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Estcourt LJ, Malouf R, Doree C, Trivella M, Hopewell S, Birchall J

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[Intervention Review]

Prophylactic platelet transfusions prior to surgery for people with a low platelet count

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ABSTRACT

Background

People with thrombocytopenia often require a surgical procedure. A low platelet count is a relative contraindication to surgery due to the risk of bleeding. Platelet transfusions are used in clinical practice to prevent and treat bleeding in people with thrombocytopenia. Current practice in many countries is to correct thrombocytopenia with platelet transfusions prior to surgery. Alternatives to platelet transfusion are also used prior surgery.

Objectives

To determine the clinical effectiveness and safety of prophylactic platelet transfusions prior to surgery for people with a low platelet count.

Search methods

We searched the following major data bases: Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2), PubMed (e-publications only), Ovid MEDLINE, Ovid Embase, the Transfusion Evidence Library and ongoing trial databases to 11 December 2017.

Selection criteria

We included all randomised controlled trials (RCTs), as well as non-RCTs and controlled before-and-after studies (CBAs), that met Cochrane EPOC (Effective Practice and Organisation of Care) criteria, that involved the transfusion of platelets prior to surgery (any dose, at any time, single or multiple) in people with low platelet counts. We excluded studies on people with a low platelet count who were actively bleeding.

Data collection and analysis

We used standard methodological procedures expected by Cochrane for data collection. We were only able to combine data for two outcomes and we presented the rest of the findings in a narrative form.

Main results

We identified five RCTs, all conducted in adults; there were no eligible non-randomised studies. Three completed trials enrolled 180 adults and two ongoing trials aim to include 627 participants. The completed trials were conducted between 2005 and 2009. The two ongoing trials are scheduled to complete recruitment by October 2019. One trial compared prophylactic platelet transfusions to no transfusion in people with thrombocytopenia in an intensive care unit (ICU). Two small trials, 108 participants, compared prophylactic platelet transfusions to

other alternative treatments in people with liver disease. One trial compared desmopressin to fresh frozen plasma or one unit of platelet transfusion or both prior to surgery. The second trial compared platelet transfusion prior to surgery with two types of thrombopoietin mimetics: romiplostim and eltrombopag. None of the included trials were free from methodological bias. No included trials compared different platelet count thresholds for administering a prophylactic platelet transfusion prior to surgery. None of the included trials reported on all the review outcomes and the overall quality per reported outcome was very low.

None of the three completed trials reported: all-cause mortality at 90 days post surgery; mortality secondary to bleeding, thromboembolism or infection; number of red cell or platelet transfusions per participant; length of hospital stay; or quality of life.

None of the trials included children or people who needed major surgery or emergency surgical procedures.

Platelet transfusion versus no platelet transfusion (1 trial, 72 participants)

We were very uncertain whether giving a platelet transfusion prior to surgery had any effect on all-cause mortality within 30 days (1 trial, 72 participants; risk ratio (RR) 0.78, 95% confidence interval (CI) 0.41 to 1.45; very-low quality evidence). We were very uncertain whether giving a platelet transfusion prior to surgery had any effect on the risk of major (1 trial, 64 participants; RR 1.60, 95% CI 0.29 to 8.92; very low-quality evidence), or minor bleeding (1 trial, 64 participants; RR 1.29, 95% CI 0.90 to 1.85; very-low quality evidence). No serious adverse events occurred in either study arm (1 trial, 72 participants, very low-quality evidence).

Platelet transfusion versus alternative to platelet transfusion (2 trials, 108 participants)

We were very uncertain whether giving a platelet transfusion prior to surgery compared to an alternative has any effect on the risk of major (2 trials, 108 participants; no events; very low-quality evidence), or minor bleeding (desmopressin: 1 trial, 36 participants; RR 0.89, 95% CI 0.06 to 13.23; very-low quality evidence; thrombopoietin mimetics: 1 trial, 65 participants; no events; very-low quality evidence). We were very uncertain whether there was a difference in transfusion-related adverse effects between the platelet transfused group and the alternative treatment group (desmopressin: 1 trial, 36 participants; RR 2.70, 95% CI 0.12 to 62.17; very-low quality evidence).

Authors' conclusions

Findings of this review were based on three small trials involving minor surgery in adults with thrombocytopenia. We found insufficient evidence to recommend the administration of preprocedure prophylactic platelet transfusions in this situation with a lack of evidence that transfusion resulted in a reduction in postoperative bleeding or all-cause mortality. The small number of trials meeting the inclusion criteria and the limitation in reported outcomes across the trials precluded meta-analysis for most outcomes. Further adequately powered trials, in people of all ages, of prophylactic platelet transfusions compared with no transfusion, other alternative treatments, and considering different platelet thresholds prior to planned and emergency surgical procedures are required. Future trials should include major surgery and report on bleeding, adverse effects, mortality (as a long-term outcome) after surgery, duration of hospital stay and quality of life measures.

PLAIN LANGUAGE SUMMARY

Platelet transfusion before surgery for people with low platelet counts

Review question

We aimed to assess the safety and clinical effectiveness of administering platelet transfusions to people with a low platelet count who require surgery. We included three comparisons: giving platelet transfusion versus no platelet transfusion; giving platelet transfusion versus an alternative treatment (medicines that reduce the risk of bleeding or increase the platelet count) or giving platelet transfusions when the platelet count is below a set number (low platelet count e.g. $20 \times 10^9/L$ versus slightly higher e.g. $50 \times 10^9/L$).

Our target population was people with a low platelet count of any age who required surgery. We excluded studies on people with a low platelet count who were actively bleeding.

Key messages

There was not enough evidence to help guide the use of platelet transfusions prior to surgery in people with a low platelet count. There is no evidence for infants and children or prior to a major operation.

What was studied in this review?

Platelets are tiny cells in the blood that form clots to help stop bleeding. If a person with a low platelet counts requires surgery they are at increased risk of bleeding during and after surgery. A number of strategies are used to reduce the risk of bleeding, these include: giving platelet transfusions (injecting platelets into the bloodstream) to increase the platelet count, giving medicines to increase the platelet count and giving medicines that reduce the risk of bleeding. The current strategies are not based on good evidence, but based on individual clinical experience and expertise.

What are the main results of this review?

We found five randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) eligible for inclusion in this review. Two of these studies are still in progress. The three completed trials were small, with a combined total of 180 people. All were in adults who required minor surgery or an invasive procedure (a procedure that is carried out through the skin or a body cavity or anatomical opening). Two trials were in adults with liver disease and one trial was in adults in the intensive care unit. One trial compared platelet transfusion to no transfusion. One trial compared platelet transfusion to drugs that increased the platelet count. One trial compared platelet transfusion to a drug that decreased the risk of bleeding. We did not find any studies that compared the use of platelet transfusions using different platelet count levels as a guide for platelet transfusion.

There was not enough evidence to determine whether platelet transfusions affected the risk of death due to any cause, minor or major procedure-related bleeding, or the risk of a serious side effect. The only available evidence was of very-low quality because: the estimates were very imprecise, the studies were at risk of bias (participants and doctors knew which treatment they were receiving) and the evidence only applied to adults with liver disease requiring a dental procedure or liver biopsy (sample of the liver taken for analysis), or adults in intensive care units requiring insertion of a tube to help breathing (tracheotomy).

None of the studies reported: death due to any cause at 90 days after surgery; death due to bleeding, infection or a blood clot; number of red cell (cells that carry oxygen in the blood) or platelet transfusions each participant received; length of hospital stay or quality of life.

None of the trials included children or people who needed major surgery or emergency surgical procedures.

How up to date is this evidence?

We searched for studies published up to December 2017.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery

Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery

Patient or population: people with a low platelet count

Setting: surgery

Intervention: platelet transfusion

Comparison: no platelet transfusion

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no platelet transfusion	Risk with platelet transfusion				
All-cause mortality within 30 days of surgery	Study population		RR 0.78 (0.41 to 1.45)	72 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b}	—
	405 per 1000	316 per 1000 (166 to 588)				
Mortality secondary to bleeding within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to thromboembolism within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to infection within 30 days of surgery – not reported	—	—	—	—	—	—
Number of participants with major bleeding within 7 days of surgery (surgical site bleeding requiring a second intervention or reoperation or surgical site bleeding that causes a haematoma or haemarthrosis of sufficient size to delay mobilisation or wound healing)	Study population		RR 1.60 (0.29 to 8.92)	64 (1 RCT)	⊕⊕⊕⊕ Very low ^{b,c}	—
	61 per 1000	97 per 1000 (18 to 541)				
The number of participants with minor procedure-related bleeding within 7 days of surgery	Study population		RR 1.29 (0.90 to 1.85)	64 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,c,d}	—

	576 per 1000	743 per 1000 (518 to 1000)		
Serious adverse events (surgery-related adverse effects within 30 days)	No events occurred in either study arm		64 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,c,d}

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aOnly adults in the intensive care unit were included in this trial (downgraded one level for indirectness).

^bThe confidence intervals included a serious risk of harm or benefit (downgraded two levels for imprecision).

^cThis is a subjective outcome and the trial was unblinded (downgraded one level for risk of bias).

^dThe confidence intervals included a risk of harm or benefit (downgraded one level for imprecision).

Summary of findings 2. Prophylactic platelet transfusion prior to surgery versus alternative treatments

Prophylactic platelet transfusion prior to surgery versus alternative treatments

Patient or population: people with a low platelet count

Setting: surgery

Intervention: platelet transfusion

Comparison: desmopressin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with desmopressin	Risk with platelet trans- fusion

All-cause mortality within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to bleeding within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to thromboembolism within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to infection within 30 days of surgery – not reported	—	—	—	—	—	—
Number of participants with major bleeding within 7 days of surgery (bleeding that required ≥ 2 units of whole blood/red blood cells within 24 hours of the bleeding)	No events in either study arm			36 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b,c}	—
Number of participants with minor procedure-related bleeding within 7 days of surgery	Study population		RR 0.89 (0.06 to 13.23)	36 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b,c}	—
	59 per 1000	52 per 1000 (4 to 778)				
Serious adverse events (transfusion-related adverse effects within 24 hours of the transfusion)	Study population		RR 2.70 (0.12 to 62.17)	36 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b,c}	—
	0 per 1000	0 per 1000 (0 to 0)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aOpen-label trial (downgraded one level for risk of bias).

^bStudy only included adults with chronic liver disease (downgraded one level for indirectness).

^cConfidence intervals included a serious risk or benefit or treatment (downgraded one level for imprecision, as already downgraded one level for indirectness and risk of bias).

Summary of findings 3. Different platelet count thresholds for administering a prophylactic platelet transfusion prior to surgery

Different platelet count thresholds for administering a prophylactic platelet transfusion prior to surgery

Patient or population: people with a low platelet count

Setting: surgery

Intervention: platelet transfusion

Comparison: TPO mimetic

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with TPO mimetic	Risk with platelet trans- fusion				
All-cause mortality within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to bleeding within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to thromboembolism within 30 days of surgery – not reported	—	—	—	—	—	—
Mortality secondary to infection within 30 days of surgery – not reported	—	—	—	—	—	—
Number of participants with major bleeding within 7 days of surgery	No bleeding in any of the study arms			65 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b}	—
Number of participants with minor procedure-related bleeding within 7 days of surgery	No bleeding occurred in any of the study arms			65 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b}	—
Serious adverse events – not reported	—	—	—	—	—	—

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio; **TPO:** thrombopoietin.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aStudy only included adults with chronic liver disease (downgraded one level for indirectness).

^bNo events occurred (downgraded two levels for imprecision).

BACKGROUND

Description of the condition

Platelets are an essential component in the formation of a blood clot (BCSH 2003). A low platelet count can lead to a range of bleeding symptoms such as bruising, nosebleeds and, rarely, life-threatening or fatal bleeding.

Thrombocytopenia is defined as a platelet count less than $150 \times 10^9/L$ (BCSH 2003). When this is dilutional, associated with an expanded blood volume, the drop is mild and rarely clinically significant. Severe thrombocytopenia is defined as a platelet count less than $50 \times 10^9/L$ (BCSH 2003). Thrombocytopenia can be caused by: reduced platelet production in the bone marrow often as a result of chemotherapy or a haematological malignancy (blood cancer) (Leguit 2010; Weinzierl 2013); increased platelet consumption as occurs in bleeding or disseminated intravascular coagulation (Levi 2009); increased platelet destruction such as immune thrombocytopenia (ITP) (Neunert 2013; Pacheco 2011; Provan 2010); or a combination of these conditions.

Mild, dilutional thrombocytopenia is common in pregnancy (7% to 12% of pregnancies), but severe thrombocytopenia is much less common (0.05% to 1% of pregnancies) and is a sign of complications (Burrows 1990; Nisha 2012; Sainio 2000). A platelet count less than $150 \times 10^9/L$ is very common in people with chronic liver disease (up to 76%) (Afdhal 2008), and people who are critically ill (up to 68%) (Hui 2011). One large UK study of people admitted to the intensive care unit (ICU) reported that 9% developed severe thrombocytopenia (Stanworth 2013). Thrombocytopenia is also frequent in people with haematological malignancies (Leguit 2010; Weinzierl 2013), and most platelet transfusions are used in people with haematological disorders (Cameron 2007; Greeno 2007; Pendry 2011).

People with thrombocytopenia often require a surgical procedure. A low platelet count is a relative contraindication to surgery due to the risk of bleeding (Estcourt 2017a; Kaufman 2015; NICE 2015). Platelet transfusions are one of a number of interventions used in modern clinical practice to prevent and treat bleeding in people with thrombocytopenia.

Description of the intervention

Platelet concentrates are the second most frequently used blood component (Bolton-Maggs 2016). Approximately 2.2 million platelet units are transfused annually in the USA (Whitaker 2013). Seventy-four per cent of platelet transfusions are given prophylactically to non-bleeding people with thrombocytopenia and 15% are given to prevent bleeding prior to surgery or a procedure in people with haematological malignancies. In many cases, platelet transfusions are given when the platelet counts are higher than the recommended triggers (Estcourt 2012; Greeno 2007).

Unlike other blood components, platelets must be kept on a shaker at room temperature, limiting the shelf life of platelet units to five to seven days. This makes it difficult for hospitals to manage their platelet stock (Fuller 2011).

Current practice in many countries is to correct thrombocytopenia with platelet transfusions prior to surgery. Guidelines often

recommend a platelet count threshold of $50 \times 10^9/L$ prior to major surgery and $100 \times 10^9/L$ prior to surgery involving the brain or eyes (Estcourt 2017a; Kaufman 2015; NICE 2015). Guidelines often do not go into further detail about risks for different types of surgery. Some low-risk surgery may not require platelet transfusions at all, other procedures may be higher risk and the risk may also be dependent on patient comorbidities.

Platelet transfusions are not risk-free. In 2014, 34% of all transfusion-related adverse events reported to the UK national reporting system (Serious Hazards of Transfusion (SHOT)) were due to platelet components. The most common adverse events due to platelet components were febrile and allergic reactions (Birchall 2015). Although most of these reactions are not life-threatening, they can be extremely distressing for the person and time consuming for health professionals to investigate and exclude a more serious cause. Rarer, but more serious sequelae, include: anaphylaxis (life-threatening allergic reaction), transfusion-transmitted infections (TTI) and transfusion-related acute lung injury (TRALI) (Blumberg 2010; Chapman 2015; Kaufman 2015; Slichter 2007; Vlaar 2013). Platelet units are stored at room temperature on a shaker, which increases the risk of bacterial growth (1:2000 to 1:3000) (Jacobs 2011). In 2015, there were four near-miss incidents (three in platelets) reported, between 2011 and 2015 and a total of 37/44 bacterial transfusion-transmissions to individual recipients (34 incidents) were caused by the transfusion of platelets (Bolton-Maggs 2016).

One prospective multicentre cohort study concluded that in critically ill people, transfusion of platelets, but not of red blood cells and plasma, is an independent risk factor for acquiring a nosocomial infection (Engele 2016).

Alternative agents that could replace or reduce platelet transfusions may be more effective than platelet transfusions at controlling bleeding and will have a different adverse effect profile. Alternatives include artificial platelet substitutes, cryosupernatant, recombinant factor VIIa (rFVIIa), fibrinogen, recombinant factor XIII (rFXIII), thrombopoietin (TPO) mimetics and antifibrinolytic drugs.

How the intervention might work

Platelet transfusions

The premise for preprocedure intervention with platelet transfusion is as follows: thrombocytopenia increases the risk of bleeding, platelet transfusion corrects thrombocytopenia, a higher platelet count prevents bleeding and overall there is benefit to the patient. However, this presumption is over simplistic.

