Abstracts

Gregory L. Moneta, MD, Section Editor

Botox Therapy for Ischemic Digits

Neumeister MW, Chambers CB, Herron MS, et al. Plast Reconstr Surg 2009;124:191-200.

Conclusion: Botox appears to provide improvement in digital perfusion and pain reduction in patients with Raynaud's syndrome when conservative management fails.

Summary: Digital ulceration associated with Raynaud's syndrome is painful, difficult to treat, and frequently results in patient debilitation and chronic depression. Reports by Sycha and Van Beek have indicated potential benefit for patients with ischemic digits with local injection of botulinum toxin (Euro J Clin Invest 2004;34:312-3; Plast Reconstr Surg 2007;119: 217-26). This was a retrospective observational study on outcomes of 19 patients with Raynaud's syndrome treated with botulinum toxin. All patients had chronic ischemic hand pain, and vascular studies had ruled out proximal occlusive disease and underlying disorders, including carpal tunnel syndrome, diabetes, renal failure, rheumatoid arthritis, hypothenar hammer syndrome, scleroderma and mixed connective tissue disease as well as lupus. Thirteen patients had chronic finger ulcers. Botox (50 to 100 U) was injected into the palm around each involved neurovascular bundle. Preinjection and postinjection laser Doppler studies were performed in most patients to assess potential changes in digital blood flow.

Of the 19 patients treated, 16 (84%) reported reduction of pain, 13 reported immediate pain relief, 3 more had gradual pain relief over 1 to 2 months, and 3 patients had no or minimal response. Laser Doppler studies demonstrated markedly increased blood flow to the treated digits. The chronic finger ulcers in the 13 patients healed ≤60 days. Twelve patients (63%) remained pain free with a single injection at 13 to 59 months after injection. Four patients (21%) required additional injections because of recurrent pain.

Comment: In addition to its cosmetic uses, Botox is receiving increased attention for treatment of widely varying disorders, from anal fissures to ischemic digital ulcers. Its mechanism of action is unclear, although some speculate that it may work through modulation of vascular tone or blockage of chronic neuropathic pain pathways. This study was not controlled, and it is well known that patients with finger ulcers often have a waxing and waning course and that many ulcers will heal with conservative therapy. However, if the results of Botox therapy for ischemic ulceration of the fingers are as truly dramatic as depicted in this report, it should not be difficult to design a blinded trial with sufficient power to definitely prove the efficacy of this treatment.

Dabigatran Versus Warfarin in the Treatment of Acute Venous Thromboembolism

Schulman S, Kearon C, Kakkar AK, et al; the RE-COVER Study Group. N Engl J Med 2009;361:2432-52.

Conclusion: A fixed dose of dabigatran, an oral anticoagulant that does not require monitoring, is as effective as warfarin in the treatment of acute venous thromboembolism (VTE) and has a similar safety profile.

Summary: Dabigatran is an orally available, potent, direct inhibitor of thrombin that is administered in a fixed dose, with no need for coagulation monitoring. Its half-life is 12 to 17 hours, and it is excreted in the urine. Dabigatran has demonstrated similar safety and efficacy as an enoxaparin in prevention of VTE in patients undergoing hip or knee arthroplasty (J Thromb Haemost 2007;52178-85; Lancet 2007;370:949-56). It has also has similar safety and, in some cases, superior efficacy in the prevention of stroke in patients with atrial fibrillation (N Engl J Med 2009;361:1139-51).

This was a double-blind, randomized, noninferiority trial comparing dabigatran with warfarin for treatment of acute VTE. Patients with acute VTE were initially given parenteral anticoagulation therapy for a median of 9 days (interquartile range, 8-11 days). Patients randomized to dabigatran received 150 mg twice daily. Patients randomized to warfarin were treated with dose adjustment to achieve an international normalized ratio (INR) of 2.0 to 3.0. The primary outcome was recurrent, symptomatic, objectively confirmed VTE and related deaths at 6 months. Safety end points included bleeding, acute coronary syndromes, liver function tests, and other adverse events.

