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Platelet Transfusion for Neonates with Thrombocytopenia: Protocol for a Systematic Review

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ABSTRACT

Introduction

Thrombocytopenia is one of the most common haemostatic abnormalities among neonates. It affects approximately one-quarter of neonates admitted into neonatal intensive care units (NICUs) and may lead to high risks of bleeding and mortality, which are great concerns of neonatologists. Platelet transfusion (PT) is a specific treatment for thrombocytopenia. To date, PT thresholds are diverse, since the associations between low platelet count and negative outcomes are not clear. We propose this protocol for a systematic review to collect and assess evidence concerning the best PT threshold to reduce mortality, bleeding and major morbidity among neonates with thrombocytopenia.

Methods and analysis

The systematic review will be performed according to the Cochrane Handbook for Systematic Review of Interventions, the PRISMA statement, and the GRADE system. Two independent researchers will perform the study selection, data extraction/coding, quality assessment and further analyses of the included studies, with disagreements being resolved by a third researcher. We will search for neonatal PT in the following electronic databases: MEDLINE, The Cochrane Library, and EMBASE. All randomized controlled trials (RCTs) and cohort studies will be included without any restrictions regarding publication date or language. The primary outcome will comprise in-hospital mortality and bleeding episodes. Endnote X9 and Review Manager V.5.3 software will be used to manage the selection process and statistical analysis, respectively. If the included studies are sufficient and homogeneous for any of the outcomes, a quantitative synthesis (meta-analysis) may be performed. Otherwise, we will conduct a narrative systematic review of the results.

Ethics and dissemination

Ethical approval is not required for this study because the data are from published studies and will not include individual patient data. The results of this study are anticipated to be published in a peer-reviewed journal.

Strengths and limitations of this study

- This study will be the first systematic review to evaluate the evidence regarding PT therapy for neonates with thrombocytopenia.
- Comprehensive outcomes including in-hospital mortality, bleeding episodes, morbidity, the adverse effects of transfusion, and length of stay will be evaluated.
- The approach of the review will be performed according to the Cochrane Handbook and the PRISMA statement.
- The quality of evidence will be affected by the bias in original studies.
- The results of this systematic review may be helpful for both clinical decisions and further study.

BACKGROUND

Thrombocytopenia, defined as a platelet count less than 150 000/μL, is a common haemostatic abnormality among neonates, especially premature infants.[1 2] The aetiology of thrombocytopenia is complicated and involves multiple factors, including abnormal immunity, infection, and asphyxia.[3-7] Thrombocytopenia may be a sole clinical manifestation or complication of other diseases, such as sepsis or necrotizing enterocolitis.[3-5 8] Approximately 9.4% to 35% of neonates admitted to neonatal intensive care units (NICUs) develop thrombocytopenia.[5 9-12] Theoretically, neonates with thrombocytopenia may develop a high risk of bleeding and mortality. Thus, this condition is a significant and unresolved problem for neonatologists.

Platelet transfusion (PT) is commonly used as a prophylactic and therapeutic treatment for bleeding episodes in neonates with thrombocytopenia. To date, the relationship between low platelet count and major bleeding or mortality is not clear, and the efficacy of PT remains controversial.[5 13-15] Current guidelines generally recommend prophylactical PT for thrombocytopenic neonates.[16-19] The recommended thresholds vary from 20 000/μL to 30 000/μL [15-17 20-25] for non-bleeding stable neonates, while the thresholds range from 30 000/μL to 50 000/μL[15 21 24-26] for non-bleeding unstable neonates. These guidelines are consensus guidelines rather than evidence-based guidelines.[19 27] Thus, there is great diversity in PT thresholds among different NICUs.[28 29]

Theoretically, compared with that at a low threshold, PT at a high threshold may reduce the risks of severe thrombocytopenia, subsequent mortality and bleeding episodes. Surprisingly, a recent randomized controlled trial (RCT) reported that PT at a high threshold increased mortality and bleeding episodes in preterm infants with severe thrombocytopenia compared with PT at a low threshold.[14] On the other hand, as an invasive therapy, PT has some acknowledged adverse events, including transfusion-transmitted infections, bacterial sepsis, febrile nonhemolytic transfusion reaction, transfusion-associated circulatory overload, transfusion-related acute lung injury, and immune-mediated platelet destruction.[3 30-32] Furthermore, PT has a higher risk of these

adverse events than transfusions of other blood products due to its pro-inflammatory function.

Recently, more clinical trials regarding PT in neonates with thrombocytopenia have been completed. To assess the best threshold and safety of PT, we will perform this systematic review and meta-analysis to summarize current evidence for PT in neonates.

Objectives

Several reports have argued that a lower transfusion threshold may reduce the incidence of unnecessary transfusion and financial costs without the extra risks of bleeding and mortality.[13 15] We propose this protocol for a systematic review to collect and assess the evidence concerning the best threshold for PT to reduce mortality, bleeding and major morbidity among neonates with thrombocytopenia. We will further explore the best thresholds for PT for neonates with thrombocytopenia due to various causes and more specific clinical characteristics. Furthermore, the safety of PT will be assessed by comparing its side effects at different thresholds.

METHODS AND ANALYSIS

This protocol will be conducted on the basis of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) 2015 guidelines,[33] and further systematic review will be performed according to the Cochrane Handbook for Systematic Review of Interventions,[34] the PRISMA statement,[35] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[36]

Data sources and search strategy

Comprehensive searches will be performed by two researchers independently in the following databases: MEDLINE, the Cochrane Library, and EMBASE. No restriction for language or publication year will be applied to the search. We will use the following keywords to search for and select relevant studies.

1. For neonates, the following combination of search terms will be used: “infant” or “newborn” or “neonatal” or “neonate” or “preterm” or “premature” or “neonatology”.
2. For thrombocytopenia, the following search terms will be used: “thrombocytopenia” or “thrombocytopenic” or “NT”.
3. For PT, the following search terms will be used: “platelet transfusion” or “platelet infusion therapy” or “platelet administration” or “PT”
4. Steps 1, 2 and 3 will be combined with “and”.

The detailed search strategy is shown in supplemental table 1.

Furthermore, we will hand-check the references of all identified trials, relevant systematic reviews, and current treatment guidelines to avoid missing important studies. Missing data will be handled by contacting relevant investigators for unreported materials or additional details.

Study eligibility

Types of studies

We will include RCTs and cohort studies and exclude animal researches, in vitro studies, cross-sectional studies, case-control studies, case reports, case series, and secondary or tertiary articles (systematic reviews and meta-analyses).

If there are enough data to answer this review's questions using only data from RCTs, we will report only data from RCTs.

Types of participants

New-born infants (less than 28 postnatal days) with thrombocytopenia (platelet counts<150 000/μL) admitted to NICUs will be included. We will exclude studies for infants with congenital malformations.[14]

Types of interventions and comparators

The intervention of the included study is PT for thrombocytopenia. We will compare the effects of different transfusion platelet count thresholds. We will also record the type and dose of the platelet component received.

Types of outcomes

The primary outcome will be in-hospital mortality or bleeding episodes [including intraventricular haemorrhage (IVH), intracranial haemorrhage (ICH), pulmonary haemorrhage (PH), frank rectal bleeding, and other bleeding].

The secondary outcomes will be morbidity [including patent ductus arteriosus (PDA), sepsis, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), etc.], adverse effects of transfusion, and length of stay (LOS).[5 14 29 37-39]

Study selection

Two researchers will independently screen the titles and abstracts of the references retrieved by the searches. If eligible, the full texts of potential references will be obtained and assessed by two researchers. Studies approved by both investigators will be included in this meta-analysis. Discrepancies in inclusion and exclusion decisions will be solved with a third senior researcher. Endnote X9 software will be used to tract and manage the selection process, and there will be a PRISMA flow diagram to help demonstrate this process (see supplemental figure 1).

Data extraction

A structured extraction sheet (see supplemental table 2) as well as Review Manager V.5.3 (Cochrane Collaboration, Oxford, UK) software will be used for data extractions by two investigators independently, and disagreement will be resolved by a third senior researcher. The included data items are as follows:

1. Publication and study details: authors, year of publication, country, study design, and number of participants.

2. Clinical characteristics: gestational age (GA), birth weight (BW), platelet count before transfusion or severity of thrombocytopenia, platelet count thresholds, type and dose of platelet component, and the number of PTs.

3. Outcomes: mortality, bleeding episodes, IVH grade, NEC, BPD, ROP, sepsis, and LOS.

4. Other information: any sponsorship or funding.

Missing information will be handled by contacting relevant investigators for unreported data or additional details.

Risk of bias in individual studies

Risk of bias will be assessed by two independent reviewers, and disagreement will be resolved by a third reviewer.

For RCTs, the 'Risk of Bias Assessment Tool' in Review Manager V.5.3 software (Cochrane Collaboration, UK) will be used. This tool includes random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. The bias of the included studies will be divided into high risk of bias, low risk of bias, or unclear in each domain (see supplemental table 3).[40]

The Newcastle-Ottawa scale (NOS) will be used for observational studies in terms of selection, comparability, and outcome, with a minimum score of 0 and a maximum score of 9. We will grade trials with scores of 9 as high quality and those with scores from 1-8 as low quality (see supplemental table 4).

Data synthesis

When the studies are sufficiently homogeneous for any of the described outcome measures, a quantitative synthesis (meta-analysis) may be performed according to the recommendations of the Cochrane handbook. If quantitative analysis cannot be performed, we will conduct a narrative systematic review of the results from the studies included, and we will not pool the data from the individual studies.

For dichotomous data (occurrence of mortality, bleeding episode, morbidity, adverse events, etc.), the risk ratio (RR) and odds ratio (OR) will be used for analysis. For continuous data (GA, BW, etc.), the mean difference (MD) or standardized mean difference (SMD) with 95% confidence intervals (CIs) will be used to represent the

summary statistics of the outcome with the same units and different scales, respectively.

Assessment of heterogeneity

The chi² test (P≤0.1 indicates substantial or considerable heterogeneity) will be used to determine whether heterogeneity is statistically significant. We will also assess the degree of statistical heterogeneity by examining I^2. The data will be pooled by applying a random-effects model following $I^2 \geq 50\%$ or P≤0.1. Otherwise, the fixed-effects model will be used.

Sensitivity analysis

We will assess the robustness of the results by excluding low-quality studies.

Subgroup analysis

If sufficient data are identified, subgroup analyses will be performed to detect possible heterogeneity based on the following participant characteristics:

1) GA (<28 w, 28 – 32 w, 32 – 37 w, >37 w)

2) BW (<1000 g, 1000 – 1500 g, 1500 – 2500 g, >2500 g)

3) The severity of thrombocytopenia [mild (100 000 – 150 000/μL), moderate (50 000 – 100 000/μL), severe (<50 000/μL)]

4) The platelet count thresholds for PT

5) The cause for thrombocytopenia

6) The design of the study (RCTs, cohort studies)

We will explore the possible heterogeneity among subgroups with I^2 and P values.

Quality of the evidence

We will use the GRADE approach[36 40] to assess the quality of evidence and propose to present "Summary of findings" tables (see supplemental table 5).

DISCUSSION

We will include RCTs and observational cohort studies in this review to strengthen the statistical power because of the limited number of relevant studies. To the best of our knowledge, this review will be the first to aim to determine the best transfusion platelet threshold for thrombocytopenic neonates admitted to NICUs. We expect to provide the best available evidence for neonatologists and guideline developers on PT, which will help both clinical practice and further study design.

ETHICS AND DISSEMINATION

Ethical approval is not required for this study because the data are from published studies and will not include individual patient data. The results of this study are anticipated to be published in a peer-reviewed journal.

