thrombosis of the inferior vena cava, without infra-inguinal DVT; Bilateral IFDVTs with or without associated thrombosis of the inferior vena cava, with unilateral infra-inguinal DVT; Bilateral IFDVTs with or without associated thrombosis of the inferior vena cava, with bilateral infra-inguinal DVT). Although various thrombus grading systems, most notably the MARDER grading system, have been used in oral anti-coagulant trials, the lack of a universally acceptable thrombus grading is lamentable. Such a thrombus grading system is desperately needed when analyzing thrombus clearance strategies.

Executive Summary

As a specific sub-group, patients with IFDVT are at the highest risk of developing the post-thrombotic syndrome (PTS). This risk is estimated at 27% at 6 months and 50% at 2 years.[2,3,6] The associated risk of leg ulcers is ~ 5% over 10 years.[4,8] Patients with IFDVT have a 2.4 fold increased risk of developing recurrent DVTs compared to less extensive DVTs.[(4/5)] The post-thrombotic syndrome has a significant negative impact on the quality of life and patient productivity, resulting in an enormous burden to health care systems. The total per-patient cost of patients with DVT who develop the PTS is double that of patients with DVT who don`t develop the PTS.[4,9,10,11,12,13] Younger patients with IFDVT with longer life expectancies are particularly prone to develop the PTS over time and therefore represent a group of patients more likely to benefit from expedited thrombus clearance strategies.

These thrombus removal strategies should be evaluated in a standardized manner. Such standardization is confounded currently by various considerations. Systemic thrombolysis has been shown to be ineffective in preventing the PTS, and furthermore has been associated with a significant bleeding risk.[4/7] Hence, systemic thrombolysis cannot be recommended currently.

Local thrombus clearance strategies for acute IFDVTs in select patients have the potential to reduce the development of the PTS and to reduce the risk of recurrent DVTs. The aim of therapy is to restore complete vein patency; to preserve valves and to treat residual venous outflow occlusive disease. It is envisaged that this would translate into significant clinical and functional outcomes: decreased procedure-related bleeding risk; decreased incidence of leg swelling; decreased incidence of chronic venous insufficiency (CVI); decreased venous claudication; and improved quality of life (QOL).

These strategies include:

- Surgical venous thrombectomy

- Catheter-directed thrombolysis (CDT)
- Percutaneous mechanical thrombectomy (PMT)
- Hybrid / combined procedures such as:
    - Hybrid venous thrombectomy
    - PMT combined with CDT (PM-CDT)

Evidence will be presented regarding the evidence base for these strategies. These literature reviews will define the safety and efficacy, as well as the strengths and weaknesses of these strategies. Only after these considerations can we formulate an approach that is relevant for local practice.

Future Directions

It is possible that sub-group analysis of current trials, and the results of ongoing and future trials will better inform indications and best practice. There is a desperate need to better define the thrombus burden in select patients being offered thrombus clearance strategies. A universally acceptable grading system is desperately needed here. It is absolutely imperative that a follow-up of 5 years or more is achieved in these studies to fully appreciate defined clinical outcomes.

Recommendations

1. The term proximal DVT should be avoided. A more anatomically appropriate, comprehensive venous-imaging informed, DVT description should be utilized, e.g. isolated ilio-femoral DVT (IFDVT), extended IFDVT, femoro-popliteal DVT (FPDVT), etc. **(Class 1; Level A)**

2. In select patients with acute IFDVT, being offered thrombus clearance strategies, some form of universally acceptable thrombus grading system is recommended

3. All patients receiving thrombus clearance strategies should be included in a national registry or in a clinical trial

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3. Surgical venous thrombectomy

Abdool-Carrim ATO

Venous thrombectomy in the modern era should be in the vascular surgeon's armamentarium as it can be a limb saving procedure. Previous surgical outcomes were poor as no arteriovenous fistula were performed and no intra-operative radiology was performed which led to poor patency and recurrent thrombosis.[11]

Venous thrombectomy has been effective in relieving ileo-femoral obstructions and may preserve the function of distal valves[1].

Early thrombus removal has been advocated for extensive Ileo-femoral Deep Vein Thrombosis. The strength of recommendation for early Thrombosis removal by the Guidelines Committee of the Society for Vascular Surgery and American venous Forum [1] have been based on the act of balancing the risk of therapy versus the prevention of the post-thrombotic syndrome and quality of life, but the quality of evidence supporting early thrombus removal is low (Grade C). [1]

On the other hand, in patients with limb threatening ischaemia due to venous obstruction, early thrombus removal is the treatment is of choice (Grade 1 A).[2]

Ilio-femoral thrombectomy has been compared with standard anticoagulation in 10 studies[1, 3,6-11] and only one was a randomized study [11]. The studies were small and follow up varying from 6 months to 10 years. Pooled analysis [16] of 5 studies[6,7,78,11,13] evaluating reflux showed thrombectomy was associated with significant reduction of reflux (RR 0,68: 95%. CI: 0.40 – 0.99).

In 4 studies[6,11,13,14] evaluating venous patency there was a non-significant trend towards less venous obstruction in the thrombectomy groups. There was also a significant reduction in the important outcome of post thrombotic syndrome (RR, 0.67: 95%, CI 0.52 – 0.87).[16]

The primary aim of therapy in Phlegmasia Cerulea Dolens (PCD) is to arrest thrombus progression and evacuating clot to avoid gangrene and limb loss which has been reported in 60% of patients with PCD [5]. The venous outflow obstruction and arterial collapse leads to critical pressure being exceeded by surrounding tissues. Compartment pressures >50mmHg have been noted in PCD [5]. The role of

fasciotomy is controversial and ACCP Guidelines [2] does not recommend it as first line therapy and it should not precede the rapid intervention to relieve ilio-femoral venous outflow obstruction as relief of obstruction will decrease compartmental pressure and avoid fasciotomy. The ACCP [2] also recommends appropriate anticoagulation and fluid resuscitation in patients with PCD. They do recommend fasciotomy if compartmental pressure remains elevated > 30mmHg after clot clearance. Fasciotomy may also be complicated by bleeding due to ongoing anticoagulation. In patients with extensive iliofemoral deep vein thrombosis with impending gangrene Pharmaco-mechanical catheter directed venous Thrombolytic therapy would be the treatment of choice, but in cases where Thrombolytic therapy is contra indicated then open surgical venous thrombectomy is performed (Grade 2c).

Surgical Thrombectomy technique is well described [16] but must include good pre-operative imaging to document the extent of clot and if Inferior Vena Cava (IVC) is involved an extended approach to remove IVC thrombus must be carried out. The use of positive pressure and expiratory ventilation is also used to reduce the risk of pulmonary embolus. Intra-operative completion Venography must be performed to exclude iliac vein stenosis (iliac vein stenting recommended if stenosis noted).

The long -term outcome of open surgical Thrombectomy versus standard anti-coagulation have shown to be favourable for early Thrombectomy in that both clinical and hemodynamic effects were superior in the surgical group [5]. The use of temporary Arterio-venous fistula must be performed to reduce risk of recurrent venous thrombus.[9,16]

The recommendations for surgical thrombectomy have largely been adopted from the Clinical Practice Guidelines of the Society for Vascular Surgery and the American Venous Forum. [1]

Recommendations:

1. Open surgical venous thrombectomy is advocated in selected patients who are not candidates for immediate anticoagulation or where thrombolytic therapy is contra-indicated. **(Class 2b / Level C)**
2. Open surgical venous thrombectomy is the treatment of choice in patients with Phlegmasia Cerulea Dolens or with impending gangrene due to acute IFDVT. **(Class 1 / Level A)**
3. The use of adjunctive arterio-venous fistula following surgical thrombectomy, with the need for more supporting evidence, must be individualized currently **(Class 2a / Level C)**
4. Comprehensive venous imaging is essential to identify extent of thrombus and to confirm clot clearance. **(Class 1 / Level C)**
5. Fasciotomy is hardly recommended currently and it`s use following thrombus clearance strategies, such as surgical venous thrombectomy, must be carefully individualized. **(Class 2b / Level C)**

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4. Catheter Directed Thrombolysis for ilio-femoral deep vein thrombosis

James Tunnicliffe

Introduction and Overview

The standard recommended treatment for Ilio-Femoral DVT (IFDVT) is anticoagulation[1]. Over the last 30 years, there has been an increasing shift towards early thrombus removal to try and minimise the incidence of Post Thrombotic Syndrome (PTS)[1,2]. Catheter Directed Thrombolysis (CDT) has emerged as one of the most popular methods for early thrombus removal. In spite of the massive numbers of DVT seen world-wide, and the large numbers of centres carrying out CDT for IFDVT, there is a striking paucity of good data to support this strategy and method for early thrombus removal. Moreover, the efficacy of early thrombus removal in preventing PTS remains controversial[3], as do the reporting standards employed, resulting in a surprisingly small body of literature to support this notion. Whether or not CDT for IFDVT for early thrombus removal results in an improvement in patient Quality of Life remains unclear.

To date there has only been one published randomised controlled trial (RCT) of CDT for IFDVT[4], with most of the literature being composed of retrospective reviews and case series.

Executive Summary

The introduction of CDT for IFDVT occurred in the early 1990s, largely in an effort to reduce the major bleeding complications of systemic thrombolysis[2]. Systemic thrombolysis and surgical thrombectomy had been used occasionally to try and improve upon the outcomes after systemic anticoagulation alone, with mixed results. Comerota and Aldridge reported a 45% rate of complete or significant thrombolysis with systemic thrombolysis, compared with a reported rate of only 10% for anticoagulation alone[2], which sparked interest in early thrombus removal. Over subsequent years the high incidence of bleeding complications of systemic thrombolysis led to the adoption of CDT.

The indications for CDT for IFDVT are generally agreed to be as follows: Symptoms < 14 days, good functional status, life expectancy >1 year and low bleeding risk. The contraindications include: malignancy, advanced age (undefined), bleeding disorders, uncontrolled hypertension and recent surgery[1-4,6].

The method of CDT for IFDVT is similar in all reports: systemic anticoagulation with unfractionated heparin is used for all patients. The CDT is administered via a multi-side-holed catheter placed within the thrombus in the IF segment. The catheter is placed via a sheath inserted under Ultrasound guidance into the popliteal vein. Low dose heparin is also infused via the sheath in most series. The choice of lytic agent is varied, but the most recent series (except from USA) all use rtPa. Urokinase is the commonest agent in the USA series. The lytic agent is usually deposited within the thrombus ("lacing"), and then a continuous infusion is employed. Alternatively, a pulse-spray technique may be used. There does not appear to be any difference in outcomes according to infusion technique, but no randomised study has been performed to assess this.

The majority of clinicians did not use Vena Caval filters unless there was free-floating Caval thrombus present. The majority of IVC filters used in such cases were retrievable, and were all retrieved at termination of the CDT. All patients were managed with anticoagulation for at least 6 months post CDT, with some authors routinely giving anticoagulation for a year. Patients found to have an Inherited Hypercoagulable state were placed on life-long anticoagulation. Without exception, any Iliac stenosis exposed by the CDT were treated with venous stenting.

The CaVenT study[4] is the only published RCT investigating the efficacy of CDT for IFDVT. 209 patients were randomised to receive either CDT (101) or anticoagulation alone (108). 24-month follow-up was obtained for 189 patients (90 CDT, 99 controls.). 41.1% of the CDT patients and 55.6% of controls at 24 months had PTS defined by a Villalta score >5. (p=0.047). Absolute risk reduction for PTS was 14.4%, with NNT of 7. Iliofemoral patency at 6 months was reported in 58 patients: 65.9% with CDT, 47.4% controls. (p=0.012). In the CDT group, there were 20 bleeding complications, of which 3 were major, and 5 were clinically relevant. The authors concluded that CDT should be considered in patients with high proximal DVT (iliac veins, common femoral vein, but NOT superficial femoral vein) and low risk of bleeding.

In a prospective, non-randomised comparison of CDT vs Pharmacomechanical Thrombectomy (PMT) for acute iliofemoral DVT, Kuo et al studied 61 patients[5]. The demographics and patient characteristics in both groups were similar, and venous outcomes (Venous Outflow Resistance – VOR, Valvular Insufficiency - VI, Thrombus Score – TS, 24-month Villalta Score, and Venous Registry Index – VRI) were not statistically different. 6 patients in each group developed PTS (Villalta >5), but in the CDT group the severity was worse than in the PMT group. All patients who developed PTS had significant venous obstruction, compared with only 14.3% in the group who did not develop PTS. No difference in the rate of valvular insufficiency was seen between the PTS and PTS – free groups. The severity of PTS (Villalta score) was highly correlated with the postoperative

TS and severity of venous obstruction. Postoperative TS also correlated highly with severity of venous obstruction.

Sillesen et al[6], in a retrospective review of 45 cases treated with CDT, reported a technical success at reopening the thrombosed segments of 93%. Partial lysis was obtained in 2 of the remaining 3 cases. The last case turned out to have a chronic previous deep vein occlusion. The utility of this study is limited by the fact that the patients were not limited to those with only IFDVT. Of the 45 patients, only 5 had isolated iliac vein thrombosis, while 34 had iliac and femoral involvement. 4 had iliac, femoral and popliteal involvement., with 1 isolated femoral and 1 isolated popliteal DVT completing the group. The authors reported 7 complications: arm compartment syndrome secondary to bleeding from a previous arterial puncture, which required fasciotomy; 4 minor bleeding complications, usually related to the catheter insertion site in the popliteal fossa; 1 skin rash; 1 re-thrombosis 48 hours after lysis, which was successfully lysed a second time and has remained patent. There were no deaths.

Baekgaard et al reported on 101 patients with 103 IFDVT treated with CDT in a prospective single-centre study[7]. Median follow up was 50 months. At 6 years, 82% of limbs had patent veins with competent valves, and no clinical signs of PTS.

Casey et al published a systematic review and meta-analysis in 2012 comparing anticoagulation alone, with CDT and Surgical Thrombectomy[8]. The meta-analysis included 22 articles, representing 15 unique studies and 2 systematic reviews. There were 1186 enrolled patients altogether, with a mean sample size of 77, and mean duration of follow-up of 55.2 months (range: 3 – 120 months). The overall quality of evidence was low (no randomisation, poor base-line group comparability, selection bias to anticoagulation alone for late presenting patients, poor follow-up rates). In the meta-analysis CDT compared to anticoagulation was associated with a statistically significant reduction in risk of PTS development (RR 0.19, 95% CI 0.07 – 0.48; I^2 = 64%) and venous obstruction (RR 0.38; 95% CI 0.18 – 0.37; I^2 = 46%) and a trend to reduction in risk of venous reflux (RR 0.39; 95% CI 0.16 – 1.00; I^2 = 92%). Indirect comparison between CDT and Surgical Thrombectomy revealed no significant difference in risk of PTS development (RR 0.33; 95% CI 0.00 – 2.28), venous reflux (RR 0.44; 95% CI 0.05 – 2.10), and venous obstruction (RR 0.30; 95% CI 0.01 – 2.13). Adverse events and outcomes were poorly reported.

PTS morbidity and Quality of Life after CDT for IFDVT remains the major concerns for patients who do not suffer from major pulmonary embolization before or during treatment of DVT. It is agreed that PTS risk is worst in patients who suffer from IFDVT rather than in the femoral, popliteal or infra-popliteal segments. Discerning the segments involved with DVT is difficult when terms such as "Proximal DVT" and Distal DVT" are used[9]. De Maeseneer et al[9]. retrospectively identified 1338 patients diagnosed with acute unilateral DVT from 1994 to 2012. The site of the DVT was described anatomically as follows: Segment 1 = Calf Veins' segment 2 = popliteal Vein, Segment 3 = Superficial Femoral Vein, Segment 4 = Common Femoral Vein, and Segment 5 = Iliac Veins. 8% of all DVT were in 1 segment only, 22% in 2 segments, 36% in 3 segments, 15% in 4 segments and 20% in 5 segments. There was a 57% incidence of Left sided DVT. "Distal DVT" applies to Calf Vein DVT (Segment 1), while "Proximal DVT" refers to the remaining segments. The study showed that 38% of DVT are isolated Iliofemoral DVT. This is generally agreed to be the group most likely to benefit from Thrombus clearance. This group also has a high incidence of correctable anatomical lesions which precipitated the DVT and which are amenable to stenting, with concomitant low recurrence rates and PTS development rates. The authors conclude that defining the site of DVT more accurately by means of segments allows a much more accurate assessment of treatment options, and also allows for a more careful assessment of subsequent venous reflux, venous obstruction, and correlation with PTS severity.

Foegh et al. reported on the factors associated with long-term treatment success after CDT for IFDVT in a prospective observational study[10]. Symptom duration less than 14 days, absence of chronic post-

thrombotic lesions, and use of Pulse-Spray technique were identified as having better primary patency including normal valve function in the long term. 191 patients (203 limbs) underwent CDT between 1999 and 2013. Median follow up was 5 years (Range 1 month - 14.3 years). Lacing of the thrombus followed by continuous infusion of rtPa was used in 55 patients; the remainder were treated with a Pulse Spray technique. Patients were monitored during lysis with PTT, daily venograms and D-Dimer estimation. All had systemic heparin. Time to lysis was recorded. Stents were placed when necessary. All patients were anticoagulated for at least 1 year. Follow-up was by means of Duplex Ultrasound at 6 weeks, 3 months, 6 months, 12 months, and annually thereafter. Pulse Spray median time to lysis was 52 hours (range 22 – 142 hours), while continuous infusion time to lysis median time was 71 hours (range 25 – 146 hours); $p<0.05$. 52% of limbs were stented. At 7 years the cumulative rate of patent and competent deep veins was 79%. The authors confirmed that "restoration of the venous outflow tract is fundamental for a successful result".

