Title: The Effectiveness of Interventions to Prevent Intraventricular Haemorrhage in Premature Infants: A Systematic Review and Network Meta-analysis

Short Title: Interventions to Prevent IVH: A NMA

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Abstract

Background: Intraventricular haemorrhage (IVH) is a common problem in preterm infants. It is a major cause of morbidity and mortality with life-long impacts for the child. To date, there have been many randomised controlled trials looking at interventions to prevent IVH. However, the effectiveness of interventions relative to each other is not known. Therefore, the aim of this study is to identify all the interventions which have aimed to reduce incidence of IVH, and to produce an order of effectiveness.
Methods: A search on MEDLINE, EMBASE, Emcare, and CENTRAL was performed. Randomised controlled trials which looked at neonatal interventions with a primary aim to reduce incidence of IVH in preterm infants were eligible, and inclusion was independently assessed by all three authors. The primary outcome of this study was incidence of IVH. A network meta-analysis was performed to produce a network map and surface under a cumulative ranking curve (SUCRA) to indicate the intervention's probability of being the most effective prevention of IVH.
Results: We found 2153 studies, of which 56 were eligible for inclusion. Over 8300 infants , indomethacin (90%), and magnesium (80%) had the highest probabilities of being the best interventions to prevent IVH in premature infants.
Conclusion: This is the first systematic review and network meta-analysis to compare all the neonatal interventions aiming to reduce IVH. Whilst vitamin E and indomethacin had the highest probability of being the most effective, many trials were conducted before routine use of antenatal corticosteroids and magnesium sulphate. While IVH remains a substantial cause of neonatal death and long-term disability, further randomised trials of potential treatments are needed to assess their ro444le in contemporary neonatal care, and including the most at risk, most preterm, infants. This study helps to prioritise the potential interventions requiring further research.

Key words: brain injury, intraventricular haemorrhage, premature, preterm birth,

prevention

Introduction

Intraventricular haemorrhage (IVH) is a major cause of morbidity and mortality in preterm infants, especially in those born before 32 weeks' gestation. (1) Despite being the largest cause of preterm brain injury, (2) the effectiveness and relative effectiveness of interventions to prevent IVH in preterm infants are not known.

IVH is defined as bleeding of the germinal matrix into the ventricles of the brain (3) and its incidence and severity are greater in the most premature infants. (4) In the short-term, IVH can progress to wider-spread haemorrhage, post-haemorrhagic ventricular dilatation (PVHD), obstructive hydrocephalus and parenchymal haemorrhagic infarction. (5, 6) These can lead to long-term adverse outcomes such as cerebral palsy, developmental delay, visual, hearing impairment, (7-9), and death, (10) meaning that IVH and its complications are one of the leading causes of neurological disability and mortality for premature infants. (2, 8, 11)

Preventative strategies have been based on the pathogenesis of IVH, which is predominantly due to the immaturity and fragility of the germinal matrix vasculature. (3, 12) Disturbances of cerebral blood flow and impaired cerebral autoregulation can damage fragile blood vessels in the germinal matrix, causing them to bleed. (3, 13) Premature infants are particularly vulnerable to respiratory distress and sepsis, which are amongst the many causes of cerebral blood flow disturbance. (13) However, even with the increasing usage of antenatal corticosteroids and surfactant for lung maturation, (14) the reported incidence of IVH has not consistently decreased. (15-18)

There have been many trials and reviews investigating the effectiveness of preventative interventions. (3, 8, 13) Interventions can be given antenatally to the mother, or postnatally to the infant after birth. The increased use of antenatal corticosteroids (14) following a Cochrane review (19) has greatly improved preterm survival and has also been studied as a prevention of IVH. (19-21) Other pharmacological examples for IVH prevention include indomethacin (22) and phenobarbital. (23, 24) More recently, procedural interventions such as midline head positioning, (25) delayed cord clamping, (26) and preventing transport of the neonate between hospitals (27) have also been studied. However, there are no guidelines which recommend the optimal management to prevent IVH in premature infants. There have been systematic reviews and meta-analyses of the effectiveness of one intervention, but none, to the best of the authors' knowledge, which compare them relative to each other. Additionally, results from older studies require review as they may not be relevant to modern clinical practice.

The aim of this study is the identify all the interventions trialed to reduce the incidence of IVH in premature infants and use direct and indirect comparisons to rank them in order of effectiveness.

METHODS

This systematic review and network meta-analysis has been conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) guidelines. (28)

Criteria for consideration for review

Randomised and quasi-randomised controlled trials, with a primary outcome of reducing the incidence of IVH in infants born before 37 weeks' gestation, were eligible for inclusion (Table 1). After initial searches, the remit of the analysis was restricted to interventions delivered to the infants (as opposed to antenatally to the mother). Any intervention, whether pharmacological or procedural was considered, but must have been compared to another

intervention, placebo, or usual care. Incidence of IVH must have been detected using imaging (ultrasound (US), computerised tomography or magnetic resonance imaging), or by post-mortem examination. Trials with multiple primary outcomes, of which incidence of IVH is one, were considered, but trials with composite primary outcomes were excluded. Trials conducted on animals and written in a language other than English were excluded.

Search methods and selection

A detailed search was performed on the 7th of January 2021 on MEDLINE (1946-2021), EMBASE (1947-2021), Emcare (1995-2021) and Cochrane Library Central Register of Controlled Trials (CENTRAL). Free words, medical subject headings, and the corresponding SIGN randomised controlled trial filters produced by InterTASC Information Specialists' Sub-group were used in MEDLINE and EMBASE. (29) The MEDLINE filter was used for Emcare due to the lack of a specific filter, and only free words were used to search in CENTRAL. The search was initially piloted to ensure studies that were already known to the authors were included. The search terms used are given in Appendix 1.

Duplicates of results were removed, and titles and abstracts were initially screened by SLY. Any abstracts that were uncertain were screened by ES and DO. Subsequently, the full texts of relevant studies were retrieved, and their eligibility independently reviewed by all the authors. Where disagreement regarding eligibility occurred, a collective decision was agreed upon amongst the authors.

Primary and secondary outcomes

The primary outcome of this systematic review and network meta-analysis was incidence of any IVH. Secondary outcomes include incidence of death, severe IVH (defined as IVH with ventricular dilatation (grade III) and parenchymal haemorrhage (grade IV) (30) or similar), death or IVH, and death or severe IVH.

Data extraction

Data was extracted by SLY. Data extracted included number of deaths, number of IVH, number of severe IVH (based on the criteria used in the study), the study's eligibility criteria, the years that the infants were recruited, and classification of IVH used.

The reference lists of the included studies and published systematic reviews which referenced our included studies, were reviewed to identify other relevant studies omitted from the original search. The systematic reviews were also used for comparison to validate the data extraction. Any discrepancies in the data extraction were resolved by consulting the other authors.

Risk of bias

The quality of every included study was assessed by SLY with respect to selection (randomisation and concealment bias), measurement (performance bias, blinding of radiologist), attrition (loss to follow-up) and reporting bias, based on the Cochrane Handbook for Systematic Reviews (31) and previous studies (11). A study's risk of bias was assessed as low, high, or unclear.

Statistical analysis

All analyses were performed by DO and SLY using Stata 16. A network map was created. A random-effects model using the STATA 'network' command was performed to give the risk ratios (RR) with 95% confidence intervals (CI), reported with $p < 0.05$ as the level of significance. The surface under a cumulative ranking curve (SUCRA) was calculated using a Markov Chain Monte Carlo method to measure the probability that an intervention would be

the most effective and produce a ranking of effectiveness at reducing the incidence of IVH, as well as the other secondary outcomes.

Sensitivity analysis
Two *a-priori* sensitivity analyses were performed. "High quality" excluded studies which had a high risk of bias on any quality measure, and "best practice care" was limited to studies published after 2009 after significant changes in perinatal management over the study period (antenatal corticosteroids, (32) magnesium sulphate, (33) and delayed cord clamping (34)) were presumed to be have been delivered as a standard of care.

RESULTS
After removing duplicates, 2153 publications were found in the search. Reference lists of included studies, as well as systematic reviews which referenced studies included in this review, (23, 25, 35-39) were also screened. Ninety-six full texts were evaluated in total, with 56 randomised controlled trials included in this review (Figure 1).We made one further amendment to the methodology after conducting the pilot search; a third sensitivity analysis was included ("wider search") which included studies using an intervention identified as trialled to reduce IVH (e.g. indomethacin) even when the study was performed for a different primary outcomes (e.g. closure of a patent ductus arteriosus or safety outcome). These were identified from the initial search and systematic reviews (23, 25, 35-37, 39, 40). Whilst other interventions trialled in neonatal care may report IVH as a secondary or safety outcome, they remained outside the remit of this review unless the treatment had been trailed in an eligible trial elsewhere.

Qualitative synthesis
The earliest publication date was 1981 (24) and the most recent was 2020 (41-43). There were 25 studies conducted in North America, 10 in Asia, one in Australia, 18 in Europe, and two across multiple countries. Around 8387 preterm infants were included in the analysis. The exact number is unclear due to incomplete reporting in some studies.