Contributors

TX contributed to the conception of the study. The framework of the systematic review was developed by all authors. The search strategy was designed by TX and will be run by YY and DJL, who will further independently screen the relevant records, extract data from included studies and assess the risk of bias. JLW will perform the data synthesis. TX and JT will arbitrate in cases of any disagreement and ensure no errors occur during the study. The manuscript for this protocol was drafted by DJL and revised by TX. All authors have approved the publication of this protocol.

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Competing interests

None declared.

Patient consent

Not required.

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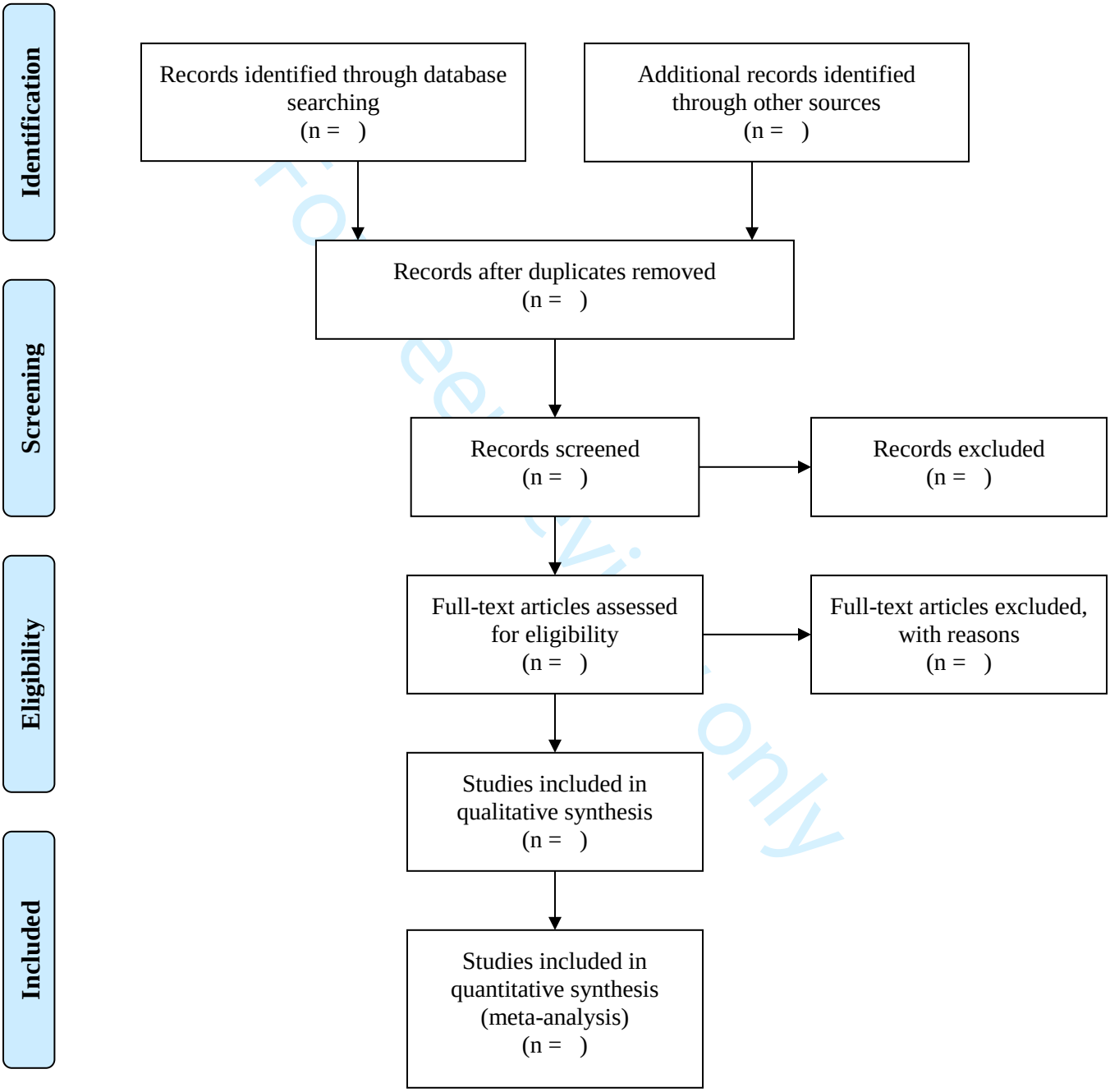
Supplemental Figure 1. Flow Diagram of Studies Selected for Inclusion in the Systematic Review (PRISMA 2009 Flow Diagram)



Supplemental Table 1. Search Strategy

(for Each Electronic Database to Be Searched)

#	Search terms	No of records returned
1	infant	
2	newborn	
3	neonatal	
4	neonate	
5	preterm	
6	premature	
7	neonatology	
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	
9	thrombocytopenia	
10	thrombocytopenic	
11	NT	
12	#9 OR #10 OR #11	
13	platelet transfusion	
14	platelet infusion therapy	
15	platelet administration	
16	PT	
17	#13 OR #14 OR #15 OR #16	
18	#8 AND #12 AND #17	
19	limit #18 to humans	

Supplemental Table 2. Data Extraction Sheet

Publication and study details						
Authors						
Year of publication						
Country						
Study design						
Number of participants						
Groups	Group 1 platelet count threshold (*10-3 per cubic millimeter)			Group 2 platelet count threshold (*10-3 per cubic millimeter)		
Clinical characteristics						
	Group 1 median (or mean)	Group 1 IQR (or SD)	Group 1 total	Group 2 median (or mean)	Group 2 IQR (or SD)	Group 2 total
GA (w)						
BW (g)						
Platelet count (*10-3 per cubic millimeter)						
Number of platelet transfusions						
Primary outcomes						
	Group 1 event	Group 1 total	Group 2 event	Group 2 total		
In-hospital mortality or major bleeding						
Bleeding episodes						
IVH						
ICH						
PH						

Frank rectal bleeding				
Other bleeding				
Secondary outcomes				
Major morbidity				
	Group 1 event	Group 1 total	Group 2 event	Group 2 total
PDA				
BPD				
Sepsis				
NEC				
ROP				

Other outcome measures						
LOS (days)	Group 1 median (or mean)	Group 1 IQR (or SD)	Group 1 total	Group 2 median (or mean)	Group 2 IQR (or SD)	Group 2 total

Adverse effects of transfusion	Group 1 event	Group 1 total	Group 2 event	Group 2 total
Other information				
Type and dose of platelet component				
Any sponsorship or funding				

IQR: interquartile range; SD: standard deviation; GA: gestational age; BW: birth weight; IVH: intraventricular haemorrhage; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; LOS: length of stay

Supplemental Table 3. The Risk of Bias Assessment Tool for Randomized Controlled Studies

Supplemental Table 3.1 The Risk of Bias Table

Item	Judgement	Support for judgement
Random sequence generation (selection bias)		
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)		
Blinding of outcome assessment (detection bias)		
Incomplete outcome data addressed (attrition bias)		
Selective reporting (reporting bias)		
Other bias		

Supplemental Table 3.2 The Recommended List of Items in the Risk of Bias Tool

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

		blinding was effective	
Detection bias	Blinding of outcome assessment*	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants),	Attrition bias due to amount, nature, or handling of incomplete outcome data

		reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review	
Reporting bias	Selective reporting	State how selective outcome reporting was examined and what was found	Reporting bias due to selective outcome reporting
Other bias	Anything else, ideally prespecified	State any important concerns about bias not covered in the other domains in the tool	Bias due to problems not covered elsewhere

*Assessments should be made for each main outcome or class of outcomes.

Supplemental Table 3.3 Approach to Formulating Summary Assessments of Risk of Bias for Each Important Outcome (Across Domains) within and Across Trials

Risk of bias	Interpretation	Within a trial	Across trials
Low risk of bias	Bias, if present, is unlikely to alter the results seriously	Low risk of bias for all key domains	Most information is from trials at low risk of bias
Unclear risk of bias	A risk of bias that raises some doubt about the results	Low or unclear risk of bias for all key domains	Most information is from trials at low or unclear risk of bias
High risk of bias	Bias may alter the results seriously	High risk of bias for one or more key domains	The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results

Supplemental Table 4. The Newcastle-Ottawa Scale (NOS)

Supplemental Table 4.1 The Newcastle-Ottawa Scale (NOS) – for Cohort Studies

Study	Item & score							
	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort (1)	Selection of the non-exposed cohort (1)	Ascertainment of exposure (1)	Demonstration that outcome of interest was not present at start of study (1)	Compare ability of cohorts on the basis of the design or analysis (2)	Assessment of outcome (1)	Was follow up long enough for outcomes to occur (1)	Adequacy of follow up of cohorts (1)

Supplemental 4.2 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✸
   b) somewhat representative of the average _____ in the community ✸
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview ✸
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✸
   b) record linkage ✸
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✸
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow up unlikely to introduce bias - small number lost - >____ % (select an adequate %) follow up, or description provided of those lost) ✸
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Supplemental Table 5. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach

Supplemental Table 5.1 The Summary of Findings Table

Outcomes	Illustrate comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Overall results
	Assumed risk Group 1	Corresponding risk Group 2				

Supplemental Table 5.2 GRADE Evidence Profile

Quality assessment							No. of patients		Effect	Quality
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Group 1**	**Group 2**	**Relative (95% CI)**	
Outcome 1										
Outcome 2										
Outcome 3										
Outcome 4										

Supplemental Table 5.3 Quality of Evidence Grades

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Supplemental Table 5.4 Factors that can reduce the quality of the evidence

Factor	Consequence
Limitations in study design or execution (risk of bias)	↓ 1 or 2 levels
Inconsistency of results	↓ 1 or 2 levels
Indirectness of evidence	↓ 1 or 2 levels
Imprecision	↓ 1 or 2 levels
Publication bias	↓ 1 or 2 levels

Supplemental Table 5.5 Factors that can increase the quality of the evidence

Factor	Consequence
Large magnitude of effect	↑ 1 or 2 levels
All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed	↑ 1 level
Dose-response gradient	↑ 1 level

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a under review
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1

Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	2
Support			
Sources	#5a	Indicate sources of financial or other support for the review	1
Sponsor	#5b	Provide name for the review funder and / or sponsor	1
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-6

Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7-8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6-7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8-9
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	8-9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9

Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

BMJ Open

Platelet Transfusion for Neonates with Thrombocytopenia: Protocol for a Systematic Review

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Platelet Transfusion for Neonates with Thrombocytopenia: Protocol for a Systematic Review

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ABSTRACT

Introduction

Thrombocytopenia is one of the most common haemostatic abnormalities among neonates. It affects approximately one-quarter of neonates admitted into neonatal intensive care units (NICUs) and may lead to high risks of bleeding and mortality, which are substantial causes for concern in neonatologists. Platelet transfusion (PT) is a specific treatment for thrombocytopenia. To date, PT thresholds are diverse, since the associations between low platelet count and negative outcomes are not clear. We propose this protocol for a systematic review to collect and assess evidence concerning the best PT threshold to reduce mortality, bleeding and major morbidity among neonates with thrombocytopenia.

Methods and analysis

The systematic review will be performed according to the Cochrane Handbook for Systematic Review of Interventions, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Two independent researchers will perform the study selection, data extraction/coding, quality assessment and further analyses of the included studies, with disagreements being resolved by a third researcher. A systematic search of the literature will be conducted in the PubMed, Cochrane Library, and Embase databases from database inception through October 13, 2020. All randomized controlled trials (RCTs), cohort studies and case control studies will be included without any restrictions regarding publication date or language. The primary outcome will comprise in-hospital mortality and bleeding episodes. Endnote X9 and Review Manager V.5.3 software will be used to manage the selection process and statistical analysis, respectively. If the included studies are sufficient and homogeneous for any of the outcomes, a quantitative synthesis (meta-analysis) may be performed. Otherwise, we will conduct a narrative systematic review of the results.

