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Heparin for the treatment of thrombosis in neonates (Review)

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[Intervention Review]

Heparin for the treatment of thrombosis in neonates

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ABSTRACT

Background

Among pediatric patients, newborns are at highest risk of developing thromboembolism. Neonatal thromboembolic (TE) events may consist of both venous and arterial thromboses and often iatrogenic complications (eg, central catheterization). Treatment guidelines for pediatric patients with TE events most often are extrapolated from the literature regarding adults. Options for the management of neonatal TE events include expectant management; nitroglycerin ointment; thrombolytic therapy or anticoagulant therapy, or a combination of the two; and surgery. Since the 1990s, low molecular weight heparin (LMWH) has become the neonatal anticoagulant of choice. Reasons for its appeal include predictable dose response, no need for venous access, and limited monitoring requirements. The overall major complication rate is around 5%. Whether preterm infants are at increased risk is unclear. No data are available on the frequency of osteoporosis, heparin-induced thrombocytopenia (HIT), or other hypersensitivity reactions in children and neonates exposed to LMWH.

Objectives

To assess whether heparin treatment (both unfractionated heparin [UFH] and LMWH) reduces mortality and morbidity rates in preterm and term newborn infants with diagnosed thrombosis. The intervention is compared with placebo or no treatment. Also, to assess the safety of heparin therapy (both UFH and LMWH) for potential harms.

Subgroup analyses were planned to examine gestational age, birth weight, mode of thrombus diagnosis, presence of a central line, positive family history for genetic disorders (thrombophilia, deficiency of protein S and protein C, methylenetetrahydrofolate reductase [MTHFR] mutation), route of heparin administration, type of heparin used, and location of thrombus (see "Subgroup analysis and investigation of heterogeneity").

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 4), MEDLINE via PubMed (1966 to May 9, 2016), Embase (1980 to May 9, 2016), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to May 9, 2016). We searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomized controlled trials and quasi-randomized trials**.**

Selection criteria

Randomized, quasi-randomized, and cluster-randomized controlled trials comparing heparin versus placebo or no treatment in preterm and term neonates with a diagnosis of thrombosis.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group. Two review authors independently assessed studies identified by the search strategy for inclusion.

Main results

Our search strategy yielded 1160 references. Two review authors independently assessed all references for inclusion. We found no completed studies and no ongoing trials for inclusion.

Authors' conclusions

We found no studies that met our inclusion criteria and no evidence from randomized controlled trials to recommend or refute the use of heparin for treatment of neonates with thrombosis.

PLAIN LANGUAGE SUMMARY

Heparin for treatment of the neonate with thrombosis (blood clot formation)

Review question: In newborn infants with evidence of thrombosis (blood clot formation), does administration of heparin improve survival and other important outcomes?

Background: Among pediatric patients, newborns are at highest risk of thrombosis owing to differences in the neonatal hemostatic system (the system that helps bleeding to stop). Abnormal blood clot formation might start in an artery (blood going away from the heart) or in a vein (blood going toward the heart). Different management strategies have been described, ranging from "wait and see" to active management aimed at dissolving clots (fibrinolytic) and preventing clot formation (anticoagulant). Possible side effects of active management include secondary bleeding. However, in some cases, thrombosis can be a life-threatening event requiring active management. Despite limited evidence on anticoagulant treatment in neonates, heparin has become a standard therapy. Current recommendations and dosing regimens for anticoagulative treatment are based on uncontrolled studies and have been adapted from data derived from reports on adult and pediatric patients. The evidence is current to May 2016.

Study characteristics and results: We included no studies in this review, and we identified no ongoing studies.

BACKGROUND

Description of the condition

Owing to unique peculiarities in development of the neonatal hemostatic system, newborns are at highest risk of developing thromboembolism among pediatric patients (Andrew 1995; Chalmers 2006; Stein 2004). The incidence of neonatal thromboembolic (TE) events is variable, ranging from 2.4 to 6.8 events per 1000 neonatal intensive care unit (NICU) admissions (Schmidt 1995; van Elteren 2011a). Other studies report a similar incidence of 5.1 events per 100,000 live births (Nowak-Göttl 1997).

Thromboembolic events may consist of both venous and arterial thromboses. Arterial thromboses (AT) account for nearly 50% of all TE episodes. With few exceptions, AT are iatrogenic complications that occur secondary to catheterization of the umbilical artery, the femoral artery, and peripheral arteries (Monagle 2012). The other form of arterial thrombosis is perinatal arterial ischemic stroke, which occurs at an incidence of between 1 in 1600 and 1 in 5000 live births (Laugesaar 2007; Raju 2007). It has been suggested that perinatal arterial ischemic stroke is more frequent among preterm infants, but this might merely reflect the routine use of cranial ultrasonography in these newborns (Benders 2007). The wide range of reported incidences may be explained by differences in the definition and diagnosis of perinatal arterial ischemic stroke. Both short-term and long-term outcomes depend mainly on the extent and location of the stroke. Mortality rates are low among infants who have sustained perinatal arterial ischemic stroke. The most frequently observed sequelae - in up to 50% of all infants with perinatal arterial ischemic stroke - include unilateral spastic cerebral palsy (USCP) and recurrence of seizures after the neonatal period (Rutherford 2012; van der Aa 2014).