Intervention and Control groups
We found 13 interventions which had a primary aim to reduce IVH. There were 11 which trialled delayed cord clamping (DCC), (41, 44-53) one cord milking, (43) one erythropoietin, (54) four ethamsylate, (55-58) three gave plasma concentrates (one giving fresh frozen plasma (FFP), (59) one giving antithrombin III, (60) and one coagulation factor concentrate (61)), three ibuprofen, (62-64) 12 indomethacin, (22, 63, 65-74) one magnesium sulphate, (42) three were nursing interventions, (75-77) nine used sedation (seven phenobarbitone (24, 78-83) and two in morphine (84, 85)), one tranexamic acid, (86) one heparin, (87) and seven vitamin E. (88-94) All studies compared an intervention to placebo or usual care, apart from one which randomised three ways to ibuprofen, indomethacin and usual care. (63) Whilst the length of DCC varied from 30-120 seconds delay, all these trials used immediate cord clamping as the comparison, which was taken to be the control.

Outcome
The incidence of IVH was assessed using cranial ultrasound in 51 studies, with the remaining five not explicitly stating their method of diagnosis. (53, 61, 69, 72, 73) There were 30 studies which used the Papile grading, (22, 24, 41, 44, 46-48, 51, 54, 57-60, 62, 63, 67, 70, 71, 73, 74, 76, 80, 82-84, 86, 87, 92, 94, 95) three which used the Volpe classification, (42, 65, 77) two which used Shankaran, (64, 79) two which used Levene, (56, 81) one which

used Krishanmoorthy, (66) and one which used Kuban. (75) There were 17 which did not state which classification was used. (43, 49, 50, 52, 53, 55, 61, 69, 72, 78, 85, 88-91, 93, 96)

Risk of bias
We defined "adequate quality" as no bias domain marked as "high". Therefore, 47 studies were deemed to be of adequate quality (Table 2). A detailed quality appraisal is given in Appendix 2. Many of the studies marked as "unclear" for randomisation bias did not explicitly state the method of randomisation. However, two were rated as "high risk" for randomisation bias as they used alternate treatment allocation. (61, 82) The same two studies also had a high risk of concealment bias, along with another study which did not specify who was told the allocation of intervention. (56) The studies which had an unclear risk of concealment bias omitted the method of concealment (e.g. sealed opaque envelope) or randomisation (e.g. lottery randomisation). Often, unclear risk of detection bias was due to failure to state blinding of radiologist.

Individual study findings

Indomethacin
Indomethacin is a cyclo-oxygenase inhibitor which inhibits prostaglandin synthesis and was originally used for the closure of a patent ductus arteriosus. However, upon finding its ability to stabilises cerebral blood flow (65) and mature germinal matrix vasculature, (22) trials have been undertaken to quantify its efficacy at reducing IVH. We found seven studies which looked at reducing IVH as a primary outcome, (22, 63, 65-67, 70, 95) and three which looked at IVH secondary to incidence of patent ductus arteriosus, (71-73) reduction of prostacyclin concentration, (69) and oxygen and surfactant requirement. (74) Out of 12 studies, six found that indomethacin significantly reduced the incidence of all grades of IVH. (22, 63, 65, 67, 70, 95) However, there were concerns regarding effect of indomethacin on urine output and fluid management, (95) but these were later found not to be significant. (22)

Ibuprofen
Ibuprofen, like indomethacin, is a cyclo-oxygenase inhibitor of prostaglandin synthesis and was used for the treatment of patent ductus arteriosus. It was found to enhance cerebral blood flow autoregulation, decreasing disturbance, and thus theoretically reduces the incidence of IVH. (62, 64) Out of the three studies, one found that ibuprofen significantly reduced the incidence of IVH. (63) Kalani et al. was the only trial in this review to compare two interventions, indomethacin and ibuprofen, against standard care. They found that both interventions were effective at reducing IVH when compared to standard care (32.3% vs 6.5% vs 6.5% p=0.049), but there was no significant difference between their effectiveness. (63)

Vitamin E
Vitamin E is an antioxidant and reduces oxidative damage from oxygen free radicals. (88, 91) It was initially used to prevent retinopathy of prematurity, (94) but now has been trialled to prevent IVH. In this review, one study out of seven looked at incidence of IVH as a secondary outcome to incidence of retinopathy. (94) Incidence of IVH was significantly reduced in three studies, (90, 92, 93) but not in the other four. (88, 89, 91, 94)

Ethamsylate
Ethamsylate was initially used to reduce capillary bleeding during surgery without increasing the risk of thrombosis, (58) but has been trialled specifically as a prevention for IVH in four

studies. (55-58) It was found to significantly reduce IVH in two trials without any side effects. (55, 58)

Sedation
"Sedation" encompassed two morphine (84, 85) and seven phenobarbitone studies. (24, 78-82, 97) Reducing pain and physiological fluctuations in blood pressure has been suggested to reduce IVH. (84) One trial studied the effect of morphine on IVH as a primary outcome and found no significant reduction, (84) whereas the other, which assessed IVH as a secondary outcome, found the contrary. (85) Phenobarbitone may also ameliorate the effect of hypoxic-ischaemic brain injury, (80) and two out of the seven phenobarbitone studies found a significant difference in incidence of IVH. (24, 82)

Nursing
Nursing interventions were trialled in three studies with the primary aim of reducing IVH. (75-77) Reduction of frequent handling of the neonate (76), observational individualised care, (75) and elevated midline head position compared to flat supine position, (77) were trialled. Observational individualised care was the only study out of the three which found a significant difference in incidence of IVH (5% vs 56%, p=0.01). (75)

Magnesium
There was one study which looked at the effect on the incidence of IVH after giving magnesium sulphate postnatally. (42) Although the incidence of IVH in the intervention group was lower than in the control group, this was not statistically significant (11% vs 19% p=0.25). In this study, more mothers in the intervention group received antenatal corticosteroids, but this had no effect on the outcome either.

Fresh frozen plasma
We found three studies which gave plasma concentrate (grouped under "fresh frozen plasma (FFP)"in the tables). This included antithrombin III, (60) coagulation factor concentrate, (61) and FFP. (59) Infants often experience deficiencies in antithrombin III, and therefore supplementation was hypothesised to reduce IVH, (60) however, no significant difference was found (27.5% given antithrombin III vs 32% in placebo group). (60) Another study also found no significant difference after giving coagulation-factor concentrate consisting of factors II, VII, XI, and X. (61) However, one study gave fresh frozen plasma to those randomised to the intervention group, and found that it significantly reduced incidence of IVH (14% vs 41% p=0.022). (59)

Erythropoietin
Erythropoietin is thought to be required for neurodevelopment and has been suggested to help with repair after brain injury caused by hypoxaemia during birth, circulatory, or respiratory disorders. (54) We found one study which looked at the neuroprotective effects of erythropoietin but found no significant difference between the intervention and placebo group (19% given erythropoietin had IVH compared to 21% in placebo group). (54)

Tranexamic acid
Tranexamic acid is an inhibitor of plasminogen activators, and has been suggested to reduce fibrinolytic activity in the germinal matrix. (86) A study used tranexamic acid but did not find a statistically significant difference in incidence of IVH (44% in intervention vs 40% in control group), nor in severity. (86)

Heparin
The effect of heparin, which was routinely given to maintain umbilical catheter patency, was investigated by one study. (87) They found no significant difference in the incidence of IVH (36% given heparin had IVH vs 32% in the control group p=0.154). These infants were also routinely given vitamin K in the study.

Delayed cord clamping (DCC)
The association between DCC and IVH was investigated by 11 studies. DCC appears to increase placental blood flow to the neonate, which improves the transition from foetal to new-born life, (52) as well as stabilising blood pressure and thus reducing IVH. (44) However, there are concerns with increasing the risk of jaundice, and polycythaemia, as well as delay in commencing respiratory support, and development of hypothermia during the period of DCC. (44, 52) We found three studies which looked at incidence of IVH as a primary outcome, (41, 44, 96) and the remaining as a secondary outcome. (46-53) Delay time ranged from greater than 30 seconds, to greater than 120 seconds, and all studies compared DCC to immediate cord clamping, which ranged from immediate clamping to clamping within 20 seconds. Out of 11 studies, one found that DCC significantly reduced incidence of IVH. (46)

Cord milking
Cord milking is a method of placental transfusion which has been suggested to improve post-natal transition whilst reducing the risk of other conditions such as bronchopulmonary dysplasia. (43) However, there have been concerns regarding disturbance of cerebral blood flow and increasing the risk of cerebral haemorrhage. (43) Therefore, one study looked at the effect of cord milking on disturbance of cerebral blood flow, and incidence of IVH as a safety outcome. They found that the intervention group had a higher incidence of IVH, although this was not significant (35% vs 28% p=0.5). (43)

Quantitative synthesis
Figure 2 is the network map displaying the comparisons of the interventions which had a primary aim of reducing IVH in preterm infants. Table 3 shows the relative risk (RR) and 95% confidence interval (CI) for direct and indirect comparisons between all interventions. Three comparisons reached conventional levels of statistical significance: ibuprofen compared to vitamin E (RR 1.59 95% CI 1.01-2.51), ibuprofen compared to indomethacin (RR 1.57 95% CI 1.57), and sedation compared to vitamin E (RR 1.58 95% CI 1.10-2.26). Only 1 study reported direct evidence between interventions (indomethacin and ibuprofen) and a test for consistency and found that caution is needed when interpreting the results (p=0.05).
Table 4 and Figure 3 show the non-cumulative ranking of the interventions. The SUCRA shows that vitamin E and indomethacin have the highest probability of being the most effective intervention to prevent IVH in premature infants (0.9). This is followed by magnesium (0.8), nursing, ethamsylate and interventions grouped as FFP (0.5), DCC, erythropoietin (Epo), ibuprofen and sedation (0.4), then tranexamic acid and control (0.3), leaving heparin to be the least likely to be the best treatment (0.2).