Broholm et al assessed PTS symptoms and Quality of Life[11]. Between 1999 and 2008, 109 patients with DVT completed SF-36 scores, and had Duplex assessment of venous patency and valve function. PTS was assessed using the Villalta Scale, and the disease specific VEINES – QoL and VEINES – Sym scores. Median follow-up was 71 months. PTS developed in 16.5%. In these patients CDT had been successful in 13. Patients with PTS had significantly worse mean +/- SD scores than those without PTS on VEINES – QoL (34.2 =/- 9.6 vs. 53.1 =/- 6.6, $p < 0.0001$), VEINES – Sym (34.0 +/- 8.8 vs. 53.2 +/- 6.6, $p < 0.0001$), SF – 36 MCS (44.2 +/- 15.5 vs. 52.3 +/- 11.0, $p = 0.005$) and SF – 36 PCS (42.3 +/- 9.1 vs. 53.5 +/- 7.8, $p < 0.0001$). Patients with reflux or chronic occlusions, or both, had significantly lower mean +/- SD scores than patients with patent veins without reflux on VEINES-Qol (43.5 +/- 14.3 vs. 51.0 +/- 8.8, $p = 0.044$ and SF – 36 PCS (47.2 +/- 10.9 vs. 52.4 +/- 8.5, $p = 0.049$) scales. This study demonstrated that PTS was associated with worse QoL, and that relatively few (16,5%) developed PTS after CDT for IFDVT. Patent, non-refluxing veins were associated with QoL scores.

Comerota et al. demonstrated that PTS after CDT for IFDVT was related to residual thrombus. When thrombus clearance was complete PTS was avoided, but residual thrombus was associated with increased PTS risk. 71 patients with CDT for IFDVT were studied. Pre- and post – treatment venograms were assessed for presence of residual thrombus by Physicians blinded to clinical outcome. PTS was assessed using CEAP and Villalta Scores. 63 of the 71 patients completed the CEAP and Villalta analyses. Group 1 (< 50% residual thrombus) and Group 2 (> 50% residual thrombus) had median CEAP scores of 1 and 4 respectively ($p = 0.025$) and mean Villalta Scores of 2.21 and 7.13 respectively ($p = 0.011$) There was a significant correlation between CEAP score and amount of residual thrombus ($R^2 = 0.74$, $p = 0.004$) and a highly significant correlation between Villalta score and residual thrombus ($R^2 = 0.61$, $p = 0.0014$). The conclusion that the cause of PTS was residual thrombus. However, a significant limitation of this study was that no assessment of venous reflux was done, meaning that no assessment of the contribution of venous reflux to PTS symptoms could be made.

Future Directions

It should be clear from the foregoing review of the recent and relevant literature that there is a distinct lack of good quality evidence to allow a true assessment of the role of CDT for IFDVT. This is surprising, given the frequency of IFDVT, and the large number of centres offering endovascular therapy for IFDVT.

The existing literature also highlights the vastly different standards of reporting of the anatomical segments involved with DVT, and the assessment of residual thrombus and valve function after CDT.

What is abundantly clear is that CDT is here to stay, along with other endovascular modalities and surgical thrombectomy for management of IFDVT. In order to establish the role of each of these modalities (and, indeed, the role of anticoagulation alone), there needs to be agreement on uniform standards of reporting: duplex ultrasound, anatomical segments involved, the method of lysis, the follow up intervals, and reporting on degree of residual thrombus and vein reflux. CEAP and Villalta scores have been widely accepted as scoring methods for venous disease, and should be used at all time.

A large, multicentre, randomised control trial of anticoagulation, CDT, PMT and Surgical thrombectomy would provide the necessary good quality evidence to allow the roles of each modality to be determined, as well as the quality of life data associated with those outcomes. Hopefully this will be forthcoming.

The development of adjunctive devices (such as Ekos – ultrasonic infusion catheters) to speed up clot lysis may also improve outcomes – bleeding complications become more frequent with increasing duration of lysis, meaning that the risk of bleeding can be minimised by rapid clot lysis. The improvement of sheath design may make aspiration thrombectomy easier to perform, thus adding a further adjunct to the clot removal armamentarium.

In the absence of a suitably designed and executed RCT, it would be hoped that Clot Removal for IFDVT could be recorded in a prospective fashion in a National Registry. If the data fields of different national Registries were the same, then useful volumes of data would allow more accurate conclusions to be drawn as to the place of early clot removal, and the role of individual methods of cot removal.

Recommendations

1. CDT should be considered for Acute IFDVT in selected patients (**Class 1 / Level C)**
2. Retrievable IVC filters may be utilised during CDT for IFDVT (**Class 2b / Level C)**
3. Pulse Spray CDT is recommended over Continuous Infusion techniques of CDT (**Level 2b / Level C)**
4. All patients should be fully anticoagulated after CDT for IFDVT (**Class 1 / Level B)**

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5. Pharmaco-mechanical catheter-directed thrombolysis (PM-CDT)

Van Marle J

Introduction

Pharmaco-mechanical catheter-directed thrombolysis (PM-CDT) is currently recommended as the treatment of choice for the management of acute ilio-femoral deep vein thrombosis.[1, 2] PM-CDT combines catheter-directed infusion of a thrombolytic agent with a mechanical device which fractures the thrombus and/or enhances penetration of the lytic agent into the thrombus. The rheolytic thrombectomy device, the Angiojet power pulse system (Boston Scientific Marlboro, Massachusetts), is available in SA.

Executive summary

Initial studies reported that PM-CDT was safe and effective with regards to thrombus removal, decreased thrombolytic infusion time and early improvement of clinical symptoms.[3,]

Studies comparing PM-CDT to CDT found no difference in efficacy and safety, but reported a significant reduction in lytic infusion times, dose of lytic agent used, ICU and total length of hospital stay, and costs with PM-CDT.[4] The PEARL Registry, a multicenter prospective observational study, reported PM-CDT to be safe and effective with the possibility to reduce the need for CDT and intensive care.[5]

Various studies attested to the safety and efficacy of PM-CDT in patients with relative contra-indications to thrombolysis, in children and in pregnancy related ilio-femoral DVT.[6, 7, 8]

The TORPEDO Trial, a prospectively randomised study, compared percutaneous endovenous intervention plus anticoagulation to anticoagulation alone in the reduction of recurrent VTE and PTS.[9] Recurrent VTE and PTS developed in 2.3% and 3.4% respectively in the interventional group versus 14.8% and 27,2% in the anticoagulation only group (p-0.003 en p<0.001). The benefit which appeared early in the course of therapy extended to more than 2½ years.

A recent South African study reported on the development of PTS, quality of life and venous function in patients with extensive IFDVT who were treated with PM-CDT. After a mean follow up period of 31 months (3-18 months), 97% of patients had no evidence of PTS (Vilalta score < 5), the mean QOL score was 87% (VEINES-QoL/VEINES-SYM score) and 75% of patients had no abnormality on venous duplex Doppler examination.[10]

The ATTRACT (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis) study is a RCT to determine whether PM-CDT added to standard anticoagulation therapy will reduce the development of PTS in patients with acute deep vein thrombosis involving the femoral, common femoral and/or iliac veins.[11] Preliminary results were released in a press statement on 06-03-2017. PM-CDT reduced the severity of early DVT symptoms and the severity of subsequent PTS. Data from sub-groups and secondary analyses suggest that PM-CDT may have a benefit in patients with acute ilio-femoral DVT and were considered encouraging for this subset of patients.[12]

The DUTCH CAVA-trial (CAtheter Versus Anticoagulation Alone). (NL28394) is an ongoing multicenter RCT to determine whether ultrasound assisted CDT is superior to anticoagulation alone in preventing PTS, in patients with acute iliofemoral DVT.[13]

Future directions
New devices should be developed that are minimally invasive, fast, avoiding the use of thrombolytics and thereby bleeding complications, should be capable of removing clot older than 3 weeks and be easy to use.[14]

Recommendations[1, 2, 15]
Recommendations are given pending the final results of the ATTRACT and DUTCH CAVA-trials and may therefore be revised.

1. Presence of thrombus in the iliac veins ± IVC should be documented, using CT venography or MR venography as necessary. (**Class 1 / Level C)**
2. Early thrombus removal is indicated in patients with venous ischaemia due to IFDVT (phlegmasia cerulea dolens). (**Class 1 recommendation / Level A evidence)**
3. PM-CDT should be offered to patients with:
    1. First episode of acute IFDVT
    2. Symptoms of less than 14 days in duration
    3. Low risk of bleeding
    4. Good functional capacity
    5. Life expectancy of more than 1 year.

    (**Grade 2a / Level C)**
4. The relative risks versus benefits of peri-procedural retrievable IVC filter placement should be considered in patients undergoing PM-CDT with thrombus extending into the IVC or in patients with a limited cardiac pulmonary reserve **(Class 2b / Level C)**
5. Self-expanding metallic stents should be used to treat chronic ilio-caval compression for obstructive lesions that are uncovered by PM-CDT. (**Class 1 / Level C)**
6. Patient with isolated fem-pop DVT should be treated with conventional anticoagulation because there is clinically insufficient evidence to support early thrombus removal strategy **(Class 1 / Level C)**

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6. IVC filters and peri-procedural venous embolic protection devices

Ramnarain A

Introduction

Historically IVC (inferior vena cava) interruption was managed by IVC ligation via laparotomy with resultant significant morbidity and mortality rates ranging 19% - 39%. Percutaneous techniques and filter technology have revolutionized the approach to IVC interruption. IVC filters were first introduced in 1973[1].

The American college of chest physician's guidelines 2016 only recommend the use of IVC filters in patients with acute proximal lower extremity deep vein thrombosis (DVT) or pulmonary embolus (PE) who cannot receive anticoagulation therapy[2].

Executive Summary

The benefit of filters should be assessed in 2 groups of patients

- patients with VTE
- patients undergoing endovenous intervention for DVT

Even though there has been no randomized trial assessing the benefit of IVC filters in patients who have a contra indication to anticoagulation, it is the only therapy available in this group of patients. Untreated VTE is associated with 50% risk of recurrent PE and 25% mortality within the first 14 days[3].

The PREPIC trial compared the use of permanent IVC filters in patients with confirmed DVT who also received anticoagulation. Results at 12 days showed a decreased risk of PE with an increased risk of recurrent DVT, but none statistically significant. At 2 years mortality was equivalent in both groups with an increased risk of recurrent DVT in the filter group[4]. 8 year follow up showed no difference in mortality (48.1% filter group, 51% no filter group, *P* 0.008), increased risk of recurrent DVT (35.7% vs 27.5% *P* 0.042). This suggested that IVC filters may be beneficial in selected patients at high risk of fatal PE[5].

PREPIC 2 assessed the outcomes of retrievable filters in patients with acute pulmonary embolism. At 3 months PE occurred in 3% of the control group and 1.5% of the filter group. This result was consistent at 6 months and showed no benefit of filter placement. There was no increase in risk of recurrent DVT as 91.1% underwent filter retrieval at 3 months[6].

The FILTER-PEVI study assessed the benefit of IVC filters in patients undergoing percutaneous endovenous intervention (PEVI) for DVT. PE developed in 1 of the 14 symptomatic patients in the filter group and 8 of the 22 patients in the control group (P = 0.048). IVC filter implantation during PEVI reduces the risk of iatrogenic PE by eightfold without a mortality benefit. It was suggested that a selective approach may be exercised in filter implantation during PEVI[7].

Filter design affects outcomes in terms of IVC thrombosis, PE and limb penetration. Zhou et al[8] found 86.1% limb penetration through the IVC wall in 620 patients, even though a small number were symptomatic. A systematic review of 9002 patients identified IVC penetration to be present in 19% of patients. Of these, 19% showed organ/structure involvement of which 5% required surgical management[9].

The incidence of IVC thrombosis post filter placement varies from 0.6% to 18% based on different publications and attributed to several factors – central position of filter, clot formation within filter and filter design[1]. The risk of IVC penetration varies with filter type, indwelling time and the imaging modality used to assess the filter. Conical-shaped filters appear to have the highest rate of IVC perforation ranging from 13-100%[10].

In summary

- IVC filters are the only therapy available in patients with DVT who cannot receive anticoagulation
- Current randomized trials are flawed and do not definitively show general benefit in the use of IVC filters in patients who can be anticoagulated
- Possible benefit with retrievable filters during PEVI, but no mortality benefit
- Filters are associated with significant complications

Recommendations

1. The use of IVC filters in patients with acute IFDVT, with or without pulmonary embolism, should be considered when anticoagulation is contraindicated or when severe side-effects or bleeding complications attributable to the use of anticoagulants develop. **(Class 2b / Level B)**
2. The use of retrievable IVC filters during PEVI in select patients may reduce the risk of demonstrable procedure-related pulmonary embolism **(Class 2b / Level C)**

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7. Venous imaging (Acute and chronic venous disorders)

Naidoo NG

Introduction (Basic overview and problem statement)

Clinical appraisal, even with the use of hand-held Doppler, for the diagnosis of both acute and chronic venous disorders, is totally inadequate to inform treatment of especially symptomatic and complicated venous disorders in comtemporary vascular practice. Comprehensive venous imaging is absolutely essential in comtemporary venous practice to inform management decision algorithms. Unfortunately there is no gold standard venous imaging modality available currently. Modern venous practice employs the utility of one or more venous imaging modalities prior to venous intervention. The purpose of comprehensive venous imaging is to provide both functional and anatomical diagnostic data for various acute and chronic venous pathologies. These tests must provide information: on the pattern and distribution of superficial vein reflux in patients with varicose veins; on the anatomical distribution of thrombus burden in patients with acute deep vein thrombosis; on the pattern, and distribution, of deep vein and superficial vein occlusive and reflux disease in patients with the post-thrombotic syndrome; to diagnose primary and secondary venous outflow obstruction; to diagnosis central vein occlusive disease; to determine the superficial and deep extent of venous malformations; to diagnose pelvic vein reflux. This data is then utilized to inform single or multi-modal venous treatment strategies. Comtemporary venous practice employs one or more of the following venous imaging modalities:

- Venous Duplex Ultrasound (VDUS)
- Venography
    - Multi-Detector Computed Tomography Venography (MDCTV)
        - Indirect
        - Direct
    - Magnetic Resonance Venography (MRV)
        - Uncontrasted
        - Contrast-enhanced (Blood pool agents)
    - Catheter-based Venography (CV)
        - Ascending Venography
        - Descending Venography
        - Varicography
- Intravascular Ultrasound (IVUS)
- Trans-Vaginal Ultrasound (TVUS)

Executive Summary

Venous Duplex Ultrasound (VDUS)

Venous DUS has evolved as the first line, non-invasive, imaging modality for the diagnostic appraisal of both acute and chronic venous disorders in contemporary venous practice. It is used for pre-operative diagnosis, post-operative surveillance and during interventions. [1,2,3,4] Venous DUS, however, is operator and equipment dependent. It is less effective in ilio-caval venous imaging where imaging is limited by large body habitus (abdominal adiposity), excessive bowel gas, in-situ inferior vena cava (IVC) filter or post-laparotomy patient. Venous DUS is ideally suited for infra-inguinal venous imaging with sensitivity of 95% and specificity of 96%. [5] When compared to MDCTV diameters of the great saphenous vein (GSV) > 6mm generally correlate well with reflux. [6] It is highly imperative that venous DUS imaging be performed by experienced and accredited individuals.

Summary evidence from various varicose veins guidelines and studies found clinical evaluation and hand-held Doppler to be insufficient for evaluation of the deep and superficial veins of the lower extremity compared to DUS. [7,8,9] Venous DUS provides information on superficial and/or deep

venous thrombosis, deep venous reflux, saphenous junctional and truncal reflux, perforator reflux, and anomalous venous anatomy. Venous DUS should only be performed in patients with symptomatic or complicated varicose veins. In all patients with chronic venous disorders employing venous DUS, imaging must interrogate the inferior vena cava, iliac veins and both lower limbs completely. The infra-inguinal veins must be evaluating with the patient standing upright. It is important to completely document reflux and occlusive disease at all venous segmental levels. The standard reference for pathological venous reflux is > 0.5 seconds for superficial, profunda femoral, and calf veins; > 1 second for common femoral, femoral and popliteal veins; and > 0.35 seconds for perforating veins. [8] Venous DUS can also provide useful information to suggest the post-thrombotic syndrome, especially in patients who do not have a history of DVT: small caliber, thick-walled veins; the presence of traberculations or synechiae, often described as "venous channels"; and no flow detected in the deep veins.