Venous thromboses make up the remaining 50% of TE events, especially deep vein thrombosis (DVT) arising as a complication of central line positioning. When diagnosed clinically, DVT is estimated to occur as a complication in 1% of catheters used for total parenteral nutrition; rate rises to 35% when the condition is diagnosed by echocardiography, and to 75% when it is detected by venography (Thornburg 2006). Venous thromboses may involve different parts of the venous system. Renal venous thromboses account for approximately 20% of neonatal TE episodes and have been associated with males and with preterm birth (Schmidt 1995). Acute complications of renal venous thromboses consist of adrenal hemorrhage, extension of the clot into the inferior vena cava, renal failure, hypertension, and death (Lau 2007). Chronic complications include cortical or segmental infarction of the affected kidney(s), hypertension, or both. Portal vein thrombosis tends to be asymptomatic during the neonatal period (30% to 70% of the time) (Williams 2011). Nevertheless, long-term outcomes at five years might include asymptomatic left lobar atrophy of the liver, progressive hepatomegaly, or portacaval shunting due to portal hypertension (Morag 2011). Right atrial thrombosis is common among newborns with central catheters and can present as a new cardiac murmur, persistent sepsis, or cardiac failure (Cartwright 2004). The presence of patent foramen ovale may cause cerebral embolism through passage of venous thrombi into the systemic circulation (Mas 2001). Although it is a rare fatal complication, pulmonary embolism can occur. Incidence rates for neonatal cerebral sinovenous thrombosis vary greatly - from 0.6 to 12 cases per 100,000 live births (Berfelo 2010; deVeber 2001; Ramenghi 2009) - implying that the disorder often remains undiagnosed as the result of lack of awareness among clinicians to the nonspecific clinical presentation, or to the difficulty of radiologic diagnosis. Cerebral sinovenous thrombosis is a serious condition with a mortality rate of 2% to 12% and an adverse outcome in approximately 50% of cases (Raets 2013; Ramenghi 2009; Wasay 2008). Survivors often experience motor and cognitive impairments as well as epilepsy (Fitzgerald 2006; Kersbergen 2011; Ramenghi 2009; Roach 2008; Wasay 2008). Several studies have demonstrated that cerebral sinovenous thrombosis is the most frequently recognized cause of symptomatic intraventricular hemorrhage (IVH) and is associated with basal ganglia and thalamic hemorrhage in term neonates. Deep venous thrombosis can be accompanied by hemorrhage into the ventricles as a result of blockage and hypertension in the deep venous drainage system, leading to hydrocephalus (Kersbergen 2009; Wu 2002; Wu 2003).

Description of the intervention

Treatment guidelines for TE events in pediatric patients most often are extrapolated from literature on and experiences of adults. The goal of treatment is to prevent life-threatening consequences, thrombus extension and recurrence, and long-term complications, without significantly increasing the risk of bleeding. Options for the management of neonatal TE events include expectant management (observation only); nitroglycerin ointment (vasospasm); thrombolytic or anticoagulant therapy, or a combination of the two; and surgery. Expectant management is a reasonable alternative, given that recommendations and dosing regimens for anticoagulant/thrombolytic therapy in neonates are based on findings of uncontrolled studies, extrapolations from adult and pediatric data, small case series, cohort studies, or expert opinion (Monagle 2012). However, in severe cases, limb, organ, and possibly life may be threatened and antithrombotic treatment warranted after potential benefits and risks for serious complications, such as intracranial hemorrhage, have been weighed.

How the intervention might work

Treatment with unfractionated heparin (UFH) should be provided with the goal of preventing clot expansion or embolism and should be limited to patients with clinically significant thromboses. Therapy is usually continued for five to 30 days (Monagle 2012), but data are not available to support this as a recommendation. Owing to low levels of antithrombin and an increased rate of heparin clearance, neonates tend to require higher doses to achieve therapeutic levels (Male 1999). Bleeding is the major complication of UFH therapy in neonates; one study reported a 2% rate of major hemorrhage (Nowak-Göttl 1997). A common cause of fatal heparin-induced bleeding is accidental overdose most often due to erroneous selection of vial concentration. No data have been gathered so far regarding the potential risk of osteoporosis due to heparin treatment in neonates, and few cases of pediatric UFH-induced thrombosis have been reported in the literature (Murphy 1992; Sackler 1973). Heparin-induced thrombocytopenia (HIT), described in a pediatric population at rates of almost zero in unselected heparinized children to 2.3% among those in the pediatric intensive care unit (Schmugge 2002), has not been reported in neonatal newborns.

