BASL Portal Hypertension SIG Meeting
1st May 2019

CALIBRE Trial.

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Honorary Reader, University of Birmingham
Disclosures

• None
Background

- Variceal bleeding accounts for 11% admissions with a GI Bleed in the UK with 4 week mortality 15%
- 50% of all cirrhotic patients have varices
- Prevention of variceal bleeding is an important clinical goal
- Recent UK guidelines have fuelled the debate about optimal therapy for primary prevention

Pathogenesis of portal hypertension

Systemic circulation

↓ bioavailability to vasodilators
↑ sensitivity to vasoconstrictors
↑ fibrogenesis
↑ angiogenesis

↑ intrahepatic vascular resistance

↑ splanchnic blood flow

Portal hypertension

myocardial hypertrophy
↓ ventricular compliance
electrophysiological abnormalities

varices

sepsis

encephalopathy

angiogenesis (↑VEGF)

Opening of pre-existing vessels

Portosystemic collateral vessel formation

Dhaliwal, Armstrong, Tripathi.
Natural history of varices

Cirrhosis → Small varices → Medium/Large varices → Bleeding

- Cirrhosis: 5-12% yr
- Small varices: 10% yr
- Medium/Large varices: ~1%
- Bleeding: 30%


?NSBB → NSBB or VBL
# Non-selective beta-blockers

<table>
<thead>
<tr>
<th>PROPOSED MECHANISM OF ACTION</th>
<th>PROPAHOL, NADOLOL</th>
<th>CARVEDILOL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-1 activity to reduce cardiac output and reduce portal blood flow through splanchnic vasoconstriction via β-2 blockade.</strong></td>
<td>1/3 respond haemodynamically</td>
<td>x2-4 greater beta-blocking action of propranolol</td>
</tr>
<tr>
<td><strong>Additional intrinsic α1-adrenergic activity. Greater portal hypotensive effect than propranolol</strong> (Banares, Hepatol 2002; Sinagra APT 2014)</td>
<td>2/3 respond haemodynamically. Effective in propranolol non-responders</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIDE EFFECTS/CAUTIONS</th>
<th>Hypotension, bradycardia, caution in peripheral vascular disease/asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDICATIONS</strong></td>
<td><strong>To be discontinued at time of SBP, renal impairment and hypotension?</strong></td>
</tr>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; prophylaxis in grade II or larger varices. With VBL for 2&lt;sup&gt;nd&lt;/sup&gt; prevention.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DOSE</th>
<th>Propranolol: 40mg BD, titrated up if tolerated or once HR &lt; 50-55bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nadolol: 40mg OD (maximum dose 240mg) or once HR &lt; 50-55bpm</td>
</tr>
<tr>
<td></td>
<td>12.5mg OD if tolerated (HR &lt; 50-55bpm, SBP &lt; 90 mmHg)</td>
</tr>
</tbody>
</table>

Reiberger, Gut 2012, Rajoriya, Tripathi, WJP 2016
Variceal band ligation (VBL)

- VBL: reduced local complication over sclerotherapy and better outcomes
- Compared with placebo 64% reduction in variceal bleeding and 45% reduction in mortality (Imperiale, Hepatol 2001)
- Technique very important with multibanders.
- Not for small varices
### VBL vs NSBB – Variceal bleeding

#### Study or subgroup

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Banding</th>
<th>Beta-blockers</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk of selection bias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jutahka 2005</td>
<td>0/31</td>
<td>4/31</td>
<td>0.9%</td>
<td>0.11</td>
<td>[0.01, 1.98]</td>
</tr>
<tr>
<td>Lo 2004</td>
<td>10/50</td>
<td>16/50</td>
<td>10.5%</td>
<td>0.63</td>
<td>[0.31, 1.24]</td>
</tr>
<tr>
<td>Lui 2002</td>
<td>3/44</td>
<td>9/66</td>
<td>4.1%</td>
<td>0.50</td>
<td>[0.14, 1.74]</td>
</tr>
<tr>
<td>Norberto 2007</td>
<td>5/31</td>
<td>4/31</td>
<td>4.3%</td>
<td>1.25</td>
<td>[0.37, 4.22]</td>
</tr>
<tr>
<td>Perez 2010</td>
<td>5/39</td>
<td>9/36</td>
<td>6.1%</td>
<td>0.51</td>
<td>[0.19, 1.39]</td>
</tr>
<tr>
<td>Schepke 2004</td>
<td>19/75</td>
<td>22/77</td>
<td>14.4%</td>
<td>0.89</td>
<td>[0.52, 1.50]</td>
</tr>
<tr>
<td>Tripathi 2009</td>
<td>17/75</td>
<td>8/77</td>
<td>8.8%</td>
<td>2.18</td>
<td>[1.00, 4.75]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>345</td>
<td>368</td>
<td>49.1%</td>
<td>0.84</td>
<td>[0.53, 1.33]</td>
</tr>
</tbody>
</table>

