Experimental insights into post thrombotic syndrome

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NO DISCLOSURES

PTS Pathophysiology

Mainstays of therapy
• Rapid and therapeutic anticoagulation
• Leg elevation
• Compression
• Invasive techniques to clear thrombus

But does compression work?

Removal of the obstruction

Can we prevent PTS by actively removing the acute thrombotic obstruction?
Catheter-directed Thrombolysis vs.  AC Ca VenT Study

<table>
<thead>
<tr>
<th></th>
<th>Thrombolysis (n=20)</th>
<th>Standard treatment only (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-thrombotic</td>
<td>22 (36.4%)</td>
<td>35 (68.8%)</td>
<td>0.042</td>
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<tr>
<td>Syndrome at 6 months</td>
<td></td>
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<tr>
<td>Referral pending at 6 months</td>
<td>52 (65.4%)</td>
<td>56 (93.5%)</td>
<td>0.032</td>
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<tr>
<td>Post-thrombotic syndrome at 6 months</td>
<td>27 (32.4%)</td>
<td>32 (35.3%)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Table 3: Short and long-term outcomes

Models of VT

Diaz JA, et al. ATVB 2012;32:3256;

Balance of thrombosis-resolution at vessel wall interface

• uPA-plasmin
• tPA-plasmin
• PAI-1 inhibition

Henke, PK. Rutherford, 9E

Thrombus Fibrosis-contraction

2d 8d 21d

EIM

Human chronic PTS CFV segment

Courtesy of Dr A. Comerota

VT dependence on Plasmin Axis:
PAI-1-/- to increase plasmin

Stasis model

WT
Plasmin Axis and Vein Wall Fibrosis: Disconnect

How about increased PAI-1 on vein wall fibrosis?

• Stasis model
• Late time point at 14d
• Vn is a cofactor for PAI-1

PAI-1 deletion is associated with decreased VT size, but increased fibrosis – possibly due to MMP activation

MMPs and vein wall fibrosis – MMP2/-

• Another example of VT resolution and vein wall injury disconnect
• Larger VT, less fibrosis at d8

MMP2/9/- and vein wall injury

• Stasis model
• Midterm d8
Potential Experimental PTS mechanism

\[ \text{PAI-1} \rightarrow \text{Plasmin} \rightarrow \text{MMP2/9} \rightarrow \text{Fibrosis} \rightarrow \text{VT size} \]

? Translatable

Other factors

- IL-6
  - Biomarker, proinflammatory
- P-selectin – PSGL-1 axis
  - Biomarker, cell adhesion and thrombosis
- Role of endothelial preservation
  - Not yet definitively answered; could be area of statin benefit

Potential Translation

- Administering PAI-1 to prevent PTS is not translatable
- Use of MMP2/9 inhibitor in time specific manner?
- LMWH and decreased vein wall injury
  - Supported by limited clinical data
- Vn blockade decreases vein wall fibrosis but does not impair VT resolution—deserves further evaluation

Thank you

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