Phlegmasia cerulea dolens (PCD) is an uncommon, severe form of lower extremity deep venous thrombosis characterized by extremity swelling, cyanosis, and pain. Progression of the thrombotic process may result in extremity gangrene, amputation, and death. The relative value of specific therapeutic regimens in the treatment of this disease remains uncertain. Twelve patients, 9 females and 3 males, with PCD were treated during a 10-year period. Eighteen lower extremities were involved. Pre-existing conditions included malignancy (eight), postoperative state (four), diabetes (three), previous deep venous thrombosis (three), and hypercoagulable (two). Venous gangrene was present in four patients. All patients were treated initially with bedrest, fluid resuscitation, extremity elevation, and systemic high-dose heparin therapy. Five patients had complete resolution with this regimen alone. One patient required cessation of heparin therapy due to heparin-induced thrombocytopenia and development of gangrenous toes. Two patients whose condition failed to respond to heparin therapy underwent catheter-based delivery of urokinase with marked clinical improvement. Four patients, two with venous gangrene, died, three of whom had disseminated malignant disease. A significant percentage of patients with PCD will respond to extremity elevation, fluid resuscitation, and aggressive systemic anticoagulation therapy. Thrombolytic therapy selectively administered is beneficial in patients whose disease fails to respond promptly. Venous thrombectomy should be reserved for patients with contraindications to thrombolysis.

Phlegmasia cerulea dolens (PCD) is a fulminant form of deep venous thrombosis, characterized by pain, edema, and cyanosis of the affected extremity. Up to 55% of these patients may have venous gangrene. A significant percentage require extremity amputation, and mortality has been reported to be 25% to 41%.[1]

Therapeutic options suggested in the treatment of PCD have included sympathectomy, fasciotomy, anticoagulation, venous thrombectomy, and thrombolysis. In a recent review, Weaver et al.[2] recommended treatment of uncomplicated early cases with bedrest, extremity elevation, and heparin therapy. They suggested that failure to achieve a clinical response in 6 to 12 hours should be followed by ilipectoral venous thrombectomy or possibly thrombolysis. For patients presenting with severe ischemia or impending venous gangrene, venous thrombectomy was recommended as the primary intervention. In this report, we describe our experience using this treatment algorithm and the use of thrombolytic therapy rather than thrombectomy for clinical progression and advanced cases of PCD.

PATIENTS AND METHODS

From 1982 to 1992, 12 patients (18 extremities) with PCD were evaluated at the University of Southern California Health Sciences Campus. Nine patients were women, and three were men. Mean age was 56 years, with a range of 34 to 74 years.

Associated conditions known to predispose to thrombotic events were present in 11 patients. Malignancy was the most common, being present in eight. Documented primary sites included cervix (two), pancreas (one), lung (one), bladder (one), and brain (one). Two patients had presumed malignancy of unknown origin. One of these patients presented with metastatic carcinoma, and the other had retroperitoneal and hepatic masses of presumed malignant etiology documented by computed tomographic (CT) scan. A prior history of lower extremity deep venous thrombosis was elicited in three patients. One had therapeutic anticoagulation with warfarin at presentation, and two had previously placed bird’s nest caval filters. Both patients with bird’s nest filters had extensive new iliac and caval thrombosis documented with the clinical onset of PCD (Figure 1). Four patients were within 1 month postoperation. Operative procedures included coronary artery bypass, biliary enteric bypass, crianiotomy, and radical cystectomy. Diabetes mellitus was present in three patients, being the only associated illness in two. A single patient had Sjögren’s syndrome with documented anticardiolipin antibodies, and another had a protein S deficiency. Other associated conditions included chronic obstructive pulmonary disease, renal...
failure, ulcerative colitis, atrial fibrillation, and coronary artery disease. More than 1 associated condition was present in 8 of 12 patients.

All patients had pain, massive edema, and cyanosis of the affected extremity at the time of initial evaluation. Disease was present bilaterally in six patients. Venous gangrene was present at initial evaluation in three patients (four extremities). Pedal pulse deficits were present in eight limbs.

A presumptive diagnosis of PCD was made on clinical grounds in all patients and confirmed by either continuous wave Doppler venous examination in 17 extremities, venous color-flow duplex scan in 4, venography in 4, and impedance plethysmography in 1 (Figure 2). Abdominal CT scan documented extensive inferior vena cava and iliac vein thrombosis in three patients.