Secondary outcomes
Vitamin E and interventions grouped as “FFP” appeared to be the most effective at reducing severe IVH. Reports of deaths were inconsistent across studies and unable to be combined into a summary analysis; however, for reducing death or IVH, heparin had the highest SUCRA of 0.5.

Sensitivity analyses
When only including "high quality" studies, interventions grouped as "FFP" were suggested to be most effective (0.9), followed by indomethacin (0.8) and then vitamin E (0.7). When only studies which presumed to have used "best practice care" were included, vitamin E and indomethacin had the highest probability of being the most effective. After including studies found in the "wider search" as well, vitamin E was most likely to be the best (0.9). However, cord milking, which was not included in the main analysis as it looked at IVH as a secondary outcome, was least likely to be the best intervention (0.2). Finally, we intended to review the effect of interventions on reducing death, but due to limited data, we were unable to run the analysis.

DISCUSSION

Study findings
This systematic review and network meta-analysis collated and compared the results of all randomised controlled trials which aimed to reduce the incidence of IVH in premature infants. In total over 8300 infants have been enrolled in trials aiming to reduce IVH but a consensus on the most effective, has yet to be achieved. The time period over which the studies were performed, and the evidence of inconsistency within the network analysis, makes drawing firm conclusions difficult.
We found that vitamin E and indomethacin were the most likely to be the best at preventing IVH. However, our sensitivity analysis shows that vitamin E became third best when only adequate quality studies were included, and fourth best when only including studies conducted with "best practice care". High attrition bias was observed in two vitamin E studies as they had incomplete data due to loss at follow-up and were therefore omitted from the "high quality" analysis. (88, 91) Whilst neither originally found that vitamin E had a significant effect on IVH incidence, nor did they have particularly large sample sizes, their omission affected the overall efficacy of vitamin E. This suggests that the evidence for vitamin E needs to be reviewed to add high quality results trialled in the modern era of neonatal medicine before it can be recommended as an intervention to prevent IVH.
Indomethacin appears to be equally as effective as vitamin E in the primary analysis and none of the trials were omitted on the grounds of poor quality. The main analysis suggested that magnesium was second most effective. Magnesium sulphate is recommended to be given to every woman at risk of preterm birth for neonatal neuroprotection in the UK(98, 99) although the mechanism through which this improves developmental outcomes is unclear [Cochrane of Mg]. This work suggests a possible role in IVH prevention, and raises the possibility that neonatal delivery of Magnesium may provide some benefit, although perhaps now limited those unable to receive it prior to birth. Further work in neonatal care may be warranted to investigate this further.
Nursing interventions fell in the middle of the ranking order. Whilst not the most effective, nursing interventions are cheap and easy to implement and concurrent delivery, alongside pharmacological interventions should be considered.
Our results suggest that heparin and cord milking were the least effective at preventing IVH, with both scoring worse than giving a placebo or usual care, and thus are not recommended to be given to preterm neonates.

Strengths and limitations
Previous meta-analyses only evaluate the efficacy of one intervention, but a strength of this study is the indirect comparison of all interventions in respect to each other to propose a

ranking order. To the best of the authors' knowledge, this is the first network meta-analysis conducted in this field. We were only able to look at neonatal interventions, excluding antenatal interventions, such as vitamin K (100, 101) and corticosteroids, (102) even though they are likely to be effective in reducing IVH. (101) Furthermore, interventions currently untrialled in randomised controlled trials were excluded. These include inter-hospital transport of neonates weighing <1500g, which has been described to increase IVH, and neonatal care bundles, which typically include several interventions, and may decrease IVH with odds ratios of 1.75 (27) and 0.42 (103) respectively; both interventions appear deliverable and modifiable. These omitted interventions may reduce IVH, potentially with little cost, but were not included in this work. Additionally, we found clinical heterogeneity between the studies. Differences included IVH classifications, inclusion of out-born infants, and inclusion of pre-existing IVH. Some studies gave open-label medications additional to the study drug, which may have also affected incidence of IVH (for example, Benson et al. was studying the effect of ethamsylate, but administered prophylactic vitamin E for retrolental fibroplasia as well (55)). Also, since there was only one direct comparison between two interventions, (63) we could also not validate indirectly calculated risk ratios. The test of consistency showed that our model may be inconsistent, in part due to the likely heterogeneity between populations enrolled, and therefore interpretation should be done with caution. Nevertheless, this systematic review and network meta-analysis has suggested an order of effectiveness of neonatal interventions to prevent IVH in preterm infants and highlighted areas which may justify further work.

Wider context

Brion et al. found that vitamin E significantly reduced the incidence of IVH (RR 0.85 95% CI 0.73-0.99), but increased the risk of sepsis (RR 1.52 95% CI 1.13-2.04) in a systematic review and meta-analysis in 2003. (37) They also found that administration intravenously did not have a significant effect on reducing IVH. Therefore, the adverse effects of vitamin E, and optimum route of administration need to be reviewed before it can be recommended as an intervention for preterm infants. Fowlie et al. also found that indomethacin significantly reduced IVH (RR 0.88 95% CI 0.80-0.98) in a meta-analysis in 2010, (39) but at present indomethacin remains unavailable in the UK for neonatal use. However, all trials of vitamin E and indomethacin, aside from one, (88) were conducted before 2000. As commented by Brion et al., very, and extremely premature infants were less likely to survive when compared to current survival data, and magnesium sulphate and antenatal corticosteroids were not yet routinely used. Therefore, more up to date research is required due to increased survival at lower gestational ages and adoption of antenatal corticosteroids and magnesium sulphate. Temporal trends of preterm birth have not decreased, however there is a recent move towards offering active management to infants at lower gestational ages, with many developed countries now adopting guidelines of active management consideration from 22 weeks gestational age and resulting increase in IVH. (16) Since the incidence of IVH is closely linked with prematurity and is commonly associated with death in the neonatal period, it is important to continue research into its prevention. IVH is one of the largest causes of childhood disability, (2) and long-term neurodevelopmental consequences impact the child's entire life. (8) Cognitive, visual, hearing, and motor consequences affect the child's readiness for school, (104, 105) school performance, and job attainment. (106) Additionally, childhood disability could affect social outcomes such as intimate relationships, moving out of the family home, as well as financial and personal independence. Therefore, continuing research into the prevention of IVH is required.

Conclusion

IVH is one of the largest causes of childhood disability in the UK, and its prevention is paramount given the significant social, medical, and economic effects on the individual, family, and society. This review has found that many interventions have been trialled to prevent IVH. The results from this study suggest that IVH may be effectively prevented with vitamin E or indomethacin when given postnatally, although neither of these medications have been trialled recently in the modern era of neonatal care. Therefore, more up to date research is required to quantify their effectiveness now, and to evaluate their impact on long-term childhood outcomes.

Conflict of Interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions
Conception: DO and ES. Design: DO, ES, and SLY. Collection of data: SLY. Assembly, analysis, and interpretation of data: SLY, DO, ES. Drafting article: SLY. Reviewing, and editing of article: DO, ES, SLY.

Funding
No specific funding was obtained for this work.

Acknowledgments
Si Liang Yao would like to thank Delyth Morris (Cardiff University Library Service) for her advice on literature searching for systematic reviews

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Table 1. The population, intervention, control, and outcomes for consideration for review

Types of studies	Randomised and quasi-randomised controlled trials that have investigated the effectiveness of an intervention (compared to another, or to a placebo) to reduce the incidence of IVH were included. Trials must have been published in a peer-reviewed journal. Trials conducted on animals and written in a language other than English were excluded.
Population	Infants born before 37 weeks' gestation or with a birth weight of less than 1500 grams. Infants diagnosed with a coagulation disorder were excluded.
Interventions	Any intervention with the primary aim to reduce intraventricular haemorrhage in preterm infants were included. The intervention could have been given or performed antenatally, perinatally or neonatally.
Control	Comparisons to another intervention, a placebo, or usual care.
Outcome	Trials must have had the primary outcome as incidence of IVH, of any grade, identified by imaging (ultrasound, computerised tomography, or by magnetic resonance imaging) or post-mortem examination. Studies where IVH is one of multiple outcomes were considered, however, composite outcomes which include IVH were excluded. Trials with incidence of IVH as a secondary outcome were excluded as IVH is unlikely to have been investigated or discussed sufficiently, and to reduce the number of studies included.

