A Prospective, Randomized Trial of Sliding-Scale Hydration for Prevention of Contrast Nephropathy

The POSEIDON (Prevention of Contrast Renal Injury with Different Hydration Strategies) trial

Somjot S. Brar, MD, MPH

on behalf of the POSEIDON investigators
I, Somjot S. Brar DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Contrast Nephropathy

Common complication of contrast exposure associated with increased:

- Morbidity
- Mortality
- Cost

Hallmark of therapy is prevention yet preventive strategies remain limited.
Hydration, with normal saline (0.9% saline), remains the cornerstone of CN prevention, yet important questions remain:

- **Rate** of hydration?
- **Duration** of hydration?
- Uniform rate for everyone or can the rate be optimized to the patients needs?
Study Hypothesis

*Personalized Hydration for Prevention of Contrast Nephropathy*

Does LVEDP guided hydration reduce the incidence of contrast induced acute kidney injury in patients undergoing coronary angiography or PCI?
LVEDP

Left Ventricular End Diastolic Pressure

- Hemodynamic parameter routinely measured in the cardiac cath lab
- Provides insight into volume status
Methods

Investigator Initiated RCT

**Masking:** Single blind

**Study period:** November 2010 to July 2012

**Population:** Patients undergoing coronary angiography or PCI (inpatient & outpatient)

**Location:** High volume tertiary care center in Los Angeles, CA

**Funding:** Kaiser Permanente (KP-RCCL-5718)

**Principal Investigator:** Somjot S. Brar, MD, MPH
Methods

Inclusion Criteria

Estimated GFR < 60 mL/min/1.73 m^2 (by MDRD equation)

And at least one of the following:

- Diabetes mellitus
- Age > 75
- Hypertension (>140/90 or treatment)
- History of CHF
Methods

**Exclusion Criteria**

- Pulmonary edema or acute decompensated heart failure
- Contrast exposure within 48 hours
- Severe valvular heart disease or mechanical aortic valve
- Heart or Kidney transplant status
- Primary PCI
- >15% change in serum creatinine in previous 2 days
Methods

Study Design & Endpoints

Coronary Angiography or PCI
(Age >18 & eGFR < 60)

1:1

LVEDP guided hydration
0.9% saline

Stratification
Diabetes
NAC

Standard hydration
0.9% saline

25% or 0.5 mg/dL increase in serum creatinine
(at least two values measured on days 1-4)

Primary Endpoint

Secondary Endpoint

30-day Major Adverse Event
(Death, MI, and dialysis)
## Methods

**Sliding Scale Hydration Protocol**

<table>
<thead>
<tr>
<th></th>
<th>LVEDP Guided Hydration</th>
<th>Standard Hydration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-procedure</strong></td>
<td>3 mL/kg x 1 hr</td>
<td>3 mL/kg x 1 hr</td>
</tr>
<tr>
<td><strong>During procedure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDP</td>
<td>Rate</td>
<td></td>
</tr>
<tr>
<td>&lt;13</td>
<td>5 mL/kg/hr</td>
<td>1.5 mL/kg/hr</td>
</tr>
<tr>
<td>13-18</td>
<td>3 mL/kg/hr</td>
<td></td>
</tr>
<tr>
<td>&gt;18</td>
<td>1.5 mL/kg/hr</td>
<td></td>
</tr>
<tr>
<td><strong>Post-procedure</strong></td>
<td>Continued x 4hrs</td>
<td>Continued x 4hrs</td>
</tr>
</tbody>
</table>

LVEDP assessed prior to contrast administration
Methods

Additional Protocol Details

- LVEDP measured systematically using a pigtail catheter (prior to contrast administration).
- Ioxilan, a non-ionic, low-osmolar contrast medium used for all procedures.
- Power injector (Acist medical) used for contrast administration and measuring contrast volumes in 1mL increments.
- N-Acetylcysteine use at discretion of referring physician. If started, 2 day course was continued.
Methods

