With DCBs for CLTI Distal Drug Migration May Adversely Affect Wound Healing: Has It Ever Happened?

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Paclitaxel properties

• Paclitaxel of the taxane class, has been the primary drug of choice used to coat balloons because of its long-lasting effects even after short single-dose applications, with loss of SMC in the media and minimal neointimal thickening.

• Mechanism of action is through the interruption of microtubule assembly in the S/G2/M phase of the cell cycle, resulting in cytotoxic effects.

• Cytotoxicity may result in the theoretic disadvantage of inducing necrosis and increasing inflammation, although it has been speculated that paclitaxel may be primarily cytostatic at lower concentrations.

Drug-coated balloon therapy in coronary and peripheral artery diseases

• Nonstent-based local drug delivery with DCBs can achieve rapid transfer of a drug to surrounding tissue, and durable antirestenotic efficacy.

• Advantages of DCBs over DESs include:
  - Broad surface contact
  - Homogenous drug distribution
  - Absence of stent footprint or polymer residue
  - Restoration of normal vessel anatomy and function.

• Preclinical studies have shown that DCB delivery of paclitaxel combined with a hydrophilic spacer (excipient) results in clinically effective local tissue drug concentrations and sustained inhibition of neointimal growth.

Large particles of PTX have the potential to occlude microvessels downstream following balloon inflation.

What could it limit the drug absorption and impede the distribution of drug into the arterial wall?

• Endothelium
• Presence of atherosclerosis
• Calcium
• Thrombus
• Intimal hyperplasia

Mechanisms Underlying Drug Delivery to Peripheral Arteries

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Preferred excipients for DCBs are nonpolymeric carriers (usually hydrophilic) that help to provide a uniform coating and enhance the transfer of lipophilic drugs (PTX) onto the arterial wall.

Different excipients utilized to date, include:
  - iopromid (Paccocath®)
  - urea (IN.PACT®)
  - shellac (e.g. Freeway®)
  - butyrylhexacitrat (BTHC) (BIO-LUX®)
  - citric ester (Ranger®)
  - polysorbat (Lutonix®)
  - resveratrol (Sequent Please OTW®)
  - polyethylenglycol (Stellarex®).

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DCB in BTK arteries

- Results from clinical trials have shown DCBs to be safe and highly efficacious in the SFA.
- Contrary to expectations, the role of DCBs for below-the-knee (BTK) interventions remains to be elucidated.

Two weeks after DCB angioplasty

- Minor amputation and tissue biopsy
- Arterial and capillary vessel proliferation
- Collagen fibers dissected by intense vascular proliferation
Drug-Coated Balloons for Revascularization of Infrapopliteal Arteries

• Meta-Analysis to investigate the clinical and angiographic outcomes of patients with atherosclerotic disease and DCB based revascularization in infrapopliteal vessels.

- DCB vs UnCoated Balloon or DES
- 641 patients (378 pts DCB) in 5 trials
- Follow up 12 month

The occurrence of incomplete wound healing was reported for 107 limbs (26.2%; data available for 408 limbs treated in 3 trials [6,8,10]).

No significant difference in terms of risk for incomplete wound healing was found with DCB therapy in comparison with control therapy (24.5% vs. 28.7%; RR: 0.84; 95% CI: 0.45 to 1.58; p = 0.60; I² = 47%; phet = 0.05).

No evidence of significant downstream embol or systemic toxicity of DCB with PTA.
• Randomized, multi-center, non-inferiority trial (NCT00728895)
• Inclusion criteria:
  - Age ≥ 18 years
  - History of CLI
  - Rutherford class > 4
• Exclusion criteria:
  - Diabetes mellitus
  - History of amputation

Table 3: Clinical and Angiographic Outcomes at 12 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PCB</th>
<th>PTA</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length (mm)</td>
<td>57</td>
<td>64</td>
<td>0.012</td>
</tr>
<tr>
<td>Binary restenosis</td>
<td>25</td>
<td>35</td>
<td>0.002</td>
</tr>
<tr>
<td>Clinical target lesion closure</td>
<td>25</td>
<td>25</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Table 4: 12-Month Efficacy Endpoints

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>PCB</th>
<th>PTA</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length (mm)</td>
<td>60</td>
<td>65</td>
<td>0.001</td>
</tr>
<tr>
<td>Binary restenosis</td>
<td>30</td>
<td>40</td>
<td>0.003</td>
</tr>
<tr>
<td>Occlusion rate (%)</td>
<td>15</td>
<td>20</td>
<td>0.45</td>
</tr>
<tr>
<td>Longitudinal restenosis (%)</td>
<td>67</td>
<td>72</td>
<td>0.18</td>
</tr>
<tr>
<td>Clinically driven TLR (%)</td>
<td>5</td>
<td>10</td>
<td>0.21</td>
</tr>
<tr>
<td>Clinically driven TLR (all PTs)</td>
<td>11</td>
<td>11</td>
<td>0.66</td>
</tr>
</tbody>
</table>

The paradox that angiographic efficacy did not correlate with clinical benefit might be explained by the heterogeneity of the study population in terms of disease severity, different follow-up protocols, lack of standardized wound protocols.

The goal of treatment is to prevent disease progression, thereby preserving limbs.

- Success of this strategy is influenced by several factors:
  - Wound care
  - Sustained blood supply to the wound
  - The correlation between vessel patency and limb salvage/ulcer healing
  - Improved distal flow can noticeably improve the clinical outcomes.

No evidence of delay in wound healing or more tissue loss.
Conclusions

- Uncoated balloon angioplasty (POBA) remains the recommended gold standard therapy in patients with BTK disease.
- It seems that tibial vessels may behave differently compared to femoro-popliteal arteries but still this hypothesis remains unanswered.
- Local toxic effects of paclitaxel and significant drug loss on the way to the lesion are theoretical considerations.
- Therefore, these effects should not be overestimated.
- The local toxic effect being discussed could affect the endothelium, collateral growth or wound healing itself by inhibiting cell proliferation and function of clearing cells and mechanism.