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Use of platelet transfusions prior to lumbar punctures or epidural anaesthesia for the prevention of complications in people with thrombocytopenia (Review)

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[Intervention Review]

Use of platelet transfusions prior to lumbar punctures or epidural anaesthesia for the prevention of complications in people with thrombocytopenia

Lise J Estcourt[1], Reem Malouf[2], Sally Hopewell[3], Carolyn Doree[4], Joost Van Veen[5]

[1]Haematology/Transfusion Medicine, NHS Blood and Transplant, Oxford, UK. [2]National Perinatal Epidemiology Unit (NPEU), University of Oxford, Oxford, UK. [3]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, UK. [4]Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK. [5]Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

Contact address: Lise J Estcourt, Haematology/Transfusion Medicine, NHS Blood and Transplant, Level 2, John Radcliffe Hospital, Headington, Oxford, OX3 9BQ, UK. lise.estcourt@nhsbt.nhs.uk, lise.estcourt@ndcls.ox.ac.uk.

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ABSTRACT

Background

People with a low platelet count (thrombocytopenia) often require lumbar punctures or an epidural anaesthetic. Lumbar punctures can be diagnostic (haematological malignancies, subarachnoid haematoma, meningitis) or therapeutic (spinal anaesthetic, administration of chemotherapy). Epidural catheters are placed for administration of epidural anaesthetic. Current practice in many countries is to correct thrombocytopenia with platelet transfusions prior to lumbar punctures and epidural anaesthesia, in order to mitigate the risk of serious procedure-related bleeding. However, the platelet count threshold recommended prior to these procedures varies significantly from country to country. This indicates significant uncertainty among clinicians regarding the correct management of these patients. The risk of bleeding appears to be low, but if bleeding occurs it can be very serious (spinal haematoma). Consequently, people may be exposed to the risks of a platelet transfusion without any obvious clinical benefit.

This is an update of a Cochrane Review first published in 2016.

Objectives

To assess the effects of different platelet transfusion thresholds prior to a lumbar puncture or epidural anaesthesia in people with thrombocytopenia (low platelet count).

Search methods

We searched for randomised controlled trials (RCTs), non-randomised controlled trials (nRCTs), controlled before-after studies (CBAs), interrupted time series studies (ITSs), and cohort studies in CENTRAL (the Cochrane Library 2018, Issue 1), MEDLINE (from 1946), Embase (from 1974), the Transfusion Evidence Library (from 1950), and ongoing trial databases to 13 February 2018.

Selection criteria

We included RCTs, nRCTs, CBAs, ITSs, and cohort studies involving transfusions of platelet concentrates, prepared either from individual units of whole blood or by apheresis, and given to prevent bleeding in people of any age with thrombocytopenia requiring insertion of a lumbar puncture needle or epidural catheter.

The original review only included RCTs.

Data collection and analysis

We used standard methodological procedures expected by Cochrane for including RCTs, nRCTs, CBAs, and ITSs. Two review authors independently assessed studies for eligibility and risk of bias and extracted data. Results were only expressed narratively.

Main results

We identified no completed or ongoing RCTs, nRCTs, CBAs, or ITSs. No studies included people undergoing an epidural procedure. No studies compared different platelet count thresholds prior to a procedure.

In this update we identified three retrospective cohort studies that contained participants who did and did not receive platelet transfusions prior to lumbar puncture procedures. All three studies were carried out in people with cancer, most of whom had a haematological malignancy. Two studies were in children, and one was in adults.

The number of participants receiving platelet transfusions prior to the lumbar puncture procedures was not reported in one study. We therefore only summarised in a narrative form the relevant outcomes from two studies (150 participants; 129 children and 21 adults), in which the number of participants who received the transfusion was given.

We judged the overall risk of bias for all reported outcomes for both studies as 'serious' based on the ROBINS-I tool.

No procedure-related major bleeding occurred in the two studies that reported this outcome (2 studies, 150 participants, no cases, very low-quality evidence).

There was no evidence of a difference in the risk of minor bleeding (traumatic tap) in participants who received platelet transfusions before a lumbar puncture and those who did not receive a platelet transfusion before the procedure (2 studies, 150 participants, very low-quality evidence). One of the 14 adults who received a platelet transfusion experienced minor bleeding (traumatic tap; defined as at least 500 x 10^6/L red blood cells in the cerebrospinal fluid); none of the seven adults who did not receive a platelet transfusion experienced this event. Ten children experienced minor bleeding (traumatic taps; defined as at least 100 x 10^6/L red blood cells in the cerebrospinal fluid), six out of the 57 children who received a platelet transfusion and four out of the 72 children who did not receive a platelet transfusion.

No serious adverse events occurred in the one study that reported this outcome (1 study, 21 participants, very low-quality evidence).

We found no studies that evaluated all-cause mortality within 30 days from the lumbar puncture procedure, length of hospital stay, proportion of participants who received platelet transfusions, or quality of life.

Authors' conclusions

We found no evidence from RCTs or non-randomised studies on which to base an assessment of the correct platelet transfusion threshold prior to insertion of a lumbar puncture needle or epidural catheter. There are no ongoing registered RCTs assessing the effects of different platelet transfusion thresholds prior to the insertion of a lumbar puncture or epidural anaesthesia in people with thrombocytopenia. Any future study would need to be very large to detect a difference in the risk of bleeding. A study would need to be designed with at least 47,030 participants to be able to detect an increase in the number of people who had major procedure-related bleeding from 1 in 1000 to 2 in 1000. The use of a central data collection register or routinely collected electronic records (big data) is likely to be the only method to systematically gather data relevant to this population.

PLAIN LANGUAGE SUMMARY

Use of platelet transfusions prior to a lumbar puncture or epidural anaesthetic in people with a low platelet count

Review question

We evaluated the evidence for whether people with a low platelet count (increases risk of bleeding) require a platelet transfusion prior to insertion of a lumbar puncture needle or epidural catheter, and if so what is the platelet count level at which a platelet transfusion is required.

Background

Platelets are found in the blood and are an essential part of a blood clot. A low platelet count increases the risk of bleeding. People with a low platelet count often require a lumbar puncture or epidural anaesthetic for administration of treatment or to aid in diagnosis.

A lumbar puncture is usually performed by inserting a needle between the bones (vertebrae) of the spine in the lower back into the fluid surrounding the spinal cord (the bundle of nerves that runs down the spine and connects the brain with the body). Lumbar punctures are performed either to obtain a sample of this fluid or to administer treatment into the fluid (chemotherapy or an anaesthetic). The lumbar puncture needle is removed immediately after any fluid samples have been taken or treatment administered.

An epidural involves inserting a needle with a larger diameter than a lumbar puncture needle. The epidural needle passes through the same tissues as the lumbar puncture needle, but stops short of penetrating the fluid sac surrounding the spinal cord. Instead any treatment is injected into the space just outside the fluid sac (called the epidural space). A small tube (an epidural catheter) is often passed through the epidural needle and left in position so that additional local anaesthetic medicines can be given.

Current practice in many countries is to increase the platelet count above a prespecified level with platelet transfusions (platelets given by injection into a vein) to prevent serious bleeding due to the lumbar puncture or epidural anaesthetic. Although the risk of bleeding appears to be low, if bleeding does occur, it can be very serious. Due to a lack of evidence the platelet count level recommended prior to lumbar puncture or epidural anaesthetic varies significantly from country to country. This means that doctors are uncertain about what is the correct platelet count level, or if a platelet transfusion is required. Consequently, people may be exposed to the risks of a platelet transfusion (e.g. allergic reaction, infection) without any obvious clinical benefit.

Study characteristics

We searched scientific databases for clinical studies of people of any age with low platelet counts requiring a lumbar puncture or epidural anaesthesia. The evidence is current to 13 February 2018. In this review, we found only three cohort studies. Only two of these studies reported outcomes relevant to this review. Both studies included people with low platelet counts and blood cancer; one included 21 adults and the other included 129 children. Both studies compared people who had and had not received platelet transfusions before the insertion of a lumbar puncture needle. No studies assessed the use of platelet transfusions prior to insertion of an epidural catheter or different platelet count thresholds for platelet transfusion administration prior to a procedure.

Key results

There were no major procedure-related bleeding complications in either study. No serious adverse events occurred in the one study (21 participants) that reported this outcome.

There was little or no difference in the number of minor bleeding complications in either adults or children who received or did not receive platelet transfusions.

None of the studies reported on death, number of platelet transfusions given after the procedure, length of hospital stay, or quality of life.

Quality of the evidence

The quality of the evidence from the included studies was very poor.

We found no evidence from randomised controlled trials to answer our review question.

A study would need to be designed with at least 47,030 participants to be able to detect an increase in the number of people who had bleeding after lumbar puncture or epidural anaesthetic from 1 in 1000 to 2 in 1000. A study that uses routinely collected electronic medical records (big data) is likely to be the only study design that could answer our review question.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Platelet transfusion compared with no platelet transfusion for lumbar puncture procedures

Patient or population: People with thrombocytopenia
Intervention: Platelet transfusion
Comparison: No platelet transfusion

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No platelet transfusions	Platelet transfusion				
Major procedure-related bleeding within 24 hours of the procedure	No cases of major bleeding		Not estimated	150 (2 studies)	⊕◯◯◯ Very low [1,2]	
All-cause mortality up to 30 days after the procedure	-	-	-	-	-	Not reported
Transfusion-related complications within 24 hours of the procedure	-	-	-	-	-	Not reported
Procedure-related (lumbar puncture or epidural anaesthetic) complications within 7 days of the procedure	No serious adverse events		Not estimated	21 (1 study)	⊕◯◯◯ Very low [1,2]	

Quality of life (as defined by the individual studies)	-	-	-	-	-	Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. The initial rating was 'low' as all included studies were non-randomised studies.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision (low event rate). No events occurred.
[2]We would also have downgraded due to risk of performance and detection bias, but could not because the quality of the evidence was already very low.

BACKGROUND

Please see Published notes for a glossary of technical terms.

Description of the condition

Thrombocytopenia

Thrombocytopenia is defined as a platelet count less than 150 x 10^9/L (BCSH 2003), and severe thrombocytopenia as a platelet count less than 50 x 10^9/L. Thrombocytopenia can occur due to reduced platelet production in the bone marrow as a result of chemotherapy or a haematological malignancy (blood cancer) (Leguit 2010; Weinzierl 2013); increased platelet consumption, for example due to bleeding or disseminated intravascular coagulation (Levi 2009); or increased platelet destruction, for example due to immune thrombocytopenia or neonatal alloimmune thrombocytopenia (Neunert 2013; Pacheco 2011; Provan 2010). 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.

