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Long-term safety of prenatal and neonatal exposure to paracetamol: a protocol for a systematic review

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Long-term safety of prenatal and neonatal exposure to paracetamol: a protocol for a systematic review

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What is known about the subject

- In recent years, use of paracetamol in neonatal intensive care units has increased.
- Currently available evidence on efficacy and short-term safety of paracetamol in ill neonates of NICUs appears favourable.
- There is growing concerns regarding long-term safety of prenatal and neonatal exposure to paracetamol.

What this study hopes to add

- Timely and comprehensive overview of the available information on long-term safety of prenatal and neonatal exposure to paracetamol
- Insight into the perceived safety of paracetamol in neonatal population.
- Evidence-based information that can contribute to the optimal use of this drug in neonatal population.

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Abstract

Introduction: A surge in the use of paracetamol in neonates has resulted in growing concerns about its potential long-term adverse events. In this study, we conduct a systematic review of the long-term safety of prenatal and neonatal exposure to paracetamol in newborn infants.

Methods and analysis: We will follow the Joanna Briggs Institute Manual for Evidence Synthesis and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements to conduct and report this review. We will conduct a systematic search of Embase, Medline, Web of Science, and Google Scholar for studies with data on long-term adverse events in neonates that were exposed to paracetamol in the prenatal and neonatal period. We will not apply language or design limitations. We will use standardized risk of bias assessment tools to perform a quality assessment of each included article.

Ethics and dissemination: This systematic review will only involve access to publicly available data, and therefore ethical approval will not be required. The results of this study will be communicated to the target audience through peer-reviewed publication and as well as other knowledge exchange platforms, such as conferences, congresses or symposia.

Trial registration: The protocol for this systematic review is submitted for registration to international database of prospectively registered systematic reviews (PROSPERO, awaiting registration number).

Keywords: Paracetamol, Neonates, Long-term safety

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1. Introduction

Paracetamol (para-acetylaminophenol), is one of the most widely used antipyretics and analgesics worldwide, and the most common medication encountered in paediatric care.[1] In recent years, the use of paracetamol in neonatal intensive care units (NICU) has also increased. The limited available evidence supporting the potential narcotic-sparing effect of paracetamol in term and preterm neonates, along with promising evidence for its efficacy for the closure of a hemodynamically significant patent ductus arteriosus (hsPDA) have resulted in a rapid increase in its use by many neonatal specialists.[2] Data from two small randomized controlled trials support the use of intravenous (IV) paracetamol in the immediate postoperative period to decrease the use of narcotics without an increase in pain score.[3,4] Of interest, available evidence for oral or rectal administration of paracetamol for control of mild to moderate pain did not provide a similar benefit.[5] Nevertheless, paracetamol continues to be used for pain control among neonates in a variety of formulations and routes to decrease the use of narcotics.

Over the past decade, the use of paracetamol as an alternative pharmacotherapy to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for the treatment of hsPDA has been evolving. A recent systematic review and meta-analysis that examined the association of various pharmacotherapeutic options for closure of hsPDA in preterm infants showed that oral paracetamol ranked highest in efficacy in terms of reducing the need for repeat pharmacotherapy.[6] With the increasing use of paracetamol in neonates, specifically ill neonates of NICUs, the need for pharmacokinetics (PK), pharmacodynamics (PD), and optimal dosing and safety data has become paramount.

Although data exist on the PK and optimal dosing of paracetamol for pain relief in extremely and very preterm infants, there is no paracetamol population PK data for neonates with hsPDA.[2] Furthermore, there is a considerable paucity of PD studies, incorporation of the available evidence-based dosing recommendations, and reports on efficacy and safety outcomes of paracetamol in neonates. Although currently available evidence on short-term safety of paracetamol in ill neonates of NICUs might be

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favourable, its long-term safety remains an area of debate.[2,7] Despite this significant lack of data, the perceived superior safety of paracetamol as compared to narcotics for the treatment of pain and NSAIDs for the closure of a hsPDA, has resulted in a strong desire for its use.

