Sphincter of Oddi Dysfunction Type III, Manometry and Sphincterotomy: Sham Won, Game Over

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Ruggero Ferdinando Antonio Guiseppe Vincenzo Oddi

Arch Ital Biol 1887
History

- Sphincter of Oddi described 120 years ago
- 1980 Geenen performed sphincter mano confirming a physiologic zone
- SOM manometric dyskinesia identified (tachyodia), but later felt not causative
- Three types of SOD
- Post-chole pain ≈ 30%; SOD often attributed

Gastroenterology 1980; Gastroenterology 1985

Geenen et al Gastroenterology 1980
**Problems with the Problem**

- Few normals studied to establish norms
- Retrospective outcome studies
- 2 controlled, blinded studies (Type II)
- Major conflict of interest
- Open access sphincterotomy is a business

**How did we get in this mess?**

- Sold the entity by people who are respected
- Appears to be a science ie you can measure it
- Other tests (scintigraphy) compared to mano for predicting disease and outcome of sphincterotomy
- Desire to help chronic pain patient--desperation
- Poor understanding of the entity in primary care
- SOM became “standard of care” for any pain below the diaphragm
The Vagaries of Manometry

- Catheter position, use of wire increase pressure
- Medications

- Of 5352 patients → 80% positive

repeat mano in 30 patients

60% positive

So extrapolating to entire cohort -> 93% may be positive!

Endoscopy 2010

This is nuts!

Postcholecystectomy Pain Syndrome: Pathophysiology of Abdominal Pain in Sphincter of Oddi Type III

**Figure 1.** (A) Duodenal pain perception in patients with type III SOD [●] and control subjects [□]. Values expressed as mean ± SEM. (B) Duodenal compliance in patients with type II SOD [●] and control subjects [□]. Values expressed as mean ± SEM.

Gastroenterology 1999
It’s the Sphincter Stupid

Long-term outcome of endoscopic dual pancreatobiliary sphincterotomy in patients with manometry-documented sphincter of Oddi dysfunction and normal pancreatogram

Sang-Heum Park, MD, James L. Watkins, MD, Evan L. Fogle, MD, Stuart Sherman, MD, Laura Lazzell, RN, Lois Buckso, RN, Glen A. Lehman, MD

*Indianapolis, Indiana*

- Combined types I and II sphincter of Oddi dysfunction ($p = 0.105$). When compared with endoscopic biliary sphincterotomy alone in historical control patients from our unit, endoscopic dual pancreatobiliary sphincterotomy had a lower reinervention rate in patients with pancreatic sphincter of Oddi dysfunction alone and a comparable outcome in those with sphincter of Oddi dysfunction of both ducts.
- Conclusion: Endoscopic dual pancreatobiliary sphincterotomy is useful in patients with pancreatic sphincter of Oddi dysfunction. Prospective randomized trials of endoscopic biliary sphincterotomy alone versus endoscopic dual pancreatobiliary sphincterotomy based on sphincter of Oddi manometry findings are in progress. (Gastrointest Endosc 2005;57:489-91)

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E. Diagnostic Criteria for Functional GB and SO Disorders

- Must include episodes of pain located in the epigastrum and/or right upper quadrant and all of the following:
- 1. Episodes lasting 30 minutes or longer
- 2. Recurrent symptoms occurring at different intervals (not daily)
- 3. The pain builds up to a steady level
- 4. The pain is moderate to severe enough to interrupt the patient’s daily activities or lead to an emergency department visit
- 5. The pain is not relieved by bowel movements
- 6. The pain is not relieved by postural change
- 7. The pain is not relieved by antacids
- 8. Exclusion of other structural disease that would explain the symptoms

**Supportive criteria**

- The pain may present with 1 or more of the following:
- 1. Pain is associated with nausea and vomiting
- 2. Pain radiates to the back and/or right infraspinacular region
- 3. Pain awakens from sleep in the middle of the night
Functional Abdominal Pain

D. Diagnostic Criteria* for Functional Abdominal Pain Syndrome

Must include all of the following:
1. Continuous or nearly continuous abdominal pain
2. No or only occasional relationship of pain with physiological events (eg, eating, defecation, or menses)
3. Some loss of daily functioning
4. The pain is not feigned (eg, malingering)
5. Insufficient symptoms to meet criteria for another functional gastrointestinal disorder that would explain the pain