A platelet count less than 150 x 10^9/L occurs commonly in pregnancy (7% to 12% of pregnancies), but severe thrombocytopenia (platelet count less than 50 x 10^9/L) is much less common (0.05% to 1% of pregnancies) (Burrows 1990; Nisha 2012; Sainio 2000). A platelet count less than 150 x 10^9/L is very common in people with chronic liver disease (up to 76%) (Afdhal 2008), people who are critically ill (up to 68%) (Hui 2011), and people with haematological malignancies (Leguit 2010; Weinzierl 2013).

Lumbar puncture

Diagnostic

A diagnostic lumbar puncture (LP) is an invasive procedure to obtain samples of cerebrospinal fluid (Doherty 2014). Cerebrospinal fluid is the fluid that bathes and protects the brain and spinal cord. An LP is usually performed by inserting a needle into the lower back (underneath the spinal L4 bony process) (Williams 2008). The cerebrospinal fluid obtained can then be used in the investigation of haematological malignancies (Vavricka 2003), subarachnoid haemorrhages, meningitis (Riordan 2002), or neurological disorders. Lumbar punctures are performed by doctors or specially trained nurses.

Therapeutic

Therapeutic LPs administer drugs into the cerebrospinal fluid. This can be for the administration of therapeutics such as intrathecal chemotherapy or antibiotics, or the administration of local anaesthetic to the nerves of the lower spine (spinal anaesthetic) (Doherty 2014). This usually involves insertion of a fine needle into the lower back, administration of the therapeutic agent, and then removal of the needle (Ng 2004).

Diagnostic or therapeutic LPs are relatively common hospital procedures in people with haematological disorders who are thrombocytopenic (up to 10% of all procedures) (Estcourt 2012).

Epidural anaesthesia

The most common indication for epidural anaesthesia is in pregnant women to aid in pain relief during labour (Venn 2015). However, epidural anaesthesia can also be used in postoperative pain management, especially for people with lower limb ischaemia (Venn 2015), and people undergoing thoracic surgery (Mendola 2009), as alternatives to general anaesthesia. Epidural anaesthesia typically involves inserting a needle that is larger in diameter than a spinal needle. The epidural needle passes through the same tissues as a spinal needle but stops short of penetrating the dura (tissue sac that contains cerebrospinal fluid). An epidural catheter is often passed through the needle and left in position so that additional local anaesthetic medications can be administered (Ng 2004).

Spinal haematoma

The risk of a spinal haematoma in the general population is very low (1 in 200,000 epidural anaesthetic procedures during labour to 1 in 3600 epidural anaesthetic procedures in older women having knee surgery) (Li 2010; Moen 2004; Ruppen 2006; Vandermeulen 1994). Risk factors for major bleeding are multifactorial and include: increasing age (the procedure is more difficult in older people due to changes to the spine that occur with age), low platelet count, abnormal coagulation (including anticoagulant medication), and traumatic needle or catheter insertion (Erbay 2014; Li 2010; Moen 2004; Vandermeulen 1994). Performing an LP or administration of epidural anaesthesia is a relative contraindication in people with thrombocytopenia due to this perceived higher risk of complications (van Veen 2010). However, there are no current reliable estimates of the risks of adverse effects such as spinal haematomas in people with thrombocytopenia overall (van Veen 2010).

Description of the intervention

Current practice in many countries is to correct thrombocytopenia with platelet transfusions prior to an LP or epidural anaesthesia in order to mitigate the risk of serious peri- or postprocedural bleeding. Up to 4% of all platelet components issued in the UK prior to a procedure are given to people with thrombocytopenia who need an LP (Qureshi 2007). The safe platelet count threshold recommended prior to an LP or epidural anaesthesia varies significantly from country to country.

For example, the platelet count threshold for LP in the US is 50 x 10^9/L (Kaufman 2015); in the UK it is 50 x 10^9/L in adults

(BCSH 2003), but 20 to 40 x 10^9/L in children (BCSH 2004); and in Germany it is 20 x 10^9/L unless it is an urgent procedure (e.g. diagnosing bacterial meningitis), when an LP should be performed irrespective of the platelet count (GMA 2009).

The platelet count threshold for epidural anaesthesia also varies. In Italy and the UK, a platelet count of at least 50 x 10^9/L is recommended (BCSH 2003; Liumbruno 2011), while the recommendation in France is a platelet count of at least 80 x 10^9/L (Samama 2005).

As there is currently no consensus on the standard platelet count threshold prior to an LP or epidural anaesthesia, we compared the most commonly recommended platelet count threshold in national guidelines (50 x 10^9/L) against other recommended thresholds (10 x 10^9/L, 20 x 10^9/L, 30 x 10^9/L, 40 x 10^9/L, 80 x 10^9/L).

If guidelines recommend a platelet count threshold higher than is necessary to perform an LP or epidural anaesthesia safely, this will mean that people are exposed to the risks of a platelet transfusion unnecessarily. 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). While most of these reactions are not life-threatening, they can be extremely distressing for the person. Rarer, but more serious sequelae include anaphylaxis (life-threatening allergic reaction), transfusion-transmitted infections, and transfusion-related acute lung injury (Blumberg 2010; Chapman 2015; Kaufman 2015; Slichter 2007; Vlaar 2013).

If guidelines recommend a platelet count threshold higher than is necessary to perform an LP safely, it may delay the start of lifesaving treatments, which can be time-critical in conditions such as bacterial meningitis or subarachnoid haemorrhage.

Epidural anaesthesia allows for a safer and more controlled, localised anaesthesia to be administered, reducing the complications associated with general anaesthesia and reducing patient time in hospital. If guidelines recommend a platelet count threshold higher than is necessary to administer an epidural anaesthetic, it may mean that a person is not offered an epidural anaesthetic and instead receives a general anaesthetic.

If guidelines recommend a platelet count threshold lower than is necessary to perform an LP or epidural anaesthesia safely, then people with thrombocytopenia are put at a higher risk of serious or life-threatening bleeding such as a spinal haematoma.

How the intervention might work

Platelet transfusions are given to people with low platelet counts to increase the platelet count and, therefore, reduce the risk of bleeding during invasive procedures.

However, the risk of bleeding during or after an LP may be low in people with a low platelet count. One systematic review of platelet transfusion indications showed that bleeding events were rare in people who had thrombocytopenia undergoing diagnostic LPs; however, the quality of the evidence was low (Kumar 2015). In the review, there were five case series in children who needed an LP, nearly all of whom had acute lymphocytic leukaemia. In three of these studies, children were grouped by platelet count: 243 LPs were performed at a count less than 20 x 10^9/L and 817 at a platelet count between 21 x 10^9/L and 50 x 10^9/L, and no bleeding complications occurred (van Veen 2010). People may therefore be exposed to the risks of a platelet transfusion without any obvious clinical benefit.

Why it is important to do this review

The platelet count threshold recommended prior to an LP or epidural anaesthesia varies significantly from country to country (BCSH 2003; BCSH 2004; GMA 2009; Kaufman 2015). This indicates significant uncertainty in clinicians of the correct management for safely performing an LP or administering an epidural anaesthetic.

Avoiding the need for unnecessary platelet transfusions in people with thrombocytopenia will have significant logistical and financial implications for national health services as well as decreasing people's exposure to the risks of transfusion. These factors are perhaps even more important in the development of platelet transfusion strategies in low-income countries, where access to blood components is much more limited than in high-income countries (Verma 2009).

OBJECTIVES

To assess the effects of different platelet transfusion thresholds prior to a lumbar puncture or epidural anaesthesia in people with thrombocytopenia (low platelet count).

METHODS

Criteria for considering studies for this review

Types of studies

We included the following study designs, irrespective of language or publication status.

- randomised controlled trials (RCTs)
- non-randomised controlled trials (non-RCTs)
- controlled before-after studies (CBAs)
- interrupted time series studies (ITSs)

- cohort studies with a concurrent control.

We excluded cross-sectional studies, case-control studies, case series, and case reports.

Types of participants

We included people of any age with thrombocytopenia (as defined by the studies) requiring an LP or epidural anaesthesia. We excluded people who were experiencing clinically significant bleeding at the time of the procedure because such people are routinely given platelet transfusions to treat the bleeding.

Types of interventions

We planned to include studies comparing the following two types of procedure: LP needle insertion or epidural catheter insertion; however, we included only studies involving people undergoing LP needle insertion in the review.

We compared platelet transfusion prior to the procedure versus no platelet transfusion.

We planned to compare platelet transfusion prior to the procedure when the platelet count was less than 50 x 10^9/L versus platelet transfusion prior to the procedure when:

- platelet count was less than 10 x 10^9/L;
- platelet count was less than 20 x 10^9/L;
- platelet count was less than 30 x 10^9/L;
- platelet count was less than 40 x 10^9/L;
- platelet count was less than 80 x 10^9/L.

However, no studies compared different platelet count thresholds. Had we identified relevant studies, we planned to report each analysis separately, as subgroups within the main comparisons.

Types of outcome measures

Primary outcomes

- Major procedure-related bleeding within 24 hours of the procedure, e.g. spinal haematoma; intraventricular, intracerebral, or subarachnoid haemorrhage; or major bleeding (not further defined) as reported by individual studies.
- All-cause mortality up to 30 days after the procedure.
- Serious adverse events:
    - transfusion-related complications within 24 hours of the procedure (including transfusion-related acute lung injury, transfusion-transmitted infection, transfusion-associated circulatory overload, transfusion-associated dyspnoea, acute transfusion reactions);
    - LP-related or epidural anaesthetic-related complications within seven days of the procedure (infection, headache, cerebral herniation, neurological symptoms such as radicular pain or numbness, back pain).

Secondary outcomes

- Minor LP-related or epidural anaesthetic-related bleeding within 24 hours of the procedure (defined as prolonged bleeding at the insertion site that only required treatment with a pressure bandage) or minor bleeding (not further defined) as reported by individual studies.
- Duration of hospital stay (total number of days in hospital).
- Proportion of people receiving platelet transfusions.
- Quality of life, as defined by individual studies

Search methods for identification of studies

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

Electronic searches

We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 1) (13 February 2018) (Appendix 1).
- MEDLINE (1946 to 13 February 2018) (Appendix 2).
- Embase (1974 to 13 February 2018) (Appendix 3).
- PubMed (e-publications only) (Appendix 4).
- Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1950 to 13 February 2018); this includes a search of grey literature (Appendix 5).
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/ictrp/en/) (13 February 2018) (Appendix 6).
- ClinicalTrials.gov (clinicaltrials.gov) (13 February 2018) (Appendix 7).

We combined searches in MEDLINE and Embase with the recommended Cochrane RCT search filters and with systematic review and observational studies filters based on those of the Scottish Intercollegiate Guidelines Network (SIGN) (sign search filters) (Lefebvre 2011). We did not limit searches by language, year of publication, or publication type.

We performed a new search for this update of the review.

