Research Topics Pertaining to Cardiorespiratory Health in Newborn Medicine

by

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Abstract

Preterm infants face many challenges, particularly concerning their cardiorespiratory health. Within this context, the management of apnea of prematurity (AOP) and the control of patent ductus arteriosus (PDA) emerge as paramount concerns. This thesis consists of 2 projects. Chapter 2 is a randomized controlled trial protocol, that investigates the use of caffeine therapy in moderate and late premature infants (MLPT). Caffeine is a common medication in neonatal intensive care units (NICUs) that is effective in reducing apnea episodes. This project aims to fill knowledge gaps related to the impact of caffeine on respiratory outcomes and long-term neurodevelopmental outcomes in MLPT infants, a population at risk that represents a substantial proportion of preterm births. Chapter 3 is a systematic review and meta-analysis of randomized controlled trials that explore the use of acetaminophen versus indomethacin for managing PDA in preterm infants. While indomethacin is a common treatment for PDA, acetaminophen offers an alternative that may have fewer side effects. The study demonstrates that acetaminophen is as effective as indomethacin in closing PDA, with the added benefit of reducing the risk of necrotizing enterocolitis and post-treatment azotemia. These two projects highlight crucial aspects of the management of preterm infants. Caffeine may play a substantial role in improving both short- and long-term outcomes in MLPT. With its promising safety profile, acetaminophen emerges as a practical alternative for closing PDA. Both initiatives highlight the value of additional studies to enrich evidence and guide decision-making in neonatal cardiorespiratory care.

Preface

This thesis is an original work by Eyad Bitar.

There are two different projects in this thesis. Chapter 2 is a protocol for a randomized controlled trial on caffeine therapy in moderate and late preterm infants. Chapter 3 is a systematic review and meta-analysis of a randomized controlled trial comparing acetaminophen versus indomethacin for patent ductus arteriosus management in premature infants. Chapter 3 has been published in Paediatrics & Child Health (1). The main author, Eyad Bitar, contributed to all review stages, including research question formulation, protocol development, literature search, study selection, data extraction, and manuscript development. Data synthesis and interpretation of results were done in conjunction with the study supervisor, Manoj Kumar.

(1) Bitar E, Hyderi A, Campbell SM, Kumar M. Acetaminophen versus indomethacin for patent ductus arteriosus management in premature infants: systematic review and meta-analysis of randomized controlled trials. Paediatr Child Health. 2023;28(5):291-298. Published 2023 Apr 4. doi:10.1093/pch/pxac130

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List of Abbreviations

AOP: apnea of prematurity

BW: birth weight

BPD: bronchopulmonary dysplasia

DA: ductus arteriosus

GA: gestational age

HsPDA: hemodynamically significant patent ductus arteriosus

IVH: intraventricular hemorrhage

MLPT: moderate and late preterm

NICU: neonatal intensive care unit

NEC: necrotizing enterocolitis

NSAIDs: non-steroidal anti-inflammatory drugs

OR: odds ratio

PDA: patent ductus arteriosus

PG: prostaglandin

PMA: Post-menstrual age

RCT: randomized controlled trial

ROP: retinopathy of prematurity

RR: risk ratio

Chapter 1: Introduction

1.1 Caffeine for Apnea of Prematurity (AOP)

AOP is a common and clinically significant condition that affects premature infants born less than 37 weeks gestational age (GA) (1). It is characterized by the cessation of breathing for longer than 20 seconds, or less if associated with a decrease in heart rate and oxygen saturation (2). AOP creates considerable challenges in neonatal care requiring close monitoring and appropriate intervention to ensure optimal outcomes. GA has an inverse relationship with its incidence. Among infants who are born prematurely, extremely preterm infants born before 29 weeks GA infants have the highest incidence rate. Nearly all extremely premature infants have apneas (3), compared to 85% of infants born at 30 weeks GA. Even moderate to late preterm (MLPT) infants born between 32 weeks gestation and 36 weeks and 6 days (commonly written as 36^{+6} weeks) gestation may experience apneas. 20% of those born at 34 weeks GA may develop AOP (4).

