Colchicine for Post-operative Pericardial Diseases


Les Grands Prés
Conflict of Interest related to this presentation: None

- Colchicine pills, 1 mg, and matching placebo were manufactured by Laboratoires Sanofi Paris France and provided by Laboratoires Mayoly-Spindler, marketing authorization holder of the drug in France.

- The study funders (French Society of Cardiology and French federation of Cardiology) had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.
Post-Operative Pericardial Diseases

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

✓ After post-op day 7: Phase 2
  - Post pericardiotomy syndrom (PPS): COPPS-1¹ and 2 studies
  - Persisting moderate to large POPE: POPE-1² and 2 studies

What is a POPE?

It is a banal Post Operative Pericardial Effusion

By definition, a POPE is asymptomatic (otherwise it is a tamponade)

What is a Post Pericardiotomy syndrom (PPS)?

It is a pericarditis

- **Pericardial « Post injury syndrom » family:**
  - Initial pericardial injury followed by a pericarditis 1 to 6 weeks later
    - auto-immune mechanism¹
      - antibodies anti-heart, anti-pericardium....
  - Another well known post injury syndrom: Dressler syndrome after myocardial infarction

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What is a PPS?: a nosologic problem

1°) Wrong definition:

At least 2 of the following criteria:

- Fever
- Pericardic or Pleuritic Chest Pain
- Pericardial or pleural Rub
- New or Worsening Pleural Effusion
- New or Worsening Pericardial Effusion

According to this wrong definition, 30% of the patients would « suffer » from a PPS!

2°) Clinical PPS = Pericarditis

- After post-op day 7
- Fever 37°8
- Chest Pain
- pericardial rub or effusion

1-2% of the patients suffer from a real PPS

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

**Symptoms:**
- (real) PPS: yes  □
- POPES ≈ no

**Effusions:**
- PPS ≈ no or small  □
- POPES: yes, large

(2) Imazio et al. COPPS-1 Study. Eur Heart J 2010.
(3) Imazio et al. Am J Cardiol. 2011

POPES = High Tamponade Risk
The COPPS-2 study: a Trial of Prevention

Colchicine for prevention of post-pericardiotomy syndrome and post-operative atrial fibrillation: the COPPS-2 randomized clinical trial.

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COPPS-2 Design

Figure 1. Screening, Enrollment, Randomization, and Follow-up of Study Participants in the COPPS-2 Trial

758 Patients undergoing cardiac surgery assessed for eligibility

398 Excluded
143 Urgent cardiac surgery
108 Atrial fibrillation
86 Declined to participate
61 Other reasons

360 Randomized

180 Randomized to receive placebo
180 Received allocated intervention
32 Discontinued study
180 Included in primary analysis

180 Randomized to receive colchicine
180 Received allocated intervention
39 Discontinued study
180 Included in primary analysis

Placebo/Colchicine 0.5mg BID or 0.5mg once daily (<70kg) till 1 months after surgery

PPS within 3 months
COPPS-2 Results: Clear « PPS » incidence reduction with colchicine
But what for? Is it clinically meaningful?

No: it is not clinically meaningful: « The overall prognosis of PPS in the trial was good; therefore its preoperative prevention maybe unnecessary given the rate of adverse effects of colchicine ».

It is useless to prevent or to treat a « syndrom » which has neither symptoms nor complication
Colchicine for Post-operative Pericardial Effusion: The Post-Operative Pericardial Effusion (POPE-2) Study.
A Multicenter, Double-blind, Randomized Trial

POPE-2 Study: Is colchicine effective in treating POPES and in preventing cardiac tamponade?
## Methods (1)

### 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</td>
<td>&lt; 10 mm</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-Moderate</td>
<td>10-14 mm</td>
<td>&lt; 10 mm</td>
<td>2-7%</td>
</tr>
<tr>
<td>3-Medium</td>
<td>15-19 mm</td>
<td>10-14 mm</td>
<td>15%</td>
</tr>
<tr>
<td>4-Large</td>
<td>≥ 20 mm</td>
<td>≥ 15 mm</td>
<td>25-45%</td>
</tr>
</tbody>
</table>

Methods (2)

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 A: 3 patients
- Patient n°1: Grade 2
- Patient n°2: Grade 3
- Patient n°3: Grade 4

Mean Pericardial Effusion Grade of this fictional Group:
- \( \frac{(2+3+4)}{3} = 3 \)
Results
From April 2011 to March 2013

Echocardiography at admission (16 ± 6 days after surgery)

252 Grade ≥ 2

7888 Grade 0 or 1: STOP

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)

197 pts randomized

197 pts randomized

Colchicine
N = 98

Placebo
N = 99

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

Treatment duration: 14 days
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group</th>
<th>Colchicine Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n = 99</strong></td>
<td></td>
<td><strong>n = 98</strong></td>
</tr>
<tr>
<td><strong>POPE mean grade: MPEG</strong></td>
<td><strong>2.9±0.8</strong></td>
<td><strong>3.0±0.8</strong></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 and Subgroups

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

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n = 99)</th>
<th>Colchicine Group (n = 98)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation at the end of the study</td>
<td>12%</td>
<td>15%</td>
<td>0.51</td>
</tr>
<tr>
<td>MPEG decrease in Patients With CRP level &gt; 30mg/l (n=82)</td>
<td>-1.3±1.4</td>
<td>-1.4±1.4</td>
<td>0.81</td>
</tr>
</tbody>
</table>
Conclusion (1)

1°) moderate to large persisting (> 7 days) POPE: banal but dangerous effusion
   - High risk of tamponade
   - Colchicine administration is useless (POPE-2 study)
   [PS: NSAID administration seems to be useless (POPE-1 study)]

2°) PPS: post-op auto-immune pericarditis
    very rare but benign disease
    - “Syndrom” Overdiagnosed in studies,
    - Real PPS: post op acute pericarditis (≈ post MI dressler syndrome)
      - rare
      - the association aspirin + colchicine is effective
## Take Home Message

<table>
<thead>
<tr>
<th></th>
<th>incidence</th>
<th>treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pericardial Effusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-op pericardial effusion: POPE(^1,2)</td>
<td>40-60% post op</td>
<td>No drug&lt;br&gt; Echo twice a week</td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>Acute Pericarditis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute viral Pericarditis(^3)</td>
<td>1-2% post op</td>
<td>Aspirine : 1 month&lt;br&gt;-3g/day 10 days&lt;br&gt;-2 g/day 10 days&lt;br&gt;- 1g/day 10days +&lt;br&gt;Colchicine : 3 months&lt;br&gt;- 0,5 to 1mg/day</td>
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</tr>
</tbody>
</table>

Thanks to

✓ **POPE study investigators:**

- **Hopital Corentin Celton:** **MC Iliou.** P Cristofini, Devaux N, Sissman J.
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- **Clinique des Fauvettes:** **JL Bussiere.**

✓ **Patients**