High-Dose-Rate Brachytherapy for the Treatment of In-Stent Restenosis in the Lower Extremity

Karen J. Ho, Phillip M. Devlin, Ann L. Madenci, Marcus E. Semel, Louis L. Nguyen, Michael Belkin, Edwin C. Greaveraux, Matthew T. Menard, Brigham and Women’s Hospital, Boston, Mass

Objectives: The effectiveness of endovascular brachytherapy (EVBT) for in-stent restenosis (ISR) after percutaneous transluminal angioplasty (PTA) and stenting (PTAS) has been limited by edge stenosis and late thrombosis. We evaluated a novel protocol of PTA and EVBT for ISR in lower extremity occlusive disease.

Methods: We conducted a retrospective, single-center review of patients treated with PTA and EVBT for ISR in the iliac and femoropopliteal segments between 11/2004 and 11/2012. Twenty Gy in a single fraction was prescribed to 0.5 mm beyond the radius of the largest balloon and with proximal and distal margins of at least 2 cm. Stents were duplexed at 1, 3, 6, 9, 12, and 18 months, and then yearly. The primary endpoint was freedom from ≥75% restenosis in the treated segment. Patency data were estimated using the Kaplan-Meier method.

Results: Forty-two consecutive cases of EVBT for ISR in iliac (24%; n = 10) and femoropopliteal (38%; n = 32) arteries were performed. Twenty patients (47.6%) had claudication, five (11.9%) had critical limb ischemia, and 17 (40.4%) were asymptomatic. Median time from stenting to EVBT was 594 days (interquartile range, 324-1124 days). Thirteen (31%) patients underwent additional stent placement at time of EVBT. Mean treated length was 23.5 ± 12.3 cm over mean duration of 16.1 ± 9.6 months. Median post-EVBT follow-up time was 675 days (interquartile range, 272-967 days). There were two periprocedural and five late thrombotic occlusions. There was one death, thought to be unrelated to EVBT. Post-EVBT patency data are shown in the Fig. Primary-assisted patency rates for recurrent ISR of ≥50% were identical to that of ≥75%.

Conclusions: EVBT appears to be a promising option for ISR in the iliac and femoropopliteal arteries, particularly with a strategy of intervening upon at-risk stents prior to occlusion. Future studies may help delineate which patients will benefit maximally from EVBT.

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Cost-Effectiveness of Exercise Therapy Versus Primary Stenting for Patients with Intermittent Claudication and Iliofemoral Disease

Marcus E. Semel, Karen J. Ho, C. Keith Ozaki, Michael Belkin, Brigham and Women’s Hospital, Boston, Mass

Objectives: Supervised exercise (SE) is an evidence-based treatment for intermittent claudication (IC). While primary stenting (PS) for iliofemoral occlusive disease may improve outcomes over angioplasty alone, it may do so at increased cost. Although prior reports have failed to show superiority of angioplasty over SE, we hypothesize that PS is cost-effective when compared with SE.

Methods: We conducted a retrospective, single-center review of 203 patients treated with primary stenting (PS) or angioplasty (PTA) at our institution between 11/2004 and 11/2012. Twenty Gy in a single fraction was prescribed to 0.5 mm beyond the radius of the largest balloon and with proximal and distal margins of at least 2 cm. Stents were duplexed at 1, 3, 6, 9, 12, and 18 months, and then yearly. The primary endpoint was freedom from ≥75% restenosis in the treated segment. Patency data were estimated using the Kaplan-Meier method.

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Conclusions: EVBT appears to be a promising option for ISR in the iliac and femoropopliteal arteries, particularly with a strategy of intervening upon at-risk stents prior to occlusion. Future studies may help delineate which patients will benefit maximally from EVBT.

However, it is not known whether this pathway is active and can be manipulated in human vein grafts. Thus our objective was to demonstrate that activation of Eph-B4 with exogenous Ephrin-B2/Fc would reduce neointimal hyperplasia in human saphenous veins in an in vitro model of neointimal hyperplasia.

Methods: Excess saphenous vein was obtained from patients undergoing bypass surgery. Vein rings were cultured for 14 days with Ephrin-B2/Fc at concentrations between 0 and 2 μg/mL. Each ring was compared with its matched control for expression of intimal hyperplasia and quantitative real-time polymerase chain reaction was performed to assess gene expression. Human umbilical vein endothelial cells were treated with Ephrin-B2/Fc and receptor phosphorylation was detected with western blot.