Table 2. Risk of bias of all included studies.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of clinicians (performance bias)	Blinding of outcome (detection bias)	Incomplete data (attrition bias)	Selective reporting (reporting bias)
Als, 1994	?	-	?	-	-	-
Anand, 2004	-	-	?	-	+	?
Anwar, 1986	?	?	?	?	-	-
Bada, 1989	-	?	-	-	-	-
Bada, 1990	?	?	?	-	-	-
Bandstra, 1988	?	-	-	-	-	-
Barekatain, 2018	?	?	-	?	+	?
Bedard, 1984	-	-	?	-	-	-
Benson, 1986	-	?	-	?	-	-
Beverley 1985	?	-	-	?	-	-
Chang, 1997	-	?	?	-	-	-
Chiswick, 1983	?	?	-	-	-	-
Chiswick, 1989	?	-	?	?	-	-
Dani, 2005	-	-	-	-	-	-
Donn, 1981	-	-	?	-	-	-
Duley, 2018	-	-	-	-	-	-
Elborne, 1994	-	+	?	-	+	?
Fauchere, 2015	-	-	-	?	-	?
Fish, 1990	?	?	?	-	+	?
Fulia, 2003	-	-	?	?	?	?
Hanigan, 1988	-	-	-	?	-	-
Hemmati, 2020	?	?	-	-	+	?
Hensey, 1984	?	?	-	?	-	-
Kalani, 2016	?	?	?	?	-	-
Kazemi, 2017	?	?	-	?	-	-
Kochan, 2019	-	?	-	-	-	-
Kuban, 1986	-	-	?	?	-	-
Ment, 1985	-	?	-	-	-	?
Ment, 1988	-	?	-	-	-	-
Ment, 1994	-	?	-	-	-	-
Mohammadzadeh, 2020	?	?	-	-	-	?
Morgan, 1981	?	-	-	?	-	-
Morgan, 1982	+	+	?	-	-	-
Ruth, 1988	-	-	?	-	?	-
Sanghvi, 1999	?	-	?	-	-	?
Sinha, 1987	?	-	?	?	-	-
Speer, 1984	?	?	-	-	-	-
van Overmeire, 2004	-	?	-	?	-	-
Waltl, 1973	+	+	+	?	-	-
Whitelaw, 1983	?	?	?	-	-	-
Studies which had IVH as a secondary outcome						
Armanian, 2017	?	?	-	?	?	-
Backes, 2016	-	-	-	-	+	-
Courser, 1996	?	?	-	?	-	-
El-Naggar, 2020	-	-	?	-	-	-
Krueger, 1987	?	?	-	?	-	-
Kugelman, 2007	?	-	-	?	-	-
Mahony, 1985	?	-	-	?	-	-
Mercer, 2003	?	-	-	?	-	-
Mercer, 2006	-	?	-	-	-	-
Oh, 2011	?	?	?	?	-	-

Phelps, 1987	?	-	-	?	-	-
Ranjit, 2015	-	-	-	?	?	-
Rennie, 1986	?	?	-	?	-	-
Simons, 2003	?	?	?	?	-	-
Tarnow-Mordi, 2017	?	?	-	+	?	-
Yaseen, 1997	?	?	-	?	-	-

- = low risk, ? = unclear risk, and + = high risk of bias

Table 3. Network meta-analysis for comparisons between all trialled interventions to reduce IVH in preterm infants. A lower RR suggests the intervention is better at reducing IVH than its comparator.

	DCC	Epo	Eth	FFP	Hep	Ibu	Indo		Mag	Nur	Sed	TXA	VitE	Cont
Cont	0.91 (0.59-1.41)	0.98 (0.57-1.68)	0.85 (0.64-1.11)	0.88 (0.42-1.84)	1.18 (0.61-2.28)	0.95 (0.65-1.40)	0.61 (0.46-0.81)		0.62 (0.25-1.51)	0.85 (0.58-1.24)	0.95 (0.73-1.24)	1.10 (0.61-2.00)	0.60 (0.47-0.77)	1
VitE	1.51 (0.92-2.51)	1.63 (0.90-2.96)	1.41 (0.97-2.05)	1.47 (0.68-3.20)	1.96 (0.97-3.97)	**1.59 (1.01-2.51)**	1.01 (0.69-1.48)		1.02 (0.40-2.61)	1.41 (0.89-2.23)	**1.58 (1.10-2.26)**	1.83 (0.96-3.50)	1	
TXA	0.83 (0.40-1.73)	0.89 (0.40-2.00)	0.77 (0.40-1.48)	0.80 (0.31-2.07)	1.07 (0.44-2.60)	1.07 (0.44-2.60)	0.55 (2.09-1.07)		0.56 (0.19-1.64)	0.77 (0.38-1.56)	0.86 (0.45-1.65)	1		
Sed	0.96 (0.58-1.59)	1.04 (0.57-1.88)	0.89 (0.62-1.29)	0.93 (0.43-2.04)	1.24 (0.61-2.52)	1.24 (0.61-2.52)	0.64 (0.45-0.93)		0.65 (0.26-1.65)	0.90 (0.57-1.40)	1			
Nur	1.07 (0.60–1.91)	1.16 (0.60-2.23)	1.00 (0.63-1.58)	1.04 (0.45-2.39)	1.39 (0.65-2.97)	1.39 (0.65-2.97)	0.72 (0.45-0.93)		0.73 (0.27-1.93)	1				
Mag	1.48 (0.54-4.01)	1.59 (0.56-4.54)	1.38 (0.54-3.52)	1.44 (0.45-4.59)	1.92 (0.63-5.84)	1.92 (0.63-5.84)	0.99 (0.39-2.54)		1					
Indo	1.49 (0.89-4.01)	1.61 (0.88-2.96)	1.39 (0.95-2.04)	1.45 (0.66-3.21)	1.94 (0.95-3.96)	**1.57 (1.00-2.46)**	1							
Ibu	0.95 (0.54-1.70)	1.03 (0.53-2.00)	0.89 (0.56-1.41)	0.93 (0.40-2.13)	1.24 (0.58-2.46)	1								
Hep	0.77 (0.35-1.70)	0.83 (0.36-1.95)	0.72 (0.35-1.47)	0.75 (0.28-2.10)	1									
FFP	1.03 (0.44-2.43)	1.11 (0.42-2.75)	0.96 (0.44-2.10)	1										
Eth	1.07 (0.64-1.80)	1.16 (0.63-2.12)	1											
Epo	0.93 (0.46-1.86)	1												
DCC	1													

Comparisons between interventions should be read with the intervention (x axis) first (e.g. the RR of incidence of IVH when using indomethacin compared to vitamin E is 1.01 (95% CI 0.69-1.48))

Bolded numbers reached statistical significance.

DCC = delayed cord clamping; Epo = erythropoietin; Eth = ethamsylate; FFP = fresh frozen plasma; Hep = heparin; Ibu = ibuprofen; Ind = indomethacin; Mag = magnesium; Nur = nursing; Sed = sedation; TXA = tranexamic acid; VitE = vitamin E; Cont = control.

Table 4. Surface under the cumulative ranking curve (SUCRA) for the primary, secondary and sensitivity analyses.

Rank	Treatment													
	Control	DCC	Epo	Eth	FFP	Hep	Ibu	Ind	Mag	Nur	Sed	TXA	VitE	Cord
Primary outcome														
IVH	0.3	0.4	0.4	0.5	0.5	0.2	0.4	0.9	0.8	0.5	0.4	0.3	0.9	N/A
Secondary outcomes														
Severe IVH	0.3	0.6	0.2	0.6	0.8	0.4	0.4	0.7	0.7	0.7	0.2	0.3	0.8	N/A
Death or IVH	0.5	N/A	N/A	N/A	N/A	0.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Death or Severe IVH	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sensitivity analyses														
High quality	0.2	0.5	N/A	0.5	0.9	0.2	0.4	0.8	0.6	0.5	0.4	N/A	0.7	N/A
Best practice care	0.3	N/A	0.3	N/A	N/A	N/A	0.8	0.8	N/A	0.2	N/A	N/A	0.6	N/A
Wider Search	0.3	0.5	0.4	0.6	0.5	0.3	0.4	0.8	0.8	0.6	0.5	0.3	0.9	0.2

Values closer to 1 (or 100%) suggests greater efficacy of the intervention to reduce the incidence of intraventricular haemorrhage in preterm infants.
DCC = delayed cord clamping; Epo = erythropoietin; Eth = ethamsylate; FFP = fresh frozen plasma; Hep = heparin; Ibu = ibuprofen; Ind = indomethacin; Mag = magnesium; Nur = nursing; Sed = sedation; TXA = tranexamic acid; VitE = vitamin E; Cont = control; Cord = cord milking; N/A = not available; SUCRA = surface under the cumulative ranking curve); Sev IVH = severe IVH.

