The impact of Distal Drug Migration on Wound Healing after PTAs with DCB

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Disclosures

• Clinical Advisor for Boston Scientific

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.

Determinants of DCB Biological Effect

• Loss to circulation (insertion-transit-inflation) and its effect
  - Particulate embolization
  - Systemic effects

• Paclitaxel tissue residency
  - Resorption during restenotic cascade
  - Homogeneity of distribution

Adverse Event secondary to Drug Coated Balloons

Downstream Panniculitis Secondary to Drug-Eluting Balloon Angioplasty

Adverse Event secondary to Drug Coated Balloons

Vasculitis resulting from a superficial femoral artery angioplasty with a paclitaxel-eluting balloon

Granada JF, TCT 2013.
Granada JF, TCT 2014.


Antiproliferative Agents

• Reduce inflammation
• Arrest mitosis
• Inhibit SMC migration

Intervent Cardiol Clin 6 (2017) 197–216
Local Biological Effects and Downstream Vascular Changes with the use of DCB and DES

Finn A, LINC 2018.

Preclinical results may not necessarily be indicative of clinical performance. Ranger DCB is an investigational device and not available for sale in the US. Lutonix ™ Drug Coated Balloon Catheter is a trademark of C.R. Bard Inc. Lutonix™Bard is co-distributed by Boston Scientific. IN.PACT ™ is a trademark of Medtronic Inc.

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 . 67%; phet . 0.05).

- Randomized Trial,
- Single-center,
- Head-to-head clinical trial comparing DCB with PTA in patients with Diabetes mellitus, CLI with a Rutherford class of greater than 4,
- Significant stenosis or occlusion greater than 40 mm in at least 1 IPA vessel (n = 132).79
- The mean lesion length was 130 mm.
- Mean diameter stenosis of 97% in both arms.
- Patients underwent ultrasound duplex and angiography.
- Follow-up at 12 months.
- Restenosis of greater than 50% and clinically driven TLR were both more favorable in the PCB group.
- Restenosis: 27% vs 74%, PCB vs PTA  (P<.001)
- TLR: 18% vs 43%, DCB vs PTA  (P = .002)

No evidence of significant downstream embol or systemic toxicity of DCB with PTA.
Prospective, multicenter, randomized study,
• Passeo-18 Lux DCB (Biotronik) (N=36)
• Passeo-18 PTA (N=36).
• The primary hypothesis was a 45% relative risk reduction for binary restenosis
• Angiographic follow-up 6-month and 12 months

The IN.PACT DEEP Trial did not direct the wound care by protocol, which definitely will have influenced safety endpoints

More diseased patients Rutherford 5
• 72.2% BIOLUX PII vs 84.1% IN.PACT DEEP
• BIOLUX PII excluded Rutherford 5 patients
DCB arm of IN.PACT DEEP 1.7%

IN.PACT Amphirion balloon is manually coated after it is folded, resulting in non-uniform paclitaxel distribution on the balloon

The Journal of Cardiovascular Surgery 2016 October;57(5):667-76

Objective
To examine patient outcomes following the use of the drug-coated balloon (DCB) in patients with CLI and DM with Complex Real World lesions undergoing endovascular intervention in below-the-knee (BTK) arteries

Device: Ranger™ Paclitaxel Coated PTA Balloon Catheter
(Paclitaxel dose 3.5 µg/mm²)

Study Design
• Two-Center Experience
• National Medical Center ISSSTE, México City
• Medica Sur Hospital, Mayo Clinic Network, Mexico City
• Universidad Nacional Autónoma de México
• Prospective,
• Phase 1: (30 patients)
• Phase 2: Extension (>100 patients) Longer follow up (24 months)
• Follow-up: clinical visits at 1,3,6,9,12 months

Inclusion and Exclusion criteria
• Symptomatic PAD Rutherford 4-6
• Stenosis >70% or occlusion of infrapopliteal vessels
• Complete angioplasty of tibial vessels at least to the ankle
• Any calcification grade

• Exclusion
• Stroke < 3 months
• MI or angina < 30 days
• GFR < 30ml/min per 1.73m²
• Acute limb ischemia
• In-stent restenosis of target lesion
Inflow Treatment (if needed)

PTA Pre-dilatation

Suboptimal PTA

Treatment with no DCB

Optimal PTA with DCB

Follow up

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**Study Endpoints**

- **Efficacy**
  - **Efficacy rate after 12 months**
    - Successful self-closure rate
    - ABI drop > 20% or 0.15 when compared with post-procedure
    - Absence of stenosis in US image or increase of ABI
    - Freedom from Target vessel revascularization
    - **Technical success defined:** PVR > 2.4
  - **SAFe 2**
    - Freedom above ankle amputation
    - Sustained clinical improvement (Rutherford classification improvement ≥ 1 category)
    - Wound healing rate (assessment of ulcer size and depth, was documented at each follow-up visit)
    - Technical success (restoration of at least 1 BTK artery with <30% residual stenosis in the final angiogram)