Long-term safety of prenatal and neonatal exposure to paracetamol has been an area of concern since the early 2000s.[8] In vivo and in vitro animal studies have shown evidence of neuroapoptosis with chronic use of paracetamol at therapeutic doses, causing altered neurotransmission with possible subsequent neuro-behavioural changes.[12] It has been suggested that prenatal use of paracetamol may interfere with endogenous hormones and signaling pathways in the developing fetus, leading to a reduction of fetal testicular testosterone production and alteration of the brain endocannabinoid system, resulting in developmental disruption and the associated behavioural changes.[13] Results of ecologic and cohort studies supported by biological plausibility have raised questions if the use of paracetamol during pregnancy or the early neonatal period can result in reproductive and immunological disruption and long-term adverse events such as cryptorchidism, atopic disorders, attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD).[9,10]

Although the mechanism of action of paracetamol is not yet clearly understood, it is believed that paracetamol's PD effects are mainly through central pathways. Besides inhibition of prostaglandin and nitric oxide biosynthetic pathways, augmentation of descending inhibitory serotonergic pain pathways and effects on cannabinoid (CB) receptors through active metabolites are its other hypothesized mechanisms of action.[11] Whether paracetamol's interference with neurohormonal regulatory mechanisms can result in long-term neurological, immunological, or hormonal disruption remains an important question and is an area that requires additional information.

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1. Objective:

We aim to conduct a systematic review of the available evidence on the long-term safety of prenatal and neonatal exposure to paracetamol in newborn infants.

2. Materials and Methods:

3.1. Protocol registration

The protocol for this systematic review is submitted for registration to international database of prospectively registered systematic reviews (PROSPERO, awaiting registration number). We will follow the Joanna Briggs Institute Manual for Evidence Synthesis and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements to conduct and report this review, respectively.[14,15]

3.2. Search strategy

A search strategy will be developed in consultation with a professional librarian, using the following electronic databases: Embase (Ovid), Medline (Ovid), Web of Science (Ovid), and Google Scholar from their inception to October 2020. We will use a combination of the following controlled terms in Ovid Medline: (exp Infant/ or exp Infant, Small for Gestational Age/ or exp Infant, Low Birth Weight/ or exp Infant, Premature/ or exp Infant, Very Low Birth Weight/ or exp Infant, Newborn/ AND exp acetaminophen/ or exp Paracetamol/ or exp APAP/ or exp Tylenol). This strategy will be translated, as appropriate, for the other databases. The bibliographies of any relevant articles for additional references will be reviewed. Using Google Scholar, we will also search for any relevant studies that are not commercially published, such as dissertations, policy documents, conference abstracts, and book chapters. We aim to contact authors of published trials and unpublished work to clarify information when necessary.

3.3. Eligibility criteria

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All randomized controlled trials (RCTs), prospective and retrospective cohort studies, and case reports describing the use of paracetamol in neonates that reported long-term safety outcomes will be eligible for inclusion, irrespective of the dose, route, frequency of administration and duration of treatment. In the studies with a control group, the provided intervention(s), placebo or standard practice will be the comparator. In studies with no comparator group, the observational report of the long-term safety of paracetamol during the study period will be collected. We will not apply any language or study design limitations. Animal studies and duplicate studies will be excluded.

3.4. Study selection and Data extraction

We will use Covidence as the primary screening and data extraction tool.[16] Two independent reviewers (KS and SSZ) will screen the resulting articles at the title and abstract level for eligibility. Eligible articles will then be reviewed at the full-text level by the two specified independent reviewers (KS and SSZ). We will extract data related to population, intervention, control and outcome from each study (Table 1). We will pilot test the data extraction form prior to its use. Any identified discrepancies will be resolved through discussion between three reviewers (JVDA, KS and SSZ).

3.5. Assessment of risk of bias and quality of evidence

Qualitative assessment of articles will be done using an appropriate standardized risk of bias assessment tool for each study design. These tools include the Cochrane risk-of-bias assessment tool for randomized trials (RoB 2), the Newcastle-Ottawa Quality Assessment Scale for cohort and case control studies, and the modified Newcastle-Ottawa scale for cross-sectional studies to assess cross-sectional studies. The quality of case reports will be evaluated using the Checklist for Case Reports by the Joanna Briggs Institute (JBI).[14,17,18] The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be used by the two reviewers (KS, SSZ) for rating the quality of included evidence.[19]

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3. Outcomes and variables

Our primary outcome is the presence of long-term adverse events, defined as neurodevelopmental adverse events, atopic disorders, and reproductive disorders. Our secondary outcomes are PK data, PD data, and short-term adverse events. Short-term adverse events include increased hepatic transaminases, gastrointestinal hemorrhage, necrotizing enterocolitis, feeding intolerance, defined as the presence of abdominal distention, increased gastric residuals, or any other gastrointestinal symptom that results in a decreased or held feed (Table 2).

