in both groups (P = .703, Mann-Whitney U test). The SF36 mental scoring over 3 years improved in group S (P = .04). However, there was no change in the physical scores in both groups (S: P = .361; F: P = .889) or the mental score in group F (P = .285). Furthermore, there was no difference in the changes on the physical and mental score between the treatment groups due to treatment (physical P = .724, mental P = .354, Mann-Whitney U test).

Conclusions: At 3 to 5 years follow up, the treatment was equally effective between the two groups, as demonstrated with VSDS, VCCS, and AVVQ score improvements. The additional foam sessions were also similar. Since surgery may not provide a definitive solution, foam sclerotherapy could be offered like a dental care treatment model (ie, "treat as and when the problem appears").

A New Approach to the Genetics of Varicose Veins: A Genome-wide Association Study

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Background: The exact nature of the genetic basis of varicose veins remains unclear. A number of genetic associations have been described. These have, however, all been relatively small, limited-candidate gene studies, none of which have been validated. The aim of this study was to consider these current reported genetic associations with varicose veins and to carry out a case control analysis to validate them, using the approach of a more comprehensive nonbiased genome-wide association study (GWAS).

Methods: An indirect, in silico, GWAS of varicose veins was undertaken. This was based on our abdominal aortic aneurysm GWAS in which the frequency of varicose veins was similar in cases and controls. Genetic polymorphisms associations with venous disease to date were identified through a literature search. All known single nucleotide polymorphisms, with >5% allele frequency in the genes previously implicated, were analyzed. Genotyping was carried out using Affymetrix genome-wide human single nucleotide polymorphisms array 6.0.

Results: Three hundred forty-nine patients with varicose veins and 857 controls were included. Genes which have been implicated in venous disease so far include *FOXC2*, *HFE C282Y*, factor XIII V34L, estrogen receptor B, TNF-A, *MTHFR*, and thrombomodulin. None of the single-nucleotide polymorphisms in these genes have shown to have significant association in this study. However, there were a number of other single-nucleotide polymorphisms that were found to be associated with varicose veins. Some of these are quite novel and previously not linked to venous disease. These are being further validated in another larger and more strictly phenotyped cohort.

Conclusions: This is the first GWAS applied to varicose veins. The previous candidate genes implicated in common venous disease have not been confirmed. A GWAS approach has been shown to be useful in validation and discovery of novel genes in venous disease. Further larger cohorts are required to confirm these.

Thrombolytic Therapy with Tissue Plasminogen Activator: Why Prolonged Continuous Infusion is not the Best Approach

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Background: Continuous infusion has been assumed to be the optimal way of administering every thrombolytic agent approved for clinical use. However, this simplistic approach fails to take advantage of differences in properties of thrombolytic agents that could be exploited to increase efficacy as well as safety. In particular, continuous infusion is not necessary when using thrombolytic agents with strong fibrin binding and is not the optimal way of administering recombinant tissue plasminogen activator (r-tPA or alteplase). Once given by intraclot injection, alteplase binds to fibrin clot, and once bound to clot, its activity as a plasminogen activator increases several hundred-fold, also known as fibrin selectivity. Once the clot has been laced with tPA, prolonged fibrinolysis ensues, obviating the need for prolonged infusions.

Methods: Forty-five patients with subclavian, jugular, or central venous thrombosis (SJ-CVT) and 56 patients with acute deep vein thrombosis of the lower extremity (DVT-LE) were treated with once daily intraclot pulse spray injection of tPA without prolonged infusions of tPA, but with full systemic anticoagulation. Initial protocols used high doses of tPA (20-40 mg/day for SJ-CVT, and up to 50 mg/day for DVT-LE) but were reduced five- to ten-fold to a maximum of 4 mg/day tPA for SJ-CVT and a maximum of 10 mg/day tPA for DVT-LE after pharmacokinetic studies indicated the higher doses greatly exceeded the amount of tPA that could bind to acute fibrin clot.

Results: Venous patency was restored in 34 of 45 (76%) SJ-CVT patients after an average of 2.1 days/treatments and 51 of 56 (91%) of acute DVT-LE patients after an average of 2.7 days/treatments. There was no loss of efficacy with decrease in dose of tPA. No major bleeding complications requiring transfusion were found at either dosing schedule.