Ethics and dissemination

Ethical approval is not required for this study because the data will be obtained from published studies and will not include individual patient data. The results of this study are anticipated to be published in a peer-reviewed journal.

PROSPERO registration number: CRD42020169262.

Strengths and limitations of this study

- This study will be the most recent systematic review to evaluate the PT threshold for neonates with thrombocytopenia based on recent evidence. We will include RCTs and observational studies and separately combine the results of each study design.
- Comprehensive and extensive analyses of the outcomes, including in-hospital mortality, bleeding events, morbidity, the adverse effects of transfusion, and length of stay, will be performed.
- The approach of the review will be performed according to the Cochrane Handbook and the PRISMA statement.
- Formal risk of bias analyses will be performed. The quality of evidence will be affected by the bias in original studies.
- The results of this systematic review may be helpful for both clinical decisions and further study.

BACKGROUND

Thrombocytopenia, defined as a platelet count less than 150 000/μL, is a common haemostatic abnormality among neonates, particularly premature infants.[1 2] The aetiology of thrombocytopenia is complicated and involves multiple factors, including abnormal immunity, infection, and asphyxia.[3-7] Thrombocytopenia may be a sole clinical manifestation of alloimmune thrombocytopenia or a complication of other diseases, such as intrauterine growth restriction, polycythaemia, sepsis or necrotizing enterocolitis.[3-5 8] Approximately 9.4% to 35% of neonates admitted to neonatal intensive care units (NICUs) develop thrombocytopenia.[5 9-12] Theoretically, neonates with thrombocytopenia may develop a high risk of bleeding and mortality. This increased risk is attributed to the important role of platelets in the whole process of haemostasis, and thrombocytopenia may lead to dysfunctional haemostasis. Thus, this condition is a significant and unresolved problem for neonatologists.

Platelet transfusion (PT) is commonly used as a prophylactic and therapeutic treatment for bleeding episodes in neonates with thrombocytopenia. To date, the relationship between a low platelet count and major bleeding or mortality is not clear, and the efficacy of PT remains controversial, as supported by the evidence from recent trials.[5 13-15] Current guidelines generally recommend prophylactic PT for neonates with thrombocytopenia.[16-19] The recommended thresholds vary from 20 000/μL to 30 000/μL [15-17 20-25] for non-bleeding stable neonates, while the thresholds range from 30 000/μL to 50 000/μL[15 21 24-26] for non-bleeding unstable neonates. These guidelines are consensus guidelines rather than evidence-based guidelines.[19 27] Thus, a wide range of PT thresholds has been reported among different NICUs.[28 29]

Theoretically, compared with that at a low threshold, PT at a high threshold may reduce the risks of severe thrombocytopenia, subsequent mortality and bleeding episodes. Surprisingly, a recent randomized controlled trial (RCT) reported that PT at a high threshold increased the mortality rate and bleeding events in preterm infants with severe thrombocytopenia compared with PT at a low threshold.[14] On the other hand, as an invasive therapy, PT results in some acknowledged adverse events,

including transfusion-transmitted infections, bacterial sepsis, febrile nonhemolytic transfusion reaction, transfusion-associated circulatory overload, transfusion-related acute lung injury, and immune-mediated platelet destruction.[3 30-32] Furthermore, PT has a higher risk of these adverse events than transfusions of other blood products due to its pro-inflammatory function.

Recently, more clinical trials regarding PT in neonates with thrombocytopenia have been completed. Several reports have argued that a lower transfusion threshold may reduce the incidence of unnecessary transfusions and financial costs without the extra risks of bleeding and mortality.[13 15] We will perform this systematic review and meta-analysis to summarize current evidence for PT in neonates and to assess the best threshold and safety of PT.

Objectives

We propose this protocol for a systematic review to collect and assess the evidence concerning the best threshold for PT to reduce mortality, bleeding and major morbidity among neonates with thrombocytopenia. We will further explore the best thresholds for PT for neonates with thrombocytopenia due to various causes and more specific clinical characteristics. Furthermore, the safety of PT will be assessed by comparing its side effects at different thresholds.

METHODS AND ANALYSIS

This protocol will be conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) 2015 guidelines,[33] and a subsequent systematic review will be performed according to the Cochrane Handbook for Systematic Review of Interventions,[34] the PRISMA statement,[35] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[36]

Data sources and search strategy

Comprehensive searches will be separately performed by two independent researchers in the PubMed, Cochrane Library, and Embase databases from database inception through October 13, 2020. No restrictions on the language will be applied to the search. We will use the following keywords to search for and select relevant studies.

1. For neonates, the following combination of search terms will be used: “infant” or “newborn” or “neonatal” or “neonate” or “preterm” or “premature” or “neonatology”.

2. For thrombocytopenia, the following search terms will be used: “thrombocytopenia” or “thrombocytopenic” or “NT”.

3. For PT, the following search terms will be used: “platelet transfusion” or “platelet infusion therapy” or “platelet administration” or “PT”

4. Steps 1, 2 and 3 will be combined with “and”.

The detailed search strategy is shown in supplemental table 1.

Furthermore, we will hand-check the references of all identified trials, relevant systematic reviews, and current treatment guidelines to avoid missing important studies. Missing data will be handled by contacting relevant investigators for unreported materials or additional details.

Study eligibility

Types of studies

We will include RCTs, cohort studies, and case control studies, and exclude animal studies, in vitro studies, cross-sectional studies, case reports, case series, and secondary or tertiary articles (systematic reviews and meta-analyses).

If there are enough data to answer this review's questions using only data from RCTs, we will report only data from RCTs.

Types of participants

New-born infants with thrombocytopenia (platelet counts<150 000/μL, the diagnosis was established at less than 28 postnatal days and the follow-up time may extend to a postnatal age > 28 days) admitted to NICUs will be included. We will exclude studies of infants with congenital malformations.[14]

Types of interventions and comparators

The intervention of the included study is PT for thrombocytopenia. We will compare the effects of different transfusion platelet count thresholds. We will also record the type and dose of the platelet component received.

Types of outcomes

The primary outcome will be in-hospital mortality or bleeding episodes [including intraventricular haemorrhage (IVH), intracranial haemorrhage (ICH), pulmonary haemorrhage (PH), frank rectal bleeding, and other bleeding].

The secondary outcomes will be morbidity [including patent ductus arteriosus (PDA), sepsis, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), etc.], adverse effects of transfusion, and the length of stay (LOS).[5 14 29 37-39] The minimum length of follow-up for assessing these outcomes will be 7 days. Detailed descriptions of the definitions of the outcomes are provided in supplemental table 2.

If the studies provided both adjusted and unadjusted results, we will only present the adjusted results in the review.

Study selection

Two researchers will independently screen the titles and abstracts of the references retrieved by the searches. If eligible, the full texts of potential references will be obtained and assessed by two researchers. Studies approved by both investigators will be included in this meta-analysis. Discrepancies in inclusion and exclusion decisions will be solved with a third senior researcher. Endnote X9 software will be used to tract and manage the selection process, and a PRISMA flow diagram will be constructed to depict this process (see supplemental figure 1).

Data extraction

Structured extraction sheets (see supplemental tables 3.1-3.3) and Review Manager V.5.3 (Cochrane Collaboration, Oxford, UK) software will be used for data extraction

by two independent investigators, and disagreements will be resolved by a third senior researcher. The included data items are as follows:

1. Publication and study details: authors, year of publication, country, study design, and number of participants.

2. Clinical characteristics: gestational age (GA), birth weight (BW), platelet count before transfusion or severity of thrombocytopenia, platelet count thresholds, type and dose of platelet component, and the number of PTs.

3. Outcomes: mortality, bleeding episodes, IVH grade, NEC, BPD, ROP, sepsis, and LOS.

4. Other information: any sponsorship or funding.

Missing information will be handled by contacting relevant investigators for unreported data or additional details.

Risk of bias in individual studies

Risk of bias will be assessed by two independent reviewers, and disagreement will be resolved by a third reviewer.

For RCTs, the 'Risk of Bias Assessment Tool' in Review Manager V.5.3 software (Cochrane Collaboration, UK) will be used. This tool includes random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. The bias of the included studies will be divided into a high risk of bias, low risk of bias, or unclear risk of bias in each domain (see supplemental table 4).[40]

The Newcastle-Ottawa scale (NOS) will be used for observational studies in terms of selection, comparability, and outcome, with a minimum score of 0 and a maximum score of 9. We will grade trials with scores of 9 points as high quality and trials with scores of 1-8 points as low quality (see supplemental table 5).

Data synthesis

When the studies are sufficiently homogeneous for any of the described outcome measures, a quantitative synthesis (meta-analysis) may be performed according to the recommendations of the Cochrane handbook. If quantitative analysis cannot be performed, we will conduct a narrative systematic review of the results from the studies included, and we will not pool the data from the individual studies.

For dichotomous data (occurrence of mortality, bleeding events, morbidity, adverse events, etc.), the risk ratio (RR) will be used in the analysis of RCTs and cohort studies and the odds ratio (OR) will be used for case control studies. For continuous data (GA, BW, etc.), the mean difference (MD) or standardized mean difference (SMD) with 95% confidence intervals (CIs) will be used to represent the summary statistics of the outcome with the same units and different scales, respectively.

Assessment of heterogeneity

The chi² test (P≤0.1 indicates substantial or considerable heterogeneity) will be used to determine whether heterogeneity is statistically significant. We will also assess the degree of statistical heterogeneity by examining I^2. The data will be pooled by applying a random-effects model following $I^2 \geq 50\%$ or $P \leq 0.1$. Otherwise, the fixed-effects model will be used.

Sensitivity analysis

We will assess the robustness of the results by including or excluding the controversial studies, such as low-quality studies or studies with temporal ambiguity (whether the bleeding event occurred after PT is unknown).

Subgroup analysis

If sufficient data are identified, subgroup analyses will be performed to detect possible heterogeneity based on the following participant characteristics:

1) GA (<28 w, 28 – 32 w, 32 – 37 w, and >37 w)

2) BW (<1 000 g, 1 000 – 1 500 g, 1 500 – 2 500 g, and >2 500 g)

3) The severity of thrombocytopenia [mild (100 000 – 150 000/μL), moderate (50 000 – 100 000/μL), and severe (<50 000/μL)]

4) The platelet count thresholds for PT

5) The cause of thrombocytopenia and

6) The design of the study (RCTs and cohort studies)

We will explore the possible heterogeneity among subgroups with I^2 and P values.

Quality of the evidence

We will use the GRADE approach[36 40] to assess the quality of evidence and propose to present "Summary of findings" tables (see supplemental table 6). We will construct funnel plots and perform Egger's test to assess publication bias for each of the pooled outcomes when more than 10 included studies are available. Asymmetry may arise as a result of publication bias or of a relationship between the trial size and effect size. Egger's linear regression analysis will be performed to test for funnel plot asymmetry.

Patient and public involvement

No patients are involved.

DISCUSSION

Due to the limited number of RCTs, observational studies are a great source of potentially high-quality data. Furthermore, observational studies have additional benefits that may justify the evidence obtained from RCTs as well. We will include RCTs and observational studies in this review because of the limited number of relevant RCTs examining neonates with thrombocytopenia. We will separately combine the results of RCTs and observational studies. To the best of our knowledge, this review will be the most recent systematic review to aim to determine the best PT

threshold for neonates with thrombocytopenia who are admitted to NICUs. We expect to provide the best available evidence for neonatologists and guideline developers on PT, which will help both clinical practice and further study design.