Data Quality & Analysis

- Intention-to-treat analysis
- All events adjudicated (blinded to treatment allocation)
- Independent oversight & auditing
- Sample size: assumed an event rate of 18% in control and 8% in treatment; with an $\alpha$ 0.05 and $\beta$ 0.20; 10% loss to follow-up; => ~390 patients.
Methods

Study Flow

1,594 Eligible (by age & eGFR)

Exclusions:
- Severe valve disease, n=371
- ADHF, n=341
- Change in renal function, n=234
- Transplant status, n=145
- Other exclusions, n=107

396 Randomized

196 LVEDP guided hydration
- 178
- 196

200 Standard hydration
- 172
- 200

Contrast nephropathy analysis (88%)
30-d clinical follow-up (100%)
## Baseline Characteristics

### Demographics

<table>
<thead>
<tr>
<th></th>
<th>LVEDP Guided (n=196)</th>
<th>Control (n=200)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>71 ± 9</td>
<td>72 ± 8</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>36%</td>
<td>41%</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Race / Ethnicity</strong></td>
<td></td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>White</td>
<td>57%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>14%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>9%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>14%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td>30 ± 6</td>
<td>29 ± 6</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>52%</td>
<td>51%</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>98%</td>
<td>98%</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td>11%</td>
<td>10%</td>
<td>0.54</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

### Laboratory Data & Medications

<table>
<thead>
<tr>
<th></th>
<th>LVEDP Guided (n=196)</th>
<th>Control (n=200)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.4 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>0.87</td>
</tr>
<tr>
<td>Estimated GFR</td>
<td>48 ± 9</td>
<td>47 ± 9</td>
<td>0.39</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.7 ± 1.8</td>
<td>12.7 ± 2.1</td>
<td>0.78</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>38%</td>
<td>37%</td>
<td>0.80</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>79%</td>
<td>72%</td>
<td>0.13</td>
</tr>
<tr>
<td>ACE inhibitor / ARB</td>
<td>81%</td>
<td>77%</td>
<td>0.39</td>
</tr>
<tr>
<td>Diuretic, thiazide</td>
<td>20%</td>
<td>19%</td>
<td>0.63</td>
</tr>
<tr>
<td>Diuretic, loop</td>
<td>25%</td>
<td>22%</td>
<td>0.55</td>
</tr>
</tbody>
</table>
## Hemodynamics & Procedural Data

<table>
<thead>
<tr>
<th></th>
<th>LVEDP Guided</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=196)</td>
<td>(n=200)</td>
<td></td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>12 ± 7</td>
<td>12 ± 7</td>
<td>0.36</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>136 ± 20</td>
<td>134 ± 21</td>
<td>0.40</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>69 ± 12</td>
<td>68 ± 13</td>
<td>0.49</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>56 ± 12</td>
<td>57 ± 11</td>
<td>0.60</td>
</tr>
<tr>
<td>Contrast volume, mL</td>
<td>105 (84-188)</td>
<td>111 (79-209)</td>
<td>0.73</td>
</tr>
<tr>
<td>Procedure dur., min</td>
<td>35 ± 23</td>
<td>37 ± 25</td>
<td>0.77</td>
</tr>
<tr>
<td>PCI</td>
<td>24%</td>
<td>32%</td>
<td>0.08</td>
</tr>
<tr>
<td>No. of stents</td>
<td>1.2 ± 0.6</td>
<td>1.3 ± 0.6</td>
<td>0.55</td>
</tr>
<tr>
<td>Acute coronary syn.</td>
<td>39%</td>
<td>45%</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Primary Endpoint

25% or 0.5 mg/dL increase in Serum Creatinine

Event Rate, %

<table>
<thead>
<tr>
<th>LVEDP guided</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.7</td>
<td>16.3</td>
</tr>
</tbody>
</table>

\[ P = 0.005 \]

RR (95% CI):
0.41 (0.22 – 0.79)

RD (95% CI):
-9.5% (-16.3 to -2.9)

NNT = 11
Hydration Volume

\[ P < 0.001 \]