Figure 1. PRISMA flowchart

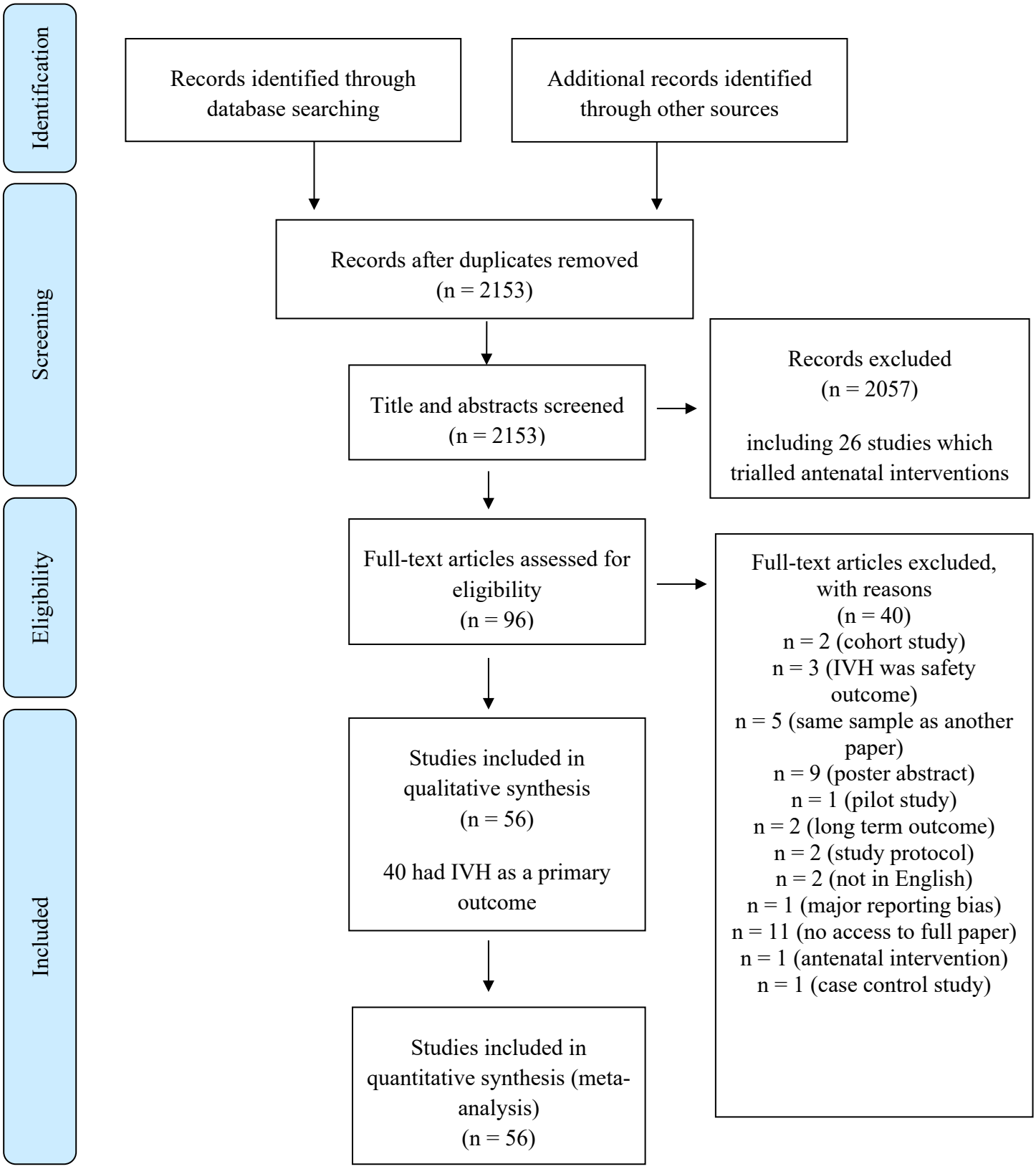
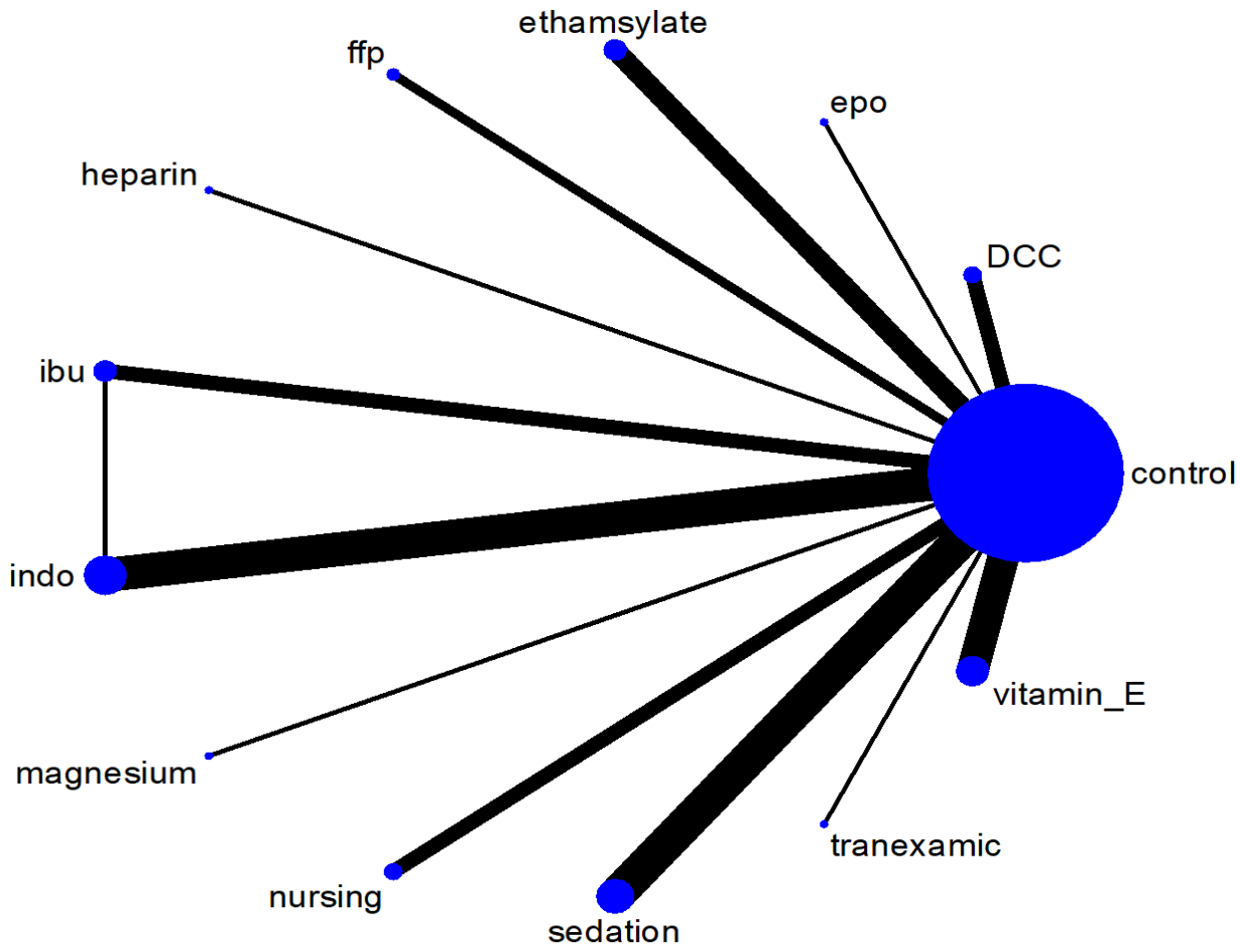


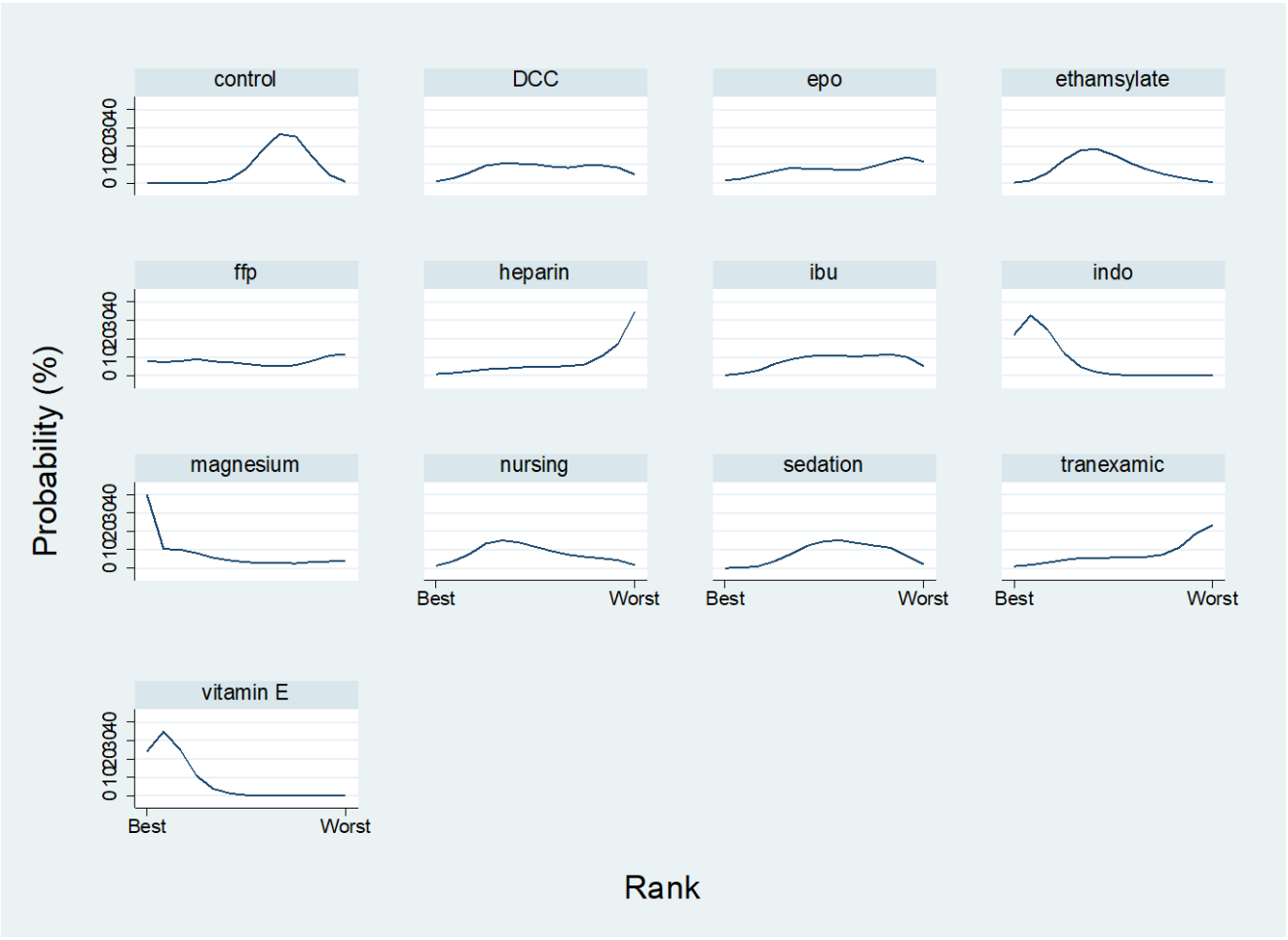
Figure 2. Network map. Comparisons of interventions which had a primary aim of reducing intraventricular haemorrhage in preterm infants.