Dabigatran was given to 1274 patients, and 30 (2.4%) had a recurrent thromboembolic event. Warfarin was given to 1265 patients, and 27 (2.1%) had recurrent VTE. The difference in risk was 0.4% points (95% confidence interval [CI], −0.8 to 1.5; $P < .001$) for the prespecified not inferiority margin. The hazard ratio for dabigatran was 1.10 (95% CI, 0.65-1.84). Major bleeding occurred in 20 patients (1.6%) assigned to dabigatran and in 24 (1.9%) treated with warfarin. The hazard ratio with dabigatran was 0.82 (95% CI, 0.45-1.48). Any bleeding was observed in 205 patients assigned to dabigatran (16.1%) and in 277 patients assigned to warfarin (21.9%), and the hazard ratio with dabigatran was 0.71 (95% CI, 0.59-0.85). The two groups had similar numbers of deaths, acute coronary syndromes, and abnormal liver function test results. The drug was discontinued due to adverse events in 9% of patients assigned to dabigatran and in 6.8% of patients assigned to warfarin ($P = .05$).

Comment: The data indicate dabigatran is not inferior to warfarin when used to treat patients with acute VTE when warfarin is adjusted to maintain an INR of 2.0 to 3.0. The only previously available oral, direct thrombin inhibitor was ximelagatran. This was also not inferior to warfarin for treatment of recurrent VTE, but there were infrequent but serious hepatic toxic effects thus far not seen with dabigatran. Dabigatran is cleared in the urine, and >90% of the patients in this study had a creatinine clearance of >50 mL/min. Obviously, additional patients with varying levels of renal dysfunction will need to be studied. Accumulating evidence supports dabigatran as a fixed-dose alternative to warfarin. The drug has no known interactions with foods and minimal reactions with other drugs. The days of using rat poison to treat VTE may be drawing to a close.

Heparin Induced Thrombocytopenia and Thrombosis in a Tertiary Care Hospital

Ban-Hoefen M, Francis C. Thromb Res 2009;124:189-92.

Conclusion: The occurrence of heparin-induced thrombocytopenia (HIT) can be decreased by reducing the exposure to unfractionated heparin. The diagnosis can be improved by reporting the optical density of the enzyme-linked immunosorbent assay (ELISA) test result.

Summary: HIT results from the development of an antibody reacting with a complex of heparin and platelet factor 4 that results in thrombocytopenia and a hypercoagulable state. Clinical diagnosis depends on a combination of a decline in platelet count, the duration of platelet therapy, and the occurrence of thrombotic events. The most widely used diagnostic test for HIT is an ELISA that detects the presence of antibodies reactive with the heparin platelet factor 4 complex. The tests are very sensitive but lack specificity. A negative test is useful for excluding the diagnosis.

The authors sought to determine the frequency, clinical characteristics, and laboratory correlates of HIT in a tertiary care hospital. They undertook a retrospective record review of all adults hospitalized during a 30-month period. Patients who had a positive antiplatelet factor 4 ELISA assay were identified through an institutional laboratory database. Data were analyzed for the type, dosage, and route of administration of heparin associated with HIT.

HIT was diagnosed in 136 patients, including 114 of 28,091 patients (0.48%) who received only unfractionated heparin. It was diagnosed in 22 of 6559 patients (0.33%) who received both unfractionated and low-molecular-weight (LMW) heparin. HIT was diagnosed in 2 of 2498 patients (0.8%) who received only LMW heparin ($P = .02$ compared with those who received only unfractionated heparin). HIT occurred in 62 of 16,939 patients receiving subcutaneous heparin or LMW heparin compared with 69 of 11,152 patients receiving intravenous therapy ($P = .003$). Of the 34,650 patients exposed to heparin products, symptomatic thrombosis developed in 41 (0.1%). The optical density of the ELISA assay was 1.2 ± 0.8 in patients with HIT and thrombosis and 0.9 ± 0.6 in those without thrombosis ($P = .03$).

Comment: The data in this study indicate HIT develops in about 0.4% of all patients exposed to heparin in a tertiary care hospital and is significantly less frequent in those treated only with LMW heparin. These authors' findings are consistent with previous reports. A new bit of information is the association of the optical density value of the ELISA assay with thrombotic complications of HIT. The Food and Drug Administration requires ELISA assays for HIT to be reported as positive or negative based on a certain threshold value. The data suggest that reporting of the actual optical density may be useful in determining which patients with HIT are at most risk for a thrombotic complication.

Prediction of Hypertension Improvement After Stenting of Renal Artery Stenosis: Comparative Accuracy of Translesional Pressure Gradients, Intravascular Ultrasound, and Angiography

Leesar MA, Varma J, Shapira A, et al. J Am Coll Cardiol 2009;53:2363-71.

Conclusion: A hyperemic systolic pressure gradient ≥21 mm Hg predicts improvement in hypertension after stenting of renal artery stenosis.

Summary: Correlation is poor between the percentage of renal artery stenosis measured by renal angiography and translesional pressure gradients across the renal artery stenosis. It is postulated therefore that the discordance