Total events: 59 (Banding), 72 (Beta-blockers)

Heterogeneity: Tau^2 = 0.15, Chi^2 = 10.42, df = 6 (P = 0.11); I^2 = 42% Test for overall effect: Z = 0.74 (P = 0.46)

#### Unclear risk of selection bias

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Banding</th>
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<th>Weight</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Abdel fattah 2006</td>
<td>4/51</td>
<td>13/52</td>
<td>5.5%</td>
<td>0.31</td>
<td>[0.11, 0.90]</td>
</tr>
<tr>
<td>Abu fittah 2003</td>
<td>4/44</td>
<td>10/66</td>
<td>5.2%</td>
<td>0.60</td>
<td>[0.20, 1.79]</td>
</tr>
<tr>
<td>Chen 1998</td>
<td>1/26</td>
<td>2/30</td>
<td>1.3%</td>
<td>0.58</td>
<td>[0.06, 6.00]</td>
</tr>
<tr>
<td>De 1999</td>
<td>2/15</td>
<td>2/15</td>
<td>2.1%</td>
<td>1.00</td>
<td>[0.16, 6.20]</td>
</tr>
<tr>
<td>Drastich 2005</td>
<td>2/40</td>
<td>2/33</td>
<td>1.9%</td>
<td>0.83</td>
<td>[0.12, 5.54]</td>
</tr>
<tr>
<td>Gheorghe 2002</td>
<td>3/25</td>
<td>13/28</td>
<td>4.9%</td>
<td>0.26</td>
<td>[0.08, 0.80]</td>
</tr>
<tr>
<td>Lay 2006</td>
<td>11/50</td>
<td>12/50</td>
<td>9.9%</td>
<td>0.92</td>
<td>[0.45, 1.88]</td>
</tr>
<tr>
<td>Mora 2000</td>
<td>1/12</td>
<td>2/12</td>
<td>1.4%</td>
<td>0.50</td>
<td>[0.05, 4.81]</td>
</tr>
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<td>4/30</td>
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<td>5.4%</td>
<td>0.44</td>
<td>[0.15, 1.29]</td>
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<td>4/46</td>
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<td>0.32</td>
<td>[0.11, 0.91]</td>
</tr>
<tr>
<td>Psilopoulos 2005</td>
<td>6/31</td>
<td>7/30</td>
<td>6.3%</td>
<td>0.83</td>
<td>[0.32, 2.18]</td>
</tr>
<tr>
<td>Song 2000</td>
<td>2/16</td>
<td>1/15</td>
<td>1.4%</td>
<td>1.88</td>
<td>[0.19, 18.60]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>386</td>
<td>405</td>
<td>50.9%</td>
<td>0.57</td>
<td>[0.40, 0.80]</td>
</tr>
</tbody>
</table>

Gluud, Cochrane 2012
Primary prevention in medium/large varices - UK Guidelines Conundrum

NICE 2016:
Use VBL as first line

BSG 2015:
Recommends VBL and NSBB (propranolol (nadolol/carvedilol)) and suggests NSBB as first line. VBL if contraindications of NSBB

NICE 2016, Tripathi 2015
Primary prevention of variceal bleeding in patients with liver cirrhosis

Introduction

The aim of the HTA Programme is to ensure that high quality research information on the effectiveness, costs and broader impact of health technology is produced in the most efficient way for those who use, manage, provide care in or develop policy for the NHS. Topics for research are identified and prioritised to meet the needs of the NHS. Health technology assessment forms a substantial portfolio of work within the National Institute for Health Research and each year about fifty new studies are commissioned to help answer questions of direct importance to the NHS. The studies include both primary research and evidence synthesis.

Research Question:

What is the clinical and cost effectiveness of non-selective beta-blockers compared to endoscopic variceal band ligation for primary prevention of variceal bleeding?

