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Mini Review

Perspectives on Phlegmasia Caerula Dolens

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Abstract

Iliofemoral Deep Vein Thrombosis (DVT), particularly with Phlegmasia Caerula Dolens (PCD) or venous gangrene, is a limb and life-threatening condition. Pulmonary embolism is common, particularly with venous gangrene. Aggressive treatment of phlegmasia caerula dolenswith catheter- directed thrombolysisor venous thrombectomy and arterial venous fistula, yieldgood results particularly when treatment begins as early as possible after the onset. These treatments are complementary with thrombectomy best reserved where thrombolysis is contraindicated or has failed. Early and aggressive treatment will achieve the goals of restored venous patency, limb viability and reduce mortality in comparison to the standard conservative treatment alone.

Keywords: Deep vein thrombosis; Hypercoagulable states; Venous gangrene; Pulmonary embolism;Treatment; Vena cava filter

Abbreviations

IVC: Inferior Vena Cava; DVT: Deep Vein Thrombosis; PCD: Phlegmasia Caerulae Dolens;PAD: Phlegmasia Alba Dolens;PTS: Post Thrombotic Syndrome; APTT: Activated Plasminogen Thrombotic Time;rTPA: Recombinant Tissue Plasminogen Activator; PTFE: Polytetrafluoroethylene

Introduction

Severe and extensive iliofemoral DVT causes a swollen and painful leg typically pale secondary to arterial insufficiency from dramatically elevated compartment pressures below the knee, but often erythematous, a syndrome known as Phlegmasia Alba Dolens (PAD). Phlegmasia Caerulea Dolens (PCD) on the other hand is characterized by cyanosis in an acutely swollen limb classically with an extreme bursting pain which is constant. This latter condition results when there is extension of thrombosis to the venular and capillary levels with secondary development of acute arterial ischaemia. PCD always involves the distal limb progressing proximally. Both PAD and PCD can be complicated by venous gangrene.In 50% of cases of PCD venous gangrene may develop and this invariably starts distally in the toes and foot and progresses proximally [1]. There is a high risk of massive pulmonary embolism, particularly with venous gangrene even under anticoagulation.PCD is associated with an underlying malignancy in 50% of cases, usually in those afflicted by a life-threatening illness associated with dehydration and cachexia [2]. It is also important tonote as a differential diagnosis thatabout60% of patients with acute iliofemoral DVT recover without further symptoms but40% will have some degree of Post Thrombotic Syndrome (PTS) which includes oedema, pain, hyperpigmentation, lipodermatosclerosis and ulceration,and4% will develop severe PTS [2,3].

Pathophysiology and natural history

PCD results from near total occlusion of venous outflow from the limb which occurs most importantly at the microvascular level. Complete occlusion of the major leg veins will result in a syndrome of phlegmasia alba dolens and not in PCD [4]. Thus at the tissue level venous thrombosis results in a massive increase in capillary hydrostatatic pressure causing outpouring of fluid and massive interstitial oedema.Pressures in the tissues may increase up to fivefold with major sequestration of plasma into an affected limb of up to 6-10 litres which explains the shock commonly seen in this condition [5]. Where there is either little or moderate compromise of the arterial circulation a reversible syndrome of PCD without venous gangrene develops. Typically after a period of 1-2 days and in up to 50% of patients venous gangrene will supervene secondary to arterial impairment. The mechanism of arterial compromise seems to be mainly hydrostatic. Capillary flow is is further compromised by the high interstitial (intramuscular or compartment) pressures overcoming the critical closing pressures of the arterioles and small peripheral arteries resulting in their collapse [6]. This probably explains the late development of venous gangrene commonly seen in untreated PCD. Arterial spasm has been implicated but there is little evidence to support this as an important pathophysiological mechanism [7,8]. The major amputation rate is 25-40% [9] PCD develops in hypercoagulable states with an underlying cause being found in 90% of cases [7]. Underlying malignant disease is the major cause of hypercoagulability particulary where there is venous gangrene.Indeed, as part of a paraneoplastic syndrome it may be a presenting symptom of a previously unsuspected malignancy [9]. In the absence of a malignant cause an underlying thrombophilia should be suspected, particularly activated protein C resistance and/or antiphospholipid syndrome. PCD can complicate the secondary hypercoagulable states after major surgery or trauma [10], the puerperial period, radiotherapy, prolonged immobilization and in chronic inflammatory conditions, particularly relapse of ulcerative colitis [11,12]. Although not PCD, a persistent venous outflow obstruction after an iliofemoral thrombosis may cause the symptom of a Post-Thrombotic Syndrome (PTS) in a large majority of patients [8]. A persistent swelling of the leg and venous claudication may signify a limitation in quality of life for young patients with PTS.

