The role of the appendix in Ulcerative Colitis

- Vestigial no more...?

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Ulcerative Colitis

- Chronic relapsing disease
- Young population
- Long-term health burden to patient + NHS
- 50,000 people in the UK
- £££Millions spent on drug research
- Interventions that may reduce the rate or severity of relapse would provide considerable benefits to patients and the health service.
The appendix
The appendix

‘vestigial organs’ = evidence for evolution
I GAVE EACH HUMAN AN APPENDIX

SO THEY CAN RANDOMLY EXPLODE AND KILL THEM. SOMETIMES I CRACK MYSELF UP
The role of the appendix in UC
Appendicectomy and the development of UC

Appendicectomy as child results in

↓↓ lifetime risk of developing UC in the future
Peri-Appendiceal Red Patch (PARP)

Case reports – emergency appendicectomy for appendicitis in UC patients

• Lifetime population risk of developing appendicitis is around 9%

• Patients with UC developed appendicitis, had an appendicectomy and noticed symptoms of UC seemed to improve
### Deliberate therapeutic appendicectomy in UC pts

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Inclusion</th>
<th>Findings/success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolin</td>
<td>2009</td>
<td>30</td>
<td>Active ulcerative proctitis with unremitting symptoms despite medical therapy</td>
<td>Improvement in CAI in 27 of 30 (90%). 12 of 30 (40%) had full resolution of symptoms and came off medication</td>
</tr>
<tr>
<td>Radford-Smith</td>
<td>2003</td>
<td>15</td>
<td>Refractory UC</td>
<td>“Significant improvements in CAI (P=0.015), endoscopic activity (P=0.02) and need for medication (P=0.02) at 12mths”</td>
</tr>
<tr>
<td>Okazaki</td>
<td>2000</td>
<td>1</td>
<td>Distal active UC</td>
<td>Asymptomatic at 3yrs (100%)</td>
</tr>
<tr>
<td>Kim</td>
<td>2006</td>
<td>1</td>
<td>Severe pancolitis</td>
<td>No relapse at 1yr; came off medication (100%)</td>
</tr>
<tr>
<td>Jarnerot</td>
<td>2001</td>
<td>6</td>
<td>UC refractory to standard treatment in whom proctocolectomy was being considered.</td>
<td>Unclear. Not reported - most patients (5 of 6) got better; but they could find other possible ‘reasons’ for this improvement (eg restarting smoking, change of maintenance medication)</td>
</tr>
<tr>
<td>Bageacu</td>
<td>2011</td>
<td>8</td>
<td>Refractory ulcerative proctitis</td>
<td>All patients had mucosal healing. 4 patients (50%) experienced only one flare-up post-appendectomy then nil further.</td>
</tr>
</tbody>
</table>
Can we test this intervention properly?
Can we run an RCT?
- Chronic relapsing disease; health burden to pt + state
- Large proportion remain on maintenance medication
- 1 year relapse rate on medication ≈ 40%

- Some promising data that this novel intervention might work to decrease disease relapses
Questions raised.....

• Can we recruit patients to such a trial?
• Is this an attractive treatment option to patients?
• Will gastroenterologists buy into it?
• Are surgeons be willing to be involved?

• How safe is appendicectomy in this context?

• What is the best way of measuring beneficial effects on disease activity?
The ACCURE-UK Trial Feasibility study
The feasibility of undertaking Appendicectomy to impact upon the Clinical Course of Ulcerative colitis
INCLUSION CRITERIA

- Aged over 18 with histologically confirmed UC
- Disease relapse within last 12 months
- Currently in clinical remission

Exclusions – previous appendicectomy, or comorbidities/previous surgery which precludes safe appendicectomy.
STUDY DESIGN

- Randomised 1:1 between:
  - Laparoscopic day-case appendicectomy + standardised medical treatment or
  - Standardised medical treatment alone

- Endpoints:
  **Primary**
  - Completion of recruitment on schedule
  **Secondary**
  - 1-year control arm relapse rate
  - Adverse events relating to appendicectomy
  - Number of relapses; time to relapse; QoL
  - Qualitative research stream
RESULTS

- **Acceptable ✓**
  - 57% (60/106) eligible patients were willing to participate

- **Safe ✓**
  - 19/25 (76%) completed as day case procedures.
  - No major complications
Minimal morbidity ✔

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain from operation within <strong>first week</strong></td>
<td>7 (5-8)</td>
</tr>
<tr>
<td><strong>Negative impact</strong> on life within <strong>first week</strong></td>
<td>5 (3-8)</td>
</tr>
<tr>
<td>Pain from operation at <strong>6 weeks</strong></td>
<td>1 (1-2)</td>
</tr>
<tr>
<td><strong>Negative impact</strong> on life at <strong>6 weeks</strong></td>
<td>1 (1-2)</td>
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QOL

Mean Scores Over Time for the EQ-5D EuroQoL Score

<table>
<thead>
<tr>
<th>EQ-5D assessment</th>
<th>Control (N)</th>
<th>Surgery (N)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>19</td>
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<td>3</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>
Mean Scores Over Time for the EORTC QLQ-C30 Global Score

Control
Surgery

Patients

<table>
<thead>
<tr>
<th>Assessment</th>
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<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>15</td>
</tr>
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</table>

Global Score
Conclusion – ACCURE-UK

- Appendicectomy was an acceptable treatment for both patients and clinicians.
- Day case appendicectomy was a safe treatment option in UC patients.
- Some signal of a clinical effect(?)

→ Proceed to full phase III RCT...
UC with flare in past 12 months (currently in remission)

Standard medical therapy

Therapeutic appendicectomy & standard medical therapy

Followed up at 3 /6 /9 /12 months
1y: 1 year cumulative UC relapse rate
2y: QOL; Resource usage; safety

NIHR EME-funded 2018-2021

- 10 UK centres
- 90 patients
- Identical protocol
What are the alternatives for my UC treatment?

If you choose not to go into this trial, you are likely to simply continue your tablet medication for UC into the future to try to prevent further relapses (flare-ups) of your disease activity.

Your gastroenterologist may recommend increasing your treatment by adding in new or different medications in the future, as they would normally. There may be other new treatments developed for UC in the future, and this trial is not designed to interfere with any of these in any way.

What are the possible disadvantages and risks of taking part?

If you enter the trial and are allocated to undergo appendicectomy, this operation would be an additional treatment compared to the routine care of patients with UC. The procedure is outlined above, and like any surgery there is always the possibility of complications. We have done our best to reduce the chances of these by ensuring that only experienced and specialised colorectal consultant surgeons undertake operations during the trial. All adverse events relating to the operations within ACCURE-UK 2 will be carefully recorded as this is important information to know if we are to propose that this operation be offered more widely to UC sufferers.

For patients who enter the control arm there will be no disadvantages from a medical point of view as they will receive standard treatment with tablet medications as they would anyway if they were not involved in the trial. Additionally, the reviews planned every 3 months throughout the trial (with the exception of the final review) will give you an opportunity to discuss your condition freely with the team.
Do you suffer from UC? Have you had a flare-up in the last 12 months? Are you interested in taking part in an NHS based study for patients suffering with UC?

ACCURE-UK 2 aims to find out whether removing the appendix impacts UC flare-ups in the future.

Visit our website for further information and to find out how you can get involved: www.birmingham.ac.uk/ACCURE-UK2/info
Thank you

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