Colchicine for Post-operative Pericardial Effusion: The Post-Operative Pericardial Effusion (POPE-2) Study.

A Multicenter, Double-blind, Randomized Trial

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Disclosures

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Background and Objectives
Post-Operative Pericardial Diseases

✓ Before post-op day 7: Phase 1
- Post-operative pericardial effusion (POPE): 50-80% patients
  • Early tamponades: haemopericardium: 0.5 to 1% of the patients

✓ After post-op day 7: Phase 2
- Post pericardiotomy syndrom (PPS): COPPS-1\(^1\) and 2 studies
- Persisting moderate to large POPE: POPE-1\(^2\) and 2 studies

Post Operative Pericardial Diseases after day 7: PPS and POPES are very different

Symptoms:

- **PPS**: yes
- **POPES**: no

Effusions:

- **PPS**: no or small
- **POPES**: yes, large

To sum-up:

- **PPS**: acute *Pericarditis*, but low Tamponade Risk
- **POPES**: *Effusion* initially asymptomatic, but high Tamponade Risk

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Treatment of POPEs

✓ Non Steroidal Anti Inflammatory Drugs (NSAIDs) are useless¹

✓ What about colchicine?
- Very efficient to treat acute pericarditis²
  • (Add-on NSAID or aspirin)
- Efficient to prevent Post Pericardiotomy Syndrome³
- Efficient to treat post operative pericardial effusions?

POPE\textsuperscript{-2} Study: Methods
Objective: to assess whether colchicine was effective in reducing post operative pericardial effusion (POPE) volume.

Design: multicenter, randomized, double-blind, placebo-controlled study

Setting: Ten post operative cardiac rehabilitation centers (POCRC).

Patients: 197 patients at high risk of tamponade

Treatment administration: 14 days (colchicine or placebo)
- Pts ≥ 70kg: 2.0 mg for the first day followed by a maintenance dose of 1 mg daily
- Pts <70 kg 1 mg per day without a loading dose
### Methods (2)

Quantification of POPEs: echocardiographic classification 1,2

<table>
<thead>
<tr>
<th>Grade at Day 15 (8-29)</th>
<th>Loculated</th>
<th>Circumferential</th>
<th>Estimated Late Tamponade Risk at Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1- Small &lt; 10 mm</td>
<td>&lt; 10 mm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-Moderate 10-14 mm</td>
<td>&lt; 10 mm</td>
<td>2-7%</td>
<td></td>
</tr>
<tr>
<td>3-Medium 15-19 mm</td>
<td>10-14 mm</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>4-Large 20 mm ≥ 15 mm</td>
<td>≥ 15 mm</td>
<td>25-45%</td>
<td></td>
</tr>
</tbody>
</table>

≈ 10%

Inclusion criteria:
- Persistent pericardial effusion ≥ grade 2 on the echocardiography performed at admission in POCRC (8 to 30 days after surgery)

Exclusion criteria:
- Colchicine contra-indication (allergy, pregnancy, renal failure, …)
- Cardiac transplantation or correction of congenital heart anomalies
Methods (4)
Quantification of POPEs Volume

Main endpoint:
Mean (echographic) Pericardial Effusion Grade (MPEG) evolution in the 2 groups (colchicine and placebo)

Example:
Determination of the Mean Pericardial Effusion Grade of a group of patients:
(Fictional) Group: 3 patients
Patient n°1: Grade 2 POPE
Patient n°2: Grade 3 POPE
Patient n°3: Grade 4 POPE

Mean Pericardial Effusion Grade of this fictional Group = \( \frac{2+3+4}{3} = 3 \)
Methods (5)

Spontaneous evolution of the Mean pericardial Effusion Grade: Data from a previous study

Follow up of POPEs in 1277 consecutive patients


\[
\text{Day 15 grade: } 2.54 \pm 0.73 \\
\text{Day 30 grade: } 1.90 \pm 0.60
\]

\[\downarrow \text{MPEG=0.6 } \pm 0.6 \text{ grades}\]
Methods (6):
Statistical Power

- Mean pericardial effusion grade (MPEG) decrease
  - Between the inclusion and the final echocardiographies
  - Expected to be of 0.6 grades in the placebo group

- Sample size assessment: 86 patients per group
  - 80% power to detect a supplementary reduction of 50% of the MPEG with colchicine (versus placebo)
  - Two-sided type 1 error of 5%
Results
From April 2011 to March 2013

Total patients: 8140

Echocardiography at admission (16 ± 6 days after surgery)

252 Grade ≥ 2

7888 Grade 0 or 1: STOP

197 pts randomized

Colchicine: N = 98
Placebo: N = 99

Excluded (n=55)
- Refused consent (n=18)
- Indication for immediate pericardial drainage (n=12)
- Colchicine contraindication (n=3)
- Long-term colchicine treatment (n=3)
- Investigator decision (n=18)
- Participation in another study (n=1)