Searching other resources

We handsearched reference lists of included studies and reviews in order to identify further relevant studies. We found four additional studies via handsearching other sources. We contacted lead authors of the included studies in order to identify any unpublished material, missing data, or information regarding ongoing studies.

Data collection and analysis

Selection of studies

We selected studies according to the recommendations described in Chapter 7 of 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 all those that were clearly irrelevant. Thereafter, two review authors (RM, LE) independently screened all the remaining references for relevance against the full eligibility criteria using Covidence. We retrieved full-text articles for all references for which a decision on eligibility could not be made based on title and abstract alone. We requested additional information from study authors as necessary to assess 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 (JVV). We reported the results of study selection using a PRISMA flow diagram (Moher 2009).

Data extraction and management

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), two review authors (RM, LE) independently extracted data onto standardised forms using Covidence.

For all studies, we extracted the following information.

- Source: study identity (ID), report ID, review author ID, date of extraction, ID of author checking extracted data, citation of paper, contact authors 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, setting, number of centres, 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, type of LP needle used, and any co-interventions.
- Characteristics of participants: age, gender, primary diagnosis, type of procedure (diagnostic LP, therapeutic LP, epidural anaesthesia), 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.
- Outcomes: major procedure-related bleeding within 24 hours of the procedure, minor procedure-related (LP or epidural anaesthetic) bleeding within 24 hours of the procedure, transfusion-related complications within 24 hours of the procedure, procedure-related complications within seven days of the procedure, duration of hospital stay, proportion of participants receiving platelet transfusions within 24 hours of the procedure, all-cause mortality up to 30 days from the procedure, quality of life (as defined by the individual studies).

For studies that were not RCTs, we also extracted the following information.

- Study design.
- Confounding factors.
- Comparability of groups on confounding factors.
- Method of assigning the intervention(s).
- Method of data analysis: methods used to control for confounding and on multiple effect estimates (both unadjusted and adjusted estimates) as recommended in Chapter 13 of the*Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011).

Assessment of risk of bias in included studies

Randomised controlled trials

We planned to perform an assessment of all RCTs using the Cochrane 'Risk of bias' tool according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). However, we included no completed RCTs in the review.

If in future updates RCTs are included in the review, two review authors will independently assess each domain of potential bias listed below as 'high', 'low', or 'unclear' risk of bias. We will provide a brief description of support for our judgements of potential bias in the 'Characteristics of included studies' table. We will ensure that a consensus on the degree of risk of bias is met through comparison of the review authors' statements and where necessary, through consultation with a third review author. We will use Cochrane's tool for assessing risk of bias, which includes the following domains.

- Selection bias: random sequence generation and allocation concealment.
- Performance bias: blinding of participants and personnel.
- Detection bias: blinding of outcome assessment.
- Attrition bias: incomplete outcome data.
- Reporting bias: selective reporting.
- Other bias.

Non-randomised studies

We used the ROBINS-I tool (formerly known as ACROBAT-NRSI) to rate the quality of non-randomised studies (non-RCTs, CBAs, ITSs, cohort studies) (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: two occur in the pre-intervention phase (bias of confounding and bias in the selection of participants into the study); one domain covers the intervention phase (bias in the classification of the interventions); and the final four domains cover the postintervention phase (bias due to deviations from intended interventions, bias due to missing data, bias in measuring the outcomes and selective reporting).

We judged the quality of evidence for each domain in the tool as 'low risk of bias', 'moderate risk of bias', 'serious risk of bias', or 'critical risk of bias or no information'. The response options for the list of the signalling questions for each domain were 'yes', 'probably yes', 'no', 'probably no', and 'no information'.

We then assigned an overall risk of bias judgement, mapping all the seven domains, for each outcome reported in the review.

- For 'low risk of bias' the study is judged to be at low risk of bias in all seven domains.
- For 'moderate risk of bias' the study is judged to be at low to moderate risk of bias in all seven domains.
- For 'serious risk of bias ' the study is judged to be at serious risk of bias in at least one of the seven domains.
- For 'critical risk of bias' the study is judged to be at critical risk of bias in at lease one of the seven domains.
- For 'no information on bias' when information in one or more key risk of bias domains is lacking.

We prespecified the following main potential confounding factors that could influence the intervention.

- Primary diagnosis of participants (e.g. pregnancy, immune thrombocytopenia, acute lymphoblastic leukaemia)
- Age: variability in the age of included participants (e.g. paediatric (less than 16 years) versus adult (> 16 years) versus older adult (> 60 years))
- Gender: male-to-female ratio
- History of previous severe bleeding (e.g. World Health Organization (WHO) Grade 3 or 4 or equivalent)
- Anticoagulants
- Antiplatelet agents
- Haemostasis
- Type of platelet component
- Dose of platelet component

We prespecified the following co-interventions.

- Plasma transfusions
- Red cell transfusions
- Haemostatic agents

Measures of treatment effect

Randomised controlled trials

We did not perform any of the planned analyses because the search identified no RCTs. In future updates of this review we will perform the following.

- For continuous outcomes, we will record the mean, standard deviation, and total number of participants in both the treatment and control groups.
- For dichotomous outcomes, we will record the number of events and total number of participants in both the treatment and control groups.

We planned the following analyses for this review, which we will perform in future updates of this review.

- For continuous outcomes using the same scale, we will perform analyses using the mean difference (MD) with 95% confidence intervals (CIs).
- For continuous outcomes measured with different scales, we will perform analyses using the standardised mean difference (SMD).
- We will extract and report hazard ratios (HRs) for time-to-event data (mortality or time in hospital) if this information is available. 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 will use HRs in favour of risk ratios (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 will report the pooled RR with a 95% CI (Deeks 2011). Where the number of observed events is small (less than 5% of sample per group), and where treatment groups in the trials were balanced, we planned to report the Peto odds ratio (OR) with 95% CI (Deeks 2011).
- 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 Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

Non-randomised studies

For dichotomous outcomes, we planned to 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 RRs (i.e. the RR postintervention/RR pre-intervention) if this information was available. None of the studies reported adjusted analyses.

For continuous variables, we planned to extract and report the absolute change from a statistical analysis adjusting for baseline dif-

ferences (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 pre-intervention difference between the intervention and control groups/the postintervention level in the control group) if this information was available (EPOC 2017). However, none of the studies reported continuous variables.

All studies

If data allowed, we planned to undertake quantitative assessments using Review Manager 5 (RevMan 2014). However, we were unable to perform a quantitative assessment.

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

As we could not report the available data in any of the formats described above, we presented a narrative report, but due to the paucity of data we did not need to present the data in tables.

Unit of analysis issues

We planned to treat any unit of analysis issues in accordance with the recommendations in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). However, no unit of analysis issues arose.

If in future updates of this review any unit of analysis issues arise, we will treat them in accordance with the recommendations in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). If participants are randomised more than once, we will contact the authors of the study to obtain data associated with the initial randomisation. For studies with multiple treatment groups, two review authors (RM and LE) will exclude subgroups that are considered irrelevant to the analysis. We will tabulate all subgroups in the 'Characteristics of included studies' table. When appropriate, we will combine groups to create a single pair-wise comparison. If this is not possible, we will select the most appropriate pair of interventions and exclude the others (Higgins 2011c).

Dealing with missing data

We tried to contact the primary authors of two of the included studies in this review to obtain participants' individual data across these studies, as we were unable to record the subgroup of participants who had platelet counts less than 80 x 10^9/L and also the subgroup of participants who received platelet transfusion before undergoing the LP procedure (Howard 2000; van Veen 2004). van Veen 2004 responded to our request, but the data were no longer available.

Assessment of heterogeneity

We did not perform any of the planned analyses. We planned to analyse the data in RCTs, non-RCTs, CBAs, ITSs, and cohort studies separately. However, we included only cohort studies in the review.

In future updates of this review we will:

- combine the data to perform a meta-analysis, if the clinical and methodological characteristics of individual studies are sufficiently homogeneous;
- evaluate the extent of heterogeneity by visual inspection of forest plots as well as by utilising statistical methods;
- assess statistical heterogeneity of treatment effects between studies using a Chi^2 test with a significance level at $P < 0.1$. We will use the I^2 statistic to quantify the degree of potential heterogeneity, classifying it as low if the I^2 is less than or equal to 50%, moderate if the I^2 is 50% to 80%, or considerable if the I^2 is greater than 80%. We will use the random-effects model for low to moderate heterogeneity;
- if statistical heterogeneity is considerable, and we cannot identify an explanation for the heterogeneity, 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 potential publication bias (small-trial bias) by generating a funnel plot and statistically test using a linear regression test because no meta-analyses were performed in this review (Sterne 2011). We identified no other unpublished studies for inclusion after searching the clinical trial registries.

Data synthesis

We planned to perform analyses according to the recommendations in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions,* using aggregated data for analysis (Deeks 2011). We did not perform any of the planned analyses because the search identified only two cohort studies that reported any of the outcomes of this review. None of the outcomes reported in these two studies were reported as adjusted effect estimates.

In future updates of this review we will perform the following.

If studies are sufficiently homogenous in their study design, we will conduct a meta-analysis according to the recommendations in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We will not conduct meta-analyses that involve both RCTs and non-RCTs. We will conduct separate meta-analyses for each comparison. We will group different thresholds within the same comparisons together only if they are considered to be clinically similar.

Randomised controlled trials

If meta-analysis is feasible for RCTs, we will use the random-effects model for pooling data. For binary outcomes, we will base the estimation of the between-study variance using the Mantel-Haenszel method. We will use the inverse-variance method for continuous outcomes; outcomes that include data from cluster-RCTs; or outcomes where HRs are available. If heterogeneity is found to be above 80%, and an explanation for the heterogeneity is identified, we will explore this with subgroup analyses. If we cannot find an explanation for the heterogeneity, then we will not perform a meta-analysis, but comment on the results narratively with the results from all studies presented in tables.

Non-randomised studies

If meta-analysis is feasible for non-RCTs, CBAs, ITSs, and cohort studies, we will analyse the different types of 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 Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2011).

All studies

We will use the random-effects model for all analyses, as we anticipate that true effects will be related but will not be the same for included studies. If we cannot perform a meta-analysis, we will comment on the results narratively with the results from all studies presented in tables.

'Summary of findings' table

We used the GRADE approach to create a 'Summary of findings' table, as suggested in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). We used the GRADE approach to rate the quality of the evidence as 'high', 'moderate', 'low', or 'very low', employing the five GRADE considerations. We only included three observational studies in this review, therefore the quality of evidence started as 'low' and was downgraded to 'very low'.

- 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.

We planned to report separate 'Summary of findings' tables for LPs and epidural anaesthesia, but we only included studies involving participants undergoing LPs in this review. We planned to report the subgroup for each comparison that contained the largest number of studies, however we only identified studies comparing platelet transfusions versus no platelet transfusions.
We included the following outcomes.