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

Table 2. Symptom-Related Behaviors Often Seen in Patients With FAPS

<table>
<thead>
<tr>
<th>Behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expressing pain of varying intensity through verbal and nonverbal methods, may diminish when the patient is engaged in distracting activities, but increase when discussing a psychologically distressing issue or during examination</td>
</tr>
<tr>
<td>Urgent reporting of intense symptoms disproportionate to available clinical and laboratory data (eg, always rating the pain as “10” on a scale from 1 to 10)</td>
</tr>
<tr>
<td>Minimizing or denying a role for psychosocial contributors, or of evident anxiety or depression, or attributing them to the presence of the pain rather than to understandable life circumstances</td>
</tr>
<tr>
<td>Requesting diagnostic studies or even exploratory surgery to validate the condition as “organic”</td>
</tr>
<tr>
<td>Focusing attention on complete relief of symptoms rather than adaptation to a chronic disorder</td>
</tr>
<tr>
<td>Seeking health care frequently</td>
</tr>
<tr>
<td>Taking limited personal responsibility for self-management, while placing high expectations on the physician to achieve symptom relief</td>
</tr>
<tr>
<td>Making requests for narcotic analgesics when other treatment options have been implemented</td>
</tr>
</tbody>
</table>

Gastroenterology 2006
If it’s only the sphincter, why does cutting not cure?

Figure 1. Patients with SOD and sphincterotomy. Average pain scores.
Before Sphincterotomy  After Sphincterotomy

Figure 2. Patients with sphincterotomy. Berthelot score (in - 19).
Before Sphincterotomy  After Sphincterotomy

Am J Gastroenterol 2003

Can patient and pain characteristics predict manometric sphincter of Oddi dysfunction in patients with clinically suspected sphincter of Oddi dysfunction?

Results: The cohort was 92% female with a mean age of 38 years. Baseline pancreatic enzymes were increased in 5%; 9% had minor liver enzyme abnormalities. Pain was in the right upper quadrant (RUQ) in 90% (48% also epigastric); 51% reported daily abdominal discomfort. Fifty-six took narcotics an average of 33 days (of the past 90 days). Less than 10% experienced depression or anxiety. Functional disorders were common. At ERCP, 64% had abnormal pSOM findings (34% both sphincters, 21% biliary normal), 36% had normal pSOM findings, and 75% had at least abnormal 1 sphincter. Demographic factors, gallbladder pathology, increased pancreatobiliary enzymes, functional disorders, and pain patterns did not predict abnormal SOM findings. Anxiety, depression, and poorer coping were more common in patients with normal SOM findings (not significant on multivariate analysis).

Conclusions: Patient and pain factors and psychological comorbidity do not predict SOM results at ERCP in suspected type III SOD. (Clinical Trial registration number: NCT00681682.) (Gastrointest Endosc 2014;79:765-72.)

GIE 2014
Outcomes of Single Center Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>P,R</th>
<th>% improved (positive outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>46</td>
<td>R</td>
<td>31/46</td>
</tr>
<tr>
<td>1988</td>
<td>40</td>
<td>R</td>
<td>63</td>
</tr>
<tr>
<td>1994</td>
<td>73</td>
<td>R</td>
<td>60 (type II); 8 (type III)</td>
</tr>
<tr>
<td>1996</td>
<td>64</td>
<td>R</td>
<td>70 (type II); 39 (type III)</td>
</tr>
<tr>
<td>2011</td>
<td>72</td>
<td>R</td>
<td>75 (type II); 50 (type III)</td>
</tr>
</tbody>
</table>

RCT’s

- Rome type 3
- Concealed assignment
- Blinded f/u
- Type I, (N%)
- Type II, N (%)
- Type III, N (%)
- Sham EBS
- Mano Directed
- Response
  - + mano (EBS vs S),% 91, 25
  - - mano (EBS vs S),% 33,42

Geenen ('89) | Toouli (2000)
- | -
? | +
yes | yes
0 | 0
47 (100) | 81 (100)
0 | 0
yes | yes
no | yes
91, 25 | 85, 38
33,42 | 62,42
Table 1. Patients' Symptom Scores after Endoscopic Sphincterotomy (ES) or Sham Endoscopic Sphincterotomy at One-Year Follow-up.

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Type of Treatment</th>
<th>Symptom Scores*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Good</td>
</tr>
<tr>
<td>23</td>
<td>ES</td>
<td>10</td>
</tr>
<tr>
<td>24</td>
<td>Sham ES</td>
<td>4</td>
</tr>
</tbody>
</table>

*Symptom scores after one year, based on a comparison with the score of "poor" for all patients at the time of study entry.