ITT: n = 197
(Per Protocol: n = 182)

Treatment duration: 14 days
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n = 99)</th>
<th>Colchicine Group (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Age (SD), years</strong></td>
<td>65±10.</td>
<td>64±12</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>88 (89%)</td>
<td>82 (84%)</td>
</tr>
<tr>
<td><strong>Surgery performed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CABG</td>
<td>52%</td>
<td>59%</td>
</tr>
<tr>
<td>- Ao Valve Replacement</td>
<td>48%</td>
<td>35%</td>
</tr>
<tr>
<td>- Mitral Valve Surgery</td>
<td>39%</td>
<td>27%</td>
</tr>
<tr>
<td>- Root Aorta Surgery</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Delay surgery-inclusion</strong></td>
<td>16 ±5</td>
<td>16±5</td>
</tr>
<tr>
<td><strong>Oral anticoagulants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- INR at inclusion (SD)</td>
<td>51 % 2.4 ± 0,7</td>
<td>53 % 2.4 ± 0,79</td>
</tr>
<tr>
<td><strong>POPE mean grade: MPEG</strong></td>
<td>2.9 ± 0.8</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>Grade 2</td>
<td>35%</td>
<td>27%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>36%</td>
<td>43%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>28%</td>
<td>28%</td>
</tr>
</tbody>
</table>
**Primary Endpoint:** Mean Pericardial Effusion Grade Decrease

<table>
<thead>
<tr>
<th>Grade</th>
<th>Placebo</th>
<th>Colchicine</th>
<th>Mean (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>2.9±0.8</td>
<td>3.0±0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>1.8±1.3</td>
<td>1.7±1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>-1.1±1.3</td>
<td>-1.3±1.3</td>
<td>-0.19 (-0.55 to 0.16)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Difference between groups: -0.19 (-0.55 to 0.16)
Secondary Endpoints

Tamponades after 14 days treatment:
N = 13 (6.6%)

Pericardial drainages within 6 months
N = 22 (11.2%)

<table>
<thead>
<tr>
<th>患者至少1级下降</th>
<th>Placebo Group (n = 99)</th>
<th>Colchicine Group (n = 98)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>67%</td>
<td>74%</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>-4.7 ± 6.9</td>
<td>-5.8 ± 6.1</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>12%</td>
<td>15%</td>
<td>0.51</td>
<td></td>
</tr>
</tbody>
</table>
## Prespecified Sub-Groups Analysis

<table>
<thead>
<tr>
<th>MPEG decrease (grades) in Patients</th>
<th>Placebo Group (n=99)</th>
<th>Colchicine Group (n=98)</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>With CRP level ≥ 30mg/l (n=82)</td>
<td>-1.3±1.4</td>
<td>-1.4±1.4</td>
<td>-0.11 (-0.72 to 0.49)</td>
<td>0.81</td>
</tr>
<tr>
<td>Receiving an oral anticoagulant (n=102)</td>
<td>-0.9±1.3</td>
<td>-1.4±1.2</td>
<td>-0.48 (-0.99 to 0.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>Per Protocol Analysis (n=182)</td>
<td>-1.1±1.3</td>
<td>-1.3±1.3</td>
<td>0.18 (-0.56 to 0.20)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Conclusion:
Moderate to large persisting (> 7 days) post operative pericardial effusion:
What does this study add?

1- High risk patients: 11.5% reoperation within 6 months:
   - 6.6% tamponades in the 2 following weeks
   - Another 5% will require pericardial drainage within 6 months

2- Colchicine administration seems to be useless

[PS: NSAID administration seems to be useless (POPE-1]
Thanks to

☑ POPE study investigators:

- **Hopital Corentin Celton:** MC Iliou, P Cristofini, Devaux N, Sissman J.
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- **Clinique de la Mitterie:** J De Monte, JP Beuvin, C Defrance, ME Lopes.
- **Centre Dieuleufit santé:** L Briota, R Brion, S Devaud, C Kugler-Chambron, R Auberger.
- **La Maison du Mineur:** A Bellemain-appaix, H Chevassus-Lescaut.
- **Clinique de châtillon:** JL Bussiere.

Patients
High power of the study to assess Colchicine effectiveness
- Theoretical sample size: 172
  • Included: 197

Study underpowered to test colchicine safety:
- 13 patients did not complete the study
  • 10 in the colchicine group:
    ✓ Diarrhea (n = 7), constipation (n = 1), digestive haemorrhage (n = 1), leucopenia (n = 1)
  • 3 in the placebo group
    ✓ Stroke (n = 1), constipation (n = 1), consentment withdrawal (n = 1)