In one small randomised controlled trial (RCT) of 23 participants with thrombocytopenia who required 35 procedures and 84 teeth removed, bleeding complications were minimal without blood product support (Perdigão 2012).

One study including 1720 participants with thrombocytopenia undergoing coronary artery bypass graft (CABG) surgery pooled individual patient data from one pilot study and six RCTs. Platelet transfusion compared with no platelet transfusion was associated with a significant increase in mortality among people undergoing CABG surgery (odds ratio (OR) 4.76, 95% confidence interval (CI) 1.65 to 13.73; $P = 0.009$). Although the authors used propensity score analysis, it was unclear if the increased mortality was due

to platelet transfusion or because people who were more unwell received platelet transfusions (Spieess 2004).

Alternatives to platelet transfusions

Alternatives to platelet transfusion simulate the effects of platelets (artificial platelet substitutes), stimulate additional fibrin formation (cryosupernatant, rFVIIa and fibrinogen), promote von Willebrand factor release and platelet function (desmopressin), increase platelet production (TPO mimetics), strengthen clot structure (rFXIII) or decrease clot breakdown (antifibrinolytics). These agents aim to promote haemostasis without the adverse effects associated with platelet transfusions. Their main adverse effect is excessive clotting and thrombosis.

In this review, we excluded trials that assessed the use of: rFVIIa; fibrinogen concentrate; rFXIII; prothrombin complex concentrate and desmopressin as these are the subject of other Cochrane Reviews that compared these interventions to an active comparator in people requiring a surgical procedure (Desborough 2017; Fabes 2013; Simpson 2012).

Artificial platelet substitutes

Artificial platelet substitutes such as microspheres of human albumin coated with fibrinogen, lyophilised platelets, infusible plasma membranes and liposomes with inserted platelet receptors aim to reproduce the active components of platelets without associated adverse events (Desborough 2016). Artificial platelets are not yet in routine clinical use, so their costs and adverse events are at present unclear.

Cryosupernatant

Cryosupernatant is a source of clotting factors and can be administered intravenously. It is a blood component and is associated with a small risk of transfusion reactions and TTIs.

Thrombopoietin mimetics

TPO is made by the liver and is the key regulator of bone marrow platelet production. TPO mimetics have been used in several disease states to promote both an increase in the cells that produce platelets (megakaryopoiesis) and the production of platelets themselves (thrombopoiesis) (Kuter 2014). The two main TPO mimetics in current use are romiplostim (weekly injection) and eltrombopag (daily oral tablet), both of which are recommended by the National Institute for Health and Care Excellence (NICE) for use in adults with ITP who have severe disease and a high risk of bleeding (NICE 2011; NICE 2013). While a systematic review found that these agents improved platelet counts, there was no evidence that they reduced the risk of significant bleeding for people with ITP (Zeng 2011). TPO mimetics are more expensive than platelet transfusions (Joint Formulary Committee 2016). Interleukin 6 and interleukin 11 may also act as stimulants of thrombopoiesis (Gordon 1995; Kurzrock 2011; Tsimberidou 2005). They are not in routine clinical use, so their costs are unclear at present.

Antifibrinolytic drugs

Fibrinolysis is the process by which blood clots are broken down after they have been formed. Antifibrinolytic drugs block this process, resulting in greater clot strength. The three most commonly used antifibrinolytic drugs are tranexamic acid, aprotinin and epsilon-aminocaproic acid. Other Cochrane

systematic reviews have assessed these agents in people undergoing surgical procedures (Henry 2011; McNicol 2016), or in people with haematological disorders (Estcourt 2016a).

Why it is important to do this review

People with a low platelet count often require surgery. Current guidelines are mainly based on expert opinion rather than good evidence and frequently do not go into detail about the risks for different types of surgery or define a specific platelet count threshold. Some low-risk surgery, for example dental extraction, may not require platelet transfusions at all. Platelet transfusions may cause immediate- or longer-term harm and delay the start of life-saving treatments. Alternatives to platelets may be more effective and safer. Therefore, there is a need to assess the likely benefit of platelet transfusion and their alternatives, in different procedures, against known risks.

In this review we aimed to answer the following questions.

- Do people require prophylactic platelet transfusion prior to certain types of surgery?
- If platelet transfusions are required, which platelet count threshold should be used to trigger the transfusion of prophylactic platelets prior to surgery?
- Are prophylactic platelet transfusions superior to other alternative treatments?

OBJECTIVES

To determine the clinical effectiveness and safety of prophylactic platelet transfusions prior to surgery for people with a low platelet count.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs, non-randomised controlled trials (non-RCTs) and controlled before-and-after studies (CBAs), irrespective of language or publication status. We excluded uncontrolled studies, cross-sectional studies and case-control studies.

We only included cluster-RCTs, non-randomised cluster trials, and CBAs with at least two intervention sites and two control sites. In studies with only one intervention or control site, the intervention (or comparison) is completely confounded by study site making it difficult to attribute any observed differences to the intervention rather than to other site-specific variables.

Our plan was that if there were sufficient data to answer this review's questions using only data from RCTs we would only report data from RCTs.

Types of participants

People of all ages with a low platelet count who were due to have surgery including invasive procedures.

We excluded studies on people with a low platelet count who were actively bleeding because they would receive platelet transfusions as part of the treatment of bleeding.

Types of interventions

We compared three types of platelet transfusion regimens.

- **Comparison 1:** prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery (placebo or no treatment).
- **Comparison 2:** prophylactic platelet transfusion prior to surgery versus alternative treatments (cryosupernatant, antifibrinolytics, TPO mimetics). In this review, we excluded trials that assess the use of rFVIIa; fibrinogen concentrate, rFXIII, prothrombin complex concentrate and desmopressin as these are the subject of other Cochrane Reviews that compared these interventions to an active comparator in people requiring a surgical procedure (Carless 2004; Fabes 2013; Simpson 2012).
- **Comparison 3:** different platelet count thresholds for administering a prophylactic platelet transfusion prior to surgery.

We recorded type of platelet component and dose of platelet component received.

Types of outcome measures

Primary outcomes

- Mortality (all-causes, secondary to bleeding, secondary to thromboembolism and secondary to infection) within 30 days and 90 days of surgery.
- Number of participants with major procedure-related bleeding within seven days of surgery, defined as:
 - surgical site bleeding requiring a second intervention or reoperation or surgical site bleeding that causes a haematoma or haemarthrosis of sufficient size to delay mobilisation or wound healing;
 - bleeding of sufficient size to cause delayed wound healing, or wound infection or surgical site bleeding that was unexpected and prolonged or caused haemodynamic instability (as defined by the study) that was associated with a 20 g/L drop in haemoglobin (Hb);
 - bleeding that required two or more units of whole blood/red cells within 24 hours of the bleeding;
 - bleeding defined by the study with no further details.

Secondary outcomes

- Number of participants with minor procedure-related bleeding within seven days of surgery (e.g. haematoma, prolonged bleeding at surgical site that did not fulfil the definition for major bleeding).
- Number of platelet transfusions per participant and number of platelet components per participant.
- Number of red cell transfusions per participant and number of red cell components per participant.
- Proportion of participants requiring additional interventions to stop bleeding (surgical; medical, e.g. tranexamic acid; other blood products, e.g. fresh frozen plasma (FFP), cryoprecipitate, fibrinogen) within seven days of surgery.
- Quality of life assessment using validated tools.
- Serious adverse events due to:
 - transfusion (transfusion reactions, TRALI, transfusion-related infection, transfusion-associated circulatory overload,

transfusion-related dyspnoea) within 24 hours of the transfusion;

- surgery (e.g. delayed wound healing, infection) within 30 days after the operation.
- Length of hospital stay and length of ICU stay.
- Venous and arterial thromboembolism (including deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction).

Search methods for identification of studies

The Systematic Review Initiative's Information Specialist (CD) developed the search strategies in collaboration with the Cochrane Haematological Malignancies Group.

Electronic searches

We searched the following databases.

Bibliographic databases

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, 2017, Issue 12) (Appendix 1).
- MEDLINE (OvidSP, Epub Ahead of Print, In-Process and other Non-Indexed Citations, and 1946 to 11 December 2017) (Appendix 2).
- PubMed (for e-publications ahead or print only) (www.ncbi.nlm.nih.gov/pubmed) (Appendix 3).
- Embase (OvidSP, 1974 to 11 December 2017) (Appendix 4).
- CINAHL (EBSCOHost, 1937 to 11 December 2017) (Appendix 5).
- Transfusion Evidence Library (www.transfusionevidencelibrary.com; 1950 to 11 December 2017 – this included a search of grey literature) (Appendix 6).
- LILACS (1982 to present) (lilacs.bvsalud.org/en/) (Appendix 7).
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to 11 December 2017) (Appendix 8).

Online databases of ongoing trials

We searched for ongoing studies to 11 December 2017 in the following databases:

- ClinicalTrials.gov (clinicaltrials.gov) (Appendix 9);
- World Health Organization (WHO) International Clinical Trials Registry Search Platform (ICTRP) (apps.who.int/trialsearch/AdvSearch.aspx) (Appendix 10).

We combined searches in MEDLINE and Embase with the recommended Cochrane RCT search filters (Lefebvre 2011), systematic review filters based on those of the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/filters.html), and CBA study filters based on those used in reviews of the Cochrane Effective Practice and Organisation of Care Group (EPOC 2015) (epoc.cochrane.org/). Searches in CINAHL were combined with the SIGN systematic review and RCT filter and an EPOC-based filter. We did not limit searches by language, year of publication or publication type.

Once we identified studies for inclusion, we searched MEDLINE (OvidSP) for errata or retraction statements for the reports of these studies.

Searching other resources

We handsearched the reference lists of included studies and any relevant systematic reviews to identify further relevant studies. We made contact with lead authors of relevant studies to identify any unpublished material, missing data or information regarding ongoing studies.

Data collection and analysis

We summarised data in accordance with standard Cochrane methodologies. We planned to analyse data from different study designs separately.

Selection of studies

We selected studies with reference to the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The Systematic Review Initiative's Information Specialist (CD) initially screened all search hits for relevance against the eligibility criteria and discarded those that were clearly irrelevant. Thereafter, two review authors (LE, RM) independently screened all the remaining references for relevance against the full eligibility criteria. We retrieved full-text papers for all references for which a decision on eligibility could not be made from only screening the title and abstract. If necessary, we requested additional information from study authors to assess the eligibility for inclusion of individual studies. The two review authors discussed the results of study selection and resolved any discrepancies between themselves, without the need for a third review author (MT). We reported the results of study selection using a PRISMA flow diagram (Moher 2009). We also recorded the reasons for excluding studies based on full-text assessment and added those to the [Characteristics of excluded studies](#) table.

We collated multiple reports of one study so that the study, and not the report, was the unit of analysis

Data extraction and management

Two review authors (RM, LE) independently extracted data as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), using standardised forms available in Covidence software (Covidence 2016). We planned to pilot two different data extraction forms for included RCTs and non-RCTs separately, however we included only RCTs in this review. The two review authors came to consensus agreements without the need for a third review author (MT). The review authors were not blinded to names of authors, institutions, journals or the study outcomes. They extracted the following information for each study.

Randomised controlled trials

- Source: study ID, report ID, review author ID, date of extraction, ID of author checking extracted data, citation of paper, contact author's details.
- General study information: publication type, study objectives, funding source, conflict of interest declared, other relevant study publication reviewed.
- Study details and methods: location, country, clinical setting, number of centres, study design, total study duration, recruitment dates, length of follow-up, power calculation, primary analysis (and definition), stopping rules, method of sequence generation, allocation concealment, blinding

(of clinicians, participants and outcome assessors) and any concerns regarding bias.

- Characteristics of interventions: number of study arms, description of experimental arm, description of control arm, type of platelet component (e.g. apheresis or pooled), dose of platelet component, thresholds of platelets transfusions, type of surgery.
- Characteristics of participants: age, gender, primary diagnosis, surgery types procedure (minor, major, surgery to sensitive areas as ocular surgery or neurosurgery), platelet count, coagulation abnormalities, anticoagulant medications, antiplatelet medications.
- Participant flow: total number screened for inclusion, total number recruited, total number excluded, total number allocated to each study arm, total number analysed (for review outcomes), number of allocated participants who received planned treatment, number of dropouts with reasons (percentage in each arm), protocol violations, missing data.
- Method of data analyses.
- Outcomes: mortality (all-causes, secondary to bleeding, secondary to thromboembolism and secondary to infection) within 30 days and 90 days of surgery; number of participants with major procedure-related bleeding within seven days of surgery; number of participants with minor procedure-related bleeding within seven days of surgery; number of platelet transfusions per participant and number of platelet components per participant; number of red cell transfusions per participant and number of red cell components per participant; proportion of participants requiring additional interventions to stop bleeding within seven days of surgery; quality of life assessment using validated tools; serious adverse events due to transfusion (within 24 hours of the transfusion) or surgery (within 30 days after the operation); length of hospital stay and length of ICU stay, venous and arterial thromboembolism.

Non-randomised controlled trials

There were no non-RCTs eligible for inclusion in this review.

In future updates of this review, we plan to extract all the data collected for RCTs and additional information on the following.

- Study design.
- Method of selecting participants: sample source, sample size, participants eligibility criteria, number of participants at each follow-up point, and the source of study control group and baseline differences between the two groups.
- Confounding factors: baseline confounding factors and cointerventions that might lead potentially to bias are identified in the study and relevant confounding factors and cointerventions that could introduce bias after the starting of platelets transfusions; the comparability of groups on confounding factors.
- Method of assigning the intervention.
- Cointervention status: this is in order to document if any other cointerventions are considered in the study.
- Method of data analysis: methods used to control for confounding and on multiple effect estimates (both unadjusted and adjusted estimates) as recommended in the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011).

Assessment of risk of bias in included studies

Randomised controlled trials

We assessed the risk of bias for all included RCTs using the Cochrane 'Risk of bias' tool according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). Two review authors (LE, RM) independently assessed each element of potential bias listed below as 'high', 'low' or 'unclear' risk of bias. We reported a brief description of the judgement statements upon which the review authors assessed potential bias in the [Characteristics of included studies](#) table. We ensured that a consensus on the degree of risk of bias was met through comparison of the review authors' statements and, where necessary, through consultation with a third review author (SH). We used Cochrane's tool for assessing risk of bias, that included the following domains.

- Selection bias: we described for each included study if and how the allocation sequence was generated and if allocation was adequately concealed prior to assignment. We described the method used to conceal the allocation sequence in detail and determine if intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment.
- Performance bias: we described for each included study, where possible, if the study participants and personnel were adequately blinded from knowledge of which intervention a participant received. We judged studies as low risk of bias if they were blinded, or if judged that lack of blinding could not have had affected the results.
- Detection bias: was blinding of the outcome assessors effective in preventing systematic differences in the way in which the outcomes were determined?
- Incomplete outcome data: we described for each included study the attrition bias due to amount, nature or handling of incomplete outcome data. We also tried to evaluate whether intention-to-treat analysis were performed or could have been performed from published information.
- Selective outcome reporting or reporting bias: we described for each included study the possibility of selective outcome reporting bias.
- Other bias: was the study apparently free of other problems that could put it at risk of bias?

We summarised the risk of bias for each key outcome for each included study. We judged studies with at least one domain of high risk at high risk of bias overall.

Non-randomised controlled trials

There were no non-RCTs eligible for inclusion in this review.

In future updates of this review, we plan to use the ROBINS-I tool to rate the quality of non-randomised controlled trials (non-RCTs) and CBAs (Sterne 2016). This tool is based on the Cochrane 'Risk of bias' tool for rating the quality of RCTs (Higgins 2011c). The tool covers seven domains and the quality of evidence is rated 'low', 'moderate', 'serious', 'critical or no information', and the response options were 'yes', 'probably yes', 'no', 'probably no' and 'no information' (see [Appendix 2](#) for a copy of the tool) and uses signalling questions for the assessment of:

- bias due to confounding;
- bias in the selection of participants;

- bias in measurement of interventions;
- bias due to departure from intended interventions;
- bias due to missing data;
- bias in measurement of outcomes;
- bias in the selection of the reported result.

For 'low risk of bias,' the study was judged at low risk of bias on all the tool seven domains.

For 'moderate risk of bias,' the study was judged at low-to-moderate risk of bias on all tool seven domains.

For 'serious risk of bias' the study is judged to be at serious risk of bias in at least one of the tool seven domains.

For 'critical risk of bias,' the study was judged at critical risk of bias in at least one domain of the tool seven domains.

