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[Intervention Review]

Antiplatelet and anticoagulant agents for primary prevention of thrombosis in individuals with antiphospholipid antibodies

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ABSTRACT

Background

Antiphospholipid syndrome (APS) is an autoimmune disease characterised by the presence of antiphospholipid (aPL) antibodies that have prothrombotic activity. Antiphospholipid antibodies are associated with an increased risk of pregnancy complications (recurrent miscarriage, premature birth, intrauterine growth retardation) and thrombotic events (both arterial and venous). The most common thrombotic events include brain ischaemia (stroke or transient ischaemic attack) and deep vein thrombosis. To diagnose APS, the presence of aPL antibodies in two measurements and at least one thrombotic event or pregnancy complication are required. It is unclear if people with positive aPL antibodies but without any previous thrombotic events should receive primary antithrombotic prophylaxis.

Objectives

To assess the effects of antiplatelet or anticoagulant agents versus placebo or no intervention or other intervention on the development of thrombosis in people with aPL antibodies who have not had a thrombotic event. We did not address obstetric outcomes in this review as these have been thoroughly addressed by other Cochrane Reviews.

Search methods

We searched the Cochrane Vascular Specialised Register (4 December 2017), the Cochrane Central Register of Controlled Trials (CENTRAL) (last search 29 November 2017), MEDLINE Ovid, Embase Ovid, CINAHL, and AMED (searched 4 December 2017), and trials registries (searched 29 November 2017). We also checked reference lists of included studies, systematic reviews, and practice guidelines, and contacted experts in the field.

Selection criteria

We included randomised controlled trials (RCTs) that compared any antiplatelet or anticoagulant agents, or their combinations, at any dose and mode of delivery with placebo, no intervention, or other intervention. We also included RCTs that compared antiplatelet or anticoagulant agents with each other or that compared two different doses of the same drug. We included studies performed in people of any age and with no history of thrombosis (as defined by APS Sapporo classification criteria or updated Sydney classification criteria), but with aPL antibodies confirmed on at last two separate measurements. The studies included both pregnant women who tested positive for

aPL antibodies and had a history of recurrent obstetric complications, as well as non-pregnancy related cases with positive screening for antibodies, in accordance with the criteria mentioned above.

Data collection and analysis

Pairs of authors independently selected studies for inclusion, extracted data, and assessed the risk of bias for the included studies and quality of evidence using GRADE. Any discrepancies were resolved through discussion or by consulting a third review author when necessary. In addition, one review author checked all the extracted numerical data.

Main results

We included nine studies involving 1044 randomised participants. The studies took place in several countries and had different funding sources. No study was at low risk of bias in all domains. We classified all included studies as at unclear or high risk of bias in two or more domains. Seven included studies focused mainly on obstetric outcomes. One study included non-pregnancy-related cases, and one study included both pregnancy-related cases and other patients with positive results for aPL antibodies. The remaining studies concerned women with aPL antibodies and a history of pregnancy failure. Four studies compared anticoagulant with or without acetylsalicylic acid (ASA) versus ASA only and observed no clear difference in thrombosis risk (risk ratio (RR) 0.98, 95% confidence interval (CI) 0.25 to 3.77; 4 studies; 493 participants; low-quality evidence). No major bleeding was reported, but minor bleeding risk (nasal bleeding, menorrhagia) was higher in the anticoagulant with ASA group as compared with ASA alone in one study (RR 22.45, 95% CI 1.34 to 374.81; 1 study; 164 participants; low-quality evidence). In one study ASA was compared with placebo, and there were no clear differences in thrombosis (RR 5.21, 95% CI 0.63 to 42.97; 1 study; 98 participants; low-quality evidence) or minor bleeding risk between the groups (RR 3.13, 95% CI 0.34 to 29.01; 1 study; 98 participants; low-quality evidence), and no major bleeding was observed. Two studies compared ASA with low molecular weight heparin (LMWH) versus placebo or intravenous immunoglobulin (IVIG), and no thrombotic events were observed in any of the groups. Moreover, there were no clear differences in the risk of bleeding requiring transfusion (RR 9.0, 95% CI 0.49 to 164.76; 1 study; 180 participants; moderate-quality evidence) or postpartum bleeding (RR 1.30, 95% CI 0.60 to 2.81; 1 study; 180 participants; moderate-quality evidence) between the groups. Two studies compared ASA with high-dose LMWH versus ASA with low-dose LMWF or unfractionated heparin (UFH); no thrombotic events or major bleeding was reported. Mortality and quality of life data were not reported for any of the comparisons.

