



Centre for Clinical Effectiveness

Enhancing patient outcomes through clinical application of the best available evidence

EVIDENCE CENTRE
CRITICAL APPRAISAL
Series 2002: Therapy

Do cardiac surgical patients on Clopidogrel bleed more and require more blood transfusions than those not on Clopidogrel?

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SUMMARY STATEMENT:

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REQUEST:

Do cardiac surgical patients on Clopidogrel bleed more and require more blood transfusions than those not on Clopidogrel?

REQUESTED BY:

Anne Mennen, Nurse Unit Manager, 32 South/specialty, Monash Medical Centre, Clayton.

METHODOLOGY

Search Strategy

The Centre for Clinical Effectiveness defines the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined National Health and Medical Research Council (NHMRC, 2000) criteria (see Appendix 1).

First, we search for systematic reviews, evidence based clinical practice guidelines, health technology assessments and randomised controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable or have other methodological difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Such studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

Details of Evidence Request

Patient/condition: Cardiac surgical patients
Intervention: Clopidogrel (plavix, Iscover)
Comparison: No Clopidogrel, placebo
Outcomes: Bleeding complications, transfusion requirements, death

Search terms (see Appendix 2 for exact search strategy)

Table 1. Search terms used in the retrieval of articles from electronic databases and websites

Field of focus	Search term
Patient/condition-related	Exp Coronary Artery Bypass/ or Coronary Artery Bypass.tw, CABG.tw, exp Cardiopulmonary Bypass/ or Cardiopulmonary Bypass.tw, CPB.tw, heart-lung bypass.tw, cardiac surgery patients.Tw
Intervention-related	Exp Platelet Aggregation Inhibitors/ or Platelet Aggregation Inhibitor\$, (Iscover or Plavix or Clopidogrel).tw.
Outcome-related	Exp Blood Transfusion/ or Blood Transfusion\$.tw, exp Hemorrhage/ or (Hemorrhage or bleed\$.tw, exp Postoperative Hemorrhage/, death\$.tw.

Resources Searched

We searched the following databases and Internet websites:

Cochrane Library CD-ROM- Issue 1, 2002

Medline (OVID)- 1966 to February week 4 2002

CINAHL (OVID) – 1982 to December week 2 2001

Current contents (OVID) – 1993 week 26 to 2002 week 10

PreMedline (OVID)- March 4, 2002

Australasian Medical Index – February 2002

National Guideline Clearinghouse – March 4, 2002

Refinements, Searching & Reporting Constraints:

We included items of evidence that were available to us on 5 March 2002. Our search was restricted to adults aged over 19 years and articles published in English in the last 6 years (1995-2002). Our search was also restricted to studies that compared Clopidogrel and placebo treatments in cardiac surgery.

RESULTS:

From our sources we identified 6 articles related to the request and was categorised as follows:

Table 2. Study designs of articles retrieved by search

Study Design	Number
Systematic reviews or meta-analyses	0
Evidence-based clinical practice guidelines	0
Randomised controlled trials	0
Pseudo-randomised controlled trials	0
Comparative studies	1
Case series, case report, Narrative reviews	5

Articles were excluded from further appraisal as follows:

Table 3: Reason for exclusion of article retrieved by search

Reason for exclusion	Number
Level IV studies	5

This left one article for appraisal. We are reasonably confident this article represents the most relevant finding published to date based on our refinements, searching and reporting constraints.

EVIDENCE SUMMARIES

Format

Evidence summaries are presented as spreadsheets attached to this report. Each spreadsheet contains the article citation, details of the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

REFERENCES

ARTICLE CRITICALLY APPRAISED

Yende, S. and R. G. Wunderink (2001). "Effect of clopidogrel on bleeding after coronary artery bypass surgery." Critical Care Medicine **29**(12): 2271-5.

ARTICLES NOT CRITICALLY APPRAISED

- **Level IV evidence (case series, case report, narrative review)**

1. Dunlop, H. (2001). "Clopidogrel (Plavix): hematological reactions." Cmaj (Canadian Medical Association Journal) **164**(1): 92-3, 95-7.

2. Kilaru, P. K., M. J. Schweiger, et al. (2001). "Diffuse alveolar hemorrhage after clopidogrel use." Journal of Invasive Cardiology **13**(7): 535-7.

3. Lee, L. Y., W. DeBois, et al. (2002). "The effects of platelet inhibitors on blood use in cardiac surgery." Perfusion **17**(1): 33-37.

4. Levy, J. H. (2000). "Platelet inhibitors and bleeding in cardiac surgical patients." Annals of Thoracic Surgery **70**(2 Suppl): S9-11

5. Milas, B. L., D. R. Jobses, et al. (2000). "Management of bleeding and coagulopathy after heart surgery." Seminars in Thoracic & Cardiovascular Surgery **12**(4): 326-36.