Fundamental mechanics are complex and still not fully understood. Both central and peripheral mechanisms could be involved in the development of apnea in premature infants. Central Mechanisms may include decreased central chemosensitivity, hypoxic ventilatory depression, upregulated inhibitory neurotransmitters and delayed central nervous system development. Abnormal carotid body activity, laryngeal chemoreflex and excessive bradycardic response are factors that represent the peripheral pathways involved in the pathophysiology of apnea (5-8). The infant's inability to maintain regular breathing patterns is influenced by these factors (Figure 1.6.1).

AOP episodes can be detected clinically by the parents or the health care providers and are confirmed through continuous cardiorespiratory monitoring in the neonatal intensive care unit (NICU). AOP presents both short-term and long-term consequences. In the short term, premature infants may experience desaturation and bradycardic episodes alongside apnea. Prolonged apnea and bradycardia can lead to a decrease in systemic blood pressure, potentially resulting in cerebral hypoperfusion, which may contribute to hypoxic-ischemic injury in the immature brain (9). The long-term effects of AOP remain a topic of debate, primarily due to the difficulty in establishing a direct link between AOP

and long-term outcomes. It was found that there is no direct evidence of a causal relationship between AOP and sudden infant death syndrome (SIDS) (10). In addition, no significant differences in neurodevelopmental outcomes were found between infants with AOP and control groups (11). However, recent evidence suggests that a higher number of days with AOP may be associated with neurodevelopmental impairments such as cerebral palsy and blindness at the age of 3 (12). However, it was not definitively established whether the neurodevelopmental consequences result from AOP-related events or if a pre-existing abnormality in the premature infant's brain makes them more prone to experiencing such events.

The management of AOP involves several strategies. Positioning techniques and optimizing the NICU environment can help prevent the events (13). Applying positive pressure through non-invasive respiratory support helps keep the airways open, leading to decreased atelectasis, improved oxygen levels, and reduced occurrences of apnea (14). The most frequently prescribed medication for the treatment of AOP is caffeine, a central nervous system stimulant. Caffeine primarily operates by inhibiting adenosine receptors, thereby prompting stimulation of the central nervous system and the respiratory centers located in the brainstem (15). This results in several positive effects, including heightened minute ventilation, increased responsiveness to carbon dioxide, elevated skeletal muscle tone, reduced fatigue in the diaphragm, and improved diaphragmatic contractility (16,17). Caffeine reduces the frequency and severity of apnea episodes, stimulates the infant's respiratory drive, and may improve several respiratory outcomes (18). Up to this point, most of the research concerning caffeine's impact on newborns has centred around extremely preterm infants due to their susceptibility to health issues and higher morbidity and mortality (19). However, there is a substantial gap in our understanding regarding how caffeine affects MLPT infants, who are born between 32^{+0} and 36^{+6} weeks GA even though they constitute the largest proportion of premature births.

1.2 Patent ductus arteriosus (PDA)

The ductus arteriosus (DA) is an essential vascular shunt in the human fetus. It allows for communication between the pulmonary and systematic circulations. In utero, about

