Endotherapy for GERD and Acid Related Disorders – Advances in Endoscopy

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Deep Thoughts!

“The hope is that the future will bring us more studies about data generating equipment instead of equipment generating data”

Prevalence of GERD

- In a 2005 systematic review, prevalence was 10–20% in Europe and USA.
- In a 2013 updated review, prevalence was:
  - 8–26% in Europe
  - 18–28% in USA
- More prevalent in Northern than Southern Europe.
- Prevalence also increasing in Middle East, Asia and Australia.
Recent Trends in Treatment Development for GERD

Non-medical techniques

Drug Development
What are the Areas of Unmet Needs in GERD?

- Advance grading of erosive esophagitis (15-30% → 20%)
- Nonerosive reflux disease (70% → 40%)
- Postprandial heartburn (OTC market)
- Nighttime heartburn (50% → 38%)
- Maintenance treatment (30%)
- On-demand / intermittent (80-90%)
- Refractory GERD (30-40%)
- Atypical manifestations of GERD (noncardiac chest pain)
- Extraesophageal manifestations of GERD
- PPIs—Dependence on food for efficacy
- Alternative approaches to chronic PPI treatment
- Barrett’s esophagus
Downsides of Current Treatment Modalities for GERD

Medical therapy

- Daily, chronic use of medication (no cure)
- Risk of side effects: 1–10%
- Incomplete or lack of response (30–40%)
- High cost

Downsides of Current Treatment
Modalities for GERD (con’d)

Surgery (laparoscopic fundoplication)
• Invasive, hospital stay, absence from work
• Risk of severe early complications: 2–5%; mortality: 0–0.8%
• Risk of insufficient symptom relief: 10–13%
• Risk of developing new symptoms (e.g., gas bloating, severe dysphagia, diarrhea): up to 67%
• Risk of re-operation: 3–15%
• Restart of anti-reflux medication: 11–62%
• High costs

The Rate of Antireflux Procedures Using the Nationwide Inpatient Sample

The Role of New Technology in GI
First Generation Endoscopic Treatments for GERD

- Stretta
- EndoCinch
- Full-thickness plication
- Enteryx
- Plexiglass
- Gatekeeper prosthesis
Mechanisms of Action

- Decrease proximal migration of acid reflux
- Decrease TLESR rate (scarring of cardia/lower esophagus)
- Mechanical obstruction of reflux (scarring, bulking or stitching effect)
- Increase LES basal pressure (scarring)
- Decrease esophageal sensitivity (?)
The Gatekeeper Prosthesis
The Gatekeeper
Enteryx Injection (Pretreatment)
Injection

Enteryx Is Injected Circumferentially Within and Along the Muscle Layer of the LES
Foreign Body Response
The Presence of Enteryx Elicits an
Acute Inflammatory Reaction

Davila & Fennerty; Gastroenterology & Endoscopy News; Jan 2004:36-40
Enteryx Injection Procedure

Reflux Barrier

The Encapsulated Material Results in Decreased Muscle Distensibility and Increased Yield Pressure, Which Enables the LES to Form a More Effective Gastroesophageal Reflux Barrier

Davila & Fennerty; Gastroenterology & Endoscopy News; Jan 2004:36-40
Studies of Injection Therapy in Patients with GERD

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Device</th>
<th>Follow-up (months)</th>
<th>Patients off PPI (%)</th>
<th>pH4 pre/post (%)</th>
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<tr>
<td>Cohen</td>
<td>2005</td>
<td>59</td>
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<td>24</td>
<td>67</td>
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<td>Enteryx</td>
<td>6</td>
<td>68</td>
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<td>69</td>
<td>Gatekeeper</td>
<td>6</td>
<td>53</td>
<td>9/6</td>
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</tbody>
</table>

NA* = not available

EndoCinch
Reflux Score Before and 3 and 12 Months After the EndoCinch Procedure

* $P < 0.05$ Compared to the Score off PPI Before the Procedure

[Graph showing reflux score changes over time]
The Plicator System

Rothstein R et al. Gastroenterol 2006
Comparison of PPI Use at Baseline and after 3 Months in Patients Undergoing Plication vs. Sham (ITT)

$P = .002^a$

$P$ values for treatment comparison are from Fisher exact test.