Conclusions: Elimination of prolonged continuous infusion from thrombolytic regimens using tPA has two advantages. When many venous divisions are thrombosed, the catheter can be moved from one division to the next to load each segment of clot with tPA quickly, instead of having to leave the catheter in one division for prolonged infusion. This allows thrombolysis of many divisions in almost parallel fashion instead of the serial fashion required with conventional thrombolytic therapy. The second advantage is safety, because with termination of intraclot injection, any tPA that reached the systemic circulation during injection is cleared rapidly due to its short half-life ($T_{.5} \approx 5$ min) shortening the duration of circulating tPA, whereas with conventional thrombolytic therapy, elevated systemic tPA levels and suppressed plasminogen activator inhibitor-1 levels are likely to persist as long as the prolonged infusion continues.

Postoperative Deep Vein Thrombosis in Total Knee or Hip Replacement Operation is Associated with Preoperative Increased Calf Muscle Deoxygenation

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Background: To assess whether preoperative calf muscle deoxygenated hemoglobin (HHb) level during light-intensity exercise is useful for identifying patients at risk of developing postoperative deep vein thrombosis (DVT).

Methods: Sixty-three patients receiving either total knee or total hip replacement operation were enrolled. Preoperative screening using compression ultrasound of the bilateral lower extremities was performed if study patients already had deep vein thrombosis. The mean flow velocity of the popliteal vein (POPV) was assessed. Moreover, prevalence of venous reflux in the POPV was evaluated preoperatively. Near-infrared spectroscopy was used to measure calf muscle HHb levels. Calf venous blood filling index (HHbFI) was calculated on standing, then the calf venous ejection index (HHbEI) was obtained after one tiptoe movement and the venous retention index (HHbRI) after ten tiptoe movements. All patients received fondaparinux for postoperative thromboprophylaxis.

Results: There were no preoperative DVT. Of 63 patients evaluated, postoperative compression ultrasound confirmed DVT in 13 (20.6%) patients. There were no significant differences in mean age, body mass index, and gender distributions between patients with postoperative DVT and those without. There was no significant difference in the mean flow velocity in the POPV between patients with postoperative DVT and these without (P = .062). Reflux in the POPV was found in three patients with postoperative DVT and 12 without postoperative DVT, and there was no significant difference between the groups (P = .945). The preoperative near-infrared spectroscopy-derived HHbRI was significantly increased in patients who developed deep vein thrombosis in comparison with those who did not (7.78 ± 8.65, 1.83 ± 2.30; P = .006, respectively). There were no significant differences in the values of HHbFI and HHbEI between the study groups.

Conclusions: These results suggest that HHbRI, as measured by near-infrared spectroscopy, may be a promising parameter for identifying patients at risk of developing postoperative DVT despite pharmacologic deep vein thrombosis prophylaxis. These findings might be very helpful for physician in detecting patients who require more extensive thromboprophylaxis.

Patient Characteristics, Referral Patterns and Associated Risk Factors in Patients Referred to an Outpatient Vascular Laboratory to Rule out Deep Venous Thrombosis

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Background: Previous studies utilizing national or regional data demonstrated that a significant proportion of deep vein thrombosis (DVT) is diagnosed in the outpatient setting. Little is known, however, about patient characteristics, referral patterns, and percentage of positive DVT in patients referred to outpatient vascular laboratories. The study objective was to examine demographics, risk factors, presenting symptoms, and referring physician specialties in patients referred to outpatient vascular laboratories (OVL) and to delineate clot extent in patients diagnosed with DVT.

Methods: Data was retrospectively collected from an OVL database of 1506 patients referred to rule out DVT over a 13-month period. Data collected included patient age, gender, risk factors, presenting symptom(s), and referring physician specialty. In patients with positive findings, the DVT were categorized (acute or chronic), and extent of DVT was classified on a scale of 1 to 4 (4 = gastronemius vein, 3 = tibial vein, 2 = femoral and/or popliteal vein, and 1 = common femoral and/or more proximal veins). Logistic regression was used to quantify association of risk factors with the presence of acute DVT.