Contributors

TX contributed to the conception of the study. The framework of the systematic review was developed by all authors. The search strategy was designed by TX and will be completed by YY and DJL, who will further independently screen the relevant records, extract data from included studies and assess the risk of bias. JLW will perform the data synthesis. TX and JT will arbitrate in cases of any disagreement and ensure that no errors occur during the study. The manuscript describing this protocol was drafted by DJL and revised by TX. All authors have approved the publication of this protocol.

Competing interests

None declared.

Patient consent

Not required.

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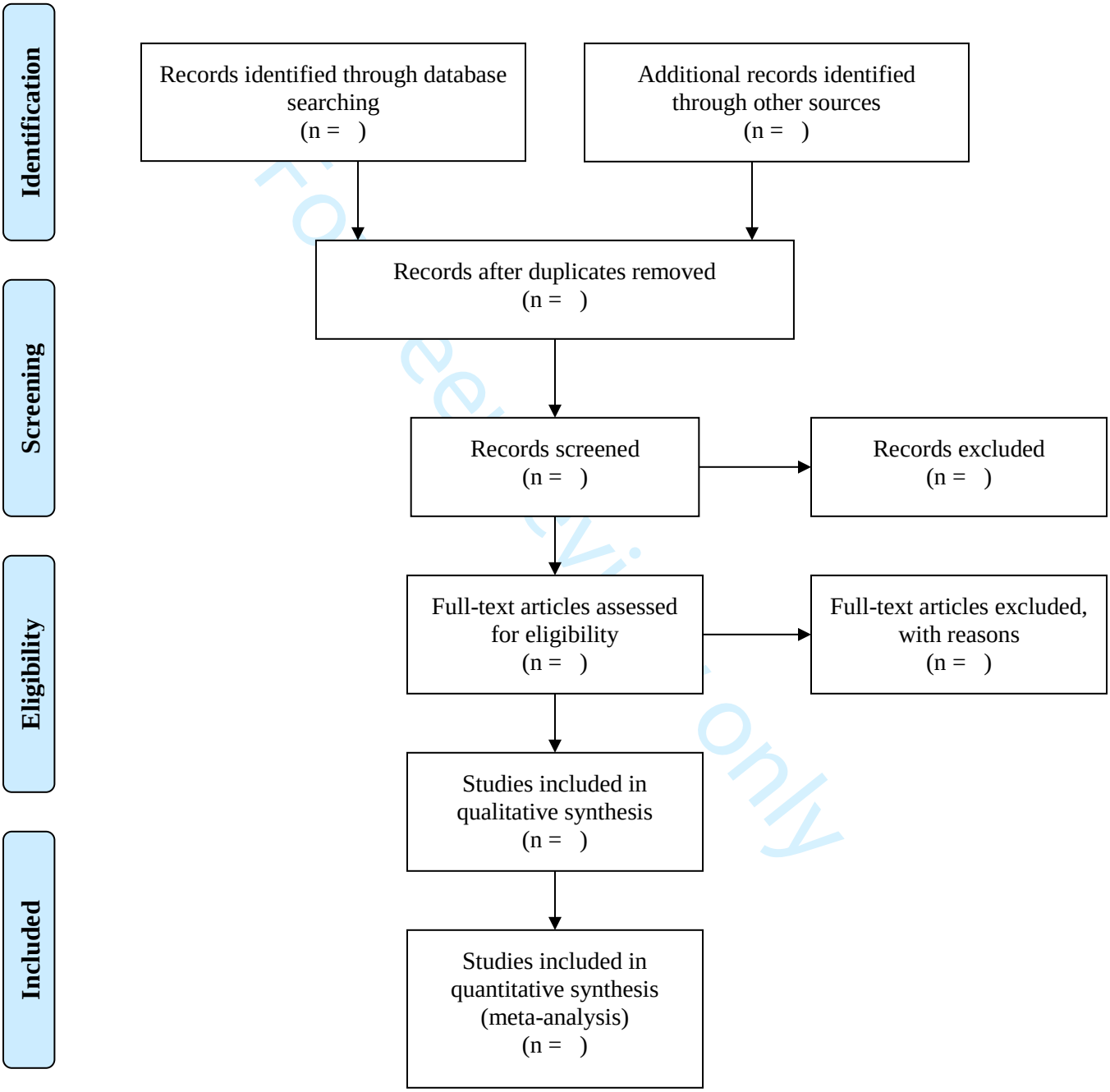
Supplemental Figure 1. Flow Diagram of Studies Selected for Inclusion in the Systematic Review (PRISMA 2009 Flow Diagram)



Supplemental Table 1. Search strategy used for the following databases: PubMed, The Cochrane Central Register of Controlled Trials and Embase.

Table 1.1 PubMed

Query	
#1	"Platelet Transfusion" [MeSH]
#2	platelet transfusion
#3	platelet transfus*
#4	platelet infusion therapy
#5	platelet infus*
#6	platelet administration
#7	platelet administrat*
#8	PT
#9	thrombocyte transfusion
#10	thrombocyte transfus*
#11	thrombocyte infusion therapy
#12	thrombocyte infus*
#13	thrombocyte administration
#14	thrombocyte administrat*
#15	"Thrombocytopenia" [MeSH]
#16	thrombocytopenia
#17	thrombocytopenic
#18	thrombocytopen*
#19	NT
#20	"Infant, Newborn" [MeSH]

#21	infant
#22	newborn
#23	neonatal
#24	neonate
#25	neonatology
#26	neonat*
#27	preterm
#28	premature
#29	prematur*
#30	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#31	#15 or #16 or #17 or #18 or #19
#32	#20 or #21 or #22 or #22 or #23 or #24 or #25 or #26 or #26 or #27 or #28 or #29
#33	#30 and #31 and #32 Filters: Humans

Table 1.2 The Cochrane Central Register of Controlled Trials

Query	
#1	MeSH descriptor: [Platelet Transfusion] explode all trees
#2	(platelet transfusion): ti, ab, kw (word variations have been searched)
#3	(platelet transfus*): ti, ab, kw (word variations have been searched)
#4	(platelet infusion): ti, ab, kw (word variations have been searched)
#5	(platelet infus*): ti, ab, kw (word variations have been searched)
#6	(platelet administration): ti, ab, kw (word variations have been searched)
#7	(platelet administrat*): ti, ab, kw (word variations have been searched)
#8	(PT): ti, ab, kw (word variations have been searched)
#9	(thrombocyte transfusion): ti, ab, kw
#10	(thrombocyte transfus*): ti, ab, kw
#11	(thrombocyte infusion therapy): ti, ab, kw
#12	(thrombocyte infus*): ti, ab, kw
#13	(thrombocyte administration): ti, ab, kw
#14	(thrombocyte administrat*): ti, ab, kw
#15	MeSH descriptor: [Thrombocytopenia] explode all trees
#16	(thrombocytopenia): ti, ab, kw (word variations have been searched)
#17	(thrombocytopenic): ti, ab, kw (word variations have been searched)
#18	(thrombocytopeni*): ti, ab, kw (word variations have been searched)
#19	(NT): ti, ab, kw (word variations have been searched)
#20	MeSH descriptor: [Infant, Newborn] explode all trees
#21	(infant): ti, ab, kw
#22	(newborn): ti, ab, kw

#23	(neonatal): ti, ab, kw
#24	(neonate): ti, ab, kw
#25	(neonatology): ti, ab, kw
#26	(neonat*): ti, ab, kw
#27	(preterm): ti, ab, kw
#28	(premature): ti, ab, kw
#29	(prematur*): ti, ab, kw
#30	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#31	#15 or #16 or #17 or #18 or #19
#32	#20 or #21 or #22 or #22 or #23 or #24 or #25 or #26 or #26 or #27 or #28 or #29
#33	#30 and #31 and #32 in Trials

Table 1.3 Embase

Query	
#1	'thrombocyte transfusion'/exp
#2	'thrombocyte transfusion'
#3	thrombocyte transfus*
#4	'thrombocyte infusion therapy'
#5	thrombocyte infus*
#6	'thrombocyte administration'
#7	thrombocyte administrat*
#8	'platelet transfusion'/exp OR 'platelet transfusion'
#9	platelet transfus*
#10	'platelet infusion therapy'
#11	platelet infus*
#12	'platelet administration'
#13	platelet administrat*
#14	pt
#15	'thrombocytopenia'/exp
#16	'thrombocytopenia'
#17	thrombocytopenic
#18	thrombocytopen*
#19	nt
#20	'newborn'/exp
#21	infant
#22	newborn

#23	neonatal
#24	neonate
#25	neonatology
#26	neonat*
#27	preterm
#28	premature
#29	prematur*
#30	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#31	#15 or #16 or #17 or #18 or #19
#32	#20 or #21 or #22 or #22 or #23 or #24 or #25 or #26 or #26 or #27 or #28 or #29
#33	#32 AND ('clinical article'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'clinical trial topic'/de OR 'cohort analysis'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'feasibility study'/de OR 'human'/de OR 'human experiment'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'observational study'/de OR 'open study'/de OR 'outcomes research'/de OR 'phase 2 clinical trial'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de OR 'retrospective study'/de)

Supplemental Table 2. Definitions of outcome measures

Outcome measures	Definitions
IVH	The presence of blood inside the ventricles on CT or cranial ultrasonography. Grading of IVH (as described by J. Volpe): -Grade I: Bleeding confined to the periventricular area (germinal matrix) -Grade II: Intraventricular bleeding (10-50% of the ventricular area on a sagittal view) -Grade III: Intraventricular bleeding (>50% of the ventricular area or distends the ventricle) -Intra-parenchymal echodensity (IPE) represents periventricular haemorrhagic infarction and is often referred to as Grade IV IVH.
ICH	The presence of blood within the skull on CT or cranial ultrasonography.
PH	The presence of frank tracheal blood and multi-lobular opacity on chest X-rays.
Frank rectal bleeding	Macroscopic faecal bleed.
PDA	The ductus arteriosus remains open on the echocardiography or associated Doppler studies.
BPD	Treated with more than 21% oxygen for at least 28 days.
Sepsis	A bacterial bloodstream infection (blood culture-proven infection).
NEC	At least one clinical finding (bilious gastric aspirate or emesis, abdominal distension, or occult or gross blood in the stool in the absence of anal fissures) and at least one radiographic finding (pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum).
ROP	Diagnosed by the ophthalmologist according to the International Classification of Retinopathy of Prematurity, first published in 1985 and revised in 2005.

IVH: intraventricular haemorrhage; CT: computed tomography; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity.

