A Randomized Trial of Rectal Indomethacin and Sublingual Nitrates to Prevent Post-ERCP Pancreatitis

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ERCP is a frequently lifesaving tool in selected cases.

A feared complication is post-ERCP pancreatitis (PEP).

There are a few methods which might prevent or reduce the severity of PEP.
High-Risk Groups

- SOD
- Precut
- PD cannulation
- Balloon dilatation of the ampulla
- Two of the following:
  - Female sex
  - Age<60 years
  - Non-dilated CBD
  - Normal serum bilirubin
  - Pancreatic duct injection
  - Difficult cannulation
  - Incomplete stone extraction
NSAIDs

- Rectal NSAIDs (diclofenac or indomethacin) are among the few agents shown to be effective in preventing PEP
- Routine rectal administration of 100mg of diclofenac or indomethacin, immediately before or after ERCP is recommended
Nitrates

- A few researchers have suggested the possible beneficial effect of nitrates in preventing PEP
  - Maybe through relaxing the sphincter of Oddi or causing vasodilation and thus better blood flow
Aim

- To evaluate the efficiency of adding sublingual nitrate to rectally administered indomethacin for the prevention of PEP.
Ethics

- The study was approved by the IRB and ethics committee of the Digestive Disease Research Center of Tehran University of Medical Sciences.
- All subjects signed the consent form.
Design

- Two arms:
  - Indomethacin 100 mg rectal suppository + isosorbide dinitrate 5 mg sublingual (study group)
  - Indomethacin 100 mg rectal suppository + placebo sublingual (control group)
- Randomized
  - Blocked (blocks of two)
- Double blind (sealed envelopes)
Sample Size

- Originally planned to include 750 subjects
- To detect a reduction in PEP of 5%  
  - Significance level of 5%
  - Power of 80%
Inclusion Criteria

- Age above 18
- Consenting to the study
Exclusion Criteria

- Recent acute pancreatitis (one month)
- Recent upper GI bleeding (two weeks)
- Chronic pancreatitis
- Glaucoma
- Ampulla of Vater tumor
- Active proctitis with rectal bleeding
- Previous sphincterotomy
- Known allergy to study medications
Outcomes

- **Primary:**
  - Frequency of PEP

- **Secondary**
  - Adverse events
  - Ease of CBD cannulation
  - Severity of PEP
Definition of PEP

- Abdominal pain
- Elevated amylase level above 3 times of ULN
  - Amylase level checked 2 and 24 hours after the procedure
- Within 24 hours after ERCP.
Ease of CBD Cannulation

- Fluoroscopy time
- Time to CBD cannulation
- Requiring papillotomy
- Number of attempts
- Number of PD cannulations
- Failed cannulation
Severity of PEP

- **Mild:**
  - Requiring admission or prolongation of planned admission for 2–3 days

- **Moderate:**
  - Hospitalization for 4–10 days

- **Severe:**
  - Hospitalization for more than 10 days or
  - Hemorrhagic pancreatitis or
  - Pseudocyst or
  - Requiring intervention
Interim Analysis

- Four points for analysis were planned at 150, 300, 500, and 750 subjects.
- During the second analysis at 300 patients a significant benefit was observed towards the study group.
- The Pocock boundary was 0.0182, the p value at 300 subjects was 0.016.
- The ethics committee recommended early termination of the study.
Results

- 572 subjects evaluated for eligibility
- 272 excluded:
  - Previous sphincterotomy: 185 (88%)
  - Not consenting: 56 (21%)
  - Recent pancreatitis: 16 (6%)
  - Tumor of ampulla: 10 (4%)
  - Other: 5 (2%)
Results

- A total of 300 patients entered the trial, 150 in each group
- 242 (80.7%) were high-risk for PEP
  - Mean number of risk factors: 2.9
- PEP observed in 33 patients (11%)
Results, Primary Outcome

- 33 patients developed PEP
  - Study group: 10 cases (6.7%)
  - Control group: 23 cases (15.3%)
- p value: 0.016
- NNT: 12
Patient Flow

- Evaluated for inclusion: n=572
- Excluded patients: n=272
- Eligible patients underwent ERCP: N=300

Group A: n=150
- Pancreatitis: n=10
- No pancreatitis: n=140

Group B: n=150
- Pancreatitis: n=23
- No pancreatitis: n=127
Results, Secondary Outcomes

- No adverse events in either group
- No difference in ease of cannulation
- Among subjects with PEP
  - No difference in severity of pancreatitis
  - No difference in hospital stay
- Among all subjects
  - Significantly less hospital stay in the study group (1.2 days vs. 1.8, p: 0.016)
Amylase levels

- 2 hours after the procedure
  - Study: 97 IU/L, Control: 130 IU/L
  - P: 0.39

- 24 hours after the procedure
  - Study: 108 IU/L, Control: 130 IU/L
  - P: 0.83
## Results

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>74 (49.3)</td>
<td>80 (53.3)</td>
<td>0.49</td>
</tr>
<tr>
<td>Age</td>
<td>58.4 ± 17.8</td>
<td>58.6 ± 17.5</td>
<td>0.92</td>
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<tr>
<td>Incomplete stone extraction</td>
<td>16 (11.1)</td>
<td>18 (12.9)</td>
<td>0.63</td>
</tr>
<tr>
<td>Balloon dilation</td>
<td>38 (26.0)</td>
<td>41 (29.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Number of attempts</td>
<td>4.5 ± 3.8</td>
<td>4.1 ± 3.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Precut required</td>
<td>63 (43.4)</td>
<td>49(35.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Peri-ampullary diverticuli</td>
<td>18 (12.0)</td>
<td>25 (16.7)</td>
<td>0.19</td>
</tr>
<tr>
<td>Failed cannulation</td>
<td>28 (18.7)</td>
<td>26 (17.3)</td>
<td>0.80</td>
</tr>
<tr>
<td>PD cannulation</td>
<td>50 (33.3)</td>
<td>60 (40.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>PD dye injection</td>
<td>35 (23.3)</td>
<td>38 (25.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>Final diagnosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>4 (2.7)</td>
<td>0 (0.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>CBD stone</td>
<td>101 (67.3)</td>
<td>101 (67.3)</td>
<td></td>
</tr>
<tr>
<td>SOD</td>
<td>4 (2.7)</td>
<td>4 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Biliopancreatic tumors</td>
<td>27 (18.0)</td>
<td>23 (15.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14 (9.3)</td>
<td>22(14.7)</td>
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Conclusion

- The addition of sublingual nitrate to rectal indomethacin given before ERCP further reduces the incidence of PEP
Researchers

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