65% good or fair vs 39%)

P<0.001

Geenen et al NEJM 1989

Figure 3. Symptom Score (Graded Good, Fair, or Poor) at Four-Year Follow-up after Endoscopic Sphincterotomy (ES) or the Sham Procedure, in Relation to Normal Basal Sphincter-of-Oddi (SO) Pressure (<40 mm Hg) as Compared with Elevated Basal Sphincter-of-Oddi Pressure (>40 mm Hg).

Table 2. Assessment of pain at 24 months in patients treated with either endoscopic sphincterotomy (ES) or a sham procedure.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
<th>Improved</th>
<th>No change</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>13</td>
<td>5</td>
<td>8</td>
<td>0.041</td>
</tr>
<tr>
<td>ES</td>
<td>13</td>
<td>11</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>SO dyskinesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>0.670</td>
</tr>
<tr>
<td>ES</td>
<td>11</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Normal manometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham</td>
<td>19</td>
<td>8</td>
<td>11</td>
<td>0.473</td>
</tr>
<tr>
<td>ES</td>
<td>13</td>
<td>8</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Patients with resolution of their pain are included in the improved group. SO, sphincter of Oddi.

Toouli et al Gut 2000
EPISOD TRIAL

EPISOD timeline

- Jan 2002 NIH ERCP conference
- Jan 2002 Internal discussion MUSC
- Sep 2004 Planning grant approved
- Sep 2007 Grant funded
- Mar 2008 First subject enrolled at MUSC
- Mar 2012 Last subject enrolled at St Louis
- Apr 2013 DSMB preliminary results
Baseline characteristics

- 92% female, mean age 38
- Less distressed than expected
  - 9% anxiety, 7.5% depression, 17% trauma
- 85% had an FGID, 34% had IBS
- 26% had taken narcotics for abdominal pain in prior month
- 38% on anti-depressants
Pain Reduced in Both Groups

Success of Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Success N (%)</th>
<th>95% CI for Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>73</td>
<td>27 (37%)</td>
<td>(21.6, 33.6)</td>
</tr>
<tr>
<td>Sphincterotomy</td>
<td>141</td>
<td>32 (23%)</td>
<td>(15.8, 29.6)</td>
</tr>
<tr>
<td>Biliary</td>
<td>94</td>
<td>18 (19%)</td>
<td>(11.2, 27.1)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>47</td>
<td>14 (30%)</td>
<td>(16.7, 42.9)</td>
</tr>
</tbody>
</table>
Success Based Upon Mano and Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Biliary manometry</th>
<th>Pancreatic manometry</th>
<th>N</th>
<th>Success</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>positive</td>
<td>negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary and pancreatic Sphincterotomy</td>
<td>x</td>
<td>x</td>
<td>27</td>
<td>9 (33%)</td>
</tr>
<tr>
<td></td>
<td>x</td>
<td>x</td>
<td>17</td>
<td>4 (23%)</td>
</tr>
<tr>
<td>Biliary Sphincterotomy</td>
<td>x</td>
<td>x</td>
<td>25</td>
<td>5 (20%)</td>
</tr>
<tr>
<td></td>
<td>x</td>
<td>x</td>
<td>14</td>
<td>3 (21%)</td>
</tr>
<tr>
<td></td>
<td>x</td>
<td>x</td>
<td>25</td>
<td>5 (20%)</td>
</tr>
<tr>
<td></td>
<td>x</td>
<td>x</td>
<td>30</td>
<td>5 (17%)</td>
</tr>
</tbody>
</table>

Complications

The ERCP procedures at randomization caused pancreatitis in 26 subjects, 10.6% in the sphincterotomy arm and 15.1% in the sham arm (Unadjusted Relative Risk: 0.71, 95% CI, 0.34–1.46). Two of the events were defined as severe, 10 moderate and 14 mild. Two subjects suffered retro-duodenal perforations at ERCP, one of which required surgical treatment. There were no procedure-related episodes of bleeding or infection, and no deaths.
Reasons for failure

- Rapid score
- Re-intervene
- Narcotics
**Studies Evaluating ERCP in Recurrent Idiopathic Pancreatitis**