1. Intervention: Oral non-selective beta-blockers (NSBB), choice to be justified by applicants.
2. Patient group: Adults with cirrhosis and medium or large oesophageal varices, no history of variceal haemorrhage and no contraindications to beta blocker use.
5. Study design: A randomised non-inferiority trial to compare NSBB against VBL. When appropriate subgroup analyses should be performed. The trial data should also be incorporated into a new or updated systematic review with meta-analyses. A model of cost effectiveness is required.
6. Important outcomes: Time to first variceal bleeding event; overall mortality.
   Other outcomes: Adverse effects; an updated meta-analysis; patient preference; QoL; cost effectiveness.
7. Minimum duration of follow-up: Duration of study sufficient to accumulate enough events to inform the model.
### Trial Design
- A multicentre randomised controlled, open-label, self-evident two-arm trial with internal pilot.

### Aim
- To investigate the clinical and cost-effectiveness of carvedilol versus variceal band ligation in patients with cirrhosis and medium to large oesophageal varices that have not bled.

### Sample size 2630 - CALIBRE largest ever Phase III trial in cirrhosis
- Based on superiority hypothesis – 33% proportional difference in 1 year bleeding with carvedilol (absolute 12% (VBL), 8% (carvedilol)).

### NIHR HTA funded - £2.3m
- Sponsor University of Birmingham
- Over 75 months

### Recruitment over 4 years nationally
- All acute NHS trusts and health boards in UK potentially eligible

### Primary end point
- Any variceal bleeding within 1 year of randomisation
Varices are banded at 2–4-weekly intervals until eradication. After successful eradication of the varices, repeat endoscopy at 3 months, then 6 monthly thereafter. Any recurrent varices should be treated with further VBL until eradication.
Study protocol for a randomised controlled trial of carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis (CALIBRE trial)

Dhiraj Tripathi,1,2 Peter Hayes,3 Paul Richardson,4 Ian Rowe,5 James Walter Fersuon,1,2 Peter Devine,6 Jonathan Mathers,7 Christopher Poyner,7 Sue Jowett,7 Kelly Handley,8 Margaret Grant,8 Gemma Slinn,8 Peter Brocklehurst,8 Khaled Ahmed,8 on behalf of CALIBRE trial collaborative group

To cite: Tripathi D, Hayes P, Richardson P, et al. Study protocol for a randomised controlled trial of carvedilol versus variceal band ligation in primary prevention of variceal bleeding in

abstract

Introduction Liver cirrhosis is the fifth largest cause of adult deaths, and a major complication, variceal bleeding is associated with a 1-year mortality of 40%. There is uncertainty on the first-line therapy for prevention of variceal bleeding owing to a lack of adequately powered hypertension and variceal bleeding. In patients with cirrhosis, varices develop at a rate of 5% per year with 10 year cumulative incidence of 44%.3 At least 3000 patients are admitted to hospital in England per year with variceal bleeding, with inpatient mortality
Grant activation: March 2018

0 - 6 months:
- Application for ethical and governance approval through REC and MHRA with appropriate documents. For sites outside of England the appropriate processes will be followed.
- Ethical approval obtained.
- Trial included on the NIHR portfolio study.
- Sites identified for pilot phase of study with site-specific documentation completed by nominated PIs.
- Trial steering committee (TSC) and Data Monitoring Committee (DMC) formed.
- Randomisation methods finalised.
- Trials registered with ISRCTN and Eudra-CT.

6-18 months:
- Pilot sites begin screening and recruitment with aim of 20 sites over 12 months.
- Once recruitment target of at least 240 patients is met trial to be rolled out nationally through CRN network leads for Gastroenterology & Hepatology.

19-54 months:
- This will be assessed by the trial management group and TSC.

55-66 months:
- Follow up of patients recruited.

67-75 months:
- Analysis of data and dissemination.
CALIBRE - Carvedilol versus variceal band ligation in primary prevention of variceal bleeding in liver cirrhosis

Email: calibretrial@trial.bham.ac.uk

Twitter: @CalibreTrial
Conclusions

• Prevention of variceal bleeding is an important clinical goal
• Controversy regarding efficacy of banding vs NSBB in primary prevention of medium/large varices.
• CALIBRE aims to provide conclusive evidence in primary prevention.
THANK YOU!

CALIBRE TRIAL MANAGEMENT GROUP

Clinical
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Prof Peter C Hayes, Edinburgh

PPI Representative
Mr Peter Devine

BCTU, University of Birmingham (Sponsor)
Prof Peter Brocklehurst (Director)
Dr Margaret Grant (Director of Operations and Trials Management)
Dr Jonathan Mathers, Mr Christopher Poyner (Qualitative research)
Dr Susan Jowett (Health Economics)
Dr Kelly Handley (Medical statistics)
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