Despite limited evidence on the safety and efficacy of anticoagulant treatment in neonates, low molecular weight heparin (LMWH) (specifically enoxaparin) has since the 1990s become the neonatal

anticoagulant of choice (Malowany 2008; van Elteren 2011a). Reasons for its appeal include predictable dose response, no need for venous access, and limited monitoring requirements (Thornburg 2006). Low molecular weight heparin predominantly exerts an anti–factor Xa action with little anti–factor IIa (thrombin) activity. Although adverse effects of LMWH are considered rare, several major complications have been described (Malowany 2007; Obaid 2004; Saxonhouse 2012; van Elteren 2011b). Minor bleeding events including bruising and minor leaking at the injection site have been documented in up to 56% of cohorts (Malowany 2008). Major adverse outcomes of bleeding have included major bleeding and hematoma at the administration site; gastrointestinal bleeding; intracranial hemorrhage (one case; Streif 2003); hemorrhagic infarction (one case; Streif 2003); hemorrhagic pericardial effusion (one case; Bontadelli 2007); and compartment syndrome (one case; Obaid 2004). In each case, the plasma anti-factor Xa level was in the therapeutic range (0.5 to 1.0 units/mL). The overall major complication rate has been reported at around 5% (Malowany 2008). Whether preterm infants are at increased risk is unclear. No available data show the frequency of osteoporosis, HIT, or other hypersensitivity reactions in children and neonates exposed to LMWH. Overall, LMWH therapy has been effective in the NICU setting, and centers have reported partial or complete resolution of TE events in 59% to 100% of cases (Saxonhouse 2012).

Why it is important to do this review

One published Cochrane review examined treatment of the neonate with thrombosis (John 2005). Another Cochrane review addressed the topic of prevention of catheter-related thrombosis in children, including term and preterm neonates (Shah 2006). In contrast, the present review includes studies on the use of heparin for treatment of neonates with thrombosis because heparin is now widely used in NICUs to treat patients with this condition.

OBJECTIVES

To assess whether heparin treatment (both UFH and LMWH) reduces mortality and morbidity rates in preterm and term newborn infants with diagnosed thrombosis. The intervention is compared with placebo or no treatment. Also, to assess the safety of heparin therapy (both UFH and LMWH) for potential harms.

Subgroup analyses were planned to examine gestational age, birth weight, mode of thrombus diagnosis, presence of a central line, positive family history for genetic disorders (thrombophilia, deficiency of protein S and protein C, methylenetetrahydrofolate reductase [MTHFR] mutation), route of heparin administration, type of heparin used, and location of thrombus (see Subgroup analysis and investigation of heterogeneity).

METHODS

Criteria for considering studies for this review

Types of studies

We included prospective randomized controlled clinical trials (RCTs) and quasi-randomized trials. We included cluster-RCTs if definitions of participants and clusters were sufficiently clear.

We did not include cross-over trials.

Types of participants

Participants were newborns of any gestational age and any birth weight with arterial or venous thrombosis, including any localization and perinatal arterial ischemic stroke. Imaging modalities for the detection of thrombosis included Doppler ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) with or without magnetic resonance angiography or venography, and venography. CT and MRI are likely to provide information similar to that obtained by ultrasonography, and no additional clinical benefit is derived from the increased anesthetic risks associated with these procedures. Recommended imaging generally varies by institution and by patient and is based on availability and the clinical condition of the infant. The incidence of symptomatic cases is estimated to be only 1% to 3%, and symptoms include catheter dysfunction, hypertension, limb ischemia, mesenteric ischemia, renal dysfunction, and congestive heart failure. Signs and symptoms suggestive of a central line thrombus include persistent infection of the line, persistent thrombocytopenia, and dysfunction of the line. Therefore, we planned to include studies of newborns with a clinical or imaging diagnosis of TE (see Subgroup analysis and investigation of heterogeneity).

Types of interventions

We looked for studies comparing heparin (both UFH and LMWH) versus placebo or no treatment.

We did not include in this review studies comparing heparin with thrombolytic agents, as these comparisons have been reported elsewhere (John 2005).

We included in this review any dose, mode of administration, and duration of heparin therapy.

