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

Estcourt LJ, Ingram C, Doree C, Hopewell S, Trivella M, Stanworth SJ

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 12

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

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

Lise J Estcourt[1], Callum Ingram[2], Carolyn Doree[3], Sally Hopewell[4], Marialena Trivella[4], Simon J Stanworth[5]

[1]Haematology/Transfusion Medicine, NHS Blood and Transplant, Oxford, UK. [2]School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK. [3]Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK. [4]Centre for Statistics in Medicine, University of Oxford, Oxford, UK. [5]National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust and the University of Oxford, Oxford, 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.

Editorial group: Cochrane Haematological Malignancies Group.
Publication status and date: New, published in Issue 12, 2015.

Citation: Estcourt LJ, Ingram C, Doree C, Hopewell S, Trivella M, Stanworth SJ. Use of platelet transfusions prior to lumbar punctures or epidural anaesthesia for the prevention of complications in people with thrombocytopenia. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.: CD011980. DOI: 10.1002/14651858.CD011980.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

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

BACKGROUND

Please see Published notes for an explanation of some 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 (DIC) (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.

Lumbar puncture

Diagnostic

A diagnostic lumbar puncture (LP) is an invasive procedure to obtain samples of cerebrospinal fluid (CSF) (Doherty 2014). CSF 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 CSF obtained can then be used for the investigation of haematological malignancies (Vavricka 2003), subarachnoid haemorrhages, meningitis (Riordan 2002), or neurological disorders. LPs are performed by doctors or specially trained nurses.

Therapeutic

Therapeutic LPs administer drugs into the CSF. This can be for the administration of therapeutics such as intrathecal chemotherapy or antibiotics, or administration of local anaesthetic to the nerves of the lower spine when a spinal anaesthetic is administered (Doherty 2014). This usually involves inserting 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 larger diameter needle 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 CSF). 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

In the general population, the risk of a spinal haematoma 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, overall, there are no current reliable estimates of the risks of adverse effects such as spinal haematomas in people with thrombocytopenia (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 post-procedural 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 a 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 in France a platelet count of at least 80 x 10^9/L is recommended (Samama 2005).

As there is currently no consensus on the standard platelet count threshold prior to an LP or epidural anaesthesia, we will compare 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 then 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). Most of these reactions are not life-threatening but can be extremely distressing for the person. Rarer, but more serious sequelae include: anaphylaxis (life-threatening allergic reaction), transfusion-transmitted infections (TTI) and transfusion-related acute lung injury (TRALI) (Blumberg 2010; Chapman 2015; Kaufman 2015; Slichter 2007; Vlaar 2013).

If guidelines recommend a platelet count threshold higher than is necessary to perform an LP safely, it may delay the start of life-saving 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 complica-

tions 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 this is putting people with thrombocytopenia 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 the children 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). Therefore, people may 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 by 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 the insertion of 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 will include only randomised controlled trials (RCTs), irrespective of publication status.

Types of participants

We will include people of any age with thrombocytopenia (as defined by the studies) requiring an LP or epidural anaesthesia. We will exclude people who are 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 will include RCTs comparing the following two types of procedure: LP needle insertion or epidural catheter insertion.

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

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

We will 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.

For example: 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 (TRALI), transfusion-transmitted infection (TTI), transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions);
- LP-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 bleeding within 24 hours of the procedure (defined as prolonged bleeding at the insertion site that only requires 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 the individual studies

Search methods for identification of studies

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

Electronic searches

We will limit our searches to five main electronic databases and two ongoing trial databases.

- Cochrane Central Register of Controlled Trials (CENTRAL; latest issue) (Appendix 1).
- MEDLINE (1946 to present) (Appendix 2).
- EMBASE (1974 to present) (Appendix 3).
- PubMed (e-publications only) (Appendix 4).
- Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1950 to present) (Appendix 5).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (Appendix 6).
- ClinicalTrials.gov (Appendix 7).

We will combine searches in MEDLINE with the Cochrane RCT search filter, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We will combine searches in EMBASE with the relevant Scottish Intercollegiate Guidelines Network (SIGN) RCT studies filter (www.sign.ac.uk/methodology/filters.html). We will exclude studies published in languages other than English. We will not limit searches by year of publication or publication type.

