Clinical endpoints

Mike Poullis
Ask Mum

- Renal failure
- LV function
- Age
- Pulmonary function
- Hct
- Transfusion

- Remember stats determines association NOT causation
What determines hct?

- Bone marrow function
- Losses
Variation and Quality

• Variation is bad – can’t all be right

• Look at the best not the highest or lowest

• Eg Beta blockers quality marker
Perioperative beta-blocker therapy and mortality after major noncardiac surgery.

Lindenauer PK', Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM.

Author information

Abstract

BACKGROUND: Despite limited evidence from randomized trials, perioperative treatment with beta-blockers is now widely advocated. We assessed the use of perioperative beta-blockers and their association with in-hospital mortality in routine clinical practice.

METHODS: We conducted a retrospective cohort study of patients 18 years of age or older who underwent major noncardiac surgery in 2000 and 2001 at 329 hospitals throughout the United States. We used propensity-score matching to adjust for differences between patients who received perioperative beta-blockers and those who did not receive such therapy and compared in-hospital mortality using multivariable logistic modeling.

RESULTS: Of 782,969 patients, 663,635 (85 percent) had no recorded contraindications to beta-blockers, 122,338 of whom (18 percent) received such treatment during the first two hospital days, including 14 percent of patients with a Revised Cardiac Risk Index (RCRI) score of 0 and 44 percent with a score of 4 or higher. The relationship between perioperative beta-blocker treatment and the risk of death varied directly with cardiac risk; among the 580,665 patients with an RCRI score of 0 or 1, treatment was associated with no benefit and possible harm, whereas among the patients with an RCRI score of 2, 3, or 4 or more, the adjusted odds ratios for death in the hospital were 0.88 (95 percent confidence interval, 0.80 to 0.98), 0.71 (95 percent confidence interval, 0.63 to 0.80), and 0.58 (95 percent confidence interval, 0.50 to 0.67), respectively.

CONCLUSIONS: Perioperative beta-blocker therapy is associated with a reduced risk of in-hospital death among high-risk, but not low-risk, patients undergoing major noncardiac surgery. Patient safety may be enhanced by increasing the use of beta-blockers in high-risk patients.

Meta-analysis of secure randomised controlled trials of β-blockade to prevent perioperative death in non-cardiac surgery.

Bouri S', Shun-Shin MJ, Cole CD, Mayet J, Francis DP.

Author information

Abstract

BACKGROUND: Current European and American guidelines recommend the perioperative initiation of a course of β-blockers in those at risk of cardiac events undergoing high- or intermediate-risk surgery or vascular surgery. The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) family of trials, the bedrock of evidence for this, are no longer secure. We therefore conducted a meta-analysis of randomised controlled trials of β-blockade on perioperative mortality, non-fatal myocardial infarction, stroke and hypotension in non-cardiac surgery using the secure data.

METHODS: The randomised controlled trials of initiation of β-blockers before non-cardiac surgery were examined. Primary outcome was all-cause mortality at 30 days or at discharge. The DECREASE trials were separately analysed.

RESULTS: Nine secure trials totalling 10 529 patients, 291 of whom died, met the criteria. Initiation of a course of β-blockers before surgery caused a 27% risk increase in 30-day all-cause mortality (p=0.04). The DECREASE family of studies substantially contradict the meta-analysis of the secure trials on the effect of mortality (p=0.05 for divergence). In the secure trials, β-blockade reduced non-fatal myocardial infarction (RR 0.73, p=0.001) but increased stroke (RR 1.73, p=0.05) and hypotension (RR 1.51, p<0.00001). These results were dominated by one large trial.

CONCLUSIONS: Guideline bodies should retract their recommendations based on fictitious data without further delay. This should not be blocked by dispute over allocation of blame. The well-conducted trials indicate a statistically significant 27% increase in mortality from the initiation of perioperative β-blockade that guidelines currently recommend. Any remaining enthusiasts might best channel their energy into a further randomised trial which should be designed carefully and conducted honestly.
ART

• Don’t assume factors you measure are the only important factors
• You can’t measure some

• How can you quantitate how good a picture is
Case 1

- Dry on closing
- No CVA / MI
- Narrow mediastinum
- Mediastinal drainage 400mL
- No resternotomy
- No blood

Case 2

- Wet on closing
- No CVA / MI
- Wide mediastinum
- Mediastinal drainage 400mL
- No resternotomy
- Blood transfusion
Treat the cause

NOT

The effect
Is single-unit blood transfusion bad post-coronary artery bypass surgery?

