PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and safety of treatments used for the management of patent ductus arteriosus (PDA) in preterm infants: a protocol for a systematic review and network meta-analysis
AUTHORS	Mitra, Souvik; Florez, Ivan D; Tamayo, Maria Eulalia; Aune, Dagfinn; Mbuagbaw, Lawrence; Veroniki, Areti Angeliki; Thabane, Lehana

VERSION 1 - REVIEW

REVIEWER	Dr Ravikumar Parikh Consultant Neonatologist with interest in Neonatal Cardiology Setu Newborn Care Centre Ahmedabad, India
REVIEW RETURNED	14-Feb-2016

GENERAL COMMENTS	It is very well intentioned and drafted study to be done. The results are going to guide the researchers and protocol makers in right direction.

REVIEWER	Gina Rosito California Pacific Medical Center United States of America
REVIEW RETURNED	04-Mar-2016

GENERAL COMMENTS	There are a few editing corrections that are necessary. See attached file . The reviewer also provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Douglas Schneider University of Kentucky United States
REVIEW RETURNED	11-Apr-2016

GENERAL COMMENTS	Excellent project- thorough, well-thought out, and clinically important.

REVIEWER	Mary Brindle University of Calgary, Canada
REVIEW RETURNED	13-May-2016

GENERAL COMMENTS	The authors present a protocol examining various medical therapies used for closure of the patent ductus arteriosus in the premature neonate. The authors have followed the PRISMA-P reporting guidelines appropriately in developing this manuscript. They propose using a network meta-analysis for this study which has been previously applied to address the question of the most appropriate medical therapy for PDA closure. The authors assert (and I agree) that the newer publications including those that explore acetaminophen as a therapy for PDA closure warrant a new look at the question. Overall, the protocol is very well-considered and well-written. The description of the methods is very clear. I am familiar with network meta-analysis but do not have great expertise in this field and would, therefore, recommend statistical review. Overall, there are only a few comments and questions/suggestions I would make. When the authors discuss exclusion criteria, would it be appropriate to exclude studies in which prior medical therapy for PDA has already been attempted? In many studies, ductal closure is defined as an endpoint without a specific timeline proposed. Although effectiveness of therapy is very likely to be seen within the 7 day time frame, do the authors feel that studies will sufficiently identify studies that examine PDA closure within one week of treatment? If studies do not define time until closure, will they be excluded? It may also be appropriate, within the limitations, to acknowledge that, if a large number of inconsistencies remain after adjusting for effect modifiers, a network meta-analysis may not be appropriate for the data. This is unlikely. A previous meta-analysis has suggested that the studies concerning acetaminophen use are low quality. Do the authors plan to perform any sensitivity analyses to assess for the impact of study quality. There are a couple of minor typos/wording issues In the abstract under ethics and dissemination, the phrase “the results… will find knowledge gaps” might be better stated as “will expose” or “identify”. In the discussion, the opening statement reads “The present systematic review will provide the relative effectiveness and safety of the medical treatments for closure of PDA in preterm babies”. The authors may want to change this to “evidence of effectiveness” or a similar term. In addition. “Its results will be of interest for a broad audience” might be better written as “of interest to” In the discussion, saying that the published work will be from “the most important” databases might be better worded as “the most comprehensive”.

REVIEWER	David Osborn University of Sydney, Australia
REVIEW RETURNED	22-May-2016

GENERAL COMMENTS	This protocol for a systematic review and network meta-analysis has

	the potential to provide important guidance to the management of the ductus arteriosus, one of the most controversial topics in neonatology. It is highly likely the benefits of closing a ductus and reducing shunts are balanced by the disadvantages of increased after load and the side effects of medications used to close the ductus. Large, trials are needed and overdue to answer important questions with little substantial progress in this area since the TIP trial except from relatively small trials of various agents often without a placebo group. This review has the potential to inform a new trial. The review has not prespecified how it will deal with the use of prophylactic treatment with may not differ in timing from early targeted treatment. The review would be strengthened by describing the different treatment strategies of the ductus – prophylactic, early targeted, presymptomatic and symptomatic in regards to the prespecified subgroup analysis regarding timing. The objective should consider the possibility no treatment is superior in terms of overall infant morbidity. The review is not considering long term outcomes. The lack of reported long term outcomes will limit the utility of this review. Again, the TIP trial highlighted the lack of association between ductal closure and change in mortality and neurodevelopmental outcomes. It is a step backwards to omit these outcomes. Clinical criteria were used to enrol infants in treatment in many trials, not just the presence of a ductus with echo confirmation. How will the review deal with differences in patient populations with regards illness severity? With regards side effects, trials may or may not have excluded infants at increased risk of toxicity (eg with renal impairment). The review has not prespecified the cutpoints for assessing timing of treatment (see above), PDA size and left Atrium:Aortic root ratio. The most important is timing. PDA size and A:Ao ratio are only a subset of measures of ductal significance. It is likely the reviewers will find this narrow consideration will limit the usable data. Trials may have enrolled previously treated infants. In addition, cross-over rates were frequently very high. Both factors are likely to influence response rates and produce heterogeneity. Primary outcome: Ductal closure is not necessarily the goal of treatment – the ductus tends to close spontaneously even without treatment over time. It should be considered that attempts to close the ductus instead of constricting the ductus (ie aimed at controlling 'symptoms') may be associated with increased side effects – eg long versus short courses of indomethacin. Time of measurement of outcome is also important – the ductus tends to close spontaneously even without treatment. Another source of potential heterogeneity. In conclusions, the protocol as it stands is a minimal approach to exploring potential heterogeneity between studies and needs further input from content experts. The use of the random effects model estimates the next trial estimates. This is consistent with an