Types of outcome measures

Primary outcomes

- Neonatal death (during first 28 days of life)
- Failure of resolution of the thrombus on imaging within 30 days after treatment initiation
- Failure of reperfusion of an affected limb clinically (ie, failure of capillary refill time to return within two seconds, determined by Doppler ultrasonography)

Secondary outcomes

- Death during initial hospitalization (all-cause mortality)
- Cranial abnormalities seen on ultrasound: any intraventricular hemorrhage (IVH) of grade 3 or 4 according to the Papile classification (Papile 1978) with cystic periventricular leukomalacia; any intracranial bleeding (in any cerebral and cerebellar regions)
- Clinically apparent bleeding during treatment
- Failure of normalization of kidney or liver function, defined as persistent thrombocytopenia, alterations on coagulation tests, alterations in transaminase level, elevation of creatinine, microalbuminuria, proteinuria, hematuria, and electrolyte alterations. All newborns with renal or hepatic TE would be included, regardless of laboratory findings at treatment initiation

- Chronic renal failure due to renal venous thrombosis, defined by glomerular filtration rate (GFR) according to the Schwartz formula (Schwartz 1976): chronic renal insufficiency (GFR 20 to 40 mL/min/1.73 m^2), chronic renal failure (GFR 10 to 20 mL/min/1.73 m^2), and end-stage renal disease (GFR < 10 mL/min/1.73 m^2) (Kher 2002)
- Portal hypertension due to portal TE in normotensive infants at initiation of heparin treatment, defined as splenomegaly without liver disease, without reversal of portal vein flow, and without gastric/esophageal varices (Vos 1974)
- Hypertension in normotensive infants at initiation of heparin treatment, defined as blood pressure higher than the 95th centile for age, sex, and height (Task Force 1987); or as requirement for antihypertensive medication
- Hypotension in normotensive infants at initiation of heparin treatment, defined as blood pressure lower than the 5th centile for age, sex, and height (Task Force 1987)
- Discrepancy in length of limbs (mm) after TE due to umbilical catheter or central line positioning among infants with a limb thrombus at 18 months and at 36 months of age
- Duration of hospital stay (days)
- Retinopathy of prematurity: any and severe (stage 3 or greater; ICROP 1984)
- Necrotizing enterocolitis: any grade, requiring surgery, classified according to Bell (Bell 1978)
- Need for blood transfusions during initial hospitalization
- Central catheter (umbilical line or peripherally inserted central catheter) occlusion: failure to resolve an occlusion by treatment
- Central catheter (umbilical line or peripherally inserted central catheter) occlusion: after therapy in any enrolled participant
- Hydrocephalus due to cerebral sinovenous thrombosis
- Hydrocephalus due to major bleeding as an adverse effect of heparin treatment
- Major neurodevelopmental disability, that is, (1) cerebral palsy on physician assessment (yes/no); (2) developmental delay or intellectual impairment: Bayley or Griffith assessment more than two standard deviations (SD) below the mean, or intellectual impairment (IQ more than two SD below the mean); neuromotor development (Bayley Scales of Infant Development - Psychomotor Development Index (BSID PDI)) assessed in survivors; mental development (Bayley Scales of Infant Development - Mental Development Index (BSID MDI)) assessed in survivors; (3) blindness vision (< 6/60 in both eyes); or (4) sensorineural deafness requiring amplification. We will report these components of this long-term outcome for all trials that have assessed children after 18 months' chronological age. We will perform separate analyses for children aged 18 to 24 months and for those aged three to five years

Search methods for identification of studies

Electronic searches

We used criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group (see the Cochrane Neonatal Group search strategy for specialized register).

We conducted a comprehensive search that included the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 4) in the Cochrane Library; MEDLINE via PubMed (1996 to May 9, 2016); Embase (1980 to May 9, 2016); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to May 9, 2016), using the following search terms: (heparin AND (thrombosisOR thromb*)), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). We applied no language restrictions.

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; the International Trials Registry and Platform of the World Health Organization [www.whoint/ictrp/search/en/]; the ISRCTN Registry).

Searching other resources

We searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; www.whoint/ictrp/search/en/; controlled-trials.com).

Data collection and analysis

We used standard methods of the Cochrane Neonatal Review Group. Each review author independently conducted trial searches, assessed methods, and extracted data while comparing and resolving any differences found at each stage. We assessed methods regarding blinding of randomization, interventions, and outcome measurements as well as completeness of follow-up (ie, > 80%). We planned to request additional data from the authors of each study when data on important outcomes were missing or required clarification. We planned to use standardized Cochrane statistical methods. For categorical data, we planned to calculate risk ratio (RR), absolute risk difference (RD), number needed to treat for an additional beneficial outcome (NNTB), and number needed to treat for an additional harmful outcome (NNTH). For continuous data, we planned to calculate mean difference (MD) and the 95% confidence interval (CI).

