Equipoise, Innovation and the Role for Comparative Studies

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NO DISCLOSURES
How Have We Trained Our Surgeons?
How Have We Trained Our Surgeons?
Figure 1. Levels of evidence
“New therapeutic procedures should be always supported by randomized controlled trials.”

A.L. Cochrane, 1989
RANDOMIZED TRIALS CAN NOT BE DONE IN PEDIATRIC SURGERY

- Parents would never consent
- Surgeons would never have equipoise
EQUIPOISE

“the condition in which the physician is indifferent to the therapeutic value of an experimental treatment versus a control”

Charles Fried
EQUIPOISE

Personal equipoise is “overwhelmingly fragile…disturbed by a slight accretion of evidence” favoring one treatment over another

Benjamin Freedman
CLINICAL EQUIPOISE

- Justification to support 2 treatment paths
- No proof of superiority

You don’t need personal equipoise to support, participate in or design a trial
INSTITUTIONAL DISCREPANCY
TO ESTABLISH CLINICAL
EQUIPOISE
Treatment of Empyema

FIBRINOLYSIS

- Had been shown to be superior to chest tube alone

VATS

- Had been shown to be superior to chest tube alone

We were a house divided
VATS v Fibrinolysis for Empyema

Convinced fibrinolysis is effective

Convinced thoracoscopy is better
How can we conduct a study?

- There are no comparative data
- Our assumptions require proof
- A fixed management protocol

If patients are going down 2 pathways regardless, we have an ethical obligation to perform a trial
STUDY POPULATION

Inclusion Criteria
VATS v Fibrinolysis for Empyema

**FIBRINOLYSIS**

- 12 Fr tube placed by IR or surgery in procedure room
- 4mg tPA in 40ml NS given into tube on insertion and each day for 3 doses

**VATS**

- Thoracoscopic debridement with chest tube left behind on – 20 cm H$_2$O suction
London Prospective Trial
- 60 pts

VATS v Fibrinolysis w/Urokinase

- No difference in LOS (6 v 6 days)
- VATS more expensive (11.3K v 9.1K)

16% failure rate for fibrinolysis
### CMH STUDY RESULTS

#### Outcomes – 36 pts

<table>
<thead>
<tr>
<th></th>
<th>VATS</th>
<th>tPA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS (Days)</td>
<td>6.9</td>
<td>6.8</td>
<td>0.96</td>
</tr>
<tr>
<td>O2 tx (Days)</td>
<td>2.2</td>
<td>2.3</td>
<td>0.89</td>
</tr>
<tr>
<td>PO Fever (Days)</td>
<td>3.1</td>
<td>3.8</td>
<td>0.46</td>
</tr>
<tr>
<td>Analgesic doses</td>
<td>22.3</td>
<td>21.4</td>
<td>0.90</td>
</tr>
<tr>
<td>Proc Charges</td>
<td>$11,660</td>
<td>$7,575</td>
<td>0.01</td>
</tr>
</tbody>
</table>

16.6% failure rate for fibrinolysis
VATS v Fibrinolysis

Summary

- No recovery advantages to VATS
- Fibrinolysis is less costly
- Avoids an operation in the majority
ALL PATIENTS

EMPYEMA

(Locations or > 10,000 WBC/µL)

12 Fr chest tube with 3 doses of tPA

Drainage decreased without clinical improvement

Ultrasound or CT

Persistent pleural space disease

No pleural space disease

VATS

Continue Antibiotics
VATS v Fibrinolysis for Empyema
AFTER THE TRIAL

102 consecutive patients same protocol

Duration of stay
- All Patients: 7 +/- 3 days
  - Fibrinolysis only: 6.3 +/- 2.0 days
- Fibrinolysis then VATS: 11.8 +/- 4.3 days
  - Mean stay 5.9 +/- 3.7 days after VATS

Avg VATS operative time
- 62 +/- 13 minutes

15.7% failure rate for fibrinolysis
After the Observational Study

Redefining Failure

Sept, 2014 – March, 2019

48 patients

- All Patients – LOS: 6 days (IQR 5, 7.2)

Only 2 patients underwent VATS (4%)

- Both in the first 2 years of the study period

4% failure rate for fibrinolysis
ENEMY OF PRACTICE
EVOLUTION

SURGICAL DOGMA
TRADITION
JUST BECAUSE YOU’VE ALWAYS DONE IT THAT WAY
doesn’t mean it’s not incredibly stupid.
SURGICAL DOGMA

Fig. 2. Laparoscopic view of the esophagogastric junction with the liver retracted.