Supplemental Table 3.1 Data extraction sheet for RCTs

Publication and study details						
Authors						
Year of publication						
Country						
Study design						
Number of participants						
Groups	Experimental platelet count threshold (*10^{-3} per cubic millimeter)			Control platelet count threshold (*10^{-3} per cubic millimeter)		
Clinical characteristics						
	Experimental median (or mean)	Experimental IQR (or SD)	Experimental total	Control median (or mean)	Control IQR (or SD)	Control total
GA (w)						
BW (g)						
Platelet count (*10^{-3} per cubic millimeter)						
Number of platelet transfusions						
Primary outcomes						
	Experimental event	Experimental total	Control event	Control total		
In-hospital mortality or major bleeding events						
Bleeding episodes						
IVH						
ICH						
PH						
Frank rectal bleeding						
Other bleeding						
Secondary outcomes						
Major morbidity						

	Experimental event	Experimental total	Control event	Control total
PDA				
BPD				
Sepsis				
NEC				
ROP				

Other outcome measures						
LOS (days)	Experimental median (or mean)	Experimental IQR (or SD)	Experimental total	Control median (or mean)	Control IQR (or SD)	Control total

Adverse effects of transfusion	Experimental event	Experimental total	Control event	Control total

Other information	
Type and dose of platelet component	
Any sponsorship or funding	

IQR: interquartile range; SD: standard deviation; GA: gestational age; BW: birth weight; IVH: intraventricular haemorrhage; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; LOS: length of stay

Supplemental Table 3.2 Data extraction sheet for cohort studies

Publication and study details									
Authors									
Year of publication									
Country									
Study design									
Number of participants									
Groups	Group 1 platelet count threshold (*10^{-3} per cubic millimetre)			Group 2 platelet count threshold (*10^{-3} per cubic millimetre)			Group N platelet count threshold (*10^{-3} per cubic millimetre)		
Clinical characteristics									
	Group 1 median (or mean)	Group 1 IQR (or SD)	Group 1 total	Group 2 median (or mean)	Group 2 IQR (or SD)	Group 2 total	Group N median (or mean)	Group N IQR (or SD)	Group N total
GA (w)									
BW (g)									
Platelet count (*10^{-3} per cubic millimetre)									
Number of platelet transfusions									

Primary outcomes						
	Group 1 event	Group 1 total	Group 2 event	Group 2 total	Group N event	Group N total
In-hospital mortality or major bleeding events						
Bleeding episodes						
IVH						
ICH						
PH						
Frank rectal bleeding						
Other bleeding						

Secondary outcomes									
Major morbidity									
	Group 1 event		Group 1 total	Group 2 event		Group 2 total	Group N event		Group N total
PDA									
BPD									
Sepsis									
NEC									
ROP									
Other outcome measures									
LOS (days)	Group 1 median (or mean)	Group 1 IQR (or SD)	Group 1 total	Group 2 median (or mean)	Group 2 IQR (or SD)	Group 2 total	Group N median (or mean)	Group N IQR (or SD)	Group N total
Adverse effects of transfusion	Group 1 event		Group 1 total	Group 2 event		Group 2 total	Group N event		Group N total
Other information									
Type and dose of platelet component									
Any sponsorship or funding									

IQR: interquartile range; SD: standard deviation; GA: gestational age; BW: birth weight; IVH: intraventricular haemorrhage; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; LOS: length of stay

Supplemental Table 3.3 Data extraction sheet for case control studies

Publication and study details						
Authors						
Year of publication						
Country						
Study design						
Number of participants						
Groups	Exposed group platelet count threshold (*10^{-3} per cubic millimetre)			Unexposed group platelet count threshold (*10^{-3} per cubic millimetre)		
Clinical characteristics						
	Exposed group median (or mean)	Exposed group IQR (or SD)	Exposed group total	Unexposed group median (or mean)	Unexposed group IQR (or SD)	Unexposed group total
GA (w)						
BW (g)						
Platelet count (*10^{-3} per cubic millimetre)						
Number of platelet transfusions						
Primary outcomes						
	Exposed group event	Exposed group total	Unexposed group event	Unexposed group total		
In-hospital mortality or major bleeding events						
Bleeding episodes						
IVH						
ICH						

PH				
Frank rectal bleeding				
Other bleeding				
Secondary outcomes				
Major morbidity				
	Exposed group event	Exposed group total	Unexposed group event	Unexposed group total
PDA				
BPD				
Sepsis				
NEC				
ROP				
Other outcome measures				

LOS (days)	Exposed group median (or mean)	Exposed group IQR (or SD)	Exposed group total	Unexposed group median (or mean)	Unexposed group IQR (or SD)	Unexposed group total

Adverse effects of transfusion	Exposed group event	Exposed group total	Unexposed group event	Unexposed group total

Other information	
Type and dose of platelet component	
Any sponsorship or funding	

IQR: interquartile range; SD: standard deviation; GA: gestational age; BW: birth weight; IVH: intraventricular haemorrhage; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; LOS: length of stay

Supplemental Table 4. The risk of bias assessment tool for randomized controlled studies

Supplemental Table 4.1 The risk of bias table

Item	Judgement	Support for judgement
Random sequence generation (selection bias)		
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)		
Blinding of outcome assessment (detection bias)		
Incomplete outcome data addressed (attrition bias)		
Selective reporting (reporting bias)		
Other bias		

Supplemental Table 4.2 The recommended list of items in the risk of bias tool

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describes the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to the inadequate generation of a randomised sequence
	Allocation concealment	Describes the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describes all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provides any information related to	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

		whether the intended blinding was effective.	
Detection bias	Blinding of outcome assessment*	Describes all measures used, if any, to blind outcome assessments from knowledge of which intervention a participant received. Provides any information related to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describes the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. States whether attrition and exclusions were reported, the numbers in each intervention group (compared with the total number of randomised	Attrition bias due to the amount, nature, or handling of incomplete outcome data

		participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review.	
Reporting bias	Selective reporting	States how selective outcome reporting was examined and what was found.	Reporting bias due to selective outcome reporting
Other bias	Anything else, ideally prespecified	States any important concerns about bias not covered in the other domains of the tool.	Bias due to problems not covered elsewhere

*Assessments of each main outcome or class of outcomes should be performed.

Supplemental Table 4.3 Approach to formulating summary assessments of the risk of bias for each important outcome (across domains) within and across trials

Risk of bias	Interpretation	Within a trial	Across trials
Low risk of bias	Bias, if present, is unlikely to alter the results seriously	A low risk of bias for all key domains	Most information is obtained from trials at low risk of bias
Unclear risk of bias	A risk of bias that raises some doubt about the results	A low or unclear risk of bias for all key domains	Most information is obtained from trials at low or unclear risk of bias
High risk of bias	Bias may substantially alter the results	A high risk of bias for one or more key domains	The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results

Supplemental Table 5. The Newcastle-Ottawa Scale (NOS) for cohort studies and case control studies

Supplemental Table 5.1 The Newcastle-Ottawa Scale (NOS) for cohort studies

Study	Item & score							
	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort (1)	Selection of the non-exposed cohort (1)	Ascertainment of exposure (1)	Demonstration that the outcome of interest was not present at start of study (1)	Compare the ability of cohorts based on the design or analysis (2)	Assessment of outcome (1)	Was the follow-up period long enough for outcomes to occur (1)	Adequacy of the follow-up of cohorts (1)

Supplemental 5.2 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE FOR COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars are possible for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____(describe) in the community ✸
   b) somewhat representative of the average _____(describe) in the community ✸
   c) selected group of users, e.g., nurses and volunteers
   d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a) secure record (e.g., surgical records) ✸
   b) structured interview ✸
   c) written self-report
   d) no description

4) Demonstration that the outcome of interest was not present at the start of the study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts based on the design or analysis
   a) study controls for _____(select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate a specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blinded assessment ✸
   b) record linkage ✸
   c) self-report
   d) no description

2) Was the follow-up period long enough for outcomes to occur
   a) yes (selected an adequate follow-up period for the outcome of interest) ✸
   b) no

3) Adequacy of the follow-up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow-up, unlikely to introduce bias - small number lost - >____ % (select an adequate %) follow-up, or description provided of those individuals lost to follow-up) ✸
   c) follow-up rate < ____% (select an adequate %) and no description of those individuals lost to follow-up
   d) no statement

Supplemental Table 5.3 The Newcastle-Ottawa Scale (NOS) for case control studies

Study	Item & score							
	Selection				Comparability	Exposure		
	Is the case definition adequate? (1)	Representativeness of the cases (1)	Selection of Controls (1)	Definition of Controls (1)	Comparability of cases and controls based on the design or analysis (2)	Ascertainment of exposure (1)	Same method of ascertainment for cases and controls (1)	Non-response rate (1)

Supplemental 5.4 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE FOR CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars is possible for Comparability.

Selection

1) Is the case definition adequate?
a) yes, with independent validation ✸
b) yes, e.g., record linkage or based on self-reports
c) no description
2) Representativeness of the cases
a) consecutive or obviously representative series of cases ✸
b) potential for selection bias or not stated
3) Selection of Controls
a) community controls ✸
b) hospital controls
c) no description
4) Definition of Controls
a) no history of disease (endpoint)
b) no description of the source

Comparability

1) Comparability of cases and controls based on the design or analysis
a) study controls for _____ (Select the most important factor.) ✸
b) study controls for any additional factor ✸ (This criteria could be modified to indicate a specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
a) secure record (e.g., surgical records) ✸
b) structured interview where the interviewer was blinded to the case/control status ✸
c) interviewer was not blinded to the case/control status
d) written self-report or medical record only
e) no description
2) Same method of ascertainment for cases and controls
a) yes ✸
b) no
3) Non-response rate
a) same rate for both groups ✸
b) non-respondents described
c) rates differed and no designation was provided

Supplemental Table 6. The GRADE approach

Supplemental Table 6.1 The summary of findings table

Outcomes	Illustrates comparative risks (95% CI)		Relative effect (95% CI)	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Overall results
	Assumed risk Group 1	Corresponding risk Group 2				

Supplemental Table 6.2 GRADE evidence profile

Quality assessment							No. of patients		Effect	Quality
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Group 1**	**Group 2**	**Relative (95% CI)**	
Outcome 1										
Outcome 2										
Outcome 3										
Outcome 4										

Supplemental Table 6.3 Quality of evidence grades

Grade	Definition
High	We are very confident that the true effect lies is similar to the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but it may be substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

Supplemental Table 6.4 Factors that may reduce the quality of the evidence

Factor	Consequence
Limitations in the study design or execution (risk of bias)	↓ 1 or 2 levels
Inconsistency of the results	↓ 1 or 2 levels
Indirectness of the evidence	↓ 1 or 2 levels
Imprecision	↓ 1 or 2 levels
Publication bias	↓ 1 or 2 levels

Supplemental Table 6.5 Factors that may increase the quality of the evidence

Factor	Consequence
Large magnitude of effect	↑ 1 or 2 levels
All plausible confounding factors would reduce the described effect or increase the effect if no effect was observed	↑ 1 level
Dose-response gradient	↑ 1 level

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1

Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	2
Support			
Sources	#5a	Indicate sources of financial or other support for the review	1
Sponsor	#5b	Provide name for the review funder and / or sponsor	1
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-8
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	2, 8

Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8-9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

BMJ Open

Platelet Transfusion for Neonates with Thrombocytopaenia: Protocol for a Systematic Review

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Platelet Transfusion for Neonates with Thrombocytopaenia: Protocol for a Systematic Review

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ABSTRACT

Introduction

Thrombocytopaenia is one of the most common haemostatic abnormalities among neonates. It affects approximately one-quarter of neonates admitted into neonatal intensive care units (NICUs) and may lead to a high risk of bleeding and mortality, which are substantial causes for concern by neonatologists. Platelet transfusion (PT) is a specific treatment for thrombocytopaenia. To date, PT thresholds are diverse since the associations between low platelet count and negative outcomes are not clear. We propose this protocol for a systematic review to collect and assess evidence concerning the best PT threshold to reduce mortality, bleeding and major morbidity among neonates with thrombocytopaenia.

Methods and analysis

The systematic review will be performed according to the Cochrane Handbook for Systematic Review of Interventions, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Two independent researchers will perform the study selection, data extraction/coding, quality assessment and further analyses of the included studies, with disagreements being resolved by a third researcher. A systematic search of the literature will be conducted in the PubMed, Cochrane Library, and Embase databases from database inception through October 13, 2020. All randomized controlled trials (RCTs), cohort studies and case-control studies will be included without any restrictions regarding publication date or language. The primary outcomes will comprise in-hospital mortality and bleeding episodes. Endnote X9 and Review Manager V.5.3 software will be used to manage the selection process and statistical analysis, respectively. If the included studies are sufficient and homogeneous for any of the outcomes, a quantitative synthesis (meta-analysis) may be performed. Otherwise, we will conduct a narrative systematic review of the results.