It is widely acknowledged, based on existing literature, that venous duplex ultrasound should only be performed in high pretest probability cases suspected with acute DVT. Clinical decision rules (e.g. Well`s score) and D-dimer should be utilized for low pretest probability cases of suspected DVT initially. A low clinical pretest probability by the Wells rule for DVT in combination with a normal D-dimer blood test result safely rules out a first DVT. The following features are highly suggestive of a diagnosis of DVT: distended, non-compressible femoral and/or popliteal veins; no flow detected in the deep veins imaged, or alternatively loss of phasic flow; filling defects in the deep veins. The options between two point VDUS imaging (common femoral vein and popliteal vein) vs. whole leg VDUS imaging should be informed by institutional protocol, expertise and resource availability. [9] Venous DUS is the ideal imaging tool for first episode DVT. It is not, however, a reliable imaging tool to diagnose recurrent DVTs because of the residual organized thrombus that is invariably present. Ultrasound abnormalities may persist in ~ 80% of patients 3 months, and in 50% of patients 1 year after a DVT despite adequate anticoagulation. [11] Availability of a previous reported ultrasound scan may assist in improving the diagnostic yield of DUS under these circumstances. Venous DUS is unable to accurately age DVTs in all cases, even in the hands of experienced ultrasonographers.

Currently venous DUS cannot reliably confirm or exclude ilio-caval venous occlusive disease in all cases. A few venous centers of excellence in some countries have suggested the use of venous DUS to diagnose pelvic vein reflux. In the author`s experience this is too cumbersome and challenging for universal real-world application. Other complementary non-invasive venous imaging modalities are required for both the later considerations.

Multi-Detector Computed Tomography Venography (MDCTV) and Magnetic Resonance Venography (MRV)

In the recent past both MDCTV and MRV have evolved as extremely valuable venous imaging tools. They definitely provide much more information than venous DUS in suspected abdomino-pelvic venous pathology and central vein occlusive disease. [12] Both provide useful information regarding primary or secondary pelvic venous outflow obstruction (e.g. May-Thurner syndrome, post-thrombotic iliac vein occlusive disease, suspected pelvic tumors or iliac aneurysms resulting in venous compression); suspected central vein occlusive disease (e.g. superior vena cava syndrome, post central vein catheter-related occlusive disease); Nutcracker syndrome; and pelvic vein reflux disease. The utility of these tests should be restricted to the indications mentioned here. MDCTV has proven to be an invaluable navigational imaging tool to inform treatment strategies for varicose veins, especially, the need to interrogate and treat ipsilateral venous outflow obstruction, and to direct operative approaches for complex and variable sapheno-popliteal junctional pathologies. [13] MDCTV is more popular because it is more accessible than MRV, but utility generally is informed by institutional expertise, preference and experience. Indirect MDCTV is the preferred method when using this modality for venous imaging. For the following indications MRV has proven superior to MDCTV imaging: recurrent DVT; and for better visualization of intra-luminal venous pathology.

Both MDCTV and MRV are invaluable in the diagnosis of pelvic vein reflux with associated dilated vulval and peri-vulval veins; dilated buttock veins, and dilated posterior thigh and calf veins. These atypical veins are generally associated with the pelvic congestion syndrome (chronic pelvic pain, dysmenorrhea; severe dyspareunia, and exertional pelvic pain radiating down the inner thighs). Highly suggestive features include dilated left gonadal vein (> 6mm); dilated left and right gonadal veins; dilated para-uterine veins. More importantly significant gynecological pathologies can be identified or excluded. This is extremely important when considering gonadal or pelvic vein trans-catheter embolization.

Atypical varicose veins, both saphenous and non-saphenous, can present significant diagnostic challenges. Much information regarding the pattern and distribution of these unusual clinical entities has been provided by 2D and 3D reformatted MDCTV imaging. This has expanded our knowledge base in this regard tremendously, simultaneously informing innovative treatment strategies or treatment algorithms. [14]

Both MDCTV and MRV are capable of ageing and defining the extent of acute DVTS more accurately than venous DUS. [15] This is invaluable when considering venous removal strategies, where the results of intervention are far superior for fresh DVTS < 14 days. The following features are highly suggesting of a fresh DVT < 14 days: A distended CFV, or other deep veins, with hypoechoic thrombus and inflammatory enhancement of the vein wall, compared to the contralateral normal deep veins. Small caliber CFV, or other deep veins, with thickened walls, and/or partial recanalization, and/or intraluminal filling defects are highly suggestive of more long-standing DVTs. Both MDCTV and MRV are more than capable of accurately delineating the extent of DVT. This is extremely important to standardize outcomes when comparing various thrombus clearance strategies for acute ilio-femoral DVTs (IFDVT).

Catheter-based Venography (CV)

Conventional phlebography for diagnostic purposes has been largely superseded by non-invasive imaging (VDUS; MDCTV and MRV). Catheter-based venogram is currently employed predominantly in venous interventions such as iliac vein angioplasty and stenting, central vein angioplasty and stenting, trans-catheter embolization for pelvic vein reflux, and for percutaneous catheter-based thrombus clearance strategies such as catheter-directed thrombolysis (CDT) and catheter-based pharmaco-mechanical thrombectomy (PMT) for acute IFDVTs.

Intravascular Ultrasound (IVUS)

Intravascular ultrasound is extremely invaluable in evaluating and directing the endovascular treatment of primary and secondary iliac vein occlusive disease, as well as central vein occlusive disease. [16] It is more accurate than VDUS, catheter-based venography, MDCTV and MRV in describing and calculating the degree of venous stenosis. In the VIDIO trial IVUS was superior to three-projection catheter venography in identifying and treating iliac vein occlusive disease. [17] In cases of significant chronic post-thrombotic ilio-caval occlusive disease IVUS is invaluable in directing the extent of iliac vein stenting, where multiple overlapping iliac vein stents may be requiring, and equally importantly identifying where stenting across the inguinal ligament is required.

Intravascular ultrasound is invaluable in cases employing thrombus removal strategies for acute IFDVT. In these cases it is used for diagnosing high grade ilio-caval occlusive disease requiring iliac vein stenting.

It is not cost-effective, however, to use IVUS as a purely screening diagnostic imaging modality. It`s use must be informed by good quality VDUS, MDCTV, MRV or a combination of pre-operative imaging modalities.

Trans-vaginal Ultrasound (TVUS)

Trans-vaginal ultrasound (TVUS) is an important adjunct in the evaluation of patients with atypical varicose veins suggestive of pelvic vein reflux. Suggestive features include dilated para-uterine veins or ovarian veins > 6mm.

Future Directions

Until a "one-stop imaging shop" venous imaging modality becomes available, a combination of tests are generally required for diagnostic and interventional purposes in contemporary venous practice. It is not unusual for two or more venous imaging modalities to be used to diagnose and treat various venous pathologies in current practice. Good quality studies are needed to evaluate costly imaging modalities such as MDCTV; MRV and IVUS.

Recommendations

1. Hand-held CW Doppler should not be used in the evaluation of chronic venous disorders **(Class 1; Level B)**
2. Venous DUS is the initial investigation of choice for all patients with symptomatic or complicated chronic venous disorders **(Class1; Level A)**
3. Venous DUS should be the first line investigation for recurrent varicose veins following surgery or endovenous vein ablation **(Class 1; Level C)**
4. Venous DUS should be the first line investigation for a high pretest probability acute DVT **(Class 1; Level B)**
5. When indicated venous DUS must scan the IVC, iliac veins and both lower limbs completely **(Class 1; Level C)**
6. Additional venous imaging for acute DVT, such as MDCTV or MRV, should be reserved for the following:
    a. Acute IFDVT requiring thrombus removal interventions **(Class IIa; Level B)**
    b. Prior to IVC filter insertion **(Class IIa; Level C)**
    c. Pulmonary thromboembolism with a normal venous DUS **(Class IIa; Level C)**
7. No venous imaging is required for asymptomatic chronic venous disorders e.g. asymptomatic primary varicose veins **(Class 1; Level C)**
8. Additional venous imaging for symptomatic or complicated chronic venous disorders should be reserved for the following:
    a. Suspected pelvic vein reflux **(Class 1; Level B)**
    b. Suspected lower extremity venous outflow obstruction **(Class 1; Level B)**
    c. Suspected central vein stenosis / occlusion **(Class 1; Level B)**
    d. Atypical varicose veins **(Class IIa; Level B)**
9. Trans-vaginal ultrasound should be used to evaluate suspected pelvic vein reflux where such expertise is available **(Class IIa; Level C)**
10. Catheter-based venography should be reserved for venous interventions **(Class IIa; Level B)**
11. Intravascular ultrasound should be used in the evaluation and interventional treatment of lower extremity venous outflow obstruction **(Class 1; Level B)**
12. Intravascular ultrasound should be used in the evaluation and interventional treatment of central vein occlusive disease **(Class 1; Level C)**

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8. Venular, reticular and varicose veins: Overview, Medical treatment & Compression therapy

Dube B

Introduction

Venular (telangiectasias), reticular and varicose veins are part of the spectrum of chronic venous disorders (CVD). Telangiectases are hyphen intradermal web veins one millimetre (mm) or less, impalpable and associated with blanching.[1] Reticular veins lie deep to the dermis (2-3mm in diameter) and are also not palpable. Varicosities are defined as palpable abnormal, tortuous dilated veins more than 3mm in diameter. These can be classified as congenital, primary, secondary or recurrent, with primary varicose veins being the most prevalent and thus the focus of this guide-line. When associated with advanced clinical manifestations (oedema, skin changes and ulcers), such disorders are termed Chronic Venous Insufficiency (CVI).[2]

Executive Summary

Varicose veins are extremely common, with a variable reported incidence ranging from 20% to 64%.[3] Risk factors for varicose veins and subsequent CVI include; age, gender, obesity, family history, occupation and ethnicity.[4] Varicose veins are associated with a wide range of symptoms; pain, restless legs, heaviness, itching, and swelling of the limbs. Primary varicose veins may also be complicated by superficial vein thrombosis and bleeding, both resulting in significant morbidity. The more advanced stages of venous disease affect about 5% of the population, with the prevalence of the end stages of CVI (active and healed venous ulcers) estimated at 1-2%.[2]

The natural history of primary varicose veins is very variable although aging, family history and a maladaptive lifestyle are all associated with clinical progression. A study including 116 limbs with varicose veins used a second duplex scan a median 19 months after the initial examination in the period waiting for surgery.[5] Approximately one-third of the patients had progression, and in 95% of the patients the changes were noted after 6 months or more. In the large-scale Bonn Vein study, the progression rate from varicose veins to CVI was 4% per year.[6]

The pathophysiology of CVD is characterized by reflux, obstruction, or a combination of both. This results in reduced ability to empty the leg veins efficiently during exercise, which means the ambulatory venous pressure remains high and this eventually leads to all the clinical features of venous hypertension. Whereas most patients with uncomplicated varicose veins still have normal venous pressures during ambulation, all those with more advanced stages of CVD progressively develop venous hypertension, characterized by symptoms and signs of CVI. The spectrum of presentation of varicose veins is best described and assessed using the CEAP (Clinical, Etiological, Anatomical, Pathophysiological) classification with the clinical class ranging from C0 to C6.[7]

COMPRESSION

Elastic stockings have been the cornerstone of conservative management of varicose for decades. They are available in 4 classes: 10 to 15 mmHg (class 1), 20 to 30 mmHg (class 2), 30 to 40 mmHg (class 3) and 40 to 50 mmHg (class 4). The mechanism of action includes compression of the superficial and deep veins and improvement of the muscle pump function, both leading to reduction in ambulatory venous pressure and reduction of oedema.

Compression stockings for Early Venous Disease (C1 – C2)

In a review of 11 randomised controlled trials (RCTs) and 12 observational studies, there was no agreement on the appropriate class of compression for early venous disease.[8] Compression was noted to improve patient symptoms and quality of life (QoL) when high compliance rates were attained. However, use of compression stockings was not shown to prevent progression of varicose veins or recurrence of varicose veins after treatment.

Compression stockings in C2 – C3 Disease

The Randomised Clinical Trial, Observation Study and Assessment of Cost-Effectiveness of the Treatment of Varicose Veins (REACTIV) trial randomised 246 patients with to conservative management or surgery.[9] The hallmark of conservative treatment was the use of compression stockings. In the first 2 years after treatment, the authors observed more symptomatic relief, better quality of life in the surgical group as compared to conservative management. The surgical arm was noted to be more cost effective as compared to conservative management.

Compression Stockings in C4 – C6 Disease

A Cochrane review in 2012 of 4 RCTs (979 patients) in overall showed a decrease in venous ulcer recurrence with use of Class 2 and 3 stockings[10]. Only 1 study showed lower recurrence with a higher compression (Class 3), but however due to the large heterogeneity of the studies, a meta-analysis could not be performed.

Medical Treatment

Medical treatment has been used for decades but its role in the treatment of CVD remains very controversial and poorly defined. There are no drugs that alter the natural progression of minor and established varicose veins. A wide variety of drugs are available (phlebotonic drugs), and these are thought to reduce symptoms and oedema. These are broadly divided into natural and synthetic drugs. They exert their effects by, decreasing capillary permeability, inhibiting release of inflammatory mediators and improving venous tone.

Four groups of drugs have been evaluated in the treatment of CVD; coumarins (alfa-benzopyrones), flavonoids (gamma-benzopyrones), saponosides (horse chestnut seed extracts/aescin) and other herbal extracts. Coumarins are derived from many plants and are thought to have anti-inflammatory activities. Flavonoids exert their actions on leukocytes and the endothelium with a reduction in both inflammation and capillary permeability. Aescin is a mixture of saponins derived from Aesculus Hippocastum and have both anti-inflammatory and vasoconstrictor effects.

A Cochrane review of the efficacy of the above drugs was published in 2005 and has still not been updated.[11] A total of 110 studies were reviewed but only 44 studies had valid methodology suitable for analysis. Micronized Purified Flavonoid Fraction (MPFF), a mixture of Diosmin and Hesperidin was the most effective at reducing symptoms of oedema and restless legs. Rutosides resulted in a decrease in venous oedema and calcium dobesilate was noted to reduce cramps and restless legs. This meta-analysis, however, concluded that there was insufficient evidence to support the global use of all veno-active drugs in the treatment of CVD.

A Cochrane review of 17 randomised controlled studies (RCTs) showed that horse chestnut seed extract (HSCE) was effective at decreasing oedema, pain and itching.[12] The RELIEF study investigated the effects of MPFF on 5,052 CVD patients with C0 to C4 venous disease. MPFF significantly reduced oedema, pain, heaviness and cramps in the limbs.[13] In other reviews, use of MPFF or Pentoxifylline (a competitive non-selective adenylate cyclase inhibitor) combined with compression was associated with faster healing of venous ulcers.[14-15]

Future Directions

There is still a need to develop an anatomical classification of varicose veins that can be applied consistently in studies assessing effectiveness of stockings. Further high-quality studies are needed to determine the appropriate class of compression required including the length of stockings (knee or thigh length) in the management of varicose veins. Given the limitations of the current evidence regarding medical therapy for CVD, there is a need for further randomised controlled trials with greater attention paid to methodological quality.

Recommendations

- Class 2 compression stockings (20 – 30 mmHg) are recommended for patients with symptomatic primary varicose veins **(Class IIb / Level C)**.
- Compression stockings alone may be used in the treatment of some patients with isolated non-truncal varicose veins. A trial of a short course of compression may be appropriate when alternative pathology is suspected **(Class IIb / Level C)**.
- Compression stockings are not recommended as the primary treatment modality in patients who are candidates for saphenous vein ablation **(Class I / level B)**.
- Compression stockings should be used after healing of venous ulcers to decrease the risk of recurrence **(Class IIa / Level B).**
- Phlebotonic drugs should be considered as a treatment option for patients with symptomatic varicose veins and leg swelling when available **(Class IIb / Level B)**.
- Long-standing or large venous ulcers may benefit from treatment with either pentoxifylline or MPFF (Daflon) in combination with compression therapy **(Class IIb / Level B)**.

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9. Saphenous Ligation; CHIVA and ASVAL

Michalowski K

Introduction

Despite the high prevalence of venous disease, the aetiology and pathogenesis of varicose veins is still poorly understood. Improvement in technology, particularly duplex ultrasonography, has enabled physicians to map the venous system, gaining anatomical and functional information that can accurately describe patterns of reflux. The features of chronic venous disease (CVD) are secondary to high venous pressure in the lower limb, resulting in development of varicosities, skin changes, and in the ulceration. However, the steps leading up to the development of venous hypertension are still poorly understood. There are two fundamentally opposite aetiological concepts: firstly Descending/saphenocentric, and secondly Ascending/multifocal. The Descending theory supports traditional treatment where ablation of Greater and Lesser Saphenous Veins is carved in stone for management. Whereas, the Ascending theory has inspired development of a surgical approach with the aim of correcting abnormal haemodynamic pathways in the venous system, resulting in targeted interventions like CHIVA (cure conservatries et hemodynamique de l'insuffisance veineuse en ambulatiore-ambulatory conservative haemodynamic management of varicose veins) and ASVAL (ablation selective des varices sous anesthesia locale- ambulatory selective varicose vein ablation under local anesthesia). The old technique of preserving Greater Saphenous Veins, like simple high ligations, has proven to be ineffective. The Simple Ligation of insufficient Lesser Saphenous Vein remains one of the recommended methods of treatment.