Fig. 4. Approximation of the crus during laparoscopic Nissen fundoplication.
HERNIATION
BACKGROUND

- We had begun doing less dissection and placing more stitches and were seeing less herniations – Whit Holcomb

- The UAB group was bipolar on the topic - Keith Georgeson v Mac Harmon
INTERVENTIONS

Maximal Mobilization (MAX)  Minimal Mobilization (MIN)
INTERVENTIONS

At Least 4 Esophagocrural Sutures Placed in All Patients
Dissection vs No Dissection

Study Design

- Primary Outcome Variable - Hiatal Hernia
- 2 centers – CMH and UAB
- All patients get upper GI study at 1 yr
QUALITY ASSURANCE

- Photograph after dissection to confirm minimal or maximal mobilization

- Photographs were reviewed by participating surgeons at APSA when we reviewed the data

- No patients were removed because photograph didn’t confirm randomization allotment
# OUTCOMES

## During Study Follow-Up

(16 Months – 3.5 Years)

<table>
<thead>
<tr>
<th></th>
<th>MAX (N = 70)</th>
<th>MIN (N = 64)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrap Herniation</td>
<td>30.0%</td>
<td>7.8%</td>
<td>0.002</td>
</tr>
<tr>
<td>Re-Operation</td>
<td>18.4%</td>
<td>3.3%</td>
<td>0.006</td>
</tr>
</tbody>
</table>
LONG-TERM FOLLOW-UP

- 122 patients in original study at CMH
  - 67% telephone contact (43 MAX, 39 MIN)
  - 11.5% deceased (4MAX, 10MIN)
  - 21.3% lost to follow-up (14 MAX, 12 MIN)

- Median time to follow-up: 6.5yrs

- Mean age: 8.4 ± 2.8yrs
# Rate of Post-Operative Herniation at 1 and 5 Yrs

<table>
<thead>
<tr>
<th></th>
<th>1 yr</th>
<th>5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAX</td>
<td>12%</td>
<td>37%</td>
</tr>
<tr>
<td>MIN</td>
<td>3%</td>
<td>12%</td>
</tr>
<tr>
<td>P=0.01</td>
<td></td>
<td>P=0.01</td>
</tr>
</tbody>
</table>
NISSEN FUNDOPPLICATION
STUDY #2
Crural Stitches vs No Stitches
Stitches vs No Stitches

- Randomized 120 patients
- No herniations in either group
  - 1 reoperation for failed fundo in stitch group
- Far shorter operating time with no stitches

“It was the dissection causing the problem”
Prosp Observational Study

No Crural Stitches
GROUP PRACTICE = CLINICAL EQUIPOISE
PERFORATED APPENDICITIS

Should we irrigate?
“Dilution is the solution to pollution”
NO IRRIGATION

“Macrophages can’t swim”
STUDY POPULATION

Inclusion Criteria

- Under 18 years of age
- Perforated appendicitis at the time of appendectomy
  - Stool in the abdomen
  - Hole in the appendix

Exclusion Criteria

- Severe concomitant process
INTERVENTIONS

**Irrigation**

- 1 bag of saline attached to the suction/irrigator
  - Minimum irrigation volume of 500cc

**Suction Only**

- No bag attached to the suction/irrigator

Battery Powered Suction Irrigator Used in All Cases
STANDARDIZED SUCTION
Battery Powered Suction Irrigator
MANAGEMENT

- One computer order set for both groups
- Standard PCA was utilized for pain control
- Foley catheter placed, no nasogastric tubes
- Once daily dosing of IV ceftriaxone (50 mg/kg) and metronidazole (30 mg/kg)
- When tolerating diet, discharged home to complete 7 day course with oral amoxicillin/clavulanate
RESULTS

Irrigation

- 1 suction patient received irrigation
  - Analyzed with the no irrigation patients

