Which tocolytic for pre-term delivery?

A novel approach to evidence synthesis in obstetrics

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Outline of talk

• Introduction to tocolysis and epidemiology of pre-term delivery,
• Problem of multiple treatment decision making,
• Methodology of indirect comparisons and network meta-analysis,
• Results, conclusions and future directions.
Tocolysis for pre-term delivery

- In the UK, 8% of live births are preterm (<37\textsuperscript{0} weeks). Evidence suggests incidence is increasing.
- Preterm delivery associated with increased mortality and lifelong morbidity. Estimated cost NHS of £9.4 m.
- Tocolytics can prolong pregnancy by up to 7 days to administer corticosteroids or enable maternal transfer.
- There are several tocolytic classes e.g. Prostaglandin Inhibitors, Betamimetics, Oxytocin receptor blockers, Calcium channel blockers, Magnesium sulphate, Nitrates.
Summary of pairwise evidence

Review: Calcium channel blockers for inhibiting preterm labour
Comparison: 1 Any calcium channel blocker compared with any other tocolytic agent
Outcome: 4 Birth within 48 hours of treatment

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ca++CB n/N</th>
<th>Other tocolytic n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferguson 1990</td>
<td>6/33</td>
<td>10/33</td>
<td></td>
<td>11.3%</td>
<td>0.60 [0.25, 1.46]</td>
</tr>
<tr>
<td>Garcia-Velasco 1998</td>
<td>3/26</td>
<td>2/26</td>
<td></td>
<td>2.3%</td>
<td>1.50 [0.27, 8.25]</td>
</tr>
<tr>
<td>Glock 1993</td>
<td>3/39</td>
<td>3/41</td>
<td></td>
<td>3.3%</td>
<td>1.05 [0.23, 4.90]</td>
</tr>
<tr>
<td>Koks 1998</td>
<td>15/32</td>
<td>6/24</td>
<td></td>
<td>7.7%</td>
<td>1.88 [0.86, 4.11]</td>
</tr>
<tr>
<td>Kupferminc 1993</td>
<td>6/36</td>
<td>9/35</td>
<td></td>
<td>10.3%</td>
<td>0.65 [0.26, 1.63]</td>
</tr>
<tr>
<td>Larmon 1999</td>
<td>2/57</td>
<td>3/65</td>
<td></td>
<td>3.2%</td>
<td>0.76 [0.13, 4.39]</td>
</tr>
<tr>
<td>Papatsonis 1997</td>
<td>21/95</td>
<td>33/90</td>
<td></td>
<td>38.2%</td>
<td>0.60 [0.38, 0.96]</td>
</tr>
<tr>
<td>Read 1986</td>
<td>4/20</td>
<td>11/20</td>
<td></td>
<td>12.4%</td>
<td>0.36 [0.14, 0.95]</td>
</tr>
<tr>
<td>Weerakul 2002</td>
<td>14/45</td>
<td>10/44</td>
<td></td>
<td>11.4%</td>
<td>1.37 [0.68, 2.75]</td>
</tr>
</tbody>
</table>

Total (95% CI): 383 / 378
Total events: 74 (Ca++CB), 87 (Other tocolytic)
Heterogeneity: $\chi^2 = 12.05$, df = 8 ($P = 0.15$); $I^2 = 34$
Test for overall effect: $Z = 1.59$ ($P = 0.11$)

Favours Ca++CB | Favours Other tocol.
Summary of pairwise evidence

Compared to placebo, “Tocolytics decreased the risk of delivery within 7 days (OR 0.60, 95% CI 0.38, 0.95).” (Gyetvai 1999)

Compared to placebo, “Tocolytics were associated with significant decreases in the odds of delivery within 48 hours (OR 0.47, 95% CI 0.30-0.75)” (Tan 2006)

“Calcium channel blockers appear to be more effective than betamimetic agents in prolonging pregnancy for 7 days or longer” (King 2003).

“In the magnesium sulphate versus control (all studies) no difference was seen for the risk of birth within 48 hours”. (Crowther 2002).
Network meta-analysis of tocolytics

• We conducted a systematic review and network meta-analysis (NMA).
  – NMA an extension of standard meta-analysis to include multiple treatments, not just two.
  – Allows a simultaneous combination of all available evidence in a single analysis.
• Literature searches conducted up to 17/02/2012.
• 8 classes of tocolysis, 95 RCTs of women at risk of pre-term labour, outcomes:
  – delivery delayed by 48 hours, all cause maternal side effects, neonatal respiratory distress syndrome and neonatal mortality.
Direct comparisons

\[ LOR_{Pl \, v \, MS} \]
Direct comparisons

$LOR_{Pl \, v \, P-I}$
Indirect comparisons

Indirect Comparison of MS vs PI formed using relative treatment effects

$$= LOR_{Pl \text{ v } PI} - LOR_{Pl \text{ v } MS}$$
Mixed comparisons

Combining direct and indirect estimates of treatment effect (weighted average)
- Makes use of all available evidence on MS vs PI
- Inference based on more evidence = more robust
Network meta-analysis

Placebo

Calcium channel blocker

Prostaglandin Inhibitor

Magnesium Sulphate

Nitrates

Prostaglandin Inhibitor

Oxytocin receptor blocker

Other

Betamimetic
Results: rank-o-grams of tocolytics

Prostaglandin Inhibitors

Betamimetic

Placebo

Oxytocin receptor blocker

Other

Calcium Channel Blocker

Nitrates

Magnesium Sulfate

48hr delay
NRDS
Neonatal mortality
Maternal side effects
Prostaglandin inhibitors had highest probability of being most effective class for delaying preterm delivery and had a favorable maternal side effect profile.

For the two neonatal outcomes, calcium channel blockers had highest probability of being best class.
Summary: novel evidence synthesis in obstetrics

• Network meta-analysis
  – Is an extension of standard, pairwise meta-analysis
  – Uses all available evidence: indirect & direct
  – Enables comparison of treatments not directly compared in head-to-head trials
  – Increases precision of treatment effect estimates
  – Answers policy relevant questions via rankings of treatments
  – Identifies gaps in evidence base...

Next steps: RCT of prostaglandin inhibitor vs calcium channel blocker with cost-effectiveness analysis?