- Major procedure-related bleeding within 24 hours of the procedure.
- All-cause mortality up to 30 days after the procedure.
- Transfusion-related complications within 24 hours of the procedure.
- Procedure-related (LP or epidural anaesthetic) complications within seven days of the procedure.
- Quality of life (as defined by the individual studies).

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses for each of the following outcomes to assess the effect on heterogeneity.

- Type of procedure (diagnostic LP, therapeutic LP, epidural anaesthesia).
- Type of participant (intensive care, liver disease, obstetric, leukaemia, other).
- Age of participant (neonate, child (aged one to 15 years), adult (aged 16 years or older)).
- Whether participants had associated clotting abnormalities, including disseminated intravascular coagulation, or concomitant use of anticoagulant or antiplatelet agents.

If appropriate, we also planned to investigate heterogeneity between studies as follows.

- Type of platelet component.
- Dose of platelet component.

However, we could not perform any subgroup analyses due to insufficient data.

Sensitivity analysis

We planned to assess the robustness of our findings by performing the following sensitivity analyses where appropriate.

- Including only 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 only studies with less than a 20% dropout rate.
- Including only studies that were published in full.

However, we could not perform any sensitivity analyses due to insufficient data.

RESULTS

Description of studies

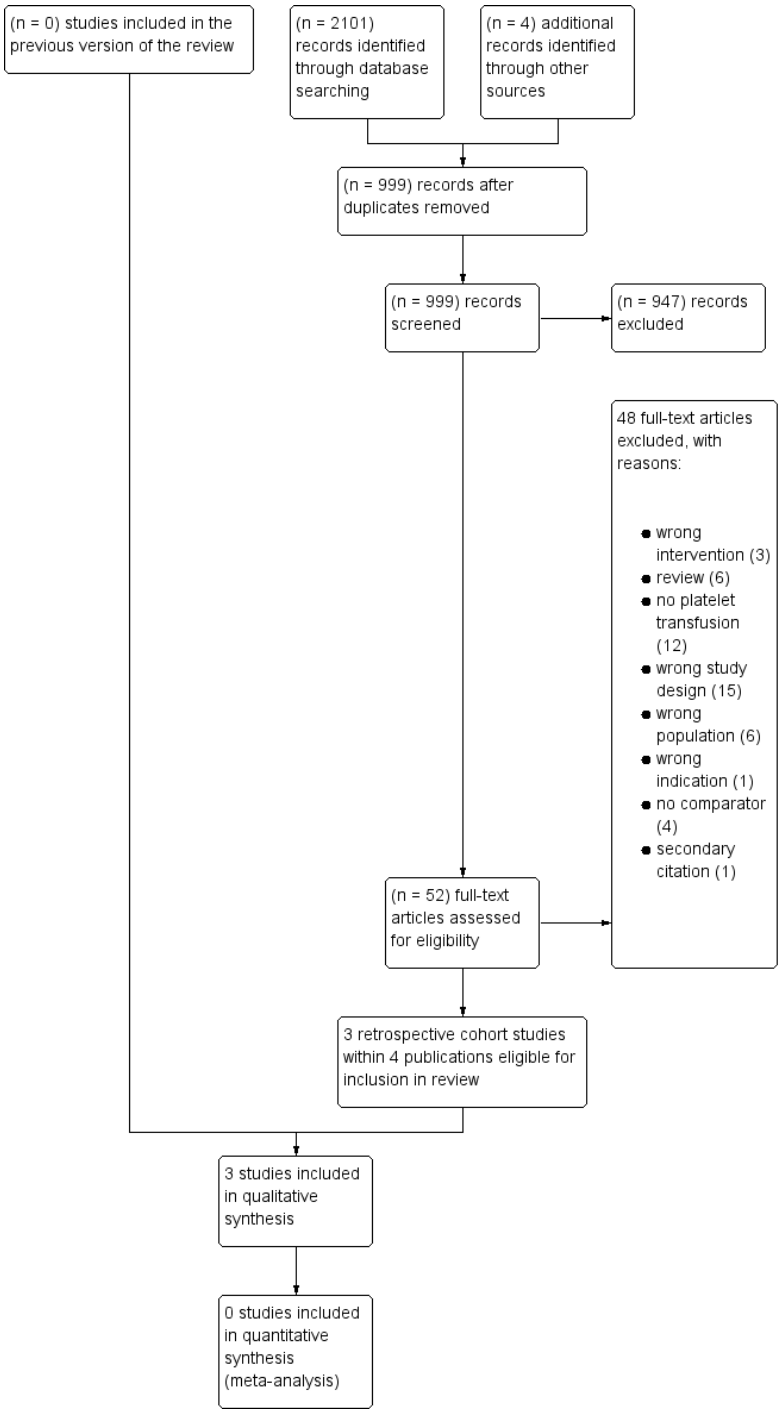
See Characteristics of excluded studies.

Results of the search

The original search (conducted on 3 March 2016) identified 1060 potentially relevant records, of which 596 records remained after removal of duplicates. We excluded 592 records based on the abstract, and four records based on the full text (Foerster 2015; Howard 2000; Ning 2016; van Veen 2004.

In this update of the review we performed a new search using the review's original search strategy, with no language restriction. The search (conducted on 13 February 2018) retrieved a total of 2101 references, and handsearching other sources identified four additional studies. Two review authors (LE and RM) independently screened the titles and abstracts of the 999 records left after removal of duplicate records. We excluded 947 records based on the abstract. We checked 52 full-text articles for eligibility, excluding 47 studies within 48 records. We identified three completed studies for inclusion in this update (Howard 2000; Ning 2016; van Veen 2004). No registered, ongoing, or completed but not yet published studies were identified for inclusion in this update. (See the PRISMA flowchart for study selection in Figure 1.)

Figure 1. Study flow diagram.



Included studies

See Characteristics of included studies.

Study setting

The three included studies were published in English between 2000 and 2016 (Howard 2000; Ning 2016; Van Veen 2004). One study was based in Canada (Ning 2016), one in the UK (Van Veen 2004), and one in the USA (Howard 2000). Howard 2000 reviewed health records from 1984 to 1998; van Veen 2004 reviewed health records from 1989 to 2003; and Ning 2016 reviewed health records from January 2013 to December 2014.

Study design

All three included studies were retrospective, single-centre cohort studies.

Participants

Two studies assessed the safety of lumbar puncture procedures (LPs) in children with a low platelet count (Howard 2000; Van Veen 2004). Overall, 1184 children with acute lymphocytic leukaemia (aged up to 18 years old at diagnosis) underwent 5571 LPs (Howard 2000; Van Veen 2004). Of these, 1070 LPs were performed when the platelet count was 50 x 10^9/L or less.
The third study assessed the safety of LPs in adults with thrombocytopenia (Ning 2016). Overall, 135 adults with cancer and a platelet count below 150 x 10^9/L were included in the study. Twenty-nine LPs were performed (21 adults) when the platelet count was 50 x 10^9/L or less. Coagulopathy was an exclusion criterion.

Platelet transfusion before lumbar puncture

In Howard 2000, despite the fact that platelet transfusions were recorded during induction and consolidation therapy, no further information was available in the published paper.
Two studies administered platelet transfusions to a proportion of participants with a platelet count of 50 x 10^9/L or less (Ning 2016; Van Veen 2004). These two studies contained 150 participants with a platelet count of 50 x 10^9/L or less.

Study outcomes

In Howard 2000 the primary outcomes were serious complications defined as as the presence of any neurological, infectious, or haemorrhagic complications after performing LPs.
Participants in Ning 2016 were followed up to one week after undergoing the LP procedure. All haemorrhagic complications, including spinal, subdural, and epidural haematoma and traumatic taps (defined as red blood cells in the cerebral spinal fluid equal to or greater than 500 x 10^6/L) were monitored.
Van Veen 2004 reported on the occurrence of traumatic tap.

Excluded studies

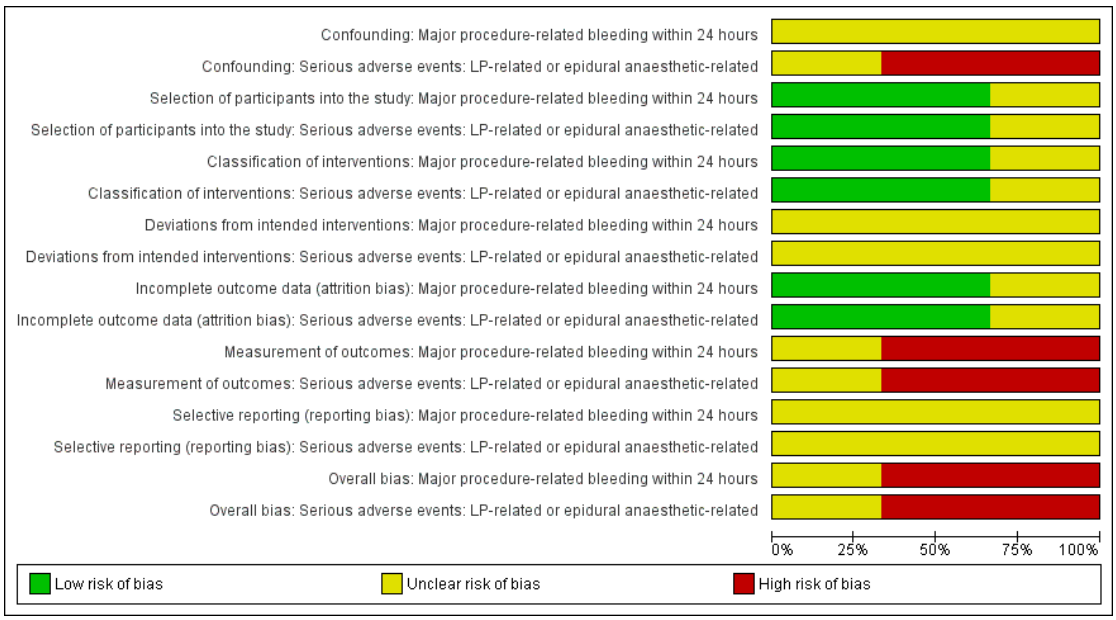
We excluded 47 studies within 48 full-text papers. See Characteristics of excluded studies for further details.

- Three studies compared the wrong intervention (NCT01972529; NCT01976104; Hasegawa 2012).
- Six studies were reviews (Choi 2009; Feusner 2004; Hua 2014; Mitchell 2012; Valent 2011; Wolfe 2016).
- Fifteen studies were the wrong study design; the majority were case reports (Breuer 1982; Dresner 2010; Kandemir 2016; Kasama 1997; Kimura 2001; Kotelko 1989; Kotera 2010; Kuczkowski 2006; Lee 2007; Liu 2014; Mayumi 1983; Moller 2015; Pivalizza 2005; Steer 1993; Wirtz 2000).
- Twelve studies involved no platelet transfusions (Beilin 1997; Bernstein 2016; Foerster 2015; McLure 2003; Noris 2014; Palit 2008; Ramanathan 1988; Rolbin 1988; Ruell 2006; Totadri 2014; Waldman 1987; Welter 2008).
- Six studies involved the wrong population (Eriksson 2007; Lecompte 2003; McLendon 2011; Moeschler 2016; Self 2007; Wong 1989).
- Four studies had no comparator (Frenk 2005; Osmanagaoglu 2006; Vavricka 2003; Webert 2003).
- One study involved the wrong indication (Meneses 2009).

