STUDY PROTOCOL

What is the association between common medications (indomethacin, ibuprofen and acetaminophen) and spontaneous intestinal perforations in premature infants? A systematic review protocol [version 1; peer review: awaiting peer review]

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Abstract

Background: Spontaneous intestinal perforation (SIP) affects very low birth weight preterm neonates and accounts for 44% of gastrointestinal perforations. Commonly used medications such as indomethacin, ibuprofen and acetaminophen for PDA closure, increases the risk of intestinal perforation. Unfortunately, the majority of the data combine SIP with those affected by necrotizing enterocolitis (NEC) despite them being separate entities. This systematic review aims to explore the association between the use of common medications and SIP in the premature infant cohort independently from NEC.

Methods: Our study will focus on preterm infants with exposure to either indomethacin, ibuprofen or acetaminophen where SIP is a reported outcome. A health science librarian will search Medline and Medline in Process via OVID, Embase Classic + Embase via OVID, the LILACS database, the SciELO database and the Cochrane Library including EBM Reviews - Cochrane Central Register of Controlled Trials. Search dates for each database will be from their respective dates of inception to March 2022. All articles will undergo screening by two independent reviewers, and if selected, data extraction with risk of bias assessment by two independent reviewers. A third reviewer will settle any disagreements that may occur. Incidence of
SIP will be measured as a proportion. Individual proportions will be pooled using a random effects logistic regression model. The comparative incidence of SIP by treatment group will be measured using the odds ratio. Odds ratios will be pooled using the DerSimonian and Laird random effects model for meta-analysis.

**PROSPERO Registration:** CRD42017058603

**Keywords**
Systematic review, Premature neonates, Spontaneous intestinal perforation, Focal intestinal perforation, Ibuprofen, Indomethacin, Acetaminophen
Introduction
Spontaneous intestinal perforation (SIP) is the perforation of the gastrointestinal tract of a premature infant without an attributable cause.¹ SIP and necrotizing enterocolitis (NEC) are two major gastrointestinal entities in premature infants that can have profound adverse effects on long term outcomes.² While clinically they are separate entities, similarities in their initial presentations are overlapping which initially led to them being reported together as intestinal perforation.² However, teasing them apart underscores their differences in pathophysiology, management and outcome. After many years of aggressive interventions targeting the incidence of NEC, it is now declining.² SIP however, is emerging as more prevalent in the extremely low birth weight cohort that are being fed with human milk.²,³ This trend further emphasizes the need to not only understand how SIP and NEC differ but also to better understand potential modifiable risk factors for SIP.

The incidence of SIP is bimodal with an early presentation at 0-3 days and a second peak at 7-10 days of life.⁴ SIP clinically presents with sudden onset of abdominal distension. In addition, the abdomen can be shiny and bluish in color. Pneumoperitoneum is seen on abdominal imaging.⁵ Historically definitive diagnosis is made surgically. As the prevalence of SIP is increasing other means for clinical diagnosis have been suggested.² NEC in premature infants typically occurs from day of life 13-20.⁶ Clinical presentation of NEC can be varied from subtle and nonspecific to fulminant.⁶ It can present with feed intolerance, bloody stools and numerous abdominal signs including distension, visible bowel loops and discoloration. On blood work there can be neutropenia, thrombocytopenia, metabolic acidosis, electrolyte abnormalities and coagulopathy. Radiographically NEC can demonstrate intestinal distension, thickened bowel walls, pneumatosis intestinalis and pneumoperitoneum. Both NEC and SIP independently increase the risk of adverse outcomes including Grade 3-4 intraventricular hemorrhage, severe retinopathy of prematurity and nosocomial infections.⁷ SIP alone is less likely to adversely affect neurodevelopmental outcome when compared to NEC.⁷