Results: Treatment of vein rings with Ephrin-B2/Fc led to an average of 30.8% (95% confidence interval, 6.56-55.0; n = 20) decrease in neointimal hyperplasia compared with controls. Eph-B4 and ephrin-B2 expression significantly decreased in organ culture while osteopontin expression increased (n = 7). Cultured endothelial cells demonstrated a significant increase in Eph-B4 phosphorylation when treated with Ephrin-B2/Fc as well as increased phosphorylated of downstream signaling proteins AKT and ERK.

Conclusions: The Eph-B4 signaling pathway is active in human venous cells and stimulation of Eph-B4 in vitro leads to reduced neointimal hyperplasia in saphenous vein rings. Stimulation of the Eph-B4 pathway may be a promising candidate for a clinical trial to reduce vein graft neointimal hyperplasia.

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Table 1: Model Inputs

<table>
<thead>
<tr>
<th>Model Inputs</th>
<th>Base Case</th>
<th>Range for Sensitivity Analysis</th>
<th>References</th>
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<tr>
<td>Costs</td>
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</tr>
<tr>
<td>SE</td>
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<tr>
<td>PS</td>
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<tr>
<td>Cost of Intervention</td>
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<td>Surgery</td>
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<td>$2,000-4,500</td>
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<tr>
<td>Renovation</td>
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</tr>
<tr>
<td>Maximum Waiting Time</td>
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</tr>
<tr>
<td>450</td>
<td>54,15-112</td>
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</table>

*If consisted of 3-6 h sessions per week for 26 weeks. NS patients were assumed to exercise with the same frequency and compliance. We assumed that 6.25% of patients who did not benefit from exercise were non-compliant with their exercise regimen.

Methods: We performed a cost-effectiveness analysis comparing SE and ilio-femoral PS with a baseline strategy of nonsupervised exercise (NSE). Estimates for costs and outcomes were obtained from the medical literature (Table) and the Bureau of Labor Statistics. Costs were adjusted to 2012 US Dollars. Effectiveness was measured as the maximum walking distance (MWD) in meters by treadmill testing performed at 1 year. The primary endpoint was cost-effectiveness measured in dollars per meter walked. Because of a 1-year time horizon, discounting was not used.

Results: The average cost-effectiveness of NSE/SE/PS in dollars per meter walked was 15.4/19.8/51.6, respectively. When compared with NSE, the incremental cost-effectiveness ratio for SE was $242.96/m. For PS, it was $881.1/m. One-way sensitivity analyses (Table, Column 3) demonstrated that SE was a robust strategy in that it was more cost-effective than PS in all scenarios. PS was both more costly and less effective (ie, dominated) if MWDPS <207 m or MWDSE >424 m.

Conclusion: When compared with NSE, SE is a more cost-effective strategy than PS for the treatment of iliofemoral disease in IC.

Determinants of Amputation-Free Survival After Peripheral Vascular Intervention for Critical Limb Ischemia

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Objectives: Our objective was to identify independent predictors of overall (OS) and amputation-free survival (AFS) in patients undergoing peripheral vascular intervention (PVI) for critical limb ischemia (CLI).

Methods: We reviewed 1253 patients who underwent 1414 PVI for CLI within the Vascular Study Group of New England (VSGNE) from January 2010 to December 2011. A univariate screen of potential predictors of the primary (AFS) and secondary (OS) end points was performed to construct a Cox proportional hazards model of survival at 1 year.

Results: All PVI were performed for CLI (rest pain 29%, tissue loss 71%). During each procedure, the number of arteries treated were one (49%), two (35%), three (12%) and >four (5%). Target arterial segments and TASC classifications were aorto-iliac (27%; A 49%, B 25%, C 11%, D 15%), femoral-popliteal (48%; A 36%, B 33%, C 20%, D 17%) and infrapopliteal (25%; A 17%, B 15%, C 27%, D 41%). Technical success was high (92%), while complication rates were low (access site hematoma [5.0%] or occlusion [0.3%], distal embolization [2.4%]). Mortality and major amputation rates were 2.8% and 2.2% at 30 days, respectively. Overall percutaneous or open reintervention rate was 8.0% at 1 year. The Kaplan-Meier estimates of 1-year OS and AFS were 82% and 76%, respectively. Independent predictors of AFS included male gender, age <80 years, dependent living status, congestive heart failure, dialysis dependence, and tissue loss; smoking was protective (Table).