Diagnosis and investigations

PCD is most common in the fifth and sixth decades of life. There is an equal sex distribution and the left leg is involved almost thrice

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as often as the right probably as a result of left iliac vein compression syndrome [13]. There is usually a progression of symptoms in the lower limb from phlegmasia alba dolens to the cyanosis and extreme pain of PCD, which may be rapid but usually takes place over 1-2 days. The affected limb becomes massively swollen and very tense with distal cyanosis a constant feature. The skin may have cutaneous bullae and in venous gangrene, there is a striking purplish/ black discolouration or mottling of the skin, which does not blanch. The pain involves the entire limb and is typically intense and bursting in nature. Peripheral pulses are extremely difficult to feel because of the oedema but may be detected with the Doppler probe.The differential diagnosis includes venous gangrene, lymphatic obstruction, acute cellulitis, PAD and acute arterial obstruction. Arterial hypotension secondary to hypovolaemia, which may be severe, complicates this condition and the literature overall reports an amputation rate of 50% with a mortality of 25-40% [14]. Pulmonary embolism is common, particularly in venous gangrene, with an incidence of 12-40% [7]. Diagnosis is largely clinical although duplex venography is extremely useful in documenting the extent of venous thrombosis and is now the investigation of choice. Venography is technically extremely difficult and meaningful information in the presence of extensive ileofemoral thrombosis can only be obtained by descending venography via a contralateral femoral or branchial approach. Angiography is of little diagnostic value usually showing only peripheral arterial constriction in severe cases but is often performed where the diagnosis of PCD and venous gangrene has not been considered or where there is doubt [2].

Management

Conservative treatment: Initial management is directed at improving tissue perfusion by aggressive resuscitation with intravenous fluids to treat the hypovolaemic shock, and bed rest with high limb elevation to reduce limb oedema and thus the high interstitial pressures. Adequate limb elevation on a wedge or by some form of gallows traction would optimize venous and lymphatic drainage. Immediate anticoagulation with intravenous heparin to achieve and maintain an APTT of 1.5-2.0 will prevent further thrombus propagation. Simple conservative treatment along these lines together with investigation for any underlying cause will suffice in early cases without progression to venous gangrene and clinical improvement will be evident within 12-24 hours. However, conservative treatment does not work alone in severe PCD particularly with gangrene and more definitive treatments must be employed [15]. In addition to anticoagulation the use, either singly or combined, of thrombolysis and thrombectomy may be necessary [14,16].

Definitive treatment

Thrombolytic therapy: Thrombolytic therapy delivered by catheter directly into the thrombus has given better results than systemic thrombolysis [17,18], with success reported in 10 out of 12 patients in one series and five out of seven patients in another [19,20]. Urokinase or recombinant Tissue Plasminogen Activator (rTPA) are the main agents used and their combined use reported in successful treatment of a particularly severe case of PCD [21]. The risk of valve damage associatedwith mechanical thrombectomy is also reduced. The delivery catheter is usually placed either from the contralateral femoral vein if patent, or from the internal jugular vein or frequently both. Because of the high risk of pulmonary embolism during the treatment it is advisable to place a temporary filter in the infrarenal IVC via either of these approaches although the internal jugular or brachial vein approach is the most convenient, The infusion catheter can safely be passed through the filter and imbedded into the thrombus. Delivery of thrombolytic agent via intra-arterial catheters to the affected limb has recently been reported to have excellent results in severe PCD [12,21]. This approach delivers thrombolysis to the capillary and venular thrombus as previously discussed, andin the small number of patients so treated relief from pain, swelling and hypotension was rapid (within 6-12h) and dramatic. Thus thrombolytic therapy tailored to both components of PCD namely the large venous and the microvenous occlusions via intravenous and intra-arterial catheters is a logical advance and appears to have promising results. Further experience is required of this combined approach [2].

