Efficacy and safety of unfractionated heparin plus glycoprotein IIb/IIIa inhibitors during revascularization for an acute coronary syndrome: a meta-analysis of randomized trials performed with stents and thienopyridines

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CRD summary

The review found adding glycoprotein IIb/IIIa inhibitors to unfractionated heparin reduced myocardial infarction and revascularisation rates without increasing major bleeding among patients undergoing revascularisation for acute coronary syndrome using stents and thienopyridine. The intervention increased minor bleeding. Groups had similar mortality rates. These conclusions are probably reliable but the review included poor quality and non placebo-controlled trials.

Authors' objectives

To assess the benefits and risks of adding glycoprotein IIb/IIIa inhibitors to unfractionated heparin among patients who underwent revascularisation for acute coronary syndrome using coronary stents and periprocedural thienopyridines.

Searching

MEDLINE (from inception to July 2010), the Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were searched without language restriction. Search terms were reported. The reference lists of systematic reviews were checked.

Study selection

Eligible studies were randomised controlled trials (RCTs) that compared unfractionated heparin plus glycoprotein IIb/IIIa inhibitors versus unfractionated heparin plus placebo or other control in patients who underwent revascularisation for acute coronary syndrome using coronary stents and periprocedural thienopyridine.

Participants in the included studies had a median age of 62 years, 24% (median) were women, 19% (median) had diabetes mellitus and 69% presented with ST-elevation myocardial infarction. All participants received a thienopyridine, which was usually administered before the intervention. Glycoprotein IIb/IIIa inhibitors were given as a bolus followed by infusion, usually for 12 hours post-procedure. Those used most commonly were abciximab or tirofiban. Doses of unfractionated heparin varied, and in some studies a higher dose was used in the control arm than in the intervention arm. The definition of myocardial infarction varied across studies. The primary review outcomes were myocardial infarction and major bleeding. Other outcomes were minor bleeding, revascularisation, thrombocytopenia and total stroke (all assessed at 30 days) and all-cause mortality (assessed at 30 days and six to 12 months).

The authors did not state how the papers were selected for the review or how many reviewers performed the selection.

Assessment of study quality

The following aspects of study quality were assessed: reporting of randomisation methods, completeness of follow up, and blinded outcome assessment. The authors did not state how many reviewers performed the assessment.

Data extraction

Risk ratios (RRs) and 95% confidence intervals (CIs) were extracted from each study. Primary study authors were contacted for more data as required.

Two authors independently extracted the data and discrepancies were resolved by the consensus of another two authors.

Methods of synthesis

Data were combined to calculate pooled risk ratios and 95% confidence intervals, using a random-effects DerSimonian and Laird model. Analyses were stratified by type of glycoprotein inhibitor used (abciximab or small molecule). Begg's test and funnel plots were used to assess for publication bias, and the I^2 and Q statistics were used to assess statistical heterogeneity. Subgroup analyses were conducted by type of myocardial infarction (ST-elevation or non-ST-elevation).

Sensitivity analyses were used to assess the effect of including only placebo-controlled studies, including only those clearly using Thrombosis in Myocardial Infarction bleeding criteria, and excluding the largest study.

Results of the review

Sixteen RCTs were included (7,612 participants, range 31 to 2,022), of which only seven were placebo-controlled.

Nine RCTs used computer-generated randomisation or sealed containers for allocation concealment, two allocated the intervention by order of enrolment and four provided no relevant details. Seven studies used blinded outcomes assessment, and 15 reported no or minimal drop-outs.

At 30 days the intervention group had a significantly lower risk of myocardial infarction (RR 0.74, 95% CI 0.59 to 0.94; 11 RCTs; I^2=0%) and revascularisation (RR 0.64, 95% CI 0.46 to 0.89; 11 RCTs), compared to controls. In subgroup analysis, abciximab was associated with a significant reduction in risk of myocardial infarction (RR 0.74, 95% CI 0.58 to 0.96) or revascularisation (RR 0.55, 95% CI 0.36 to 0.86). Small-molecule glycoprotein IIb/IIIa inhibitors did not differ significantly from controls in risk of myocardial infarction (RR 0.66, 95% CI 0.26 to 1.68) or revascularisation (RR 0.91, 95% CI 0.39 to 2.10). When analysis was restricted to placebo-controlled trials, for the outcome of myocardial infarction there was a trend favouring glycoprotein IIb/IIIa inhibitors which was not quite statistically significant (RR 0.78, 95% CI 0.61 to 1.002).

At 30 days the incidence of major bleeding did not differ significantly between the groups (RR 1.21, 95% CI 0.89 to 1.63; 11 RCTs; I^2=0%) but minor bleeding was higher in the intervention group (RR 1.37, 95% CI 1.06 to 1.78; 11 RCTs; I^2=13.5%). In subgroup analysis, abciximab did not differ significantly from controls in risk of minor bleeding (RR 1.46, 95% CI 0.82 to 2.60) but small-molecule glycoprotein IIb/IIIa inhibitors were associated with a significantly higher risk than controls (RR 1.42, 95% CI 1.03 to 1.94).The risk of thrombocytopenia (nine RCTs) or stroke (five RCTs) at 30 days did not differ significantly between the groups, and the incidence of all-cause mortality did not differ significantly at either 30 days (12 RCTs) or six to 12 months (10 RCTs).

No publication bias was detected for any outcome. The results of other subgroup and sensitivity analyses were also reported in the review.

Authors' conclusions

Adding glycoprotein IIb/IIIa inhibitors to unfractionated heparin reduced myocardial infarction and revascularisation rates without increasing major bleeding among patients undergoing revascularisation for acute coronary syndrome using stents and thienopyridines. The intervention increased minor bleeding, but the groups had similar mortality rates.

CRD commentary

The objectives and inclusion criteria of the review were clear and relevant sources were searched for published and unpublished studies without restriction by language. Publication bias was appropriately assessed and was not detected. At least two trials used inadequate methods of randomisation and only seven of the sixteen trials were placebo-controlled. The control condition in non placebo-controlled studies was not reported. It was unclear whether study selection and quality assessment were undertaken with sufficient attempts to minimise reviewer error and bias.

Appropriate statistical techniques were used to pool the studies and assess differences between them. Heterogeneity was generally low. The authors noted limitations to the review, including variation across studies in the definition of myocardial infarction and differences within some studies in the dose of heparin given to each arm. A large number of randomised controlled trials were included, with a large number of participants, and so the authors' conclusions are probably reliable. There remain some concerns over the inclusion of poor quality trials and non placebo-controlled trials, however there is no evidence that these trials led to bias in the results.

Implications of the review for practice and research

The authors did not state any implications for practice and research.

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