All patients were initially managed with bedrest, extremity elevation, fluid resuscitation, and systemic anticoagulation therapy. Anticoagulation was established by an initial intravenous bolus of 10,000 to 15,000 U of heparin, followed by a constant infusion to maintain the activated partial thromboplastin time at least twice the control value. Heparin therapy, if successful, was continued for a mean of 8 days, after which long-term oral anticoagulation therapy was instituted. Thrombolytic therapy was initiated in selected patients whose condition failed to respond to these initial measures. Thrombolysis was accomplished using a 250,000-U bolus of urokinase followed by 100,000 U/h selectively delivered via transvenous catheters placed into the thrombus. Two Greenfield and one bird's nest caval filters were placed as a prophylactic measure in three patients. Calf and thigh fasciotomies were done in one patient due to elevated compartmental pressures.

RESULTS

Five patients (nine extremities), following initial therapeutic maneuvers, had complete resolution of pain and cyanosis with a reduction in limb swelling.

In two patients, clinical progression prompted the initiation of thrombolytic therapy at 6 and 36 hours after the start of heparin therapy. One patient had a thrombotic occlusion of the inferior vena cava below a previously placed bird's nest caval filter, which had been inserted for a documented pulmonary embolus 1 month previously. She was treated with heparin without improvement and, subsequently, underwent bilateral lower extremity fasciotomies for measured compartment pressures in the calf of greater than 80 mm Hg. Thrombolytic therapy was then initiated when distal tissue viability became questionable. This patient ultimately required a right below-knee amputation and amputation of the left toes, but thrombolytic therapy did arrest the progression of ischemia. The other patient rapidly progressed with heparin therapy and developed pregangrenous changes in the toes. Thrombolysis resulted in dramatic improvement and prevented tissue necrosis (Figures 3 and 4).

The clinical condition of the remaining five patients did not respond to heparin therapy. Heparin infusion had to be stopped after 3 days in one patient due to the development of thrombocytopenia. Antiplatelet heparin-induced antibody was documented as the etiology of the decreased platelet count. This patient began receiving dextran and subsequently underwent anticoagulation with oral warfarin. She developed gangrene of all toes, but limb perfusion and venous outflow stabilized. She underwent a transmetatarsal amputation.

The other four patients died at 1 to 10 days after initial evaluation. All were treated with heparin only. Autopsy was not performed in any of the four. Three had disseminated carcinoma at the time of presentation, and the other presented in extremis with a 2-week history of symptoms, renal failure, and atrial fibrillation; this patient died within 24 hours of admission.

COMMENTS

The pathophysiology of PCD has been outlined by Brockman, Vasco, and others [3-6]. Following near-total or total occlusion of extremity venous outflow, there is a rapid rise in venous and capillary hydrostatic pressures. Massive sequestration of fluid in the affected extremity produces hypovolemia, systemic hypotension, and a dramatic rise in interstitial tissue pressure. If untreated, the increasing transmural arterial pressure and hypovolemia lead to arterial collapse and distal tissue hypoxemia. The development of tissue necrosis and venous gangrene is a late sign and has been associated with significant morbidity and mortality [2].

The patients in this series had a variety of conditions...
that predispose the patient to the development of venous thrombosis. These are not dissimilar to those reported by Weaver et al [2] in their collective review. However, a striking finding was the development of PCD in two patients in whom bird's nest filters had been placed. In both instances, extensive caval and iliofemoral thrombosis developed after placement. This complication of the bird's nest filter has been reported previously, and it has been described in patients with Greenfield filters as well [7,8]. The awareness of this complication following vena caval interruption must be considered by those contemplating the placement of filter devices.

The finding of a painful, edematous, cyanotic extremity, with or without gangrenous changes, is virtually pathognomonic for PCD. Confirmation can be attained by several noninvasive methods. Continuous-wave Doppler examination of the femoral veins is portable and provides a rapid bedside assessment. The diagnosis of extensive iliofemoral venous thrombosis is possible with a relatively high degree of accuracy [9,10]. The addition of ultrasound imaging to Doppler technology provides the optimal modality for diagnosis. Duplex scanning, with or without color capabilities, can be brought to the patient's bedside and has the added advantage of documenting the anatomic extent of the thrombus. Sensitivity of duplex scanning for the detection of proximal deep vein thrombosis is essentially 100%, with a specificity of 99% [11]. These noninvasive methods for diagnosis of venous
versed the thrombotic process, preserving extremities in occlusion. If so, thrombectomy would have been the only option due to the recent cardiac procedure. Fortunately, decreased thrombocytopenia. Thrombolysis was contraindicated due to the least efficacious option, given the advantages of selective local thrombolysis. An aggressive approach to anticoagulation immediately saturates available antithrombin III, arrests thrombus progression, and preserves patent collateral venous pathways. Ancillary therapy involves fluid resuscitation, bed rest, and extremity elevation. There can be massive sequestration of fluid in the legs with subsequent renal failure if fluid resuscitation is inadequate. This approach alone provided resolution of clinical symptoms in 5 of 12 (42%) patients. All five patients had early PCD with no evidence of venous gangrene at presentation.