Risk of bias in included studies

We did not perform a 'Risk of bias' assessment for RCTs using the Cochrane 'Risk of bias' tool because no completed RCTs were eligible for inclusion in the review.
We evaluated the risk of bias of the non-randomised studies included in this review using the ROBINS-I tool (formerly known as ACROBAT-NRSI). Only two included studies reported outcomes relevant to this review (Ning 2016; van Veen 2004), therefore we only evaluated the ROBINS-I assessment for these two studies. Only three outcomes could be assessed using ROBINS-I (Figure 2).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



- Major LP-related or epidural anaesthetic-related bleeding within 24 hours of the procedure (reported by Ning 2016 and van Veen 2004).
- Serious adverse events (reported by Ning 2016).
- Minor LP-related or epidural anaesthetic-related bleeding within 24 hours of the procedure (reported by Ning 2016 and van Veen 2004).

Bias due to confounding

We judged the risk of bias due to confounding factors as 'serious' for all reported outcomes in both studies (Ning 2016; van Veen 2004). Only counts were reported.

In Ning 2016, a list of potential confounding factors was provided including the age of participants in the cohort, gender distribution, primary diagnosis, anticoagulants, antiplatelet agents, coagulopathy status, number of participants with end-stage renal disease and congenital bleeding. However, no information was provided to suggest that data analysis was adjusted for these factors. In van Veen 2004, information relevant to potential confounding factors before the intervention (at baseline) and the method of data analysis were missing.

Allocation

We judged the risk of bias of selection of participants as 'low' for all reported outcomes in both studies (Ning 2016; van Veen 2004). Selection of participants was based on the pre-procedure platelet count and that a lumbar puncture had been performed.

Bias in classification of interventions

We judged the risk of bias in classification of the intervention (platelet transfusion or receiving no platelet transfusion) as 'low' for both studies (Ning 2016; van Veen 2004). Presence or absence of a platelet transfusion was clearly defined and would have been recorded in medical records at the time of transfusion.

Bias due to deviations from intended interventions

We judged the risk of bias due to deviations from intended interventions as 'no information' for both studies. No information was available as to whether any deviations from intended intervention had occurred that were beyond those expected in usual practice.

Incomplete outcome data

We judged the risk of bias due to missing data as 'low' for all reported outcomes for both studies. There was no evidence of missing data for the reported outcomes.

Bias in measurement of outcomes

We judged the risk of bias in measurement of outcomes as 'serious' for both studies. The outcome assessors were aware of the participants' intervention status in both studies. Neither study reported methods of assessing bleeding.

Selective reporting

We judged the risk of bias due to selective reporting as 'low' for both studies, as results for all reported outcomes were equally reported between the groups.

Overall bias

Our overall judgement of risk of bias for all reported outcomes in both studies was 'serious'. For each outcome we considered more than one domain to be at 'serious' risk of bias and none to be at 'critical' risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Platelet transfusion compared with no platelet transfusion for lumbar puncture procedures

We have narratively described the outcomes reported in the two studies that reported outcomes separately for participants who did and did not receive platelet transfusions (Ning 2016; van Veen 2004). Both studies provided information on outcomes when the participants' platelet count was 50 x 10^9/L or below.

Primary outcomes

Major procedure-related bleeding within 24 hours of the procedure

No cases of major procedure-related bleeding occurred (2 studies, 150 participants, no events, very low-quality evidence).

All-cause mortality up to 30 days after the procedure

Neither study reported mortality during 30 days from the LP procedure.

Serious adverse events

Ning 2016 reported serious adverse events. No transfusion-related or LP-related serious adverse events occurred (1 study, 21 participants, no events, very low-quality evidence).

Secondary outcomes

Minor LP-related or epidural anaesthetic-related bleeding within 24 hours of the procedure

Ning 2016 and van Veen 2004 reported the proportion of LPs with minor bleeding (traumatic taps) (2 studies, 150 participants, very low-quality evidence).

In Ning 2016, one traumatic tap (defined as at least 500 x 10^6/L red blood cells in the cerebrospinal fluid) occurred in the platelet transfusion group (14 participants), and no traumatic taps occurred in the no-platelet transfusion group (7 participants).

In van Veen 2004, two traumatic taps (more than 1000 x 10^6/L red blood cells in the cerebrospinal fluid) occurred in the platelet transfusion group (57 participants), and one traumatic tap occurred in the no-platelet transfusion group (72 participants). Also, four traumatic taps (100 to 1000 x 10^6/L red blood cells in the cerebrospinal fluid) occurred in the platelet transfusion group (57 participants), and three traumatic taps occurred in the no-platelet transfusion group (72 participants).

Duration of hospital stay (total number of days in hospital)

No studies reported on the duration of hospital stay.

Proportion of participants receiving platelet transfusions

No studies reported on whether platelet transfusions were given after the procedure.

Quality of life, as defined by individual studies

No studies measured quality of life of the participants.

DISCUSSION

Summary of main results

We found no completed or ongoing RCTs, nRCTs, CBAs, or ITSs that were relevant to this review.

No studies assessed the use of platelet transfusions prior to the insertion of an epidural catheter.

No studies compared different platelet count thresholds prior to an LP procedure.

In this update of the review we identified three retrospective cohort studies that compared giving platelet transfusions versus not giving platelet transfusions when the platelet count was 50 x 10^9/L or below prior to an LP procedure. Two studies were conducted in children (Howard 2000; van Veen 2004), and one in adults

with haematological malignancies (Ning 2016). The number of children who received platelet transfusions before the LP procedure was not specified in Howard 2000, therefore we reported the findings from the two studies that reported outcomes separately for participants who did and did not receive platelet transfusions (Ning 2016; van Veen 2004).

The only available evidence for the use of platelet transfusions prior to LPs was from two retrospective cohort studies that involved only 150 participants (129 children and 21 adults) with thrombocytopenia and haematological malignancy:

- no procedure-related major bleeding occurred in the two studies that reported this outcome (2 studies, 150 participants);
- there was no evidence of a difference in the risk of minor bleeding (traumatic tap) in participants who received platelet transfusions before an LP and those who did not receive a platelet transfusion before the procedure (2 studies, 150 participants);
- no serious adverse events occurred in the one study that reported this outcome (21 participants);
- we found no studies that evaluated all-cause mortality within 30 days from the procedure; length of hospital stay; proportion of participants who received platelet transfusions; or quality of life.

Overall completeness and applicability of evidence

We are unable to answer our review question using evidence from RCTs, and there is insufficient information to answer this question using the available data from non-randomised studies.

It is unlikely that any RCTs will be performed in the future with a primary outcome of major bleeding because the event is rare, and if major bleeding does occur it can cause significant neurological impairment.

Any future non-randomised study would need to be very large to detect a difference in the risk of bleeding. For example, if it was assumed that major bleeding occurred in 1 out of 1000 people who had an LP when their platelet count was raised to 50 x 10^9/L or above, and that the risk of major bleeding doubled to 2 out of 1000 when their platelet count was only raised to 20 x 10^9/L or above, we would need to design a study with at least 47,030 participants to be able to detect this difference with 80% power and 5% significance (calculated using a power calculator at Sealed Envelope).

Quality of the evidence

We identified no completed RCTs, nRCTs, CBAs, or ITSs that were relevant to this review. We included three retrospective cohort studies, of which only two studies reported outcomes relevant to this review. Both studies suffered from serious methodological limitations due to their retrospective design, small sample size, the absence of analytic method, and inappropriate reporting of the results. The validity of the results from both studies is therefore questionable.

Overall we rated the quality of the evidence for the two reported outcomes as very low according to GRADE methodology (Summary of findings for the main comparison) because all data were from non-randomised studies (low-quality evidence), and the quality of the evidence was downgraded for imprecision. We were unable to further downgrade the quality of the evidence because it was already classified as very low, but the evidence was at serious risk of bias.

We could assess only three outcomes reported in two studies for risk of bias using the ROBINS-I tool: major LP-related or epidural anaesthetic-related bleeding within 24 hours of the procedure (reported in Ning 2016 and van Veen 2004); serious adverse events (reported in Ning 2016); and minor LP-related or epidural anaesthetic-related bleeding within 24 hours of the procedure (reported in Ning 2016 and van Veen 2004).

All outcomes in both studies were at serious risk of bias due to:

- confounding, as factors known to increase the risk of bleeding were not clearly documented and adjusted for. Potential haemostatic confounding factors such as the coagulopathy status and the intake of anticoagulants were only reported in Ning 2016 as part of this population's baseline characteristics, but it was unclear if the analysis adjusted for these cofounders;
- lack of blinding, as all studies were open-label.

There were also limitations due to lack of information reported in both studies with regard to the number of attempts at placing an LP needle and detailed list of medications at baseline. The optimal indication to determine platelet transfusions as well as to perform LP was platelet counts prior to LPs in both studies. The methodology and the reporting of both studies were lacking details. Both studies had a similar design, and data were collected by reviewing medical records of a small sample size.

Potential biases in the review process

To our knowledge, our review process was free from bias. We conducted a comprehensive search, searching data sources (including multiple databases and clinical trial registries) to ensure that we would capture all relevant studies, including any ongoing studies. We carefully assessed the relevance of each paper identified and performed all screening in duplicate. We prespecified all outcomes and subgroups prior to analysis. We could not perform a formal assessment of publication bias as we conducted no meta-analyses.

Agreements and disagreements with other studies or reviews

We know of two systematic reviews that were relevant to this review (Kumar 2015; van Veen 2010).

The review by Kumar 2015 assessed the evidence for the use of platelet transfusions prior to LPs but did not assess the evidence prior to epidural anaesthesia. Like our review, Kumar 2015 found no RCTs that were relevant to this review's question. The Kumar 2015 review also assessed evidence from non-randomised studies. They identified seven observational, retrospective, single-centre studies (1536 participants; 6440 LPs) with varying platelet count thresholds. The studies did not report outcomes separately for those participants who received prophylactic platelet transfusions and those who did not. In addition, the studies did not describe the eligibility criteria or the criteria for transfusion. However, although of poor quality, the studies seemed to indicate a lack of severe bleeding associated with the insertion of an LP needle. There were no serious bleeding complications in five case series of 1450 children with thrombocytopenia. There were two cases of spinal haematoma (86 participants) in two case series of adults with thrombocytopenia. The van Veen 2010 review identified the same seven non-randomised studies because Kumar 2015 used the search performed by van Veen 2010 that was first published online in September 2009. The van Veen 2010 review also assessed the evidence for the use of platelet transfusions prior to epidural anaesthetics. There were no RCTs; six observational studies included only participants receiving an epidural anaesthetic, and no spinal haematomas occurred. Only one of the included studies included participants who were not pregnant.