For 'no information on bias,' when information in one or more key risk of bias domains were lacking.

Two review authors independently assessed each domain of potential bias listed and also tabulated a brief description of the judgement statements upon which they assessed potential bias in the [Characteristics of included studies](#) table. We ensured that a consensus on the degree of risk of bias was met through comparison of the review authors' statements and where necessary, through consultation with a third review author. We highlighted the highest quality evidence for each outcome.

We prespecified the following main potential confounding factors.

- Primary diagnosis of participant (e.g. liver disease, critical illness, pregnancy).
- Age: variability in the age of participants included, for example, paediatric (under 16 years) versus adult (older than 16 years) versus older adult (older than 60 years).
- Gender: male to female ratio.
- Previous severe bleeding (e.g. WHO grade 3 or 4 or equivalent).

Measures of treatment effect

Randomised controlled trials

For dichotomous outcomes, we recorded the number of events and the total number of participants in both the treatment and control groups.

For continuous outcomes, we recorded the mean, standard deviation and total number of participants in both the treatment and control groups. For continuous outcomes using the same scale, we performed analyses using the mean difference (MD) with 95% CIs. If continuous outcomes were reported using different scales, we used standardised mean difference (SMD).

None of the studies reported hazard ratios (HR) and no HRs could be estimated using the available data. In future updates of this review, if available, we plan to extract and report HRs for time-to-event data (mortality or time in hospital) data. If HRs are not available, we will make every effort to estimate as accurately as possible the HR using the available data and a purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007). If sufficient studies provide HRs, we plan to use HRs in favour of RRs or MDs in a meta-analysis, but for completeness, we will also perform

a separate meta-analysis of data from studies providing only RRs or MDs for the same outcome.

For dichotomous outcomes, we reported the pooled risk ratio (RR) with a 95% CI (Deeks 2011). No outcomes required an analysis using the Peto's odds ratio (OR). In future updates of this review, where the number of observed events is small (less than 5% of sample per group), and where trials have balanced treatment groups, we plan to report the Peto's OR with 95% CI (Deeks 2011).

There were no cluster-randomised trials. In future updates of this review, for cluster-randomised trials, we will extract and report direct estimates of the effect measure (e.g. RR with a 95% CI) from an analysis that accounts for the clustered design. We will obtain statistical advice to ensure the analysis is appropriate. If appropriate analyses are not available, we will make every effort to approximate the analysis following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d).

If data allowed, we undertook quantitative assessments using Review Manager 5 (Review Manager 2014).

Non-randomised studies

There were no non-randomised studies eligible for inclusion in this review.

In future updates of this review, for dichotomous outcomes, if available we will extract and report the RR with a 95% CI from statistical analyses adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of risk ratios (i.e. the risk ratio postintervention/risk ratio preintervention). For continuous variables, if available we will extract and report the absolute change from a statistical analysis adjusting for baseline differences (such as regression models, mixed models or hierarchical models), or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute postintervention difference between the intervention and control groups, as well as the absolute preintervention difference between the intervention and control groups/the postintervention level in the control group) (EPOC 2015). If data allows, we will undertake quantitative assessments using Review Manager 5 (Review Manager 2014).

All studies

Where appropriate, we planned to report the number needed to treat for an additional beneficial outcome (NNTB) and harmful outcome (NNTH) with 95% CIs.

If we could not report the available data in any of the formats described above, we performed a narrative report, and if appropriate, we presented the data in tables.

Unit of analysis issues

There were no unit of analysis issues in this review.

In future updates of this review if any unit of analysis issues arise, we will treat these in accordance with the advice given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). If participants are randomised more than once, we plan to contact the authors of the study to provide us with data associated with the initial randomisation. For studies with multiple treatment

groups, we excluded subgroups that were considered irrelevant to the analysis. We tabulated all subgroups in the [Characteristics of included studies](#) table. When appropriate, we combined groups to create a single pair-wise comparison. If this was not possible, we selected the most appropriate pair of interventions and excluded the others (Higgins 2011c).

Dealing with missing data

Where we identified data to be missing or unclear in published literature, we contacted study authors directly. We contacted the authors of all three completed studies for additional information, but no additional information was provided (Basu 2012; Stanca 2010; Veelo 2012).

Assessment of heterogeneity

We planned to analyse the data in RCTs, non-RCTs, and CBA studies separately. However, we only identified three RCTs for inclusion in this review.

We did not perform any meta-analyses and, therefore, could not assess heterogeneity of the included RCTs (Deeks 2011).

In future updates of this review, if the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will combine the data and perform a meta-analysis. We will assess the extent of heterogeneity by both visual inspection of forest plots and utilising statistical methods. We will assess statistical heterogeneity of treatment effects between studies using a χ^2 test with a significance level at P less than 0.1. We will use the I^2 statistic to quantify the degree of potential heterogeneity and classify it as low if the I^2 statistic is 50% or less, moderate if the I^2 statistic is 50% to 80% or considerable if the I^2 statistic is greater than 80%. We will use the random-effects model for low-to-moderate heterogeneity. If statistical heterogeneity is considerable, we will not report the overall summary statistic. We will assess potential causes of heterogeneity by sensitivity and subgroup analyses (Deeks 2011).

Assessment of reporting biases

We did not perform a formal assessment of publication bias because we did not perform any meta-analyses (Sterne 2011).

Data synthesis

We did not perform any meta-analyses.

In future updates of this review, If studies are sufficiently homogenous in their study design, we will conduct a meta-analysis according to the recommendations of Cochrane (Deeks 2011). We will not conduct meta-analyses that include both RCTs and non-RCTs. We will conduct separate meta-analyses for each comparison. Different thresholds within the comparisons will only be grouped together if they were considered to be clinically similar.

Randomised controlled trials

For RCTs where meta-analysis is feasible, we will use the random-effects model for pooling the data. For binary outcomes, we will base the estimation of the between-study variance on the Mantel-Haenszel estimator. We will use the inverse-variance method for continuous outcomes, outcomes that include data from cluster-RCTs, or outcomes where HRs are available. If there is heterogeneity

above 80%, and we identify a cause for the heterogeneity, we will explore this with subgroup analyses. If we cannot find a cause for the heterogeneity, then we will not perform a meta-analysis, but comment on the results as a narrative with the results from all studies presented in tables.

Non-randomised studies

We identified no non-RCTs for inclusion in this review. In future updates, if meta-analysis is feasible for non-RCTs or CBA studies, we will analyse non-RCTs and CBA studies separately. We will only analyse outcomes with adjusted effect estimates if these are adjusted for the same factors using the inverse-variance method as recommended in the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011).

All studies

We used the random-effects model for all analyses as we anticipated that true effects were related but were not the same for included studies. If we could not perform a meta-analysis, we commented on the results as a narrative with the results from all studies presented in tables.

'Summary of findings' tables

We used the GRADE tool (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of evidence for each outcome. We presented 'Summary of findings' tables as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b).

We applied the GRADE approach to rate the quality of the evidence as 'high,' 'moderate,' 'low' or 'very low' using the five GRADE considerations.

- Risk of bias: serious or very serious.
- Inconsistency: serious or very serious.
- Indirectness: serious or very serious.
- Imprecision: serious or very serious.
- Publication bias: likely or very likely.

The outcomes we included were listed below in order of most relevant endpoints for participants.

- All-cause mortality.
- Mortality secondary to bleeding.
- Mortality secondary to thromboembolism.
- Mortality secondary to infection.
- Number of participants with major procedure-related bleeding within seven days of surgery.

- Number of participants with minor procedure-related bleeding within seven days of surgery.
- Serious adverse events due to platelet transfusions.

Subgroup analysis and investigation of heterogeneity

There were insufficient data to perform any subgroup analyses. In future updates of this review, we plan to perform subgroup analyses for each of the following outcomes in order to assess the effect on heterogeneity.

- Age of participant (neonate, infant, child, adult).
- Type of surgery: minor or major (cardiac, eye, neurosurgery, dental, orthopaedic, liver, obstetric, gynaecological, plastic, gastrointestinal).
- Underlying cause of thrombocytopenia (bone marrow failure due to disease or treatment, increased destruction of platelets or increased consumption of platelets).
- Dose of platelet component.
- Coexisting coagulopathy.
- Coexisting platelet dysfunction (inherited or acquired).

Sensitivity analysis

We planned to assess the robustness of the results by performing the following sensitivity analyses when possible; however, no meta-analyses were performed.

- Including studies with a 'low risk of bias' (e.g. RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation).
- Including studies with less than a 20% dropout.

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); and [Characteristics of ongoing studies](#) tables for more details.

Results of the search

The search (conducted on 11 December 2017) identified 10,564 potentially relevant records (Figure 1). There were 8091 records after we removed duplicates. One reference was identified from other sources. We excluded 8032 references on the basis of the abstract and checked the eligibility of 60 full-text papers. We identified five RCTs eligible for inclusion in this review, three completed RCTs (Basu 2012; Stanca 2010; Veelo 2012) and two ongoing RCTs (NTR5653; Rocha 2017).

Figure 1. Study flow diagram.

Included studies

See [Characteristics of included studies](#) table for full details of the included studies.

Of the three completed RCTs, two trials were published in full ([Stanca 2010](#); [Veelo 2012](#)), and one was only available as an abstract ([Basu 2012](#)).

Study design and setting

All included trials were single-centre parallel-group RCTs. Two trials were conducted in the USA ([Basu 2012](#); [Stanca 2010](#)), and one was conducted in the Netherlands ([Veelo 2012](#)).

Trials comparing platelet transfusions with no transfusion before the surgical procedure

One trial (72 participants) compared platelet transfusion to no platelet transfusion before a surgical procedure ([Veelo 2012](#)). It included people requiring mechanical ventilation who had mild coagulation disorders (defined as prothrombin time (PT) 14.7 seconds to 20.0 seconds, or platelet count $40 \times 10^9/L$ to $100 \times 10^9/L$, or active treatment with aspirin (acetylsalicylic acid), or any combination) who required a percutaneous dilational tracheotomy (PDT). Eight participants did not undergo the tracheotomy after randomisation. About 60% of all participants had a prolonged PT and just over a third had a low platelet count and another third had received aspirin. There was more than one coagulation disorder was present in about 20% of the participants.

Study interventions

[Veelo 2012](#) randomised participants into two groups. Group A received one unit of FFP if the PT was between 14.7 seconds and 18 seconds and two units of FFP when the PT was between 18 seconds and 20 seconds, as well as five units of buffy coat prepared platelets if they had a low platelet count or had received aspirin. Group B received neither plasma nor platelets; however, in the event of bleeding during or after the procedure, immediate transfusion of FFP or platelets was available.

Study outcomes

The primary outcomes were volume of blood loss during the PDT procedure, severity of intratracheal bleeding and time until no blood was visible in tracheal aspirates. [Veelo 2012](#) assessed bleeding during and within the first 12 hours after the PDT procedure. Bleeding was defined as "minor" for blood loss of less than 100 g from the site of the procedure that could be controlled by applying local pressure and did not require the transfusion of red blood cells. "Major" bleeding was defined as the presence of blood in the airways which required repeated suction or emergency surgery or red blood cell transfusion, or both.

Trials comparing platelet transfusion to alternative treatments before the surgical procedure

Two trials (108 participants) compared platelet transfusions to different alternative treatments ([Basu 2012](#); [Stanca 2010](#)). Both included adults with liver disease, and excluded people with bleeding disorders, hepatocellular carcinoma and treatment with antiplatelet medications. Participants in [Basu 2012](#) had severe thrombocytopenia (no further details). [Stanca 2010](#) included people with moderate coagulopathy (defined as platelet count of

$30 \times 10^9/L$ to $50 \times 10^9/L$) (22 participants), or an international normalised ratio (INR) of 2.0 to 3.0, or both.

In [Basu 2012](#), the procedure was percutaneous liver biopsy, and in [Stanca 2010](#), the procedure was dental extractions.

Study interventions

[Basu 2012](#) randomly assigned participants to three groups: group A received seven units of platelets the night before the procedure; group B received romiplostim 500 µg subcutaneously given once two weeks before the procedure and group C received eltrombopag 57 mg per day by mouth for two weeks before the procedure.

[Stanca 2010](#) randomised participants were to two groups: group A received intranasal desmopressin (one spray in each nostril, total of 300 µg) and group B received FFP 10 mL/kg if the INR was 2.0 to 3.0 or one single unit of donor platelets when the platelet count was between $30 \times 10^9/L$ and $50 \times 10^9/L$.

Study outcomes

[Basu 2012](#) reported on the incidence of bleeding and haematoma after the procedure, and adverse effects and cost effectiveness. [Stanca 2010](#) reported incidence of bleeding and adverse effects at 24 hours to 48 hours after dental extraction, and a cost comparison between the two interventions.

Excluded studies

We excluded 46 studies for the following reasons:

- wrong study design: 20 studies ([Abdelfatah 2016](#); [Al-Zaabi 2014](#); [Barrera 1996](#); [Cai 2014](#); [Chantarangkul 2013](#); [Chen 2011](#); [Embrey 2006](#); [Fayed 2014](#); [Hibbert 2013](#); [Khair 2015](#); [Napolitano 2017](#); [NCT02200419](#); [NCT02987712](#); [NCT03011827](#); [NCT00549484](#); [Park 2016](#); [Pereboom 2009](#); [Perek 2016](#); [Ray 1997](#); [Tripodi 2013](#));
- wrong intervention: 14 studies ([Afdhal 2012](#); [De Pietri 2016](#); [EudraCT 2007-005851-40](#); [Karkouti 2016](#); [Kultufan 2006](#); [NCT00678587](#); [NCT01919840](#); [NCT02042898](#); [NCT02352181](#); [NCT02990273](#); [Perl 2016](#); [Pietri 2014](#); [Tripodi 2013](#); [Smart 2017](#));
- wrong patient population: 12 studies ([Backos 1999](#); [Harding 1975](#); [Hess 2015](#); [Holcomb 2015](#); [NCT00521664](#); [NCT01291290](#); [NCT01402739](#); [NCT02074436](#); [NCT03022253](#); [Simon 1982](#); [Simon 1984](#); [Tanaka 2014](#)).

Ongoing studies

We found two ongoing clinical trials ([NTR5653](#); [Rocha 2017](#)). See [Characteristics of ongoing studies](#) for further details.

NTR5653

This multicentre RCT is currently enrolling participants and aims to complete recruitment by October 2019 ([NTR5653](#)). The study is being conducted in the Netherlands and plans to enrol 462 adults on the ICU with a platelet count of $50 \times 10^9/L$ or less who require insertion of a central venous catheter. Participants will be randomised to receive or not receive a platelet transfusion.

Rocha 2017

The POCKET trial (point-of-care versus standard coagulation tests versus restrictive strategy to guide transfusion in chronic liver failure patients requiring central venous line) is a single-centre, double-blind RCT that is currently enrolling participants and aims

to complete recruitment by December 2018 (Rocha 2017). The study is being conducted in Brazil and plans to enrol 165 adults with chronic liver disease, randomised to receive transfusion of FFP, platelets or cryoprecipitate, or any combination guided by the use of standard tests of coagulation (INR greater than 1.5, activated partial thromboplastin time (aPTT) greater than 50 seconds or platelet count less than $50 \times 10^9/L$) versus thromboelastometry (ROTEM) versus standard tests of coagulation with a restrictive threshold (INR greater than 5, platelets less than $25 \times 10^9/L$) prior to central venous catheterisation.

Risk of bias in included studies

Allocation

Sequence generation

We rated two trials at low risk of bias for sequence generation because they used a computer-generated technique (Stanca 2010; Veelo 2012).

We rated Basu 2012 at unclear risk of bias because it was only available as an abstract and there were no further details available.

Allocation concealment

We rated two trials at low risk of bias for allocation concealment as both trials used opaque sealed envelopes to allocate the treatment to participants (Stanca 2010; Veelo 2012).

We rated Basu 2012 at unclear risk of bias due to lack of relevant information in the published abstract.

Blinding

We rated Basu 2012 at low risk of performance and detection bias because it was described as a double-blind trial with no further information available.

We rated two trials at high risk of bias for both performance and detection bias because they were both open-label trials (Stanca 2010; Veelo 2012).

Incomplete outcome data

We rated one trial at low risk of attrition bias because all participants who received platelet transfusions were included in the analysis (Veelo 2012).