Clinical response should be apparent within 6 to 12 hours, or consideration should be given to proceeding with thrombectomy or thrombolysis [2]. The development of safer and more effective thrombolytic agents enhances the use of this option. Many trials comparing standard systemic anticoagulation with thrombolytic therapy for uncomplicated lower extremity deep vein thrombosis have been performed [13–17]. However, reports concerning thrombolytic therapy in patients with PCD are few and anecdotal [18–20]. Of the reports available in the literature, the lytic agent used has either been undefined or streptokinase. In all instances, delivery was systemic. The two patients in this report are the first specific cases in which the thrombolytic agent was urokinase and delivered by catheter-based techniques. Catheter delivery has the advantage of ensuring a high concentration of lytic agent directly into the thrombus and minimizing systemic lytic effects. In both patients, the thrombolytic therapy, when instituted, arrested and reversed the thrombotic process, preserving extremities in one patient and lowering the amputation level in the other. In the latter patient, it is quite possible that bilateral above-knee amputations would have been required without the use of thrombolytic therapy.

Venous thrombectomy has been recommended as a primary or secondary treatment for PCD [21]. This option was not utilized in this series and would appear to be the least efficacious option, given the advantages of selective local thrombolysis. In our present algorithm, we would reserve thrombectomy for patients in whom thrombolysis is contraindicated. An example of this would be the patient who developed PCD after coronary artery bypass. Heparin therapy resulted in heparin-induced thrombocytopenia. Thrombolysis was contraindicated due to the recent cardiac procedure. Fortunately, after cessation of heparin, clinical progression did not occur. If so, thrombectomy would have been the only treatment option.

The incidence of pulmonary embolism is 12% to 41% in patients with PCD [1]. For this reason, inferior vena cava filters were prophylactically placed in four patients after initial anticoagulation therapy. With potentially one third of patients having a major pulmonary embolus, we adopted a more liberal approach to placing caval filters prophylactically [22].

In conclusion, PCD is a potentially lethal but treatable disease. Most patients, when diagnosed early, respond to bedrest, extremity elevation, fluid resuscitation, and systemic anticoagulation. If there is no response to these measures within 12 hours, thrombolytic therapy with catheter-based delivery should be instituted. If there is a contraindication to thrombolytic therapy, venous thrombectomy should be undertaken. For patients whose condition is far advanced at presentation, thrombolytic therapy or venous thrombectomy should be considered as part of the initial therapeutic plan.

REFERENCES

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DISCUSSION

J. Dennis Baker (Sepulveda, CA): Did any of your patients undergo thrombectomy?
Douglas B. Hood: To my knowledge, we haven’t done thrombectomy in 10 years.

J. Dennis Baker: You have reported cases of lytic therapy. What is your end point for this lytic therapy? Some of these patients have major iliofemoral occlusions and some multi-level occlusions below that point as well.
Douglas B. Hood: The end point would be clinical improvement, with a reduction of cyanosis and pain. We try to free the major outflow.

Richard Spence (Camden, NJ): You have not figured fasciotomy into your algorithm. When do you perform fasciotomy? Do you measure compartment pressures?
Douglas B. Hood: We do not perform fasciotomy routinely. The patient in whom a fasciotomy was performed had minimal edema and cyanosis. She had previously had a pulmonary embolus and had a bird’s nest filter in place. The thought of venous thrombosis was on our minds. She did not respond to anticoagulation therapy, and we measured compartment pressures, which were elevated, so a fasciotomy was performed. Even with the fasciotomy, her condition continued to deteriorate, and she developed gangrene of both feet. Consequently, at 36 hours, we performed lysis, and her clinical status rapidly stabilized.

John Corson (Iowa City, IA): Was lysis performed through a transjugular approach?
Douglas B. Hood: Lysis was performed through a transjugular approach as well as through a transfemoral route. We attack from both sides.

John Corson: We are concerned that these bird’s nest filters may cause significant problems with caval thrombosis. With your transjugular approach, are you able to get through with the other filters, and can you get through the bird’s nest filter?
Douglas B. Hood: When there was a bird’s nest filter, we used the transfemoral route.