Both of these reviews concluded that there is a scarcity of evidence supporting prophylactic platelet transfusions prior to the insertion of a spinal needle for an LP or for the delivery of anaesthetic (Kumar 2015; van Veen 2010).

The most recently published platelet transfusion guidelines from the American Association of Blood Banks used this non-randomised evidence (Kaufman 2015; Kumar 2015). Another recently published guideline based its recommendations on expert opinion (NICE 2015).

AUTHORS' CONCLUSIONS

Implications for practice

We are unable to make any firm recommendations to support or refute platelet transfusions before performing lumbar punctures on children and adults with thrombocytopenia. We are also unable to define a trigger for platelet transfusions for this population.

Implications for research

It is unlikely that any randomised controlled trials will be performed in the future with a primary outcome of major bleeding because the event is rare. To detect a doubling in the number of participants with major bleeding from 0.1% to 0.2% would require a study with more than 47,000 participants. The possibility of establishing a central data collection register where data are systematically documented across different platelet thresholds categories and other relevant demographic data of this population is likely to be the only method to systematically gather data relevant to this population.While platelet counts have been used as the optimal method to advise on the need for platelet transfusion for this population, other haemostasis indicators should also be considered.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Howard 2000

Methods	**Type of study:** Retrospective cohort study **Type of publication**: Full **Setting and country**: USA **Number of centres**: 1 centre, St Jude Children's Research Hospital, Memphis, TN **Recruitment dates (start and end)**: February 1984 to July 1998 **Study duration**: 14 years **Was a power calculation performed?** No **Platelet counts collected within 24 hours before lumbar puncture:** Not from all children: 208 LPs were performed without platelet counts within 1 day of performing LPs
Participants	**Inclusion criteria:** Children with newly diagnosed ALL **Exclusion criteria:** Not reported **Number of potentially eligible participants:** 958 children undergoing 5442 LPs **Number of participants analysed:** 956 children. 1 child was excluded due to early death from sepsis before initiation of intrathecal therapy, and another was excluded because an intracranial haemorrhage at the time of diagnosis resulted in grossly bloody CSF at each of 11 LPs performed to relieve pressure **Number of participants with platelet counts < 50 x 10^9/L:** Not reported **Age:** Median 5.5 years (range 1 month to 18 years) **Gender:** 524 boys (55%) and 434 girls (45%) **Ethnicity:** 83% white, 13% black, 4% other races **Coagulopathy:** No information **Platelet dysfunction:** No information **End-stage renal disease:** No information **Diagnosis:** ALL **Number of lumbar punctures:** 5223, 895 LPs performed at diagnosis. 41 LPs were excluded because no platelet count was performed within 1 day of LP, and 167 LPs were excluded because no platelet count was documented after transfusion of platelets **Number of lumbar punctures per participant:** Median 5 LPs. Each child received 2 to 9 LPs during the study period for the administration of intrathecal chemotherapy in addition to 1 diagnostic LP **Platelet counts levels and number of lumber punctures:** 1 to 5 x 10^9/L (6 LPs), 6 to 10 x 10^9/L (23 LPs), 11 to 20 x 10^9/L (170 LPs), 21 to 30 x 10^9/L (234 LPs), 31 to 40 x 10^9/L (235 LPs), 41 to 50 x 10^9/L (273 LPs) **Treatment:** Induction chemotherapy (prednisone, asparaginase, vincristine, daunorubicin, etoposide (or teniposide), and cytarabine with or without methotrexate) **Co-intervention (plasma transfusions, haemostatic agents):** No information **Were participants with active bleeding explicitly excluded?** No information
Interventions	Platelet transfusion with all relevant information was missing; this included number of children who received the transfusion, number of children who did not receive the transfusion, platelet thresholds, dose, and frequency All LPs were performed by paediatric oncologists, paediatric oncology fellows, paediatric

Howard 2000 (*Continued*)

	residents, and nurse practitioners
Outcomes	**Primary outcomes:** Serious complications including any neurological, infectious, or haemorrhagic problems apart from headache, nausea, irritability, or somnolence. Red blood cells per high-powered microscopic field of 500 or more in the CSF was an indication of traumatic LP
Notes	**Trial register ID:** Not reported **Supported by:** Cancer Center Support (CORE) **Conflicts-of-interest statement:** Not declared **Ethical approval body:** No information **Contact email:** scott.howard@stjude.org **Address:** Department of Hematology-Oncology, ALSAC Bldg, Room C6005, St Jude Children's Research Hospital, Memphis, TN

Risk of bias

Bias	Authors' judgement	Support for judgement
Confounding Major procedure-related bleeding within 24 hours	Unclear risk	ROBINS-I not performed, outcome not reported.
Confounding Serious adverse events: LP-related or epidural anaesthetic-related	Unclear risk	ROBINS-I not performed, outcome not reported.
Selection of participants into the study Major procedure-related bleeding within 24 hours	Unclear risk	ROBINS-I not performed, outcome not reported.
Selection of participants into the study Serious adverse events: LP-related or epidural anaesthetic-related	Unclear risk	ROBINS-I not performed, outcome not reported.
Classification of interventions Major procedure-related bleeding within 24 hours	Unclear risk	ROBINS-I not performed, outcome not reported.
Classification of interventions Serious adverse events: LP-related or epidural anaesthetic-related	Unclear risk	ROBINS-I not performed, outcome not reported.
Deviations from intended interventions Major procedure-related bleeding within 24 hours	Unclear risk	ROBINS-I not performed, outcome not reported.
Deviations from intended interventions Serious adverse events: LP-related or epidural anaesthetic-related	Unclear risk	ROBINS-I not performed, outcome not reported.

Howard 2000 (*Continued*)

Incomplete outcome data (attrition bias) Major procedure-related bleeding within 24 hours	Unclear risk	ROBINS-I not performed, outcome not reported.
Incomplete outcome data (attrition bias) Serious adverse events: LP-related or epidural anaesthetic-related	Unclear risk	ROBINS-I not performed, outcome not reported.
Measurement of outcomes Major procedure-related bleeding within 24 hours	Unclear risk	ROBINS-I not performed, outcome not reported.
Measurement of outcomes Serious adverse events: LP-related or epidural anaesthetic-related	Unclear risk	ROBINS-I not performed, outcome not reported.
Selective reporting (reporting bias) Major procedure-related bleeding within 24 hours	Unclear risk	ROBINS-I not performed, outcome not reported.
Selective reporting (reporting bias) Serious adverse events: LP-related or epidural anaesthetic-related	Unclear risk	ROBINS-I not performed, outcome not reported.
Overall bias Major procedure-related bleeding within 24 hours	Unclear risk	ROBINS-I not performed, outcome not reported.
Overall bias Serious adverse events: LP-related or epidural anaesthetic-related	Unclear risk	ROBINS-I not performed, outcome not reported.

Ning 2016

Methods	**Type of study:** Retrospective cohort study **Type of publication**: Full **Setting and country**: Sunnybrook Health Sciences Centre - Canada **Number of centres**: 1 centre in Toronto **Recruitment dates (start and end)**: January 2013 until December 2014 **Study duration**: 23 months **Was a power calculation performed?** No **Platelet counts collected within 24 hours before lumbar puncture:** Yes
Participants	**Inclusion criteria:** • Adults (≥ 18 years) with malignancy undergoing LPs from January 2013 until December 2014 **Exclusion criteria:** • People with coagulopathy INR ≥ 1.5, aPTT ≥ 40 s, fibrinogen ≤ 1.0 g/L **Number of participants included:** 135

	Number of participants with platelet counts < 50 x 10^9/L: 21; platelet transfusion group (n = 14) and no-platelet transfusion group (n = 7) **Number of participants analysed:** 21 **Age:** Mean (range): platelet transfusion group: 50 (38 to 70) years; no-platelet transfusion group: 57 (20 to 80) years **Gender:** Platelet transfusion group: female (n = 4) (22%); no-platelet transfusion group: female (n = 5) (71.4%) **Ethnicity:** Not reported **Coagulopathy:** Platelet transfusion group (n = 0); no-platelet transfusion group (n = 0) **Platelet dysfunction:** Platelet transfusion group (n = 0); no-platelet transfusion group (n = 0) **End-stage renal disease:** Platelet transfusion group (n = 0); no-platelet transfusion group (n = 0) **Diagnosis:** Platelet transfusion group: lymphoma (n = 7), leukaemia (n = 7), other malignancies (n = 0); no-platelet transfusion group: lymphoma (n = 4), leukaemia (n = 2), other malignancies (n = 1) **Number of lumbar punctures:** 28; platelet transfusion group (n = 18); no-platelet transfusion group (n = 10) **Number of lumbar punctures per participant:** median 1 **Number of lumber punctures and platelet counts:** • Pre-LP platelet count ≤ 10 x 10^9/L: platelet transfusion group (n = 1); no-platelet transfusion group (n = 0) • Pre-LP platelet count 11 to 20 x 10^9/L: platelet transfusion group (n = 5); no-platelet transfusion group (n = 2) • Pre-LP platelet count 21 to 30 x 10^9/L: platelet transfusion group (n = 3); no-platelet transfusion group (n = 2) • Pre-LP platelet count 31 to 40 x 10^9/L: platelet transfusion group (n = 6); no-platelet transfusion group (n = 1) • Pre-LP platelet count 41 to 50 x 10^9/L: platelet transfusion group (n = 3); no-platelet transfusion group (n = 5) **Co-intervention (plasma transfusions, haemostatic agents):** No information **Were participants with active bleeding explicitly excluded?** Yes, but participants with risk of bleeding were included: • antiplatelet agents: platelet transfusion group (n = 2); no-platelet transfusion group (n = 0) • anticoagulants - prophylactic: platelet transfusion group (n = 8); no-platelet transfusion group (n = 1) • anticoagulants - therapeutic: platelet transfusion group (n = 1); no-platelet transfusion group (n = 1)
Interventions	• Platelet transfusion: single transfusion with either a pool of 4 units of buffy coat-derived platelet or 1 unit of single-donor apheresis platelet when platelet count ≤ 50 x 10^9/L • No platelet transfusion: no transfusion when platelet count ≤ 50 x 10^9/L
Outcomes	• Haemorrhagic complications (spinal, subdural, subarachnoid, and epidural haematomas) • Traumatic tap: ≥ 500 x 10^6/L red blood cells in the CSF