4. Patient and public involvement

Patients are not directly involved in the design or conduct of this study. We will plan public involvement mostly concerned with the interpretation of the review findings and the development of reporting plans and associated guidance.

5. Amendments

We will document any amendments to this protocol, with reference to saved searches and analysis methods, which will be recorded in bibliographic databases (Ovid), EndNote and Covidence.

6. Dissemination

The results of this study will be communicated to the target audiences, such as paediatricians, neonatologists, pediatric surgeons, anesthesiologists, policymakers and researchers, through peer-reviewed publication as well as other knowledge exchange platforms, such as conferences, congresses or symposia.

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7. Discussion

Growing evidence suggests possible associations between exposure to paracetamol during the fetal or neonatal period and neurodevelopmental, immunological, or hormonal adverse effects. Increasing use of paracetamol in neonatal populations, specifically ill neonates of NICUs, may have long-term outcome implications. The current systematic review will present a comprehensive overview of the available information on the long-term safety of prenatal and neonatal exposure to paracetamol and will provide insight into the perceived safety of paracetamol in this vulnerable population. The results of this review will be of interest to a broad range of audiences; including paediatricians, neonatologists, pediatric surgeons, anesthesiologists, policymakers, and researchers, as it could provide clinical guidance on the optimal prescription of this widely used drug. The methodological strengths of our review include a comprehensive search to locate all available evidence, published and unpublished, in the major electronic databases. We will use the systematic approach recommended by the GRADE working group to rate the certainty of evidence. In conducting this review, we also anticipate some methodological challenges. We foresee methodological weaknesses of the available literature, as we will not apply any study design limitations. Our review, therefore, might include studies that are not at the highest level of medical evidence and may be subject to vulnerabilities such as publication bias, a lack of ability to generalize, and inability to conclude a cause-effect relationship.

We believe this systematic review will provide timely evidence-based information on the long-term safety of prenatal and neonatal exposure to paracetamol and that it can contribute to the optimal use of this drug in the neonatal population.

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Data availability statements

All data relevant to the study will be included in the article or will be uploaded as supplementary information.

Authors' contributions

SSZ and JVDA contributed to the conception and design of the protocol and its scientific writing. SSZ, KS and JVDA contributed to the critical review of the protocol and review of its scientific content. All authors give final approval on the version to be submitted.

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Competing interests statement

Authors attest they have no conflict of interest to declare.

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Table 1 Data extraction form

Study ID	
Title	
Author	
Country of Study Conduct	United States UK Canada Australia Other
Study Characteristics	
Aim	
Design	RCT Non-randomized experimental study Cohort study Cross-sectional study Case-control study Systematic review Qualitative study Prevalence study Case series Case report Diagnostic test accuracy study Clinical prediction rule Economic evaluation Text and opinion Other
Start Date	
End Date	
Funding Source	
Conflict of Interest	
Participant Characteristics	
Population Description	
Inclusion Criteria	
Exclusion Criteria	
Sample Size (n)	
Birthweight (gram)	
Gestational Age (week)	
Postnatal Age (week)	
Underlying Condition	
Comorbidities	
Concurrent Medications	
Intervention/Exposure Details	
Paracetamol Dosing regimen (mg/kg/dose)	
Paracetamol Duration (days)	
Paracetamol Route of Administration	
Control Details	
Pharmacotherapy	Sedative-analgesic Epidural NSAID Other
Non-Specified-Standard Treatment	
Outcomes	
Primary Outcomes	
Long-Term Adverse Effects	
Neurodevelopmental Adverse Events	
Atopic Disorders	

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Reproductive Disorders	
Others	
Secondary Outcomes	
Pharmacokinetic Data	
Pharmacodynamic Data	
Short-Term Adverse Events	
Increased Hepatic Transaminases	
Gastrointestinal Hemorrhage	
Necrotizing Enterocolitis	
Feeding Intolerance	

Table 2 Primary and secondary outcome variables

Primary Outcome	
Long-Term Adverse Events	
Primary Outcome Variables	Neurodevelopmental adverse events Atopic disorders Reproductive disorders
Secondary Outcomes	
Secondary Outcome Variables	Pharmacokinetic variables Pharmacodynamic variables Short-Term Outcomes o Increased hepatic transaminases o Gastrointestinal hemorrhage o Necrotizing enterocolitis o Feeding intolerance

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- Currently available evidence on efficacy and short-term safety of paracetamol in ill neonates of neonatal intensive care units appears favourable.
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What this study hopes to add

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- Insight into the perceived safety of paracetamol in neonatal population.
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Abstract

Introduction: A surge in the use of paracetamol in neonates has resulted in growing concerns about its potential long-term adverse events. In this study, we conduct a systematic review of the long-term safety of prenatal and neonatal exposure to paracetamol in newborn infants.

