The Future of DVT Therapy

Examining the origin and current state of treatment to predict the future of DVT.

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Prediction is folly but great fun nonetheless. It reminds me of sandcastles on the beach, growing in splendid magnificence, then falling to ruin in the face of the inexorable forces of nature. When building sandcastles out of our scientific future, the inexorable force is the creativity of the human mind, and as powerful as nature sometimes reveals itself to be, human creativity is a far greater force, which can move mountains that nature can only gently nudge.

ORIGIN OF THE DEEP VEIN THROMBOSIS DEBATE

To have any chance of guessing the future, one must at least have a sense of the direction from which our collective scientific past has moved. The origin of the modern debate about deep vein thrombosis (DVT) began with the incredibly thoughtful and prescient observations of Professor Rudolf Virchow (1821-1901), who, in a bold move against the prevailing currents of his time in 1856, wrote the following concerning venous blockage by clot:[1]

> "Accordingly, the sequence of the possible stages and consequences of blockage may be classified and studied under three headings: the phenomena associated with the irritation of veins and their vicinity; the phenomena of blood clotting; the phenomena of interrupted blood flow."

Although, evident in his wording, Virchow did not say that these three phenomena were the cause of DVT; his observations implied that he believed DVT was limited in its expression to phenomena in these three classes. The general agreement with this postulate more than 150 years later is astonishingly good—a sandcastle, we must all admit, that was built on a high rock and quite a ways out of the wind.

Many analytic thinkers years later still returned to this postulate as the starting block for their thoughts on DVT. One such person, trying to push the understanding of the etiology of DVT to a new level in 1924, wrote that the first two arms of the triad could best be understood by examining the question, "Why do platelets and leukocytes adhere to vessel walls?…on the answer to this question stands or falls any explanation of thrombosis."[2]

Fifty years later, as we entered the modern era in which we were developing our understanding of the molecular basis for clotting, the force of the triad still held sway over the thinking on DVT as reflected in the title of the article, "Hypothesis Concerning the Aetiology of Venous Thrombosis in Terms of Virchow's Triad," in which the author opines that,

> "stasis induces hypoxic endothelial injury, especially in valve cusps…which lack *vaso vasorum*, …and are dependent on pulsatile flow, …which induces platelet and [white blood cell] adhesion and induces thrombosis."[3]

TREATING THE CLOT

Subpar Treatment Options

Parallel to our development of a greater understanding of the pathophysiology of venous clot has come an appreciation for the need to develop safe and effective ways to treat that clot. Anticoagulation, as safe and effective as it has been in preventing death from pulmonary embolus, has left us as individuals and as a society with the huge costs and anguish of postphlebitic syndrome. Although thrombolytics entered the treatment armamentarium more than 40 years ago with incredibly positive results in small prospective randomized studies comparing anticoagulation to systemic streptokinase, their acceptance has lagged behind their clear-cut potential due to their perceived risk of bleeding and the lack of any large-scale, multi-institutional study comparing the newer drugs delivered with catheter-based techniques to standard anticoagulation therapy. Developing new

thrombolytic drugs does not seem to be the answer because most new drugs have been targeted toward coronary syndrome and stroke intervention without any clear definition of what is needed to make a drug safe and effective for the typical DVT patient. In addition, only a few of the novel or newer agents including the direct fibrinolytics, such as plasmin and metalloproteinases (snake venoms), have even small DVT series with which to judge their effectiveness or safety in this diverse and challenging patient population.

Direct Fibrinolytics

Nonetheless, there are some powerful theoretical reasons that direct fibrinolytics should be useful in DVT, including the fact that they are uniformly faster in their lytic effect than tissue plasminogen activator (tPA). All of the theoretical and tested attributes of plasmin as the model direct fibrinolytic drug seem beneficial in lysing clot quickly, completely, and safely including the fact that its action is independent of plasminogen in clot,[4,5] that it had a sixfold safety margin versus tPA in a rabbit ear bleeding model,[6] and that is both less dependent on the inflow of blood for its activity and is immediately neutralized if it escapes into the general circulation.[7]

Effectiveness

For DVT patients, the question of effectiveness may be extremely difficult to answer because there are so many variations in the response to treatment. For instance, patients with homocysteinemia form tighter clots that resist urokinase (UK) but not tPA,[8] and chronic pulmonary thromboembolic patients make a fibrin clot that is significantly more resistant to plasmin degradation.[9] In addition, given the multifactorial causes that precipitate most DVT cases and its protean forms of expression, there is even a serious question if thrombolysis by itself would ever be sufficient as a stand-alone treatment. An aggressive and thorough treatment of DVT needs to address at least three clinical requirements: speed, completeness, and durability (Table 1).

