The effect of pre-operative aspirin on bleeding, transfusion, myocardial infarction, and mortality in coronary artery bypass surgery: a systematic review of randomized and observational studies


CRD summary
The authors concluded that pre-operative aspirin increased bleeding after coronary artery bypass grafting; doses under 325 mg/day may prevent this increase. Most studies were old and further research was required in current practice settings. This was generally a well-conducted and clearly reported review. The authors’ conclusions incorporating the relevance of studies to current clinical practice appeared reliable.

Authors’ objectives
To evaluate the efficacy and safety of pre-operative aspirin in patients undergoing coronary artery bypass grafting.

Searching
MEDLINE, EMBASE, CINAHL, ACP Journal Club, The Cochrane Library and DARE were searched from inception to the first quarter of 2007. Search terms were reported. Non-English articles were translated. Reference lists of relevant papers were screened.

Study selection
Randomised controlled trials (RCTs) and observational studies that compared aspirin prior to first-time coronary artery bypass grafting with cardiopulmonary bypass with or without combined procedures versus with control (aspirin discontinued or placebo) in adults (aged 18 or more) were eligible for inclusion. Studies in which one treatment group received other anticoagulants or antiplatelet drugs were excluded. Studies had to assess postoperative blood loss, packed red blood cell transfusion, reoperation, perioperative myocardial infarction (MI) or death. The review classified pre-operative aspirin as aspirin discontinued less than seven days before surgery.

Where reported, the included studies evaluated varying doses of aspirin (80 mg to 2,600 mg daily). Most RCTs did not report the use of perioperative fibrinolytic drugs; about half of the observational studies reported antifibrinolytic use. Most RCTs did not report use of postoperative antiplatelet regimens; aspirin (150 mg to 325 mg daily) was given postoperatively to both treatment groups in two RCTs. The mean age of patients ranged from 54 to 69 years. The percentage of women ranged from 0 to 34 per cent. Most patients were undergoing elective surgery. Publication dates ranged from 1978 to 2005.

Two reviewers independently selected studies and resolved disagreements through consensus.

Assessment of study quality
Two reviewers independently assessed validity using the Jadad scale (reporting of randomisation, blinding and withdrawals) and resolved disagreements through consensus. The maximum possible score was 5 points.

Data extraction
Authors were contacted if required for missing data. Packed red blood cell transfusions reported as millilitres were converted to number of units. Where there were multiple aspirin groups, the number in the control group was divided between them. Two reviewers independently extracted data and resolved disagreements through consensus.

Methods of synthesis
RCTs and observational studies were analysed separately. Pooled mean differences (MD) and odds ratios (OR) with 95% confidence intervals (CI) were calculated using random-effects models. A value of 0.5 was added to cells with zero events in one or both treatment groups. Heterogeneity was assessed using the $X^2$ and the $I^2$ statistics. Pre-specified subgroup analysis was used to examine the influence of aspirin dose (<325 mg versus ≥325 mg) and date of publication. RCTs were analysed by Jadad score. Publication bias was assessed using a funnel plot and Egger’s test.
Results of the review
Eight RCTs (n=805) and 14 observational (n=4,485) studies were included. Four RCTs were low quality (Jadad score 1 or 2 out of 5) and four were high quality (Jadad score 4). Four RCTs reported blinded outcome assessment.

RCTs
Pre-operative aspirin was associated with a statistically significant increase in postoperative bleeding MD 104.9 mL (95% CI: 19.2, 190.6; p=0.016; seven studies) and reoperation, OR 2.52 (95% CI: 1.18, 5.38; p=0.017; six studies) compared to control. There was moderate heterogeneity for bleeding (p=0.093, $I^2=41.2\%$). This was no longer present when studies were grouped by aspirin dose. Aspirin >325 mg was associated with a statistically significant increase in postoperative bleeding, MD 229.6 mL (95% CI: 18.7, 440.5; p=0.033; three studies). There was no significant difference between aspirin < 325 mg and control, MD 65.3 mL (95% CI: -20.2, 150.8; p=0.134; four studies). There was significant heterogeneity between these subgroups (p=0.094). Heterogeneity in the main analyses remained after grouping studies by publication date and quality. There was no statistically significant difference between aspirin and control in transfusion requirements (four studies), perioperative MI (three studies) or death (five studies).

Observational studies
Pre-operative aspirin was associated with a statistically significant increase in postoperative bleeding (10 studies) and transfusion requirements (11 studies) compared to control; statistically significant heterogeneity was found for both analyses (p<0.01, $I^2=71.3\%$ for postoperative bleeding and p =0.007, $I^2=54.7\%$ for transfusion requirements). There was no statistically significant difference between aspirin and control in reoperation rates (eight studies) or perioperative MI (one study).

Funnel plots were asymmetrical for bleeding and mortality among RCTs suggesting publication bias.

Authors' conclusions
Pre-operative aspirin increased postoperative bleeding in patients undergoing coronary artery bypass grafting; using doses under 325 mg/day may prevent this increase. Most RCTs were old and further research was required to evaluate pre-operative aspirin in current practice settings.

CRD commentary
The review question was clearly stated. Several relevant sources were searched and attempts were made to minimise language bias. No specific attempts to minimise publication bias were reported and some evidence of this bias was found. Appropriate methods were used to minimise reviewer error and bias during the review process. The validity of RCTs was assessed, but no comments were made on the quality of observational studies. Studies were appropriately grouped by design and combined in meta-analyses. Heterogeneity was assessed and various predefined subgroup analyses were conducted. This was generally a well-conducted and clearly reported review. The authors’ conclusions incorporating the relevance of studies to current clinical practice were likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that a large RCT was required to evaluate the safety and efficacy of perioperative aspirin in coronary artery bypass grafting patients who also routinely receive perioperative fibrinolytics.

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