Methods and analysis: We will follow the Joanna Briggs Institute Manual for Evidence Synthesis and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements to conduct and report this review. We will conduct a systematic search of Embase, Medline, Web of Science, and Google Scholar for studies with data on long-term adverse events in neonates that were exposed to paracetamol in the prenatal and/or neonatal period. We will not apply language or design limitations. We will use standardized risk of bias assessment tools to perform a quality assessment of each included article.

Ethics and dissemination: This systematic review will only involve access to publicly available data, and therefore ethical approval will not be required. The results of this study will be communicated to the target audience through peer-reviewed publication as well as other knowledge exchange platforms, such as conferences, congresses or symposia.

Trial registration: The protocol for this systematic review is submitted for registration to international database of prospectively registered systematic reviews (PROSPERO, awaiting registration number).

Keywords: Paracetamol, Neonates, Long-term safety

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1. Introduction

Paracetamol (para-acetylaminophenol, also known as acetaminophen), is one of the most widely used antipyretics and analgesics worldwide, and the most common medication encountered in paediatric care.[1] In recent years, the use of paracetamol in neonatal intensive care units (NICU) has also increased. The limited available evidence supporting the potential narcotic-sparing effect of paracetamol in term and preterm neonates, along with promising evidence for its efficacy for the closure of a hemodynamically significant patent ductus arteriosus (hsPDA) have resulted in a rapid increase in its use by many neonatal specialists.[2] The results from a cohort study and a small randomized clinical trial support the use of intravenous (IV) paracetamol in the immediate postoperative period to decrease the use of narcotics without an increase in pain score.[3,4] Of interest, available evidence for oral or rectal administration of paracetamol for control of mild to moderate pain did not provide a similar benefit.[5] Nevertheless, paracetamol continues to be used for pain control among neonates in a variety of formulations and routes to decrease the use of narcotics.

Over the past decade, the use of paracetamol as an alternative pharmacotherapy to Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for the treatment of hsPDA has been evolving. A recent systematic review and meta-analysis that examined the association of various pharmacotherapeutic options for closure of hsPDA in preterm infants showed that oral paracetamol ranked highest in efficacy in terms of reducing the need for repeat pharmacotherapy.[6] With the increasing use of paracetamol in neonates, specifically ill neonates of NICUs, the need for pharmacokinetics (PK), pharmacodynamics (PD), and optimal dosing and safety data has become paramount.

Although data exist on the PK and optimal dosing of paracetamol for pain relief in extremely and very preterm infants, there is no paracetamol population PK data for neonates with hsPDA.[2] Furthermore, there is a considerable paucity of PD studies, incorporation of the available evidence-based dosing recommendations, and reports on efficacy and safety outcomes of paracetamol in neonates. Although

currently available evidence on short-term safety of paracetamol in ill neonates of NICUs might be favourable, its long-term safety remains an area of debate.[2,7] Despite this significant lack of data, the perceived superior safety of paracetamol as compared to narcotics for the treatment of pain and NSAIDs for the closure of a hsPDA, has resulted in a strong desire for its use.

Long-term safety of prenatal and neonatal exposure to paracetamol has been an area of concern since the early 2000s.[8] In vivo and in vitro animal studies have shown evidence of neuroapoptosis with chronic use of paracetamol at therapeutic doses, causing altered neurotransmission with possible subsequent neuro-behavioural changes.[9] It has been suggested that prenatal use of paracetamol may interfere with endogenous hormones and signaling pathways in the developing fetus, leading to a reduction of fetal testicular testosterone production and alteration of the brain endocannabinoid system, resulting in developmental disruption and the associated behavioural changes.[10] Results of ecologic and cohort studies supported by biological plausibility have raised questions if the use of paracetamol during pregnancy or the early neonatal period can result in reproductive and immunological disruption and long-term adverse events such as cryptorchidism, atopic disorders, attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD).[11,12]

Although the mechanism of action of paracetamol is not yet clearly understood, it is believed that paracetamol's PD effects are mainly through central pathways. Besides inhibition of prostaglandin and nitric oxide biosynthetic pathways, augmentation of descending inhibitory serotonergic pain pathways and effects on cannabinoid (CB) receptors through active metabolites are its other hypothesized mechanisms of action.[13] Whether paracetamol's interference with neurohormonal regulatory mechanisms can result in long-term neurological, immunological, or hormonal disruption remains an important question and is an area that requires additional information.