Treatment Options and Their Safety Concerns

When debating the safety of thrombolytics, the only significant question concerns bleeding. One very clear fact, given the wide range of doses that have been proposed for DVT thrombolysis with tPA and the newer plasminogen activators, is that a rational understanding of an appropriate dose range for this use of these drugs is lacking. Nonetheless, it has become equally clear over time that lower doses than ever expected are quite effective and, when used appropriately, can achieve high rates of success with limited complications. For instance, at the University of Minnesota, during the course of our first 2 years using tPA for DVT, we decreased our dose from approximately .02 mg/kg per hour to .005 mg/kg per hour, resulting in an average dose of .1 to .5 mg/kg per hour, depending on the size of the patient and our concern for bleeding risk.

TABLE 1. CLINICAL REQUIREMENTS OF DVT TREATMENT

Speed: Time to flow and time to complete lysis, both of which have a direct effect on two problems:
1. Symptoms: pain and swelling
2. Limb loss: associated with phlegmasia cerulea dolens

Completeness: Ability to preserve valves and completely remove clot from the main veins of the deep system and also the branches and collaterals associated with the deep system, all of which will be the primary determinant of the severity of any postphlebitic syndrome.

Durability: Ability to prevent recurrent DVT, which is also a powerful predictor of the development and severity of postphlebitic syndrome.

In addition, our understanding of and appropriate use of adjunctive medications has also lagged behind similar efforts for stroke and coronary syndromes. In a large animal arteriole and venule injury model, both argatroban and activated protein C markedly enhanced staphylokinase lysis.[10] In a dog microvasculature thrombosis model comparing heparin and argatroban in the prevention and treatment of DVT, argatroban was superior to heparin in both the time to thrombosis and the time to complete cessation of flow, and when used with tPA, argatroban at doses of .1 to .2 mg/kg per hour accelerated thrombolysis with no change in partial thromboplastin time.[11]

Lower doses of plasminogen activator, combined with pulse-spray techniques and appropriate adjuvant drugs, such as direct thrombin inhibitors and even additional plasminogen, have been studied in a series of animal model articles by Joseph Bookstein, MD, at the University of California, San Diego, proving that there are distinct chances of moving toward a more rational comprehension of thrombolysis in the future.

In terms of the future use of thrombolysis for DVT, people often question the need for and safety of simultaneous anticoagulation. Anecdotally, all interventional radiologists who treat DVT have clearly witnessed failures due to rethrombosis when anticoagulation is not used, and the rationale for using it has been clearly shown in several animal studies. One of the best of these was a study that examined the effect of heparin anticoagulation on thrombolysis and, by comparing it to fibrinogen depletion, came to the conclusion that heparin's positive effect on throm-

bolysis is primarily due to its inhibition of rethrombosis.[12] In their dog model, Cercek et al had a group of animals that received tPA thrombolysis alone with 27% clot clearance, compared to 79% in the group with tPA plus heparin and 68% in the group with tPA plus ancrod, which is a strong fibrinogen depletor.

The other class of drugs that has been experimentally tested but has remained surprisingly almost invisible clinically is those that either decrease or somehow modulate the type of inflammatory reaction that occurs in the vein wall during any DVT episode. Studies in a baboon model of venous thrombosis in 2000, for instance, showed that inhibition of P-selectins by a monoclonal antibody that inhibits platelet and polymorphonuclear neutrophils (PMN) interaction with the endothelial cell, prevented thrombosis, promoted a more rapid thrombolysis, decreased vein wall edema, and decreased vein wall cytokine release, all without changing any coagulation parameters and surprisingly without decreasing overall PMN migration capability.[13]

In general, given the present state of our experience and knowledge, it seems safe to say that the safety and efficacy of a thrombolytic agent are less dependent on the agent and more dependent on dose, timing, and technique, including the appropriate use of adjunctive medications and possibly temporary inferior vena cava filters and adjunctive mechanical devices. In some recent studies, devices, especially the AngioJet (Possis Medical, Inc., Minneapolis, MN), have proven quite effective as the only treatment. In one recent study, 20 patients with extensive lower-extremity DVT and three others who had recurrent disease were treated with the AngioJet using various dilutions of thrombolytics in the infusate. Fifteen of 23 had complete removal, while only eight of 23 had partial removal that required additional thrombolysis.[14] It is clear, however, that most devices currently in use will leave clot behind, especially in critical areas, such as behind valve cusps, and either additional thrombolytic therapy or the use of one of the new novel ultrasound devices will be required to clear the vein completely. Ultrasound as an adjunct to thrombolysis is emerging as an unexpectedly powerful tool. Pulsed ultrasound promotion of tPA thrombolysis has been shown to be more extensive with stable cavitation than inertial cavitation and, when used at energies that do not promote cavitation, is not better than thrombolysis alone.[15]