	appropriate objective of the review, to identify the patient population and treatment that will be assessed in the next large trial of treatment or non-treatment.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
It is very well intentioned and drafted study to be done. The results are going to guide the researchers and protocol makers in right direction.

R/ Thanks for your comment. No additional comments or changes to introduce.

Reviewer 2
There are a few editing corrections that are necessary. See attached file

R/ Thanks for your comments. All your comments and editions have been made in the manuscript. Across the document in red font with the changes made in response to other reviewers.

Reviewer 3
Excellent project- thorough, well-thought out, and clinically important.

R/ Thanks for your comment. No changes to introduce to the document

Reviewer 4

-When the authors discuss exclusion criteria, would it be appropriate to exclude studies in which prior medical therapy for PDA has already been attempted?

R/ Thanks for your comment. We believe “prior medical therapy” here indicates “prophylactic therapy” or prior pharmacotherapy for a hemodynamically significant PDA (hs-PDA). Regarding “prophylactic therapy” we would like to mention thatin our protocol only those studies in which prophylactic treatment has been attempted will be excluded. Any study which has attempted to close the PDA by pharmacological means after the establishing the diagnosis clinically and/or echocardiographicallywill be included. However, we can definitely explore the outcomes in that subgroup where infants were randomized after having received an open labeled treatment following establishment of a diagnosis of hs-PDA. We expect this to be an uncommon case, but in case they exist we will perform subgroup analysis to assess the differences in the effect. [page 10, line 17,18]

-In many studies, ductal closure is defined as an endpoint without a specific timeline proposed. Although effectiveness of therapy is very likely to be seen within the 7 day time frame, do the authors feel that studies will sufficiently identify studies that examine PDA closure within one week of treatment? If studies do not define time until closure, will they be excluded?

R/ Thanks for your comment. We will take this recommendation into account since some studies could have measured closure at different days. Accordingly, we will include all the studies that have measured the outcome and we will analyze the data based on the time of closure. [page 10, line 17]

- It may also be appropriate, within the limitations, to acknowledge that, if a large number of inconsistencies remain after adjusting for effect modifiers, a network meta-analysis may not be appropriate for the data. This is unlikely.

R/ Yes, in case of presence of large heterogeneity and large incoherence that could not be addressed

using the strategies proposed (subgroup, sensitivity analysis), we will have to stop the process and avoid running the NMA.We added this idea in the manuscript in the section The Network Meta-analysis

-A previous meta-analysis has suggested that the studies concerning acetaminophen use are low quality. Do the authors plan to perform any sensitivity analyses to assess for the impact of study quality.

R/ We agree with the reviewer regarding the need to perform sensitivity analyses based on the risk of bias. Because of that we planned and described it in the protocol (at the bottom of page 10): “We will perform meta-regression or subgroup analysis as appropriate using these hypotheses as the study level covariates and we will perform a sensitivity analysis based on the studies with high ROB”. Although we expect that the most recent studies with paracetamol likely will be of better quality of the ones published before.

- There are a couple of minor typos/wording issues
--In the abstract under ethics and dissemination, the phrase “the results… will find knowledge gaps” might be better stated as “will expose” or “identify”.

R/ We agree with the comment. We have changed the sentence using ‘will identify’

-In the discussion, the opening statement reads “The present systematic review will provide the relative effectiveness and safety of the medical treatments for closure of PDA in preterm babies”. The authors may want to change this to “evidence of effectiveness” or a similar term.

R/ We Agree. We will use instead:‘Evidence of comparative effectiveness’

- In addition. “Its results will be of interest for a broad audience” might be better written as “of interest to”

R/ Agreed. Changes performed in the manuscript

- In the discussion, saying that the published work will be from “the most important” databases might be better worded as “the most comprehensive”.

R/ Agree; we have changed the sentence.

Reviewer5

-The review has not prespecified how it will deal with the use of prophylactic treatment with may not differ in timing from early targeted treatment.