DCC = delayed cord clamping; Epo = erythropoietin; Eth = ethamsylate; FFP = fresh frozen plasma; Hep = heparin; Ibu = ibuprofen; Ind = indomethacin; Mag = magnesium; Nur = nursing; Sed = sedation; TXA = tranexamic acid; VitE = vitamin E.

Node size corresponds to the number of studies in reporting this intervention while line thickness is proportional to the number of studies comparing the two interventions.

Figure 3. Non-cumulative ranking curves.



DCC = delayed cord clamping; Epo = erythropoietin; Eth = ethamsylate; FFP = fresh frozen plasma; Hep = heparin; Ibu = ibuprofen; Ind = indomethacin; Mag = magnesium; Nur = nursing; Sed = sedation; TXA = tranexamic acid; VitE = vitamin E.

Supplementary Material

Supplementary Table 1. Non-cumulative probabilities of an intervention being the most effective prevention of intraventricular haemorrhage in preterm infants.

Rank	Treatment													
	Cont	DCC	Epo	Eth	FFP	Hep	Ibu	Ind	Mag	Nur	Sed	TXA	VitE	Cord
Best	0.0	1.0	1.5	0.8	7.8	0.9	0.2	22.2	39.8	1.4	0.0	1.0	24.0	N/A
2nd	0.0	1.0	1.5	0.3	7.8	0.9	0.2	22.2	39.8	1.4	0.0	1.0	24.0	N/A
3rd	0.0	5.7	4.5	5.4	7.8	2.4	2.7	25.2	10.0	7.5	0.9	3.0	24.8	N/A
4th	0.0	9.5	6.6	12.6	9.0	3.5	6.3	12.4	8.2	13.3	3.7	4.4	10.7	N/A
5th	0.4	10.7	8.2	17.9	7.6	3.9	8.8	4.8	5.6	15.1	7.8	5.5	3.7	N/A
6th	2.2	10.6	7.7	18.5	7.3	4.4	10.5	1.9	4.1	14.0	12.2	5.4	12.3	N/A
7th	7.9	10.2	7.8	15.3	6.4	5.1	11.2	0.6	3.3	11.5	14.7	5.8	0.4	N/A
8th	18.2	9.0	7.2	10.9	5.5	4.9	10.8	0.3	2.8	9.2	15.0	6.1	0.1	N/A
9th	26.6	8.4	7.0	7.5	5.0	5.2	10.5	0.1	2.7	7.2	13.6	6.1	0.0	N/A
10th	25.2	9.6	9.2	5.0	5.6	6.1	11.1	0.0	2.5	6.1	12.2	7.4	0.0	N/A
11th	14.2	9.6	11.9	3.2	8.1	10.4	11.6	0.0	3.4	5.4	11.0	11.3	0.0	N/A
12th	4.6	8.4	14.1	1.6	10.8	17.3	10.0	0.0	3.7	1.6	2.1	23.4	0.0	N/A
Worst	0.7	4.7	11.8	0.5	11.7	34.7	5.2	0.0	3.7	1.6	2.1	23.4	0.0	N/A

DCC = delayed cord clamping; Epo = erythropoietin; Eth = ethamsylate; FFP = fresh frozen plasma; Hep = heparin; Ibu = ibuprofen; Ind = indomethacin; Mag = magnesium; Nur = nursing; Sed = sedation; TXA = tranexamic acid; VitE = vitamin E; Cont = control; Cord = cord milking; N/A = not available.

Supplementary Table 2. Summary of included studies and the author's judgement of their risk of bias.

IVH investigated as a primary outcome

Als, 1994

Methods	Randomised controlled trial
Participants	Inborn infants, either <1250g or born 24-30 weeks' gestation
Intervention	Specialised care which consisted of specially trained nurses who observed and documented infants' behaviour and gave individualised care, and psychologists advised on developmental care
Comparison	Usual care
Primary outcome	Medical observations, medical conditions, incidence of IVH (Kuban) by CUS, neurodevelopmental outcome.

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Used a random assignment procedure
Concealment bias	Low	Allocation sequence was in a sealed envelope
Performance bias	Unclear	Nurses may have acted different as they could not be blinded
Detection bias	Low	Radiologist was blinded when assessing US
Attrition bias	Low	Low loss-to-follow up
Reporting bias	Low	None

Anand, 2004

Methods	Randomised controlled trial
Participants	Infants born between 23-32 weeks' gestation
Intervention	Morphine
Comparison	Placebo
Primary outcome	Composite outcome of neonatal death, severe IVH, or PVL (but were reported separately as well)

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Automated telephone response, stratified by gestational week
Concealment bias	Low	Automated telephone response
Performance bias	Unclear	Can visibly see infant is sedated
Detection bias	Low	Radiologist was unaware of assignment
Attrition bias	High	Different outcomes had different number of participants, so has some missing data.
Reporting bias	Unclear	Different outcomes had a different number of participants, so has some missing data.

Anwar, 1986

Methods	Randomised controlled trial
Participants	Preterm infants <1500g
Intervention	Phenobarbital
Comparison	Usual care
Outcomes	Incidence of IVH (unclear classification) using CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Says randomly allocated but does not say how
Concealment bias	Unclear	Does not specify
Performance bias	Unclear	No placebo so they know which infants are in control group
Detection bias	Unclear	Did not say radiologist was blinded
Attrition bias	Low	All infants were accounted for
Reporting bias	Low	None

Bada, 1989

Methods	Randomised controlled trial
Participants	Infants weighing <1500g
Intervention	Indomethacin
Comparison	Placebo
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Block randomisation
Concealment bias	Unclear	Unclear whether blocks were different sizes
Performance bias	Low	No reason for performance bias
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Bada, 1990

Methods	Randomised controlled trial
Participants	Preterm infants <1500g
Intervention	Reduced manipulation
Comparison	Standard care
Primary outcome	Incidence of IVH (Papile) by CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomly allocated but does not say how
Concealment bias	Unclear	Does not specify concealment

Performance bias	Unclear	Nurses were not blinded. In discussion, some said they were biased to its benefits
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Bandstra, 1988

Methods	Randomised controlled trial
Participants	Preterm infants 500-1300g
Intervention	Indomethacin
Comparison	Placebo
Primary outcomes	Incidence of IVH (modified Volpe) CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Low	Enveloped but did not say opaque
Performance bias	Low	Drugs looked the same
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Barekatain, 2018

Methods	Randomised controlled trial
Participants	Infants <30 weeks' gestation
Intervention	Vitamin E
Comparison	Placebo
Primary outcome	Incidence of IVH (classification unclear) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Unclear	Does not specify
Performance bias	Low	Did not appear to have a reason to have a risk of performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	High	Number of participants do not add up so must be some lost to follow-up
Reporting bias	Unclear	Numbers do not add up

Bedard, 1984

Methods	Randomised controlled trial
Participants	Infants <37 weeks' gestation
Intervention	Phenobarbital
Comparison	Placebo

Primary outcomes	Incidence of IVH (Shankaran) on CUS

Risk of bias	Author's judgement	Justification
Randomisation bias	Low	Used card deck
Concealment bias	Low	Card deck
Performance bias	Unclear	Clinician could tell whether baby is sedated
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Benson, 1986

Methods	Randomised controlled trial
Participants	Infants <1500g
Intervention	Ethamsylate
Comparison	Placebo
Primary outcomes	Incidence of IVH (classification unclear) on CUS

Risk of bias	Author's judgement	Justification
Randomisation bias	Low	Block randomisation
Concealment bias	Unclear	Did not specify
Performance bias	Low	Placebo, drugs looked the same
Detection bias	Unclear	Did not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Beverley, 1985

Methods	Randomised controlled trial
Participants	Infants <1500g or born before 32 weeks' gestation
Intervention	Fresh frozen plasma
Comparison	Placebo
Primary outcomes	Coagulation studies, incidence of IVH (Papile) on CUS

Risk of bias	Author's judgement	Justification
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Low	Sealed envelope
Performance bias	Low	No reason to have a risk of performance bias
Detection bias	Unclear	Did not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Chang, 1997