Executive Summary

High ligation alone to preserve saphenous vein was proven to be an inadequate method of treatment when compared to high ligation and stripping (HL/S). 133 legs of 100 patients were randomized to high ligation or high ligation and stripping. The need for reoperation was 6% in patients who underwent HL/S vs 20% in those patients who underwent high ligation alone. The reason for this is that patients with high ligation have recurrent reflux in the residual GSV, which causes new symptoms and increased risk of reoperation.

Complete stripping of Lesser Saphenous Vein (LSV) is rarely performed today because of possible injury to the Sural Nerve, but ligation of the LSV in popliteal fossa guided by Duplex Doppler is recommended for treating CVD caused by reflux in this vein. There is no evidence that flush ligation is better than simple ligation of the vein when performed at a location closer to the skin.

Modern preservation of the saphenous vein was described by Paul Pittaluga in the ASVAL and by Francesci in the CHIVA.

ASVAL eliminates varicose veins tributaries by simply performing extensive phlebotomies. Contrary to the "descending" theory, ASVAL advocates the belief that we must catch the problem early before the "suction" from the varicose veins has damaged the saphenous vein. Removal of varicosities reduces the haemodynamic load on the saphenous vein.

The procedure is performed as a day surgery case. Varicosities are marked pre-operatively with the patient standing. Phlebotomies are performed with micro-incisions and the varicosities are removed with a phlebotomy hook, whilst preserving saphenous trunk.

A retrospective analysis on patients treated with ASVAL and saphenous vein sparing revealed good midterm results – saphenous reflux reduced in more than two-thirds of cases over a four year period, whilst symptoms improved or disappeared in the majority of cases. There was no recurrence in 95% of patients at one year and 88,5% at four years. Recurrence was more likely to occur if the varicosities were extensive. In haemodynamic study's authors clarified that patients with limited disease progression and mild haemodynamic alternations were most likely to benefit from this approach.

CHIVA is a surgical approach with the aim of correcting abnormal haemodynamic pathways in the venous system, resulting in targeted intervention. A classification with so-called abnormal haemodynamic "shunts" is the crux of the CHIVA approach. Proponents of this theory have illustrated four patterns of deviant flow in the saphenous, varicose and perforating veins. Intervention requires simple ligation (thereby disconnecting the abnormal shunts) at either the saphenous vein junction or the origin of the varicose veins at the point where they come off the saphenous vein. Sometimes a combination of ligations is required. Normal flow then returns without destroying any veins at all. After appropriate ligations, abnormal high-pressure veins are reportedly remodelled and return to their normal size. After targeted ligations, normal flow from the superficial to deep veins is re-established. No phlebotomies, sclerotherapy, or saphenous ablations are required. Importantly, CHIVA cannot be performed on patients with deep venous incompetence, as there is no competent channel through which the venous flow can be re-routed.

A Cochrane review published in 2013 found 3 randomized controlled trials comparing CHIVA vs saphenous stripping and one comparing CHIVA vs compression. The authors reported that CHIVA had reduced recurrence rates, improved quality of life and reduced side effect profile compared to both stripping and compression. Direct comparison between CHIVA and stripping or endovenous laser ablation (EVLA) found that CHIVA and EVLA patients had improved cosmetic results and reduced pain scores compared to those undergoing open surgery. Reported recurrence rates (reflux in GSV) ranging from as high as 91% at 3 years to 18% at 10 years. The consensus appears to be that CHIVA is less reproducible than traditional methods and good results are difficult to achieve.

It is possible that the financial advantages of ablating saphenous vein are the real driver for not saving the saphenous vein in many countries when treating varicose veins.

Future Directions

Currently ASVAL is performed for patients with minimal or no symptoms of CVD, competent sapheno-femoral valve and segmental saphenous reflux. It will be very difficult to design randomized studies to evaluate it against any proven and well-validated surgical techniques.

CHIVA is a very complex approach and a high level of dedication and training is required to perform it with the results achieved in small-randomized trials.

New directions are reported with CHIVA combined with endoluminal heat techniques.

Recommendations

1. High ligation of GSV alone should not be performed for treatment of CVD **(Class 1 / Level A)**

2. ASVAL can be used selectively for patients with minimal symptoms of CVD **(Class 2b / Level C)**
3. CHIVA can be recommended for patients with varicose veins but only when performed by a suitably trained venous interventionists **(Class 2a / Level B)**

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10. Endovenous vein ablation (EVA) – Thermal Strategies

Ntloko S

Introduction

The traditional treatment for saphenous vein insufficiency has been high ligation with or without stripping of the great saphenous vein (GSV) for GSV insufficiency and ligation of the sapheno-popliteal junction in small saphenous vein (SSV) insufficiency. This is usually performed under general or epidural anaesthesia and is an effective method to eliminate reflux in the short term as 5 year recurrence rates have been quoted between 20-28%. Endovenous techniques eg, endovenous laser ablation (EVLA), radiofrequency ablation (RFA) and ultrasound-guided foam sclerotherapy (UGFS) are commonly performed now with the advantage, over traditional surgery, of minimal scarring, obviating general or epidural anaesthesia, having fewer complications, faster recovery times and less post-procedural pain. The two most commonly performed endovenous thermal ablations (EVTA) are EVLA and RFA and they have demonstrated clinical superiority to stripping and surgical ligation, as well as significantly reduced the post-operative pain and recovery time [1]. All the thermal techniques require injection with tumescent fluid around the target vein to protect the perivenous tissue from the heat during treatment; create spasm of the vein and to obtain local compression and anaesthesia. While withdrawing the catheter or fibre, energy is emitted intraluminally to cause

irreversible thermal destruction of the endothelium of the vein wall. Compression post intervention is recommended but the duration is not clearly defined. Recordered post-operative complications in EVTA include thrombophlebitis (7%), thermal skin injury (<1%), bruising and hyperpigmentation (5%) and paresthesia (1-2%).

Executive Summary

EVLA wavelengths and fibres

To reduce the possible side effects of EVLA, higher laser wavelengths have been introduced and different fibre tips have been developed. There are low (810nm/940nm/980nm/1064nm) and high (1320nm/1470nm/1500nm) wavelengths depending on their absorption characteristic in the blood. Proebstle et al [3] found that the wavelengths were equally effective in producing occlusive rates but there was significantly less pain and ecchymosis post procedurally with the 1320nm laser.

The use of bare-tip fibres creates unequal energy delivery at the vein wall resulting in local vein wall perforations and perivenous tissue destruction which are associated with increased post procedural pain. The jacket-tip fibre has been designed to sheath the distal tip of the laser fibre thus enabling the delivered energy to be diffused over a greater surface area. Kabnick et al[4] showed that using a jacket tip is more significant in reducing pain and bruising compared to using a laser with longer wavelength.

Effectiveness and safety of EVTA vs surgery

EVLA and RFA effectively eliminate superficial venous reflux and the permanent obliteration rate is as high as 87-100%. Wozniak[2] showed that EVLA and RFA offered comparable efficacy and safety of lower extremity varicose vein management in a 5 year follow up. This has been corroborated by previously published meta-analyses and a current Cochrane review [5] which concluded that RFA and EVLA are at least as effective as surgery in the treatment of GSV varicose veins.

RFA vs EVLA

RFA and EVLA have the same occlusion rates, but patients treated with RFA have less post-operative pain and bruising which can result in equal or faster return to work[7]. In most trials comparing the two, the Closure Fast catheter is compared to lower wavelength lasers using a bare tip fibre and there are no trials that have compared the RFA with higher wavelengths and the new fibre designs.

Both RFA and EVLA have been described as safe and effective options for the treatment of recurrent varicose veins. EVLA was found to have a higher technical success rate and lower complication rate compared to surgery especially relating to sural nerve neuralgia (20% vs 9%). RFA was found to be superior to redo groin surgery with respect to lower pain scores, bruising and procedure times.

Small saphenous vein treatment

EVTA of the SSV has excellent early and midterm results. Compared to surgery, EVTA, seems to be more efficient and results in fewer post-operative side effects. EVLA of the SSV is associated with a significantly higher incidence of sensory disturbance compared to EVLA of the GSV. Access at the lateral malleolus results in higher paresthesia rates compared to mid-calf access because of the proximity of the sural nerve to the SSV in the distal part of the calf

Future Directions

Endovenous Steam ablation (EVSA)

Van den Bos [8] published a RCT that showed that EVSA was inferior to RFA, however patients treated with high dose EVSA reported similar results with EVLA. Further studies are required to assess its midterm efficacy.

Recommendations

1. For the treatment of GSV reflux in patients with symptoms and signs of chronic venous disease, EVTA techniques are recommended in preference to surgery and foam sclerotherapy **(Class 1 / Level A)**
2. For the treatment of small saphenous vein reflux in patients with symptoms and signs of chronic venous disease, EVTA techniques should be considered, but access to the SSV should be gained no lower than the mid-calf **(Class 2b / Level B)**
3. EVTA should be considered for the treatment of symptomatic recurrent varicose veins in select patients with endo-suitable venous pathology **(Class 2a / Level B)**
4. Tumescent anaesthesia is recommended for EVTA procedures **(Class 1 / Level B)**
5. Concomitant phlebectomy along with EVTA should be considered especially if the refluxing tributary is >3mm **(Class 2b / Level C)**
6. Post-operative compression stocking for at least 7 days is recommended **(Class 1 / Level B)**
7. Post-operative oral Rivaroxaban (10mg/d) for a period of 5-10 days for eHIT prophylaxis in EVLA may be considered **(Class 2a / Level C)**

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11. Endovenous vein ablation- Non-Thermal Strategies

Redman L

Introduction

Non-thermal endovenous ablations are minimally invasive endovenous techniques for the treatment of chronic venous insufficiency created to minimise unwanted side effects of thermal endovenous techniques, such as pain, skin burns and nerve damage. Additionally, venous incompetence can be treated to the ankle without the risk of associated nerve injury.

Non-thermal endovenous ablations consist of Mechanical Occlusive Chemically Assisted (MOCA) closure, or Clarivein, which uses mechanical and chemical methods to ablate the saphenous vein, Cyanoacrylate Adhesive Ablation (CAA) or VeneSeal and foam sclerotherapy.

The former two endovenous techniques have been compared to the current gold standard of RadioFrequency Ablation (RFA) and have shown non-inferiority.

Foam sclerotherapy is an adjunctive non-thermal ablative technique.

Executive Summary

Indications and Current treatments

Venous insufficiency affects 20–30% of the adult population. Symptoms may or may not be present but include: heaviness, swelling, throbbing, itching, muscle cramps and restless legs. In more advanced cases, hyperpigmentation, eczema, lipodermatosclerosis and ulceration may develop.

Treatments traditionally included saphenous ligation and stripping which have largely been replaced by thermal endovenous techniques.

The newer non-thermal modalities have been developed to achieve the same results as thermal ablation, but to minimise the negative aspects.

Mechanochemical Ablation (MOCA) - Clarivein

The Procedure

Mechanochemical ablation is performed under ultrasound guidance, through a 4 French sheath. Catheter placement is 2 cm from the sapheno-femoral or sapheno-popliteal junction. The first 3mm is mechanical only. Thereafter, liquid sclerosant is injected at 0.2 ml per cm. The catheter is pulled back at 1cm every 6 seconds.

The sclerosant is injected at a calculated dose according to vein size (typically 1.5% of sodium tetradecyl sulphate above the knee and 1.0% below the knee).

Efficacy

1. Vein Closure Rates

A randomised controlled trail (RCT) has been performed looking at closure rates comparing MOCA to RFA. At one month these showed a non-significant difference of complete occlusion rates of 83% and 92% respectively (p=0.79). [2]

Two cases series have reported one year occlusion rates of 88% and 94%.

2. Pain Scores

The RCT comparing RFA and MOCA in both the great and small saphenous veins, showed a significant difference in pain favouring MOCA.

In a non-randomised comparative study of 68 patients with great saphenous vein incompetence treated by MOCA or RFA showed non-significant differences in pain scores during the procedure, a significant difference after 3 days and a highly statistically significance over the first two weeks post procedure in favour of MOCA.[6]

3. Quality of Life Scores

A comparison of MOCA to RFA showed similar Venous Clinical Severity Scores (VCSS) and Aberdeen Varicose Vein Questionnaire (AVVQ) improvements of outcome at one month follow up, with no statistical difference noted between the two, with statistically significant improvements from baseline in both groups at 6 weeks. [2,6]

A case series of 92 patients reported significant improvement in the median VCSS and AVVQ score at 1-year follow-up ($p<0.001$). [3]

4. Time to return to activity

There is no significant difference in mean times to return to work between RFA and MOCA with the mean times to return to being 3.5 days.[2] In a case series of 92 patients (106 legs), the median time to return to usual activities was 1.0 day.[3]

<u>Safety</u>

Adverse events were very low in all reports.

The RCT of 117 patients showed no patients treated by MOCA and 1 patient treated by RFA had deep vein thrombosis. [2]

A large case series of 449 patients showed 1 patient had deep vein thrombosis and 2 had pulmonary embolism – all patients were treated without any sequelae.

Thrombophlebitis has been reported in 0% -14% in various case studies.

Very low incidences of other adverse events have been reported in MOCA and include: sural nerve injury, pain and erythema, pain at the injection site, induration, infection (at puncture site), haematoma, ecchymosis and hyperpigmentation.

Retrograde inversion stripping of a small saphenous vein was reported in 1 patient in a case report due to the catheter becoming stuck – there were no long-term sequelae.

Theoretical adverse events not reported in the literature include: vein perforation, migraine, visual disturbance and stroke.

Cyanoacrylate Adhesive Ablation (CAA) - VeneSeal [7, 8, 9]

The Procedure

The VeneSeal system works through a 7 Fr sheath. The catheter needs preparation.

The catheter is placed 5 cm from the sapheno-femoral or sapheno-popliteal junction. At the start, 0.1mls of cyanoacrylate is delivered to the first 1 cm and pressure maintained on the vein and a 3 cm segment is treated and pressure maintained for 3 minutes. Thereafter 3 cm segments are treated and pressure maintained for 30 seconds.

Efficacy

1. Vein Closure Rates

RFA and CCA have been compared in an ongoing study - closure rates were initially compared at 3 months with 99% and 95.4% closure in the Veneseal and RFA group respectively. This has been extended to a 36 month assessment of closure showing closure rates of 94.4% and 91.9% in the VeneSeal and RFA group respectively, showing statistically significant non-inferiority of VeneSeal to RFA.[7, 8, 9]

The WAVES study looked at outcomes of treating large veins with cyanoacrylate – up to 20 mm, as well as treating multiple segments. The great saphenous veins, accessory saphenous vein and small saphenous vein were assessed for closure at 1,3 and 12 months. These showed overall excellent closure rates of 100%, 99% and 98% respectively. [10]

2. Pain Scores

Pain scores were not significantly different compared to RFA in a randomized control trial. There was also no difference in narcotic or non-steroidal anti-inflammatory use between RFA and Veneseal. [7, 8, 9]

Pain scores in the WAVES study, which treated more advanced disease were low. Pain scores were 0 in 36% of patients at one week and 86% of patients at one month. [10]

There was significantly less bruising in Veneseal group versus RFA group at day 3.

3. Quality of Life Scores

Venous Clinical Severity Scores showed that there was significant improvement in scores up to 6 months and this was obtained throughout 3 years. There was also no significant difference between RFA and VeneSeal. The same outcomes were seen in the Aberdeen Questionnaire and the EQ5D scoring system.

All scoring evaluations for quality of life in patients treated in multiple segments with cyanoacrylate showed significant improvement at12 months. [10]

4. Time to return to activity

Return to work was shown to be on the day of the procedure or the day after. (0.2 +/- 1.1 days). Return to normal activities including full exercise workouts was a mean of 2.4 days.[9]

Safety

Up to three months all adverse events were mild and included paraesthesia in treatment zone, irritation from stockings, phlebitis, access site infection and superficial thrombophlebitis. Phlebitis was more common in the VeneSeal group, but not statistically significantly so. Between 3 and 12 months, there was no difference in adverse events between the two groups – again, most being mild. Of note, there was no thrombus extension in the VeneSeal group but two reported in the RFA group. Between 2-3 years, two mild adverse events occurred in the 36-month follow up in the Veneseal group. These were mild (phlebitis and prominent scar) and not related to device or procedure. [7, 8, 9]

When multiple segments were treated in more advanced disease, at one year adverse events were still minimal and mild – there was one episode of phlebitis and a possible allergy. [10 this as]

Other

Treating multiple segment showed that adjunctive procedures (phlebectomy and sclerotherapy) could be significantly reduced at 3 months.

Foam Sclerotherapy

Foam sclerotherapy is made by mixing a sclerosant with 1:4 or 1:5 mls part sclerosant to air using the Tessari method.

It has been previously shown to be inferior to surgical techniques, but can be used as an adjunct for endovenous procedures, where catheter ablations are not technically possible and around ulcerations.

Future Directions

Non-thermal catheter ablations are comparable to the current gold standard of thermal ablations in terms of safety and efficacy and their use has adequate support. There are also seemingly added advantages and some of the end points of the trials showed a trend towards superiority.

They are useful for treating small saphenous veins, great saphenous veins below the knee, lipodermatosclerotic skin and MOCA is useful to treat ulcerations.

Continued long-term follow up is essential.