- Mean volume of irrigation was 867 +/- 327 ml
  - Range 500 – 2000 ml

And the results are……..
## Results

### Outcomes

<table>
<thead>
<tr>
<th></th>
<th>No Irrigation (n = 110)</th>
<th>Irrigation (n = 110)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abscess (%)</strong></td>
<td>19.1%</td>
<td>18.3%</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Op Time (mins)</strong></td>
<td>38.7 +/- 14.9</td>
<td>42.8 +/- 16.7</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Initial PO’s (dys)</strong></td>
<td>2.6 +/- 1.5</td>
<td>2.5 +/- 1.3</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Reg Diet (hrs)</strong></td>
<td>3.4 +/- 1.7</td>
<td>3.5 +/- 1.5</td>
<td>0.63</td>
</tr>
<tr>
<td><strong>Narcotic Doses</strong></td>
<td>11.4 +/- 5.4</td>
<td>11.6 +/- 6.3</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Days of Stay</strong></td>
<td>5.5 +/- 3.0</td>
<td>5.4 +/- 2.7</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Charges ($K)</strong></td>
<td>48.1 +/- 20.1</td>
<td>48.1 +/- 18.2</td>
<td>0.97</td>
</tr>
</tbody>
</table>
TEMPERATURES

- Irrigation
- Suction Only

<table>
<thead>
<tr>
<th>Day</th>
<th>Mean Max Daily Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38.5 ± 0.2</td>
</tr>
<tr>
<td>2</td>
<td>38.2 ± 0.3</td>
</tr>
<tr>
<td>3</td>
<td>38.0 ± 0.4</td>
</tr>
<tr>
<td>4</td>
<td>37.8 ± 0.5</td>
</tr>
<tr>
<td>5</td>
<td>37.5 ± 0.6</td>
</tr>
</tbody>
</table>
## RESULTS

Outcomes of Patients with Postoperative Abscess

<table>
<thead>
<tr>
<th></th>
<th>No Irrigation (n = 21)</th>
<th>Irrigation (n = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drain Placed (%)</td>
<td>52%</td>
<td>40%</td>
<td>0.54</td>
</tr>
<tr>
<td>Days of Drainage</td>
<td>2.3 +/- 2.2</td>
<td>1.8 +/- 2.8</td>
<td>0.58</td>
</tr>
<tr>
<td>Days of Stay</td>
<td>8.7 +/- 4.4</td>
<td>9.4 +/- 3.8</td>
<td>0.56</td>
</tr>
<tr>
<td>Reg Diet (hrs)</td>
<td>19.5 +/- 3.9</td>
<td>21.4 +/- 8.6</td>
<td>0.37</td>
</tr>
<tr>
<td>Days Home Health</td>
<td>10.4 +/- 4.5</td>
<td>13.0 +/- 7.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Charges ($K)</td>
<td>28.3 +/- 22.7</td>
<td>24.6 +/- 13.8</td>
<td>0.54</td>
</tr>
</tbody>
</table>
LOCATION OF ABSCESSES

<table>
<thead>
<tr>
<th></th>
<th>No Irrigation</th>
<th>Irrigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboes (No.)</td>
<td>14.6</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>29.1</td>
<td>31.0</td>
</tr>
<tr>
<td></td>
<td>47.3</td>
<td>45.3</td>
</tr>
<tr>
<td>Aboes (Yes)</td>
<td>1.8</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>7.3</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>47.3</td>
<td>45.3</td>
</tr>
</tbody>
</table>
CONCLUSION

Irrigation = Suction Alone
HOW CAN WE INVESTIGATE DURING INNOVATION?
PROGRESSION OF INNOVATION

Figure 1. Levels of evidence
Acceptance of Laparoscopy

- Cholecystectomy, splenectomy, nephrectomy, adrenalectomy, fundoplication, others
- Same operation - no laparotomy
- Shorter LOS, shorter convalescence, improved patient satisfaction, improved cosmesis, improved visualization/ease of operation

Disruptive Innovation
WHAT’S THE PROBLEM?