90% of right ventricular output travels through the duct bypassing the pulmonary circulation (20). Patency of the DA is predominantly maintained by prostaglandins (PGs). PGs are produced by the placenta and the DA itself (21). Prostaglandin E2 (PGE2) is the most biologically active PG (22). PGE2 is synthesized from membranous phospholipids. This process is mediated by 2 enzymes: cyclooxygenase (COX) which generates prostaglandin G2 (PGG2) from arachidonic acid and then converts it to prostaglandin H2 (PGH2) by the peroxidase (23). PGE2 induces the formation of cyclic adenosine monophosphate (cAMP). As a result, vasoconstriction is prevented, and vasodilation is maintained (24). Similarly, nitric oxide (NO) which is synthesized in the wall of the DA enhances the production of cyclic guanosine monophosphate (cGMP) which subsequently induces vasodilation (25). In utero closure of DA in the human fetus has poor fetal impact, ranging from right ventricle failure to hydrops fetalis and fetal demise (26). Functional closure of the DA starts in the first hours of life in the majority of term infants and by 48-72 hours almost 100% are closed (27). This process is determined by several changes starting in late gestation which lead to a change in ductal tone. Postnatally, the drop in pulmonary vascular resistance leads to a decrease in the pressure within the lumen of the DA. On the other hand, the production of PGE2 declines with the removal of the placenta and the breakdown of PG in the lungs (28). In addition, the sensitivity of the DA to PGE2 is reduced by the increase in oxygen concentration (29). Increased arterial oxygen pressure also has a direct constrictive effect on smooth muscles and ductus walls (31). These changes trigger the functional closure of the DA. Permanent anatomic closure of the DA, on the other hand, occurs through a process of remodeling which is essential to prevent the reopening of the duct (31). In premature infants, in addition to the functional immaturity of the DA, endogenous PG is probably responsible for the persistent patency of the DA due to its relaxing effect (32). The catabolism of PGE2 is reduced in smaller gestation (33). Furthermore, the sensitivity of the DA to circulating PGE2 and nitric oxide is higher in preterm infants (34,35). As a result, closure of the DA is delayed or even fails to occur in premature infants.

It is well known that infants born prematurely experience difficulties in achieving a permanent ductal closure. 87% of infants born at 24 weeks are found to have PDA at 7

days of age (36). PDA is linked to significant morbidity and mortality in premature neonates (37). The optimal management for PDA in extremely premature infants remains unclear (38). Non-steroidal anti-inflammatory drugs (NSAIDs) work by reducing the production of PGs by blocking the conversion of arachidonic acid into PGG2 (Figure 1.6.2). Indomethacin is a widely used NSAID for medical closure of the PDA. The role of indomethacin in closing the duct was first described in 1976 (39,40). The evidence shows that it does significantly increase rates of PDA closure but with no benefit on PDA-related outcomes (41). A meta-analysis on the use of prophylactic indomethacin for PDA treatment in preterm infants reported only short-term benefits (decreased risk of severe intraventricular hemorrhage and the need for surgical ligation) but with no long-term neurodevelopmental benefit (42). Indomethacin could have several side effects, most commonly the adverse vasoconstrictive effects on renal, cerebral and mesenteric vessels (43,44). Acetaminophen, on the other hand, has gained more interest lately based on the assumption that it is as effective but with fewer side effects. It works by blocking the PG pathway preventing the formation of PGH2. Acetaminophen may serve as an alternative to indomethacin if it demonstrates comparable effectiveness in closing the PDA.

1.3 Summary

The existing body of evidence currently lacks comprehensive insights into the true impact of caffeine administration on MLPT. Notably, there is an absence of randomized controlled trials (RCTs) that have specifically investigated both short-term and long-term outcomes within this distinctive population. Furthermore, while indomethacin has demonstrated efficacy in achieving PDA closure, its application is accompanied by a notable array of adverse effects. In contrast, acetaminophen offers a compelling alternative, characterized by a more favorable side effect profile. These essential trials are important for providing guidance to clinicians and informing guidelines committees. This thesis serves as a focal point for the development of an RCT protocol designed to explore the effects of caffeine in MLPT. Additionally, it aims to conduct a comprehensive systematic review and meta-analysis comparing the efficacy of acetaminophen versus indomethacin for PDA management in preterm infants.

1.4 Objectives

This thesis aims to contribute to the understanding of these critical aspects of neonatal cardiorespiratory care by addressing two key objectives:

Objective 1: To investigate the use of caffeine therapy in MLPT infants. This investigation will fill knowledge gaps regarding the efficacy, and short- and long-term outcomes associated with caffeine therapy in this specific population. We hypothesize that caffeine therapy reduces the duration of respiratory support in this specific population.

