BMJ Open

Steroid use for established bronchopulmonary dysplasia: study protocol for a systematic review and meta-analysis

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To cite: Strashun S, Seliga-Siwecka J, Chioma R, *et al*. Steroid use for established bronchopulmonary dysplasia: study protocol for a systematic review and meta-analysis. *BMJ Open* 2022;**12**:e059553. doi:10.1136/bmjopen-2021-059553

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-059553).

Received 29 November 2021
Accepted 25 March 2022

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ABSTRACT

Introduction Postnatal steroids during the first few weeks of life have been demonstrated to be effective in decreasing the incidence of bronchopulmonary dysplasia (BPD), a serious chronic respiratory condition affecting preterm infants. However, this preventive option is limited by the concern of neurological side effects. Steroids are used to treat established BPD in an attempt to reduce mortality, and length of stay and home oxygen therapy, both of which associated with high levels of parental stress and healthcare costs. Moreover, a late timing for steroid treatment may show a more favourable safety profile in terms of neurodevelopment outcomes, considering the added postnatal brain maturation of these infants. Here, we report a protocol for a systematic review, which aims to determine the efficacy and long-term safety of postnatal steroids for the treatment of established BPD in preterm infants.

Methods and analysis MEDLINE, Embase, Cochrane databases and sources of grey literature for conference abstracts and trial registrations will be searched with no time or language restriction. We will include case–control studies, cohort studies and non-randomised or randomised trials that evaluate postnatal steroids for infants diagnosed with moderate or severe established BPD at 36 weeks' postmenstrual age. We will pool data from studies that are sufficiently similar to make this appropriate. Data extraction forms will be developed a priori. Observational studies and non-randomised and randomised clinical trials will be analysed separately. We will combine OR with 95% CI for dichotomous outcomes and the mean difference (95% CI) for continuous outcomes. We will account for the expected heterogeneity by using a random-effects model. We will perform subgroup analysis based on the a priori determined covariate of interest.

Ethics and dissemination Systematic reviews are exempted from approval by an ethics committee. Attempts will be sought to publish all results.

PROSPERO registration number CRD42021218881.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study designed to systematically investigate the use of steroids for established bronchopulmonary dysplasia, which is a serious respiratory condition associated with premature birth, currently lacking an effective therapy.
⇒ One limitation of this meta-analysis is that the data on this topic are few and the level of the evidence is not expected to be of very high quality.
⇒ We will make the search as comprehensive as possible with no time or language restriction throughout MEDLINE, Embase and Cochrane databases, also including sources of grey literature, and we will contact the authors of articles that included mixed data to obtain the information relevant to our research question.
⇒ Another limitation is that there is a variety of possible formulations, routes and dosage for steroids, and this may possibly increase the heterogeneity of the analysis.
⇒ We planned for meta-regressions and subgroup analysis to account for the expected heterogeneity in case a sufficient number of studies are found.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a serious chronic respiratory condition that affects many preterm infants.[1–4] Despite improvements in neonatal care, the rates of BPD have not decreased over the last few decades.[1] Approximately 60% of infants born at less than 27 weeks' gestation are diagnosed with BPD.[2 3 5] BPD definition has changed over the years. The current definition of BPD is based on the need for supplemental oxygen and/or respiratory support at 36 weeks' postmenstrual age (PMA).[6] BPD is classified into three grades of severity depending on the amount of oxygen and the type of respiratory support needed.[6] BPD is also often non-specifically referred to as chronic lung disease of prematurity. The pathogenesis of BPD is considered multifactorial. Prematurity itself and the subsequent arrest of lung maturation at the early stages of lung development

is the major determinant of the disease. In addition, prenatal events, including placental dysfunction, pre-eclampsia, intrauterine growth restriction, chorioamnionitis, maternal smoking and postnatal iatrogenic insults, such as nutritional deficiencies, direct injury from mechanical ventilation and oxygen toxicity, further worsen the picture, all playing a role in the resulting pulmonary inflammation.[2 7] Infants suffering from severe BPD are difficult to wean from respiratory support, they often experience feeding intolerance and intermittent hypoxic episodes,[8] requiring a prolonged hospital stay and often needing discharge on home on oxygen.[6] BPD is also burdened by long-term consequences, which include impaired lung function and architecture, recurrent respiratory infections and poor neurodevelopmental outcomes. Respiratory difficulties may continue well into adolescence and adulthood.[9–12] Mortality rate is up to 3% during first admission in infants diagnosed with severe BPD and 20% within 2 years of life in infants requiring tracheostomy.[13–15]