APPENDIX 1

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Levels of Evidence

Based on "How to use the evidence: assessment and application of scientific evidence" (National Health & Medical Research Council, Canberra, 2000):

- | | |
|-------------|--|
| Level I | Evidence obtained from a systematic review of all relevant randomised controlled trials. |
| Level II | Evidence obtained from at least one properly designed randomised controlled trial. |
| Level III-1 | Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method). |
| Level III-2 | Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized, cohort studies, case control studies, or interrupted time series with a control group. |
| Level III-3 | Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group. |
| Level IV | Evidence obtained from case series, either post-test or pre-test/post-test. |

APPENDIX 2

Search strategy (Search terms for Medline database is shown below. Search terms for other databases is not shown)

1. exp Coronary Artery Bypass/
 2. Coronary Artery Bypass.tw.
 3. CABG.tw.
 4. exp Coronary Disease/
 5. Coronary Disease.tw.
 6. exp Cardiac Surgical Procedures/
 7. Cardiac Surgical Procedure\$.tw.
 8. exp Cardiopulmonary Bypass/
 9. Cardiopulmonary Bypass.tw.
 10. CPB.tw.
 11. heart-lung bypass.tw.
 12. (cardiac or heart or cardiothoracic or coronary).tw.
 13. exp SURGERY/
 14. Surgery.tw.
 15. 13 or 14
 16. 12 and 15
 17. or/1-11
 18. 17 or 16
 19. exp Platelet Aggregation Inhibitors/
 20. (Platelet Aggregation Inhibitor\$ or iscover or plavix or clopidogrel).tw.
 - 21.19 or 20
 - 22.18 and 21
 - 23.exp Blood Transfusion/
 - 24.Blood Transfusion\$.tw.
 - 25.exp Hemorrhage/
 26. (Hemorrhage or bleed\$.tw.
 27. exp Postoperative Hemorrhage/
 28. death\$.tw. or exp death/ or exp death, sudden/ or exp death, sudden, cardiac/
 29. or/23-28
 30. 22 and 29
 31. limit 30 to (human and English language and all adult <19 plus years> and yr=1995-2002)
- \$ Wildcard indicating truncation

<p style="text-align: center;">Evidence Summary Therapy/Intervention</p> <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: fit-content;"> <p style="text-align: center;">Effects of clopidogrel versus placebo in cardiac surgery patients</p> </div>	<p style="text-align: center;">Study</p> <p>Yende, S. and R. G. Wunderink (2001). Effect of clopidogrel on bleeding after coronary artery bypass surgery. Critical Care Medicine 29(12): 2271-5</p>
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p style="text-align: center;">Level III-2 – A prospective observational cohort study</p>
<p>DESCRIPTION: Patients (subjects), Intervention, Comparisons, Outcomes, Inclusion & Exclusion Criteria</p>	<p>Setting: Tertiary Care centre, Methodist Healthcare Central Hospital, Memphis, TN, USA. Patients: Consecutive patients undergoing conventional or off-pump coronary artery bypass (CABG) between June 1999 and January 2000 (n=247). Patients were identified before surgery. Intervention: None. The study evaluated the effects of clopidogrel on bleeding complications after coronary artery bypass graft surgery. Outcomes: Need for reexploration secondary to bleeding (primary end point), and need for transfusion of blood products, number of units of blood products transfused and chest tube output were secondary end points. Incl & Excl Criteria: All patients undergoing conventional CABG or off-pump coronary artery bypass surgery and those undergoing combined valve surgery and CABG were included. Patients undergoing valvular surgery alone were excluded.</p>
<p>VALIDITY: Methodology, rigour, selection</p>	<p>Randomisation: No. Blinding: Surgeons were not aware of data collection and the preliminary results were not available to them during the study. Surgeons were not blinded to antiplatelet medications received by patients. All patients accounted for: Yes. Two patients who died within the first 24 hrs after surgery were excluded from analysis. Patients treated equally: During the postoperative period, patients received transfusions of PRBC, platelets, fresh frozen plasma, or cryoprecipitate at the discretion of the surgeon. Use of aspirin, clopidogrel, ticlopidine, heparin, and glycoprotein IIb/IIIa inhibitors (epitifibate or tirofiban) during the 5 days before surgery was recorded. Similar groups: Baseline characteristics of clopidogrel recipients and nonrecipients was similar.</p>
<p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<ul style="list-style-type: none"> • Eight (3%) of 247 patients required reexploration secondary to bleeding. Bleeding was from a single vessel in 3 patients and secondary to diffuse oozing, or was not identified in the remaining 5 patients. • 37 (15%) of 247 patients had chest tube output. • At baseline, 51 (21%) patients used clopidogrel and 194 (79%) didn't. All but three patients who received clopidogrel also received aspirin. Only one (0.4%) patient received ticlopidine, 15 (6.6%) patients received glycoprotein IIb/IIIa, and 103 (45.4%) patients received heparin. Recipients of clopidogrel preoperatively had higher incidence of reexploration for bleeding (9.8% vs. 1.6%, p=0.01; Odds Ratio=6.9, 95% CI 1.6-30). When the 3 patients who bled from a single source were excluded, the risk of reexploration for clopidogrel recipients was 6.1% vs. 1.0%, p=0.058. Clopidogrel also increased the percentage of patients receiving packed red blood cell transfusion (72.6 vs. 51.6%, p =0.007), the number of packed red blood cell units (3 vs. 1.6, p=0.0004), and the number of cryoprecipitate units (2.4 vs. 1.2, p =0.04) transfused after coronary artery bypass graft surgery. Among clopidogrel recipients, a trend for increased transfusion of platelet units (4.3 vs. 1.7, p =0.05) and fresh frozen plasma units (1.1 vs. 0.6, p =0.08) also was found. No significant difference in mortality, length of ICU stay and length of hospital days between those receiving clopidogrel and those who didn't.