Ning 2016 (*Continued*)

Notes	**Trial register ID:** Not reported **Supported by:** Not reported **Conflicts-of-interest statement:** Not reported **Ethical approval body:** Study was approved by the Institution's Research Ethics Board **Contact email:** yulia.lin@sunnybrook.ca **Address:** Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Rm B-204, Toronto, ON M4N 3M5, Canada

Risk of bias

Bias	Authors' judgement	Support for judgement
Confounding Major procedure-related bleeding within 24 hours	Unclear risk	**ROBINS-I judgement (Serious)** The following confounders were measured but not adjusted for: participants' diagnosis, age, gender, antiplatelet, anticoagulants, haemostasis
Confounding Serious adverse events: LP-related or epidural anaesthetic-related	High risk	**ROBINS-I judgement (Serious)** The following confounders were measured but not adjusted for: participants' diagnosis, age, gender, antiplatelet, anticoagulants, haemostasis
Selection of participants into the study Major procedure-related bleeding within 24 hours	Low risk	**ROBINS-I judgement (Low)** Selection of participants into the study was not based on participant characteristics observed after the start of the intervention. We were not aware of the exclusion of any participants from the analysis for this outcome
Selection of participants into the study Serious adverse events: LP-related or epidural anaesthetic-related	Low risk	**ROBINS-I judgement (Low)** Selection of participants into the study was not based on participant characteristics observed after the start of the intervention
Classification of interventions Major procedure-related bleeding within 24 hours	Low risk	**ROBINS-I judgement (Low)** Both the group who received platelet transfusion and the group who did not receive platelet transfusion before LPs were clearly defined, and all the information used to define each group was equally reported
Classification of interventions Serious adverse events: LP-related or epidural anaesthetic-related	Low risk	**ROBINS-I judgement (Low)** Both the group who received platelet transfusion and the group who did not receive platelet transfusion before LPs were clearly defined, and all the information used to de-

Ning 2016 (*Continued*)

		fine each group was equally reported
Deviations from intended interventions Major procedure-related bleeding within 24 hours	Unclear risk	**ROBINS-I judgement (No information)** No information reported.
Deviations from intended interventions Serious adverse events: LP-related or epidural anaesthetic-related	Unclear risk	**ROBINS-I judgement (No information)** No information reported.
Incomplete outcome data (attrition bias) Major procedure-related bleeding within 24 hours	Low risk	**ROBINS-I judgement (Low)** Data for this outcome were available for all participants, and it is likely that no participants were excluded due to missing data
Incomplete outcome data (attrition bias) Serious adverse events: LP-related or epidural anaesthetic-related	Low risk	**ROBINS-I judgement (Low)** Data for this outcome were available for all participants, and it is likely that no participants were excluded due to missing data
Measurement of outcomes Major procedure-related bleeding within 24 hours	High risk	**ROBINS-I judgement (Serious)** Outcome assessors were aware of the intervention received by each participant in the study, which could have influenced the assessment of this outcome. No information on whether the methods of assessing major bleeding were comparable across the platelet-transfused and not-transfused groups
Measurement of outcomes Serious adverse events: LP-related or epidural anaesthetic-related	High risk	**ROBINS-I judgement (Serious)** Outcome assessors were aware of the intervention status of the participants in the study, which could have influenced the assessment of this outcome. Information on outcome assessment methods was missing
Selective reporting (reporting bias) Major procedure-related bleeding within 24 hours	Unclear risk	**ROBINS-I judgement (No information)** No information reported.
Selective reporting (reporting bias) Serious adverse events: LP-related or epidural anaesthetic-related	Unclear risk	**ROBINS-I judgement (No information)** No information reported.
Overall bias Major procedure-related bleeding within 24 hours	High risk	**ROBINS-I judgement (Serious)**

Ning 2016 (*Continued*)

Overall bias Serious adverse events: LP-related or epidural anaesthetic-related	High risk	**ROBINS-I judgement (Serious)**

van Veen 2004

Methods	**Type of study:** Retrospective cohort study **Type of publication**: Full **Setting and country**: Department of Haematology, Sheffield Children's Hospital, UK **Number of centres**: 1 centre **Recruitment dates (start and end)**: 1989 and 2003 **Study duration**: 14 years **Was a power calculation performed?** No **Platelet counts collected within 24 hours before lumbar puncture:** Unknown
Participants	**Inclusion criteria:** • 226 children newly diagnosed acute lymphoblastic leukaemia (ALL) **Exclusion criteria:** • Not reported **Number of participants included:** 226 children **Number of participants with platelet counts < 50 x 10^9/L:** 135 children; 129 underwent LPs, 72 without a platelet transfusion **Number of participants analysed:** 129 **Age:** All were children, but not reported further. **Gender:** Not reported **Ethnicity:** Not reported **Coagulopathy:** Not reported **Platelet dysfunction:** Not reported **End-stage renal disease:** Not reported **Diagnosis:** ALL **Number of lumbar punctures:** 129 **Median of the number of lumbar punctures per participant:** Not reported **Number of lumber punctures and platelet counts:** • Platelet count < 10 x 10^9/L: 22 LPs; 13 LPs platelet transfusion, 9 LPs no transfusion • Platelet count 10 to 20 x 10^9/L: 42 LPs; 20 LPs platelet transfusion, 22 LPs no transfusion • Platelet count 21 to 50 x 10^9/L: 65 LPs; 24 LPs platelet transfusion, 41 LPs no transfusion **Treatment:** Intrathecal chemotherapy **Co-intervention (plasma transfusions, haemostatic agents):** No information **Were participants with active bleeding explicitly excluded?** No information
Interventions	• Platelet transfusion: n = 57 children • No platelet transfusion: n = 72 children
Outcomes	• Traumatic tap • Minor bleeding

Notes	**Trial register ID:** Not reported **Supported by:** Not reported **Conflicts-of-interest statement:** Not reported **Ethical approval body:** Not reported **Contact email:** jenny.welch@sch.nhs.uk **Address:** Department of Haematology, Sheffield Children's Hospital, Western Bank, Sheffield S10 2TH, UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Confounding Major procedure-related bleeding within 24 hours	Unclear risk	**ROBINS-I judgement (Serious)** No information was provided to suggest that potential confounding factors were considered and adjusted for in the analysis
Confounding Serious adverse events: LP-related or epidural anaesthetic-related	High risk	**ROBINS-I judgement (Serious)** No information was provided to suggest that potential confounding factors were considered and adjusted for in the analysis
Selection of participants into the study Major procedure-related bleeding within 24 hours	Low risk	**ROBINS-I judgement (Low)** Selection of participants into the study was not based on their characteristics
Selection of participants into the study Serious adverse events: LP-related or epidural anaesthetic-related	Low risk	**ROBINS-I judgement (Low)** Selection of participants into the study was not based on their characteristics
Classification of interventions Major procedure-related bleeding within 24 hours	Low risk	**ROBINS-I judgement (Low)** The assignment to the interventions (platelet transfusion or no platelet transfusion) was not based on characteristics
Classification of interventions Serious adverse events: LP-related or epidural anaesthetic-related	Low risk	**ROBINS-I judgement (Low)** The two groups were clearly defined with regard to the number of participants in each group, platelet counts, and the number of LP procedures
Deviations from intended interventions Major procedure-related bleeding within 24 hours	Unclear risk	**ROBINS-I judgement (No information)** No information to suggest a cross-contamination between platelet transfusion group and no-platelet transfusion group occurred
Deviations from intended interventions Serious adverse events: LP-related or epidural anaesthetic-related	Unclear risk	**ROBINS-I judgement (No information)** No information to suggest a cross-contam-

		ination between platelet transfusion group and no-platelet transfusion group occurred
Incomplete outcome data (attrition bias) Major procedure-related bleeding within 24 hours	Low risk	**ROBINS-I judgement (Low)** Data for this outcome were probably available for all participants
Incomplete outcome data (attrition bias) Serious adverse events: LP-related or epidural anaesthetic-related	Low risk	**ROBINS-I judgement (Low)** Data for this outcome were probably available for all participants
Measurement of outcomes Major procedure-related bleeding within 24 hours	High risk	**ROBINS-I judgement (Serious)** The outcomes assessors were aware of participants' intervention status. However, the assessors knowledge of the intervention status would likely have had no influence on the reporting of this outcome
Measurement of outcomes Serious adverse events: LP-related or epidural anaesthetic-related	High risk	**ROBINS-I judgement (Serious)** The outcomes assessors were aware of participants' intervention status
Selective reporting (reporting bias) Major procedure-related bleeding within 24 hours	Unclear risk	**ROBINS-I judgement (No information)**
Selective reporting (reporting bias) Serious adverse events: LP-related or epidural anaesthetic-related	Unclear risk	**ROBINS-I judgement (No information)**
Overall bias Major procedure-related bleeding within 24 hours	High risk	**ROBINS-I judgement (Serious)**
Overall bias Serious adverse events: LP-related or epidural anaesthetic-related	High risk	**ROBINS-I judgement (Serious)**

ALL: acute lymphoblastic leukaemia
aPPT: activated partial thromboplastin time
CSF: cerebral spinal fluid
INR: International normalised ratio
LP: lumbar puncture

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beilin 1997	No platelet transfusions
Bernstein 2016	No platelet transfusions
Breuer 1982	Wrong study design: case report and review of vascular sources of needle-induced bleeding in lumbar puncture
Choi 2009	Review
Dresner 2010	Wrong study design: commentary
Eriksson 2007	Wrong population: a case report on a woman with pre-eclampsia and normal platelet counts
Feusner 2004	Review
Foerster 2015	No platelet transfusions
Frenk 2005	No comparator: all parturients with platelets count less than 50 x 10^9/L received platelet transfusion before regional anaesthesia
Hasegawa 2012	Wrong intervention
Hua 2014	Review
Kandemir 2016	Wrong study design: case report
Kasama 1997	Wrong study design: case report
Kimura 2001	Wrong study design: case report (2 people with essential thrombocythaemia)
Kotelko 1989	Wrong study design: case report (a 31-year-old primigravida with previously diagnosed May-Hegglin anomaly)
Kotera 2010	Wrong study design: case report (a 31-year-old woman with aplastic anaemia was admitted for the management of delivery at 33 weeks of gestation)
Kuczkowski 2006	Wrong study design: case report (a parturient with immune thrombocytopenic purpura)
Lecompte 2003	Wrong population: Von Willebrand disease
Lee 2007	Wrong study design: case series (4 patients); 2 cases of spinal epidural haematoma and 2 cases of intracranial subdural haematoma after lumbar puncture in children receiving chemotherapy for acute lymphoblastic leukaemia and non-Hodgkin lymphoma
Liu 2014	Wrong study design: case report

(*Continued*)