Objective 2: To conduct a systematic review and meta-analysis comparing the use of acetaminophen and indomethacin in the management of PDA in preterm infants. This review will assess the efficacy and safety of acetaminophen as an alternative treatment for PDA and provide a comprehensive overview of the available evidence.

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1.6 Figures

Figure 1.6.1. Possible mechanisms of apnea of prematurity

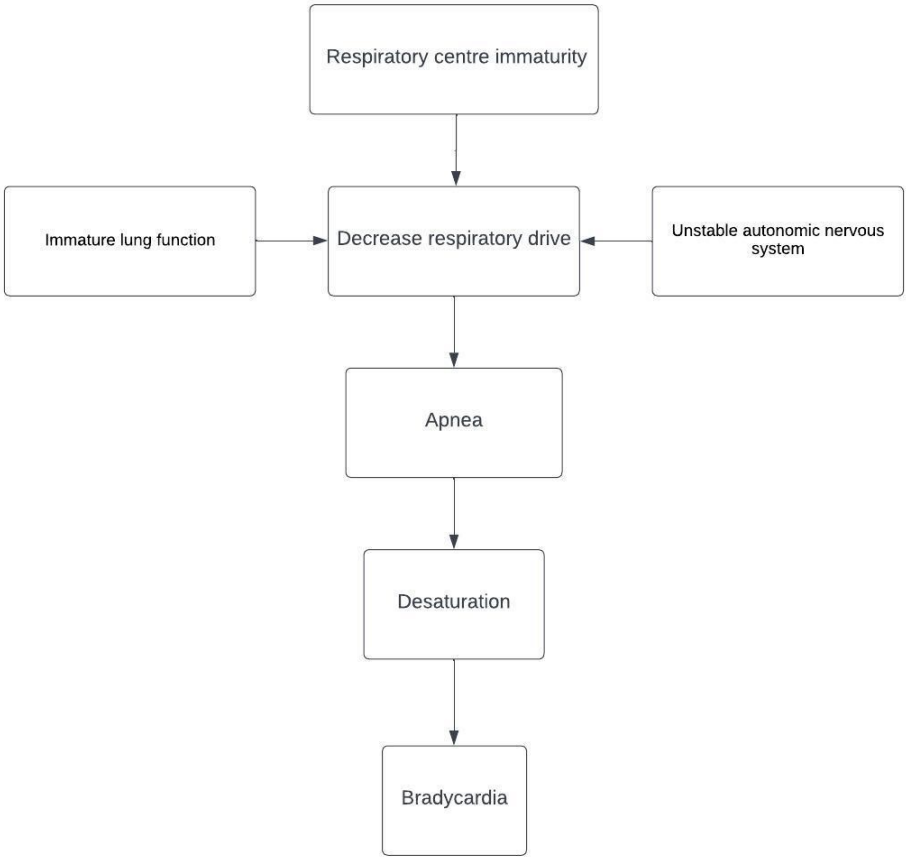
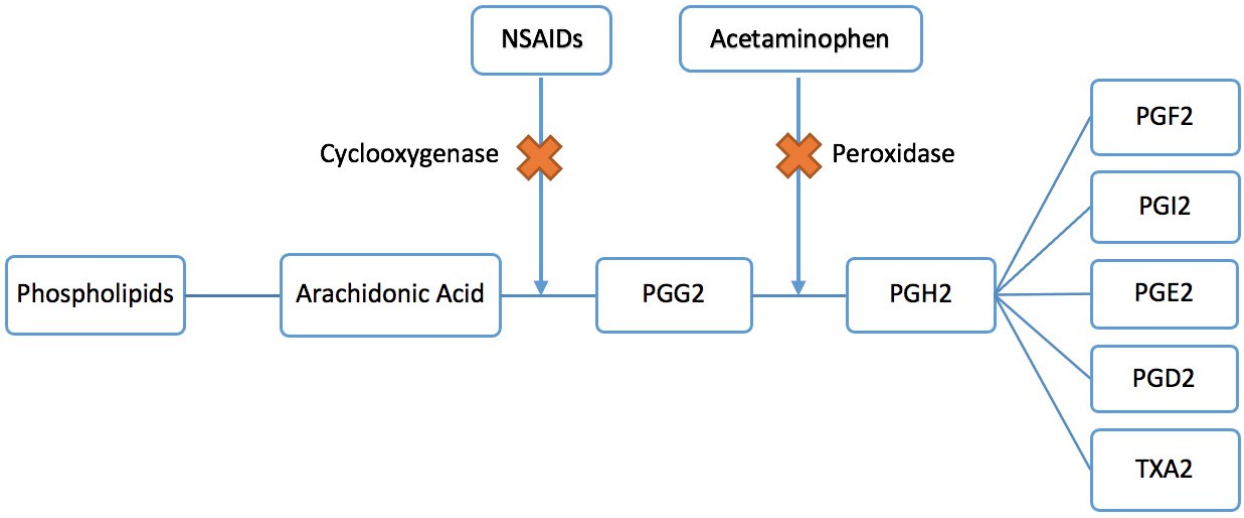