SIP and NEC also differ in pathophysiology. NEC is the result of the numerous interactions leading to the imbalance of the intestinal microflora and damage to the intestinal wall resulting in inflammatory necrosis.⁶ SIP is related to an exacerbation of the imbalance of intestinal mucosal hyperplasia and submucosal hypoplasia, leading to a thin bowel wall resulting in perforation.¹ Both low birth weight and prematurity are risk factors for both SIP and NEC but those with SIP are typically more immature and/or smaller.³ Both lower gestational age and birth weight correlate to thinner bowel walls secondary to decrease in insulin-like growth factor-1 which is responsible for increasing the bowel wall submucosa.² Common medications such as indomethacin ibuprofen and acetaminophen are thought to increase the risk of intestinal perforation. Non-steroidal anti-inflammatory medications lead to decreased nitric oxide synthase resulting in decreased peristalsis and in animal studies this can lead to a dilated ileus.³

Given the rise in SIP incidence it is imperative to assess potential modifiable risk factors in this fragile population such as medication exposure. The goal of this systematic review is to characterize the association of SIP with exposure to common medications including indomethacin, ibuprofen and acetaminophen. The population will be premature infants or infants with a birth weight less than 2.5 kg. The intervention will be exposure to indomethacin, ibuprofen or acetaminophen compared to no medication exposure or comparison between different medication exposures. The outcome of interest primarily is SIP.

Methods
The protocol of this review has been registered on PROSPERO (registration number: CRD42017058603).³ The strategy involves a comprehensive systematic review of the literature and meta-analysis. The procedures will follow the methods outlined in the Cochrane handbook for systematic reviews.⁶ This includes guidance in planning the review, searching and selecting studies, collecting data, as well as the risk of bias and prospective meta-analysis. The protocol of this systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) Statement.⁸

Study selection criteria
Study population
The eligible population will involve preterm infants less than 37 weeks or birth weight less than 2.5 kg. Exclusion criteria are any studies that do not meet inclusion criteria.

Types of intervention
The intervention is exposure to one of the following medications: indomethacin, ibuprofen or acetaminophen. Medications can be delivered via oral, rectal or intravenous routes.
Outcomes

The primary outcome is spontaneous intestinal perforation with comparisons between those exposed to one of the listed medications compared to either no medication or to an alternate medication from that list (For example Indomethacin versus no indomethacin or indomethacin versus ibuprofen). If the diagnosis of SIP is not unclear the study will be excluded.

Study types

We will consider studies with the following retrospective or prospective designs in any language worldwide:

- Randomized controlled trials
- Controlled trials
- Cohort studies
- Case control
- Case report/series with five or more cases

Study settings

Given the premature patient population the studies will be in the inpatient hospital setting.

Information sources

The following databases will be searched by a health sciences librarian: Medline and Medline in Process via OVID, Embase Classic + Embase via OVID, the LILACS database, the SciELO database and the Cochrane Library including EBM Reviews - Cochrane Central Register of Controlled Trials via Ovid. Search timeline will be from database inception to October 2022.

Search strategy

A search strategy will be developed in Medline, and then translated into the other databases, as appropriate (see extended data). There will be no language exclusion criteria, nor any other publication restrictions. All references will be entered into an Endnote file for processing.

Selection process

All studies found through the search algorithms will be placed in reference management programs (EndNote and Covidence) and duplicates will be removed. The remaining studies will undergo screening to identify studies that meet the inclusion criteria. This will initially be done with an abstract screen performed by two independent reviewers and followed by a full text screen to assess study eligibility. Reasons for exclusion will be documented and reported using a PRISMA flow diagram.

Data collection process

All primary and secondary data will be extracted from each eligible study and incorporated into excel (See https://doi.org/10.17605/OSF.IO/QB9JY for a list of data extraction points). This process will be conducted independently by two reviewers and any inconsistencies or queries will be resolved with the assistance of a biostatistician. Records and data will be managed using Microsoft Word and Excel and shared with the team.

Data items

Primary outcome

Spontaneous intestinal perforation as defined by either radiological (pneumoperitoneum, intramural echogenicity and echogenic extramural material on abdominal ultrasonography as pathognomonic signs with no evidence of pneumatosis intestinalis) or histopathologic evidence (focal hemorrhagic necrosis, possible hypoplasia of the muscularis layer and thinning of the submucosa) or surgical evidence of isolated intestinal perforation in the absence of histopathological features of necrotizing enterocolitis.13–15
Secondary outcomes

- NEC: Radiological (pneumatosis intestinalis, distended intestinal loops, thickened walls, portal venous gas, pneumoperitoneum) or surgical evidence of NEC with or without the Bell staging
- Acute kidney injury (AKI): Oliguria < 1ml/kg/hr of urine output
- Intraventricular hemorrhage (IVH): Papile criteria of IVH
- Retinopathy of prematurity (ROP): Using the International Classification of ROP
- Neonatal death: Number of reported deaths either prior to discharge
- Bronchopulmonary dysplasia (BPD): Requirement of oxygen and/or positive pressure at 28 days or 36 weeks postmenstrual age or at time of discharge

If a study does not fit the above definitions, then the outcome will not be used for analysis.