Currently, BPD lacks a safe and effective treatment. The use of postnatal steroids within the first few weeks of life has been proven to be effective in reducing the incidence of BPD.[16–19] However, their use is limited due to the possible long-term neurodevelopmental consequences.[20] Steroid treatment for established BPD could be tried in an attempt of reducing mortality, and length of stay and home oxygen therapy, which are both associated with a high level of parental stress and health economic burden. The rationale for the use of steroids in established BPD is based on evidence of inflammation in histology and transcription analyses of lung biopsies derived from patients with BPD,[21] and animal models of established BPD.[22] Inflammation can be found in the alveolar and the peripheral or central airways.[23] Possible benefits for corticosteroids in this population include decreasing inflammation and airway oedema and decreasing lung fibrosis.[24] Inhaled and systemic corticosteroids are used commonly for infants with established BPD, with notable variability in the use of inhaled corticosteroids between centres[25] and can be considered for long-term treatment of infants and children with BPD.[26 27] Although the concern about the risk of neurodevelopmental impairment remains, a late timing for steroid treatment may show a more favourable safety profile in terms of neurodevelopment outcomes, considering the added postnatal brain maturation of these infants. Data on the use of steroids in preterm infants suffering from established BPD and the inability to wean off oxygen/ventilation are sparse and inconsistent. However, the available evidence, analysed through a meta-analytical methodology, may assist the clinical choices, and help in designing future clinical trials. A systematic approach to the evidence synthesis towards this potential treatment approach could be beneficial. Here, we report a protocol for a systematic review to determine if the late treatment with postnatal steroids in preterm infants suffering from established BPD affects survival up to 1 year compared with those receiving no treatment.

METHODS AND ANALYSIS

Protocol and registration

We followed the reporting guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015.[28] The completed PRISMA-P checklist is provided in the online supplemental file 1. The protocol is registered with the PROSPERO international prospective register of systematic reviews (registration number: CRD42021218881). The final review will be reported following the updated PRISMA statement.[29] Important amendments to this protocol will be reported and published with the results of the review.

Population Intervention Comparator Outcome (PICO) question

This study aims to answer the following PICO question: In preterm infants suffering from established BPD, does rescue treatment with postnatal steroids versus no treatment affect survival up to 1 year of life?

Study selection criteria

Studies will be included or excluded if they meet our inclusion or exclusion criteria, respectively, as outlined below.

Types of participants

Inclusion criteria

- Preterm babies born <32 weeks' gestational age (GA).
- Infants diagnosed with moderate or severe established BPD at 36 weeks' PMA. All current definitions of BPD at 36 weeks' PMA are eligible for this study.[6 30 31]

Exclusion criteria

- Infants with lung malformations, lung haemorrhage or non-prematurity-related lung disease.

Where relevant studies including a mixed sample of patients (eg, patients receiving steroid treatment for both evolving and established BPD) are identified, the study authors will be contacted to provide data on all the patients treated starting from 36 weeks' PMA. If the authors are unwilling or unable to provide this information, the study will not be included.

Types of studies

Inclusion criteria

This systematic review will include case–control studies, cohort studies and non-randomised or randomised trials that evaluate postnatal steroids for preterm infants with established BPD. Both prospective and retrospective studies will be included.

We chose to include non-randomised and retrospective studies especially to investigate safety and report possible side effects, since safety is rightfully the major concern when approaching steroid treatment in preterm infants.

Analysis of randomised clinical trials (RCTs) will not be combined with the observational studies.

Exclusion criteria

Studies will not be included in this systematic review if they are qualitative thematic analysis, narrative reviews, editorials, systematic reviews or expert opinions.

Type of intervention

Inclusion criteria

The type of intervention measured in this systematic review is the late use of steroids in the treatment of established BPD in preterm infants in the neonatal intensive care unit (NICU) from 36 weeks' PMA to discharge. Steroid treatments include, but are not limited to, betamethasone, hydrocortisone, dexamethasone, methylprednisolone and prednisolone. Interventions are eligible regardless of the dose, route of administration (eg, orally, parenterally or via nebuliser), duration and intensity.

Exclusion criteria

Studies focused on steroid administration before 36 weeks of PMA or on other interventions for established BPD.