Figure 1.6.2. Prostaglandins synthesis pathway



Chapter 2: Caffeine Therapy in Moderate and Late Premature Infants: A Protocol for a Randomized Controlled Trial

2.1 Introduction

Caffeine is a commonly used medication in the NICU for the treatment of AOP in newborn infants (1). Apnea refers to a pause in breathing that lasts longer than 20 seconds or is accompanied by a decrease in heart rate and oxygen levels (2). AOP is a common condition among preterm infants and can lead to significant complications if not treated promptly (3). The incidence of AOP increases as GA decreases and could reach 100% of infants born before 28 weeks GA (4). AOP is linked to physiological immaturity and poor myelination of the higher breathing centers in premature infants (5). The frequency of apnea gradually decreases as preterm infants grow; however, it may persist until the age of 44 weeks after conception (6). Several studies have shown that multiple persistent hypoxic and bradycardic spells may be associated with multiple morbidities, including long-term neurodevelopmental problems (7). However, a causal relationship has not been proven yet. Caffeine acts primarily by blocking adenosine receptors leading to the stimulation of the central nervous system and respiratory centers in the brainstem (8). It leads to an increase in minute ventilation, increased sensitivity to carbon dioxide, an increase in skeletal muscle tone, decreased diaphragmatic fatigue, and enhanced diaphragmatic contractility (9,10). The use of caffeine in premature infants has been shown to have several clinical benefits. It reduces the frequency and severity of apnea episodes, which could help to prevent the need for resuscitation and improve oxygenation (11). Caffeine can also help reduce the duration of non-invasive respiratory support and minimize the need for mechanical ventilation (12,13). This is important, as mechanical ventilation could be associated with many complications in preterm infants (14). Furthermore, the use of caffeine in very premature infants has been associated with a shorter duration of hospitalization, mainly due to the reduction in apnea episodes and respiratory support (15). Studies have shown that the use of caffeine therapy in very premature infants is associated with improved long-term neurodevelopmental outcomes. It is effective in preventing

bronchopulmonary dysplasia (BPD), cerebral palsy, and cognitive impairment in extremely preterm infants (16-18).

MLPT infants refer to those who are born between 32^{+0} and 36^{+6} weeks GA (19). Globally, an estimated 13.8 million infants were born preterm in 2020 and 85% were MLPT (20). While these infants are generally more developed than extremely preterm infants, they can face many unique challenges compared to full-term infants. They are at risk for respiratory disease, apnea, hypoglycemia, temperature instability, hyperbilirubinemia, intraventricular hemorrhage (IVH), infection, and feeding difficulty (21). MLPT infants are reported to be at greater risk of death and cerebral palsy compared to term infants (22, 23).