Selection of studies

Two review authors (OR, MB) independently searched for eligible trials that met the inclusion criteria. Review authors screened titles and abstracts to identify potentially relevant citations. We planned to retrieve the full texts of all potentially relevant articles and to independently assess the eligibility of studies by filling out eligibility forms designed in accordance with the specified inclusion criteria. We planned to review studies for relevance on the basis of study design, types of participants, interventions provided, and outcomes measured. We planned to resolve disagreements by discussion and, if necessary, by consultation with a third review author (MGC). We planned to list studies excluded from the review in the "Characteristics of excluded studies" table along with reasons for exclusion. We planned to contact trial authors if the details of primary trials were not clear.

Data extraction and management

Two review authors (MB, OR) undertook data abstraction independently using a data extraction form developed ad hoc and integrated with a modified version of the Cochrane Effective Practice and Organisation of Care Group (EPOC) data collection checklist.

We planned to extract the following characteristics from each included study.

- Administrative details: study author(s); published or unpublished; year of publication; year in which study was conducted; details of other relevant papers cited.
- Details of the study: study design; type, duration, and completeness of follow-up (ie, > 80%); country and location of study; informed consent and ethics approval.
- Details of participants: sex, birth weight, gestational age, and number of participants.
- Details of the intervention: any type of heparin, dose, duration of therapy, and mode of administration.
- Details of outcomes: as listed above.

We planned to resolve disagreements by discussion between review authors. We planned to describe ongoing trials, when available, by detailing primary authors, research question(s), methods, and outcome measures, together with an estimated reporting date.

When any queries arose, or when we required additional data, we planned to contact trial authors. MGC planned to use Review Manager 5 software (RevMan 2014) to enter all study data.

Assessment of risk of bias in included studies

Two review authors (SZ, MB) planned to independently assess the methodological quality of all included studies. We planned to assess the risk of bias using the Cochrane "Risk of bias" tool (Higgins 2011).

We planned to appraise the following items.

- Selection bias: random sequence generation and selection bias, that is,
  - random sequence generation (biased allocation to interventions) due to inadequate generation of a randomized sequence; and
  - allocation concealment: selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment.
- Blinding of participants and personnel: performance bias due to knowledge of allocated interventions by participants and personnel during the study.
- Blinding of outcome assessment: detection bias due to knowledge of allocated interventions by outcome assessors.
- Incomplete outcome data: attrition bias due to quantity, nature, or handling of incomplete outcome data.
- Selective reporting: reporting bias due to selective outcome reporting.
- Other bias: bias due to problems not covered elsewhere in the table.

See Appendix 2 for the complete "Risk of bias" tool.

Measures of treatment effect

We followed standard methods of the Cochrane Neonatal Review Group when performing data synthesis. We planned to extract categorical data for each intervention group and to calculate risk ratios (RRs) and absolute risk differences (RDs). We planned to obtain means and standard deviations for continuous data and to perform analyses using weighted mean differences (WMDs). For each measure of effect, we planned to provide 95% confidence intervals (CIs) and to present numbers needed to treat for an additional beneficial outcome and numbers needed to treat for an additional harmful outcome (NNTB/NNTH), as appropriate.

Unit of analysis issues

We planned to describe, for each included study, observations of participants at selected time points until hospital discharge. In cluster trials, groups of individuals are randomly allocated to study arms, then outcomes are measured for individual cluster members. Under such circumstances, it is necessary to adjust results to account for the fact that individuals rather than clusters were randomized. As many cluster-randomized trials fail to report appropriate analyses, corrections for clustering are needed before they can be included in a meta-analysis.

To calculate adjusted (inflated) CIs that account for clustering, we planned to proceed to an approximate analysis as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to multiply the standard error of the effect estimate (from an analysis ignoring clustering) by the square root of the design effect. We calculated the design effect from the average cluster size and the intracluster correlation coefficient and planned to borrow intracluster correlation coefficient(s) from similar studies. If this correction was not possible, we planned to include cluster trials in the review but not in the meta-analysis.

Dealing with missing data

We planned to obtain a drop-out rate for each included study and to consider as significant a drop-out rate that was equal to or greater than the event rate of the control group. If we found a significant drop-out rate, we planned to contact study author(s) to request additional data. We planned to perform a sensitivity analysis to evaluate overall results with and without inclusion of studies with a significant drop-out rate. If a study reported outcomes only for participants completing the trial or only for participants who followed the protocol, we planned to contact study author(s) to ask them to provide additional information that would facilitate an intention-to-treat analysis; when this was not possible, we planned to perform a complete case analysis.

Assessment of heterogeneity

We planned to assess clinical heterogeneity by comparing the distribution of important participant factors (eg, age) and trial factors (eg, randomization concealment, blinding of outcome assessment, losses to follow-up, treatment type, co-interventions) across trials. We planned to assess statistical heterogeneity by examining the I^2 statistic (Higgins 2011), a quantity that describes the proportion of variation in point estimates that is due to variability across studies rather than to sampling error. We planned to interpret the I^2 statistic as described by Higgins 2003.