Type of comparator

We will include studies that have control groups with placebo, other drugs or no drug administration. In case the comparator is another drug, comparators are eligible regardless of the dose, route of administration (eg, orally, parenterally or via nebuliser), duration and intensity.

Time frame

The time frame for outcome evaluation will differ depending on the outcomes.

The time frame for the primary outcome (mortality) and the short-term safety outcomes will be considered starting from 36 weeks' PMA, to make sure they reflect the effect of the steroid treatment and not the pre-existing conditions. The primary outcome will be studied up to 1 year of age while the secondary safety outcome will be studied up to NICU discharge.

All the secondary short-term efficacy outcomes will be considered from birth to discharge from the NICU. The long-term efficacy and safety outcomes will be considered from 18 months up to 6 years of age.

In the case the time frame of the listed complications is not specified or unclear, the study authors will be contacted to provide the specific data. If the authors are unwilling or unable to provide this information, the additional outcome will not be included in the analysis for that study.

Setting

Study setting will be NICU stay and postdischarge follow-up clinics.

Language and publication time

No time or language restriction will be applied.

Outcome measurement

Primary outcome

The primary outcome of interest of this systematic review is the efficacy of postnatal steroid use for preterm infants with established BPD in terms of mortality from 36 weeks' PMA up to 1 year of age.

Secondary outcomes

The secondary outcomes are grouped in efficacy and safety, and short-term and long-term outcomes. The complete list of the secondary outcomes can be consulted in the online supplemental material. Our list tried to comprehensively cover and define all the possible short-term and long-term efficacy and safety outcomes of the steroid treatment. Since no core outcome sets have currently been approved for steroids in neonates, we report all the possible outcomes of interest to limit the reporting bias. Moreover, as recommended,[32] we are not going to exclude studies from this systematic review solely based on the lack of relevant outcome data or definitions. However, we will specify what secondary outcomes are eventually added to our predetermined list.

Search strategy

The databases MEDLINE and Embase will be searched for this systematic review. In consultation with a research librarian (KW), a standardised search strategy has been employed using a standardised set of keywords and operators. No other filtering or restrictions have been applied to the search strategy. Additional strategies to identify studies included manual reviews of reference lists from key articles that fulfilled our eligibility criteria and the use of 'related articles' feature in PubMed. Studies included in relevant systematic reviews searched in MEDLINE, Embase and Cochrane database will be used as well if they fulfil our eligibility criteria.

The electronic database search will be supplemented by searching for grey literature: trial protocols through clinical registers (ISRCTN registry and ClinicalTrials.gov), thesis dissertation (sourced through NDLTD and EThOS), conference proceedings (searched by Web of Science and Embase) and other grey literature databases (OpenGrey and Trip database). The search strategy is detailed in the online supplemental material.

Data management

Literature search results will be uploaded to the Distiller Systematic Review (DistillerSR) software (Ottawa, Canada), an internet-based software program that facilitates the study selection process. Screening questions and forms for level 1 (title and abstract screening) and level 2 (full-text screening), based on the inclusion and exclusion criteria, will be developed and tested. For level 2 screening, full-text articles will be uploaded with screening items to DistillerSR. Before each screening step, a calibration exercise will be performed to pilot and refine the screening items.

Study selection process

The articles will be split into two sequential groups for feasibility reasons. Each group will be assessed for titles and abstracts independently by two authors for a total of four authors. First, the two independent reviewers will screen article titles and abstracts in duplicate using an initial screening questionnaire. Subsequently, full-text screening for all the articles retained will be conducted against our eligibility criteria. For each screening step (title and abstract and full text), calibration exercises will be performed on 10 random articles to ensure adequate inter-reviewer correlation. A match between authors will need to be reached before an article enters the full-text review. Any disagreement will be settled by consensus and when not possible a third author will be contacted for resolution (MP). We will seek additional information from study authors where necessary to resolve questions about eligibility. For level 2, we will record the reasons for excluding trials. The review authors will not be blinded to the journal titles or the study authors or institutions.

Data extraction

Data extraction forms will be developed a priori and pilot tested by our team using a standardised extraction form on DistillerSR. Two independent reviewers will perform the data extraction using a single charting and audit approach using the quality control function in DistillerSR. The extraction forms will be piloted on five random studies to ensure the approach to data charting will be consistent and in line with the research question and purpose. Each reviewer will chart half of the articles and audit the other half. In case of disagreement between the reviewers, a third independent reviewer will be consulted. The team will discuss the results, and the data charting form will be continuously updated in an iterative process to be inclusive of other aspects of the treatment that may not be listed a priori in the first place.