Recommendations

1. Non-thermal endovenous ablation is an acceptable treatment modality for treating venous incompetence and may be preferred in select cases such as below the knee and ulcer intervention **(Class 2a / level B)**

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12. Management of the varicose reservoir, telangiectasia and reticular veins

Moydien R, Naidoo NG

Introduction

The varicose reservoir refers to the dilated subcutaneous veins > 3mm in diameter located in the calf, thigh or both. These varicose veins may be primary, secondary or recurrent. Recurrent varicose veins may develop years after surgery (REVAS) or endovenous thermal vein ablation (REVATA). Primary varicose veins may be associated with junctional and truncal saphenous vein reflux, non-junctional, truncal saphenous vein reflux, isolated perforator vein reflux, or may be totally non-saphenous altogether e.g. postero-lateral thigh perforator. The management of this varicose reservoir has always remained a matter of debate: should their management be synchronous or staged with truncal vein

treatment strategies? Should we be using phlebectomies or sclerotherapy, or both to treat this varicose reservoir?

Telangiectasia, or spider veins, are dilated intra-dermal venules (small superficial veins) measuring less than 1.0 mm in diameter. Reticular veins have a diameter 1 to 3 mm and are often tortuous and located in the subdermal or subcutaneous tissue. The cause is unknown. These veins may or may not be associated with saphenous vein reflux. Patients may be asymptomatic or may report pain, burning or itching. Risk factors include family history, pregnancy, local trauma, and hormonal factors. The diagnosis is made clinically and according to the CEAP classification. Telangiectasias and reticular veins are classified as C1 disease. The incidence increases with age. They are very common in the lower extremities, being found in 41% of women over the age of 50 years. It represents an important aesthetic or cosmetic problem and may be associated with major venous system insufficiency. [1] Treatment for telangiectasia and reticular veins include sclerotherapy, transcutaneous laser therapy, intense pulsed light treatment, microphlebectomy and thermocoagulation. These treatments can be used individually or in combination to maximise the effects and avoid any harm of the individual techniques.

Executive Summary

Sclerotherapy

The most common treatment for telangiectasias and reticular veins is sclerotherapy.[2] This technique causes destruction of the vein by injection of a sclerosing agent that destroys the vein endothelium, leading to vessel occlusion, fibrosis and disappearance of the vessel. Sodium tetradecyl sulphate (STS), polidocanol (POL), sodium morrhuate, glycerine, and hypertonic saline, either as liquid or foam (this is created using a detergent sclerosant such as STS) is injected into the vein with a hypodermic needle until the area around the puncture site blanches or resistance is felt. The injection is discontinued if there is extravasation. [2,3,4]

There is no consensus on when to use liquid or foam, however, telangiectasias are best treated with liquid sclerotherapy, whereas reticular veins and the varicose reservoir are more effectively treated with foam sclerotherapy [4,5,6] For varicose veins 3mm-8mm in diameter foam sclerotherapy appears to be particularly effective.

The optimal treatment approach is to match vessel diameter with the lowest concentration and least volume of sclerosant, with larger volumes for larger veins. It is recommended that <1ml at a single site be injected and <10ml in a single session when using STS. There is no strict consensus on sclerosing agent concentration and volume and target vessel size. [4,5,6]

Liquid sclerotherapy is more effective than placebo injection for telangiectasia and reticular veins. There is no evidence suggesting superior efficacy of any one sclerosant over another. [3]

Foam sclerotherapy mixes gas and liquid sclerosing agents (STS or POL) using the Tessari method. Foam sclerotherapy, usually ultrasound guided, is more effective than liquid sclerotherapy in the varicose reservoir because of the enhanced sclerosing properties of foam formulation due to the increased dwell time and contact area between sclerosing agent and vessel wall. This improved therapeutic effect can be achieved with a lower concentration and volume of sclerosant, with the added benefit of reducing potential side effects. Foam tends to degrade within 1-2 minutes, so it should be mixed just before injection. [3,4,5,6] For varicose veins 3mm-8mm in diameter foam sclerotherapy appears to be particularly effective. Foam can be used in larger varicose veins (> 8mm), usually in a staged approach because of the volumes needed, but the recurrence rate here is increased. More recently fill and foam sclerotherapy (FAFS) has been described for treating large varicose veins concurrently with endovenous vein ablation (EVA). [8]

Post-sclerotherapy compression

Post-sclerotherapy compression improves the clinical clearance of vessels and reduces post-sclerotherapy pigmentation and bruising. Three weeks of continuous compression led to the best

results in 1 study, although 3 days of compression resulted in greater improvement than no compression. Compression is an integral part of treatment and should be instituted immediately after treatment [3,4]

Knee-high, thigh-high, and pantyhose can be used depending on the treatment area under consideration. Data is lacking to directly compare knee-high versus thigh-high compression. At least class 1 (20-30 mmHg) compression is necessary when treating telangiectasia, whereas larger veins may need class 2 (30-40 mmHg) compression [3,4]

Transcutaneous laser therapy

Transcutaneous laser therapy (TCL) is used for veins with diameter less than a 30 gauge needle. This technique causes endothelial injury of the vein by exposing haemoglobin to light energy. Light energy is converted to thermal energy, causing photocoagulation, mechanical injury, thrombosis and occlusion of the target vessel [3,7]

Varying wavelengths between 532 – 1064nm are available for treatment of different diameter vessels and different skin types and/or colour. No single TCL can predictably treat all telangiectasias with equal efficacy. Each system has its own advantages and disadvantages. [3,7]

TCL is an effective treatment for telangiectasias and reticular veins, although less effective than sclerotherapy. TCL may be used as a primary treatment modality for certain indications or as secondary adjunctive therapy after sclerotherapy. Multiple treatment sessions may be required to achieve total clearance. Improved results are achieved when combined with sclerotherapy. Compression therapy after TCL is not common practice. [3,7]

Indications for TCL include: fine, superficial telangiectasias not suitable for sclerotherapy; primary telangiectatic matting; telangiectatic matting secondary to sclerotherapy; vessels below the ankle, prone to ulceration with sclerotherapy; previous poor response to sclerotherapy; patients with adverse reactions or allergy to sclerosant or needle phobias. [3,7]

Phlebectomies

A phlebectomy is a surgical procedure employing a 2-3mm skin incision over a varix, and a phlebo-hook. Multiple incisions are generally used to treat varicose clusters. These should be marked pre-operatively with the aid of a Duplex Ultrasound (DUS). These varices are teased out sequentially and avulsed.

Phlebectomies may be performed synchronously with saphenous vein surgery (high ligation and stripping) or endovenous vein ablation (EVA). Phlebectomies may also be staged following truncal vein ablation using either modality. Whether these phlebectomies should be staged or performed concurrently as always been a matter of debate. The balance of evidence currently, however, appears to favour synchronous phlebectomies.[9,10,11] In the author`s practice phlebectomies are preferred for varicose clusters > 8mm in diameter.

Phlebectomies may also be performed as an office-based procedure under local anaesthesia (ambulatory phlebectomy).[12] Tumescent anaesthesia using bicarbonate may reduce the pain associated with these procedures.

Future Directions

Sclerotherapy is still the mainstay for treatment of larger and deeper visible veins, including telangiectasias and reticular veins, but laser devices are fast becoming the preferred treatment of fine, superficial telangiectasias, which do not respond well to sclerotherapy.

Successful long-term treatment of telangiectasias and reticular veins requires elimination of refluxing feeder veins. A combination of sclerotherapy for larger veins and feeder veins and laser therapy for all other telangiectasias provides the best results. [6]

Intense Pulsed Light (IPL), microphlebectomy and thermocoagulation/radiofrequency energy are newer techniques. 1 IPL is similar to laser therapy and emits a spectrum of light, ranging from 515 – 1200nm, rather than a specific wavelength to obliterate the vein. The advantage of IPL is selective photothermolysis, in which thermal damage is confined to a specific epidermal or dermal targets, sparing surrounding tissue. Telangiectasias demonstrate the best response. Microphlebectomy uses hooks which enable venous extraction through minimal or even needle punctures. The advantage is minimal or no scarring, no skin necrosis and no residual hyperpigmentation. Thermocoagulation or radiofrequency energy uses high frequency waves, 4 MHz, transmitted through a thin needle, causing thermal damage in the veins. The advantages include immediate disappearance of veins, no allergic manifestations, no pigmentation and necrosis, and applicability to all skin types. [1] There is insufficient evidence to recommend these newer techniques over traditional sclerotherapy and laser devices.

Recommendations

1. The varicose reservoir should be treated at the same time as the refluxing saphenous vein, irrespective of saphenous vein ablation modality. **(Class 1; Level A)**
2. Both phlebectomies and/or ultrasound-guided foam sclerotherapy may be used to treat the varicose reservoir **(Class 1; Level B)**
3. Ambulatory phlebectomy should employ tumescent anaesthetic with bicarbonate to decrease pain severity. **(Class 1; Level C)**
4. Saphenous vein pathology (junctional and/or truncal reflux, and/or perforator vein reflux) should be treated before treating telangiectasias and reticular veins **(Class 1; Level B)**
5. Sclerotherapy is recommended for the treatment of telangiectasias and reticular veins **(Class 2a; Level B)**
6. Compression therapy with compression stocking or compression bandage is recommended after sclerotherapy treatment **(Class 2a; Level B)**
7. Laser devices for venuler veins may be used as primary treatment for certain indications or as secondary treatment after sclerotherapy **(Class 2a; Level B)**

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13. Pelvic congestion syndrome (PCS)

Mistry PP, le Roux DA

Introduction

Chronic pelvic pain can be caused by multiple pathologies which include irritable bowel syndrome, endometriosis, adenomyosis, typical menstrual pain, urologic disorders, and psychosocial issues.[1,2] It is essential that these pathologies are excluded before a diagnosis of pelvic congestion syndrome (PCS) is considered. PCS is often associated dysuria, heaviness, dyspareunia and non-specific lower abdominal and pelvic pain. Symptoms are generally worse during menstruation and often occur after previous pregnancies. Clinically patients presents with varicose veins in pelvic and perineum areas.

Executive summary

The choice of non-invasive testing largely depends on institutional expertise. Transabdominal and transvaginal ultrasonography showing ovarian veins > 6mm in diameter is associated with a 96% positive predictive value for pelvic varices.[3,4] CTV and MRV criteria include 4 or more tortuous parauterine veins, parauterine veins measuring 4 mm or ovarian vein diameter of > 8mm.[5] While non-invasive testing is useful, retrograde catheter directed venography is the gold standard for diagnosis of pelvic congestion syndrome. Venography should generally be used to confirm the diagnosis with intervention being performed at the same setting. Criteria for pelvic congestion syndrome with venography include: (1) an ovarian vein diameter :6 mm, (2) contrast retention >20 seconds, (3) congestion of the pelvic venous plexus and/or opacification of the ipsilateral (or contralateral) internal iliac vein, or (4) filling of vulvovaginal and thigh varicosities.[6] Endovascular therapies are now the preferred approach for pelvic congestion syndrome. These techniques include a combination of embolization of internal iliac vein tributaries and ovarian varices using coils, plugs, and/or sclerosing agents and relieving mechanical obstruction of the iliac vein (May-Thurner Syndrome), nutcracker syndrome and retro-aortic left renal vein with venous stents. Most women (73-78%) have relief of symptoms or cure within 2 weeks of treatment.[7] In a review of

over a 1000 patients in 20 studies the overall technical success rate was as high as 99%. With a mean follow up of 15months, 80% of the patients reported benefit from the procedure while 13% experienced little or no relief of the symptoms. 8 While these results may seem encouraging, there is a lack of high quality evidence in this field with no randomised trials, no proper control arms in a largely heterogenous group of patients. Thus, careful assessment of the cause of symptoms and selection of patients for endovascular management is of paramount importance.

Recommendations

1. Non-invasive imaging with ultrasound (transabdominal and/or transvaginal), CT or MR venography is recommended in patients with symptoms of pelvic congestion syndrome or symptomatic varices in the distribution of the pubis, labia, perineum, or buttocks. **(Class 2a / Level C)**
2. Catheter venography of ovarian and internal iliac veins is recommended in patients with suspected or confirmed pelvic congestion syndrome in whom intervention is planned. **(Class 1 / Level C)**
3. Catheter venography of ovarian and internal iliac veins is recommended in patients with suspected pelvic congestion syndrome in patients when non-invasive testing is equivocal **(Class 2b / Level C)**
4. Endovascular therapies which include vein stenting, coils, plugs and sclerosants can be used alone or in combination to treat pelvic congestion syndrome and pelvic varices. **(Class 2a / Level B)**

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14. SVC / BCV / Subclavian-Axillary veins (Surgical and Endovascular treatment)

Mulaudzi TV

The wide spread use of central venous catheter, ports, pacemakers and defibrillators has increased the incidence of superior vena cava syndrome, subclavian and axillary vein occlusions from benign causes(1). Symptoms depends on the rate at which occlusion occurs, a slow developing obstruction will allow for collaterals to develop with patients having absent or minimal symptoms. Those with sudden occlusion will present with swollen face, neck and upper limb, may have dyspnoea or convulsions due to brain oedema.
Stanford and Doty described four types of superior vena cava syndrome(2). Type I has high grade superior vena cava (SVC) stenosis with normal direction flow through SVC and azygos vein, type II has >90% stenosis or occlusion of SVC but with normal direction flow in azygos vein, type III has occlusion of SVC with retrograde flow in the hemi azygos vein and type IV is extensive occlusion of SVC, innominate and azygos veins with chest wall and epigastric venous collaterals.

Open surgical repair for benign occlusion is known to be effective and with durable long term patency(3). In the last decade endovascular intervention has become the first choice due to it being less invasive and also with midterm results similar to open surgery(3). Endovascular therapy could either be balloon angioplasty alone or with stenting. The current recommendations are for stenting.

Percutaneous transluminal angioplasty (PTA) has a technical success of 70% to 90%(4). Central veins are prone to recoil and restenosis after balloon angioplasty than peripheral veins(5). The long term results of PTA have previously been poor mainly due to the type of balloons that were in use. The results of PTA alone have improved with the use of high pressure balloons and repeated intervention without use of stents(4).
The not so good long term results obtained from PTA alone has led to the use of stents(6). The use of stents is adviced in those with significant stenosis post PTA or those who presents with restenosis within three months(7). Stenting has a primary patency rate of 27% at 24 months and a secondary patency rate of 81% at 48 months(8). Repeated intervention is needed to maintain long term patency. Stents in these low flow venous system are less likely to remain patent without repeated angioplasty. Complications related to stents could be stent migration, fracture or intrastent neointimal hyperplasia.

Open surgical repair is indicated for those where endovascular intervention is not possible or those with failed endovascular interventions. These are mainly those with Type IV superior vena cava syndrome. Surgery for correction of central venous disease is very difficult and should be considered as a last resort. Reconstruction of the central veins may be done with the use of a spiral saphenous vein or polytetrafluoroethylene grafts and may require a median sternotomy. The long term results are better than those of endovascular intervention as shown in figure 1 but with a higher complication rate(3). The primary patency rate was 61% at one year and a secondary patency rate of 74% at five years(3, 9). There is also a need for reinterventions but this are mainly performed endovascularly.

Recommendations

1. Patients with asymptomatic central veins obstruction should be should not be managed with any intervention **(Class III / Level C)**
2. Only patients with symptomatic central vein obstruction should be offered intervention **(Class IIa / Level C)**
3. Percutaneous transluminal angioplasty and stenting should be the first line intervention for symptomatic central vein occlusive disease **(Class I / Level C)**

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15. Iliac vein obstruction: Perspectives and surgical treatment

Sikhosana B

Introduction

Chronic iliac obstruction will lead to limb swelling, venous claudication, skin hyperpigmentation and ulceration. Most of the patients will give a history of deep vein thrombosis. And without the acute treatment of the iliofemoral deep vein thrombosis some of these patients will develop venous hypertension due to valvular insufficiency and iliac obstruction.

Endovascular treatment has become the first line of treatment for chronic obstruction because of its higher success rate and less invasive nature.

Iliac vein bypasses have a higher failure rate due to low pressure and low flow of the venous system, competitive collateral venous circulation in chronic obstruction and external compression of the graft, e.g. high abdominal pressure and the inguinal ligament.

But even in this endovascular era there are cases where venous bypass is still indicated such as failed endovascular treatment and segmental occlusive disease with low endovascular patency rate.

Executive summary

Various open surgical options exists depending on the level and extent of disease.

Femoro-femoral bypass (Palma procedure) can be used for venous reconstruction in patients with unilateral iliac/ iliofemoral vein obstruction. Ideally autologous vein should be used or alternatively re-enforced 8/10mm PTFE graft. Temporary arteriovenous fistula is often created to improve inflow and patency. With this procedure short-term clinical improvement is achieved but long-term patency is poor (secondary patency at 4yrs is 83% and 0% for autologous vein and PTFE graft respectively) [1]

Ilio-femoral reconstruction can be performed for unilateral/bilateral or IVC occlusion. Primary and secondary patency rates at two years only 37% and 54% respectively [2]

Considering the high peri-procedural morbidity and poor results it is not surprising that endovascular venous recanalization has become the preferred alternative in treating FICV occlusive lesions.