Authors' conclusions

There is insufficient evidence to demonstrate benefit or harm of using anticoagulants with or without ASA versus ASA alone in people with aPL antibodies and a history of recurrent pregnancy loss and with no such history; ASA versus placebo in people with aPL antibodies; and ASA with LMWH versus placebo or IVIG, and ASA with high-dose LMWH versus ASA with low-dose LMWH or UFH, in women with aPL antibodies and a history of recurrent pregnancy loss, for the primary prevention of thrombotic events. In a mixed population of people with a history of previous pregnancy loss and without such a history treated with anticoagulant combined with ASA, the incidence of minor bleeding (nasal bleeding, menorrhagia) was increased when compared with ASA alone. Studies that are adequately powered and that focus mainly on thrombotic events are needed to draw any firm conclusions on the primary prevention of thrombotic events in people with antiphospholipid antibodies.

PLAIN LANGUAGE SUMMARY

Anticoagulant and antiplatelet drugs, or both, for reducing the risk of blood clots in susceptible individuals

Background

Anitiphospholipid (aPL) antibodies are proteins produced by the immune system in some people that are directed against components of their own cells. The presence of such antibodies may increase the risk of developing blood clots (thrombosis) in the blood vessels or pregnancy-related complications (such as recurrent miscarriage, stillbirth, premature birth, or serious illness of a pregnant woman). Blood clots within arteries can cause strokes, resulting in brain damage or reversible neurological symptoms. Blood clots in veins are associated with a buildup of fluid in the limbs (oedema) and pain, and if moved or translocated, may cause a blockage in a major vessel in the lung (pulmonary embolism).

In individuals who have previously had a thrombotic event, two types of drugs are commonly used to prevent recurrent thrombotic events: anticoagulants and antiplatelet agents. Anticoagulants prevent clots (thrombus) formation by interfering with the activity of proteins involved in blood clotting (clotting factors), while antiplatelets, usually aspirin, prevent platelet aggregation and impair clot formation. The most common side effect of anticoagulant or antiplatelet treatment is a tendency to bleed. However, little is known about the benefits and harms of using anticoagulants and antiplatelets in people who have aPL antibodies but have not previously had any thrombotic event.

Review question

This review aimed to establish the potential benefits and harms of using anticoagulants and antiplatelet drugs for preventing thrombotic events, in people who are susceptible but have not as of yet had any thrombotic event.

Study characteristics

The evidence is current as of December 2017. We searched for studies that randomly allocated people with aPL antibodies and without any previous thrombotic event to different treatments, including anticoagulants, antiplatelet drugs, or both. We identified nine studies involving 1044 participants. The studies took place in several different countries. One study was multicentred and had a variety of funding sources. In two studies aspirin was compared with placebo (dummy treatment). Four studies compared an anticoagulant with or without aspirin with aspirin alone. The remaining studies compared combinations of antiplatelet agents, anticoagulants, other treatments, or two different doses of the same drug. The majority of the studies concerned women with aPL antibodies and a history of pregnancy failure. One study included non-pregnancy-related cases, and one study included pregnancy-related cases and other patients with positive results for aPL antibodies.

Key results

We summarised the effects of the treatments using the following comparisons: aspirin only versus placebo, anticoagulant only or with aspirin versus aspirin only, aspirin with anticoagulant versus placebo or other treatment. We found no clear differences in the number of individuals with thrombotic events in the compared groups. One study revealed an increased risk of minor bleeding (such as nasal bleeding or intensified menstruation) in participants receiving aspirin and anticoagulant. All other analyses did not show any meaningful differences in the number of participants with bleeding. None of the studies reported on risk of death or quality of life. We found no clear difference between the groups in any of the comparisons for unwanted effects other than bleeding, where this information was reported; the more common of these effects included mild gastrointestinal symptoms in the aspirin group and allergic reactions in the aspirin with anticoagulant group.

Quality of the evidence

We assessed none of the studies as at low risk of bias because of methodological concerns or reporting of the results. We judged the overall quality of evidence to be low to moderate, it was downgraded due to unclear or high risk of bias, small number of studies and imprecise results.