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1. Objective:

We aim to conduct a systematic review of the available evidence on the long-term safety of prenatal and neonatal exposure to paracetamol in newborn infants.

2. Materials and Methods:

2.1. Protocol registration

The protocol for this systematic review is submitted for registration to international database of prospectively registered systematic reviews (PROSPERO, awaiting registration number). We will follow the Joanna Briggs Institute Manual for Evidence Synthesis and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements to conduct and report this review, respectively.[14,15]

2.2. Search strategy

A search strategy will be developed in consultation with a professional librarian, using the following electronic databases: Embase (Ovid), Medline (Ovid), and Web of Science (Ovid) from their inception to October 2020. The strategy will be translated, as appropriate, for each database. The bibliographies of any relevant articles for additional references will be reviewed. Using Google Scholar, we will also search for any relevant studies that are not commercially published, such as dissertations, policy documents, conference abstracts, and book chapters. We aim to contact authors of published trials and unpublished work to clarify information when necessary.

2.2.1 Prenatal exposure

We will use a combination of the following controlled terms in Ovid Medline in our search for articles related to prenatal exposure to paracetamol: (exp Infant/ or exp Infant, Small for Gestational Age/ or exp Infant, Low Birth Weight/ or exp Infant, Premature/ or exp Infant, Very Low Birth Weight/ or exp Infant, Newborn/ AND exp acetaminophen/ or exp Paracetamol/ or exp APAP/ or exp Tylenol).

2.2.1 Neonatal exposure

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We will use a combination of the following controlled terms in Ovid Medline in our search for articles related to neonatal exposure to paracetamol: (exp Pregnancy/ or exp Prenatal Exposure Delayed Effects/ or exp Fetus/ or Abnormalities, Drug-Induced/ AND exp acetaminophen/ or exp Paracetamol/ or exp APAP/ or exp Tylenol).

3.3. Eligibility criteria

All interventional and observational original research articles, including randomized controlled trials (RCTs), prospective and retrospective cohort studies, and case reports describing prenatal or neonatal use of paracetamol that reported long-term safety outcomes will be eligible for inclusion, irrespective of the dose, route, frequency of administration and duration of treatment. In the studies with a control group, the provided intervention(s), placebo or standard practice will be the comparator. In studies with no comparator group, the observational report of the long-term safety of paracetamol during the study period will be collected. We will not apply any language or study design limitations. Animal studies and duplicate studies will be excluded.

3.4. Study selection and Data extraction

We will use Covidence as the primary screening and data extraction tool.[16] Two independent reviewers (KS and SSZ) will screen the resulting articles at the title and abstract level for eligibility. Eligible articles will then be reviewed at the full-text level by the two specified independent reviewers (KS and SSZ). We will extract data related to population, intervention, control and outcome from each study (Table 1). We will pilot test the data extraction form prior to its use. Any identified discrepancies will be resolved through discussion between three reviewers (JVDA, KS and SSZ).

3.5. Assessment of risk of bias and quality of evidence

Qualitative assessment of articles will be done using an appropriate standardized risk of bias assessment tool for each study design. These tools include the Cochrane risk-of-bias assessment tool for randomized trials (RoB 2), the Newcastle-Ottawa Quality Assessment Scale for cohort and case control studies, and the modified Newcastle-Ottawa scale for cross-sectional studies to assess cross-sectional studies.[17,18] The quality of case reports will be evaluated using the Checklist for Case Reports by the

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Joanna Briggs Institute (JBI).[14] The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be used by the two reviewers (KS, SSZ) for rating the quality of included evidence.[19] Any disagreement will be solved through further discussion between three reviewers (JVDA, KS and SSZ).

3. Outcomes and variables

Our primary outcome is the presence of long-term adverse events, defined as neurodevelopmental adverse events, atopic disorders, and reproductive disorders. We defined neurodevelopmental adverse events as report of ASD, ADHD, low intelligence quotient (IQ) and communication and behavioral problems, assessed beyond 18 months of age. Our secondary outcomes are PK data, PD data, and short-term adverse events. Short-term adverse events include increased hepatic transaminases, gastrointestinal hemorrhage, necrotizing enterocolitis, feeding intolerance, defined as the presence of abdominal distention, increased gastric residuals, or any other gastrointestinal symptom that results in a decreased or held feed (Table 2).