Searching other resources

We will handsearch reference lists of included studies in order to identify further relevant studies. We will contact lead authors of the included studies to identify any unpublished material, missing data or information regarding ongoing studies.

Data collection and analysis

Selection of studies

We will select studies according to Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The Systematic Review Initiative's Information Specialist (CD) will initially screen all search hits for relevance against the eligibility criteria and discard all those that are clearly irrelevant. Thereafter, two review authors (CI, LE) will independently screen all the remaining references for relevance against the full eligibility criteria using DistillerSR software. We will retrieve full-text articles for all references for which a decision on eligibility cannot be made from title and abstract alone. We will request additional information from study authors as necessary to assess the eligibility for inclusion of individual studies. The two review authors will discuss the results of study selection and try to resolve any discrepancies between themselves. In the event that this is not possible, we will refer the decision of eligibility to a third review author (SS). We will report 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 (CI, LE) will independently extract data onto standardised forms using DistillerSR software. The data extraction form will be piloted on two included RCTs. The review authors will try to come to a consensus; if an agreement cannot be reached, they will consult a third review author (SS). The review authors will not be blinded to names of authors, institutions, journals or the study outcomes. They will extract the following information for each study.

- Source: study 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.
- Characteristics of participants: age, gender, primary diagnosis, type 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 drop-outs with reasons (percentage in each arm), protocol violations, missing data.
- Outcomes: major procedure-related bleeding within 24 hours of the procedure, minor procedure-related 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).

Assessment of risk of bias in included studies

We will 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). Two review authors (CI, LE) will work independently to assess each element of potential bias listed below as 'high', 'low' or 'unclear' risk of bias. We will report a brief description of the judgement statements upon which the authors have assessed 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 (SS). We will use Cochrane's tool for assessing risk of bias, which will include 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.

Measures of treatment effect

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 the total number of participants in both the treatment and control groups.

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 present the standardised mean difference (SMD) with 95% CIs. If available, we will extract and report hazard ratios (HRs) with 95% CIs for mortality data. If HRs are not available, we will make every effort to estimate as accurately as possible the HR using the available data and a purpose built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007).

For dichotomous outcomes, we will report the pooled risk ratio (RR) with 95% CIs. Where the number of observed events is small (less than 5% of sample per group), and where trials have balanced treatment groups, we will report the Peto's odds ratio (OR) with 95% CIs (Deeks 2011).

If data allow, we will undertake quantitative assessments using Review Manager 5 (RevMan 2014).

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

If we cannot report the available data in any of the formats described above, we will perform a narrative report, and, if appropriate, we will present the data in tables.

Unit of analysis issues

We do not expect to encounter unit of analysis issues as cluster-randomised trials, cross-over studies and multiple observations for the same outcome are unlikely to be included in this review. Should any studies of these designs arise, we will treat these in accordance with the advice given 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 provide us with data on the LP or epidural anaesthesia associated with the initial randomisation. For studies with multiple treatment groups, two review authors (CI 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

Where data are identified to be missing or unclear in published literature, we will contact study authors directly. We will record the number of participants lost to follow-up for each study. Where possible, we will analyse data on an intention-to-treat (ITT) basis, but if insufficient data are available, we will present per-protocol analyses (Higgins 2011c).

Assessment of heterogeneity

If the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will combine the data to perform a meta-analysis. We will assess statistical heterogeneity of treatment effects between studies using a Chi^2 test with a significance level at P value < 0.1. We will use the I^2 statistic to quantify the degree of potential heterogeneity and classify it as moderate if the I^2 statistic is greater than 50%, or considerable if the I^2 statistic is greater 80%. We perceive that we will identify at least moderate clinical and methodological heterogeneity within the studies selected for inclusion; in such cases, we will use the random-effects model. If statistical heterogeneity is considerable, we will not report the overall summary statistic. We will assess potential causes of heterogeneity by sensitivity and subgroup analyses (Deeks 2011).

Assessment of reporting biases

Where we identify at least 10 studies for inclusion in a meta-analysis, we will explore potential publication bias (small-trial bias) by generating a funnel plot and using a linear regression test. We will consider a P value of less than 0.1 as significant for this test (Sterne 2011).