We rated two trials at unclear risk of attrition bias (Basu 2012; Stanca 2010). In Basu 2012, the trial was only published as an abstract, and they did not report the number of participants who were randomised and included in the analyses. Stanca 2010 did not include all randomised participants in the analysis of outcome data. The study enrolled 43 participants, but the analysis included only 36 participants (19% dropout). The reasons for excluding these participants were clearly provided: two participants assigned to the blood transfusion group withdrew their consent; five participants were not included in the analysis because their blood results prior to the procedure showed they no longer met the trial eligibility criteria. Although this was a significant dropout, it was unclear what effect this would have on the study's findings, as most of the exclusions were because participants were no longer eligible.

Selective reporting

We rated two trials at unclear risk of selective reporting (Basu 2012; Stanca 2010). Basu 2012 was only available as an abstract, and there was no trial registration. The only outcome listed on the trial registration (NCT00816127) for Stanca 2010 was: "Necessity of rescue blood transfusion in patients who received DDAVP [desmopressin] or blood transfusion prior to dental extraction." There were no other secondary outcomes listed. Although this outcome was reported, there was no protocol available to assess if other outcomes were planned.

We rated Veelo 2012 at "high" risk of selective reporting, because not all the outcomes stated in the trial registration (ISRCTN31808827) were reported in the published paper such as the amount of blood products used during and after the procedure (not reported for intervention group). Some other outcomes were classified as the trial's primary outcome measures in the trial registration (ISRCTN31808827), but were reported as secondary outcomes in the published paper for example the volume of blood loss during the surgical procedure, the intensity of intra-tracheal bleeding, time until no blood was visible in tracheal aspirates.

Other potential sources of bias

We rated Stanca 2010 at low risk of other potential sources of bias, because baseline characteristics were balanced for the two groups, and there were no obvious sources of bias.

We rated two trials at unclear risk of other potential sources of bias (Basu 2012; Veelo 2012). Basu 2012 did not report adequate baseline information for the three study groups. The Veelo 2012 trial was stopped early due to increased resistance to recruitment and low rate of bleeding in either trial arm, planned recruitment was 152 participants but only 64 participants were included in the analysis.

Effects of interventions

See: [Summary of findings for the main comparison Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery](#); [Summary of findings 2 Prophylactic platelet transfusion prior to surgery versus alternative treatments](#); [Summary of findings 3 Different platelet count thresholds for administering a prophylactic platelet transfusion prior to surgery](#)

Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery

Only one trial compared prophylactic platelet transfusions versus no prophylactic platelet transfusions (Veelo 2012) ([Summary of findings for the main comparison](#)).

Primary outcomes

Mortality

All-cause mortality within 30 days of the surgery

There was no evidence of a difference in the risk of death due to any cause between participants having their coagulopathy corrected (platelets, plasma, or both) and participants who did not (1 trial, 72 participants; RR 0.78, 95% CI 0.41 to 1.45; very-low quality evidence; [Analysis 1.1](#)).

Mortality secondary to bleeding; mortality secondary to thromboembolism and mortality secondary to infection (within 30 days of surgery)

The trial did not report these outcomes.

All-cause mortality; mortality secondary to bleeding; mortality secondary to thromboembolism and mortality secondary to infection (within 90 days of the surgery)

The trial did not report these outcomes.

Number of participants with major procedure-related bleeding within seven days of surgery

[Veelo 2012](#) defined major bleeding as the presence of blood in the airways requiring repeated suction post procedure, emergency surgery, transfusion of packed red cells, or a combination of these.

There was no evidence of a difference on the incidence of procedure-related bleeding between participants having their coagulopathy corrected (platelets, plasma, or both) and participants who did not (1 trial, 72 participants; RR 1.60, 95% CI 0.29 to 8.92; very-low quality evidence; [Analysis 1.2](#)).

Secondary outcomes

Number of participants with minor procedure-related bleeding within seven days of surgery

[Veelo 2012](#) defined minor bleeding as blood loss less than 100 g that could be controlled with the application of local pressure and did not require re-exploration or transfusion of packed red cells. There was no evidence of a difference in the risk of minor bleeding during or for 12 hours after the procedure for participants having their coagulopathy corrected (platelets, plasma, or both) and participants who did not (1 trial, 64 participants; RR 1.29, 95% CI 0.90 to 1.85; [Analysis 1.3](#)).

Number of platelet transfusions per participant and number of platelet components per participant

Twenty-three participants received a platelet transfusion (five buffy coat units) prior to the procedure in the intervention arm and no participants received a platelet transfusion in the comparator arm. It was not clear whether any participant in the intervention arm received a platelet transfusion during or after the procedure.

Number of red cell transfusions per participant and number of red cell components per participant

No participants in either treatment arm received a red cell transfusion during or after the procedure (1 trial, 64 participants; no events).

Proportion of participants requiring additional interventions to stop bleeding (surgical; medical, e.g. tranexamic acid; other blood products, e.g. fresh frozen plasma, cryoprecipitate, fibrinogen) within seven days of surgery

There was no evidence of a difference in the risk of requiring additional procedures to stop bleeding between participants having their coagulopathy corrected (platelets, plasma or both) and participants who did not (1 trial, 64 participants; RR 0.35, 95% CI 0.01 to 8.38; [Analysis 1.4](#)). Bleeding occurred directly after skin incision and before opening the airway in one participant in the "no correction" group who was on active aspirin treatment, this was treated with suturing and application of local compression.

Quality of life assessment

The trial did not report this outcome.

Serious adverse events

Serious adverse events due to transfusion

The trial did not report this outcome.

Serious adverse events due to surgery

No participants in either treatment arm developed a serious adverse event due to the procedure (1 trial, 64 participants; no events; very-low quality evidence).

Length of hospital stay and length of intensive care unit stay

The trial did not report length of hospital stay.

There was no evidence of a difference in the length of ICU stay (median: 15 days (range 8 to 29) with coagulopathy correction versus median 21 days (range 14 to 26); $P = 0.21$ (analysis by study authors)).

Venous and arterial thromboembolism (including deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction)

The trial did not report these outcomes.

Prophylactic platelet transfusion prior to surgery versus alternative treatments

Two trials compared platelet transfusions to other alternative treatments before surgery ([Basu 2012](#); [Stanca 2010](#)). [Stanca 2010](#) compared platelet transfusion or plasma transfusion or both to intranasal desmopressin, whereas [Basu 2012](#) compared platelet transfusion to TPO mimetics (romiplostim and eltrombopag) ([Summary of findings 2](#); [Summary of findings 3](#)).

Primary outcomes

Mortality

All-cause mortality; mortality secondary to bleeding; mortality secondary to thromboembolism and mortality secondary to infection (within 30 days of the surgery)

The trials did not report mortality within 30 days.

All-cause mortality; mortality secondary to bleeding; mortality secondary to thromboembolism and mortality secondary to infection (within 90 days of the surgery)

The trials did not report mortality within 90 days.

Number of participants with major procedure-related bleeding within seven days of surgery

Platelet transfusion versus desmopressin

No participants had major procedure-related bleeding (1 trial, 36 participants; no events; very-low quality evidence).

Platelet transfusion versus thrombopoietin mimetic

No participants had major procedure-related bleeding (1 trial, 65 participants; no events; very-low quality evidence).

Secondary outcomes

Number of participants with minor procedure-related bleeding within seven days of surgery

Platelet transfusion versus desmopressin

There was no evidence of a difference in minor procedure-related bleeding (1 trial, 36 participants, 0.89, 95% CI 0.06 to 13.23; very-low quality evidence; [Analysis 2.1](#)).

Platelet transfusion versus thrombopoietin mimetic

No participants had minor procedure-related bleeding (1 trial, 65 participants; no events; very-low quality evidence).

Number of platelet transfusions per participant and number of platelet components per participant

The trials did not report these outcomes.

Number of red cell transfusions per participant and number of red cell components per participant

Platelet transfusion versus desmopressin

In [Stanca 2010](#), no participants required red cells transfusions to treat bleeding post dental extraction (1 trial, 36 participants; no events).

Platelet transfusion versus thrombopoietin mimetic

In [Basu 2012](#), no participants required red cells transfusions to treat bleeding post liver biopsy (1 trial, 65 participants; no events).

Proportion of participants requiring additional interventions to stop bleeding

Platelet transfusion versus desmopressin

In [Stanca 2010](#), four participants reused desmopressin at home, the amount of bleeding prior to repeat use of desmopressin administration was not measured, in comparison only one participant in the transfusion group had bleeding after the procedure and required an additional transfusion. There was no evidence of a difference between the two groups for this outcome (1 trial, 36 participants; RR 0.22, 95% CI 0.03 to 1.81; [Analysis 2.2](#)).

Platelet transfusion versus thrombopoietin mimetic

In [Basu 2012](#), no bleeding occurred in either study arm, therefore no treatments were required to stop bleeding (1 trial, 65 participants; no events).

Quality of life assessment

The trials did not report this outcome.

Serious adverse events within 30 days after the operation

Platelet transfusion versus desmopressin

There was no evidence of a difference in the risk of serious adverse reaction related to transfusion (1 trial, 36 participants; RR 2.70, 95% CI 0.12 to 62.17, very-low quality evidence; [Analysis 2.3](#)).

The trials did not report serious adverse events related to surgery.

Platelet transfusion versus thrombopoietin mimetic

The trials did not report serious adverse events related to surgery or transfusion.

Length of hospital stay and length of intensive care unit stay

The trials did not report these outcomes.

Venous and arterial thromboembolism (including deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction)

The trials did not report these outcomes.

Different platelet count thresholds for administering a prophylactic platelet transfusion prior to surgery

We found no trials comparing different platelet count thresholds for platelet transfusion.

DISCUSSION

Summary of main results

The aim of this review was to assess the efficacy and safety of prophylactic platelet transfusions in people with low platelet counts prior to surgery (including invasive procedures).

We included three completed trials in this review; two trials are still ongoing but not yet recruiting participants. All three completed trials were small single-centre RCTs (180 participants in total) ([Basu 2012](#); [Stanca 2010](#); [Veelo 2012](#)). The ongoing trials are a multicentre RCT and a single-centre RCT that plan to recruit more than 600 adults ([Characteristics of ongoing studies](#) table), which is greater than the combined number of participants included in the three completed trials. All three trials were conducted between 2005 and 2009. Two trials included people with chronic liver disorders ([Basu 2012](#); [Stanca 2010](#)), whereas one trial was set in an ICU involving people with various morbidities ([Veelo 2012](#)).

None of the included trials included children, major surgical procedures or emergency surgery.

Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery

One small trial in people in ICU requiring a tracheotomy (72 randomised, 64 had a tracheotomy) compared platelet transfusions versus no platelet transfusion before the surgical procedure ([Veelo 2012](#)).

- No cases of death reported within 30 days of the surgery.
- We were very uncertain whether there was a difference in the risk of major bleeding between the two groups during or after the surgical procedure.
- We were very uncertain whether there was a difference in the risk of minor bleeding between the two groups during or after the surgical procedure.
- We were very uncertain whether there was a difference in number of participants who required additional surgical interventions to stop bleeding.
- None of the participants had procedure-related serious adverse events.
- We were very uncertain whether there was a difference in the duration of ICU stay.

The trial did not report quality of life or length of hospital stay.

Prophylactic platelet transfusion prior to surgery versus alternative treatments

Two small trials in people with liver disease compared platelet transfusion versus alternative treatments before the surgical procedure (Basu 2012; Stanca 2010). Basu 2012 (65 participants) compared platelet transfusion to two types of TPO analogue (romiplostim, eltrombopag) in people requiring a liver biopsy. Stanca 2010 compared platelet transfusion to desmopressin in people requiring dental procedures.

- We were very uncertain whether there was a difference in the risk of major bleeding between the two groups during or after the surgical procedure.
- We were very uncertain whether there was a difference in the risk of minor bleeding between the two groups during or after the surgical procedure.
- We were very uncertain whether there was a difference in the number of participants who required blood transfusions to stop bleeding after surgery.
- We were very uncertain whether there was a difference in the number of participant who had transfusion-related serious adverse events.

Neither trial reported mortality, quality of life or length of hospital stay.

Different platelet count thresholds for administering a prophylactic platelet transfusion prior to surgery

We found no trials that compared different platelet count thresholds.

Overall completeness and applicability of evidence

The conclusions which can be drawn following this systematic review were very limited due to the inclusion of only three small RCTs (180 randomised). There was insufficient evidence to determine the effect of platelet transfusion prior to surgery on the primary outcomes of all-cause mortality or major procedure-related bleeding. There were insufficient data to determine the effect on minor procedure-related bleeding or any other secondary outcome.

There are two ongoing RCTs (anticipated to recruit 627 participants), which are scheduled to complete recruitment by October 2019 (NTR5653; Rocha 2017). One is comparing platelet transfusion versus no platelet transfusion prior to central line insertion (462 participants) (NTR5653), the other trial is comparing a restrictive versus liberal versus thromboelastography-

based transfusion algorithm (165 participants) prior to central line insertion (Rocha 2017).

The available evidence for the effectiveness and safety of prophylactic platelet transfusions only related to adults, and most of the evidence was for people with chronic liver disease. None of the included or ongoing trials included children, major surgical procedures or emergency surgery.

This review excluded studies that compared a platelet count threshold versus thromboelastography-based transfusion algorithm, or different thromboelastography-based transfusion algorithms, and several studies that were excluded at the full-text stage assessed this comparison (see [Characteristics of excluded studies](#) table), including one completed study in people with liver disease (De Pietri 2016). Thromboelastography has been suggested as an alternative to the platelet count to assess the need for a platelet transfusion by assessing the speed and strength of blood clot formation in vitro (Bolliger 2012).

Quality of the evidence

Overall, the quality of evidence was rated according to the GRADE methodology as very low across difference outcomes due to high risk of bias (unblinded studies); imprecision of the estimates, and indirectness (only adults with liver disease or adults in the ICU were included in the studies) ([Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#)).

We assessed the GRADE quality of evidence as very low for:

- all-cause mortality;
- number of participants with major procedure-related bleeding within seven days of surgery;
- number of participants with minor procedure-related bleeding within seven days of surgery;
- serious adverse events.

We could not assess the quality of the evidence for: mortality secondary to bleeding, mortality secondary to thromboembolism and mortality secondary to infection because none of the trials reported these outcomes.

All three included trials in this review were RCTs; however, none of the trials were free from methodological bias. See [Figure 2](#) for the visual summary of the risk of bias assessment on each domain. Two trials were at risk of performance and detection bias, this was due to the nature of the intervention "platelet transfusion" (Stanca 2010; Veelo 2012). Most 'Risk of bias' tool domains of one of the included trial were at unclear risk of bias as the trial was only available as an abstract (Basu 2012).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Basu 2012	?	?	+	+	?	?	?
Stanca 2010	+	+	-	-	?	?	+
Veelo 2012	+	+	-	-	+	-	?

Potential biases in the review process

We conducted a comprehensive search of multiple databases and clinical trial registries to capture all relevant studies. We did not limit the search by language or publication status. There are two ongoing studies. Two review authors carefully screened all papers identified by the search and performed data extraction and quality assessment evaluations. We prespecified all outcomes prior to undertaking the search. We were unable to undertake a meta-analysis or assess publication bias as the review included only three studies and there were significant clinical differences between the studies (comparing different interventions).

Agreements and disagreements with other studies or reviews

To our knowledge this review is the first to systematically assess the evidence related to prophylactic platelet transfusion before surgery for people with thrombocytopenia. Two reviews have assessed the evidence for prophylactic platelet transfusions prior to lumbar

punctures and epidural anaesthesia (Estcourt 2016b), and prior to central line insertion (Estcourt 2015). Neither of these reviews included non-randomised studies. Estcourt 2015 identified one of the ongoing studies identified in this review (Rocha 2017), and Estcourt 2016b did not identify any relevant studies. These other reviews highlight the lack of evidence regarding this question.

AUTHORS' CONCLUSIONS

Implications for practice

Based on only three small trials included in this review, there is insufficient evidence to determine whether prophylactic platelet transfusions before surgical procedures could reduce the risk of death and bleeding among people with a low platelet count.

Implications for research

An update of this review should consider including a platelet count threshold versus thrombelastography-based regimen as

these study comparisons have been performed and have been excluded from this version of the review.

Further trials to examine the utility of prophylactic platelet transfusions among people with thrombocytopenia before surgical procedures are still required, there are no completed or ongoing trials that:

- include neonates or children;
- include major or emergency surgery;
- include an assessment of quality of life or other participant-reported outcome measures;
- include adults with haematological disorders.

