CURITIBA trial
CUstodiol vs. RInger
whaT Is the Best Agent for renal protection during thoracoabdominal aortic aneurysm open repair?

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Disclosures

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No conflicts of interest to report:

- Consulting
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)
Any worsening in renal function impacts middle and long-term survival in aortic surgery.

AKI pathophysiology

- Hypoxia
- Ischemic acidosis (visceral and peripheral)
- Reactive vasoconstriction (RAAS)
- Membrane damage
- Endothelial cells swelling
- Interstitial edema → impaired microcirculation
Renal protection in open TAAA

- Left heart bypass
- Early revascularization
- Selective perfusion
Selective perfusion

- Normothermic blood
- Cold blood
- Cold crystalloid: Ringer’s lactate
- ...

Custodiol

H. J. Bretschneider (1922-1993)

Original manuscript (1964)
On-label use

Renal transplant

Cardioplegia

In situ perfusion in intra-renal oncologic surgery since 1995.

## Composition

<table>
<thead>
<tr>
<th>Factor</th>
<th>Custodiol (mMol/L)</th>
<th>Enriched Ringer (mMol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>15.0</td>
<td>130.0</td>
</tr>
<tr>
<td>KCl</td>
<td>9.0</td>
<td>4.0</td>
</tr>
<tr>
<td>MgCl</td>
<td>4.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Histidine</td>
<td>198.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>2.0</td>
<td>0.0</td>
</tr>
<tr>
<td>α-Ketoglutarate</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Mannitol</td>
<td>30.0</td>
<td>68.6</td>
</tr>
<tr>
<td>Methylprednisone</td>
<td>0.0</td>
<td>125 mg/L</td>
</tr>
<tr>
<td>Osmolality</td>
<td>310 mOsm/L</td>
<td>281 mOsm/L</td>
</tr>
</tbody>
</table>
## Rationale

<table>
<thead>
<tr>
<th>Factor</th>
<th>mMol/L</th>
<th>Main action</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>15.0</td>
<td>Decrease organ metabolism</td>
</tr>
<tr>
<td>KCl</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>MgCl</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Histidine</td>
<td>198.0</td>
<td>ROS scavenger / buffer</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>2.0</td>
<td>↑ Membrane integrity, antioxidant</td>
</tr>
<tr>
<td>α-Ketoglutarate</td>
<td>1.0</td>
<td>Membrane stabilization, ATP source</td>
</tr>
<tr>
<td>Mannitol</td>
<td>30.0</td>
<td>Reduces cell edema, $O_2$ requirement</td>
</tr>
<tr>
<td></td>
<td>Total  (n = 84)</td>
<td>Ringer group (n = 42)</td>
</tr>
<tr>
<td>--------------------------------</td>
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<td>-----------------------</td>
</tr>
<tr>
<td>Acute Kidney Injury (AKI)</td>
<td>64 (76.2%)</td>
<td>38 (90.5%)</td>
</tr>
<tr>
<td>Total renal ischemic time,</td>
<td>47.9 ± 16.61</td>
<td>43.6 ± 15.99</td>
</tr>
<tr>
<td>minutes, mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraplegia / paraparesis</td>
<td>14 (16.7%)</td>
<td>10 (23.8%)</td>
</tr>
<tr>
<td>Operative mortality</td>
<td>5 (5.9%)</td>
<td>4 (9.5%)</td>
</tr>
</tbody>
</table>

▲ ischemic time but ▼ AKI rate

Study design

- Single-center
- Phase 4
- Randomized
- Double-blind:
  - Custodiol
  - Enriched Ringer (mannitol + methylprednisolone)
Inclusion criteria

- >18y old
- Written informed consent
- Thoracoabdominal open repair requiring selective renal perfusion
Exclusion criteria

- Clinical trial in the last 3 months
- Urgent / Emergent procedure
- Patient incapable of consent
- Allergy / intolerance to the investigated preparation
- Patient on renal replacement therapy / dialysis
- Pregnant / lactating women
End-points

• Primary:
  – Verify reduction in post-operative AKI in the Custodiol group

• Secondary:
  – Post-operative eGFR variations
  – Independent AKI predictors
  – ICU length-of-stay
  – In-hospital length-of-stay
  – Mortality (in-hospital, 1m, 1y)
Pre-operative evaluation

- Aneurysm characteristics
- Comorbidities
- Ongoing therapy
- Standard pre-op work-up
- Baseline renal function
- Specific markers: Cystatin C, U-Albumin, U-Retinol Binding Globulin (U-RBP), U-NGAL
- Urinary system duplex US
Intra-operative evaluation

- Total procedure time
- Total clamping time
- Renal ischemic time
- Selective renal perfusion time / volume
- Intra-operative urinary output
- Fluids and blood-components infusions
- Renal artery stenting / atherectomy
- Complications
Post-operative evaluation

- ICU / in-hospital length-of-stay
- eGFR day 1-6
- LDH and CK peak value
- Specific markers: Cystatin C, U-Albumin, U-Retinol Binding Globulin (U-RBP), U-NGAL
- Urinary system duplex US
- Renal replacement therapy
- Complications / mortality
Study sample

- 90% AKI in enriched Ringer group
- 61% AKI in Custodiol group
- Power = 80%
- $\alpha < 0.05$

- Mortality $\approx 5\%$

45pts per study group
Waiting for the results...

17/01/2017: Pt #90 randomized for CURITIBA trial!

Data analysis

Follow-up
Waiting for the results...

17/01/2017: Pt #90 randomized for CURITIBA trial!

DEMAND EVIDENCE AND THINK CRITICALLY
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