Data synthesis

We will perform analyses according to the recommendations of Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* using aggregated data for analysis (Deeks 2011). For statistical analysis, we will enter data into the Review Manager 5 (RevMan 2014). One review author (CI) will enter the data and a second review author (LE) will check for accuracy.

Where meta-analysis is feasible, we will use the random-effects model for pooling the data. We will use the Mantel-Haenszel method for dichotomous outcomes, and the inverse variance method (or SMDs as necessary) for continuous outcomes. In cases where event are rare, and appropriate conditions are satisfied, we will use the Peto's OR method under the fixed-effect model. We will use the generic inverse variance method for time-to-event outcomes.

Summary of findings

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

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

We will report separate 'Summary of findings' tables for LPs and epidural anaesthesia. We will report the subgroup for each comparison that contains the largest number of studies.

The outcomes we will include are listed below.

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

Subgroup analysis and investigation of heterogeneity

If adequate data are available, we will perform subgroup analyses for each of the following outcomes in order 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 DIC, or concomitant use of anticoagulant or antiplatelet agents.

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

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

Sensitivity analysis

We will 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% drop-out rate.
- Including only studies that are published in full.

ACKNOWLEDGEMENTS

We thank the editorial base of the Cochrane Haematological Malignancies Review Group.

We thank the National Institute of Health Research (NIHR). This review is part of a series of reviews that have been funded by the

NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components. This research is also supported by the NIHR Oxford Biomedical Research Centre Programme.

REFERENCES

Additional references

BCSH 2003
BCSH. British Committee for Standards in Haematology: guidelines for the use of platelet transfusions. *British Journal of Haematology* 2003;**122**(1):10–23.

BCSH 2004
Gibson BE, Todd A, Roberts I, Pamphilon D, Rodeck C, Bolton-Maggs P, et al. Transfusion guidelines for neonates and older children. *British Journal of Haematology* 2004; **124**(4):433–53.

Birchall 2015
Birchall J, Tinegate H, Regan F. Chapter 14 Acute transfusion reactions (ATR). In: Bolton-Maggs PHB (Ed) D Poles, et al. on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group, editor(s). *The 2014 Annual SHOT Report*. Manchester, UK: SHOT, 2015: 106–12.

Blumberg 2010
Blumberg N, Heal JM, Phillips GL. Platelet transfusions: trigger, dose, benefits and risks. *F1000 Medicine Reports* 2010;**2**:1–5.

Chapman 2015
Chapman C. Transfusion-related lung injury (TRALI). www.shotuk.org/wp-content/uploads/SHOT-2014-Annual-Report_v11-Web-Edition.pdf 2015:190-5 (accessed 26 November 2015).

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

DistillerSR
Evidence Partners. DistillerSR: Data Management Software. Ottawa, ON: Evidence Partners, 2015.

Doherty 2014
Doherty CM, Forbes RB. Diagnostic lumbar puncture. *Ulster Medical Journal* 2014;**83**(2):93–102.

Erbay 2014
Erbay RH, Senoglu N, Atalay H. Spinal or epidural haematoma. *Topics in Spinal Anaesthesia*. Rijeka, Croatia: In-Tech, 2014. [DOI: 10.5772/58702]

Estcourt 2012
Estcourt LJ, Birchall J, Lowe D, Grant-Casey J, Rowley M, Murphy MF. Platelet transfusions in haematology patients: are we using them appropriately?. *Vox Sanguinis* 2012;**103** (4):284–93.

GMA 2009
The Board of the German Medical Association on the recommendation of the Scientific Advisory Board. Platelet transfusions. *Transfusion Medicine and Hemotherapy* 2009; **36**:372–82.

Higgins 2011a
Higgins JPT, Deeks JJ. Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b
Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011c
Higgins JPT, Deeks JJ, Altman DG. Chapter 16: Special topics in Statistics. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Kaufman 2015
Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. Platelet transfusion: a clinical practice guideline from the AABB. *Annals of Internal Medicine* 2015;**162**(3):205–13.