<p>AUTHOR(S) CONCLUSIONS: Limitations, implications for practice and research</p>	<p>"Preoperative use of clopidogrel in combination with aspirin is associated with increased need for surgical reexploration as well as risk of packed red blood cell and cryoprecipitate transfusions after coronary artery bypass graft surgery."</p>
<p>OUR COMMENTS: Opportunity for bias, weakness and strength</p>	<p>Potential for bias: Ten surgeons performed CABG. The need for reexploration or for blood and blood product transfusion was left to the discretion of the individual surgeon. Seven different surgeons operated on the eight patients who required reexploration.</p> <p>Weakness/es:</p> <ul style="list-style-type: none"> • An observational study • Surgeons can confound the effect of clopidogrel on outcomes by treatment bias and the authors acknowledged this. • Unclear if local ethics committee approved the study. • As acknowledged by the authors, it is difficult to determine the independent effect of clopidogrel alone in this study. Thus a further controlled study is warranted. <p>Strength/s:</p> <ul style="list-style-type: none"> • Used a clear definition for chest tube output (patients who bled >100 mL/hr for two consecutive hours). • Preoperative patient characteristics and perioperative and postoperative complications, total lengths of intensive care unit and hospital stay were recorded for all patients. • Surgeons were not aware of the data collected and were blinded to the preliminary results during the study. • Compared baseline characteristics of patients requiring reexploration and those who didn't. • Acknowledged study limitations.

EXPLANATION OF TERMINOLOGY USED IN SPREADSHEET

Level of evidence: A hierarchy of study evidence that indicates the degree to which bias has been eliminated in the study design.

Intervention: A therapeutic procedure such as treatment with a pharmaceutical agent, surgery, a dietary supplement, a dietary change or psychotherapy.

Randomisation: A process of allocating participants to treatment or control group within a controlled trial by using a random mechanism, such as coin toss, random number table or computer-generated random numbers. Study subjects have an equal chance of being allocated to an intervention or control group; thus, the two groups are comparable. Randomisation ensures that the results are not biased by the selection of particular types of patients to receive a specific therapy.

Blinding: Blinding or masking is a process used in epidemiological studies and clinical trials in which the observers and the subjects have no knowledge as to which treatment groups subjects are assigned. It is undertaken in order to minimise bias occurring in patient response and outcome measurement.

All patients accounted for: Once patients are randomly allocated to a specific group and withdraw before study conclusion, they have to be accounted for in order to ensure that patients withdrawing from the study are not significantly different from those continuing in the study. The final analysis should be conducted on an intention-to-treat basis, which includes the results of withdrawn patients in the analysis.

Patients treated equally: To be able to attribute any difference in the observed outcome to the intervention, study patients need to be treated equally in every way except for the intervention being evaluated.

Similar groups: Baseline characteristics of patients that are also likely to affect results should be evenly distributed between the intervention and control groups. Following proper randomisation, patients' attributes would be expected to be equally distributed between groups.

Validity:

Of measurement: an expression of the degree to which a measurement measures what it purports to measure; it includes construct and content validity.

Of study: the degree to which the inferences drawn from the study are warranted when account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn (internal and external validity, applicability, generalisability).

Potential for bias: Bias is a systematic deviation of a measurement from the 'true' value leading to either an over (or under) estimation of the treatment effect. Bias can originate from many different sources (including allocation of patients, measurement, interpretation, publication and review of data).