Until now, most studies on caffeine in newborns have focused on extremely preterm infants as the group with the greatest risk of morbidity and mortality (24). There is a significant knowledge gap in terms of the effect of caffeine on MLPT infants which represent the majority of infants who are born preterm. While caffeine has shown effectiveness in reducing apnea episodes and improving respiratory outcomes, more research is needed to determine the ideal dosage regimen for this specific population. Also, the potential impact of caffeine treatment on neurodevelopmental outcomes, including cognitive function, behaviour, and learning disabilities remains unknown for MLPT infants. In addition, although caffeine is generally considered safe, comprehensive studies evaluating its safety profile specifically in MLPT infants are lacking. Addressing these knowledge gaps will allow researchers to develop caffeine therapy protocols for MLPT infants, enhancing both short-term management and long-term outcomes.

A recent RCT showed that caffeine citrate (with doses of 10 and 20 mg/kg/day) was effective in preventing episodes of intermittent hypoxia in late premature infants born at 34+0–36+6 weeks GA (25). Except for tachycardia and possibly some effect on growth, caffeine did not have significant adverse effects. It is uncertain whether the reduction in hypoxic episodes would result in significant improvements in clinically important outcomes, such as long-term neurodevelopment. Another study highlighted the potential

for significant cost savings and the opportunity for quality improvement when considering outpatient caffeine management compared to inpatient observation in late premature infants with AOP (26). However, the results of this study need confirmation through prospective studies to establish the validity of these findings. Iranpour et al, showed that early prophylactic caffeine therapy in premature neonates with birth weights (BWs) between 1250g and 2000g can reduce the mean duration required for non-invasive respiratory support, duration of hospitalization in the NICU and incidence of IVH at 7 days after birth (12). However, this RCT was limited by the lack of a double-blind design and a relatively small sample size, emphasizing the need for further research.

There is a lack of consensus regarding the criteria for selecting MLPT infants who would benefit the most from caffeine therapy. Further research is needed to identify specific clinical characteristics or risk factors that can guide individualized treatment decisions, ensuring that the potential benefits outweigh any risks.

Despite caffeine therapy being commonly used in the NICU, there are still knowledge gaps regarding its short-term and long-term outcomes in MLPT infants. This trial will address these gaps by generating new data specific to this population, providing valuable insights for clinicians and researchers. Clinical practices and guidelines are very variable, and a new trial will provide contemporary evidence that aligns with current healthcare practices. By obtaining robust evidence on the effectiveness of caffeine therapy in this population, the results from the trial can guide clinical decision-making, optimize treatment strategies, and potentially improve patient outcomes.

The purpose of this study protocol is to describe how the clinical trial will be conducted and the integrity of the data collection and reporting.

If caffeine is proven effective in reducing the duration of respiratory support, this could help premature infants to establish enteral feed faster, shorten hospital stays, and could positively impact healthcare resource usage. The findings will not only benefit clinical practice but also inform future research endeavours in this field.

2.2 Methods

2.2.1 Objectives

Primary objectives: The primary objective is to determine whether caffeine therapy improves respiratory outcomes in MLPT infants. We hypothesize that caffeine therapy reduces the duration of respiratory support in this specific population.

Secondary objectives: The secondary objectives are:

- Determine the long-term neurodevelopmental outcome associated with the use of caffeine.
- Evaluate other impacts of caffeine therapy on infant respiratory stability such as frequency of significant apneas, time to wean from respiratory support, and need for invasive ventilation.
- Assess healthcare utilization patterns by analyzing the length of hospital stay and hospital readmission.

2.2.2 Trial design

This is a double-blind multi-centre RCT, analyzed by intention to treat.

2.2.3 Study setting

Multiple NICUs in Edmonton (Royal Alexandra Hospital, Grey Nuns Hospital, Misericordia Hospital, Sturgeon Community Hospital).

2.2.4 Principal Research Question

Does caffeine therapy improve respiratory outcomes in MLPT infants?