Kumar 2015
Kumar A, Mhaskar R, Grossman BJ, Kaufman RM, Tobian AA, Kleinman S, et al. Platelet transfusion: a systematic review of the clinical evidence. *Transfusion* 2015;**55**(3): 1116–27.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Leguit 2010
Leguit RJ, van den Tweel JG. The pathology of bone marrow failure. *Histopathology* 2010;**57**(5):655–70.

Levi 2009
Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. *British Journal of Haematology* 2009;**145**(1): 24–33.

Li 2010
Li S-L, Wang D-X, Ma D. Epidural hematoma after neuraxial blockade: a retrospective report from China. *Anesthesia & Analgesia* 2010;**111**(5):1322–4.

Liumbruno 2011
Liumbruno GM, Bennardello F, Lattanzio A, Piccoli P, Rossetti G. Recommendations for the transfusion management of patients in the peri-operative period. I. The pre-operative period. *Blood Transfusion* 2011;**9**(1):19–40.

Mendola 2009
Mendola C, Ferrante D, Oldani E, Cammarota G, Cecci G, Vaschetto R, et al. Thoracic epidural analgesia in post-thoracotomy patients: comparison of three different concentrations of levobupivacaine and sufentanil. *British Journal of Anaesthesia* 2009;**102**(3):418–23.

Moen 2004
Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. *Anesthesiology* 2004;**101**(4):950–59.

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-Analyses: the PRISMA Statement. *Annals of Internal Medicine* 2009; **151**(4):264–9.

Neunert 2013
Neunert CE. Current management of immune thrombocytopenia. *Hematology* 2013;**2013**:276–82.

Ng 2004
Ng KW, Parsons J, Cyna AM, Middleton P. Spinal versus epidural anaesthesia for caesarean section. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD003765.pub2]

Pacheco 2011
Pacheco LD, Berkowitz RL, Moise KJ, Bussel JB, McFarland JG, Saade GR. Fetal and neonatal alloimmune thrombocytopenia: a management algorithm based on risk stratification. *Obstetrics and Gynecology* 2011;**118**(5): 1157–63.

Parmar 1998
Parmar M, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24): 2815–34.

Provan 2010
Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010;**115**(2):168–86.

Qureshi 2007
Qureshi H, Lowe D, Dobson P, Grant-Casey J, Parris E, Dalton D, et al. National comparative audit of the use of platelet transfusions in the UK. *Transfusion Clinique et Biologique* 2007;**14**(6):509–13.

RevMan 2014
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Riordan 2002
Riordan FA, Cant AJ. When to do a lumbar puncture. *Archives of Disease in Childhood* 2002;**87**(3):235–37.

Ruppen 2006
Ruppen W, Derry S, McQuay H, Moore RA. Incidence of epidural hematoma, infection, and neurologic injury in obstetric patients with epidural analgesia/anesthesia. *Anesthesiology* 2006;**105**(2):394–99.

Samama 2005
Samama CM, Djoudi R, Lecompte T, Nathan-Denizot N, Schved JF. Perioperative platelet transfusion: recommendations of the Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSaPS) 2003. *Canadian Journal of Anaesthesia* 2005;**52**(1):30–7.

Schünemann 2011a
Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Schünemann 2011b
Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Cochrane Applicability and Recommendations Methods Group. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Slichter 2007
Slichter SJ. Evidence-based platelet transfusion guidelines. *Hematology* 2007;**1520**:172–78.

Sterne 2011
Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Tierney 2007
Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; Vol. 8, issue 16. [DOI: 10.1186/1745-6215-8-16]

van Veen 2010
van Veen JJ, Nokes TJ, Makris M. The risk of spinal haematoma following neuraxial anaesthesia or lumbar puncture in thrombocytopenic individuals. *British Journal of Haematology* 2010;**148**(1):15–25.

Vandermeulen 1994
Vandermeulen EP, Van Aken H, Vermylen J. Anticoagulants and spinal-epidural anesthesia. *Anesthesia & Analgesia* 1994; **79**:1165–77.

Vavricka 2003
Vavricka SR, Walter RB, Irani S, Halter J, Schanz U. Safety of lumbar puncture for adults with acute leukaemia and restrictive prophylactic platelet transfusion. *Annals of Hematology* 2003;**82**(9):570–73.