Authors: Richard Warwick, Neeraj Mediratta, John Chalmers, Mark Pullan, Matthew Shaw, James Mcshane, Michael Poullis

Publication date: 2013/6/1

Journal: Interactive cardiovascular and thoracic surgery

Volume: 16

Issue: 6

Pages: 765-771

Publisher: Oxford University Press

Description: OBJECTIVES Publications in the surgical literature are very consistent in their conclusions that blood is dangerous with regard to in-hospital mortality, morbidity and long-term survival. Blood is frequently used as a volume expander while simultaneously increasing the haematocrit. We investigated the effects of a single-unit blood transfusion on long-term survival post-cardiac surgery in isolated coronary artery bypass grafting patients. METHODS A prospective single-institution cardiac surgery database was analysed involving 4615...

Total citations: Cited by 7

N=4,615
Measures

• Relevant

• Cheaply and easily measurable

• Liverpool cardiac surgery database

• Univariate TOO SIMPLE
Potential measures

- Mortality
- Morbidity
- Survival
What determines minimum Hct

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Coefficient</th>
<th>t</th>
<th>P</th>
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<tr>
<td>Age</td>
<td>-0.04946</td>
<td>-10.773</td>
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<td>Pre operative Hct</td>
<td>0.2032</td>
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<td>BSA</td>
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<td>Female</td>
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<td>Operation type</td>
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<td>7.936</td>
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<tr>
<td>CPB Time</td>
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<td>-16.315</td>
<td>&lt;0.0001</td>
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<tr>
<td>Priority</td>
<td>-0.7905</td>
<td>-7.707</td>
<td>&lt;0.0001</td>
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<tr>
<td>RENAL</td>
<td>-0.5384</td>
<td>-3.325</td>
<td>0.0009</td>
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<tr>
<td>PVD</td>
<td>-0.4904</td>
<td>-3.413</td>
<td>0.0006</td>
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</table>
Mortality IHM

- **Univariate**
  - \( P < 0.0001 \)

- **Multivariate**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>( P )</th>
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<td>AGE</td>
<td>1.0730</td>
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<tr>
<td>CPB Time</td>
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<td>1.0083 to 1.0152</td>
<td>&lt;0.0001</td>
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<tr>
<td>Aortic</td>
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<tr>
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<td>Urgent</td>
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<td>1.3394 to 18.3206</td>
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<td>Salvage</td>
<td>25.5423</td>
<td>3.1498 to 207.1275</td>
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<td>Moderate LV</td>
<td>1.8746</td>
<td>1.1888 to 2.9561</td>
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<td>Poor LV</td>
<td>2.5338</td>
<td>1.4413 to 4.4545</td>
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</tbody>
</table>

30 and 90 day similar findings

**NO MIN HCT**

**NO PRE OP HCT**
Survival - Univariate

Number at risk
Group: Hct<19
1066 950 687 440 213 20
Group: Hct>19
3165 2753 2009 1216 591 74
Survival - Multivariate

Survival (Years)

Survival probability (%)

Hct > 19

Hct < 19

Survival (Years)
So

- Use evidence available

- BUT

- Use common sense
Factors a surgeon feels are important
Mortality

In hospital
30 day
90 day
180 day
360 day

Mortality (%)

IHM  30 Day  90 Day  180 Day  365 Day

Mortality (%)
Morbidity

- Renal failure
- Prolonged ventilation
- Sternal wounds
- Re operation
- Stroke

- Mediastinal blood loss
- Low cardiac output
Renal failure

• Creatinine change

• eGFR change

• RIFLE

• Kidney Disease: Improving Global Outcomes (KDIGO)

• Need for dialysis
Prolonged ventilation

- >12, 24, 48 hours
- Median
- Hct effect
- Transfusion effect
Sternal wounds

- Deep only
- STS
  - Number of patients who, within 30 days postoperatively, develop deep sternal wound infection involving muscle, bone, and/or mediastinum requiring operative intervention
  - Must have all of the following conditions:
    - Wound opened with excision of tissue (I&D) or re-exploration of mediastinum
    - Positive culture unless patient on antibiotics at time of culture or no culture obtained
    - Treatment with antibiotics beyond perioperative prophylaxis

- ? Need for VAC therapy
Re operation

- All reasons
- Bleeding
Stroke

- Neuro cognitive defects
- TIA
- RIND
- CVA

- Most CVAs post cardiac surgery are embolic
Mediastinal blood loss

- 4, 12 hours
- Total drainage

- Confounded by cell salvage of mediastinal loss

- LHCH results
Low Cardiac Output

- Cardiac enzymes
- Inotropes for > 24/48 hours
- IABP use post CPB

- ?? Surgeon messes up cardioplegia or coronary anastomosis
Problem

• Virtually impossible to untangle
  – Pre op hct
  – Lowest hct on CPB
  – Transfusion
  - Operative issues

• Other institutional / individual factors

• NEED MULTIVARIATE ANALYSIS