Population (P)**:** Premature infants born between 32+0 and 34+6 weeks of gestation with a primary admission to NICU, or transfer within 72 hours, who are receiving invasive or non-invasive respiratory support.

Intervention (I): Caffeine therapy.

Comparison (C): Placebo (normal saline).

Outcome (O): Duration of respiratory support during the hospital stay.

Time (T): Until the time of discharge from the hospital

2.2.5 Eligibility criteria

- Entry criteria: 1) Gestational age 32 0/7 – 34 6/7 weeks. 2) Postnatal age < 72 hours. 3) On invasive or non-invasive respiratory support
- Exclusion Criteria: 1) Dysmorphic features or congenital malformations that adversely affect life expectancy or neurodevelopment. 2) Known or strongly suspected cyanotic heart disease.

2.2.6 Outcomes

Primary outcome:

- Duration of respiratory support during the hospital stay. This is defined as the number of hours on invasive and non-invasive mechanical ventilation (nasal continuous positive airway pressure and high flow nasal cannula).

Secondary outcomes:

- The number of significant apneas per day (apneas that need any intervention such as stimulation, re-positioning, administration of positive pressure ventilation or free flow oxygen).
- Post-menstrual age (PMA) at successful weaning from respiratory support.
- PMA at discharge home.
- Need for invasive mechanical ventilation in those not intubated at the time of randomization.
- Length of hospital stay.
- Hospital readmission proportion up to 44 weeks PMA
- In-hospital mortality proportion
- Long-term neurodevelopmental outcomes (Cognitive function, behaviour, and occurrence of learning disabilities) assessed at 18-24 months corrected age using

standardized developmental assessments (e.g., Bayley Scales of Infant and Toddler Development).

2.2.7 The rationale for the selection of outcome measures

The main objective of the study is to evaluate the effect of caffeine on the infants' need for respiratory support, and the primary outcome, duration of respiratory support, directly addressed this goal. The study can assess whether caffeine results in a shorter period of respiratory support in this cohort by tracking the time from the start of respiratory support to effective weaning to a room air/low-flow oxygen setting. A shorter duration of respiratory support is indicative of improved lung function and respiratory stability, which are critical factors in the care of preterm infants. An important factor in determining the total impact of illness on infants and the healthcare system is the length of stay in the hospital. Infants that are born prematurely are more likely to experience neurodevelopmental delays. The study can determine whether caffeine has any effect on the long-term development of MLPT infants by analyzing neurodevelopmental outcomes at 18 and 24 months of corrected age. This outcome is essential for understanding the potential effects of caffeine beyond the immediate neonatal period.

2.2.8 Informed consent

The research team will create a clear and comprehensive document for obtaining informed consent, including details about the trial's purpose, interventions, potential benefits and risks, confidentiality measures, and the voluntary nature of participation. The consent will be approved by the Research Ethics Boards at the University of Alberta. A research assistant will meet with the parents or legal guardians, provide a detailed explanation of the trial, and address any questions or concerns raised during this discussion. Written informed consent will be obtained once the parents or guardians have agreed to the trial. The consent procedure will be conducted with a translator or interpreter if the parents or guardians do not speak the same language as the research team. The signed informed consent forms will be stored securely.