Figure 1. Levels of evidence
Subconscious Maleficence

Practicing in accepted manner to the harm of patients
Subconscious Maleficence

- Extra-intracranial artery bypass for stroke
  - Over 1000 cases by 1978
  - RCT in 1985 – then gone
- Arthroscopic debridement for osteoarthritis
  - Case series and cohort comparisons led to 650,000/yr in US by 1996
  - Trial in 2002 – no benefit over placebo
Subconscious Maleficence

- Colectomies for epilepsy
- Anglechik ring for GERD
- Reimplants for low grade VUR
- Nephrectomy/splenectomy trauma
- Jejunoileal bypass for obesity
- Swan Ganz catheters
How Do We Prevent Becoming Tomorrow’s Example?
Investigate with the launch of new treatments

- Prosp observational if the leap is disruptive

- Comparative study if equipoise exists
PECTUS EXCAVATUM
Epidural v PCA RCT

A = AM Pain Score  P = PM Pain Score

Day 0  Day 1  Day 2  Day 3  Day 4  Day 5

Pain Score

EPI  PCA
CRYOABLATION
CRYOABLATION
# EPI v PCA v Cryo

<table>
<thead>
<tr>
<th></th>
<th>Epidural (n=32)</th>
<th>PCA (n=33)</th>
<th>Cryoablation (n=35)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, Male (%)</strong></td>
<td>90.6</td>
<td>93.9</td>
<td>82.4</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>15 [14, 16]</td>
<td>14 [13,16]</td>
<td>16 [14, 17]</td>
<td>0.02*</td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
<td>1.8 [1.7, 1.8]</td>
<td>1.7 [1.7, 1.8]</td>
<td>1.7 [1.7, 1.8]</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>56.6 [52, 61.6]</td>
<td>56.1 [48, 58.4]</td>
<td>57.1 [50, 64]</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Correction Index (%)</strong></td>
<td>30 [37, 30]</td>
<td>30 [30, 40]</td>
<td>35 [30, 47]</td>
<td>0.01*</td>
</tr>
<tr>
<td><strong>Time to only oral pain meds (hr)</strong></td>
<td>71.1 [50.4, 82.7]</td>
<td>66.6 [50, 70]</td>
<td>20.9 [11.6, 28.4]</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td><strong>Length of stay (d)</strong></td>
<td>4.3 [4.1, 5.1]</td>
<td>4.2 [3.4, 5.2]</td>
<td>1 [1, 1.3]</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>
Comparison of Daily and Total Inpatient Median Morphine Equivalents (MME)

- POD 0
- POD 1
- POD 2
- POD 3
- Total Inpatient Stay

$p < 0.001$
tPA in Abdominal Abscesses Associated with Appendicitis

New Therapy (tPA) ➣

Compare to Standard ➣

IRB said “do more” ➣

New becomes Standard
## RESULTS
### Drainage Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Saline (n = 32)</th>
<th>tPA (n = 30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Drain LOS</td>
<td>3.3 +/- 1.3</td>
<td>4.5 +/- 1.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Total Days of Stay</td>
<td>6.4 +/- 4.0</td>
<td>7.1 +/- 3.8</td>
<td>0.49</td>
</tr>
<tr>
<td>Days of Drain</td>
<td>3.5 +/- 3.6</td>
<td>4.6 +/- 2.4</td>
<td>0.17</td>
</tr>
<tr>
<td>Drain Total (ml)</td>
<td>128 +/- 160</td>
<td>204 +/- 166</td>
<td>0.06</td>
</tr>
</tbody>
</table>
## RESULTS

### Downstream Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Saline (n = 32)</th>
<th>tPA (n = 30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare visits</td>
<td>5.2 +/- 2.3</td>
<td>5.9 +/- 2.3</td>
<td>0.24</td>
</tr>
<tr>
<td>Day of IV abx</td>
<td>15.6 +/- 4.0</td>
<td>16.8 +/- 5.0</td>
<td>0.30</td>
</tr>
<tr>
<td>Recurrent abscess</td>
<td>2 (6%)</td>
<td>6 (20%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Med Charges ($K)</td>
<td>4.1 +/- 2.6</td>
<td>6.5 +/- 3.1</td>
<td>0.002</td>
</tr>
</tbody>
</table>
tPA in Abdominal Abscesses Associated with Appendicitis

New Therapy (tPA)

Compare to Standard

Worse outcome with more expense

Standard Remains
Center for Prospective Trials

- Initiated in 2006
  - Randomized Trials
    - 18 Published
    - 2 Completed
    - 2 Enrolling
  - Prospective Observational Studies
    - 6 Published
    - 2 Completed
    - 6 Enrolling
Lesson Learned
Lessons Learned

"The greatest teacher, failure is."

Yoda

Star Wars: The Last Jedi
Lessons Learned
“Don’t be too timid about your actions, all life is an experiment. The more experiments you make the better”

*Ralph Waldo Emerson*

As long as you are collecting the data