Methods	Randomised controlled trial
Participants	Infants born before 30+6 weeks
Intervention	Heparin
Comparison	Usual care
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Block randomisation
Concealment bias	Unclear	Did not specify
Performance bias	Unclear	No placebo so would know who was in control group
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Chiswick, 1983

Methods	Randomised controlled trial
Participants	Infants born <37 weeks' gestation and <1751g
Intervention	Vitamin E
Comparison	Unclear, did not specify
Primary outcomes	Plasma vitamin E concentrations, incidence of IVH (unclear classification) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Unclear	Did not specify
Performance bias	Low	No reason for risk of bias
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Chiswick, 1989

Methods	Randomised controlled trial
Participants	Infants born <33 weeks' gestation
Intervention	Vitamin E
Comparison	Usual care
Primary outcomes	Plasma vitamin E concentrations, incidence of IVH (unclear classification) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how

Concealment bias	Low	Sealed envelope
Performance bias	Unclear	No placebo, could know who was in control group
Detection bias	Unclear	Did not specify radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Dani, 2005

Methods	Randomised controlled trial
Participants	Infants born <28 weeks' gestation
Intervention	Ibuprofen
Comparison	Placebo
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Random assignment procedure
Concealment bias	Low	Sealed envelope
Performance bias	Low	No reason for a risk of bias
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Donn, 1981

Methods	Randomised controlled trial
Participants	Infants <1500g
Intervention	Phenobarbitone
Comparison	Unclear, did not specify
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Lottery randomisation
Concealment bias	Low	Lottery randomisation
Performance bias	Unclear	Unsure whether there was placebo so could have known who was in the control group
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Duley, 2018

Methods	Randomised controlled trial
Participants	Infants born <32 weeks' gestation
Intervention	Delayed cord clamping (after 120s)
Comparison	Immediate cord clamping (<20s)

Primary outcomes	Death before hospital discharge and incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Computer generated sequence and block randomisation
Concealment bias	Low	Opaque envelopes
Performance bias	Low	No reason to have risk of bias
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

EC Ethamsylate, Elborne, 1994

Methods	Randomised controlled trial
Participants	Infants born <32 weeks'
Intervention	Ethamsylate
Comparison	Standard care, 'open'
Primary outcomes	Death, disability, use of health service resource, cerebral problems including incidence of IVH (Levene) on CUS was reported in this study

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Block randomisation, and stratified
Concealment bias	High	Did not say who was told over the phone
Performance bias	Unclear	It was an open trial, knew who got which intervention
Detection bias	Low	Radiologist was blinded
Attrition bias	High	Incomplete data due to loss to follow-up
Reporting bias	Unclear	Incomplete data

Fauchere, 2015

Methods	Randomised controlled trial
Participants	Infants born between 26-31+6 weeks
Intervention	Erythropoietin
Comparison	Placebo
Primary outcomes	Neuroprotective effect, reported incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Computer random allocation
Concealment bias	Low	Computer random allocation
Performance bias	Low	No reason for risk of bias
Detection bias	Unclear	Did not specify radiologist was blinded

Attrition bias	Low	All infants accounted for
Reporting bias	Unclear	Per-protocol analysis

Fish, 1990

Methods	Randomised controlled trial
Participants	Infants <1000g
Intervention	Vitamin E
Comparison	Placebo
Primary outcomes	Incidence of IVH (unclear classification) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Unclear	Unclear randomisation method
Performance bias	Unclear	Clinicians were blinded but knew vitamin E levels
Detection bias	Low	Radiologist was blinded
Attrition bias	High	8 infants died before US exam and did not have autopsy. 2 had no assessment of IVH
Reporting bias	Unclear	See attrition bias, incomplete data

Fulia, 2003

Methods	Randomised controlled trial
Participants	Infants <30 weeks' gestation
Intervention	Antithrombin III
Comparison	Placebo
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Computer generated randomised sequence
Concealment bias	Low	Computer generated randomised sequence
Performance bias	Unclear	Unsure whether clinicians knew clotting results
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Unclear	Does not say how many were included in analysis, or whether the included those who died
Reporting bias	Unclear	Number of participants and data reported don't add up. See attrition bias

Hanigan, 1988

Methods	Randomised controlled trial
Participants	Infants <1500g
Intervention	Indomethacin

Comparison	Placebo
Primary outcomes	Incidence of IVH (Krishanmoorthy) on CUS

Risk of bias	Author's judgement	Justification
Randomisation bias	Low	Block randomisation, groups of 2, 4 or 6
Concealment bias	Low	Block randomisation
Performance bias	Low	No indication of risk of bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Hemmati, 2020

Methods	Randomised controlled trial
Participants	Infants born 24-26 weeks
Intervention	Delayed cord clamping (30-45s)
Comparison	Immediate cord clamping (10-15s)
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	Author's judgement	Justification
Randomisation bias	Unclear	Infants born in the first month were allocated intervention by flipping a coin. Infants born in the next month were "put in the second group". Unsure of what the second group was and whether they were randomised.
Concealment bias	Unclear	See randomisation bias
Performance bias	Low	No reason for performance bias
Detection bias	Low	Radiologist was blinded
Attrition bias	High	39 were loss to follow-up
Reporting bias	Unclear	Does not say why some who received the allocated intervention were not analysed (study Figure 1)

Hensey, 1984

Methods	Randomised controlled trial
Participants	Infants <1250g, and infants <1500g who required respiratory support on first day of life
Intervention	Tranexamic acid
Comparison	Placebo
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	Author's judgement	Justification
Randomisation bias	Unclear	Does not specify how they were randomised

Concealment bias	Unclear	See randomisation, but manufacturer held randomisation code
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All participants accounted for
Reporting bias	Low	None

Kalani, 2016

Methods	Randomised controlled trial
Participants	Infants born <32 weeks or <1500g
Intervention	Ibuprofen and indomethacin
Comparison	Standard care
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Says simple randomisation
Concealment bias	Unclear	See randomisation, didn't specify drugs looked identical
Performance bias	Unclear	Assessors were not blinded
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Kazemi, 2017

Methods	Randomised controlled trial
Participants	Infants born <32 weeks, and <1500
Intervention	Delayed cord clamping (between 30-45s)
Comparison	Early cord clamping (<10s)
Primary outcomes	Incidence of IVH (unclear grading) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Unclear	Unclear randomisation
Performance bias	Low	Clinicians can't be blinded, but no other reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Kochan, 2019

Methods	Randomised controlled trial
Participants	Infants <1000g
Intervention	Elevated midline head positioning

Comparison	Flat head positioning
Primary outcomes	Incidence of IVH (Volpe) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Block randomisation
Concealment bias	Unclear	Does not say blocks were different sizes
Performance bias	Low	Clinicians can't be blinded by no other reason for performance bias
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Kuban, 1986

Methods	Randomised controlled trial
Participants	Infants weighing <1751g
Intervention	Phenobarbitone
Comparison	Placebo
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Table of random numbers
Concealment bias	Low	Pharmacy held randomisation
Performance bias	Unclear	Clinician could tell whether baby is sedated
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Ment, 1985

Methods	Randomised controlled trial
Participants	Infants 600-1250g
Intervention	Indomethacin
Comparison	Placebo
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Ordinal number of admission in blocks of 10
Concealment bias	Unclear	All blocks the same size
Performance bias	Low	No reason for performance bias
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	

Other bias	Unclear	Reviewed data after every block of 10 was admitted. Study terminated when statistical significance was achieved.

Ment, 1988

Methods	Randomised controlled trial
Participants	Infants 600-1250g
Intervention	Indomethacin
Comparison	Placebo
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Ordinal number of admission in blocks of 10
Concealment bias	Unclear	All blocks the same size
Performance bias	Low	No reason for performance bias
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Ment, 1994

Methods	Randomised controlled trial
Participants	Infants 600-1250g
Intervention	Indomethacin
Comparison	Placebo
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Block randomisation
Concealment bias	Unclear	Does not say blocks are different sizes
Performance bias	Low	No reason for performance bias
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Mohammadzadeh, 2020

Methods	Randomised controlled trial
Participants	Infants <1500g or <32 weeks
Intervention	Magnesium sulphate
Comparison	Placebo
Primary outcomes	Incidence of IVH (Volpe) CUS

Risk of bias	**Author's judgement**	**Justification**

Randomisation bias	Unclear	Flipping a coin – not the best way of randomisation
Concealment bias	Unclear	Know there needs to be an equal number, don't know who is flipping a coin
Performance bias	Low	No reason for performance bias
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Unclear	Numbers in table 3 and 4 do not add up

Morgan, 1981

Methods	Randomised controlled trial
Participants	Infants weighing <1500g
Intervention	Ethamsylate
Comparison	Placebo
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Low	Randomisation held by manufacturer
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Morgan, 1982

Methods	Randomised controlled trial
Participants	Infants born <1250g, and infants 1250-1500g who required artificial ventilation
Intervention	Phenobarbitone
Comparison	Usual care
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	High	Alternate allocation
Concealment bias	High	Alternate allocation
Performance bias	Unclear	No placebo and high concealment bias
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	Low

Ruth, 1988

Methods	Randomised controlled trial
Participants	Infants born >25 weeks and <1500g

Intervention	Phenobarbitone
Comparison	Placebo
Primary outcomes	Incidence of IVH (Papile) on CUS, and neurodevelopmental impairment