Rothstein R et al. Gastroenterol 2006
Comparison of Distal Esophageal Acid Exposure at Baseline and after 3 Months in Patients Undergoing Plication vs. Sham

\[ P < .001^a \quad P = .010^b \]

\[ \text{Median } \% \text{ time } \text{pH} < 4.0 \]

\[ \text{Plicator } n=53 \quad \text{Sham } n=60 \]

\[ ^a \text{P value from the Wilcoxon signed rank test} \quad ^b \text{P value for treatment comparison from Wilcoxon rank sum test} \]

Rothstein R et al. Gastroenterol 2006
# Studies of Sewing Devices in Patients with GERD

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<thead>
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<th>Patients (n)</th>
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<th>Follow-up (months)</th>
<th>Patients off PPI (%)</th>
<th>pH4 pre/ post (%)</th>
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<td>78</td>
<td>Plicator</td>
<td>3</td>
<td>50</td>
<td>6.1/4.1 active group</td>
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<td></td>
<td></td>
<td>25</td>
<td>6.1/6.1 sham group</td>
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<td>18</td>
<td>Endo-Cinch</td>
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<td>29</td>
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<td>20</td>
<td></td>
<td></td>
<td>3</td>
<td>10/8 sham group</td>
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<td></td>
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<td></td>
<td></td>
<td>3</td>
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<td>2005</td>
<td>70</td>
<td>Endo-Cinch</td>
<td>18</td>
<td>6</td>
<td>9.1/8.5 (at 12 months)</td>
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*NA* = not available

Numbers of Acid, Weakly Acidic and Weakly Alkaline Reflux Episodes at Baseline and 3 Months After Endoscopic Gastroplication as Assessed by Impedance Monitoring (N = 18)

Conchillo et al. Aliment Pharmacol Ther 2007;26:61-68
Numbers of Liquid, Gas and Mixed Reflux Episodes at Baseline and 3 Months After Endoscopic Gastropllication as Assessed by Impedance Monitoring (N = 18)

Conchillo et al. Aliment Pharmacol Ther 2007;26:61-68
Four-year Follow-up of Endoscopic Gastropllication for the Treatment of Gastroesophageal Reflux Disease.

So Why Has Endoscopic Treatment for GERD Failed?

• Procedures were time consuming
• Irreversibility of the technique
• Adverse effects (some devastating)
• Objective outcomes were not impressive
• Lack of reimbursement
• Cheaper and more successful alternatives
Endoscopic Treatment for GERD – Where Are We Now?
The Stretta Device

*Esophageal Catheter for Delivery of RFe with Bougie Tip, Expanded Basket, and Deployed Needle Electrodes*

Utley *et al.* Gastroenterol Endosc 2000;52(1):81-86
Catheter is Placed Into the Esophagus
Radiofrequency Energy Is Delivered to the Muscle of the Lower Esophageal Sphincter and Gastric Cardia

Davila & Fennerty; Gastroenterology & Endoscopy News; Jan 2004:36-40
The Esophagus Is Tighter Just a Few Days After Treatment

Davila & Fennerty; *Gastroenterology & Endoscopy News*; Jan 2004:36-40
A Randomized, Double-blinded, Sham-Controlled Trial (STRETTA)

<table>
<thead>
<tr>
<th></th>
<th>Sham (25)</th>
<th>Active (31)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Heartburn</td>
<td>-0.6</td>
<td>-1.6</td>
<td>.01</td>
</tr>
<tr>
<td>GERD-HQRL</td>
<td>-3</td>
<td>-13</td>
<td>.003</td>
</tr>
<tr>
<td>SF-36</td>
<td>1</td>
<td>7</td>
<td>.05</td>
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<tr>
<td>Daily PPI</td>
<td>-29%</td>
<td>-46%</td>
<td>.9</td>
</tr>
<tr>
<td>Median 24-pH &lt;4</td>
<td>-1.5</td>
<td>-1.8</td>
<td>.79</td>
</tr>
<tr>
<td>Median LESP</td>
<td>2.5</td>
<td>16.2</td>
<td>.72</td>
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<tr>
<td>Esophageal erosion</td>
<td>2%</td>
<td>8%</td>
<td>.88</td>
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</table>