The positive effect of ultrasound is related to the duration, intensity, and duty cycle of treatment and the pulse length, but not to the frequency.[16] When used with correct parameters, ultrasound allows deeper penetration of tPA into an experimental clot and has a wider clot thrombolysis zone, which in one study was 21 µm versus 9 µm for tPA alone.[17] In addition, ultrasound can be used to create a local pharmacomechanical pulse-spray effect by using it to destroy exogenously administered microbubbles in a selective tissue volume. By using the explosive force of the bubble destruction to break up clot and stream thrombolytic drugs deep into the clot, ultrasound can enhance the thrombolytic effect in that precise area even when the thrombolytic drugs are administered systemically. This method has been verified in a stroke model[18] and a rabbit model of peripheral artery occlusion.[19]

Future Additives

What are other investigators anticipating as the DVT thrombolysis additives for tomorrow? Metal cations, such as Sr++, have been shown to be strong enhancers of blood components that promote thrombolysis.[20] Oxygen singlet-activated PMNs mimic physiologic targeted thrombolysis without the bleeding risk.[21] When compared with UK alone, adjunctive use of lower-extremity intermittent pneumatic compression in the treatment of iliac DVT in a small sample of patients showed a marked improvement in complete lysis (5 of 14 vs 0 of 6 for UK alone) and 6-month patency (6 of 14 vs 1 of 6 for UK alone).[22] Electric potentials applied to plasminogen-coated carbon surfaces (stents, lysis sticks, etc.) markedly enhance plasmin generation and its activity.[23] Tomorrow's new additives may even include old drugs in new chimeric-like forms. One study used tPA conjugated to and inactivated by a heparin-antifibrin antibody, then activated in the clot by protamine.[24] Some old drugs may find new uses in the fight against DVT. One study that was also attempting to modulate the inflammatory reaction that accompanies all DVT used tPA plus L-arginine in an animal iliac DVT model and demonstrated that the combination preserves endothelial reactivity to nitrous oxide and reduces platelet adhesion.[25]

One special population of patients who are prone to DVT is patients with antiphospholipid syndrome. Plasmapheresis has been used in one study of patients with antiphospholipid syndrome with thrombosis to eliminate the antiannexin-2 antibodies that have been shown to inhibit plasmin generation.[26] Many other investigators are attacking the problem, each from their own perspective and each with new exciting tools and ideas. Several of them who seem to have promising avenues of research that could lead to productive clinical improvements include an attempt to modulate carboxypeptidase U and other TAFI (Thrombin Activatable Fibrinolysis Inhibitor) components to balance coagulation and fibrinolysis,[27] an attempt to decrease nitrosative stress, including macrophage-mediated nitration inactivation of plasminogen that is particularly seen in patients with atherosclerosis and diabetes,[28] and an attempt to decrease MMP-2, MMP-9, and MMP-10 expression, and collagen buildup to reduce DVT-associated inflammatory damage to the vein wall.[29]

DIAGNOSING DVT

To speculate on the future of DVT treatment, we must first uncover a more rational and accurate way to diagnose DVT. If the diagnosis can be simple, inexpensive, noninvasive, and accurate, the diagnosis will be sought much more often than before, raising our awareness and appreciation for the problem, as well as reinforcing our understanding of how easy truly fresh clot is to treat. As accurate as compression plus duplex ultrasound has been, it is very operator-dependent and has severe limitations in the pelvis, abdomen, upper chest, and all small veins. We clearly need to bring the diagnosis of DVT back into the era of molecular imaging that it left with the abandonment of 125I-labeled platelet imaging. There is no reason that positron emission tomography (PET) or single photon emission computed tomography (SPECT) couldn't be used to target fibrin, activated platelets, clotting factors, plasminogen activators, or their inhibitors. CT/PET could be used to provide anatomically accurate localization of venous clots and to guide therapy. MRI at higher field strengths and with appropriate probes to target molecular components of fresh clot could be used with subtraction views to provide both anatomic and physiological information. In addition, many other biological and imaging tools are waiting to be applied to the DVT problem, including optical and three-dimensional acoustic imaging and, in one investigator's hands, combined intravascular and extracorporeal magnetoelastic transducers to monitor viscosity changes.[30]

PREVENTING DVT

The next step involves the unequivocal development of better means of preventing DVT. Recently, the National Quality Foundation in cooperation with the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has developed a set of guidelines that should help push hospitals, practitioners, and ultimately the insurance companies to adopt behaviors, algorithms, and ways of thinking that will give the DVT problem the importance that is long deserved and will provide our patients with the degree of safe prophylaxis that they deserve. With better risk stratification schemes, more precise dosing strategies, and newer drugs, such as the oral factor-10A inhibitors, we should be able to identify the vast majority of patients at risk and provide them with a treatment that will give them a problem-free ride through the crowded and dangerous healthcare airspace.

