Cochrane Pre-hospital and Emergency Care

Pearls from the Cochrane Library for Emergency Physicians

JBMEDE
JORNAL BRASILEIRO de MEDICINA DE EMERGÊNCIA

Antiplatelet agents for preventing pre-eclampsia and its complications: a Cochrane Review

Lelia Duley[1]*, Shireen Meher[2], Kylie E Hunter[3], Anna Lene Seidler[3], Lisa M Askie[3]

[1] Nottingham Clinical Trials Unit, Nottingham Health Science Partners, Nottingham, UK
[2] Birmingham Women's Hospital, Birmingham, UK
[3] NHMRC Clinical Trials Centre, University of Sydney, Camperdown, Australia
* Corresponding author. E-mail address: *lelia.duley@nottingham.ac.uk*

Background

Pre-eclampsia is associated with deficient intravascular production of prostacyclin, a vasodilator, and excessive production of thromboxane, a vasoconstrictor and stimulant of platelet aggregation. These observations led to the hypotheses that antiplatelet agents, low-dose aspirin in particular, might prevent or delay development of pre-eclampsia.

Objectives

To assess the effectiveness and safety of antiplatelet agents, such as aspirin and dipyridamole, when given to women at risk of developing pre-eclampsia.

Search methods

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (30 March 2018), and reference lists of retrieved studies. We updated the search in September 2019 and added the results to the awaiting classification section of the review.

Selection criteria

All randomised trials comparing antiplatelet agents with either placebo or no antiplatelet agent were included. Studies only published in abstract format were eligible for inclusion if sufficient information was available. We would have included cluster-randomised trials in the analyses along with individually-randomised trials, if any had been identified in our search strategy. Quasi-random studies were excluded. Participants were pregnant women at risk of developing pre-eclampsia. Interventions were administration of an antiplatelet agent (such as low-dose aspirin or dipyridamole), comparisons were either placebo or no antiplatelet.

Data collection and analysis

Two review authors assessed trials for inclusion and extracted data independently. For binary outcomes, we calculated risk ratio (RR) and its 95% confidence interval (CI), on an intention-to-treat basis. For this update we incorporated individual participant data (IPD) from trials with this available, alongside aggregate data (AD) from trials where it was not, in order to enable reliable subgroup analyses and inclusion of two key new outcomes. We assessed risk of bias for included studies and created a 'Summary of findings' table using GRADE.

Main results

Seventy-seven trials (40,249 women, and their babies) were included, although three trials (relating to 233 women) did not contribute data to the meta-analysis. Nine of the trials contributing data were large (> 1000 women recruited), accounting for 80% of women recruited. Although the trials took place in a wide range of countries, all of the nine large trials involved only women in high-income and/or upper middle-income countries. IPD were available for 36

This review is an abridged version of a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2019, Issue 10. Art. No.: CD004659. DOI: 10.1002/14651858.CD004659.pub3. (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

trials (34,514 women), including all but one of the large trials. Low-dose aspirin alone was the intervention in all the large trials, and most trials overall. Dose in the large trials was 50 mg (1 trial, 1106 women), 60 mg (5 trials, 22,322 women), 75mg (1 trial, 3697 women) 100 mg (1 trial, 3294 women) and 150 mg (1 trial, 1776 women). Most studies were either low risk of bias or unclear risk of bias; and the large trials were all low risk of bas.

Antiplatelet agents versus placebo/no treatment

The use of antiplatelet agents reduced the risk of proteinuric pre-eclampsia by 18% (36,716 women, 60 trials, RR 0.82, 95% CI 0.77 to 0.88; high-quality evidence), number needed to treat for one women to benefit (NNTB) 61 (95% CI 45 to 92). There was a small (9%) reduction in the RR for preterm birth <37 weeks (35,212 women, 47 trials; RR 0.91, 95% CI 0.87 to 0.95, high-quality evidence), NNTB 61 (95% CI 42 to 114), and a 14% reduction infetal deaths, neonatal deaths or death before hospital discharge (35,391 babies, 52 trials; RR 0.85, 95% CI 0.76 to 0.95; high-quality evidence), NNTB 197 (95% CI 115 to 681). Antiplatelet agents slightly reduced the risk of small-for-gestational age babies (35,761 babies, 50 trials; RR 0.84, 95% CI 0.76 to 0.92; high-quality evidence), NNTB 146 (95% CI 90 to 386), and pregnancies with serious adverse outcome (a composite outcome including maternal death, baby death, pre-eclampsia, small-for-gestational age, and preterm birth) (RR 0.90, 95% CI 0.85 to 0.96; 17,382 women; 13 trials, high-quality evidence), NNTB 54 (95% CI 34 to 132). Antiplatelet agents probably slightly increase postpartum haemorrhage > 500 mL (23,769 women, 19 trials; RR 1.06, 95% CI 1.00 to 1.12; moderate-quality evidence due to clinical heterogeneity), and they probably marginally increase the risk of placental abruption, although for this outcome the evidence was downgraded due to a wide confidence interval including the possibility of no effect (30,775 women; 29 trials; RR 1.21, 95% CI 0.95 to 1.54; moderate-quality evidence).

Data from two large trials which assessed children at aged 18 months (including results from over 5000 children), did not identify clear differences in development between the two groups.

Authors' conclusions

Administering low-dose aspirin to pregnant women led to small-to-moderate benefits, including reductions in pre-eclampsia (16 fewer per 1000 women treated), preterm birth (16 fewer per 1000 treated), the baby being born small-for-gestational age (seven fewer per 1000 treated) and fetal or neonatal death (five fewer per 1000 treated). Overall, administering antiplatelet agents to 1000 women led to 20 fewer pregnancies with serious adverse outcomes. The quality of evidence for all these outcomes was high. Aspirin probably slightly increased the risk of postpartum haemorrhage of more than 500 mL, however, the quality of evidence for this outcome was downgraded to moderate, due to concerns of clinical heterogeneity in measurements of blood loss. Antiplatelet agents probably marginally increase placental abruption, but the quality of the evidence was downgraded to moderate due to low event numbers and thus wide 95% CI.

Overall, antiplatelet agents improved outcomes, and at these doses appear to be safe. Identifying women who are most likely to respond to low-dose aspirin would improve targeting of treatment. As almost all the women in this review were recruited to the trials after 12 weeks' gestation, it is unclear whether starting treatment before 12 weeks' would have additional benefits without any increase in adverse effects. While there was some indication that higher doses of aspirin would be more effective, further studies would be warranted to examine this.

Section Info

This section reproduces articles previously published by Cochrane Database of Systematic Reviews and is carried out in coordination with Patricia Jabre, Yannick Auffret, Sebastien Beroud, Julie Dumouchel, Virginie-Eve Lvovschi, Kirk Magee, Daniel Meyran, Patrick Miroux, Nordine Nekhili and Youri Yourdanov from the Cochrane Pre-hospital and Emergency Care group.