Use of placebo in surgical trials

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Disclaimer

PI on NHMRC-funded SUcceSS: SUrgery for Spinal Stenosis – randomised placebo controlled trial of surgery for spinal stenosis
Why *placebo* trials of surgery?
We lack robust evidence in the field.

- Until recently - most studies of surgery were retrospective case series
- RCTs <10%
- 2009 – 2011 83 RCTs (>9,000 orthopaedic procedures)
- 1/3 superior to non-surgical care
- 20% of procedures supported by low-risk-of-bias RCTs
  (Lim et al 2014; Lohmander & Roos 2015)

Only 2 were placebo-controlled trials!
Placebo trials are powerful!

Systematic review of placebo controlled trials of surgery

27 of 53 (51%) included placebo-controlled trials of surgery – did not support current practice

(Wartolowska et al, BMJ 2014)
7 placebo trials of surgery in MSK field

1. Arthroscopy for knee OA (Moseley trial 2002) - $3B in USA every year
2. Intradiscal electrothermal therapy for discogenic LBP (Pauza et al 2004)
3. Tidal irrigation for OA (Bradley 2002)
4. Intradiscal electrothermal therapy for discogenic LBP (Freeman 2005)
5. Vertebroplasty for VFF (Buchbinder 2009)
6. Vertebroplasty for VFF (Kallmes 2009)
7. Decompression for shoulder impingement (CSAW-Beard 2017)
## Placebo vs surgery (Wartolowska et al 2014)

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison groups</th>
<th>Outcome</th>
<th>Effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Osteoarthritis</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bradley et al 2002</td>
<td>Tidal irrigation v placebo</td>
<td>WOMAC pain</td>
<td>0.35 (0.05 to 0.65)</td>
</tr>
<tr>
<td>Bradley et al 2002</td>
<td>Tidal irrigation v placebo</td>
<td>WOMAC function</td>
<td>0.28 (-0.01 to 0.58)</td>
</tr>
<tr>
<td>Moseley et al 2002</td>
<td>Lavage v placebo</td>
<td>KSPS pain</td>
<td>0.09 (-0.4 to 0.29)</td>
</tr>
<tr>
<td>Moseley et al 2002</td>
<td>Debridement v placebo</td>
<td>KSPS pain</td>
<td>0.01 (-0.37 to 0.39)</td>
</tr>
<tr>
<td><strong>Chronic discogenic pain</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Freeman et al 2005</td>
<td>Electrothermal therapy v placebo</td>
<td>SF-36 physical</td>
<td>0.36 (-0.20 to 0.92)</td>
</tr>
<tr>
<td>Pauza et al 2004</td>
<td>Electrothermal therapy v placebo</td>
<td>Visual analogue pain</td>
<td>0.45 (-0.08 to 0.99)</td>
</tr>
<tr>
<td>Pauza et al 2004</td>
<td>Electrothermal therapy v placebo</td>
<td>ODI</td>
<td>0.69 (0.15 to 1.24)</td>
</tr>
<tr>
<td><strong>Osteoporotic vertebral fracture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kallmes et al 2009</td>
<td>Vertebroplasty v placebo</td>
<td>RMS</td>
<td>0.16 (-0.19 to 0.50)</td>
</tr>
<tr>
<td>Kallmes et al 2009</td>
<td>Vertebroplasty v placebo</td>
<td>NRS pain</td>
<td>0.24 (-0.11 to 0.59)</td>
</tr>
<tr>
<td>Buchbinder et al 2009</td>
<td>Vertebroplasty v placebo</td>
<td>NRS pain</td>
<td>0.23 (-0.24 to 0.69)</td>
</tr>
</tbody>
</table>

-3.78 0 3.78

Favours placebo  Favours treatment
CSAW (Beard et al 2017)

Figure 2: Oxford Shoulder Score in the intention-to-treat analyses
Data are mean (95% CI) shown at follow-up timepoints. OSS=Oxford Shoulder Score.
Placebo trials of surgery
When do we need a placebo trial of surgery?
Can the question be answered with:

– Controlled (no treatment) trial?
– Pragmatic (e.g. conservative care) trial?
– Sham controlled trial?
– Placebo controlled trial?
Limitations of open label trials of surgery
Lack of equipoise

- 82% of surgical trials
- Slow recruitment
- Selection bias (are trial participants similar to my patients?)
- Ethical barrier
- Treatment cross-over
Lack of blinding (unknown treatment allocation)

Why?