Further trials are required to assess the use of platelet transfusions versus no platelet transfusions in minor surgery, the use of alternatives to platelet transfusion and the use of different platelet count thresholds for all procedures.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Basu 2012

Methods	Study design: randomised, double-blind, parallel-group controlled trial Setting and country: outpatient university hospital, USA Number of centres: 1 Study duration (start to end): unclear Follow-up duration: 4 weeks Power calculation: unclear Publication type: abstract
Participants	Inclusion criteria: CLD with thrombocytopenia Exclusion criteria: ITP, drug-induced thrombocytopenia, HIV, hepatocellular carcinoma, haemangioma, autoimmune thrombocytopenia, use of steroids, MDS Number screened: unclear Number randomised: 65

Basu 2012 (Continued)

Number analysed: unclear

Number excluded: unclear

Baseline characteristics

- Number of participants: 18 in the platelet transfusion group, 23 in the romiplostim group, 24 in the eltrombopag group
- Age (years): mean 56
- Gender (male/female): 43/22
- Platelet count ($\times 10^9/L$): mean 77
- Creatinine (mg/L): not reported
- Total bilirubin (mg/dL): not reported
- ALT: not reported
- Albumin: not reported
- INR: not reported
- PT: not reported
- Primary diagnosis: hepatitis C 37/65 (57%); hepatitis B 7 (15.5%), alcoholic cirrhosis 10 (15%); non-alcoholic steatohepatitis 3 (5%), primary biliary cirrhosis 6 (9%)
- Antiplatelet agents: not reported
- Anticoagulants: exclusion criterion
- Coagulopathy: not reported

Interventions

Procedure: liver biopsy

Platelet transfusion (n = 18)

- Dose: 7 units of platelets
- Frequency: once at night for the morning liver biopsy
- Administration route: IV

Romiplostim (n = 23)

- Dose: 500 μg
- Frequency: given once 2 weeks before the liver biopsy
- Administration route: subcutaneous

Eltrombopag (n = 24)

- Dose: 57 mg/day
- Frequency: for 2 weeks before the liver biopsy
- Administration route: by mouth

Outcomes

Review outcomes

- Bleeding and haematoma

Other outcomes

- adverse effects of the eltrombopag and romiplostim: nausea, vomiting, dry mouth, headache, insomnia, irritability, local skin rash, shortness of breath, myalgia, arthralgia, erythema in postbiopsy and postinjection site
- cost effectiveness

Notes

Trial registration: none found

Sources of funding: not reported

Conflicts of interest: unclear

Basu 2012 (Continued)

Ethical approval: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Published as an abstract, no information available
Allocation concealment (selection bias)	Unclear risk	Published as an abstract, no information available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Published as an abstract, no information available
Selective reporting (reporting bias)	Unclear risk	Published as an abstract, no information available
Other bias	Unclear risk	Published as an abstract, no information available

Stanca 2010

Methods	<p>Study design: randomised, open-label, parallel-controlled trial</p> <p>Setting and country: dental clinic, Mount Sinai Hospital, USA</p> <p>Number of centres: 1</p> <p>Study duration (start to end): study enrolment occurred between October 2005 and May 2007</p> <p>Follow-up duration: 24 hours after surgery</p> <p>Study power calculation: no</p> <p>Publication type: full</p>
Participants	<p>Inclusion criteria: adults with biopsy-confirmed liver cirrhosis or clinical/radiological evidence of cirrhosis, requiring dental extraction, having a platelet count of $30 \times 10^9/L$ to $50 \times 10^9/L$, INR of 2.0 to 3.0, or a combination of these</p> <p>Exclusion criteria: presence of other bleeding disorders besides cirrhosis such as renal dysfunction (creatinine 2.0 mg/dL) or HIV, receipt of blood transfusion within 2 weeks before the study, recent acute decompensation of liver cirrhosis, malignancy excluding hepatocellular carcinoma in the absence of portal vein thrombosis, treatment with antiplatelet medications (aspirin, non-steroidal anti-inflammatory drugs or clopidogrel) within 10 days before the extraction and documented allergy to desmopressin</p> <p>Pretreatment: no difference between groups with regard to the age, gender, the severity of liver disease as reflected by MELD score, number of teeth removed and percentage of surgical extractions</p>

Prophylactic platelet transfusions prior to surgery for people with a low platelet count (Review)

Stanca 2010 (Continued)

Number screened: 43 enrolled. 2 participants assigned to the blood transfusion group withdrew their consent for the study; 1 participant wanted to be assigned to the desmopressin group, and the other participant changed his mind about having the dental extraction done at that time. 5 participants, 4 in the desmopressin group and 1 in the transfusion group, had blood drawn after being enrolled in the study but before their surgical procedure that resulted in laboratory values outside of the study parameters. These 5 participants underwent the surgical procedure but were not included in the analysis.

Number excluded: 5 participants underwent the surgical procedure but were not included in the analysis.

Baseline characteristics

Platelet transfusion group

- Number of participants: 19
- Age (years): mean 50 (range 28 to 65)
- Gender (male/female): 13/6
- Platelet count ($\times 10^9/L$): mean 45 (range 22 to 103), 11 out of 19 participants had low platelets
- Creatinine (mg/dL): mean 0.8 (range 0.5 to 1.8)
- Total bilirubin (mg/dL): mean 2.7 (range 1.5 to 24.9)
- ALT (IU/L): mean 46 (range 17 to 188)
- Albumin (g/dL): mean 2.5 (range 1.4 to 3.5)
- INR: mean 2.1 (range 1.4 to 2.9)
- PT: not reported
- Procedure: dental extraction: simple 10; surgical 7; unknown 2
- Primary diagnosis: liver cirrhosis
- Antiplatelet agents: exclusion criterion
- Anticoagulants: exclusion criteria included the presence of other bleeding disorders
- Coagulopathy: exclusion criteria included the presence of other bleeding disorders
- Platelet dysfunction: exclusion criteria included the presence of other bleeding disorders

Alternatives to platelet transfusions group

- Number of participants: 17
- Age (years): mean 51 (range 34 to 63)
- Gender (male/female): 12/5
- Platelet count ($\times 10^9/L$): mean 48 (range 30 to 147), 11 out of 17 participants had low platelets
- Creatinine (mg/dL): mean 0.9 (range 0.5 to 1.9)
- Total bilirubin (mg/dL): mean 2.7 (range 1.1 to 15.4)
- ALT (IU/L): mean 30 (range 13 to 491)
- Albumin (g/dL): mean 2.7 (range 1.9 to 4.1)
- INR: mean 2.0 (range 1.0 to 3.0)
- PT: NR
- Procedure: dental extraction: simple 9; surgical 7; unknown 1
- Primary diagnosis: liver cirrhosis
- Antiplatelet agents: exclusion criterion
- Anticoagulants: exclusion criteria included the presence of other bleeding disorders
- Coagulopathy: exclusion criteria included the presence of other bleeding disorders
- Platelet dysfunction: exclusion criteria included the presence of other bleeding disorders

Interventions

Surgical procedure: dental extraction

Platelet transfusion

- Dose: FFP 10 mL/kg for INR of 2.0 to 3.0 or 1 unit of single donor platelets if the platelet count was in the range of 30,000/L to 50,000/L (or both)

Stanca 2010 (Continued)

- Frequency: additional transfusions if bleeding post procedure
- Administration route: IV

Alternatives to platelet transfusions

- Dose: desmopressin acetate, nasal spray, 1.5 mg/mL; 25 doses in 1 container) provided by CSL Behring, Kankakee, IL
- Frequency: both nostrils, prior to surgery and after surgery if bleeding or evening after procedure if bleeding
- Administration route: intranasal

Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none">necessity of rescue blood transfusion in participants who received desmopressin or blood transfusion prior to dental extraction (time frame: 48 hours) <p>Secondary outcomes:</p> <ul style="list-style-type: none">number of participants with major procedure-related bleeding within 7 days of surgerynumber of participants with minor procedure-related bleeding within 7 days of surgerynumber of platelet transfusions per participant and number of platelet components per participantnumber of red cell transfusions per participant and number of red cell components per participantserious adverse eventscost	
Notes	<p>Trial registration number: NCT00816127</p> <p>Source of funding: Icahn School of Medicine at Mount Sinai, New York City, NY</p> <p>Conflicts of interest: unclear</p> <p>Ethical approval: yes, "The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the approval by the Mount Sinai Institutional Review Board."</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization list was generated by one member of the biomathematics team using computer software for randomization."
Allocation concealment (selection bias)	Low risk	Quote: "same member of the biomathematics team, not involved in patient enrollment, prepared sealed white randomization envelopes pre-labeled with an ID number. The content of the envelope (patient's assignment to the DDAVP [desmopressin] or blood transfusion group) matched the information in the randomization plan for that particular ID number (DDAVP or blood transfusion group). The content of the envelope was not accessible to the research coordinator who enrolled patients or to any member of the team at the time of enrollment." Judgement comment: sealed white envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design, no blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding

Stanca 2010 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	In all, 43 participants were enrolled in the study and randomised: 21 in desmopressin group and 22 in transfusion group. 36 participants (17 in desmopressin group and 19 in transfusion group) completed the study procedures. 2 participants assigned to the blood transfusion group withdrew their consent for the study; 1 participant wanted to be assigned to the desmopressin group, and the other participant changed his mind about having the dental extraction done at that time. 5 participants, 4 in desmopressin group and 1 in transfusion group, had blood drawn after being enrolled in the study but before their surgical procedure that resulted in laboratory values outside of the study parameters. These 5 participants underwent the surgical procedure but were not included in the analysis. None of these participants experienced bleeding after the procedure. 7 participants randomised were not included in the analysis. 3 in transfusion arm and 4 in desmopressin arm. This is a relative large (up to 19%) number of participants randomised who were not included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Only outcome listed on clinical trials.gov was: "Necessity of rescue blood transfusion in patients who received DDAVP [desmopressin] or blood transfusion prior to dental extraction." No other secondary outcomes listed. This outcome was reported. However, no protocol to assess if other outcomes was planned.
Other bias	Low risk	No other biases found

Veelo 2012

Methods	<p>Study design: parallel-group, open-label, RCT</p> <p>Setting and country: ICU University hospital, the Netherlands</p> <p>Number of centres: 1</p> <p>Study duration (start to end): July 2007 to October 2009</p> <p>Follow-up duration: Not reported</p> <p>Power calculation: yes, "Although a sample size of 152 patients was considered necessary to find a difference of 15% in bleeding between groups, the study was prematurely terminated."</p> <p>Publication type: full</p>
Participants	<p>Inclusion criteria: participants planned for bedside PDT with mild coagulation disorders defined as PT 14.7–20.0 seconds or platelet counts $40\text{--}100 \times 10^9/\text{L}$ or active treatment with aspirin at any dose, or a combination of these</p> <p>Exclusion criteria: aged < 18 years; need for surgical tracheotomy; contraindications to transfusion of blood products and use of clopidogrel. Participant would also be excluded from participation if the attending physician insisted on the need for transfusion of FFP or platelets (or both) before the procedure.</p> <p>Number screened: 355</p> <p>Number randomised: 72</p> <p>Number analysed: 64, 4 in each arm did not undergo PDT</p> <p>Number excluded: 283 (refused consent 27, surgical procedure 53, clopidogrel 13, PT > 20 seconds, 11, normal coagulation 179)</p> <p>Baseline characteristics</p>

Veelo 2012 (Continued)

Platelet transfusion group

- Number of participants: 35
- Age (years): median 64 (IQR 56–72)
- Gender (male/female): 22/13
- Platelet count ($\times 10^9/L$): median 81 (IQR 63–85), low platelet count 13
- Creatinine: not reported
- Total bilirubin: not reported
- ALT: not reported
- Albumin: not reported
- INR: not reported
- PT (secs): mean 16.0 (SD 1.2)
- Primary diagnosis: 9 acute renal failure, 2 chronic renal failure, 7 sepsis, 5 massive transfusion, 2 haematological malignancy, 0 liver cirrhosis
- Antiplatelet agents: 11 (aspirin)
- Anticoagulants: exclusion criterion
- Coagulopathy: 8 had > 1 coagulation disorder present
- Platelet dysfunction: not reported

No platelet transfusion group

- Number of participants: 37
- Age (years): median 68 (IQR 60–76)
- Gender (male/female): 16/21
- Platelet count ($\times 10^9/L$): median 56 (IQR 47–70), low platelet count 10
- Creatinine: not reported
- Total bilirubin: not reported
- ALT: not reported
- Albumin: not reported
- INR: not reported
- PT (secs): mean 16.6 (SD 1.1)
- Primary diagnosis: 3 acute renal failure, 2 chronic renal failure, 9 sepsis, 5 massive transfusion, 3 haematological malignancy, 0 liver cirrhosis
- Antiplatelet agents: 12 participants were on aspirin
- Anticoagulants: excluded criterion
- Coagulopathy: 7 had > 1 coagulation disorder present
- Platelet dysfunction: not reported

Interventions

Procedure: PDT

Platelet transfusion group

- Dose: participants with a prolonged PT (normal values 11.0–14.7 seconds) assigned to the "correction group" received 1 or 2 units of FFP (1 unit contained 300 mL of FFP: if the PT was between 14.7 and 18.0 seconds the participant received 1 unit of FFP; if the PT was between 18.0 and 20.0 seconds the participant received 2 units of FFP). Participants with a low platelet count or active use of aspirin (or both) assigned to the correction group received 5 units of platelet concentrates prepared from 5 pooled buffy coats.
- Frequency: before procedure
- Administration route: IV

No platelet transfusion group

- Dose: participants assigned to the "no correction" group received neither plasma nor platelets. However, FFP or platelets (or both) were made available for immediate transfusion in case bleeding occurred during or after PDT

Veelo 2012 (Continued)

Outcomes

Primary outcomes

- Volume of blood loss during PDT
- Intensity of intra-tracheal bleeding
- Time until no blood is visible in tracheal aspirates

Secondary outcome

- Amount of blood products used during and after tracheotomy

Review outcomes reported by the trial

- All-cause mortality within 30 days of surgery
- Major bleeding within 7 days of surgery
- Minor bleeding within 7 days of surgery
- Number of participants received platelet transfusions
- Number of participants received red blood cells transfusions
- Proportion of participants requiring additional interventions to stop bleeding within 7 days of surgery
- Serious adverse effects

Notes

Trial registration number: Current Controlled Trials ISRCTN31808827

Source of funding: Academic Medical Centre (AMC) (The Netherlands), Department of Intensive Care

Conflicts of interest: authors declared no conflicts of interest

Ethical approval: yes. "The study was approved by the local ethics committee."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomisation scheme was used."
Allocation concealment (selection bias)	Low risk	Quote: "Each assignment ("correction" or "no correction") was recorded on a piece of paper folded three times and enclosed in a consecutively numbered, opaque, sealed envelope."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label design RCT
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label design RCT
Incomplete outcome data (attrition bias) All outcomes	Low risk	CONSORT flow diagram clearly reported. All participants who underwent the procedure were included in the analysis. 4 in each arm did not undergo the procedure.
Selective reporting (reporting bias)	High risk	No protocol available, but registered ISRCTN31808827. Primary outcome measures: volume of blood loss during PDT2; intensity of intratracheal bleeding; time until no blood is visible in tracheal aspirates. All these were all reported in the published paper. Secondary outcome measures: amount of blood products used during and after tracheotomy – not clearly reported in the published paper

Veelo 2012 (Continued)

Other bias	Unclear risk	<p>Trial stopped early due to increase resistance to recruitment and low rate of bleeding in either arm of the study.</p> <p>Quote: "Although a sample size of 152 patients was considered necessary to find a difference of 15% in bleeding between groups, the study was prematurely terminated."</p>
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ALT: alanine transaminase; CLD: chronic liver disease; FFP: fresh frozen plasma; ICU: intensive care unit; INR: international normalised ratio; IQR: interquartile range; ITP: immune thrombocytopenia; IV: intravenous; MDS: myelodysplastic syndrome; MELD: Model for End-Stage Liver Disease; n: number of participants; PDT: percutaneous dilational tracheotomy; PT: prothrombin time; RCT: randomised controlled trial; SD: standard deviation.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abdelfatah 2016	Wrong study design, observational retrospective cohort
Afdhal 2012	Wrong intervention, no platelet transfusions
Al-Zaabi 2014	Wrong study design, single-centre observational cohort
Backos 1999	Wrong participant population, not receiving surgery or a procedure
Barrera 1996	Wrong study design, observational retrospective cohort
Cai 2014	Wrong study design, single-centre observational cohort
Chantarangkul 2013	Wrong study design, single-centre observational cohort
Chen 2011	Wrong study design, single-centre observational cohort
De Pietri 2016	wrong intervention, thrombelastography-guided blood product use
Embrey 2006	Wrong study design, observational retrospective cohort
EudraCT 2007-005851-40	Wrong intervention, no platelet transfusions
Fayed 2014	Wrong study design, observational cohort
Harding 1975	Wrong participant population (not thrombocytopenic prior to surgery)
Hess 2015	Wrong participant population (bleeding)
Hibbert 2013	Wrong study design, observational cohort
Holcomb 2015	Wrong participant population (bleeding)
Karkouti 2016	Wrong intervention, thrombelastography-guided blood product use
Khair 2015	Wrong study design, case series
Kultufan 2006	Wrong intervention, thrombelastography-guided blood product use
Napolitano 2017	Wrong study design, case series