The following information will be extracted to become Table No 1:

- Lead author, year of publication and country of origin.
- Sample size (total and per group).
- Study design.
- Inclusion and exclusion criteria.
- Setting.
- Definition of BPD.

The following information will be extracted to populate Table No 2 (observational studies), Table No 3 (interventional, non-randomised studies) and Table No 4 (interventional, randomised studies):

- Purpose of study/study objectives.
- Patient characteristics (including the type of respiratory support required).
- Details of steroid intervention implemented (including the type, duration and frequency of treatment).
- Results reported (including raw numbers, summary statistics and adjusted analysis on BPD where available).
- Outcomes of interest, as defined in the appropriate section.

For articles in which data cannot be extracted, the corresponding author of the manuscript will be contacted a total of three times. If the authors are unwilling or unable to provide this information, the study will be excluded.

Risk of bias assessment

Methodological quality will be assessed by two authors independently using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) Scale for cohort or case–control studies. The ROBINS-I tool assesses the risk of bias in six different domains (bias due to confounding, bias in the selection of participants, bias in classification of intervention, bias due to intervention deviations, bias due to missing data, bias in outcome measurement, bias in result reporting). Studies are classified as low, moderate, serious, critical and unknown risk of bias.[33] If consensus scoring on individual and total scores of the ROBINS-I Scale is not reached by the two authors, a third author will be contacted for resolution.

The Cochrane risk of bias tool will be used to assess the risk of bias of randomised trials. For each domain (allocation sequence, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, selective outcome reporting and other potential sources of bias), the risk of bias will be assessed as low, high or unclear. Potential discrepancies during the data extraction process and assessment of the risk of bias will be resolved by discussion and consensus among all reviewers.

Data analysis

Summary data for each article will be presented as means and SDs, or frequency and percentages, as appropriate. For dichotomous outcomes, the OR with 95% CI will be calculated from the data provided in the studies. ORs adjusted for potential confounders will be extracted from the studies reporting these data. We chose to use the OR for all types of studies, including RCTs. Although we are not going to combine the results of different types of studies (ie, non-randomised and randomised trials), using the same effect size measure for all types of studies may allow us to evaluate the impact of the study design on the association (ie, we may compare the OR of case–control meta-analysis with the OR of cohort meta-analysis and RCTs and see if the study design has an influence on the results).

For continuous outcomes, the mean difference (95% CI) or standardised mean differences (95% CI), if different measurement scales are used, will be calculated. When studies report continuous variables as median and range or IQR, we will estimate the mean and SD using the method of Wan *et al*.[34]

All the analyses will be performed with Comprehensive Meta-Analysis software (Biostat, Englewood, USA). We will perform the meta-analysis assuming that we will find at least two studies suitable for inclusion. When

a meta-analysis is not possible, due to an insufficient number of studies, we will provide a narrative description of the study results. We will pool data from studies that are sufficiently similar to make this appropriate. The analysis will be performed separately for observational studies and non-RCTs and RCTs. Moreover, the systemic route and inhaled route for steroid administration will be analysed separately, as they are deemed too different to be combined.

We will account for the expected heterogeneity by using a random-effects model. This model accounts for variability between studies as well as within studies. We chose to use the random-effects model, as we expect some level of heterogeneity even if we are not combining different study types. Formal tests for homogeneity based on the statistics Q and I^2 may not always be fully reliable in choosing the method for analysis.[35 36] Therefore, we chose our model a priori based on the anticipated variation among our studies. We cannot assume that in the studies the only error will be the sampling error; that would make the fixed-effects model appropriate.[37 38] Moreover, we are interested in generalising to other populations and therefore the random-effects model is more suitable.[37 38]

