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Pharmacomechanical thrombolysis treatment of DVT and preservation of valve competency

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and/or pulmonary embolism (PE), affects approximately 5% of the population at some point in their lives[1] and is estimated to occur in 300,000 – 600,000 persons in the United States each year.[2] Most patients undergo systemic anticoagulation and compression stocking therapy, a treatment strategy intended to minimize propagation of the clot and prevent pulmonary embolization.[1] The thrombus is not removed, but rather relies upon the endogenous fibrinoloytic system to eventually resolve the thrombus and recanalize the vein.[3] However when treated with anticoagulation alone, it is estimated that in only 12-47% of cases is there complete lysis the offending clot within 6 months,[4,5] increasing the risk of recurrent DVT and/or post thrombotic syndrome (PTS),[5-8] a debilitating late sequelae of DVT.

Post thrombotic syndrome (PTS) occurs in nearly 30-50% of patients following an episode of DVT[8,9] and is characterized by chronic leg pain and swelling that limits activity, the ability to work, and potentially results in leg ulcers.[9] PTS is thought to be caused by venous hypertension and impaired venous return due to the persistent (residual) venous obstruction.[9,10] Valvular reflux also frequently occurs after DVT, likely via thrombus-induced activation of inflammation, fibrous scarring by acute and resolving thrombus, or by venous dilation distal to the obstructed segment.[8] Risk factors of PTS include symptom severity at 1-month post DVT diagnosis, thrombosis of the common femoral or iliac vein, higher body mass index (BMI), previous ipsilateral venous thrombosis, older age, and female gender.[11] The occurrence of PTS has been shown to be directly related to the degree of residual clot; conversely, in cases where when there is a high degree of clot lysis, rethrombosis is avoided and patients have a minimal risk of PTS.[3,12] Furthermore, it has been recently shown that the use of compression stockings do not prevent the occurrence of PTS after DVT nor do they influence the severity of PTS or the rate of recurrent VTE.[13]

Including early clot removal in the treatment strategy for management of DVT has been shown to be associated with a significant reduction in the occurrence of persistent venous obstruction, recurrent thrombosis, PTS, valvular incompetence (reflux) and improved quality of life (QOL),[1,4,14] presumably by rapidly restoring venous patency and preserving or limiting damage to venous values.[15]

Due to the significant impact of both PTS and recurrent thrombosis on QOL and productivity as well as the cost associated with managing these conditions,[11,14] the Society for Vascular Surgery (SVS) has recently updated clinical practice guidelines suggesting early removal of thrombus in patients most likely to benefit from the procedure.[16] As defined by the SVS, early thrombus removal is indicated for patients with:

- A first episode of acute iliofemoral DVT
- Symptoms of <14 days in duration
- Low bleeding risk
- Ambulatory with good functional capacity and an acceptable life expectancy, who would benefit from a reduced long-term risk of PTS and DVT reoccurrence

First-line therapies for early thrombus removal include catheter-directed pharmacologic thrombolysis (CDT) and pharmacomechanical thrombolysis (PMT). Catheter-directed thrombolysis involves infusion of a thrombolytic agent in the region of the venous thrombus through a percutaneously placed catheter. Catheter-directed thrombolysis is limited by the risk of bleeding (5-11%),[6] prolonged infusion time required for the thrombolysis procedure (average 48-53 hours),[17] and the cost associated with the frequent requirement of patient monitoring in the ICU. Pharmacomechanical thrombolysis (PMT) was developed to address these limitations through the adjunctive use of mechanical devices, involving rotational, rheolytic or ultrasound technologies, to deliver the thrombolytic agent as well as produce some combination of thrombus fragmentation, distribution of thrombolytic drug through the thrombus and/or thrombus aspiration.[18]

Comparisons of CDT with PMT have shown that PMT is associated with[20-21]:

- Comparable rates of treatment success and risk of complications
- Shorter treatment times
- Lower doses of thrombolytic drug required
- Reduced ICU and total hospital stay and hospital costs

Recognizing the benefits of PMT over CDT, the SVS now suggests the use of PMT over catheter-directed thrombolysis alone if expertise and resources are available.[16]

Despite these advantages, concerns remain that mechanical device may damage vein valves as compared to CDT. The effect of PMT on venous valve function as compared with conventional CDT therapy has been recently evaluated by Vogel and collegues.[14] Post procedural phlebograms were reviewed to determine residual obstruction; valve function (reflux) was evaluated using duplex ultrasonography at follow-up. A total of 20 limbs were evaluated that were treated with CDT alone, 49 were treated with PMT (n=35 with the Trellis catheter, n =14 with AngioJet™ System). Similar rates of success were achieved with both CDT and PMT. At a mean length of follow-