Study	Reason for exclusion
NCT00521664	Wrong participant population, not receiving surgery or a procedure
NCT00549484	Wrong study setting, measuring thrombopoietin levels
NCT00678587	Wrong intervention, no platelet transfusions
NCT01291290	Wrong participant population (bleeding)
NCT01402739	Wrong participant population (not thrombocytopenic prior to surgery)
NCT01919840	Wrong intervention, thrombelastography-guided blood product use
NCT02042898	Wrong intervention, no platelet transfusions
NCT02074436	Wrong participant population, not receiving surgery or a procedure
NCT02200419	Wrong study design, observational study
NCT02352181	Wrong intervention, thrombelastography-guided blood product use
NCT02987712	Wrong study design, single-centre non-randomised study
NCT02990273	Wrong intervention, thrombelastography-guided blood product use
NCT03011827	Wrong study design, observational cohort study
NCT03022253	Wrong participant population, not receiving surgery or a procedure
Park 2016	Wrong study design, observational cohort
Pereboom 2009	Wrong study design, case series
Perek 2016	Wrong study design, retrospective cohort
Perl 2016	Wrong intervention, blood transfusion ratios in trauma (PROPPR study)
Pietri 2014	Wrong intervention, thrombelastography-guided blood product use
Ray 1997	Wrong study design, observational cohort
Simon 1982	Wrong participant population (not thrombocytopenic prior to surgery)
Simon 1984	Wrong participant population (not thrombocytopenic prior to surgery)
Smart 2017	Wrong intervention, thrombelastography-guided blood product use
Tanaka 2014	Wrong participant population (not thrombocytopenic prior to surgery)
Titano 2016	Wrong intervention, no platelet transfusions
Tripodi 2013	Wrong study design, observational cohort study

Characteristics of ongoing studies [ordered by study ID]

NTR5653

Trial name or title	Prophylactic platelet transfusion prior to central venous catheter placement in patients with thrombocytopenia
Methods	<p>Study design: parallel-group, single-blind, randomised controlled trial</p> <p>Country: the Netherlands</p> <p>Number of centres: multicentre</p> <p>Planned starting date: February 2016</p> <p>Planned completion date: October 2019</p> <p>Follow-up points: directly after CVC insertion, 1 hour, 24 hours</p>
Participants	<p>Target number of participants: 462</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Aged > 18 years • Need for CVC placement at the clinician's discretion • Platelet count $10\text{--}50 \times 10^9/\text{L}$ • INR < 1.5 • Informed consent <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Use of therapeutic anticoagulant therapy, except single antiplatelet therapy • Contraindication for platelet transfusion, such as thrombotic thrombocytopenic purpura, or congenital IgA deficiency • Previous randomisation in the current trial • People with a history of congenital or acquired coagulation factor deficiency or bleeding diathesis
Interventions	<p>Intervention arm: 1 unit of platelets</p> <p>Control arm: no platelets or placebo treatment</p>
Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> • A procedure-related relevant bleeding, occurring within 24 hours after the procedure. A WHO grade 2–4 bleed up to 24 hours from randomisation was defined as relevant bleeding. <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • WHO grade 1 bleeding within 24 hours of CVC placement • Adjusted WHO bleeding score, HEmorrhage MEasurement (HEME)-bleeding score • Allergic transfusion reaction within 24 hours • Onset of acute lung injury within 48 hours • Length of hospital stay • Number of RBC and platelet transfusions within 24 hours • Costs
Starting date	February 2016
Contact information	APJ Vlaar

NTR5653 (Continued)

Notes

Trial registration date: January 2016

Rocha 2017

Trial name or title	Point-of-care versus standard coagulation tests versus restrictive strategy to guide transfusion in chronic liver failure patients requiring central venous line: prospective randomized trial (POCKET)
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment (3 arms) Masking: double-blind (participant, caregiver) Primary purpose: treatment
Participants	Inclusion criteria: <ul style="list-style-type: none"> adults (aged ≥ 18 years) with chronic liver failure (cirrhosis or chronic liver graft dysfunction or both) admitted to ICU and requiring insertion of a central line. Exclusion criteria: <ul style="list-style-type: none"> acute liver failure use of therapeutic doses of oral or parenteral anticoagulants (unfractionated heparin or low molecular weight heparin or oral anticoagulants) use of oral or parenteral platelet aggregation inhibitors people with von Willebrand disease over-the-guidewire CVC changing people previously included in this study protocol during the same hospital stay
Interventions	Arm 1: coagulogram-based protocol Arm based on standard coagulation tests protocol to guide blood transfusion before central venous catheterisation. The possible components to be used include fresh frozen plasma, platelets (random or apheresis), cryoprecipitate (or a combination of these), based on INR), PTT, platelet count, fibrinogen (or a combination of these). <ul style="list-style-type: none"> INR > 1.5 or PTT > 50 seconds, fresh frozen plasma is administered (dose: 10 mL/kg) Platelets $< 50 \times 10^9/L$, platelet transfusion is administered (random or apheresis) Fibrinogen $< 1.5g/L$, cryoprecipitate is administered Arm 2: thromboelastometry-based protocol The interventions for this protocol included transfusion of fresh frozen plasma, platelets (random or aphaeresis) cryoprecipitate (or a combination of these), based on rotational thromboelastometry. <ul style="list-style-type: none"> Coagulation time (extrinsically activated) < 80 seconds and A10 (extrinsically activated) > 40 mm, then no blood transfusion is performed Coagulation time (extrinsically activated) > 80 seconds then fresh frozen plasma is administered (dose: 10 mL/kg) A10 (extrinsically activated) < 40 mm or A10 (fibrinogen polymerisation) > 10 mm platelet transfusion is administered (random or apheresis) A10 (extrinsically activated) < 40 mm or A10 (fibrinogen polymerisation) < 10 mm cryoprecipitate is administered

Rocha 2017 (Continued)

Arm 3: restrictive strategy

The interventions for this protocol include transfusion of fresh frozen plasma or platelets (random or aphaeresis), or both, based on INR and platelet count.

- INR > 5, fresh frozen plasma is administered (dose: 10 mL/kg)
- Platelets < 25 × 10⁹/L, platelet transfusion is administered (random or aphaeresis)

Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> • proportion of participants receiving a blood component transfusion, i.e. fresh frozen plasma, platelets, cryoprecipitate (or a combination of these) before central venous catheterisation (on day of randomisation) <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • incidence of haemorrhagic complications associated with central venous catheterisation procedure (up to 24 hours) • incidence of acute immunological and non-immunological adverse effects of blood transfusion (up to 24 hours) • cost assessments (laboratory and blood transfusion) between the 3 strategies (up to 24 hours) • length of stay in ICU (up to 90 days) • length of stay in hospital (up to 180 days) • mortality rate (up to 28 days)
Starting date	September 2014
Contact information	Leonardo L Rocha, MD +55-11-21511500, lrocha23@gmail.com Thiago D Correa, MD, PhD +55-11-21511500, thiagodct@gmail.com
Notes	<p>Estimated enrolment: 165</p> <p>Estimated study completion date: January 2019</p> <p>Estimated primary completion date: December 2018 (final data collection date for primary outcome measure)</p> <p>Trial registration: NCT02311985</p> <p>Location of trial: Hospital Israelita Albert Einstein, Sao Paulo, Brazil</p>

CVC: central venous catheter; ICU: intensive care unit; IgA: immunoglobulin A; INR: international normalised ratio; PTT: partial thromboplastin time; RBC: red blood cell; WHO: World Health Organization.

DATA AND ANALYSES

Comparison 1. Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality within 30 days of surgery	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of participants with major procedure-related bleeding within 7 days of surgery	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Number of participants with minor procedure-related bleeding within 7 days of surgery	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Proportion of participants requiring additional interventions to stop bleeding within 7 days of surgery	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery, Outcome 1 All-cause mortality within 30 days of surgery.

Study or subgroup	Platelet transfusion n/N	No platelet transfusion n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Veelo 2012	11/35	15/37		0.78[0.41,1.45]

Analysis 1.2. Comparison 1 Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery, Outcome 2 Number of participants with major procedure-related bleeding within 7 days of surgery.

Study or subgroup	Platelet transfusion n/N	No platelet transfusion n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Veelo 2012	3/31	2/33		1.6[0.29,8.92]

Analysis 1.3. Comparison 1 Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery, Outcome 3 Number of participants with minor procedure-related bleeding within 7 days of surgery.

Study or subgroup	Platelet transfusion n/N	No platelet transfusion n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Veelo 2012	23/31	19/33		1.29[0.9,1.85]

Analysis 1.4. Comparison 1 Prophylactic platelet transfusion prior to surgery versus no prophylactic platelet transfusion prior to surgery, Outcome 4 Proportion of participants requiring additional interventions to stop bleeding within 7 days of surgery.

Study or subgroup	Platelet transfusion	No platelet transfusion	Risk Ratio	
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Veelo 2012	0/31	1/33		0.35[0.01,8.38]
Favours Platelet transfusion			0.01 0.1 1 10 100	Favours No platelet transfusion

Comparison 2. Prophylactic platelet transfusion prior to surgery versus alternative treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with minor procedure-related bleeding within 7 days of surgery	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Desmopressin vs platelet transfusion	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Thrombopoietin mimetics vs platelet transfusion	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Proportion of participants requiring additional interventions to stop bleeding within 7 days of surgery	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Desmopressin vs platelet transfusion	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Serious adverse events (transfusion related adverse effects within 24 hours of the transfusion)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Desmopressin vs platelet transfusion	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Prophylactic platelet transfusion prior to surgery versus alternative treatments, Outcome 1 Number of participants with minor procedure-related bleeding within 7 days of surgery.

Study or subgroup	Platelet transfusion	Alternatives to platelet transfusions	Risk Ratio	
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
2.1.1 Desmopressin vs platelet transfusion				
Stanca 2010	1/19	1/17		0.89[0.06,13.23]
2.1.2 Thrombopoietin mimetics vs platelet transfusion				
Basu 2012	0/18	0/47		Not estimable
Favours Platelet transfusion			0.001 0.1 1 10 1000	Favours Alternatives to platelet transfusions

Analysis 2.2. Comparison 2 Prophylactic platelet transfusion prior to surgery versus alternative treatments, Outcome 2 Proportion of participants requiring additional interventions to stop bleeding within 7 days of surgery.

Analysis 2.3. Comparison 2 Prophylactic platelet transfusion prior to surgery versus alternative treatments, Outcome 3 Serious adverse events (transfusion related adverse effects within 24 hours of the transfusion).

APPENDICES

Appendix 1. CENTRAL (the Cochrane Library)

#1 MeSH descriptor: [Blood Platelets] explode all trees
 #2 transfus*
 #3 #1 and #2
 #4 MeSH descriptor: [Platelet Transfusion] explode all trees
 #5 MeSH descriptor: [Plateletpheresis] explode all trees
 #6 ((platelet* or thrombocyte*) near/5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product or products or component* or concentrate* or apheres* or pooled or single donor* or random donor*))
 #7 thrombo?ytopheres* or plateletpheres*
 #8 ((platelet* or thrombocyte*) near/5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utilisation or utilization))
 #9 #3 or #4 or #5 or #6 or #7 or #8
 #10 MeSH descriptor: [Specialties, Surgical] explode all trees
 #11 MeSH descriptor: [Surgical Procedures, Operative] explode all trees
 #12 MeSH descriptor: [Perioperative Care] explode all trees
 #13 MeSH descriptor: [Perioperative Period] explode all trees
 #14 surg* or presurg* or postsurg* or operat* or preoperat* or perioperat* or postoperat* or transplant* or bypass* or arthroplasty or neurosurg*
 #15 #10 or #11 or #12 or #13 or #14
 #16 #9 and #15

Appendix 2. MEDLINE (OvidSP)

1. Platelet Transfusion/
 2. Plateletpheresis/
 3. Blood Platelets/ and transfus*.mp.
 4. ((platelet* or thrombocyte*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor)).tw,kf.
 5. (thromboc?topheres* or plateletpheres*).tw,kf.
 6. ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw,kf.
 7. 1 or 2 or 3 or 4 or 5 or 6

8. exp Perioperative Care/
9. exp Surgical Procedures, Operative/
10. exp Perioperative Period/
11. exp Specialties, Surgical/
12. (preoperat* or postoperat* or perioperat* or operat* or surg* or presurg* or postsurg* or perisurg* or transplant* or bypass* or arthroplasty or neurosurg*).mp.
13. 8 or 9 or 10 or 11 or 12
14. 7 and 13
15. Meta-Analysis.pt.
16. ((meta analy* or metaanaly*) and (trials or studies)).ab.
17. (meta analy* or metaanaly* or evidence-based).ti.
18. ((systematic* or evidence-based) adj2 (review* or overview*)).tw.
19. (cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or scopus or search terms or literature search or electronic search* or comprehensive search* or systematic search* or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.
20. Cochrane Database of systematic reviews.jn.
21. (additional adj (papers or articles or sources)).ab.
22. ((electronic* or online) adj (sources or resources or databases)).ab.
23. (relevant adj (journals or articles)).ab.
24. or/15-23
25. Review.pt.
26. RANDOMIZED CONTROLLED TRIALS AS TOPIC/
27. selection criteria.ab. or critical appraisal.ti.
28. (data adj (abstraction or extraction or analys*)).ab.
29. RANDOMIZED CONTROLLED TRIAL/
30. or/26-29
31. 25 and 30
32. 24 or 31
33. exp CONTROLLED CLINICAL TRIAL/
34. exp CONTROLLED CLINICAL TRIALS AS TOPIC/
35. (randomi* or trial).tw,kf.
36. (placebo or randomly or groups).ab.
37. or/33-36
38. CONTROLLED BEFORE-AFTER STUDIES/
39. INTERRUPTED TIME SERIES ANALYSIS/
40. (nonrandom* or non random*).tw,kf.
41. (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre adj5 post)).tw,kf.
42. (controlled clinical study or controlled study or control group*).tw,kf.
43. ((before adj3 after) or "before-after" or interrupted time series or time point* or repeated measur*).tw,kf.
44. 37 or 38 or 39 or 40 or 41 or 42 or 43
45. 32 or 37 or 44
46. (ANIMALS/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/) not HUMANS/
47. Editorial.pt.
48. 46 or 47
49. 45 not 48
50. 14 and 49

Appendix 3. PubMed (epublications ahead of print only)

- #1 ((platelet* OR thrombocyte*) AND (prophyla* OR transfus* OR infus* OR administ* OR requir* OR need* OR product* OR component* OR concentrate* OR apheres* OR pooled OR single donor OR "random donor" OR "random donors" OR protocol* OR trigger* OR threshold* OR schedul* OR dose* OR dosing OR usage OR utilisation OR utilization))
- #2 (thrombo?ytopheres* OR plateletpheres*)
- #3 #1 OR #2
- #4 (preoperat*[TI] OR postoperat*[TI] OR perioperat*[TI] OR operation[TI] OR operations[TI] OR operating[TI] OR operated[TI] OR surgery[TI] OR surgical*[TI] OR presurg*[TI] OR postsurg*[TI] OR perisurg*[TI] OR transplant[TI] OR transplants[TI] OR transplanted[TI] OR transplanting[TI] OR transplantation*[TI] OR bypass*[TI] OR arthroplasty*[TI] OR neurosurg*[TI])
- #5 #3 AND #4
- #6 ((random* OR blind* OR "control group" OR placebo OR "controlled trial" OR "controlled study" OR groups OR trials OR "systematic review" OR "systematic overview" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase OR "time series" OR "repeated measures" OR "before and after" OR "before-after" OR "pre-test" OR "post-test" OR pretest* OR posttest*) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]))

#7 #5 AND #6

Appendix 4. Embase (OvidSP)