Corley DA et al. Gastroenterology 2003;125:668-676
<table>
<thead>
<tr>
<th>1st Author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Follow-up months (mean)</th>
<th>Patients off PPI (%)</th>
<th>pH &lt; 4 pre/post (%)</th>
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<tr>
<td>Torquati</td>
<td>2004</td>
<td>41</td>
<td>18–37 (27)</td>
<td>56</td>
<td>6/3 (responders, $P &lt; 0.01$) 8/10 (nonresponders)</td>
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<tr>
<td>Go</td>
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<td>50</td>
<td>3–32 (10)</td>
<td>29</td>
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<td>Cipolletta</td>
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<td>32</td>
<td>12–26 (NA*)</td>
<td>56</td>
<td>12/8</td>
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<tr>
<td>Lutfi</td>
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<td>77</td>
<td>6–36 (26)</td>
<td>43</td>
<td>8/5 (responders, $P &lt; 0.01$) 9/7 (nonresponders)</td>
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<tr>
<td>Haringsma</td>
<td>2004</td>
<td>12</td>
<td>6</td>
<td>NA*</td>
<td>10/6</td>
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<tr>
<td>Noar</td>
<td>2005</td>
<td>227</td>
<td>6–48 (NA*)</td>
<td>NA*</td>
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<tr>
<td>Arts</td>
<td>2005</td>
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<td>NA*</td>
<td>18/13</td>
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<td>Arts</td>
<td>2006</td>
<td>11 (sham)</td>
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<td>9/8 16/17</td>
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<td>31</td>
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<td>Reymunde</td>
<td>2006</td>
<td>80</td>
<td>48</td>
<td>86</td>
<td>NA*</td>
</tr>
</tbody>
</table>

NA* = not available

Stretta: 10 years results

GERD QoL

Off  On  1y  4y  10y

27  22  7  7.5  8

Esophyx
# Three-year Results of a Multicenter Prospective Study of Transoral Incisionless Fundoplication

<table>
<thead>
<tr>
<th>N = 66</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>GERD-HRQL</td>
<td>4</td>
<td>25 (off PPI)</td>
<td>9 (on PPI)</td>
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<tr>
<td>Discontinuation of Daily PPI</td>
<td>61% (ITT)</td>
<td>74% (PP)</td>
<td></td>
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<tr>
<td>Normalization of esophageal pH</td>
<td>39% (ITT)</td>
<td>82% (PP)</td>
<td></td>
</tr>
</tbody>
</table>

18.2% underwent revisional procedures

Transoral Incisionless Fundoplication 2.0 Procedure Using Esophyx™ for Gastroesophageal Reflux Disease

- N = 19
- Patients - Typical GERD SX, failed PPI, abnormal pH test, positive SI, no Hiatal hernia > 2cm
- Outcome - 3/19 (16%) – major complications
  - After follow up 10.8 months,
  - 10/19 (53%) – converted to lap fundoplication
  - 9/17 (53%) – dissatisfied with outcome
  - 13/19 (68%) – considered unsuccessful

Conclusions: Excessive early symptoms failure and a high surgical re-intervention rate.

Hoppo T et al. J Gastrointest Surg. 2010 Dec;14(12):1895-901
SRS™ Surgical Endoscope - Medigus

- Anvil
- Illumination
- Miniature camera
- Irrigation
- Suction
- Ultrasound
- Stapler
Before endoluminal SRS™ procedure

After endoluminal SRS™ procedure – A flap valve is generated
LINX™ Reflux Management System

- Reinforces the LES restoring the barrier function
- Expands during swallow allowing food to enter stomach

Highest Magnetic Resistance

Lowest Magnetic Resistance
LINX – 3-Year Follow Up

- Total participants 100
- Normalization or at least 50% reduction in acid exposure – 64%
- At least 50% reduction in PPI use – 93%
- At least 50% improvement in quality of life – 92%
- Limitations – not controlled, selective, only 50% with normal pH and dysphagia.
- Unclear long-term consequences of a foreign body around the esophagus

Comparison of the Different Procedures for GERD

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Anesthesia</th>
<th>Cost</th>
<th>Pt’s</th>
<th>Years of Exp.</th>
<th># of Ctrs</th>
<th>FDA reported Adverse Events</th>
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<tr>
<td>Stretta</td>
<td>Conscious</td>
<td>$2000-3500</td>
<td>15000</td>
<td>13</td>
<td>125</td>
<td>26</td>
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<tr>
<td>EsophyX</td>
<td>General</td>
<td>$7000</td>
<td>11000</td>
<td>7</td>
<td>200</td>
<td>96</td>
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<tr>
<td>Medigus</td>
<td>General</td>
<td>$3200</td>
<td>&gt;100</td>
<td>2</td>
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<td>0</td>
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<td>General</td>
<td>$12000</td>
<td>1000</td>
<td>5</td>
<td>70</td>
<td>48</td>
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The End