- **Safety**
  - Freedom from post-operative death POD at 30 days post-procedure
  - Freedom from device and procedure-related death in 12 months post-procedure
  - Freedom from Major adverse limb events (MALE)
  - Freedom major re-intervention (new angioplasty, thrombolysis, thrombectomy, bypass)
  - Tissue changes or wound healing rate associated to Paclitaxel drug elution

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**Baseline Demographics of patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>76.2 ± 8.1</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>31</td>
<td>60.8%</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>20</td>
<td>64.5%</td>
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<tr>
<td>Prior Myocardial Infarction</td>
<td>23/31</td>
<td>74.1%</td>
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<tr>
<td>Coronary Artery Disease</td>
<td>28/31</td>
<td>83.8%</td>
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<tr>
<td>Cerebrovascular Disease</td>
<td>7/31</td>
<td>22.5%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>20/31</td>
<td>64.5%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29/31</td>
<td>93.5%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>27/31</td>
<td>87.0%</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>31/31</td>
<td>100%</td>
</tr>
<tr>
<td>Rutherford 4</td>
<td>3/31</td>
<td>9.6%</td>
</tr>
<tr>
<td>Rutherford 5</td>
<td>20/31</td>
<td>64.5%</td>
</tr>
<tr>
<td>Rutherford 6</td>
<td>8/31</td>
<td>25.8%</td>
</tr>
<tr>
<td>Wound Present</td>
<td>24/31</td>
<td>77.4%</td>
</tr>
</tbody>
</table>
N=31
Target lesion length, mm 22.3mm ± 8.2
Mean initial stenosis % 78%± 10.2
Number of vessels with lesion 2.3 ± 1.1
Total occlusion % 22/31 (70.9%)
Number of Lesions by Vessel (n)
1= 9 patients (29.0%)
2=10 patients (33.2%)
3=12 patients (38.7%)
Femoropopliteal segment involved 10/31 (31.2%)
Pedal arch free of lesion 7/31 (22.5)
Calcification
None 1/31 (3.2%)
Mild 3/31 (9.6%)
Moderate 12/31 (38.7%)
Severe 15/31 (48.3%)
Vessel Preparation 31/31 (100%)
Atherectomy 2/31 (6.4%)
Bailout stent placement 5/31 (16.2%)
Dissection 5/31 (16.2%)
Residual stenosis 7/31 (22.5%)
Occlusion 4/31 (12.9%)
Embolic complications 4/31 (12.9%)
A/V fistulae 1/31 (3.2%)
Target vessel perforation 2/31 (6.4%)
Subintimal angioplasty 32%
Retrograde access 43%
Complete Index Wound Healing 93%
Procedural Outcomes
% Amputation Free Survival
83.9% Limb Salvage
% Patency per Kaplan Meier Estimates
Patency 96.3%

HPLC (High Pressure Liquid Chromatography)

$\text{Paclitaxel in Downstream Tissue (ng/g)}$
$7-10$ days after PTA

<table>
<thead>
<tr>
<th>Patient</th>
<th>Paclitaxel Concentration</th>
<th>Biological effect</th>
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<tbody>
<tr>
<td>1</td>
<td>112 ng/g</td>
<td>Complete Wound Healing</td>
</tr>
<tr>
<td>2</td>
<td>76 ng/g</td>
<td>Complete Wound Healing</td>
</tr>
<tr>
<td>3</td>
<td>150 ng/g</td>
<td>Major amputation</td>
</tr>
<tr>
<td>4</td>
<td>&lt;50 ng/g</td>
<td>Complete Wound Healing</td>
</tr>
<tr>
<td>5</td>
<td>*no identified</td>
<td></td>
</tr>
</tbody>
</table>
10 days after DCB angioplasty
Minor amputation and tissue biopsy

- Arterial and capillary vessel proliferation
- Collagen fibers dissected by intense vascular proliferation.

2 weeks post PTA

- Hyperplasia of the arteriole media layer
- Normal distribution of collagen and fibrin
- Low Fibrinoid necrosis
- Inflammatory cell infiltration

Conclusions

- Maintain clinical efficacy over time (12 months):
  - Patency 96.3% in 31 patients.
  - Safety: No Downstream clinical important or significant effects.
  - Safety: High rate of Limb Salvage in complex CLI patients.
  - It seems that tibial vessels may behave differently compared to femoropopliteal arteries.
  - Local toxic effects of paclitaxel and significant drug loss on the way to the lesion are theoretical considerations.
  - Therefore, these toxic effects could affect the endothelium, collateral growth or wound healing and should not be overestimated.