- < 25% – no heterogeneity.
- 25% to 49% – low heterogeneity.
- 50% to 74% – moderate heterogeneity.
- ≥ 75% – high heterogeneity.

In addition, we planned to employ a Chi^2 test of homogeneity to determine the strength of evidence showing that heterogeneity was genuine.

Assessment of reporting biases

We planned to test publication bias by using funnel plots if 10 or more clinical trials were included in the systematic review (Egger 1997; Higgins 2011).

Data synthesis

We planned to summarize all eligible studies in Review Manager 5 (RevMan 2014) and to use standard methods of the Cochrane Neonatal Review Group to synthesize data by using RRs, RDs, NNTBs, NNTHs, WMDs, and 95% CIs. We planned to perform a meta-analysis of the data from included trials by using a fixed-effect model.

Quality of evidence

We planned to use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the *GRADE Handbook* (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: neonatal death, failure of resolution of the thrombus on imaging within 30 days after treatment initiation, failure of reperfusion of an affected limb clinically, cranial ultrasound abnormalities, clinically apparent bleeding during treatment, and failure of normalization of kidney or liver function.

Two review authors planned to independently assess the quality of evidence for each of the outcomes above. We planned to consider evidence from RCTs as high quality but to downgrade the evidence one level for serious (or two levels for very serious) limitations on the basis of the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates and presence of publication bias. We planned to use the GRADEpro 2008 Guideline Development Tool to create a "Summary of findings" table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence according to one of four grades.

- High: We are very confident that the true effect lies close to that of the estimate of effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of 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.

Subgroup analysis and investigation of heterogeneity

- Gestational age (< 37 weeks vs ≥ 37 weeks)
- Birth weight (< 2500 grams vs ≥ 2500 grams)
- Mode of thrombus diagnosis: imaging studies versus clinical diagnosis
- Presence of central line versus no central line placement
- Positive family history for genetic disorders (thrombophilia, deficiency of protein S and protein C, MTHFR mutation)
- Route of heparin administration (eg, intravenous vs subcutaneous)
- UFH versus LMWH
- Location of thrombus (perinatal arterial ischemic stroke, portal venous thrombosis, renal venous thrombosis, atrial thrombosis, cerebral sinovenous thrombosis)

Sensitivity analysis

We planned to conduct sensitivity analyses to explore the effect of the methodologic quality of trials, while checking to ascertain whether studies at high risk of bias overestimated the effects of treatment.