Table 1: Summary of literature evaluating venous valve function following treatment for DVT

Author	N	DVT Therapy	Method for Determination of Venous Valve Closure Time	Length of Follow-up (months)	% with Normal Valve Function	p
Vogel, 2012	20 49	CDT PMT	Duplex Ultrasonography	44	CDT: 35% PMT: 47%	.42
Arko, 2007	30	PMT	Duplex Ultrasonography	12	88%	--
Elsharawy, 2002	17 18	Anticoagulation CDT	Photoplethysmography	6	Anticoag: 59% CDT: 89%	0.04
VanHaarst, 1996	24	Anticoagulation	Duplex Ultrasonography	33 85	52% 40%	--

up of 44 months, there was no difference in the rate of reflux demonstrated between patients treated with CDT (65%) and PMT (53%) (p=.42). Limbs treated with the Trellis catheter exhibited a reflux rate of 57% vs. 43% in limbs treated with AngioJet System (p=.53). Although the sample size was insufficient to demonstrate statistical significance, the risk of valve reflux following treatment with PMT was shown to be at least equivalent, and possibly slightly lower, than that which occurs following CDT.

Studies have reported a wide variation in rates of reflux after the use of CDT or anticoagulation alone, depending on the method of assessment and length of follow-up, as shown in Table 1. The results of the Vogel series are consistent with other reports evaluating valvular function following treatment of DVT.

The AngioJet System is a rheolytic PMT technology that is used extensively to treat DVT, acute limb ischemia and thrombosis of hemodialysis access grafts. Data collected on 329 lower extremity DVT patients as a part of the PEARL Registry, a study following AngioJet patients funded by Boston Scientific has shown that:

- Thrombectomy with Power Pulse™ or rapid lysis was utilized in 87% of the patients.
- An average reduction of 96% in thrombus immediately post AngioJet PMT therapy.
- Rates for freedom from rethrombosis at 6 and 12 months were 88% and 84%, respectively.
- Clinically and statistically significant improvements in both physical and mental components of QOL measures from baseline to 3, 6, and 12 months.
- 75% of AngioJet cases were completed in ≤ 24 hours.
- Procedure-related complications included bleeding requiring transfusion (N=1), hematoma at access site (2) arrhythmia during the AngioJet procedure (3), Acute renal failure (1) or Transient renal failure (1), and pulmonary embolism (1).

As shown in Table 2 below, the lower extremity outcomes for AngioJet PMT therapy as reported in the PEARL registry aligned favorably with the CDT experience as reported by the Venous Registry[17] with considerably less lytic drip times when CDT is used in combination with AngioJet therapy. In addition, the PEARL registry reported greater thrombus removal both acute and chronically with fewer bleeding complications with AngioJet Thrombectomy use in the treatment protocol.

Table 2: Comparison of PEARL Registry and Venous Registry patient populations and outcomesin the treatment of lower extremity DVT

	Venous Registry[17]	PEARL Registry
Number of Patients	287	329
# of sites	63	32
Prior DVT	31%	40%
Concomitant stent placement	33%	35%
Primary access	Popliteal	Popliteal
Mean age	47.5 years	52 years
% Male	48%	57%
Primary treatment	CDT	PMT with or without CDT
Primary lytic	Urokinase	TPA
CDT drip times (mean)	48 hours	17 hours (when CDT was utilized)
Procedure time (median)	NA	CDT: 41 hours CDT+PMT: 22 hours PMT: 2 hours
Acute: % thrombus removal	86%	97%
Chronic: % thrombus removal	68%	95%
Primary Patency	6 month: 65% 12 month: 60%	NA
Freedom from Rethrombosis	NA	6 month: 88% 12 month: 84%
Bleeding complications	11% major 16% minor	5% (major + minor)

Conclusions

While definitive, randomized trials evaluating the late outcomes for treatment of DVT using anticoagulation alone vs. aggressive early intervention with PMT are ongoing,[24] the consistent results reported by an accumulating, large body of research comprised of smaller studies and registries supports the benefit of early thrombus removal using PMT:

- Catheter based thrombus removal for DVT treatment has been shown to improve patient outcomes.
- Advantages of PMT treatment of DVT are not compromised by adverse effects on vein valve function.
- Studies support PMT as a safe method for the treatment of symptomatic acute DVT with excellent rates of patency reported.
- Rates of recurrent venous thromboembolism have been shown to be lower in treatment groups receiving percutaneous venous intervention.

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