Three studies were identified in the literature. A single doctor case series of venous reconstructions for chronic disease. Nineteen patients underwent venous reconstruction; Palma bypass, May Husni bypass, femoral vein transposition and axillary transplant. There was a 89% patency at 56 months [3]

Jost C et al, looked at iliofemoral and inferior vena cava reconstructions for chromic occlusive disease. Forty two patients underwent venous reconstructions; Palma bypass, ePTFE bypass, spiral vein bypass and femoral vein patch angioplasty. The three years secondary patency for all reconstructions was 62% [1]

Alimi et al, looked at ePTFE bypass for chronic iliac vein occlusions. Four patients were operated and three had patent grafts at their last different imaging dates, 10, 26 and 45 months. The fourth patient occluded after surgery [4]

All these studies are retrospective, have small numbers and short follow up. [5] And it is difficult to interpret the results as they are different bypasses and patients have different clinical severities.

Recommendation

1. In patients with venous outflow obstruction bypass surgery is not recommended as standard primary treatment (Class III / Level C)
2. Rarely in patients with severe symptomatic, complicated venous outflow obstruction e.g. patients with venous ulcers, where endovascular intervention was unsuccessful or not possible, some form of surgical bypass procedure may be considered (Class IIa / Level C)

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16. Iliac vein stenting for venous outflow obstruction

Pillai J, Natha B, Naidoo NG

Introduction

Venous outflow obstruction is recognised as a major cause of chronic venous hypertension (CVH) and chronic venous insufficiency (CVI). CVH has either a non-thrombotic (primary/idiopathic) or post-thrombotic (secondary) cause. Either type can involve reflux, obstruction or a combination of both. Obstructive lesions in the supra inguinal veins (iliocaval segment) are more likely to cause more significant CVI than obstruction isolated to the infra inguinal veins (fem-pop and crural veins). However often there is multi-level venous occlusive disease following an episode of acute deep vein thrombosis. Chronic Venous Disease (CVD) causes chronic venous hypertension in tissues proximal to the obstruction. The high venous pressures may cause a range of clinical manifestations which include pain and ulceration of the lower limb. Iliocaval obstruction may result in pain in the vulva, pelvis or lower back, as well as swelling, dermatitis and derma-sclerosis. Chronic venous disorders has been reported in 1% -5% of the adult population. [1,2,3,4,5,6]

Obstructive lesions in the iliocaval segment are responsible for high proximal venous pressures than more peripheral lesions. Iliac vein obstruction may be non-thrombotic (May Thurner Syndrome) where the obstructive process is caused by the adjacent iliac artery (usually the left iliac vein and the right iliac artery). Iliac vein obstruction is more often due to insufficient recanalization after a DVT. Post thrombotic obstruction results in variable iliac obstruction and symptoms.

Executive summary

The literature demonstrates that alleviating the venous outflow obstruction utilising endovascular/hybrid techniques in the vast majority of patients is feasible with good to excellent results in terms of stent patency, relief of symptoms and recurrent stenosis. Purely open surgical procedures are now days seen as the possible last resort when endovascular or conservative measures have failed. Guidance has been provided by Raju`s group that alleviation of venous outflow obstruction with iliac vein stenting may result in a resolution of symptoms, and in most cases may obviate the need for intervention for primary varicose veins.

There are numerous studies demonstrating the favourable outcomes with balloon angioplasty and stenting of iliac vein stenosis/occlusions in patients with CVI. Primary stent patency rates ranges from 38-100% and secondary patency rates from 79-100%. Symptom improvement was shown in 81-95.2% of patients. There are numerous factors affecting the outcome of iliac vein stent patency. In an extensive review of venous stent database performed by Drs Neglén & Raju they demonstrated that the factors that contribute to highest in-stent restenosis in braided stainless steel stents used in venous stenting was in thrombotic lesions, occluded segments and failure to stent the entire diseased area to ensure adequate in-flow and outflow. Stenting above the inguinal ligament did show better results than stenting across the inguinal ligament but when analysis the various odds ratios they demonstrated the reason for this was due to the more extensive thrombotic disease in those patients requiring stenting into the common femoral vein. Despite previously reports, they demonstrated that venous stenting across the inguinal ligament into a diseased common femoral vein had no increased risk of

stent fractures, narrowing due to external compression or focal development of severe in-stent restenosis. [7]

A study from Guy's and St Thomas' and King's College in London, presented to the American Venous Forum Annual Meeting in February 2017 demonstrated good results with venous stenting across the inguinal ligament using various first generation dedicated nitinol vein stents. There were four stent compressions and three stent fractures noted but overall results demonstrated primary patency and secondary patency rates of 52% and 82% respectively and an overall improvement in clinical outcomes. [8]

Raju's review published in 2013, analysed 1500 patients with iliac lesions: [9]

- Stent Patency 90% - 100% (non-thrombotic); 74% - 89% (post thrombotic). Follow up 3-5 years
- Relief of pain and swelling in 85%
- Ulcer healing in 80%
- Recanalization success in total occlusions in 80%

Neglen et al reported patency rates in 708 patients, some of whom had IVC occlusions: Primary and secondary patency rates were similar for patients with IVC occlusions compared to iliac occlusions. (Primary patency approximately 40% in both groups at 54 months). [10]

Rossi et al performed a randomised controlled study (40 patients) comparing clinical venous endovascular treatment of ilio-caval obstruction. Ulcer healing; QOL and patency favoured the endovascular group at 6 months. [11]

Chronic pelvic congestion syndrome may be associated with ovarian vein reflux, or iliac vein reflux/ stenosis.

Hartung reported a significant improvement in symptoms in 89 patients who were treated with iliac venoplasty and stent placement [12]

<u>Hybrid:</u>

The importance of achieving good inflow into the stented iliac venous segment is paramount in maintaining stent patency. In order to achieve this there needs to be a patent femoral or profunda vein and common femoral vein. If there is significant occlusive disease of the common femoral vein affecting the origin of the profunda or femoral vein, a surgical endovenectomy is an option to achieve inflow.

The procedure is performed by exposing the entire common femoral vein (from 2cm above the inguinal ligament) and the at least 2-3cm of the profunda and femoral vein. All large branches are controlled and after the patient is heparinised, the veins are clamped and a longitudinal anterior venotomy is made and the fibrous synechiae and endoluminal fibrous tissue is excised. The venotomy is closed using a vein patch normally harvested from ipsilateral great saphenous vein. A temporary arteriovenous fistula can be created between the distal stump of great saphenous vein and femoral artery in the groin. The occluded iliac segment can then be stented. [13] deWolf et al. reported primary patency of 77% in 19 cases where endovenectomy of the femoral vein and iliac vein stenting has been performed.

Since the benefit and low morbidity of angioplasty and stenting across the inguinal ligament, open surgical treatment of the common femoral vein has been largely replaced by endovascular treatment.

Venous obstruction after thrombolysis

Numerous retrospective and comparative studies and three randomised control studies have done looking at pharmaco-mechanical catheter directed thrombolysis (PM-CDT) of acute iliofemoral deep vein thrombosis (with stenting of unmasked high grade venous stenosis) and anticoagulation vs. anticoagulation alone.

In 1999, Mewissen, et al, reported a 473 patient multicenter registry of patients who underwent catheter-directed thrombolysis (CDT). The patients who also were treated with venous stents had a 73% 1-year patency while those who did not receive a stent had a 54 % 1-year patency. [14] These patency findings were mirrored by 3 other retrospective studies which further demonstrated significantly improved symptomatology in patients treated with CDT and stenting than those treated with anticoagulation alone (At 5 years, 78% of the CDT and stenting group was symptom free compared to 30% of the anticoagulation alone group). [15]

Both the TORPEDO and CaVenT randomized controlled studies significantly reduced recurrence/restenosis rates in the CDT and stenting arm compared to the anticoagulation arm. They also demonstrated reduced post-thrombotic syndrome symptoms in the CDT and stenting arm. [16,17]

Venous PTA/Stenting is viewed as an essential adjunct following Catheter Directed Thrombolysis (CDT) for acute iliofemoral DVT. A residual stenosis increases the risk for re-thrombosis. In up to 80% of cases with acute FICV thrombosis there is an underlying iliac vein compression or stenosis.

Randomised studies compared CDT/venous stenting with anticoagulation only. (TORPEDO, 189 patients; CaVenT, 209 patients)

The incidence and extent of post thrombotic syndrome was lower in the CDT/stenting group.

Pre-treatment Imaging

- Venous Duplex Imaging is the 1st line imaging strategy
- This may have limited value in the iliac veins/ IVC and other imaging modalities may be requested (CTV, MRV etc.).
- Ascending venography remains the most useful tool for assessing anatomy prior to intervention.

Recommendations:

1. Endovascular therapy (iliac vein stenting) should be considered in symptomatic patients with non-thrombotic and post thrombotic iliac vein occlusive lesions. Patients should be assessed using a clinical scoring system and patients with a low score should be offered a trial of compression prior to iliac vein stenting. **(Class IIa / Level B)**
2. Endovascular therapy (balloon angioplasty and stenting) may be considered for IVC obstruction. Patient may present with swelling, pain and ulceration which is not relived by compression. A clinical scoring system may be utilized and patients with a low score should be offered a trial of compression. **(Class IIa / Level B)**
3. Iliac vein stenting is recommended as an adjunct to thrombus clearance strategies (for acute IFDVT) when a residual stenosis is found on completion venous imaging. **(Class 1 / Level B)**
4. Iliac vein stenting may be considered in patients with the pelvic congestion syndrome when the iliac vein obstruction is thought to be responsible for the condition. Other causes need to be excluded prior to iliac vein stenting. **(Class 1 / Level C)**

5. Post iliac vein stenting for non-thrombotic iliac vein lesions low dose aspirin, prescribed indefinitely, is adequate anti-thrombotic therapy **(Class IIa / Level B)**
6. Post iliac vein stenting for thrombotic ilia vein stenting, full anticoagulation should be considered. Calf compressors should be considered in the early post-stenting period. Warfarin should be considered post-stenting (the rules governing the duration of anticoagulation are similar to those for acute IFDVT) **(Class IIa / Level B)**
7. Hybrid technique is a 2nd line option for treatment of ilio-(common) femoral vein obstructions in patients with symptomatic lower extremity signs & symptoms of CVI (particularly those not palliated by compression therapy). **(Class 2b, Level C)**

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17. Perforator Vein Interventions

Odendaal J

Introduction

In 1917 John Homans suggested that incompetent perforator veins (PV) play a key role in the pathophysiology of venous ulcers, but their exact role remains uncertain up to the present day. An association between perforator incompetence and increased severity of venous disease has been documented, but adequate data is lacking to conclusively prove that their treatment promotes ulcer healing or prevents ulcer recurrence. Interpretation of research is hampered by concomitant superficial vein interventions and the relative infrequency of isolated perforator vein incompetence in venous ulcer patients.[1]

Executive Summary

Perforator veins (PV) perforates the deep fascia to connect the superficial to the deep venous system. They are classified as either direct (when emptying into axial deep veins) or indirect (emptying into calf venous sinuses). They are accompanied by perforator arteries and nerves. [2] PV are classified into 6 groups with several subgroups according to location and distance from the foot while the use of names of authorities are discouraged.[3]

The guidelines for the Society for Vascular Surgery / American Venous Forum (SVS /AVF) defines a pathologic perforator as ≥ 3.5 mm at the fascial orifice with ≥ 500 miliseconds of retrograde flow.[4] PV can become incompetent either through antegrade overload secondary to superficial venous reflux or retrograde blowout due to deep venous incompetence or obstruction. Treatment of superficial axial reflux leads to resolution of incompetence in perforators in 50 – 70%, but this is less likely to occur if there is associated deep venous reflux.[5]

Treatment of pathologic PV is recommended in patients with C4b, C5 and C6 disease localized to an area near the PV if compression has failed and after axial superficial reflux has been treated.[6] The rationale is that perforators are less likely to be the primary cause of venous insufficiency, but once recruited into the disease process they may sustain and propagate the pathology[1]. The SVS/AVF guidelines suggest concurrent treatment of the superficial venous system and perforators in C6 disease.[4] Guidelines recommend against the treatment of perforators in C2 disease where perforators are more likely to recover function after treatment of superficial incompetence.[4] Perforators can be treated in association with varicose veins when they are the highest point of reflux, but not when they are the re-entry point to the deep system [1].

The original open perforator interruption as described by Linton has been abandoned mostly due to significant wound complications.[7] Less invasive open procedures includes duplex guided avulsion of perforators with a vein hook or direct ligation through a small incision. [2] Sub-fascial endoscopic perforator surgery (SEPS) uses endoscopic instruments to interrupt incompetent perforators through a

small incision placed remotely from vulnerable skin areas.[2] Even less invasive techniques are referred to as percutaneous ablation of perforators (PAPS) or transluminal occlusion of perforators (TRLOP)[8] with either (a) endovenous thermal ablation techniques (EVTA) such as radiofrequency ablation (RFA) and endovenous laser ablation (EVLA) or (b) ultrasound guided sclerotherapy (USGS) with either foam or liquid sclerosants. [6]

A randomized controlled trial (RCT) by Kianifard concluded that no additional clinical benefit could be observed by adding SEPS to high ligation and stripping in C2 patients.[9] The North American SEPS registry reported 88% ulcer healing rate at 1 year with a median ulcer healing time of 54 days and a complication rate of 6% (deep venous thrombosis, superficial thrombophlebitis, wound infection, sub-fascial space haematoma and saphenous neuralgia). Ulcer recurrence rate was 16% at 1 year and 28% at 2 years and higher in patients with postthrombotic limbs than in those with primary valvular incompetence (46% vs 20% at 2 years).[10] The Dutch SEPS RCT (SEPS vs compression) failed to show a benefit in ulcer healing or recurrence although patients with recurrent or medially located ulcers had a longer ulcer free period. A secondary analysis showed significant higher ulcer recurrence in patients who had an incomplete SEPS procedure[4]. The Swedish RCT failed to show benefit if SEPS was added to saphenous surgery in patients with venous ulcers[12]. A meta-analysis concluded that SEPS benefited most patients regarding ulcer healing and recurrence and with less complications than the open procedures.[13]The technique is limited by inability to reliably access all incompetent perforators and has a steep learning curve.[2]

Recently the use of SEPS has declined in favour of PAPS although only a few studies comparing these modalities are available in the literature. All PAPS procedures are performed under ultrasound guidance and excellent descriptions of the techniques are available in the literature.[6] Closure rates of 50 - 70% for USGS and 60 – 80% for thermal ablation techniques are reported.[7] USGS is relatively easy technically and can treat tortuous perforators as well as the associated superficial varicosities. It can be done without the use of expensive equipment and catheters. Side effect profile is wider than other PAPS procedures and include allergic reactions, phlebitis, deep vein thrombosis (DVT) and pulmonary embolism (PE), transient loss of vision, inadvertent injection of a perforator artery with extensive skin necrosis and hyperpigmentation. EVTA is more complex than USGS. Side effects include ecchymosis, induration, paraesthesia, DVT and PE. EVTA is more effective than USGS for repeat attempts to close PV. Advantages of PAPS over SEPS include a lower complication rate , that it can be done under local anaesthesia with sedation , distal perforators around the malleolus are easily treatable, there are no incisions and it can also be used in patients with obesity and lower extremity oedema.[14] Failure to close perforators has been reported in association with obesity, anticoagulation and venous pulsatility.[7] Lawrence et al demonstrated 90% ulcer healing in a subgroup of patients with recalcitrant ulcers without superficial incompetence in whom successful perforator ablation was performed(RFA)[15] as well as increased healing rates [16] and reduced ulcer recurrence in C5 patients[17]

Future Directions

Although perforator ablation is clearly beneficial in a subgroup of patients, studies with adequate power and proper design are needed to better define this role in ulcer healing and recurrence.

Recommendations

- The treatment of incompetent perforating veins in patients with simple varicose veins (CEAP class 2) is not recommended as primary therapy. **(Class IIIb / Level B evidence)**
- In patients with skin at risk for venous ulceration(C4b) or with healed (C5) or active venous ulcers (C6) located near a pathologic perforator vein , superficial venous incompetence should be addressed if present and adequate compression therapy should be applied. Treatment of perforating veins can be performed simultaneously with correction of superficial reflux or

staged after documenting persistent incompetence 4-6 weeks after correction of axial reflux. **(Class 2b / Level C)**

- PAPS should be the preferred technique to ablate pathologic perforator veins. **(Class 2b / Level C evidence)**

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18. Failing arteriovenous fistula for haemodialysis (Truncal vein issues only)

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Introduction

The goal of haemodialysis access is to achieve a functioning access that can be repetitively cannulated and provide adequate flow to sustain dialysis treatment. Once an arteriovenous (AV) access is created, it must develop to the point where it is adequate in size and depth to achieve this goal. An AV fistula (AVF) that has never been usable or that fails within three months of use is termed as failure to mature or primary failure. Late failure, on the other hand, is defined as the inability to use a matured AVF after at least three months of normal usage. (1)

Executive Summary

Detection of AV Access Dysfunction

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Practice Guidelines on Vascular Access (2) recommend that all dialysis facilities have a program in place to provide regular assessment of the AV access and haemodialysis adequacy. The goal of the program is to prospectively detect the presence of AV access dysfunction.