Thrombectomy

Venous thrombectomy will successfully clear thrombus from the major veins thus relieving the major site of venous occlusion. If there are contraindications to lytic therapy or the patient does not respond to thrombolysis, thrombectomy may be considered provided that any associateddisease does notcarry a fatal prognosis [21].Practically, in approximately 25% of patients the presence of a valve in the external iliac vein can prevent thrombectomy. This is overcomed by spreading open the valve with a long haemostat, and the distal passage of the thombectomy catheter through competent valves can be achieved by distension of the proximal vein through blowing up the balloon and gently negotiating through the valve segment.There was 85% patency rates and minimal symptoms of the post-thrombotic syndrome within 10 days of onset in ileofemoral thrombosis (without PCD or venous gangrene) [22,23]. The results in severe PCD and venous gangrene are obviously poor because surgical thrombectomy will not clear any thromboses involving the venular or capillary circulation [23]. These poor long-term results with the high morbidity and mortality of this procedurehas led to reduced enthusiasm with the main indications being failure of anticoagulant therapy or impending venous gangrene [15]. More recently much better results of venous thrombectomy have been reported from Europe with use of adjunctive temporary arteriovenous fistulae onto the superficial femoral artery using a Polytetrafluoroethylene (PTFE) graft, and attention to relieving proximal venous obstruction in the iliac veins [20,24]. Although the best results are achieved with early intervention before thrombus adherence develops, ideally within 7-10 days, there is long-term patency of the iliac vein in 80% and clinical success rates of over 60% at 120 months follow-up [20]. There was however, 52% femoral popliteal valvular competence after 6 months that deteriorated to 36% after 5 years [24]. Recently there has been the rare report of PCD with an associated compartment syndrome from markedly increased intramuscular pressure (>30mmHg) in a patient with a conservatively managed acute traumatic subdural haematoma and several cardiovascular co-morbidities. With thrombolysis being contraindicated, it was successfully managed by a combination approach of surgical thrombectomy, fasciotomy and a ray amputation of a dry gangrenous great toe 5 months later [25]. Recently endovascular stents have permitted recanalization of chronic and long-standing obstructions of inferior vena cava and the ileofemoral veins with promising safety and efficacy data [3], although long-term data are still awaited. These post –thrombotic lesions are

usually very long and frequently scarred and require longer and highly flexible stents. Because the venous dilatation and stenting are painful general anaesthesia is used. Local anaesthesia may suffice for circumscribed stenoses in the iliac region such as those with the May-Turner syndrome [3]. Such treatment would prevent valve damage from chronic venous obstruction/ insufficiency, and the sequelae of PTS. By decreasing the limb swelling and venous claudication it would improve the quality of life in these patients. Perhaps this endovascular stentingproceduremay also be useful in PCD except for the acute and rapid progression and the usually simultaneous thrombosis of the iliac, femoral, common femoral, and superficial femoral veins in PCD [26].

Vena caval filters

Although anticoagulation remains the most effective primary treatment for diagnosed venous thromboembolic disease with good outcomes in 90% of cases, in a minority of patients anticoagulation will be contraindicated, will fail or will result in complications. Before the advent of caval filters treatment was by open surgical interruption of the IVC below the renal veis by variations of suture plication (sieving) and external clip placement. These procedures to prevent PE in an invariably high risk patient population carried high morbidity and mortality. Over the last 20 years these surgical approaches have been superseded by the development of endovascularly placed vena caval filters which are not only convenient but more safe. The classical indications for vena caval filtration remain recurrent pulmonary embolism despite effective anticoagulation, complication of anticoagulation and thromboembolic disease which force discontinuation of therapy, and in patients in whom anticoagulation is contraindicated because of risk of haemorrhage. Largely because of the increased ease and safety of vena cava filter placement, there is a growing list of relative indications including recurrent pulmonary embolism with the presence of severe right heart failure in pulmonary hypertension, patients with extensive embolic occlusion of the pulmonary circulation, propagation of iliofemoral thrombus despite adequate anticoagulation and the presence of extensive free-floating ilio-femoral thrombus on contrast or duplex venography [2,27]. Increasingly, however, the use of a filter is being advocated in patients who have had a major PE in order to reduce the morbidity and mortality of a second PE [28]. With appropriate investigation and assessment of the underlying prothrombotic risk factors in a patient who has had a first PE, a considered judgement on the need for life-long anticoagulation can be made. There is no evidence to suggest that vena cava filter placement in these patients is equivalentor superior to selective use of long-term anticoagulation.

Conclusion

Phlegmasia caerula dolens is limb-threatening from venous gangrene and life-threatening from pulmonary embolism. Early and aggressive treatment is necessary.Thrombolysis or thrombectomy has a better outcome than anticoagulation alone.Vena cava filters are complementary to both conservative and definitive treatments in preventing pulmonary embolism.

Authors' Contributions

WEP is the main author and writer, ZF contributed to literature search.

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