1. Thrombocyte Transfusion/
2. Thrombocyte/ and transfus*.mp.
3. *Thrombocyte/
4. Thrombo?ytopheresis/
5. ((platelet* or thrombocyte*) adj5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product* or component* or concentrate* or apheres* or pooled or single donor or random donor)).tw.
6. (thrombo?ytopheres* or plateletpheres*).tw.
7. ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw.
8. or/1-7
9. exp Surgery/
10. (preoperat* or postoperat* or perioperat* or operati* or surg* or presurg* or postsurg* or perisurg* or transplant* or bypass* or arthroplasty or neurosurg*).mp.
11. 9 or 10
12. 8 and 11
13. Meta Analysis/
14. Systematic Review/
15. (meta analy* or metaanalys*).tw.
16. ((systematic* or literature) adj2 (review* or overview* or search*)).tw.
17. (cochrane or embase or cinahl or cinahl or lilacs or BIDS or science citation index or psyclit or psychlit or psycinfo or psychinfo or cancerlit).ti,ab.
18. ((electronic* or online) adj (sources or resources or databases)).ab.
19. (additional adj (articles or papers or sources)).ab.
20. (reference lists or bibliograph* or handsearch* or hand search* or manual* search*).ab.
21. (relevant adj (journals or articles)).ab.
22. (search term* or published articles or search strateg*).ab.
23. or/13-22
24. (data extraction or selection criteria).ab.
25. review.pt.
26. 23 or (24 and 25)
27. editorial.pt.
28. 26 not 27
29. randomized controlled trial/ or crossover-procedure/ or single-blind procedure/ or double-blind procedure/ or triple-blind procedure/
30. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or tripl* blind* or assign* or allocat*).tw.
31. (nonrandom* or non random*).tw.
32. (controlled clinical study or controlled study or control group* or trial).tw.
33. controlled clinical trial/
34. time series analysis/
35. epidemiology/
36. pretest posttest control group design/ or pretest posttest design/
37. (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre adj5 post)).tw.
38. ((before adj3 after) or "before-after" or interrupted time series or time point* or repeated measur*).tw.
39. or/28-38
40. 12 and 39
41. Animal experiment/ not (human experiment/ or human/)
42. 40 not 41
43. limit 42 to embase

Appendix 5. CINAHL (EBSCOHost)

- S1 (MH "Blood Platelets")
- S2 TX transfus*
- S3 S1 AND S2
- S4 (MH "Platelet Transfusion")
- S5 (MH "Plateletpheresis")
- S6 TX ((platelet* or thrombocyte*) N5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product or products or component* or concentrate* or apheres* or pooled or single donor* or random donor*))
- S7 TX thrombocytopheres* or plateletpheres*

S8 TX ((platelet* or thrombocyte*) N5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utilisation or utilization))
S9 S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10 (MH "Specialties, Surgical+")
S11 (MH "Surgery, Operative+")
S12 (MH "Perioperative Care+")
S13 TX (surg* or presurg* or postsurg* or operat* or preoperat* or perioperat* or postoperat* or transplant* or bypass* or arthroplasty or neurosurg*)
S14 S10 OR S11 OR S12 OR S13
S15 S9 AND S14
S16 (MH Clinical Trials+)
S17 PT Clinical Trial
S18 TI ((controlled trial*) or (clinical trial*)) OR AB ((controlled trial*) or (clinical trial*))
S19 TI ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*)) OR AB ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*))
S20 TI randomi* OR AB randomi*
S21 MH RANDOM ASSIGNMENT
S22 TI ((phase three) or (phase III)) or AB ((phase three) or (phase III) or (phase three))
S23 (TI (random* N2 (assign* or allocat*))) OR (AB (random* N2 (assign* or allocat*))))
S24 MH PLACEBOS
S25 MH META ANALYSIS
S26 MH SYSTEMATIC REVIEW
S27 TI ("meta analys*" OR metaanalys* OR "systematic review" OR "systematic overview" OR "systematic search*") OR AB ("meta analys*" OR metaanalys* OR "systematic review" OR "systematic overview" OR "systematic search*")
S28 TI ("literature review" OR "literature overview" OR "literature search*") OR AB ("literature review" OR "literature overview" OR "literature search*")
S29 TI (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit) OR AB (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit)
S30 TI placebo* OR AB placebo*
S31 MH QUANTITATIVE STUDIES
S32 S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31
S33 (MH "Controlled Before-After Studies") OR (MH "Interrupted Time Series Analysis") OR (MH "Nonrandomized Trials") OR (MH "Pretest-Posttest Design+")
S34 (MH "Quasi-Experimental Studies+") OR (MH "Repeated Measures")
S35 TX (nonrandom* or non random*)
S36 TX (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre N5 post))
S37 TX (controlled clinical study or controlled study or control group*)
S38 TX ((before N3 after) or "before-after" or interrupted time series or time point* or repeated measur*)
S39 S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38
S40 S15 AND S39

Appendix 6. Transfusion Evidence Library

Clinical Specialty: Surgery

Subject Area: Blood Components/Platelets

Appendix 7. LILACS

tw:((platelet OR platelets) AND (prophylactic OR prophylaxis OR transfusion OR transfused OR transfusing OR infused OR infusion OR administered OR required OR needed OR product OR component OR concentrate OR concentrates OR apheresis OR pooled OR donor OR donors OR protocol OR trigger OR threshold OR schedule OR dose OR doses OR dosing OR usage OR utilisation OR utilization)) AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("clinical_trials"))

Appendix 8. Web of Science CPC-IS

#1 TS=((platelet* or thrombocyte*) NEAR/5 (prophyla* or transfus* or infus* or administ* or requir* or need* or product or products or component* or concentrate* or apheres* or pooled or donor*))
#2 TS=(thrombocytopheres* or plateletpheres*)
#3 TS=((platelet* or thrombocyte*) NEAR/5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utilisation or utilization))
#4 #3 OR #2 OR #1
#5 TS=(surg* or presurg* or postsurg* or operat* or preoperat* or perioperat* or postoperat* or transplant* or bypass* or arthroplasty or neurosurg*)

#6 #5 AND #4

#7 TS=(random* OR blind* OR "control group" OR placebo OR "controlled trial" OR "controlled study" OR groups OR trials OR "systematic review" OR "systematic overview" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase OR "time series" OR "repeated measures" OR "before and after" OR "before-after" OR "pre-test" OR "post-test" OR pretest* OR posttest*)

#8 #7 AND #6

Appendix 9. ClinicalTrials.gov

Search Terms: (preoperative OR postoperative OR perioperative OR operation OR surgery OR presurgery OR postsurgery OR presurgical OR postsurgical OR transplantation OR bypass OR arthroplasty OR neurosurgery) AND (platelet transfusion OR platelet concentrate) OR

Search Terms: (preoperative OR postoperative OR perioperative OR operation OR surgery OR presurgery OR postsurgery OR presurgical OR postsurgical OR transplantation OR bypass OR arthroplasty OR neurosurgery)

Interventions: platelet transfusion OR platelet concentrate OR prophylactic platelets

Appendix 10. WHO ICTRP

Title: platelet transfusion OR platelet concentrate

Recruitment Status: ALL

OR

Title: preoperative OR postoperative OR perioperative OR operation OR surgery OR surgical OR presurgery OR postsurgery OR presurgical OR postsurgical OR perisurgical OR transplant OR transplantation OR bypass OR arthroplasty OR neurosurgery

Intervention: platelets OR platelet transfusion OR platelet concentrate OR platelet concentrates

Recruitment Status: ALL

Appendix 11. ROBINS-I

ROBINS-I tool (Stage I)

Specify the review question

Participants	People of all ages with a low platelet count who are due to have surgery
Experimental intervention 1	Prophylactic platelet transfusion before surgery
Control intervention 1	No prophylactic platelet transfusion before surgery
Control intervention 2	Artificial platelet substitutes, e.g. lyophilised platelets, infusible plasma membranes and liposomes with inserted platelet receptors
Control intervention 3	Cryosupernatant
Control intervention 4	Thrombopoietin mimetics
Control intervention 5	Antifibrinolytic drugs
Outcomes	Primary outcomes <ul style="list-style-type: none"> Mortality (all-causes, secondary to bleeding, secondary to thromboembolism and secondary to infection) within 30 days and 90 days of surgery. Number of participants with major procedure-related bleeding within 7 days of surgery, defined as: <ul style="list-style-type: none"> surgical site bleeding requiring a second intervention or reoperation or surgical site bleeding that causes a haematoma or haemarthrosis of sufficient size to delay mobilisation or wound healing; bleeding of sufficient size to cause delayed wound healing, or wound infection or surgical site bleeding that is unexpected and prolonged or causes haemodynamic instability (as defined by the study) that is associated with a 20 g/L drop in haemoglobin; bleeding that requires ≥ 2 units of whole blood/red cells within 24 hours of the bleeding; bleeding that is defined by the study with no further details.

(Continued)

Secondary outcomes

- Number of participants with minor procedure-related bleeding within 7 days of surgery (e.g. haematoma, prolonged bleeding at surgical site that does not fulfil the definition for major bleeding).
- Number of platelet transfusions per participant and number of platelet components per participant.
- Number of red cell transfusions per participant and number of red cell components per participant.
- Proportion of participants requiring additional interventions to stop bleeding (surgical; medical, e.g. tranexamic acid; other blood products, e.g. fresh frozen plasma, cryoprecipitate, fibrinogen) within 7 days of surgery.
- Quality of life assessment using validated tools.
- Serious adverse events due to: transfusion (transfusion reactions, transfusion-related acute lung injury, transfusion-related infection, transfusion-associated circulatory overload, transfusion-related dyspnoea) within 24 hours of transfusion.
- Surgery (e.g. delayed wound healing, infection) within 30 days after the operation; length of hospital stay and length of intensive care unit stay.
- Venous and arterial thromboembolism (including deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction).

List the confounding areas relevant to all or most studies

We prespecified the main potential confounding factors.

- Age (neonate, child (aged 1–15 years), adult (aged ≥ 16 years)).
- Gender: male/female ratio.
- Underlying conditions which caused thrombocytopenia.
- Minor surgery or major surgery.
- Severity of thrombocytopenia.
- Haemodynamic status at baseline.
- Participants with clotting abnormalities, such as disseminated intravascular coagulation, or concomitant use of anticoagulant or antiplatelet agents.
- Previous severe bleeding (e.g. World Health Organization grade 3 or 4 or equivalent).

List the possible cointerventions that could be different between intervention groups and could have an impact on outcomes

We prespecified the possible cointerventions that could be different between intervention groups and could have an impact on outcomes.

- Receiving corticosteroids.
- Intravenous immunoglobulin which usually is given when thrombocytopenia is caused by autoimmune disease.
- People with immune thrombocytopenia and who had their spleen removed (splenectomy).
- Transfusion of red blood cells.
- Transfusion of platelets.

The ROBINS-I tool (Stage II): for each study

Specify a target trial specific to the study

Design	Individually randomised/cluster-randomised/matched
Participants	People of all ages with a low platelet count who are due to have surgery
Experimental intervention	Prophylactic platelet transfusion prior to surgery

(Continued)

Control intervention

No prophylactic platelet transfusion prior to surgery (placebo or no treatment)

Is your aim for this study...?

- ☐ To assess the effect of initiating intervention (as in an intention-to-treat analysis)
- ☐ To assess the effect of initiating and adhering to intervention (as in a per-protocol analysis)

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the 'Summary of findings' table). Specify whether this is a proposed benefit or harm of intervention.

Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. risk ratio (RR) = 1.52 (95% confidence interval (CI) 0.83 to 2.77) or a reference (e.g. to a table, figure or paragraph) (or both) that uniquely defines the result being assessed.

Preliminary consideration of confounders

Complete a row for each important confounding area:

- listed in the review protocol; and
- relevant to the setting of this particular study, or which the study authors identified as potentially important. 'Important' confounding areas are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. 'Validity' refers to whether the confounding variable or variables fully measure the area, while 'reliability' refers to the precision of the measurement (more measurement error means less reliability).

Confounding areas listed in the review protocol

Confounding area	Measured variable (s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding area measured validly and reliably by this variable (or these variables)?	Optional: is adjusting for this variable (alone) expected to favour the experimental or the control group?
			Yes / no / no information	Favour intervention / favour control / no information

Additional confounding areas relevant to the setting of this particular study, or which the study authors identified as important

Confounding area	Measured variable (s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding area measured validly and reliably by this variable (or these variables)?	Optional: is adjusting for this variable (alone) expected to favour the experimental or the control group?

(Continued)

	Yes / no / no information	Favour intervention / favour control / no information

*In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis:

- if they are not predictive of the outcome;
- if they are not predictive of intervention; or
- because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that 'no statistically significant association' is not the same as 'not predictive.'

Preliminary consideration of cointerventions

Complete a row for each important cointervention listed in the review protocol; and relevant to the setting of this particular study, or which the study authors identified as important.

'Important' cointerventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

Cointerventions listed in the review protocol		
Cointervention	Is there evidence that controlling for this cointervention was unnecessary (e.g. because it was not administered)?	Is presence of this cointervention likely to favour outcomes in the experimental or the control group?
		Favour experimental / favour comparator / no information
		Favour experimental / favour comparator / no information
		Favour experimental / favour comparator / no information

Additional cointerventions relevant to the setting of this particular study, or which the study authors identified as important		
Cointervention	Is there evidence that controlling for this cointervention was unnecessary (e.g. because it was not administered)?	Is presence of this cointervention likely to favour outcomes in the experimental or the control group?
		Favour experimental / favour comparator / no information
		Favour experimental / favour comparator / no information
		Favour experimental / favour comparator / no information

'Risk of bias' assessment (cohort-type studies)

Bias domain	Signalling questions	Elaboration	Response options
Bias due to confounding	1.1. Is there potential for confounding of the effect of intervention in this study?	In rare situations, such as when studying harms that are very unlikely to be related to factors that influence treatment decisions, no confounding is expected and the study can be considered to be at low risk of bias due to confounding, equivalent to a fully randomised trial.	Y / PY / PN / N
	If N or PN to 1.1.: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	There is no NI option for this signalling question.	
	If Y or PY to 1.1.: determine whether there is a need to assess time-varying confounding		
	1.2. Was the analysis based on splitting participants' follow-up time according to intervention received?	If participants could switch between intervention groups then associations between intervention and outcome may be biased by time-varying confounding. This occurs when prognostic factors influence switches between intended interventions.	NA / Y / PY / PN / N / NI
	If N or PN , answer questions relating to baseline confounding (1.4. to 1.6.)		
	If Y or PY , proceed to question 1.3.		
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	If intervention switches are unrelated to the outcome, for example when the outcome is an unexpected harm, then time-varying confounding will not be present and only control for baseline confounding is required.	NA / Y / PY / PN / N / NI
	If N or PN , answer questions relating to baseline confounding (1.4. to 1.6.)		
	If Y or PY , answer questions relating to both baseline and time-varying confounding (1.7. and 1.8.)		

(Continued)

Questions relating to baseline confounding only

1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding areas?	Appropriate methods to control for measured confounders include stratification, regression, matching, standardisation, and inverse probability weighting. They may control for individual variables or for the estimated propensity score. Inverse probability weighting is based on a function of the propensity score. Each method depends on the assumption that there is no unmeasured or residual confounding.	NA / Y / PY / PN / N / NI
1.5. If Y or PY to 1.4.: were confounding areas that were controlled for measured validly and reliably by the variables available in this study?	Appropriate control of confounding requires that the variables adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domains will be specified in the review protocol but for others such a list may not be available. Study authors may cite references to support the use of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings.	NA / Y / PY / PN / N / NI
1.6. Did the authors control for any postintervention variables?	Controlling for postintervention variables is not appropriate. Controlling for mediating variables estimates the direct effect of intervention and may introduce confounding. Controlling for common effects of intervention and outcome causes bias.	NA / Y / PY / PN / N / NI

Questions relating to baseline and time-varying confounding

1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding areas and for time-varying confounding?	Adjustment for time-varying confounding is necessary to estimate per-protocol effects in both randomised trials and NRSI. Appropriate methods include those based on inverse-probability weighting. Standard regression models that include time-updated confounders may be problematic if time-varying confounding is present.	NA / Y / PY / PN / N / NI
1.8. If Y or PY to 1.7.: were confounding areas that were adjusted for measured validly and reliably by the variables available in this study?	See 1.5. above.	NA / Y / PY / PN / N / NI

'Risk of bias' judgement
Low – no confounding expected.

Low / moderate / serious / critical / NI

Moderate – confounding expected, all known important confounding domains appropriately measured and controlled for;

and

reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding.

(Continued)

Serious – ≥ 1 known important domain was not appropriately measured, or not controlled for;

or

reliability or validity of measurement of an important domain was low enough that we expect serious residual confounding.

Critical – confounding inherently not controllable, or the use of negative controls strongly suggests unmeasured confounding.