- Performance bias associated with larger treatment effects
- Lack of equipoise
- High crossover rates
# Blinding vs. unblinding in MSK RCTs

<table>
<thead>
<tr>
<th>Type of clinical condition</th>
<th>N</th>
<th>Proportion (P)</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>3</td>
<td>78% (0.01)</td>
<td>-0.54 (-0.88 to -0.20)</td>
<td></td>
</tr>
<tr>
<td>Migraine/tension headache</td>
<td>2</td>
<td>0% (0.71)</td>
<td>-0.69 (-0.92 to -0.46)</td>
<td></td>
</tr>
<tr>
<td>Low back pain</td>
<td>2</td>
<td>0% (0.37)</td>
<td>-0.63 (-0.82 to -0.44)</td>
<td></td>
</tr>
<tr>
<td>Other conditions</td>
<td>5</td>
<td>72% (0.007)</td>
<td>-0.52 (-0.89 to -0.14)</td>
<td></td>
</tr>
</tbody>
</table>
### Lack of blinding

#### Table 2: Effect of Placebo on Specific Clinical Problems

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Participants</th>
<th>No. of Trials</th>
<th>Pooled Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Binary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>182</td>
<td>3</td>
<td>0.94 (0.77 to 1.16)</td>
</tr>
<tr>
<td>Smoking</td>
<td>887</td>
<td>6</td>
<td>0.88 (0.71 to 1.09)</td>
</tr>
<tr>
<td>Depression</td>
<td>152</td>
<td>3</td>
<td>1.03 (0.78 to 1.34)</td>
</tr>
</tbody>
</table>

#### Continuous

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Participants</th>
<th>No. of Trials</th>
<th>Pooled Standardized Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>1602</td>
<td>27</td>
<td>−0.27 (−0.40 to −0.15)</td>
</tr>
<tr>
<td>Obesity</td>
<td>128</td>
<td>5</td>
<td>−0.40 (−0.92 to 0.12)</td>
</tr>
<tr>
<td>Asthma</td>
<td>81</td>
<td>3</td>
<td>−0.34 (−0.83 to 0.14)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>129</td>
<td>7</td>
<td>−0.32 (−0.78 to 0.13)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>100</td>
<td>5</td>
<td>−0.26 (−0.66 to 0.13)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>257</td>
<td>6</td>
<td>−0.06 (−0.31 to 0.18)</td>
</tr>
</tbody>
</table>

*Only problems addressed by at least three trials are included. CI denotes confidence interval.

†The relative risk was defined as the ratio of the number of patients with an unwanted outcome to the total number of patients in the placebo group, divided by the same ratio in the untreated group. A value below 1.0 indicates a beneficial effect of placebo.

‡The standardized mean difference was defined as the difference between the mean values for unwanted outcomes in the placebo and untreated groups divided by the pooled standard deviation. A negative value indicates a beneficial effect of placebo.

Placebo effect and lack of blinding SR of 130 RCTs placebo vs no treatment
Larger and significant effect – pain
Sham vs placebo
Sham vs Placebo

- Placebo = latin: *I shall please*
- Traditional definition: inert agent used to please people
- Negative connotation
- *Paradox: inert = no effect*
Design considerations
3-arm trial - adding a no treatment group

Placebo vs no treatment contrast
Inform (de) implementation of results
Estimate the size of placebo effect

Lack of blinding
Treatment cross-over
Surgery for Spinal Stenosis – a randomised placebo-controlled trial

- 160 patients randomised to decompression or placebo surgery
  - FU: 3, 6, 12 and 24 months
  - PO: Walking ability and function
- 11 surgeons and 7 participating hospitals in Melbourne and Sydney
Thank you!