Venn 2015
Venn PJH. Key points on the provision of anaesthesia services 2015. www.rcoa.ac.uk/gpas2015 (accessed 26 November 2015).

Verma 2009
Verma A, Agarwal P. Platelet utilization in the developing world: strategies to optimize platelet transfusion practices. *Transfusion and Apheresis Science* 2009;**41**(2):145–9.

Vlaar 2013
Vlaar AP, Juffermans NP. Transfusion-related acute lung injury: a clinical review. *Lancet* 2013;**382**(9896):984–94.

Weinzierl 2013
Weinzierl EP, Arber DA. The differential diagnosis and bone marrow evaluation of new-onset pancytopenia. *American Journal of Clinical Pathology* 2013;**139**(1):9–29.

Williams 2008
Williams J, Lye DC, Umapathi T. Diagnostic lumbar puncture: minimising complications. *Internal Medicine Journal* 2008;**38**(7):587–91.

* *Indicates the major publication for the study*

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
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomi*.tw,kf.
23. placebo.ab.
24. exp clinical trials as topic/
25. randomly.ab.
26. trial.tw.
27. groups.ab.
28. or/20-27
29. 19 and 28

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)).tw.
10. myelogra*.tw.
11. or/1-10
12. Thrombocyte Transfusion/
13. Thrombocytopheresis/
14. Thrombocyte/
15. ((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.

16. (thrombocyt?pheres* or plateletpheres*).tw.
17. ((platelet* or thrombocyte*) adj5 (protocol* or trigger* or threshold* or schedul* or dose* or dosing or usage or utili?ation)).tw.
18. (platelet* or thrombocyte*).ti.
19. or/12-18
20. 11 and 19
21. Randomized Controlled Trial/
22. Randomization/
23. Single Blind Procedure/
24. Double Blind Procedure/
25. Crossover Procedure/
26. Placebo/
27. exp Clinical Trial/
28. Prospective Study/
29. (randomi* or double-blind* or single-blind* or RCT*).tw.
30. (random* adj2 (allocat* or assign* or divid* or receiv*)).tw.
31. (crossover* or cross over* or cross-over* or placebo*).tw.
32. ((treble or triple) adj blind*).tw.
33. or/21-32
34. Case Study/
35. case report*.tw.
36. (note or editorial).pt.
37. or/34-36
38. 33 not 37
39. 20 and 38
40. limit 39 to embase

Appendix 4. PubMed search strategy (epublications 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 (random* OR blind* OR control group OR placebo OR controlled trial OR controlled study OR groups OR trials OR systematic review OR meta-analysis OR metaanalysis OR literature search OR medline OR cochrane OR embase) AND (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 intrathecal OR subarachnoid OR peridural OR caudal 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. Clinical.trials.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)
AND
Study Design: Intervention Studies

CONTRIBUTIONS OF AUTHORS

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

Callum Ingram: protocol development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis.

Carolyn Doree: protocol development, searching and selection of studies.

Sally Hopewell: protocol development and methodological expert.

Marialena Trivella: protocol development and statistical expert.

Simon Stanworth: protocol development and content expert.

DECLARATIONS OF INTEREST

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

Callum Ingram: none known.

Carolyn Doree: none known.

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

Marialena Trivella: partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components.

Simon Stanworth: none known.

SOURCES OF SUPPORT

Internal sources

- NHS Blood and Transplant, Research and Development, UK.

To fund the work of the Systematic Review Initiative (SRI)

External sources

- Cochrane Haematological Malignancies Group, Department for Internal Medicine, Germany.

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

NOTES

This review will be a rapid review (definition of a rapid review as previously agreed with the Haematological Malignancies Group), we will only include English language publications.

Definitions of technical terms

Disseminated intravascular coagulation (DIC)

DIC is 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 and mean that fewer platelets and clotting factors are available. This can then 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 (NAIT)

NAIT is characterised by the destruction of platelets in the fetus or newborn by antibodies produced by the mother. The fetus has proteins on the surface of the platelet that it has inherited from its father but are not present in the mother. The mother sees these proteins as "foreign" and may respond by producing antibodies against these intruders. Antibodies, 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.