Conclusions: AFS after PVI for CLI is associated with specific preoperative patient characteristics. This data may facilitate efforts to improve patient selection and, after further validation, enable risk adjusted outcome reporting for CLI patients undergoing PVI.

Table. Multivariate analysis of factors associated with 1-year AFS after PVI (N = 771).

<table>
<thead>
<tr>
<th>Preoperative characteristic</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
<th>P value</th>
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<td>Dialysis</td>
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<tr>
<td>Tissue loss</td>
<td>1.8</td>
<td>1.2-2.7</td>
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<tr>
<td>Dependent living status</td>
<td>1.8</td>
<td>1.1-2.9</td>
<td>.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.6</td>
<td>1.2-2.1</td>
<td>.01</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.5</td>
<td>1.2-2.0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Age &gt;80 years</td>
<td>1.4</td>
<td>1.0-1.9</td>
<td>.049</td>
</tr>
<tr>
<td>Smoking (prior or current)</td>
<td>0.6</td>
<td>0.5-0.9</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

AFS, Amputation-free survival; PVI, peripheral vascular intervention.

Predictors of Increased Length of Stay Following Endovascular AAA Repair


Objectives: Increased length of stay (LOS) following abdominal aortic aneurysm (AAA) repair increases costs of care and serves as an important quality metric. We sought to identify patient and procedural factors associated with increased postoperative LOS following endovascular aneurysm repair (EVAR).

Methods: All consecutive EVAR patients from a single institution (1/2010-10/2012) were evaluated for increased LOS, defined as >2 days. Predictors of increased LOS were identified by univariate and multivariate analysis.

Results: We identified 257 EVAR patients. Increased LOS was observed in 63% of patients. Univariate analysis showed that patients with increased LOS were older (78 ± 10 vs 73 ± 8 years; P < .01), female (27% vs 14%; P = .01), smokers (88% vs 77%; P = .03), had coronary artery disease (35% vs 18%; P < .01), chronic obstructive pulmonary disease (36% vs 13%; P < .01), prior AAA repair (11% vs 8%; P = .04), elevated creatinine >1.5 mg/dl (16% vs 7%; P = .05), and larger AAA (59 ± 13 mm vs 54 ± 8 mm; P < .01). They were more likely to have general anesthesia (59% vs 44%; P = .03), longer operating room time (190 ± 80 vs 130 ± 40 minutes; P < .01), receive more volume (1960 ± 980 vs 1670 ± 780 mL; P = .02), and have higher estimated blood loss (380 ± 320 vs 190 ± 140 mL; P < .01). Patients staying >2 days were more likely to require vasopressors (11% vs 3.4%; P < .05), intensive care unit stay (20% vs 1%; P < .01), and return to the operating room (5% vs 0%; P = .03). Despite these differences, risk adjusted independent predictors of increased LOS following EVAR included symptomatic coronary artery disease (odds ratio [OR] 2.3; 95% confidence interval [CI], 1.2-4.7; P = .01), chronic obstructive pulmonary disease (OR, 3.4; 95% CI, 1.4-7.9; P < .01), procedure time (per minute; OR, 1.02; 95% CI, 1.01-1.03; P < .01), age (per year; OR, 1.04; 95% CI, 1.01-1.09; P = .01), while preoperative statin use (OR, 0.29; 95% CI, 0.1-0.6; P < .01), and discharge to home (OR, 0.07; 95% CI, 0.01-0.48; P < .01) was protective. Chi-squared analysis showed that both procedure time (33%) and disposition (26%) combined accounted for more than half of the increased LOS.

Conclusions: These data highlight clinical and technical variables associated with increased LOS following EVAR and may be utilized to enact process improvement measures to improve patient care and reduce hospital costs.

Are Meta-Analyses and Systematic Reviews in Vascular Surgery Reliable?

Felix J.V. Schlösser, Bauer E. Sumpio. Yale University, New Haven, Conn.

Objectives: Meta-analyses (MAs) and systematic reviews (SRs) are considered the highest level of evidence by the Oxford Centre for Evidence-Based Medicine. The evidence-based minimum set of “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) was introduced in 2009. The objective of this protocol-driven study was to evaluate the quality of MAs and SRs published in the Journal of Vascular Surgery.