Whether an AV fistula will mature without additional intervention is generally apparent at four to six weeks and a thorough evaluation of a new fistula at this point should, therefore, be considered mandatory to detect problems as early as possible. (3)

Failure of the mature AVF is frequently suspected during monitoring designed to detect stenosis so that it can be identified and treated prior to thrombosis, usually based on physical examination findings, flow measurements, or stenosis evident on duplex examination. (2)(4) A normal mature AVF has a soft pulse and is easily compressible. There is a prominent thrill at the anastomosis that is present during systole and diastole. Findings on physical examination associated with stenotic outflow lesions include extremity oedema, AVF hyperpulsatility, and lack of AVF collapse when raising the extremity. (1)

Venous Causes of AVF Failure

Venous Stenosis

Compared to arterial lesions, venous stenoses are by far the most common cause for AVF failure. Venous lesions have a predilection for sites characterized by turbulent flow such as bifurcations, venous valves and areas that have been referred to as “swing points”. These are unique points where the course of the vein involved in the AVF or its drainage makes an extreme angle. This is seen in the juxta-anastomotic (within the first 2 to 3cm of the fistula) region of the AVF (most frequently in the radiocephalic AVF), the angle of transposition in a transposed brachial-basilic AVF, and at the cephalic arch (seen most commonly with brachiocephalic AVF). (5)

Accessory Veins

The presence of accessory veins can affect AVF development and maturation by means of diverting blood flow from the main channel. These are tributaries primarily to the forearm cephalic vein. [1]

Treatment of Venous Causes of AVF Failure

Venous Stenosis

Percutaneous angioplasty has come to be the treatment of choice for venous stenoses, however, not all stenotic lesions require treatment. To qualify for treatment, a stenotic lesion must be determined to be significant, which is defined as narrowing of the vascular lumen equal to or greater than 50 percent as well as associated clinical symptoms, abnormal physical findings, and/or abnormal blood flow measurements. [4]

For primary failure, a technique termed balloon-assisted maturation has been described the facilitate autogenous access maturation. [6] In this technique, the outflow vein is serially dilated with progressively larger balloons until a target vein diameter is achieved.

The typical angioplasty balloons used for treating dialysis vascular access stenosis are high-pressure balloons exerting pressures from 16 to 20 atmospheres. Ultra-high-pressure balloons with burst-pressure ratings in the range of 30 atmospheres are very useful for extremely resistant venous lesions, but are more expensive than standard balloons.

There is some evidence to support cutting balloon angioplasty as a treatment for resistant lesions, but larger studies are needed. [7] Although preliminary results for drug-eluting technology have been promising, studies have been small and underpowered, or uncontrolled. Additional studies are needed before any definitive conclusions can be drawn. [8]

Some method must be used to determine that an angioplasty treatment was effective, as many lesions are elastic and recoil after what appeared to initially be an effective angioplasty. There are several parameters (anatomic, clinical, and haemodynamic) that can be used to judge the success of therapy. The NKF-K/DOQI guidelines defined anatomical success as no more than 30 percent residual stenosis remaining (as compared with the adjacent normal vein on imaging) following angioplasty. [2] Furthermore, the clinical abnormalities evident on monitoring that led to treatment should no longer be apparent following treatment and the haemodynamic or physiologic abnormalities during dialysis that suggested the presence of the stenotic lesion prior to treatment should be reassessed as soon as is practical following treatment and should return to within acceptable limits.

Per the NKF-K/DOQI guidelines [2], the expected six-month patency rate following angioplasty for AV access dysfunction should be at least 50 percent. For AV access that does not meet this goal options include surgical revision or stenting.

Although a stent or stent-graft can improve the appearance of a lesion, it is unclear if this intervention provides benefits and long-term outcomes that offset its increased cost. The generally accepted indications for stent or stent-graft placement in the patient with haemodialysis AV access abnormalities include [9]:

- Acute angioplasty failure – residual stenosis following angioplasty that is greater than 30 percent
- Rapid recurrence – two interventions required within a three-month period
- Vein rupture

For patients with recurrent lesions, the recommendation of the NKF-K/DOQI guidelines further suggest that if angioplasty of the same lesion is required more than twice within three months, the patient should be referred for surgical revision if the patient is a good surgical candidate. [2] Surgical revision for stenosis is generally performed using an interposition graft or a patch angioplasty.

Accessory veins

Once it has been determined that an accessory vein is impeding the maturation of the AVF, it can be obliterated by surgical ligation (direct though the skin, or open incision) or percutaneous placement of an embolization coil. [10]

Future Directions

Even though percutaneous angioplasty is considered the treatment of choice for venous outflow stenosis, the exact technique is not clearly defined. Ultra-high-pressure, cutting and drug-eluting balloons show promise in the setting of resistant stenoses, but they require further investigation through larger, well-designed randomised trials to allow for further recommendations. Similarly, although it showed benefit in acute angioplasty failure, the indications for stents or stent-grafts in fistula salvage warrant further evaluation to ensure the benefit offsets the increased cost.

Recommendations

1. A newly created AVF should be evaluated clinically, 4 to 6 weeks after creation to detect problems with maturation **(Class 1 / Level C)**
2. A mature AVF should be evaluated monthly by a trained medical professional to pre-emptively detect potential AVF dysfunction **(Class IIa / Level B)**
3. Percutaneous balloon angioplasty is the treatment of choice for significant venous stenotic lesions **(Class 1 recommendation, Level A evidence)**
4. Balloon-assisted maturation should be considered when constructing a native AVF using sub-optimum veins **(Class IIb / Level B)**
5. Maturation of AVF can be facilitated by ligation of competing neighbourhood venous tributaries in the absence of downstream stenosis **(Class IIb / Level B)**

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19. Venous thoracic outlet syndrome

Salie M

Thoracic outlet syndrome(TOS) refers to a constellation of signs and symptoms attributable to compression of the neurovascular bundle in the thoracic outlet region of the upper extremity. Neurogenic TOS (nTOS) from brachial plexus compression, accounts for 90-95% of cases, while venous TOS(vTOS) from axillo-subclavian vein compression accounts for 5% and arterial TOS(aTOS) from subclavian artery compression around 1% of TOS cases [1,2]

Terminology: [1]
Venous thoracic outlet syndrome (vTOS) refers to compression and thrombosis of the axillo-subclavian vein and is quite frequently referred to as effort thrombosis or Paget–Schroetter syndrome(PSS). There is a subset of patients who have symptoms but no thrombosis, which is termed intermittent obstruction or McCleery syndrome.

Epidemiology: [1,2,3,6]
vTOS is a rare problem, with an incidence of 1-2/100,000 people per year. It mostly affects young, active males in their 30's. .Most often the right arm is affected, which is thought to be due to a higher proportion of right-handed dominance in society. Individuals who perform strenuous or sustained upper extremity activities, whether athletic or occupational are at prone to developing vTOS

Anatomy: [2,4,5]
vTOS occurs due to compression & eventual thrombosis of the subclavian vein, which is surrounded by four structures at the thoracic outlet: The first rib inferiorly, the subclavius tendon superiorly, the costo-clavicular ligament medially, and the anterior scalene muscle laterally.
Urshel et al, who have the largest published series to date comprising 626 upper extremities in 608 patients, suggest that in most patients with Paget-Schroetter syndrome, the costo-clavicular ligament congenitally inserts further laterally than normal. When the anterior scalene muscle, which is lateral to the vein, becomes hypertrophied through activity and exercise, the vein is significantly narrowed.

Diagnosis:
The diagnosis of vTOS is largely based on clinical findings with imaging used for confirmation
Clinical presentation: [3,4,7,10]
An acutely swollen, blue, painful upper extremity in a young active male is the hallmark presentation. Aching pain with exercise is also commonly described.
Urshel et al described clinically evident collateral circulation in 621/626 extremities in their series. The pathways for the most efficient collateral communication were between the cephalic, transverse cervical, transverse scapular, and tributaries of the internal jugular veins, producing an increased subcutaneous venous plexus around the shoulder (Urshel's sign)

Imaging: [2,3,4,8,9]
Duplex ultrasonography is the first step in confirming a clinical suspicion of vTOS. The use of colour-flow duplex in conjunction with indirect criteria such as phasicity of flow & compression manoeuvres has led a sensitivity of 81%-100% with a specificity of 82% - 100%.
Computed tomographic venography(CTV) & magnetic resonance venography(MRV) are now being increasingly used to confirm the diagnosis of vTOS. CTV provides superior analysis of the vasculature in relation to the bony structures, whereas MRV is more efficient in the depiction of accessory muscles, muscle hypertrophy and fibrous bands. Both of these imaging modalities are useful in delineating the exact location and nature of the vascular compression, and aid in surgical planning. The American College of Radiology Appropriateness Criteria recommendations of 2015 suggest that CTV and MRV are both appropriate in establishing the diagnosis of TOS.
Although catheter directed venography remains the gold standard investigation, because of its invasive nature & lack of visualisation of surrounding structures, it is generally reserved for patients selected for an intervention.

Recommendation:
History, clinical findings and duplex ultrasound should be used to establish a diagnosis of vTOS
(Class 2A Level B)

Management [2,3,4,6,7,8,10]
Clinical evidence for the approach to vascular TOS is limited to case series.

The natural history of acute primary subclavian-axillary vein thrombosis is associated with high long-term morbidity and disability. Historical series have reported persistent or recurrent symptoms in >70% of vTOS patients treated with anticoagulation alone.

Therefore treatment involves the consideration of 3 therapies in addition to anticoagulation: Thrombolysis, Decompression, and Venoplasty. Which therapy is selected depends on the clinical presentation of patients. Several contemporary series have suggested various treatment algorithms for vTOS based on their local experience.

Recommendations:

The approach to vTOS management can be summarized based on 3 patient presentations:

Acute: For patients presenting <14days **(Class 1 level B)** or < 6 weeks **(Class 2B, Level B**) since symptom onset, prompt catheter-directed thrombolysis with early surgical decompression of the thoracic outlet is suggested.

Chronic: Patients presenting > 6 weeks since symptom onset benefit from surgical decompression**.(Class 1 Level B**) Preoperative thrombolysis *may* be considered in patients with total occlusion in an attempt to restore luminal patency before decompression**(Class 2B, Level C)**.

A short post-operative course of anticoagulation is suggested until venous patency is confirmed by postoperative imaging **(Class 2B, Level C).** Venoplasty of a residual subclavian vein stenosis after decompression may be considered to reduce the risk of re-thrombosis. (**Class 2A. Level B)**

Intermittent obstruction: Patients with chronic symptoms of intermittent venous obstruction but without evidence of thrombus or significant stenosis require only surgical decompression **(Class 2B, level C)**

Operative approaches:

For adequate decompression, a first rib resection with scalenectomy and venolysis via an infraclavicular, supraclavicular or trans-axillary approach have all been well described for subclavian vein decompression. There is insufficient evidence to recommend one approach over another. There does seem to be a preference for the trans-axillary approach by several authors due to better exposure of the medial part of the first rib as well as the superior cosmetic result.

Recommendation:
Venous stenting in a non-decompressed costo-clavicular junction is associated with high rates of stent fracture and re-thrombosis. Therefore, primary stenting of the subclavian vein without thoracic outlet decompression is not indicated **(Class 3, Level B)**

Residual stenosis of the subclavian-axillary vein
Options for management include intraoperative or postoperative venography and angioplasty with or without stent insertion, vein patching, mechanical thrombectomy, or axillary-subclavian vein reconstruction. Although no study has directly compared outcomes between these different approaches, most authors prefer to perform venoplasty at the time of decompression or within 1-2weeks postoperatively **(Class 2a Level B)**

Postoperative surveillance
DUS is an efficient non-invasive imaging modality for routine postoperative surveillance, although a venogram may be performed at the first postoperative visit if residual venous stenosis is suspected and venoplasty is considered

Anticoagulation
A short course of 3-6 months may be required if there is residual thrombus on postoperative imaging.

Recommendations

1. History, clinical findings and duplex ultrasound (DUS) should be used to establish a preliminary diagnosis of vTOS **(Class IIa / Level B)**
2. In select patients presenting with acute primary axillary/subclavian vein thrombosis <14days **(Class IIa / Level B)** or < 6 weeks **(Class 2B / Level B**) since symptom onset, catheter-directed thrombolysis with early surgical decompression of the thoracic outlet is recommended

3. Patients presenting > 6 weeks since symptom onset, benefit from surgical decompression **(Class 2b / Level B).** Preoperative thrombolysis may be considered in patients with total occlusion in an attempt to restore luminal patency before decompression **(Class 2B Level C).**
4. Patients with symptoms of intermittent venous obstruction but without evidence of thrombus or significant stenosis require only surgical decompression **(Class 2b / Level C)**
5. Venography, with or without venoplasty, should be performed at the time of thoracic outlet decompression or within 1-2weeks postoperatively. **(Class 2b / Level B)**
6. Venoplasty of a stenotic segment post thoracic outlet decompression should be considered to reduce the risk of re-thrombosis **(Class IIa / Level B)**
7. A short post-operative course of oral anticoagulation should be considered until maintenance of venous patency is confirmed with venous imaging **(Class 2b / Level C)**
8. Venous stenting without thoracic outlet decompression is associated with high rates of stent fracture and re-thrombosis and should not be considered here **(Class IIIb / Level B).** The role of balloon angioplasty, with or without stenting, post thoracic outlet obstruction needs to be individualized. **(Class IIb / Level C)**

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20. Management of Venous Aneurysms

Goga R

Introduction

Venous aneurysms are rare abnormalities that can occur throughout the venous system. As they are infrequently encountered, our understanding and knowledge of them remains limited and has been derived largely from anecdotal reports and retrospective case series. The definition of a venous aneurysm remains controversial and there exists no precise size criteria to differentiate between venous dilation and aneurysm. It may best be described as a focal area of venous dilation that communicates with a main venous structure via a single channel and should not be contained within a segment of varicose vein.[1]

Executive Summary

Venous aneurysms of the lower extremity deep system carry a significant risk of thromboembolic complications; with the popliteal vein the most commonly identified location. In a systematic review of encompassing 105 patients with popliteal venous aneurysms, Bergqvist et al. reported that features of pulmonary embolism (PE) were present in 46 patients, whilst 38 patients presented with symptoms localized to the popliteal fossa.[2] There have been no reports of rupture of a popliteal venous aneurysm. Diagnosis may be accurately made with duplex ultrasonography, whilst non-invasive venography, utilizing either computed tomography (CT) or magnetic resonance (MR), further aiding operative planning. Considering the high risk of thromboembolism associated with popliteal venous aneurysms, surgical repair is recommended. This is irrespective of the size of the aneurysm as there appears to be no correlation between aneurysm size and risk of thromboembolism.[3] Anticoagulation alone should be used with caution, as fatal cases of PE have been reported, and this approach should be limited to patients with prohibitive operative risk. Aneurysmectomy with lateral venorraphy or patch angioplasty, resection with end-to-end anastomosis or interposition grafting have all produced similar results.[4] Iliac and femoral venous aneurysms also confer a high risk for PE and as such should be managed with surgical repair.

The majority of upper and lower extremity superficial venous aneurysms present as soft, blue compressible masses that are rarely symptomatic and confer a low risk for PE. The majority of cases may be managed with observation. Excision of the aneurysmal segment alone is sufficient in the majority of cases with reconstruction only indicated when concomitant thrombosis or occlusion of the deep venous system exists.

The internal jugular vein is the most common site for venous aneurysms arising in the head and neck region. The majority are congenital and display fusiform morphology. Clinical presentation includes a soft, compressible mass that enlarges on straining and Valsalva manoeuvre. Diagnosis may be confirmed with duplex ultrasound and treatment is rarely indicated unless for cosmetic indications as these aneurysms are infrequently symptomatic.

The portal vein remains the most common location intra-abdominal site for venous aneurysm formation with a 115 reported cases, of which the majority were associated with hepatic cirrhosis and portal hypertension.[4] Small portal aneurysms are often asymptomatic whilst larger aneurysms may present with abdominal discomfort, jaundice from biliary obstruction or dyspepsia from duodenal compression. Whilst the natural history of these aneurysms have not been defined spontaneous thrombosis has been described in at least a dozen cases and rupture in four. The more common occurrence of upper gastrointestinal bleeding is usually caused by portal hypertension and is often not

a consequence of the aneurysm itself.[4] Surgical repair should be considered for patients presenting with thrombosis or symptoms related to compression of surrounding structures whilst those patients presenting with features of portal hypertension, in particular upper gastrointestinal bleeding, should be considered for portal decompression.[5] As this represents major surgery, asymptomatic patients as well as those who represent a poor operative risk are best managed with observation.

Thoracic aneurysms can arise from the superior vena cava (SVC), the azygos system or the brachiocephalic or subclavian veins. The majority of SVC aneurysms are asymptomatic or are discovered incidentally in patients presenting with minor pulmonary symptoms such as cough, dyspnoea or chest pain. In a literature review Calligaro et al. reported on 19 SVC and mediastinal aneurysms. Ten of these patients, with a mean follow-up of 14 years, did not undergo surgical repair and had no complications.[6]

Future Directions

Attention should be directed to determining whether specific categories of lower extremity aneurysms may be managed with anticoagulation as primary therapy.