Ethics and dissemination

Ethical approval is not required for this study because the data will be obtained from published studies and will not include individual patient data. The results of this study are anticipated to be published in a peer-reviewed journal.

PROSPERO registration number: CRD42020169262.

Strengths and limitations of this study

- This study will be the most recent systematic review to evaluate the PT threshold for neonates with thrombocytopaenia based on recent evidence. We will include RCTs and observational studies and separately combine the results of each study design.
- Comprehensive and extensive analyses of the outcomes, including in-hospital mortality, bleeding events, morbidity, adverse effects of transfusion, and length of stay, will be performed.
- The review will be performed according to the Cochrane Handbook and the PRISMA statement.
- Formal risk of bias analyses will be performed. The quality of evidence will be affected by the bias in original studies.
- The results of this systematic review may be helpful for both clinical decisions and further study.

BACKGROUND

Thrombocytopaenia, defined as a platelet count less than 150 000/μL, is a common haemostatic abnormality among neonates, particularly premature infants.[1 2] The aetiology of thrombocytopaenia is complicated and involves multiple factors, including abnormal immunity, infection, and asphyxia.[3-7] Thrombocytopaenia may be a sole clinical manifestation of alloimmune thrombocytopaenia or a complication of other diseases, such as intrauterine growth restriction, polycythaemia, sepsis or necrotizing enterocolitis.[3-5 8] Approximately 9.4% to 35% of neonates admitted to neonatal intensive care units (NICUs) develop thrombocytopaenia.[5 9-12] Theoretically, neonates with thrombocytopaenia may develop a high risk of bleeding and mortality. This increased risk is attributed to the important role of platelets in the whole process of haemostasis, and thrombocytopaenia may lead to dysfunctional haemostasis. Thus, this condition is a significant and unresolved problem for neonatologists.

Platelet transfusion (PT) is commonly used as a prophylactic and therapeutic treatment for bleeding episodes in neonates with thrombocytopaenia. To date, the relationship between a low platelet count and major bleeding or mortality is not clear, and the efficacy of PT remains controversial, as supported by the evidence from recent trials.[5 13-15] Current guidelines generally recommend prophylactic PT for neonates with thrombocytopaenia.[16-19] The recommended thresholds vary from 20 000/μL to 30 000/μL [15-17 20-25] for non-bleeding stable neonates, while the thresholds range from 30 000/μL to 50 000/μL[15 21 24-26] for non-bleeding unstable neonates. These guidelines are consensus guidelines rather than evidence-based guidelines.[19 27] Thus, a wide range of PT thresholds has been reported among different NICUs.[28 29]

Theoretically, compared with that at a low threshold, PT at a high threshold may reduce the risks of severe thrombocytopaenia, subsequent mortality and bleeding episodes. Surprisingly, a recent randomized controlled trial (RCT) reported that compared with PT at a low threshold, PT at a high threshold increased the mortality rate and bleeding events in preterm infants with severe thrombocytopaenia.[14] On the other hand, as an invasive therapy, PT is associated with some acknowledged adverse

events, including transfusion-transmitted infections, bacterial sepsis, febrile nonhaemolytic transfusion reaction, transfusion-associated circulatory overload, transfusion-related acute lung injury, and immune-mediated platelet destruction.[3 30-32] Furthermore, PT has a higher risk of these adverse events than transfusions of other blood products due to its pro-inflammatory function.

Recently, additional clinical trials regarding PT in neonates with thrombocytopaenia have been completed. Several reports have argued that a lower transfusion threshold may reduce the incidence of unnecessary transfusions and financial costs without the extra risks of bleeding and mortality.[13 15] We will perform this systematic review and meta-analysis to summarize current evidence for PT in neonates and assess the safety and best threshold for PT.

Objectives

We propose this protocol for a systematic review to collect and assess the evidence concerning the best threshold for PT to reduce mortality, bleeding and major morbidity among neonates with thrombocytopaenia. We will further explore the best thresholds for PT in neonates with thrombocytopaenia due to various causes and specific clinical characteristics. Furthermore, the safety of PT will be assessed by comparing its side effects at different thresholds.

METHODS AND ANALYSIS

This protocol will be conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) 2015 guidelines,[33] and a subsequent systematic review will be performed according to the Cochrane Handbook for Systematic Review of Interventions,[34] the PRISMA statement,[35] and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[36]

Data sources and search strategy

Comprehensive searches will be separately performed by two independent researchers in the PubMed, Cochrane Library, and Embase databases from database inception through October 13, 2020. No restrictions on language will be applied to the search. We will use the following keywords for the search and selection of relevant studies.

1. For neonates, the following combination of search terms will be used: “infant” or “newborn” or “neonatal” or “neonate” or “preterm” or “premature” or “neonatology”.

2. For thrombocytopaenia, the following search terms will be used: “thrombocytopaenia” or “thrombocytopaenic” or “NT”.

3. For PT, the following search terms will be used: “platelet transfusion” or “platelet infusion therapy” or “platelet administration” or “PT”.

4. Steps 1, 2 and 3 will be combined with “and”.

The detailed search strategy is shown in supplemental table 1.

Furthermore, we will manually check the references of all identified trials, relevant systematic reviews, and current treatment guidelines to avoid missing important studies. Missing data will be handled by contacting relevant investigators for unreported materials or additional details.

Study eligibility

Types of studies

We will include RCTs, cohort studies, and case-control studies and exclude animal studies, in vitro studies, cross-sectional studies, case reports, case series, and secondary or tertiary articles (systematic reviews and meta-analyses).

If enough data are available from only RCTs that will answer the questions posed by this review, we will report only data from RCTs.

Types of participants

Newborn infants with thrombocytopaenia (platelet counts<150 000/μL, the diagnosis was established at less than 28 postnatal days, and the follow-up time could extend to a postnatal age > 28 days) who were admitted to the NICU will be included. We will exclude studies of infants with congenital malformations.[14]

Types of interventions and comparators

The intervention of the included studies is PT for thrombocytopaenia. We will compare the effects of different transfusion platelet count thresholds and record the type and dose of the platelet component received.

Types of outcomes

The primary outcome will be in-hospital mortality or bleeding episodes [including intraventricular haemorrhage (IVH), intracranial haemorrhage (ICH), pulmonary haemorrhage (PH), frank rectal bleeding, and other bleeding].

The secondary outcomes will be morbidity [including patent ductus arteriosus (PDA), sepsis, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), etc.], adverse effects of transfusion, and the length of stay (LOS).[5 14 29 37-39] Detailed descriptions of the outcome measures are provided in supplemental table 2. If the data are sufficient, we will conduct additional analyses according to the severity of the outcomes (for example, severe PV–IVH (grade III or IV). The minimum length of follow-up for assessing these outcomes should include the time point for their diagnosis (for example, the follow-up for BPD should extend to 28 postnatal days). If a similar outcome measure had different follow-up times in different original studies, we will try to manage the data according to the timeline.

If the studies provide both adjusted and unadjusted results, only the adjusted results will be presented in the review.

Study selection

Two researchers will independently screen the titles and abstracts of the references retrieved by the searches. If eligible, the full texts of potential references will be obtained and assessed by the two researchers. Studies approved by both investigators will be included in this meta-analysis. Discrepancies in inclusion and exclusion decisions will be solved by a third senior researcher. Endnote X9 software will be used to track and manage the selection process, and a PRISMA flow diagram will be constructed to depict this process (see supplemental figure 1).

Data extraction

Structured extraction sheets (see supplemental tables 3.1-3.3) and Review Manager V.5.3 (Cochrane Collaboration, Oxford, UK) software will be used for data extraction by two independent investigators, and disagreements will be resolved by a third senior researcher. The included data items are as follows:

1. Publication and study details: authors, year of publication, country, study design, and number of participants.
2. Clinical characteristics: gestational age (GA), birth weight (BW), platelet count before transfusion or severity of thrombocytopaenia, platelet count thresholds, type and dose of platelet component, and the number of PTs.
3. Outcomes: mortality, bleeding episodes, IVH grade, NEC, BPD, ROP, sepsis, and LOS.
4. Other information: any sponsorship or funding.

Attempts will be made to retrieve missing information by contacting relevant investigators for unreported data or additional details.

Risk of bias in individual studies

Risk of bias will be assessed by two independent reviewers, and disagreement will be resolved by a third reviewer.

For RCTs, the 'Risk of Bias Assessment Tool' in Review Manager V.5.3 software (Cochrane Collaboration, UK) will be used. This tool includes random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. The bias of the included studies will be divided into a high risk of bias, low risk of bias, or unclear risk of bias in each domain (see supplemental table 4).[40]

The Newcastle-Ottawa scale (NOS) will be used for observational studies in

terms of selection, comparability, and outcome, with a minimum score of 0 and a maximum score of 9. Trials with scores of 9 points will be graded as high quality, and trials with scores of 1-8 points will be graded as low quality (see supplemental table 5).

Data synthesis

When the studies are sufficiently homogeneous for any of the described outcome measures, a quantitative synthesis (meta-analysis) may be performed according to the recommendations of the Cochrane Handbook. If quantitative analysis cannot be performed, a narrative systematic review of the results from the studies included will be conducted, and we will not pool the data from the individual studies.

For dichotomous data (occurrence of mortality, bleeding events, morbidity, adverse events, etc.), the risk ratio (RR) will be used in the analysis of RCTs and cohort studies, and the odds ratio (OR) will be used for case-control studies. For continuous data (GA, BW, etc.), the mean difference (MD) or standardized mean difference (SMD) with 95% confidence intervals (CIs) will be used to represent the summary statistics of the outcome with the same units or different scales, respectively.

Assessment of heterogeneity

The chi² test ($P \leq 0.1$ indicates substantial or considerable heterogeneity) will be used to determine whether heterogeneity is statistically significant. Additionally, we will assess the degree of statistical heterogeneity by examining I^2. The data will be pooled by applying a random-effects model following $I^2 \geq 50\%$ or $P \leq 0.1$. Otherwise, the fixed-effects model will be used.

Sensitivity analysis

We will assess the robustness of the results by including or excluding controversial studies, such as low-quality studies or studies with temporal ambiguity (e.g., whether

the bleeding event occurred after PT is unknown).

Subgroup analysis

If sufficient data are identified, subgroup analyses will be performed to detect possible heterogeneity based on the following participant characteristics:

1) GA (<28 w, 28 – 32 w, 32 – 37 w, and >37 w);

2) BW (<1 000 g, 1 000 – 1 500 g, 1 500 – 2 500 g, and >2 500 g);

3) the severity of thrombocytopaenia [mild (100 000 – 150 000/μL), moderate (50 000 – 100 000/μL), and severe (<50 000/μL)];

4) the platelet count thresholds for PT;

5) the cause of thrombocytopaenia; and

6) the design of the study (RCTs and cohort studies).

We will explore the possible heterogeneity among subgroups using I^2 and P values.

Quality of the evidence

We will use the GRADE approach[36 40] to assess the quality of evidence and propose to present "Summary of findings" tables (see supplemental table 6). We will construct funnel plots and perform the Egger's test to assess publication bias for each of the pooled outcomes when more than 10 included studies are available. Asymmetry may arise as a result of publication bias or a relationship between the trial size and effect size. Egger's linear regression analysis will be performed to test for funnel plot asymmetry.

Patient and public involvement

No patients will be involved.