FUTURE OF DVT TREATMENT

In the future of DVT treatment, first and foremost, patients will have their DVT promptly and accurately identified within hours to days of onset and will finally be told the truth about the 20% to 30% incidence of postphlebitic syndrome with optimal anticoagulation. They will then be offered an aggressive treatment alternative that will be quick, have minimal risk, and have the potential to give them a venous system with intact valves and extremities that will function and look normal without compression garments and the daily stress and hours of effort that so many patients currently endure.

We will treat clot everywhere—not just in the one major deep vein channel into which we can most easily reach. As soon as the patient presents, we will begin with whatever risk factor modification strategies are possible, including decreasing stasis with rapid elimination of stenoses, using pumps to assist calf muscle pump dysfunction, and replacing or repairing valves to reduce problems with incompetence. In addition, we can reduce vein wall damage by enhancing oxygen delivery and decrease the severity of the effects of clot on the vein wall by administering drugs that will decrease vein wall inflammation and diminish any hypercoagulability tendencies.

As we start into the treatment phase, we will pretreat the patient with a P-selectin inhibitor, almost like aspirin for veins, administer short-acting, intravenous thrombin or factor-10A inhibitors, give nasal or mask oxygen, and possibly perform plasmapheresis to eliminate any proteins or antibodies that could delay or impair the treatment response.

Using our MRI map, we will gain access into the best vein to drive directly to the primary deep vein problem. We will deploy outflow control devices including new highly efficient retrievable filters and balloons and then macerate, sonicate, and aspirate the large bulk of the clot out of the patient in a matter of minutes. During the mechanical removal process, we will load the clot with a direct fibrinolytic drug to start the cleanup process. Concurrently, we will be drawing labs, including old standbys such as coagulation parameters and platelets, but also alpha-2 antiplasmin and alpha-2 macroglobulin levels, so that we can administer replacement therapies or modify thrombolytic and anticoagulant drug doses in a patient-specific manner to improve the safety margin.

With flow restored and the patient's veins on the way to repair, he or she will be transferred to the DVT unit where the affected extremity will be fitted with a DVT box for small vein and vein wall cleanup. If needed, the filter will be quickly exchanged for one that contains a bonded bleeding-control agent that neutralizes any excess anticoagulant or fibrinolytic drug that escapes the extremity. Targeted thrombolytic drugs with whatever additives are appropriate for the patient are administered either locally or systemically and kept in areas of maximal need with flow controllers and pumps. The thrombolytic drugs with vector or molecular tags, or encapsulated in microbubbles or trapped in nanoparticle meshes, are activated by the high-intensity

focused ultrasound programmed to activate along plotted and verified vein paths, then diffusely with nonfocused ultrasound to clear even the smallest capillary and collateral. In fact, in 2006, one team of investigators used polylactic-co-glycolic acid microspheres, containing a staphylokinase variant and exposed them to moderate-intensity ultrasound and had activity recovery of the staphylokinase that almost amounted to 100% when 2% polyvinyl alcohol was added into the aqueous phase. They also speculated on other chemical modifications that could possibly increase effectiveness even further.[31]

The final step in the new treatment of DVT involves a much more aggressive and targeted follow-up. Based on a recent study that found clotting factors in blood in abnormal amounts for up to 3 weeks after surgery,[32] our freshly treated, clot-free patients will be given a 3-week period of high-frequency lab and clinical observation and a higher dose of anticoagulation. After that, because the new oral agents are significantly safer and easier to follow than coumadin, they will be maintained on anticoagulation for at least 1 year, during which time they will have genetic evaluations and immunologic treatments, if needed, to modify any hypercoagulable tendencies. In addition, they will wear new temperature and pressure-controlled micropulsating pressure garments, which only need to be worn for 4 to 6 hours per day and be seen by a vein surgery specialist for consideration of a prosthetic valve implantation and removal or ablation of any abnormally refluxing superficial veins if needed.

Led by a nonpartisan effort at the highest levels in Washington, full funding will have been given to cancer research initiatives, eliminating all cancer. Led by an association of hospitals and insurance companies, all profits from medical care will be plowed back into a massive nationwide preventive medicine program that engages all people regardless of income, race, age, or previously demonstrated antisocial behavior, and all poor personal health habits that could contribute to DVT in the future will be extirpated from our lives. And in the gentle wind, the turrets of the sandcastle sway gently and then erode into shapelessness as the waves come ashore. ■

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