<table>
<thead>
<tr>
<th></th>
<th>LVEDP guided</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum:</td>
<td>3055 mL</td>
<td>1200 mL</td>
</tr>
<tr>
<td>Median:</td>
<td>1711 mL</td>
<td>807 mL</td>
</tr>
<tr>
<td>Minimum:</td>
<td>473 mL</td>
<td>448 mL</td>
</tr>
</tbody>
</table>
Primary Endpoint

Components

- **Primary Endpoint**
- **Event Rate, %**
  - >25% increase: 15.7%
    - Control: 6.7%
    - LVEDP guided: 15.7%
    - \( P = 0.008 \)
  - 0.5 mg/dL increase: 7%
    - Control: 3.4%
    - LVEDP guided: 7%
    - \( P = 0.13 \)
Pre-Specified Subgroups

**Primary Endpoint**

<table>
<thead>
<tr>
<th>SUBGROUP</th>
<th>RR</th>
<th>95% CI</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.54</td>
<td>0.25 – 1.16</td>
<td>0.44</td>
</tr>
<tr>
<td>Male</td>
<td>0.32</td>
<td>0.10 – 0.96</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.12</td>
<td>0.02 – 0.92</td>
<td>0.17</td>
</tr>
<tr>
<td>Yes</td>
<td>0.54</td>
<td>0.54 – 1.07</td>
<td></td>
</tr>
<tr>
<td><strong>N-acetylcysteine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.47</td>
<td>0.21 – 1.05</td>
<td>0.64</td>
</tr>
<tr>
<td>Yes</td>
<td>0.34</td>
<td>0.11 – 0.99</td>
<td></td>
</tr>
<tr>
<td><strong>Contrast volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100 mL</td>
<td>0.64</td>
<td>0.26 – 1.58</td>
<td>0.74</td>
</tr>
<tr>
<td>≥ 100 mL</td>
<td>0.54</td>
<td>0.27 – 1.06</td>
<td></td>
</tr>
</tbody>
</table>

Favors LVEDP Guided            Favors Control
30-day MAE

Composite of Death, MI, & Dialysis

- MAE: LVEDP guided = 1.0, Control = 4.0
  - P = 0.11

- Death: LVEDP guided = 0, Control = 1.5
  - P = 0.25

- MI: LVEDP guided = 0.5, Control = 2.0
  - P = 0.37

- Dialysis: LVEDP guided = 0.5, Control = 1.5
  - P = 0.62
30-day MAE by Contrast Nephropathy (CN) status

- MAE: 15.0% (No CN), 15.0% (CN), *P<0.001*
- Death: 0.3% (No CN), 5.0% (CN), *P=0.04*
- MI: 1% (No CN), 5.0% (CN), *P=0.10*
- Dialysis: 0% (No CN), 10.0% (CN), *P<0.001*
Safety

IV hydration terminated in 6 patients or 1.5% of the full study cohort (3 patients in each group).

LVEDP values:

<table>
<thead>
<tr>
<th>LVEDP guided</th>
<th>3, 7, 26 mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>3, 23, 31 mmHg</td>
</tr>
</tbody>
</table>

Reason for termination:

• Shortness of breath
• 2 patients treated with diuretics (1 LVEDP guided; 1 control group)
Conclusions

*Sliding Scale Hydration*

- This is the first trial to test the hypothesis of a LVEDP guided hydration strategy for prevention of contrast nephropathy.

- LVEDP guided hydration resulted in a significant **59% relative** and **10% absolute reduction** in contrast nephropathy (p=0.005).

- In subgroup analyses, the treatment effect was consistently in favor of LVEDP guided hydration.
Conclusions

Sliding Scale Hydration

- Easily implemented protocol that can be readily adopted in the outpatient and inpatient settings.
- Personalized strategy of sliding scale hydration guided by the LVEDP was safe. IV hydration was terminated in 1.5% of subjects.
- Reaffirm, contrast nephropathy, as defined, is associated with a significant increase in MAE (p<0.001), including mortality (p=0.04) and dialysis (p<0.001) after cardiac catheterization.
Acknowledgements

POSEIDON team

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