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Lottery randomisation
Concealment bias	Low	See randomisation
Performance bias	Unclear	Said it was not double blinded because clinicians can see if infant was sedated and needed to know in case infant had seizures
Detection bias	Low	Radiologist was blinded
Attrition bias	Unclear	Graphs had no percentages so unclear if there was loss to follow-up
Reporting bias	Low	None

Sanghvi, 1999

Methods	Randomised controlled trial
Participants	Infants born <34 weeks' gestation
Intervention	Ethamsylate
Comparison	Usual care
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Low	Opaque envelopes
Performance bias	Unclear	Had no placebo
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Unclear	Per protocol analysis, and did not analyse the infants who died

Sinha, 1987

Methods	Randomised controlled trial
Participants	Infants born <32 weeks' gestation
Intervention	Vitamin E
Comparison	Placebo
Primary outcomes	Incidence of IVH (grading unclear) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but did not say how

Concealment bias	Low	Sealed envelopes
Performance bias	Unclear	Had no placebo
Detection bias	Unclear	Does not say radiologist is blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Speer, 1984

Methods	Randomised controlled trial
Participants	Infants <1500g
Intervention	Vitamin E
Comparison	Placebo
Primary outcomes	Incidence of IVH (Papile) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Unclear	See randomisation
Performance bias	Low	No reason for performance bias
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

van Overmiere, 2004

Methods	Randomised controlled trial
Participants	Infants born between 24-30 weeks gestation
Intervention	Ibuprofen
Comparison	Placebo
Primary outcomes	Incidence of IVH (Shankaran) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Block randomisation
Concealment bias	Unclear	Same block sizes
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Waltl, 1973

Methods	Randomised controlled trial
Participants	Infants born 800-1750g
Intervention	Coagulation factor concentrate (factors II, VII, IX and X)
Comparison	Usual care
Primary outcomes	Incidence of IVH (unclear grading), unclear if on CUS

Risk of bias	Author's judgement	Justification
Randomisation bias	High	Alternate treatment and control
Concealment bias	High	Alternate treatment and control
Performance bias	High	Due to concealment bias and lack of placebo
Detection bias	Unclear	Unsure whether radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Whitelaw, 1983

Methods	Randomised controlled trial
Participants	Infants weighing <1500g
Intervention	Phenobarbitone
Comparison	Placebo
Primary outcomes	Incidence of IVH (Levene) on CUS

Risk of bias	Author's judgement	Justification
Randomisation bias	Unclear	Randomised by does not say how
Concealment bias	Unclear	Unclear how they randomised
Performance bias	Unclear	Clinician could tell whether baby is sedated
Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

IVH investigated as a secondary or safety outcome

Armanian, 2017

Methods	Randomised controlled trial
Participants	Infants born before 34 weeks' gestation
Intervention	Delayed cord clamping (30-45s)
Comparison	Immediate cord clamping (10-15s)
Primary outcomes	Multiple neonatal outcomes (including IVH)

Risk of bias	Author's judgement	Justification
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Unclear	Does not say how it was randomised
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Unclear	Some loss to follow-up
Reporting bias	Low	None

Backes, 2016

Methods	Randomised controlled trial
Participants	Infants been between 22.5-27.6 weeks' gestation
Intervention	Delayed cord clamping (30-45s)
Comparison	Immediate cord clamping (<10s)
Primary outcomes	Safety, feasibility, and efficacy of DCC

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Random number system
Concealment bias	Low	Statistician did randomisation, sealed opaque envelopes
Performance bias	Low	No reason for performance bias
Detection bias	Low	Radiologist was blinded
Attrition bias	High	Significant incomplete data
Reporting bias	Low	None

Courser, 1996

Methods	Randomised controlled trial
Participants	Infants weighing 600-1250g and aged 23-29 weeks
Intervention	Indomethacin
Comparison	Placebo
Primary outcomes	Incidence of PDA (IVH was a secondary outcome, Papile, on CUS)

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Unclear	Does not say how it was randomised
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

El-Naggar, 2020

Methods	Randomised controlled trial
Participants	Infants born between 24-30+6 weeks' gestation
Intervention	Umbilical cord milking
Comparison	Early cord clamping (<10s)
Primary outcomes	Whether milking affects cerebral blood flow, and incidence of IVH (secondary outcome, grading unclear) on CUS

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Variable block randomisation
Concealment bias	Low	Opaque sealed envelopes

Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Sonographer for SVC flow was blinded, but doesn't specify radiologist for IVH was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Krueger, 1987

Methods	Randomised controlled trial
Participants	Infants weighing 750-1500g
Intervention	Indomethacin
Comparison	Usual care
Primary outcomes	Incidence of PDA (also measured IVH)

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Unclear	Does not say how it was randomised
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Kugelman, 2007

Methods	Randomised controlled trial
Participants	Infants born between 24-34+6 weeks' gestation
Intervention	Delayed cord clamping (30-45s)
Comparison	Immediate cord clamping (<10s)
Primary outcomes	Blood pressure, haematocrit, and clinical effects (including IVH)

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Low	Sealed opaque envelopes
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Mahony, 1985

Methods	Randomised controlled trial
Participants	Infants weighing 700-1300g
Intervention	Indomethacin
Comparison	Placebo

Primary outcomes	Multiple clinical outcomes including incidence of surgical ligation, oxygen therapy, and also reported IVH

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Low	External randomisation and identical vials
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Mercer, 2003

Methods	Randomised controlled trial
Participants	Infants born between 24-31+6 weeks' gestation
Intervention	Delayed cord clamping (30-45s)
Comparison	Immediate cord clamping (5-10s)
Primary outcomes	Effect on initial blood pressure (and IVH as a secondary outcome)

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Low	Sealed opaque envelopes
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Mercer, 2006

Methods	Randomised controlled trial
Participants	Infants born between 24-31+6 weeks
Intervention	Delayed cord clamping (30-45s)
Comparison	Immediate cord clamping (10-15s)
Primary outcomes	Incidence of BPD (secondary outcome incidence of IVH (Papile) on CUS)

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Low	Block randomisation
Concealment bias	Unclear	Does not say blocks were different sizes, but allocation was in sealed envelopes
Performance bias	Low	Obstetricians could not be blinded, but no other reason for performance bias, tried to not reveal allocation to neonatologists

Detection bias	Low	Radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Oh, 2011

Methods	Randomised controlled trial
Participants	Infants born between 24-27+6 weeks' gestation
Intervention	Delayed cord clamping (30-45s)
Comparison	Immediate cord clamping (<10s)
Primary outcomes	Haematocrit at 4h, IVH was reported

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Unclear	Does not say who took the phone call
Performance bias	Unclear	Clinicians were not blinded
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Phelps, 1987

Methods	Randomised controlled trial
Participants	Infants born <33 weeks' gestation
Intervention	Vitamin E
Comparison	Placebo
Primary outcomes	Efficacy and safety of vitamin E for prevention of retinopathy, IVH was a secondary outcome

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Low	Sealed opaque envelopes
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Ranjit, 2015

Methods	Randomised controlled trial
Participants	Infants born between 30-36+6 weeks' gestation
Intervention	Delayed cord clamping (>120s)
Comparison	Immediate cord clamping (usual care)
Primary outcomes	Benefits and safety of DCC

Risk of bias	Author's judgement	Justification
Randomisation bias	Low	Random number system
Concealment bias	Low	Sealed opaque envelopes
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Unclear	Some loss to follow-up
Reporting bias	Low	None

Rennie, 1986

Methods	Randomised controlled trial
Participants	Infants <1750g
Intervention	Indomethacin
Comparison	Placebo
Primary outcomes	Relate plasma 6-ketoprostaglandin F1a, indomethacin concentrations and clinical response (but reported incidence of IVH but unsure what grading or whether it was with CUS)

Risk of bias	Author's judgement	Justification
Randomisation bias	Unclear	Says randomised in abstract but not in main text
Concealment bias	Unclear	See randomisation bias
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist is blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Simons, 2003

Methods	Randomised controlled trial
Participants	All neonates
Intervention	Morphine
Comparison	Placebo
Primary outcomes	Analgesic effect, incidence of IVH (secondary outcome, grading unclear) but CUS, and neurologic outcome

Risk of bias	Author's judgement	Justification
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Unclear	See randomisation bias
Performance bias	Unclear	Could give open label morphine, could see infants who were sedated
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None

Tarnow-Mordi, 2017

Methods	Randomised controlled trial
Participants	Infants born before 32 week's gestation
Intervention	Delayed cord clamping (>60s)
Comparison	Immediate cord clamping (usual care)
Primary outcomes	Death or major morbidity (including IVH)

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Unclear	Does not say how it was randomised
Performance bias	Low	No reason for performance bias
Detection bias	High	Radiologist was not blinded
Attrition bias	Unclear	Some loss to follow-up
Reporting bias	Low	None

Yaseen, 1997

Methods	Randomised controlled trial
Participants	Infants weighing <1750g
Intervention	Indomethacin
Comparison	Placebo
Primary outcomes	Oxygenation and surfactant requirement

Risk of bias	**Author's judgement**	**Justification**
Randomisation bias	Unclear	Randomised but does not say how
Concealment bias	Unclear	Does not say how it was randomised
Performance bias	Low	No reason for performance bias
Detection bias	Unclear	Does not say radiologist was blinded
Attrition bias	Low	All infants accounted for
Reporting bias	Low	None