<table>
<thead>
<tr>
<th>Reference/Year</th>
<th>N</th>
<th>SOD</th>
<th>Divisum</th>
<th>CBDS</th>
<th>Overall Yield (%)</th>
<th>Follow-up, mos Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>62, 1978</td>
<td>25</td>
<td>ND</td>
<td>0</td>
<td>8</td>
<td>60</td>
<td>19 (3-42)</td>
</tr>
<tr>
<td>63, 1981</td>
<td>35</td>
<td>ND</td>
<td>23</td>
<td>3</td>
<td>46</td>
<td>(6-36yrs)</td>
</tr>
<tr>
<td>10, 1982</td>
<td>11</td>
<td>ND</td>
<td>0</td>
<td>9</td>
<td>50</td>
<td>19 (3-56)</td>
</tr>
<tr>
<td>54, 1984*</td>
<td>73</td>
<td>ND</td>
<td>7</td>
<td>11</td>
<td>32</td>
<td>22 (10-48)</td>
</tr>
<tr>
<td>55, 1986</td>
<td>101</td>
<td>ND</td>
<td>1</td>
<td>18</td>
<td>64</td>
<td>ND</td>
</tr>
<tr>
<td>59, 1989</td>
<td>116</td>
<td>15</td>
<td>9</td>
<td>0</td>
<td>38</td>
<td>ND</td>
</tr>
<tr>
<td>60, 2000</td>
<td>40</td>
<td>35†</td>
<td>7.5</td>
<td>27.5</td>
<td>70</td>
<td>&gt;12 (27-73)</td>
</tr>
<tr>
<td>53, 2002</td>
<td>66</td>
<td>30</td>
<td>19</td>
<td>#</td>
<td>80</td>
<td>ND</td>
</tr>
<tr>
<td>61, 2002</td>
<td>126</td>
<td>33</td>
<td>7</td>
<td>5</td>
<td>79</td>
<td>29.6 (18-33)</td>
</tr>
</tbody>
</table>

Abbreviations used: N, number of patients; SOD, sphincter of Oddi dysfunction; CBDS, common bile duct stone; ND, not done; CP, chronic pancreatitis; PS, papillary stenosis; C, cholelithiasis: micro, microlithiasis

* Not all patients had both ERC & ERP
† SOD type 1,2
# Overall “biliary” cause including cholelithiasis, choledocholithiasis, and biliary crystals in ~ 18%; raw data not provided

Gastrointest Endosc 2006;63:1037-45.

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**Recurrent Pancreatitis After Intervention**

**Table 1. Outcome of Intervention for SOD in Recurrent Pancreatitis**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Recurrence pancreatitis (%)</th>
<th>Follow-up (mos)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES (12), S (4)</td>
<td>16</td>
<td>0</td>
<td>3 (2 ± 0.25)</td>
<td>6</td>
</tr>
<tr>
<td>ES</td>
<td>32</td>
<td>25</td>
<td>2.75</td>
<td>7</td>
</tr>
<tr>
<td>S</td>
<td>49</td>
<td>29</td>
<td>≥2</td>
<td>8</td>
</tr>
<tr>
<td>ES</td>
<td>37</td>
<td>51</td>
<td>11.5 ± 1.6</td>
<td>9</td>
</tr>
</tbody>
</table>

ES, endoscopic sphincterotomy; S, surgical sphincterotomy; SOD, sphincter of Oddi dysfunction.

Gastroenterology 2012
Role of SOD Challenged

- Commonly believed to be important
- Randomized to EBS, or EBS/EPS
  If pressure normal, EBS vs Sham
- Patients could have repeat manometry, EBS, EPS
- Primary outcome of recurrent pancreatitis

Cote G et al. Gastroenterology 2012

Figure 1. Interval development of the first episode of acute pancreatitis during the follow-up period. Patients with increased pancreatic sphincter pressure (SOM) were more likely to have at least one episode of acute pancreatitis during the follow-up evaluation compared with those with normal SOM (unadjusted HR, 3.5; 95% CI, 1.1-11.6; P = .04). Among pancreatic SOM patients, the incidence of RAP during the follow-up evaluation was nearly identical between those randomized to BES (48.3%) and DES (47.2%) (P = 1.0). Similarly, there was no difference in RAP incidence between normal SOM patients randomized to sham (11.1%) or BES (27.3%) (P = .56). Note that most RAP events occurred within 30 months of randomization in all subgroups.

Cote G et al. Gastroenterology 2012
What about the approach to Type II?

Endoscopy 2004
Conclusions

• RUQ pain has many causes
• Type 3 SOD is likely a functional and not pancreaticobiliary disease
• Sphincterotomy does not impact pain in Type III SOD any better than sham and should be abandoned
• SOD may not cause recurrent pancreatitis