Statistical heterogeneity will be assessed by Cochran's Q statistic and by the I^2 statistic, which is derived from Q and describes the proportion of total variation that is due to heterogeneity beyond chance. In case heterogeneity is significant (I^2 greater than 50%), we will take the following strategies to deal with it. To explore differences between studies that might be expected to influence the effect size, we will perform univariate random-effects meta-regression (method of moments), in case that at least 10 studies are available. A probability value of less than 0.05 (0.10 for heterogeneity) will be considered statistically significant. We will also perform subgroup analysis based on the a priori determined covariate of interest. The potential sources of variability defined a priori to analyse with subgroup analyses and/or meta-regression for short-term and long-term efficacy outcomes will be type of respiratory support (mechanical ventilation, non invasive ventilation (NIV), Biphasic intermittenet positive airway pressure (BiPAP), continuous positive airway pressure (CPAP), nasal cannula/low-flow oxygen), GA, birth weight, sex, steroid treatment course (type of steroid used, route of administration, duration and frequency of treatment), other ongoing treatments (ie, diuretics, bronchodilators, pulmonary vasodilators or vitamin A), previous treatment with steroids before 36 PMA (type of steroid used, age at treatment), neonatal morbidity (complication of prematurity, respiratory infections, late-onset sepsis, pulmonary hypertension, poor growth, difficulty feeding, developmental delay), the oxygen saturation target defined as low target (85%–89%) or high target (91%–95%), the definition of established BPD and severity of BPD (moderate vs severe forms).[30 31] For long-term neurodevelopment outcomes, socioeconomic status, time of evaluation and country of birth will be considered as well. Subgroup analyses will be conducted according to the mixed-effects model. In this model, a random-effects model is used to combine studies within each subgroup, and a fixed-effects model is used to combine subgroups and yield the overall effect. The study-to-study variance is not assumed to be the same for all subgroups. This value is computed within subgroups and not pooled across subgroups. We will use Egger's regression test and funnel plots to assess publication bias.

Data synthesis

A systematic narrative synthesis will be provided with the information presented in the text and tables to summarise and explain the characteristics and findings of the included studies. For the studies that cannot be combined in the meta-analysis, a narrative synthesis of the results will be provided. The quality of evidence for all outcomes will be judged using the Grading of Recommendations Assessment, Development and Evaluation working group methodology.[39–41] The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias. Additional domains may be considered where appropriate. Quality will be adjudicated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (very uncertain about the estimate of effect).

Patient and public involvement

Patient organisations were not involved in developing the protocol.

DISCUSSION

This is the first study designed to systematically investigate the use of steroids for established BPD. Although late steroid treatment after 50 days of life is known to be less effective in reducing the incidence of BPD,[4] there is a significant gap in research regarding the use of steroids to wean off respiratory support or oxygen therapy in established BPD and improve the overall outcome of these babies. Therefore, this systematic review and meta-analysis will focus on the validity of such an intervention. One limitation of this meta-analysis is that the data on this topic are few and the level of the evidence is not expected to be of very high quality. However, we made the search as broad as possible, and we will contact the authors of articles that included mixed data to obtain the information relevant to our research question. We believe that the results of our analysis may demonstrate where knowledge is lacking and help guiding robust clinical trials. The combination of the current evidence into a meta-analysis may provide more precise information on risks and benefits of steroid treatment for established BPD, patient values and evidence to support clinical or health

policy decision-making. This approach would fit into the research 'drive-value approach', which determines the value of different research strategies, aiming for research with the maximum value.[42] The results of our analysis may help the connection between policy making and the future clinical trials. Another limitation of our study is that there is a variety of possible formulations, routes and dosage for steroids, and this may possibly increase the heterogeneity of the analysis. We planned for meta-regressions and subgroup analysis to account for the expected heterogeneity in case enough studies are found. We believe that the systematic description of the different routes, formulations and dosing may compute the value of alternative trial designs to prioritise the trial protocol with the greatest net value.[42]

Review findings will be presented at the international neonatal meetings for early dissemination of observations and feedback. The results will also be submitted for publication in peer-reviewed journals, thus assisting neonatal professionals and parents with informed decision-making regarding the efficacy and safety of late steroid treatment in the NICU for established BPD.

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Acknowledgements We would like to thank Dr Renata Bokiniec and Dr Dariusz Madajczak for funding provision.

Contributors SS drafted the review protocol. RC and KZ reviewed the manuscript. KW has developed the search strategy. MP has led the protocol design and editing. NAA developed the project idea. JS-S obtained the funds and is the corresponding author for the review. NAA, JS-S, RKP and EV have contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. EV provided statistical and systematic review expertise. All authors contributed to intellectual content, provided feedbacks, and edited and approved the final manuscript.

Funding The systematic review process will receive funding from the Medical University of Warsaw departmental funding. This funding will support the data collection, data management, analyses and publication fees.

Disclaimer The sponsor did not take part in the study design and realisation. The funder will not be involved in any other aspect of the project, such as the design of the project's protocol and analysis plan, the collection and analyses. The funder will have no input on the interpretation or publication of the study results.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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