R/ Thanks for your comment. We agree that in terms of timing of treatment, prophylactic therapy (PT) may overlap with early targeted treatment (ETT). However conceptually ETT, as the name suggests, targets treatment of a hemodynamically significant duct, or in other words, a diagnosis of a hemodynamically significant PDA has been established. While PT has been used primarily as a means to prevent intra-ventricular hemorrhage without establishing a diagnosis of hs-PDA. Hence we have specified in our inclusion criteria that only those infants in whom a clinically/echocardiographically significant PDA has been diagnosed will be included for analysis which automatically excludes PT.

-The review would be strengthened by describing the different treatment strategies of the ductus – prophylactic, early targeted, presymptomatic and symptomatic in regards to the prespecified subgroup analysis regarding timing. The objective should consider the possibility no treatment is superior in terms of overall infant morbidity.

R/ We have intentionally left out prophylactic therapy for three reasons: a) It was primarily devised to prevent intra-ventricular hemorrhage (likely by constricting the duct) and not for "treating" an hs-PDA. Hence it does not align with our primary outcome per se; b) It is therapy which has largely fallen out of favor among most neonatologists; c) the population is completely different (i.e., otherwise 'healthy infants', while ourpopulation of interest encompasses children with a patent ductus. The analysis of this population will require a different approach, i.e., an additional systematic review.
Regarding the other strategies, we are concerned that by trying to distinguish between presymptomatic and symptomatic we would introduce subjectivity. Rather we thought it would be more prudent to explore whether ETT is better than late treatment or no treatment.In addition, we cannot agree more that "no treatment" is definitely as important as the rest (if not better) in terms of overall infant morbidity. Hence, no treatment or placebo is definitely one of the interventions of the interest included in the network. For the rest who received treatment we could look at 3 subgroups: ETT within 72 hours of life, treatment between 72 h – 7 days; treatment beyond 7 days. We will attempt to analyze these subgroups if there is enough information for doing so.

- The review is not considering long term outcomes. The lack of reported long term outcomes will limit the utility of this review. Again, the TIP trial highlighted the lack of association between ductal closure and change in mortality and neurodevelopmental outcomes. It is a step backwards to omit these outcomes.

R/ We fully agree that it is a limitation of the review. However most of the RCTs on PDA closure neither were powered to look at long term neurodevelopmental outcomes nor had long term follow-up. Hence we did not want to draw conclusions based on a meta-analysis of grossly underpowered studies and thereby introduce type II error. We would definitely highlight the need for future studies that are adequately powered to explore long term neurodevelopmental outcomes, perhaps by analyzing cohort studies that have performed long-term follow up.

- Clinical criteria were used to enrol infants in treatment in many trials, not just the presence of a ductus with echo confirmation. How will the review deal with differences in patient populations with regards illness severity? With regards side effects, trials may or may not have excluded infants at increased risk of toxicity (eg with renal impairment).

R/ We appreciate your comment. Indeed, the diagnosis of PDA based on clinical criteria is a challenging scenario that we decided to include because we were interested in including all the available information. Being aware of this challenge, we will perform sensitivity analysis based on the studies that had clinical diagnosis in order to analyze the differences in the effects (page 11, lines 1-2)

-The review has not prespecified the cutpoints for assessing timing of treatment (see above), PDA size and left Atrium:Aortic root ratio. The most important is timing.

R/ We agree that timing plays a crucial role. As mentioned above we intend to perform a subgroup analysis for the following: ETT within 72 hours of life, treatment between 72 h – 7 days; treatment beyond 7 days.

-PDA size and A:Ao ratio are only a subset of measures of ductal significance. It is likely the reviewers will find this narrow consideration will limit the usable data.

R/ We agree that we may lose some other newer and less validated echocardiographic measures to define hs-PDA. After discussing with experts in the field, we decided to include only the PDA size and the LA:Ao ratio as these are the two most common measures of ductal significance used across studies.

- Trials may have enrolled previously treated infants. In addition, cross-over rates were frequently very high. Both factors are likely to influence response rates and produce heterogeneity.

R/ Thanks for bringing up these valid points. Certainly the primary outcome may be affected by previous treatment. Hence, we would explore the outcomes in that subgroup where infants were randomized after having received an open labeled treatment following establishment of a diagnosis of hs-PDA. Regarding the problem with cross-over, if an RCT is well-conducted then this should not be an issue, at least in terms of the primary outcome being affected. And that should be taken care of by our risk of bias assessment. We intend to perform sensitivity analysis based on risk of bias which we have mentioned in the protocol.

- Primary outcome: Ductal closure is not necessarily the goal of treatment – the ductus tends to close spontaneously even without treatment over time. It should be considered that attempts to close the ductus instead of constricting the ductus (ie aimed at controlling 'symptoms') may be associated with increased side effects – eg long versus short courses of indomethacin.