DISCUSSION

Due to the limited number of RCTs, observational studies are a great source of

potentially high-quality data. Furthermore, observational studies have additional benefits that may justify the evidence obtained from RCTs. We will include RCTs and observational studies in this review because of the limited number of relevant RCTs examining neonates with thrombocytopaenia. We will separately combine the results of RCTs and observational studies. To the best of our knowledge, this review will be the most recent systematic review determining the best PT threshold for neonates with thrombocytopaenia who are admitted to NICUs. We expect to provide the best available evidence for neonatologists and guideline developers on PT, which will help both clinical practice and further study design.

Contributors

TX contributed to the conception of the study. The framework of the systematic review was developed by all authors. The search strategy was designed by TX and will be completed by YY and DJL, who will further independently screen the relevant records, extract data from the included studies and assess the risk of bias. JLW will perform data synthesis. TX and JT will arbitrate in cases of any disagreement and ensure that no errors occur during the study. The manuscript describing this protocol was drafted by DJL and revised by TX. All authors have approved the publication of this protocol.

Competing interests

None declared.

Patient consent

Not required.

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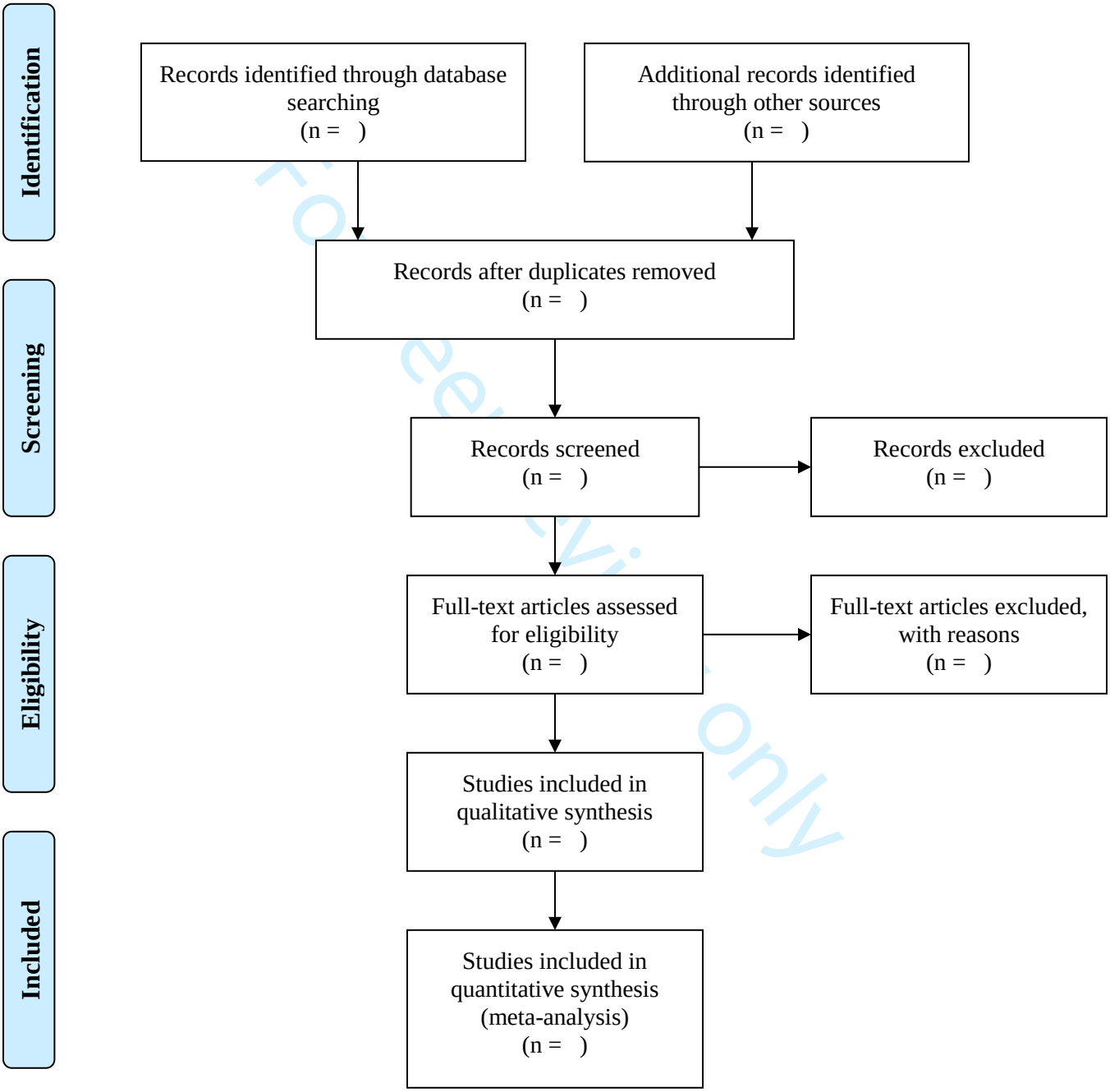
Supplemental Figure 1. Flow Diagram of Studies Selected for Inclusion in the Systematic Review (PRISMA 2009 Flow Diagram)



Supplemental Table 1. Search strategy used for the following databases: PubMed, the Cochrane Central Register of Controlled Trials and Embase

Table 1.1 PubMed

Query	
#1	"Platelet Transfusion" [MeSH]
#2	platelet transfus*
#3	platelet infus*
#4	platelet administrat*
#5	PT
#6	thrombocyte transfus*
#7	thrombocyte infus*
#8	thrombocyte administrat*
#9	"Thrombocytopenia" [MeSH]
#10	thrombocytopen*
#11	NT
#12	"Infant, Newborn" [MeSH]
#13	infant
#14	newborn
#15	neonat*
#16	preterm
#17	prematur*
#18	#1 or #3 or #4 or #5 or #6 or #7 or #8
#19	#9 or #10 or #11
#20	#12 or #13 or #14 or #15 or #16 or #17
#21	18 and #19 and #20 Filters: Humans

Table 1.2 The Cochrane Central Register of Controlled Trials

Query	
#1	MeSH descriptor: [Platelet Transfusion] explode all trees
#2	(platelet transfus*): ti, ab, kw (word variations have been searched)
#3	(platelet infus*): ti, ab, kw (word variations have been searched)
#4	(platelet administrat*): ti, ab, kw (word variations have been searched)
#5	(PT): ti, ab, kw (word variations have been searched)
#6	(thrombocyte transfus*): ti, ab, kw
#7	(thrombocyte infus*): ti, ab, kw
#8	(thrombocyte administrat*): ti, ab, kw
#9	MeSH descriptor: [Thrombocytopenia] explode all trees
#10	(thrombocytopeni*): ti, ab, kw (word variations have been searched)
#11	(NT): ti, ab, kw (word variations have been searched)
#12	MeSH descriptor: [Infant, Newborn] explode all trees
#13	(infant): ti, ab, kw
#14	(newborn): ti, ab, kw
#15	(neonat*): ti, ab, kw
#16	(preterm): ti, ab, kw
#17	(prematur*): ti, ab, kw
#18	#1 or #3 or #4 or #5 or #6 or #7 or #8
#19	#9 or #10 or #11
#20	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#21	18 and #19 and #20 in Trials

Table 1.3 Embase

Query	
#1	'thrombocyte transfusion'/exp
#2	thrombocyte transfus*
#3	thrombocyte infus*
#4	thrombocyte administrat*
#5	'platelet transfusion'/exp OR 'platelet transfusion'
#6	platelet transfus*
#7	platelet infus*
#8	platelet administrat*
#9	pt
#10	'thrombocytopenia'/exp
#11	thrombocytopen*
#12	nt
#13	'newborn'/exp
#14	infant
#15	newborn
#16	neonat*
#17	preterm
#18	prematur*
#19	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#20	#10 or #11 or #12
#21	#13 or #14 or #15 or #16 or #17 or #18
#22	#19 AND #20 AND #21 AND ('clinical article'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'clinical trial topic'/de OR 'cohort analysis'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'feasibility study'/de OR 'human'/de OR 'human experiment'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'observational study'/de OR 'open study'/de OR 'outcomes research'/de OR 'phase 2 clinical trial'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de OR 'retrospective study'/de)

Supplemental Table 2. Definitions of outcome measures

Outcome measures	Definitions	Minimum follow-up
IVH	The presence of blood inside the ventricles on CT or cranial ultrasonography Grading of IVH (as described by J. Volpe): **Grade I**: bleeding confined to the periventricular area (germinal matrix) **Grade II**: intraventricular bleeding (10-50% of the ventricular area on a sagittal view) **Grade III**: intraventricular bleeding (>50% of the ventricular area or distends the ventricle) **Grade IV**: intra-parenchymal echodensity (IPE) represents periventricular haemorrhagic infarction and is often referred to as Grade IV IVH	3 d
ICH	The presence of blood within the skull on CT or cranial ultrasonography	3 d
PH	The presence of frank tracheal blood and multi-lobular opacity on chest X-ray	3 d
Frank rectal bleeding	Macroscopic faecal bleed	3 d
PDA	PDA: open ductus arteriosus on echocardiography or associated Doppler studies after 15 postnatal hours C**linically significant PDA was suspected** in the presence of 2 or more of the following: (1) heart murmur, (2) hyperdynamic precordium, (3) bounding pulses, (4) persistent tachycardia (>160 beats per minute), (5) wide pulse pressure, (6) new-onset or increase in ventilator requirements, (7) systemic hypoperfusion (poor pulses, prolonged capillary refill time, decreased urine output, or	3 d

	hypotension), (8) chest radiographic evidence, i.e., pulmonary congestion or cardiomegaly (a cardiothoracic ratio >60%) with increased pulmonary flow. **Echocardiographic hs-PDA** was defined as the presence of transductal diameter ≥1.5 mm at the pulmonary end plus 1 of the following: (1) left-atrium/aorta ratio ≥1.4, (2) ductal velocity <2 metres per second, (3) antegrade left pulmonary artery diastolic flow >30 centimetres per second, (4) E-wave/A-wave ratio >1, (5) isovolaemic relaxation time ≤45 milliseconds, (6) absent or reversed diastolic blood flow pattern in the descending thoracic aorta.	
BPD	Treated with more than 21% oxygen for at least 28 days; Diagnostic criteria for bronchopulmonary dysplasia (as described by National Institutes of Health): **Mild** BPD: (1) breathing room air at 36 weeks post-menstrual age or discharge (for those with GA <32 weeks) (2) breathing room air by 56 days postnatal age or discharge (for those with GA ⩾32 weeks) **Moderate** BPD: (1) need for <30% O_2 at 36 weeks post-menstrual age, or discharge (for those with GA <32 weeks) (2) need for <30% O2 to 56 days postnatal age, or discharge (for those with GA ⩾32 weeks) **Severe** BPD: (1) need for >30% O2, with or without positive pressure ventilation or continuous positive pressure at 36 weeks post-menstrual age, or discharge (for those with GA <32 weeks) (for those with GA ≥32 weeks)	28 d

	(2) need for >30% O_2 with or without positive pressure ventilation or continuous positive pressure at 56 days postnatal age, or discharge (for those with GA ≥32 weeks)	
Sepsis	A bacterial bloodstream infection (blood culture-proven infection)	7 d
NEC	At least one clinical finding (bilious gastric aspirate or emesis, abdominal distension, or occult or gross blood in the stool in the absence of anal fissures) and at least one radiographic finding (pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum) are required to secure the diagnosis. Bell's stages of necrotizing enterocolitis: **I.** Suspected disease (1) Mild systemic signs (apnoea, bradycardia, temperature instability) (2) Mild intestinal signs (abdominal distention, gastric residuals, bloody stools) (3) Non-specific or normal radiological signs **II. Definite disease** (1) Mild to moderate systemic signs (2) Additional intestinal signs (absent bowel sounds, abdominal tenderness) (3) Specific radiologic signs (pneumatosis intestinalis or portal venous air) (4) Laboratory changes (metabolic acidosis, thrombocytopaenia) **III. Advanced disease** (1) Severe systemic illness (hypotension) (2) Additional intestinal signs (striking abdominal distention, peritonitis) (3) Severe radiological signs (pneumoperitoneum) (4) Additional laboratory changes (metabolic and respiratory acidosis, disseminated intravascular	7 d

	coagulopathy)	
ROP	Diagnosed by the ophthalmologist according to the International Classification of Retinopathy of Prematurity, first published in 1985 and revised in 2005.	28 d