Mayumi 1983	Wrong study design: case report
McLendon 2011	Wrong indication
McLure 2003	No platelet transfusions
Meneses 2009	Wrong indication: assessment of safety of general anaesthesia for lumbar puncture
Mitchell 2012	Review
Moeschler 2016	Wrong population: cancer patients and intrathecal drug delivery systems
Moller 2015	Wrong study design: online survey
NCT01972529	Wrong intervention: avatrombopag vs placebo
NCT01976104	Wrong intervention: avatrombobag vs placebo
Noris 2014	No platelet transfusions
Osmanagaoglu 2006	No comparator
Palit 2008	No platelet transfusions
Pivalizza 2005	Wrong study design: commentary
Ramanathan 1988	No platelet transfusions
Rolbin 1988	No platelet transfusions
Ruell 2006	No platelet transfusions
Self 2007	Wrong population: people on antiplatelet therapy
Steer 1993	Wrong study design: case report (a 26-year-old woman with idiopathic thrombocytopenia was admitted for induction of labour)
Totadri 2014	No platelet transfusions
Valent 2011	Review
Vavricka 2003	No comparator
Waldman 1987	No platelet transfusions
Webert 2003	No comparator

(*Continued*)

Welter 2008	No platelet transfusions
Wirtz 2000	Wrong study design: case report (a 12-year-old male with acute lymphoblastic leukaemia)
Wolfe 2016	Review
Wong 1989	Wrong population: children with meningococcal infection

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Blood Platelets] explode all trees
#2 (platelet* or thrombocyte*):ti
#3 MeSH descriptor: [Platelet Transfusion] explode all trees
#4 MeSH descriptor: [Plateletpheresis] explode all trees
#5 ((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*))
#6 thrombocyt?pheres* or plateletpheres*
#7 ((platelet* or thrombocyte*) near/5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utilisation or utilization))
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MeSH descriptor: [Spinal Puncture] this term only
#10 MeSH descriptor: [Anesthesia, Epidural] explode all trees
#11 MeSH descriptor: [Anesthesia, Spinal] this term only
#12 MeSH descriptor: [Injections, Spinal] explode all trees
#13 MeSH descriptor: [Myelography] this term only
#14 MeSH descriptor: [Nerve Block] explode all trees
#15 ((spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or intralumbar* or theca* or intrathecal or subarachnoid* or peridural* or caudal*) near/6 (punctur* or inject* or infus* or anesth* or anaesth* or needle* or tap* or block* or drug* or administ*))
#16 ((intrathecal or theca*) near/6 (treatment* or chemotherapy or antibiotic* or therapy or inject*))
#17 myelogra*
#18 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 #8 and #18

Appendix 2. MEDLINE (OvidSP) search strategy

1. Spinal Puncture/
2. Anesthesia, Epidural/
3. Anesthesia Spinal/
4. exp Injections, Spinal/
5. Myelography/
6. exp Nerve Block/
7. ((spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or intralumbar* or theca* or intrathecal or subarachnoid* or peridural* or caudal*) adj6 (punctur* or inject* or infus* or anesth* or anaesth* or needle* or tap* or block* or drug* or administ*)).tw,kf.
8. ((intrathecal or theca*) adj6 (treatment* or chemotherapy or antibiotic* or therapy or inject*)).tw,kf.
9. myelogra*.tw,kf.
10. or/1-9
11. Platelet Transfusion/
12. Plateletpheresis/
13. Blood Platelets/
14. ((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.
15. (thrombocytopheres* or plateletpheres*).tw,kf.
16. ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw,kf.
17. (platelet* or thrombocyte*).ti.
18. or/11-17
19. 10 and 18

Appendix 3. Embase (OvidSP) search strategy

1. Lumbar Puncture/
2. Puncture/
3. exp Intraspinal Drug Administration/
4. exp Epidural Anesthesia/
5. Spinal Anesthesia/
6. Myelography/
7. exp Nerve Block/
8. ((spine or spinal or intraspinal or dura* or intradural or epidural or lumbar* or intralumbar* or theca* or intrathecal or subarachnoid* or peridural* or caudal*) adj6 (punctur* or inject* or infus* or anesth* or anaesth* or needle* or tap* or block* or drug* or administ*)).tw.
9. ((intrathecal or theca*) adj6 (treatment* or chemotherapy or antibiotic* or therapy or inject*)).tw.
10. myelogra*.tw.
11. or/1-10
12. Thrombocyte Transfusion/
13. Thrombocytopheresis/
14. Thrombocyte/ and transfus*.mp.
15. *Thrombocyte/
16. ((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.
17. (thrombocytopheres* or plateletpheres*).tw,kf.
18. ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw,kf.
19. (platelet* or thrombocyte*).ti.
20. or/12-19
21. 11 and 20

Appendix 4. PubMed search strategy (e-publications only)

#1 ((spine OR spinal OR intraspinal OR dura OR dural OR intradural OR epidural OR lumbar* OR intralumbar* OR theca* OR intrathecal OR subarachnoid* OR peridural* OR caudal*) AND (punctur* OR inject* OR infus* OR anesth* OR anaesth* OR needle* OR tap* OR block* OR drug* OR administ*))
#2 ((intrathecal OR theca*) AND (treatment* OR chemotherapy OR antibiotic* OR therapy OR inject*))
#3 myelogra*
#4 #1 OR #2 OR #3
#5 ((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*))
#6 (thrombocytopheres* OR plateletpheres*)
#7 ((platelet* OR thrombocyte*) AND (protocol* OR trigger* OR threshold* OR schedul* OR dose* OR dosing OR usage OR utilisation OR utilization))
#8 platelet*[TI] OR thrombocyte*[TI]
#9 #5 OR #6 OR #7 OR #8
#10 #4 AND #9
#11 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
#12 #10 AND #11

Appendix 5. Transfusion Evidence Library search strategy

Search box: (lumbar OR spinal OR puncture OR injection OR needle OR epidural OR intradural OR dural OR peridural OR caudal OR intrathecal OR subarachnoid OR block OR anaesthetic OR anesthetic OR anesthesia OR anaesthesia OR drug OR tap OR administration OR procedure)
Filter: Platelets

Appendix 6. WHO ICTRP search strategy

(Title: lumbar OR spinal OR puncture OR injection OR epidural OR intradural OR dural OR peridural OR caudal OR intrathecal OR subarachnoid OR administration OR procedure) AND
(Intervention: platelet OR platelets)

Appendix 7. ClinicalTrials.gov search strategy

Search Terms: (lumbar puncture OR spinal injection OR epidural OR intradural OR dural OR peridural OR caudal OR intrathecal OR subarachnoid OR nerve block) AND (platelets OR platelet transfusion)
Study Design: All Studies

WHAT'S NEW

Last assessed as up-to-date: 13 February 2018.

Date	Event	Description
30 April 2018	New citation required but conclusions have not changed	Despite a much broader search of the literature the conclusions have not changed

(*Continued*)

13 February 2018	New search has been performed	Including non-randomised studies: as randomised controlled trials do not exist to answer the review question, we have included evidence from non-randomised studies

CONTRIBUTIONS OF AUTHORS

Lise Estcourt (LE): protocol and review development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis, and content expert.

Reem Malouf (RM): review development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis.

Sally Hopewell (SH): protocol and review development and methodological expert.

Carolyn Doree (CD): protocol and review development, searching, and selection of studies.

Joost Van Veen (JVV): review development and content expert.

DECLARATIONS OF INTEREST

Lise Estcourt (LE): partly funded by the National Institute of Health Research (NIHR) Cochrane Programme Grant - Safe and Appropriate Use of Blood Components.

Reem Malouf (RM): partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components.

Sally Hopewell (SH): partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components.

Carolyn Doree (CD): none known.

Joost Van Veen (JVV): none known.

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For editorial support

- National Institute for Health Research (NIHR) Cochrane Programme Grant, UK.

To provide funding for systematic review authors and methodological support from the Centre for Statistics in Medicine, Oxford

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are several differences between the protocol, Estcourt 2015, and this update of the review.

Because we found no eligible randomised controlled trials for inclusion in the previous version of the review (Estcourt 2016), we felt there was a particular need to expand the review scope and examine other study types to aid in answering the review question. We amended the review Methods to accommodate the inclusion of non-randomised studies in order to reflect these changes.

We made the changes in the following parts of the review.

Search strategy

In this update we did not apply any language restrictions.

Types of studies

We initially included only randomised controlled trials. However, as we did not find any such trials to include in this review update, we thought it would be appropriate to broaden our inclusion criteria and consider studies of other designs. We planned to include:

- longitudinal observational studies using appropriate concurrent comparator; this includes both prospective and retrospective cohort studies;
- non-randomised controlled trials;
- controlled before-after studies.

Data extraction and management

We extracted the following further information from studies of other designs.

- Study design
- Selection of the study sample
- Method used to allocate the intervention(s)
- A list of confounding factors reported in the paper
- Other co-intervention status
- Full description on method of analysing data in the study

Assessment of risk of bias in included studies

We added the application of the ROBINS-I tool to evaluate the risk of bias for included non-randomised studies.

Measures of treatment effect

We added details on the treatment effect measures for included non-randomised studies.

Data synthesis

We added details on the method we followed to analyse data extracted from included non-randomised studies.

We were unable perform the following due to lack of data.

- Report on all of the primary or secondary outcomes specified in the protocol
- Combine data in a meta-analysis

- Subgroup analysis
- 'Summary of findings' table with data
- Funnel plot to assess for publication bias

NOTES

Definitions of technical terms

Disseminated intravascular coagulation: a rare, life-threatening condition that prevents blood from clotting normally. The blood clots reduce blood flow and can block blood from reaching the body's organs. This increased clotting can use up the platelets and clotting factors in the blood, meaning that fewer platelets and clotting factors are available, which can lead to excessive bleeding.
Haematological malignancies: blood cancers and related diseases that primarily affect the bone marrow or blood cells. The bone marrow is the soft inner part of bones where blood is made.
The three main types of blood cells are:

- red blood cells, which carry oxygen from the lungs to every part of the body;
- white blood cells, which help the body fight infection;
- platelets, which help control bleeding.

Neonatal alloimmune thrombocytopenia: a condition characterised by the destruction of platelets in the foetus or newborn by antibodies produced by the mother. The foetus has proteins on the surface of the platelet that it has inherited from its father but that are not present in the mother. The mother sees these proteins as 'foreign' and may respond by producing antibodies against these intruders. Antibodies are an important part of the body's immune system. The antibodies produced by the mother may cross the placenta, enter the baby's bloodstream, and destroy the unborn baby's platelets.

INDEX TERMS

Medical Subject Headings (MeSH)

*Platelet Transfusion; Anesthesia, Epidural [*adverse effects]; Spinal Puncture [*adverse effects]; Thrombocytopenia [complications; *therapy]

MeSH check words

Humans