Optional: what is the predicted direction of bias due to confounding?

Can the true effect estimate be predicted to be greater or less than the estimated effect in the study because ≥ 1 of the important confounding domains was not controlled for? Answering this question will be based on expert knowledge and results in other studies and therefore can only be completed after all of the studies in the body of evidence have been reviewed. Consider the potential effect of each of the unmeasured domains and whether all important confounding domains not controlled for in the analysis would be likely to change the estimate in the same direction, or if 1 important confounding domain that was not controlled for in the analysis is likely to have a dominant impact.

Favours experimental / favours comparator / unpredictable

Bias in selection of participants into the study

2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?

This domain is concerned only with selection into the study based on participant characteristics observed after the start of intervention. Selection based on characteristics observed before the start of intervention can be addressed by controlling for imbalances between intervention and control groups in baseline characteristics that are prognostic for the outcome (baseline confounding).

Y / PY / PN / N / NI

If N or PN to 2.1.: go to 2.4.

2.2. **If Y or PY to 2.1.:** were the postintervention variables that influenced selection likely to be associated with intervention?

Selection bias occurs when selection is related to an effect of either intervention or a cause of intervention and an effect of either the outcome or a cause of the outcome. Therefore, the result is at risk of selection bias if selection into the study is related to both the intervention and the outcome.

NA / Y / PY / PN / N / NI

2.3. **If Y or PY to 2.2.:** were the postintervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?

—

NA / Y / PY / PN / N / NI

2.4. Do start of follow-up and start of intervention coincide for most participants?

If participants are not followed from the start of the intervention then a period of follow-up has been excluded, and participants who experienced the outcome soon after intervention will be missing from analyses. This problem may occur when

Y / PY / PN / N / NI

(Continued)

prevalent, rather than new (incident), users of the intervention are included in analyses.

<p>2.5.If Y or PY to 2.2. and 2.3., or N or PN to 2.4.: were adjustment techniques used that are likely to correct for the presence of selection biases?</p>	<p>It is in principle possible to correct for selection biases, e.g. by using inverse probability weights to create a pseudo-population in which the selection bias has been removed, or by modelling the distributions of the missing participants or follow-up times and outcome events and including them using missing data methodology. However, such methods are rarely used and the answer to this question will usually be 'N.'</p>	<p>NA / Y / PY / PN / N / NI</p>
<p>'Risk of bias' judgement</p>	<p>Low – all participants who would have been eligible for the target trial were included in the study and start of follow-up and start of intervention coincide for all participants.</p> <hr/> <p>Moderate – selection into the study may have been related to intervention and outcome, but the authors used appropriate methods to adjust for the selection bias; or Start of follow-up and start of intervention do not coincide for all participants, but the proportion of participants for which this was the case was too low to induce important bias; the authors used appropriate methods to adjust for the selection bias or the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time.</p> <hr/> <p>Serious – selection into the study was related to intervention and outcome;</p> <p>or</p> <p>start of follow-up and start of intervention do not coincide, and a potentially important amount of follow-up time is missing from analyses, and the rate ratio is not constant over time.</p> <hr/> <p>Critical – selection into the study was strongly related to intervention and outcome;</p> <p>or</p> <p>a substantial amount of follow-up time is likely to be missing from analyses, and the rate ratio is not constant over time.</p>	<p>Low / moderate / serious / critical / NI</p>
<p>Optional: what is the predicted direction of bias due to selection of participants into the study?</p>	<p>If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterised either as being towards (or away from) the null, or as being in favour of 1 of the interventions.</p>	<p>Favours experimental / favours comparator / towards null / away from null / unpredictable</p>
<p>Bias in classification of interventions</p>	<p>3.1. Were intervention groups clearly defined?</p> <p>A prerequisite for an appropriate comparison of interventions is that the interventions are well-defined. Ambiguity in the definition may lead to bias in the classification of participants. For individual-level interventions, criteria for considering individuals to have received each intervention should be clear and explicit, covering issues such as type, setting, dose, frequency, intensity, timing of intervention, or a combination of these. For population-level interventions (e.g. measures to control air pollution), the question relates to whether the population is clearly defined, and the answer is likely to be 'Yes.'</p>	<p>Y / PY / PN / N / NI</p>

(Continued)

	3.2. Was the information used to define intervention groups recorded at the start of the intervention?	In general, if information about interventions received is available from sources that could not have been affected by subsequent outcomes, then differential misclassification of intervention status is unlikely. Collection of the information at the time of the intervention makes it easier to avoid such misclassification. For population-level interventions (e.g. measures to control air pollution), the answer to this question is likely to be 'Yes.'	Y / PY / PN / N / NI
	3.3. Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Collection of the information at the time of the intervention may not be sufficient to avoid bias. The way in which the data are collected for the purposes of the NRSI should also avoid misclassification.	Y / PY / PN / N / NI
'Risk of bias' judgement		Low – intervention status is well-defined and based solely on information collected at the time of intervention.	Low / moderate / serious / critical / NI
		Moderate – intervention status is well-defined but some aspects of the assignments of intervention status were determined retrospectively	
		Serious – intervention status is not well-defined, or major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome.	
		Critical – (unusual) an extremely high amount of misclassification of intervention status, e.g. because of unusually strong recall biases.	
	Optional: what is the predicted direction of bias due to measurement of outcomes or interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterised either as being towards (or away from) the null, or as being in favour of 1 of the interventions.	Favours experimental / favours comparator / towards null / away from null / unpredictable
Bias due to departures from intended interventions	4.1. Was the intervention implemented successfully for most participants?	Consider the success of implementation of the intervention in the context of its complexity. Was recommended practice followed by those administering the intervention?	Y / PY / PN / N / NI
	If your aim for this study is to assess the effect of initiating and adhering to intervention (as in a per-protocol analysis), answer questions 4.2. to 4.4.		
	4.2. Did study participants adhere to the assigned intervention regimen?	Lack of adherence to assigned intervention includes cessation of intervention, cross-overs to the comparator intervention and switches to another active intervention. We distinguish between analyses where: <ul style="list-style-type: none"> intervention switches led to follow-up time being assigned to the new intervention, and intervention switches (including cessation of intervention) where follow-up time remained allocated to the original intervention, 	NA / Y / PY / PN / N / NI

(Continued)

- is addressed under time-varying confounding, and should not be considered further here.

Consider available information on the proportion of study participants who continued with their assigned intervention throughout follow-up. Was lack of adherence sufficient to impact the intervention effect estimate?

4.3. Were important cointerventions balanced across intervention groups?	Consider the cointerventions that are likely to affect the outcome and to have been administered in the context of this study, based on the preliminary consideration of cointerventions and available literature. Consider whether these cointerventions are balanced between intervention groups.	NA / Y / PY / PN / N / NI
4.4. If N or PN to 4.1., 4.2. or 4.3.: were adjustment techniques used that are likely to correct for these issues?	Such adjustment techniques include inverse-probability weighting to adjust for censoring at deviation from intended intervention, or inverse probability weighting of marginal structural models to adjust for time-varying confounding. Specialist advice may be needed to assess studies that used these approaches.	NA / Y / PY / PN / N / NI
'Risk of bias' judgement	Low – no bias due to deviation from the intended intervention is expected, for example if both the intervention and comparator are implemented over a short time period, and subsequent interventions are part of routine medical care, or if the specified comparison relates to initiation of intervention regardless of whether it is continued.	Low / moderate / serious / critical / NI
	Moderate – bias due to deviation from the intended intervention is expected, and switches, cointerventions and some problems with intervention fidelity are appropriately measured and adjusted for in the analyses. Alternatively, most (but not all) deviations from intended intervention reflect the natural course of events after initiation of intervention.	
	Serious – switches in treatment, cointerventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses.	
	Critical – substantial deviations from the intended intervention are present and are not adjusted for in the analysis.	
Optional: what is the predicted direction of bias due to departures from the intended interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterised either as being towards (or away from) the null, or as being in favour of 1 of the interventions.	Favours experimental / favours comparator / towards null / away from null / unpredictable
Bias due to missing data	5.1. Were there missing outcome data?	Y / PY / PN / N / NI
	5.2. Were participants excluded due	Y / PY / PN / N / NI

(Continued)

to missing data on
intervention status?

5.3. Were participants excluded due to missing data on other variables needed for the analysis?

This question relates particularly to participants excluded from the analysis because of missing information on confounders that were controlled for in the analysis.

Y / PY / PN / N / NI

5.4. **If Y or PY to 5.1., 5.2. or 5.3.:** are the proportion of participants and reasons for missing data similar across interventions?

This aims to elicit whether either differential proportion of missing observations or differences in reasons for missing observations could substantially impact on our ability to answer the question being addressed.

NA / Y / PY / PN / N / NI

5.5. **If Y or PY to 5.1., 5.2. or 5.3.:** were appropriate statistical methods used to account for missing data?

It is important to assess whether assumptions employed in analyses are clear and plausible. Both content knowledge and statistical expertise will often be required for this. For instance, use of a statistical method such as multiple imputation does not guarantee an appropriate answer. Review authors should seek naïve (complete-case) analyses for comparison, and clear differences between complete-case and multiple imputation-based findings should lead to careful assessment of the validity of the methods used.

NA / Y / PY / PN / N / NI

'Risk of bias' judgement
Low – data were reasonably complete; or proportions of and reasons for missing participants were similar across intervention groups; or analyses that addressed missing data are likely to have removed any risk of bias.

Low / moderate / serious / critical / NI

Moderate – proportions of missing participants differ across interventions; or reasons for missingness differ minimally across interventions; and missing data were not addressed in the analysis.

Serious – proportions of missing participants differ substantially across interventions; or reasons for missingness differ substantially across interventions; and missing data were addressed inappropriately in the analysis; or the nature of the missing data means that the risk of bias cannot be removed through appropriate analysis.

Critical – (unusual) there were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis.

Optional: what is the predicted direction of bias due to missing data?

If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterised either as being towards (or away from) the null, or as being in favour of 1 of the interventions.

Favours experimental / favours comparator / towards null / away from null / unpredictable

Bias in measurement of outcomes

6.1. Could the outcome measure have been influenced by knowledge of

Some outcome measures involve negligible assessor judgement, e.g. all-cause mortality or non-repeatable automated laboratory assessments. Risk of bias due to measurement of these outcomes would be expected to be low.

Y / PY / PN / N / NI

(Continued)

the intervention received?		
6.2. Were outcome assessors aware of the intervention received by study participants?	If outcome assessors were blinded to intervention status, the answer to this question would be 'no.' In other situations, outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators; the answer to this question would then also be 'no.' In studies where participants report their outcomes themselves, e.g. in a questionnaire, the outcome assessor is the study participant. In an observational study, the answer to this question will usually be 'Yes' when the participants report their outcomes themselves.	Y / PY / PN / N / NI
6.3. Were the methods of outcome assessment comparable across intervention groups?	Comparable assessment methods (i.e. data collection) would involve the same outcome detection methods and thresholds, same time point, same definition and same measurements	Y / PY / PN / N / NI
6.4. Were any systematic errors in measurement of the outcome related to intervention received?	This question refers to differential misclassification of outcomes. Systematic errors in measuring the outcome, if present, could cause bias if they are related to intervention or to a confounder of the intervention-outcome relationship. This will usually be due either to outcome assessors being aware of the intervention received or to non-comparability of outcome assessment methods, but there are examples of differential misclassification arising despite these controls being in place.	Y / PY / PN / N / NI
'Risk of bias' judgement	<p>Low – the methods of outcome assessment were comparable across intervention groups;</p> <p>and</p> <p>the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants (i.e. is objective) or the outcome assessors were unaware of the intervention received by study participants;</p> <p>and</p> <p>any error in measuring the outcome is unrelated to intervention status.</p> <hr/> <p>Moderate – the methods of outcome assessment were comparable across intervention groups;</p> <p>and</p> <p>the outcome measure is only minimally influenced by knowledge of the intervention received by study participants;</p> <p>and</p> <p>any error in measuring the outcome is only minimally related to intervention status.</p> <hr/> <p>Serious – the methods of outcome assessment were not comparable across intervention groups;</p> <p>or</p>	Low / moderate / serious / critical / NI

(Continued)

the outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants;

or

error in measuring the outcome was related to intervention status.

Critical – the methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups.

Optional: what is the predicted direction of bias due to measurement of outcomes?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterised either as being towards (or away from) the null, or as being in favour of 1 of the interventions.	Favours experimental / favours comparator / towards null / away from null / unpredictable
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from...	
7.1. ... multiple outcome <i>measurements</i> within the outcome domain?	For a specified outcome domain, it is possible to generate multiple effect estimates for different measurements. If multiple measurements were made, but only 1 or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
7.2. ... multiple <i>analyses</i> of the intervention-outcome relationship?	Because of the limitations of using data from non-randomised studies for analyses of effectiveness (need to control confounding, substantial missing data, etc.), analysts may implement different analytic methods to address these limitations. Examples include unadjusted and adjusted models; use of final value vs change from baseline vs analysis of covariance; different transformations of variables; a continuously scaled outcome converted to categorical data with different cut-points; different sets of covariates used for adjustment; and different analytic strategies for dealing with missing data. Application of such methods generates multiple effect estimates for a specific outcome metric. If the analyst does not prespecify the methods to be applied, and multiple estimates are generated but only 1 or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
7.3. ... different <i>subgroups</i> ?	Particularly with large cohorts often available from routine data sources, it is possible to generate multiple effect estimates for different subgroups or simply to omit varying proportions of the original cohort. If multiple estimates are generated but only 1 or a subset is reported, there is a risk of selective reporting on the basis of results.	Y / PY / PN / N / NI
'Risk of bias' judgement	Low – there is clear evidence (usually through examination of a preregistered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and subcohorts.	Low / moderate / serious / critical / NI
	Moderate – the outcome measurements and analyses are consistent with an a priori plan;	
	or	

(Continued)

are clearly defined and both internally and externally consistent;

and

there is no indication of selection of the reported analysis from among multiple analyses;

and

there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.

Serious – outcome measurements or analyses are internally or externally inconsistent; or there is a high risk of selective reporting from among multiple analyses; or the cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results.

Critical – there is evidence or strong suspicion of selective reporting of results, and the unreported results are likely to be substantially different from the reported results.

Optional: what is the predicted direction of bias due to selection of the reported result?

If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterised either as being towards (or away from) the null, or as being in favour of 1 of the interventions.

Favours experimental / favours comparator / towards null / away from null / unpredictable

Overall bias

'Risk of bias' judgement

Low – the study is judged to be at low risk of bias for all domains.

Low / moderate / serious / critical / NI

Moderate – the study is judged to be at low or moderate risk of bias for all domains.

Serious – the study is judged to be at serious risk of bias in ≥ 1 domain, but not at critical risk of bias in any domain.

Critical – the study is judged to be at critical risk of bias in ≥ 1 domain.

No information – there is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in ≥ 1 key domains of bias (a judgement is required for this).

Optional: what is the overall predicted direction of bias for this outcome?

—

Favours experimental / favours comparator / towards null / away from null / unpredictable

N: no; NA: not applicable; NI: no information; NRSI: ; PN: probably no; PY: probably yes; Y: yes.

CONTRIBUTIONS OF AUTHORS

LE: undertook the screening and selection of trials, data extraction, assessment of risk of bias, analysis of results and preparation of the protocol and final report in addition to being the content expert of the review.

RM: undertook the screening and selection of trials, data extraction, assessment of risk of bias, analysis of results and drafted the final report.

CD: created the search strategies and contributed to the preparation of the protocol and final report.

MT: statistical expert for this review and provided support with data analysis and contributed to the preparation of the protocol and final report.

SH: methodological expert for this review and provided support with data analysis and contributed to the preparation of the protocol and final report.

JB: content expert for this review and contributed to the preparation of the protocol and final report.

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SH: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no changes between the protocol ([Estcourt 2017b](#)) and the completed review.

INDEX TERMS

Medical Subject Headings (MeSH)

Benzoates [therapeutic use]; Deamino Arginine Vasopressin [therapeutic use]; Hemostatics [therapeutic use]; Hydrazines [therapeutic use]; Plasma; Platelet Transfusion [*methods]; Postoperative Care [methods]; Postoperative Hemorrhage [*prevention & control]; Pyrazoles [therapeutic use]; Randomized Controlled Trials as Topic; Receptors, Fc [therapeutic use]; Recombinant Fusion Proteins [therapeutic use]; Thrombocytopenia [complications] [*therapy]; Thrombopoietin [therapeutic use]

MeSH check words

Adult; Humans