IVH: intraventricular haemorrhage; CT: computed tomography; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; PDA: patent ductus arteriosus; hs-PDA: haemodynamically significant patent ductus arteriosus; BPD: bronchopulmonary dysplasia; GA: gestational age; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity

Supplemental Table 3.1 Data extraction sheet for RCTs

Publication and study details						
Authors						
Year of publication						
Country						
Study design						
Number of participants						
Groups	Experimental platelet count threshold (*10^3/μL)			Control platelet count threshold (*10^3/μL)		
Clinical characteristics						
	Experimental median (or mean)	Experimental IQR (or SD)	Experimental total	Control median (or mean)	Control IQR (or SD)	Control total
GA (w)						
BW (g)						
Platelet count (*10^{-3} per cubic millimeter)						
Number of platelet transfusions						
Primary outcomes						
	Experimental event	Experimental total		Control event	Control total	
In-hospital mortality or major bleeding events						
Bleeding episodes						
IVH						
ICH						
PH						
Frank rectal bleeding						
Other bleeding						
Secondary outcomes						
Major morbidity						
	Experimental	Experimental		Control event	Control total	

	event	total		
PDA				
BPD				
Sepsis				
NEC				
ROP				

Other outcome measures						
LOS (days)	Experimental median (or mean)	Experimental IQR (or SD)	Experimental total	Control median (or mean)	Control IQR (or SD)	Control total

Adverse effects of transfusion	Experimental event	Experimental total	Control event	Control total

Other information	
Type and dose of platelet component	
Any sponsorship or funding	

IQR: interquartile range; SD: standard deviation; GA: gestational age; BW: birth weight; IVH: intraventricular haemorrhage; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; LOS: length of stay

Supplemental Table 3.2 Data extraction sheet for cohort studies

Publication and study details									
Authors									
Year of publication									
Country									
Study design									
Number of participants									
Groups	Group 1 platelet count threshold (*10^3/μL)			Group 2 platelet count threshold (*10^3/μL)			Group N platelet count threshold (*10^3/μL)		
Clinical characteristics									
	Group 1 median (or mean)	Group 1 IQR (or SD)	Group 1 total	Group 2 median (or mean)	Group 2 IQR (or SD)	Group 2 total	Group N median (or mean)	Group N IQR (or SD)	Group N total
GA (w)									
BW (g)									
Platelet count (*10^{-3} per cubic millimetre)									
Number of platelet transfusions									
Primary outcomes									
	Group 1 event		Group 1 total	Group 2 event		Group 2 total	Group N event		Group N total
In-hospital mortality or major bleeding events									
Bleeding episodes									
IVH									
ICH									
PH									
Frank rectal bleeding									
Other bleeding									
Secondary outcomes									

Major morbidity						
	Group 1 event	Group 1 total	Group 2 event	Group 2 total	Group N event	Group N total
PDA						
BPD						
Sepsis						
NEC						
ROP						

Other outcome measures									
LOS (days)	Group 1 median (or mean)	Group 1 IQR (or SD)	Group 1 total	Group 2 median (or mean)	Group 2 IQR (or SD)	Group 2 total	Group N median (or mean)	Group N IQR (or SD)	Group N total

Adverse effects of transfusion	Group 1 event	Group 1 total	Group 2 event	Group 2 total	Group N event	Group N total

Other information	
Type and dose of platelet component	
Any sponsorship or funding	

IQR: interquartile range; SD: standard deviation; GA: gestational age; BW: birth weight; IVH: intraventricular haemorrhage; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; LOS: length of stay

Supplemental Table 3.3 Data extraction sheet for case-control studies

Publication and study details		
Authors		
Year of publication		
Country		
Study design		
Number of participants		
Outcome measure[a]		
Clinical characteristics		
	Case	**Control**
GA (w)		
BW (g)		
Platelet count (*10^3/μL)		
Platelet transfusion		
Platelet transfusion threshold 1 (*10^3/μL)[b]		
Platelet transfusion threshold 2 (*10^3/μL)[b]		
Number of platelet transfusions		
Other information		
Type and dose of platelet component		
Any sponsorship or funding		

a The outcome measure to distinguish the case and the control groups include: in-hospital mortality or bleeding episodes [including intraventricular haemorrhage (IVH), intracranial haemorrhage (ICH), pulmonary haemorrhage (PH), frank rectal bleeding, and other bleeding], morbidity [including patent ductus arteriosus (PDA), sepsis, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), etc.] and adverse effects of transfusion.

b If the different platelet transfusion thresholds cannot be obtained, we will record only "platelet transfusion" or "without platelet transfusion".

Supplemental Table 4. The risk of bias assessment tool for randomized controlled studies

Supplemental Table 4.1 The risk of bias table

Item	Judgement	Support for judgement
Random sequence generation (selection bias)		
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)		
Blinding of outcome assessment (detection bias)		
Incomplete outcome data addressed (attrition bias)		
Selective reporting (reporting bias)		
Other bias		

Supplemental Table 4.2 The recommended list of items in the risk of bias tool

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describes the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to the inadequate generation of a randomised sequence
	Allocation concealment	Describes the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describes all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provides any information related to	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

		whether the intended blinding was effective.	
Detection bias	Blinding of outcome assessment*	Describes all measures used, if any, to blind outcome assessments from knowledge of which intervention a participant received. Provides any information related to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describes the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. States whether attrition and exclusions were reported, the numbers in each intervention group (compared with the total number of randomised	Attrition bias due to the amount, nature, or handling of incomplete outcome data

		participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review.	
Reporting bias	Selective reporting	States how selective outcome reporting was examined and what was found.	Reporting bias due to selective outcome reporting
Other bias	Anything else, ideally prespecified	States any important concerns about bias not covered in the other domains of the tool.	Bias due to problems not covered elsewhere

*Assessments of each main outcome or class of outcomes should be performed.

Supplemental Table 4.3 Approach to formulating summary assessments of the risk of bias for each important outcome (across domains) within and across trials

Risk of bias	Interpretation	Within a trial	Across trials
Low risk of bias	Bias, if present, is unlikely to alter the results seriously	A low risk of bias for all key domains	Most information is obtained from trials at low risk of bias
Unclear risk of bias	A risk of bias that raises some doubt about the results	A low or unclear risk of bias for all key domains	Most information is obtained from trials at low or unclear risk of bias
High risk of bias	Bias may substantially alter the results	A high risk of bias for one or more key domains	The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results

Supplemental Table 5. The Newcastle-Ottawa Scale (NOS) for cohort studies and case control studies

Supplemental Table 5.1 The Newcastle-Ottawa Scale (NOS) for cohort studies

Study	Item & score							
	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort (1)	Selection of the non-exposed cohort (1)	Ascertainment of exposure (1)	Demonstration that the outcome of interest was not present at start of study (1)	Compare the ability of cohorts based on the design or analysis (2)	Assessment of outcome (1)	Was the follow-up period long enough for outcomes to occur (1)	Adequacy of the follow-up of cohorts (1)

Supplemental 5.2 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE FOR COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars are possible for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____(describe) in the community ✸
   b) somewhat representative of the average _____(describe) in the community ✸
   c) selected group of users, e.g., nurses and volunteers
   d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort ✸
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a) secure record (e.g., surgical records) ✸
   b) structured interview ✸
   c) written self-report
   d) no description

4) Demonstration that the outcome of interest was not present at the start of the study
   a) yes ✸
   b) no

Comparability

1) Comparability of cohorts based on the design or analysis
   a) study controls for _____(select the most important factor) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate a specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blinded assessment ✸
   b) record linkage ✸
   c) self-report
   d) no description

2) Was the follow-up period long enough for outcomes to occur
   a) yes (selected an adequate follow-up period for the outcome of interest) ✸
   b) no

3) Adequacy of the follow-up of cohorts
   a) complete follow up - all subjects accounted for ✸
   b) subjects lost to follow-up, unlikely to introduce bias - small number lost - >____ % (select an adequate %) follow-up, or description provided of those individuals lost to follow-up) ✸
   c) follow-up rate < ____% (select an adequate %) and no description of those individuals lost to follow-up
   d) no statement

Supplemental Table 5.3 The Newcastle-Ottawa Scale (NOS) for case control studies

Study	Item & score							
	Selection				Comparability	Exposure		
	Is the case definition adequate? (1)	Representativeness of the cases (1)	Selection of Controls (1)	Definition of Controls (1)	Comparability of cases and controls based on the design or analysis (2)	Ascertainment of exposure (1)	Same method of ascertainment for cases and controls (1)	Non-response rate (1)

Supplemental 5.4 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE FOR CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars is possible for Comparability.

Selection

1) Is the case definition adequate?
a) yes, with independent validation ✸
b) yes, e.g., record linkage or based on self-reports
c) no description
2) Representativeness of the cases
a) consecutive or obviously representative series of cases ✸
b) potential for selection bias or not stated
3) Selection of Controls
a) community controls ✸
b) hospital controls
c) no description
4) Definition of Controls
a) no history of disease (endpoint)
b) no description of the source

Comparability

1) Comparability of cases and controls based on the design or analysis
a) study controls for _____ (Select the most important factor.) ✸
b) study controls for any additional factor ✸ (This criteria could be modified to indicate a specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
a) secure record (e.g., surgical records) ✸
b) structured interview where the interviewer was blinded to the case/control status ✸
c) interviewer was not blinded to the case/control status
d) written self-report or medical record only
e) no description
2) Same method of ascertainment for cases and controls
a) yes ✸
b) no
3) Non-response rate
a) same rate for both groups ✸
b) non-respondents described
c) rates differed and no designation was provided

Supplemental Table 6. The GRADE approach

Supplemental Table 6.1 The summary of findings table

Outcomes	Illustrates comparative risks (95% CI)		Relative effect (95% CI)	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Overall results
	Assumed risk Group 1	Corresponding risk Group 2				

Supplemental Table 6.2 GRADE evidence profile

Quality assessment							No. of patients		Effect	Quality
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Group 1**	**Group 2**	**Relative (95% CI)**	
Outcome 1										
Outcome 2										
Outcome 3										
Outcome 4										

Supplemental Table 6.3 Quality of evidence grades

Grade	Definition
High	We are very confident that the true effect lies is similar to the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but it may be substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

Supplemental Table 6.4 Factors that may reduce the quality of the evidence

Factor	Consequence
Limitations in the study design or execution (risk of bias)	↓ 1 or 2 levels
Inconsistency of the results	↓ 1 or 2 levels
Indirectness of the evidence	↓ 1 or 2 levels
Imprecision	↓ 1 or 2 levels
Publication bias	↓ 1 or 2 levels

Supplemental Table 6.5 Factors that may increase the quality of the evidence

Factor	Consequence
Large magnitude of effect	↑ 1 or 2 levels
All plausible confounding factors would reduce the described effect or increase the effect if no effect was observed	↑ 1 level
Dose-response gradient	↑ 1 level

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1

Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	2
Support			
Sources	#5a	Indicate sources of financial or other support for the review	1
Sponsor	#5b	Provide name for the review funder and / or sponsor	1
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	7-8
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6-7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	2, 8

Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8-9
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11