Recommendations

1. Because of the risk of thromboembolic complications, surgical repair of all primary saccular lower extremity deep venous aneurysms is recommended **(Class IIa / Level C)**
2. Superficial venous aneurysms of the upper or lower extremity and deep venous aneurysms of the upper extremity may be managed with observation, with repair reserved for aesthetic indications or complications **(Class 2b / Level C)**
3. Jugular venous aneurysms may be managed with observation, with repair indicated for aesthetic indications **(Class 2b / Level C)**
4. Due to the risk of rupture and thromboembolism, abdominal venous aneurysms should be repaired, if the patient is of low operative risk **(Class 2b / Level C)**
5. Thoracic venous aneurysms may be managed with observation, as the risk of rupture and thromboembolism is relatively low **(Class 2b / Level C)**

NB. The data related to recommendations 3-5 remain ill-defined. Therefore recommendations need to be carefully individualized. Fusiform lower extremity deep vein aneurysms may be related to significant junctional or perforator vein reflux, or venous outflow obstruction. Treatment here should be directed at these pathologies with careful monitoring of these aneurysms with DUS.

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21. Minimally invasive strategies for acute pulmonary embolism

Paruk N

Introduction

Venous thromboembolism includes deep vein thrombosis and pulmonary embolism(PE) with an incidence of 100 per 100 000 persons in Europe and 160 per 100 000 persons in North America.[1] Pulmonary embolism is the third leading cause of death after myocardial infarction and stroke worldwide. Acute pulmonary embolism is also implicated as the commonest cause of pulmonary hypertension and R ventricular failure. In this guideline, we will use established pulmonary embolism terminology including intermediate pulmonary embolism risk (sub-massive embolism) and high risk pulmonary embolism (massive pulmonary embolus). Massive pulmonary embolism is associated with haemodynamic instability with systolic blood pressure (BP) <90mmhg. Sub-massive pulmonary embolism is haemodynamically stable with no hypotension but with R ventricular dysfunction/myocardial necrosis as evidenced by elevated cardiac biomarkers or changes in R ventricular function/dimensions as per cardiac echogram and CT imaging[2]. Systemic anticoagulation is the standard of care with treatment options escalated on the basis of mortality risk. The goals of therapy are to prevent mortality and to prevent late onset chronic thromboembolic pulmonary hypertension.

Systemic peripheral vein thrombolysis is universally recommended for massive pulmonary embolism by all guidelines but remains controversial for sub massive pulmonary embolism. The most commonly used regimen is a 100mg regimen of alteplase over 2 hours[3].

Interventional techniques in the management of acute pulmonary embolism include catheter directed thrombolysis (infusion of the lytic agent directly into the thrombus), mechanical thrombectomy with thrombus fragmentation/aspiration (which increase the surface area of thrombus to the lytic agent and physically reduce the thrombus burden) or combinations of these techniques. The simplest technique is that of thrombus fragmentation with the use of a pigtail catheter. Balloon catheters inflated/deflated within the thrombus achieve a similar result. The mechanical devices of thrombectomy include rheolytic (Angiojet-Boston Scientific), rotational (Aspirex), aspiration (Aspiration catheters, Penumbra & Angiovac), and ultrasound catheters (EKOSonic). The Angiojet system has been associated with complications including bradycardia and renal failure and is not the preferred option. Clinical results with the Aspirex(Straub) mechanical aspiration catheter are promising but with no controlled studies to support its use. The EKOSonic system is the only device approved by the United States FDA to treat pulmonary embolism.

Executive Summary

Systemic thrombolysis: A meta-analysis of 15 trials involving 2057 patients concluded that systemic thrombolysis reduced overall mortality, PE related mortality and recurrence. However, major bleed

and fatal or intracranial bleed rate was significantly increased[12]. These meta-analysis however must be interpreted with caution given the marked heterogeneity amongst these trials including trial size, severity of PE, thrombolytic agent, dose and duration of treatment. Given these limitations, there is however consensus that immediate reperfusion using systemic thrombolysis is indicated in high risk(massive) PE. This is in contrast to the controversy of benefit of systemic thrombolysis in intermediate (sub massive) risk PE. The PEITHO[13] (Pulmonary Embolism Thrombolysis) Trial compared single intravenous tenecteplase plus heparin against heparin alone in 1006 patients with intermediate risk PE. All cause death and haemodynamic decompensation at 7 days was reduced in the Tenecteplase group (2.6% vs 5.6%). However, a higher incidence of haemorrhagic stroke (2%) and major non intracranial bleed (6.3%) was noted in the Tenecteplase group. Therefore, routine systemic thrombolysis cannot be recommended for all patients with intermediate risk pulmonary embolism even in the presence of R ventricular dysfunction and myocardial necrosis. Patients in this intermediate high risk group should rather be managed with intravenous unfractionated heparin and monitored for haemodynamic instability with rescue thrombolysis available[14].

In an effort to reduce the bleed risk with systemic thrombolysis, there is weak evidence for reduced dose thrombolysis. A randomised trial of reduced dose thrombolysis[15] in patients with "massive" (severity of PE not well defined in this study), used a "half dose" tissue plasminogen activator and was non inferior to a full dose in improving pulmonary vascular obstruction with reduced bleed. The evidence for half dose systemic thrombolysis is weak at best and cannot be recommended at this time. Patients at high bleed risk should rather consider the catheter based options below.

No randomised trial compares systemic thrombolysis with contemporary catheter directed thrombolysis[9]. The American College of Chest Physicians (ACCP) recommendation favouring systemic thrombolysis in their previous 9th edition were based on a 1988 study of 34 patients with no difference in outcome between systemic and catheter directed thrombolysis[16]. The technique of catheter directed thrombolysis here however did not include positioning of the catheter within the thrombus which we would consider to be optimal catheter positioning. A greater number of cases were available to the ACCP investigators for their most recent 10th edition 2016 guideline and included the PERFECT multicentre trial[5] which included a total of 101 patients treated with catheter directed thrombolysis with clinical success rates of 85.7% for massive PE and 97.3% for sub-massive PE. However, the generally poor quality of publications results in positive recommendations in favour of therapy but with a weaker level C of evidence.

New devices for thrombus removal could improve results. The use of ultrasound with catheter directed thrombolysis(EKOS) can improve thrombus lysis. SEATTLE II[6] a prospective study of 150 patients with massive or sub massive pulmonary embolism treated with EKO-Sonic and low dose thrombolysis benefitted patients with a reduction in R ventricle /L ventricle ratio and improvement in systolic blood pressure. The Ultrasound Accelerated Thrombolysis of PE(ULTIMA) trial[11] studied 59 patients with acute main or lower lobe pulmonary embolism and a R ventricle(RV) to L ventricle(LV) dimension ratio >1. Patients were randomized to receive either unfractionated heparin or ultrasound assisted catheter directed thrombolysis. There was a statistically significant difference in favour of the ultrasound assisted thrombolysis group at 24 hours with a statistically significant reduction in RV:LV dimension ratio with no increase in bleed risk. The use of ultrasound to enhance thrombolytic permeation of thrombus holds currently the highest level of evidence in safety and efficacy[10]. However, there are publications which indicate no real difference in outcome with ultrasound versus standard catheter directed thrombolysis techniques[7].

Interventional procedures are not without complications and given the sparse availability of randomised trials and proliferation of case controlled studies with < 30 patients in each of these trials, has resulted in the weaker level of recommendation at C. With lack of background evidence on use of these technical adjuncts, a standardized technical algorithm does not exist.

Complications include intracranial haemorrhage rates of 3-5%[8](rates as high as 20% also reported), bradycardia, cardiac tamponade, pulmonary artery rupture/dissection, haemoptysis and renal failure.

There are no clinical trials comparing contemporary catheter directed interventions with systemic thrombolysis in pulmonary embolism. There is no randomised trial comparing catheter directed intervention versus anticoagulation alone for massive pulmonary embolism.

Generally, whenever thrombolysis is considered beneficial in the setting of massive pulmonary embolism, catheter directed intervention is a good alternative for patients with a high bleed risk and can be considered a reasonable alternative in low bleed risk patients provided the expertise exists. Catheter techniques may also be considered as escalation therapy when systemic thrombolysis has failed. Catheter directed interventions in sub massive pulmonary embolism may not decrease mortality but improve R ventricle function with resultant future improved exercise tolerance and improved quality of life. Catheter techniques also offer an improved safety profile (lower bleed risk).

Future Directions

Further clinical studies are required to define the optimal catheter directed thrombolysis protocol (dose and duration), the benefit obtained by increasing cost with the use of these mechanical/rotational/aspiration/ultrasound devices as compared to standard catheter thrombolysis and those patients with "sub massive" pulmonary embolism who derive benefit from intervention and if early intervention reduces the risk of chronic thromboembolic pulmonary hypertension (quality of life outcomes).

Conclusion

Full dose systemic thrombolysis should not be primary treatment for intermediate risk pulmonary embolism as its risks outweigh its benefits.

Catheter directed pharmaco-mechanical techniques are promising in PE patients with indications to reperfusion and who are at high bleed risk. However, at this time, evidence for the use of catheter directed thrombolysis compared with anticoagulation or systemic thrombolysis and catheter based treatment without thrombolysis is of low quality and therefore recommendations are weak. Recommendations favour systemic thrombolysis over catheter directed therapy not because of any direct comparison data but because there is higher quality of evidence in support of systemic thrombolysis in acute pulmonary embolism[9].

Recommendations

1. In patients with acute pulmonary embolism associated with hypotension (systolic blood pressure (BP) < 90mmhg who do not have a high bleeding risk, systemic thrombolytic therapy should be considered. **(Class I / level B)**
2. In most patients with acute pulmonary embolism not associated with hypotension, recommend against systemic thrombolytic therapy. **(Class IIIb, level B)**
3. In patients with acute pulmonary embolism, systemic thrombolytic therapy using a peripheral vein is preferred over catheter-directed thrombolysis. **(Class IIb, Level B)**
4. In patients with acute pulmonary embolism with hypotension and who have a high bleed risk; failed systemic thrombolysis or shock that is likely to cause death before systemic thrombolysis can take effect, if appropriate resources and expertise exist, catheter-directed thrombus removal strategies should be considered. Here surgery may be considered as an alternative. **(Class IIa, Level C)**
5. Close monitoring is recommended in patients with intermediate risk pulmonary embolism to permit early detection of haemodynamic decompensation and initiation of "rescue" reperfusion therapy. **(Class I / Level B)**

6. Thrombolytic therapy should be considered for patients with intermediate risk pulmonary embolism and clinical signs of decompensation. **(Class IIa / Level B)**
7. In patients with acute pulmonary embolism with no hypotension but with associated R ventricular dysfunction, myocardial necrosis, severe respiratory failure with low bleed risk, systemic thrombolysis may be used; in patients with a higher bleed risk, physicians with access to catheter directed therapy may opt for this approach. Surgery may also be considered here. **(Class IIb / Level C)**

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22. Venous leg ulcers – Wound dressings, skin grafting and compression bandaging therapy

Louwrens H

Introduction

Venous ulceration affects about 1% of the general population and can consume a considerable amount of resources due to its chronicity and labour intensive treatment. Apart from the high economic impact on healthcare systems it also causes significant long-term functional and socioeconomic morbidity and therefore it's important that patients receive the most effective and durable therapy possible.[1]

Executive summary

Wound dressings for venous ulcers

There is a large selection of different dressings available for the treatment of venous leg ulcers (VLU) , but insufficient evidence to suggest any one wound dressing resulting in significant improvement in healing rates.[1]

Foam and alginate dressings did not improve healing according to Cochrane reviews from 2013[2,3] and no advantage could be demonstrated for hydrocolloid dressings in a meta-analysis by Palfreyman.[4] Current evidence also does not support the routine use of silver donating dressings.[5,6] A Cochrane review from 2014 concluded that cadexomer iodine dressings improved healing when compared to standard care , but not when compared to hydrocolloid, paraffin gauze, dextranomer or silver impregnated dressings. [6]

In a randomized trial by Stacey et al. patients treated with zinc oxide paste bandages healed faster than those treated with zinc oxide impregnated stockings or alginate dressings under compression. Two of the groups had topical zinc oxide treatment so the difference in healing was most likely due to hemodynamic implications of the extra inelastic paste bandage.[7]

Most VLU produce a reasonable amount of exudate and any dressing that can manage the secretions and maintain a moist wound bed beneath compression should encourage healing.

Skin grafting for venous ulcers

Autologous skin grafting as a primary therapy for VLU is not supported by the literature and a Cochrane review in 2013 suggested that bilayer artificial skin in conjunction with compression increases healing, but there was insufficient evidence to support any other type of skin grafting.[8] In a randomized trial by Jankunas, 68% (27/40) had complete healing at 6 months after a skin autograft and compression versus 0% (0/31) of those who had a hydrocolloid dressing and compression. These were large ulcers that had been present for at least 6 months.[9] In a series of 100 recalcitrant ulcers of

which 72 were venous, tangential excision and split-thickness skin grafting resulted in sustained healing at 5 years of 55% of the ulcers.[10]

The use of a cultured bilayer allogeneic skin replacement (Apligraf) was reported by Falanga in a RCT of 275 patients. It was compared to a standard dressing and both groups had compression. At 6 months complete healing was achieved in 63% of Apligraf versus only 49% of standard care patients. [11] In VLU present for at least a year the use Apligraf also significantly improved healing at 6 months compared to standard care (47% vs 19%; p<0.005).[12]

Skin grafting with autografts or cultured skin replacements should only be considered for non-healing, large VLU in conjunction with appropriate compression.

Compression therapy

The primary functional abnormality in venous ulceration is ambulatory venous hypertension caused by venous reflux or obstruction. Externally applied compression in the form of stockings, elastic and inelastic bandages or multicomponent bandage systems reduces venous hypertension and remain the cornerstone of treatment.[13]

The majority of evidence suggest that VLU heal more quickly with compression therapy than with dressings alone.[14,15,16] A Cochrane review in 2012 recommended compression over no compression and a RCT from Hong Kong involving 321 patients had healing rates at 6 months that was significantly better for the compression groups (p<0.001); 72% for short stretch compression, 67% for 4 layer bandaging and 29% for moist wound dressing only.[16]

The 2012 Cochrane review also suggests that multicomponent systems are more effective than single component systems and when a multicomponent systems contains an elastic component they perform better than when only composed of inelastic constituents.[15] A RCT involving 245 patients comparing four layer vs single layer compression revealed significantly higher healing rates with 4 layer compression at 6 months (67% vs 49%; p= 0.009).[17] There is also some evidence to suggest that 4 layer bandaging (4LB) is superior to short stretch bandaging (SSB).[15,18] In a recent meta-analysis, data from 797 patients demonstrated a 30% improved healing rate with 4LB (odds ratio1,31; 95% CI, 1.09-1.58;p=0.0005).[18]

The literature does not support the use of any one specific compression system over another, as long as sustained high pressures are maintained and the wound care personnel adequately trained.[19]

The rates of recurrence after a VLU has healed is high and compression is an important part of prevention. In the Eschar trial the recurrence at 4 years was 31% vs 56% for those undergoing superficial venous surgery versus those not.[20] In a recent Cochrane review looking specifically at compression for the prevention of recurrence there is some weak evidence that suggests compression prevents recurrence. [21] In a RCT by Vondogen, 153 patients were randomized to either high compression stockings (34-46 mm Hg) or no compression. The compression group had a significantly lower recurrence at 6 months (21% vs 46%; RR 0.46; CI 95%,0.27-0.76; p=0.003).[22] A meta-analysis from 2014 also cites low quality evidence that supports the use of compression on recurrence.[14]

There is conflicting evidence on the optimal level of compression. In a RCT with 300 patients recurrence rates were compared between those allocated to moderate (Class 2 – 18-24mm Hg) or high (class 3 – 25-35mm Hg) compression stockings. There was no difference at 5 years (39% with class 2 vs 32% with class 3; RR 0.82,95% CI 0.61-1.12, p=0.22).[23] In a second study by Millic with a 3 year follow up there was a reduction in recurrence with class 3 stockings of 20,6% versus 36,7% (RR 0.57, 95%CI 0.39-0.81, p=0.002).[24] Individual patient compliance will ultimately dictate the level of compression they will be able to maintain.

Recommendations

1. A primary wound dressing should be applied under compression to manage the exudate and maintain a moist wound bed. **(Class IIa / Level B)**
2. Split-thickness skin graft should not be considered as primary treatment for VLU. **(Class III / Level B)**
3. Skin grafting with an autograft or a cultured allogeneic bilayer skin replacement should be considered, after optimum wound bed preparation, for a large or deep VLU that is not healing despite conventional treatment. **(Class 11b / Level C)**
4. Compression therapy should be offered to all patients with VLU; the method and application of such compression therapy needs to be individualized. **(Class I , Level A)**
5. Multicomponent compression should be offered over single component **(Class IIa , Level B)**
6. Compression stockings should be offered to prevent ulcer recurrence **(Class IIb, Level B)**
7. Hyperbaric oxygen cannot be recommended as a treatment modality for venous leg ulcers currently **(Class IIIa / Level C)**
8. VAC (vacuum-assist closure) dressings should be considered together with compression bandaging therapy for large or deep VLUs **(Class IIb / Level C)**

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