Missing data
In the case of missing data, we will follow the Cochrane methodology outlined in the Cochrane handbook for systematic reviews, using the traditional cut off of 5% missing as small and >20% as a large risk of bias.9 This will be conducted by two independent reviewers and any inconsistencies or queries will be resolved with the assistance of a biostatistician. If the level of missing data is considered to be high risk of bias, the corresponding author will be contacted to determine if there is any additional data prior to determining preclusion of the outcome from the analysis. Any implications resulting from missing data will be reported.

Risk of bias assessment
Each included study will be assessed for the internal validity of that study. This will be conducted independently by two reviewers with any disagreements or queries to be resolved with the assistance of third-party adjudication. To conduct the internal validity assessment the ROBINS-I will be used for the risk of bias for non-randomized trials and the Cochrane risk of bias tool-II (RoB 2) will be used for randomized trials.16,17 There is no assessment tool for case reports or for case series and we will only include those with greater than 5 cases. Those eligible case reports/series will only be included in the pooled prevalence of the outcome and not in any comparative studies.

Effect measure
The incidence of SIP will be measured as a proportion. The association of SIP with type of treatment will be measured using the odds ratio.

Synthesis methods
Descriptive statistics and tables of evidence summary will be reported. Incidence proportions will be pooled using a random effects logistic regression model.18 Odds ratios will be pooled using the DerSimonian and Laird random effects model for meta-analysis. Heterogeneity in the study estimates will be calculated using the I² statistic.19 In the event that I²>75%, the heterogeneity will be considered high and pooled estimates will not be reported. Forest plots will be used to present the meta-analysis results, while qualitative synthesis with either narrative description or tabular representation will be presented when studies could not be quantitatively combined due to unacceptable heterogeneity of missing data precluding meta-analysis. All statistical analyses will be conducted using R statistical software (version 4.0.5)20 with ‘meta’ package.21

Reporting bias assessment
Funnel plots will be used to assess publication bias provided at least 10 comparative studies of odds ratios of SIP are pooled in a meta-analysis.15 For single proportions, funnel plots have not been found to be reliable, and will therefore not be applied when pooling SIP incidence.72

Certainty assessment
For each outcome, when prognostic or effect estimates are not very wide and can be conclusively interpreted, we will grade the certainty of evidence as per the published GRADE approach (Grading of Recommendations, Assessment, Development, and Evaluation-GRADE).23
Patient and public involvement
For the systematic review there was no direct contact with patients. Studies included were all found within public library database.

Ethics and dissemination
Ethics approval will not be required for our systematic review as there is no patient contact. Any modifications to the protocol will be reported and included in the PROSPERO protocol, freely available on the internet. Our goal is to submit the findings of this review for peer-review publication with abstracts to be presented at local and international conferences.

Study status
The initial database search was completed with plans to update prior to completing analysis and risk and bias assessment. Both data extraction and risk of bias assessment are underway but not completed.

Data availability
Underlying data
No data is associated with this article.

Extended data
Open Science Framework: What is the association between common medications (indomethacin, ibuprofen and acetaminophen) and spontaneous intestinal perforations in premature infants? A systematic review protocol, https://doi.org/10.17605/OSF.IO/QB9JY.24

This project contains the following extended data:
- Data Extraction Points.pdf
- Search Strategy.pdf

Reporting guidelines
Open Science Framework: PRISMA-P checklist for ‘What is the association between common medications (indomethacin, ibuprofen and acetaminophen) and spontaneous intestinal perforations in premature infants? A systematic review protocol’, https://doi.org/10.17605/OSF.IO/QB9JY.24

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References
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