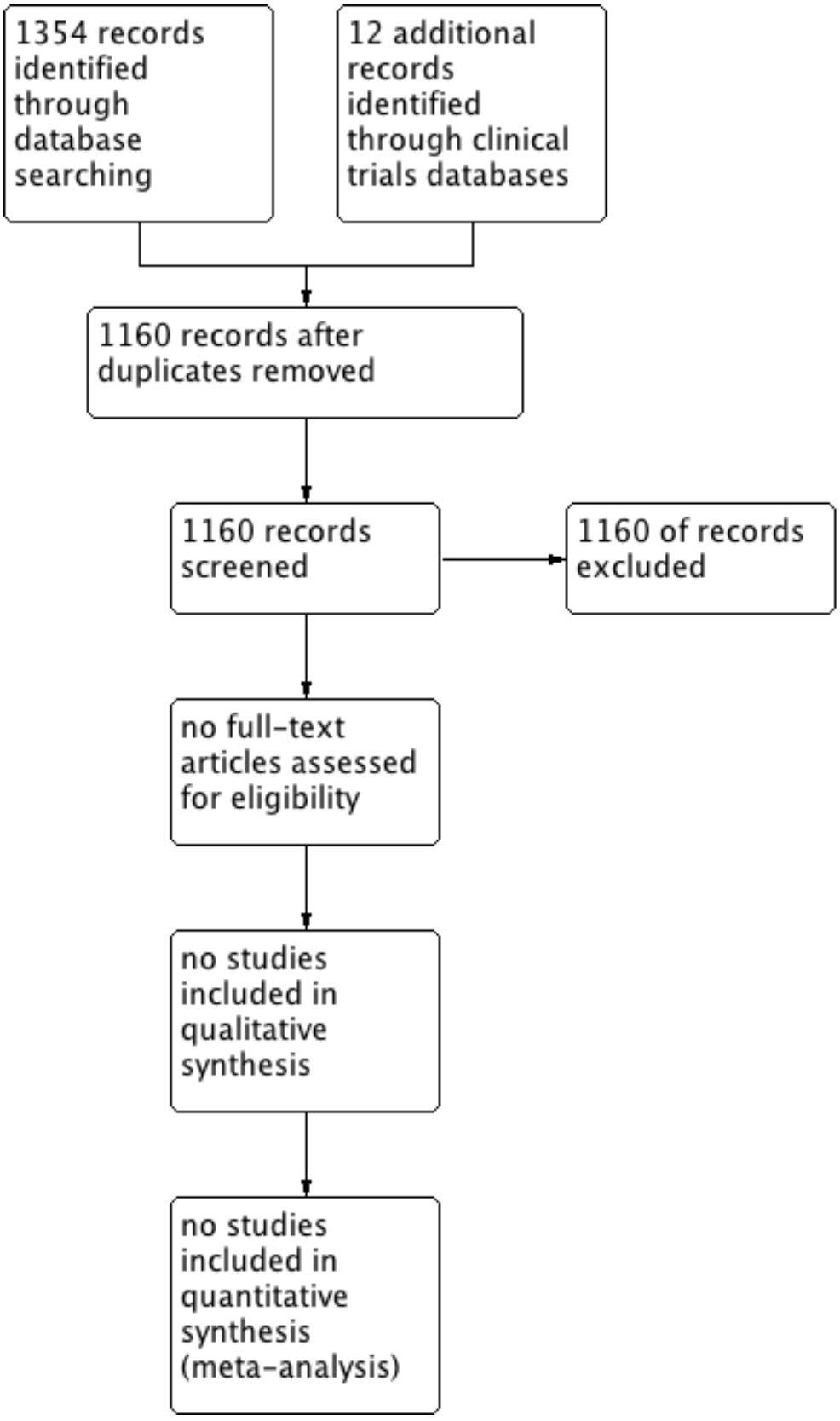
RESULTS

Description of studies

Results of the search

The literature search run in May 2016 revealed 1160 references (see Figure 1). Upon screening, we considered no trials as potentially eligible.

Figure 1. Study flow diagram.



Included studies

We identified no trials that matched our inclusion criteria and found no relevant studies on the clinical trials registries for ongoing or recently completed trials.

Excluded studies

We considered no trials as potentially eligible.

Risk of bias in included studies

No study met the eligibility criteria of this review.

Effects of interventions

No study met the eligibility criteria of this review.

DISCUSSION

Summary of main results

We identified for inclusion no eligible randomized controlled trials that examined use of heparin for the treatment of neonates with thrombosis. We found no relevant studies on the clinical trials registries for ongoing or recently completed trials.

Overall completeness and applicability of evidence

We identified no eligible trials for inclusion.

Quality of the evidence

We identified no eligible trials for inclusion.

Potential biases in the review process

We used the standard methods of the Cochrane Neonatal Review Group in conducting this systematic review. Our inclusive search strategy theoretically would have included all relevant studies. We minimized potential biases through selection of criteria for inclusion of studies in this review (see Types of interventions).

Agreements and disagreements with other studies or reviews

We have no applicable findings to report.

AUTHORS' CONCLUSIONS

Implications for practice

We found no studies that met our inclusion criteria, and hence obtained no evidence from randomized controlled trials to recommend or refute the use of heparin for treatment of neonates with thrombosis. Guidelines on antithrombotic therapy in neonates and in children published in 2012 include treatment regimen recommendations (Monagle 2012). These recommendations are based on data extrapolated from adult and pediatric patients. Authors of the guidelines raised questions regarding the weakness of existing evidence and advocated the need for a randomized controlled trial. We agree with Monagle and colleagues that randomized controlled trials are needed to evaluate the efficacy, safety, and dosage regimen of treatments. We cannot recommend or refute the use of heparin for treatment of neonates with thrombosis.

Implications for research

Randomized controlled trials are needed to evaluate the efficacy, safety, and dosage regimen of heparin for treatment of preterm and term neonates with thrombosis. Although performing an interventional study on heparin for treatment of patients with neonatal thrombosis might be challenging, ways of overcoming these difficulties have been described (Massicotte 2006), including involvement of multicenter networks of pediatric researchers and local committees that provide support such as protected time, space, resources, and recognition.

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APPENDICES

Appendix 1. Standard search methods

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. Risk of bias tool

1. Selection bias (random sequence generation and allocation concealment)

For each included study, we planned to categorize the risk of selection bias as follows.

1a. Random sequence generation

- Low risk: Investigators describe a random component in the sequence generation process such as referring to a random number table, using a computer random number generator, tossing a coin, shuffling cards or envelopes, throwing dice, drawing lots, and minimizing risk.
- High risk: Investigators describe a nonrandom component in the sequence generation process (sequence generated by odd or even date of birth, by some rule based on date or day of admission, by some rule based on hospital or clinic record number; allocation by judgment of the clinician, by preference of the participant; allocation based on results of a laboratory test or series of tests, by availability of the intervention).
- Unclear risk: No or unclear information was provided.