4. Patient and public involvement

Patients are not directly involved in the design or conduct of this study. We will plan public involvement mostly concerned with the interpretation of the review findings and the development of reporting plans and associated guidance.

5. Amendments

We will document any amendments to this protocol, with reference to saved searches and analysis methods, which will be recorded in bibliographic databases (Ovid), EndNote and Covidence.

6. Dissemination

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The results of this study will be communicated to the target audiences, such as paediatricians, neonatologists, pediatric surgeons, anesthesiologists, policymakers and researchers, through peer-reviewed publication as well as other knowledge exchange platforms, such as conferences, congresses or symposia.

7. Discussion

Growing evidence suggests possible associations between exposure to paracetamol during the fetal or neonatal period and neurodevelopmental, immunological, or hormonal adverse effects. Increasing use of paracetamol in neonatal populations, specifically ill neonates of NICUs, may have long-term outcome implications. The current systematic review will present a comprehensive overview of the available information on the long-term safety of prenatal and neonatal exposure to paracetamol and will provide insight into the perceived safety of paracetamol in this vulnerable population. The results of this review will be of interest to a broad range of audiences; including paediatricians, neonatologists, pediatric surgeons, anesthesiologists, policymakers, and researchers, as it could provide clinical guidance on the optimal prescription of this widely used drug. The methodological strengths of our review include a comprehensive search to locate all available evidence, published and unpublished, in the major electronic databases. We will use the systematic approach recommended by the GRADE working group to rate the certainty of evidence. In conducting this review, we also anticipate some methodological challenges. We foresee methodological weaknesses of the available literature, as we will not apply any study design limitations. Our review, therefore, might include studies that are not at the highest level of medical evidence and may be subject to vulnerabilities such as publication bias, a lack of ability to generalize, and inability to conclude a cause-effect relationship.

We believe this systematic review will provide timely evidence-based information on the long-term safety of prenatal and neonatal exposure to paracetamol and that it can contribute to the optimal use of this drug in the neonatal population.

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Authors' contributions

SSZ and JVDA contributed to the conception and design of the protocol and its scientific writing. SSZ, KS and JVDA contributed to the critical review of the protocol and review of its scientific content. All authors give final approval on the version to be submitted.

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Competing interests statement

Authors attest they have no conflict of interest to declare.

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Table 1 Data extraction form

Study ID	
Title	
Author	
Country of Study Conduct	United States UK Canada Australia Other
Study Characteristics	
Aim	
Design	RCT Non-randomized experimental study Cohort study Cross-sectional study Case-control study Systematic review Qualitative study Prevalence study Case series Case report Diagnostic test accuracy study Clinical prediction rule Economic evaluation Text and opinion Other
Start Date	
End Date	
Funding Source	
Conflict of Interest	
Participant Characteristics	
Population Description	
Inclusion Criteria	
Exclusion Criteria	
Sample Size (n)	
Birthweight (gram)	
Gestational Age (week)	
Postnatal Age (week)	
Underlying Condition	
Comorbidities	
Concurrent Medications	
Intervention/Exposure Details	
Paracetamol Dosing regimen (mg/kg/dose)	
Paracetamol Duration (days)	
Paracetamol Route of Administration	
Control Details	
Pharmacotherapy	Sedative-analgesic Epidural NSAID Other
Non-Specified-Standard Treatment	
Outcomes	
Primary Outcomes	
Long-Term Adverse Effects	
Neurodevelopmental Adverse Events	
Atopic Disorders	

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Reproductive Disorders	
Others	
Secondary Outcomes	
Pharmacokinetic Data	
Pharmacodynamic Data	
Short-Term Adverse Events	
Increased Hepatic Transaminases	
Gastrointestinal Hemorrhage	
Necrotizing Enterocolitis	
Feeding Intolerance	

Table 2 Primary and secondary outcome variables

Primary Outcome	
Long-Term Adverse Events	
Primary Outcome Variables	Neurodevelopmental adverse events (ASD, ADHD, low IQ, communication and behavioral problems) Atopic disorders Reproductive disorders
Secondary Outcomes	
Secondary Outcome Variables	Pharmacokinetic variables Pharmacodynamic variables Short-Term Outcomes o Increased hepatic transaminases o Gastrointestinal hemorrhage o Necrotizing enterocolitis o Feeding intolerance

ASD autism spectrum disorder, ADHD attention deficit hyperactivity disorder, IQ intelligence quotient

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