R/ Again, thanks for bringing up this extremely valid point. Unfortunately, most of the PDA studies have used closure of PDA as the main outcome. We agree that it could be a surrogate, unfortunately it is the most common and available outcome in the trials. We als ofully agree that an infant may have clinically improved following treatment but may still be labeled as treatment failure if the duct is still open. We would definitely highlight in the final paper the need to target clinically relevant outcomes (both short as well as long term) for future studies and not the surrogate outcomes like PDA size &LA:Ao ratio (where measurement errors are hardly accounted for).Examples of more critical outcomes could be short term composite outcomes including mechanical ventilation parameters + oxygen need, and long-term neurodevelopmental outcomes. Taking into account this scenario we did not restrict outcomes only to the closure or Echo findings and we tried to include a wide range not only of effectiveness but also safety outcomes. We are looking at side effects of the different modalities of treatment to drive home the point that aggressive pharmacological closure could be harmful as well.

- Time of measurement of outcome is also important – the ductus tends to close spontaneously even without treatment. Another source of potential heterogeneity.

R/ We agree with this comment. Closure is the final aim but the time is a key factor. We are going to include the time as part of our outcome and depending on how the results are described by authors we plan to develop the analyses, e.g., to perform analysis based on the closure at day 5 and at day 7.

- In conclusions, the protocol as it stands is a minimal approach to exploring potential heterogeneity between studies and needs further input from content experts. The use of the random effects model estimates the next trial estimates. This is consistent with an appropriate objective of the review, to identify the patient population and treatment that will be assessed in the next large trial of treatment or non-treatment.

R/ Thank you for your comment. We do acknowledge the limitations of the review. We are fortunate to have content experts on our team and the protocol has been formulated and fine-tuned based on their inputs. Hence while formulating the protocol, the feasibility aspect has been carefully considered,

which in a way, would bring forth the limitations of the studies done so far. We do intend to highlight those limitations. Active attempts have also been made to limit the potential heterogeneity. We agree with the reviewer that this review would help clinicians and researchers “to identify the patient population and treatment that will be assessed in the next large trial of treatment or non-treatment”.

VERSION 2 – REVIEW

REVIEWER	David Osborn University of Sydney, Australia
REVIEW RETURNED	07-Jun-2016

GENERAL COMMENTS	These comments are minor in nature regarding the response: The authors are not including trials of prophylactic treatment. This is reasonable although will mean a substantial proportion of studies/infants examining preventative treatment will be excluded. The authors have elected not to examine long term outcomes. Having excluded trials of prophylactic treatment they are correct in observing they will not have much data to extract. However, one purpose of the review is to highlight deficiencies in the evidence base. The authors run the risk of highlighting short term benefits whilst not being able to make a statement about the evidence base for long term effects. Timing of assessment of ductus – the authors may find some assessments are measured immediately at end of treatment whilst others may be weeks. Clinically we find that a ductus is frequently constricted at end of treatment and subsequently closes over the next month. Assessing ductal closure at these different time points may shed light on efficacy of treatment. I would suggest including neurodevelopment disability as an outcome to highlight the data deficiency and suggest reporting ductal closure at various time points prior to any crossover treatment.

VERSION 2 – AUTHOR RESPONSE

-The authors are not including trials of prophylactic treatment. This is reasonable although will mean a substantial proportion of studies/infants examining preventative treatment will be excluded.

R/ Thanks for the comment. We Agree. We have decided to exclude the studies as this review aims at examining the efficacy and safety of the different pharmacotherapeutic options for a hemodynamically significant PDA. We are aware of the reduction in the number of studies, but we are also interested in determining the ‘pure’ effect of the treatment. We could definitely consider examining the preventative treatment in a separate systematic review.

-The authors have elected not to examine long term outcomes. Having excluded trials of prophylactic treatment they are correct in observing they will not have much data to extract. However, one purpose of the review is to highlight deficiencies in the evidence base. The authors run the risk of highlighting short term benefits whilst not being able to make a statement about the evidence base for long term effects.

R/ We agree. This is an extremely valid point brought by the reviewer. Hence, after careful consideration we have decided to include neurodevelopmental outcomes measured at 12-24 months as one of the outcomes (see Table 1, Characteristics of the outcomes’ measures, pag. 22)

-Timing of assessment of ductus – the authors may find some assessments are measured immediately at end of treatment whilst others may be weeks. Clinically we find that a ductus is frequently constricted at end of treatment and subsequently closes over the next month. Assessing ductal closure at these different time points may shed light on efficacy of treatment.

R/ We agree. This is why we have decided to conduct a subgroup analysis based on time of assessment after the last dose for closure of the ductus (<24 h; 24h – 7 days; >7 days). (see page 10)