1b. Allocation concealment

For each included study, we planned to categorize the risk of bias regarding allocation concealment as follows.

- Low risk: Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomization), sequentially numbered drug containers of identical appearance, sequentially numbered sealed opaque envelopes.
- High risk: Participants and investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on open random allocation schedule (eg, list of random numbers), unsealed or nonopaque envelopes, alternation or rotation, date of birth, case record number.
- Unclear risk: No or unclear information was provided.

2. Blinding (performance bias)

For each included study, we planned to categorize the methods used to blind study personnel from knowledge of which intervention a participant received.

- Criteria for a judgment of "low risk of bias": No blinding or incomplete blinding occurred, but review authors judged that the outcome was not likely to be influenced by lack of blinding; blinding of participants and of key study personnel was ensured, and it was unlikely that the blinding could have been broken.
- Criteria for a judgment of "high risk of bias": No blinding or incomplete blinding occurred, and the outcome was likely to be influenced by lack of blinding; blinding of key study participants and personnel was attempted, but it was likely that blinding could have been broken, and that the outcome measurement was likely to be influenced by lack of blinding.
- Unclear risk: No or unclear information was provided.

3. Blinding (detection bias)

For each included study, we planned to categorize the methods used to blind outcome assessors from knowledge of which intervention a participant received.

- Criteria for a judgment of "low risk of bias": No blinding or incomplete blinding occurred, but review authors judged that the outcome was not likely to be influenced by lack of blinding; blinding of participants and of key study personnel was ensured, and it was unlikely that the blinding could have been broken.
- Criteria for a judgment of "high risk of bias": No blinding of outcome assessment occurred, and outcome measurement was likely to be influenced by lack of blinding; blinding of outcome assessment occurred, but it was likely that the blinding could have been broken, and that the outcome measurement was likely to be influenced by lack of blinding.
- Unclear risk: No or unclear information was provided.

4. Incomplete outcome data (attrition bias)

For each included study and for each outcome, we planned to describe completeness of data by including attrition and exclusions from the analysis.

- Criteria for a judgment of "low risk of bias."
  - No missing outcome data.
  - Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias).

- Missing outcome data balanced in numbers across intervention groups, with similar reasons provided for missing data across groups.
- For dichotomous outcome data, proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size.
- Missing data imputed by appropriate methods.

- Criteria for a judgment of "high risk of bias."
  - Reasons for missing outcome data likely to be related to true outcome, with imbalance in numbers or reasons for missing data across intervention groups.
  - For dichotomous outcome data, proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
  - For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
  - "As-treated" analysis done with substantial departure of the intervention received from that assigned at randomization.
  - Potentially inappropriate application of simple imputation.
- Unclear risk: no or unclear information provided.

5. Selective reporting (reporting bias),For each included study, we planned to describe how we investigated the risk of selective outcome reporting bias and what we found. We planned to try to access all protocols of included studies through clinical trials registries (clinicaltrials.gov; controlled-trials.com; who.int/ictrp) and through direct contact with study authors.

We planned to assess the methods as follows.

- Low risk: Study protocol is available and all of the study's prespecified (primary and secondary) outcomes of interest in the review have been reported in the prespecified way; or study protocol is not available but it is clear that published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
- High risk: Not all of the study's prespecified primary outcomes have been reported; one or more primary outcomes were reported via measurements, analysis methods, or subsets of data (eg, subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely, so that they could not be entered into meta-analysis; the study report failed to include results for a key outcome that would be expected to be reported for such a study.
- Unclear risk: No or unclear information was provided (the study protocol was not available).

6. Other potential sources of bias (other bias)

For each included study, we planned to describe any important concerns that we had about other possible sources of bias (eg, whether a potential source of bias was related to the specific study design used).

We planned to assess whether each study was free of other problems that could put it at risk of bias as follows.

- Low risk: The study appears to be free of other sources of bias.
- High risk: The study had at least one important risk of bias (eg, the study had a potential source of bias related to the specific study design used or was claimed to have been fraudulent or to have some other problem).
- Unclear risk: Risk of bias may be present, but information is insufficient to assess whether an important risk of bias exists; or rationale or evidence is insufficient to show that an identified problem will introduce bias.

We planned to use a "Risk of bias" graph to illustrate risk across studies.

We planned to resolve disagreements by consensus and, if necessary, by adjudication with a third review author (MGC).

CONTRIBUTIONS OF AUTHORS

OR and MB reviewed the literature and wrote the manuscript.

SZ and MGC assisted in the review of literature and in writing of the manuscript.

LAR reviewed and commented on the manuscript.

DECLARATIONS OF INTEREST

All review authors declare that they have no competing financial conflicts of interest.

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INDEX TERMS

Medical Subject Headings (MeSH)

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