2.2.9 Intervention

The study will be a randomized, double-blinded controlled trial. Parents of potentially eligible infants will be approached to discuss the study and obtain informed consent. Ideally, this will take place before birth once a diagnosis of threatened preterm delivery at 32 to 34+6 weeks has been made. After obtaining consent and confirmation of eligibility after birth, randomization will occur. The infants will be randomized to receive intravenous or enteral caffeine base or placebo (equivalent volume of normal saline) starting within 72 hours of birth and continuing until the infant is off respiratory support or 34 weeks corrected GA whichever is later. Keeping in consideration safe discharge practices with an apnea-free period before discharge as per local recommendations. Caffeine will be given in a loading dose (10 mg/kg of caffeine base dose), followed by a daily maintenance dose (4-5 mg/kg of caffeine base dose). The dosage will be adjusted weekly based on weight gain. The drug will be administered intravenously (IV), orally or through a gastric tube based on the individual's feeding route. We assume that the efficacy of oral caffeine is comparable to IV form given that the bioavailability of caffeine is nearly 100% (27). In case of symptoms suggestive of caffeine-induced toxicity (e.g., tachycardia, tachypnea, jitteriness, tremors, and unexplained seizures and vomiting), doses of the study drug may be held or reduced, depending on the discretion of the attending physician. Table 2.5.1 shows the schedule of enrolment, interventions, and assessments. Figure 2.6.1 presents the flow of participants through various stages of a trial.

2.2.10 Randomization Method and Blinding:

A block stratification approach that includes both center and GA as stratification factors will be used. This is to maximize the likelihood that the groups are balanced with respect to these important variables. Randomly sized blocks of treatment allocations will be created within each center. These blocks vary in size to add an element of unpredictability to the treatment assignments. A randomization list will be created using a computer-based random block generator to ensure the participants are assigned to the intervention and control groups in an unbiased manner. Participants are randomized using the predetermined block size and randomization list for each centre. A central

phone number is assigned to ensure the concealment of the allocation sequence of eligible participants. The sequence will be generated by a person not directly involved in the conduct of the trial. Also, the randomization list will be kept secure and hidden from the researchers, medical staff, and the participant's parents or guardians to maintain allocation concealment. The list is password-protected and encrypted to prevent unauthorized access. Unique allocation codes will be assigned to eligible participants without revealing the treatment group they belong to. These codes are linked to the treatment group in the randomization system and are confidential. The trial employs a double-blind design, where both the participants and the research team, including healthcare providers and data collectors, are unaware of the treatment assignments. A designated individual in the pharmacy department of the hospital who is not directly involved in the trial will be responsible for preparing the drug for administration. Both caffeine and placebo will have identical packaging, texture, colours, and administration routes to prevent clues that could reveal the treatment. The generic labels on the containers will not reveal the contents or treatment group. Adherence to blinding will be monitored by the study team throughout the trial.

2.2.11 Procedure for unblinding

The trial team will assign a person in the pharmacy who is responsible for unblinding if needed. This member will not be directly involved in patient care or outcome assessment. Unblinding will generally be avoided to maintain the validity of the trial. However, unblinding might be considered if there is a severe or life-threatening adverse event or medical emergency to inform the clinical team about the intervention and ensure that the patient will receive the most appropriate medical care. Other scenarios where unblinding may be considered are when there is an ethical concern about the safety of the intervention. In this case, unblinding may inform the study team about the need to terminate the trial.

2.2.12 Measures to reduce the Risk of Bias

- Selection Bias: A computer-generated randomization sequence will be created using a randomization software or tool. This sequence will assign participants to either the intervention group (caffeine therapy) or the control group (placebo). The

randomization sequence will be kept concealed from the researchers and healthcare providers involved in participant recruitment and assignment. This ensures that the allocation process remains unbiased and free from influence.

- Sampling Bias: To minimize the risk of sampling bias, clearly defined inclusion and exclusion criteria are implemented. The trial population is chosen so it is truly representative of the intended population to ensure the generalizability of the results.
- Performance Bias: Caregivers, healthcare providers, and outcome assessors will be blinded to the treatment allocation. This reduces the differences in treatment and care based on knowledge of an intervention. Adherence to the study protocol will be monitored to ensure consistency in the application of the intervention and the measurement of outcomes.
- Information Bias: The research team will closely monitor the study to ensure the accuracy of data collection to reduce the risk of information bias.
- Attrition Bias: To ensure the integrity of the randomization process and avoid attrition bias, individuals will be analyzed according to their randomized group assignment, regardless of adherence to the intervention (intention to treat analysis)
- Investigator Bias: The investigator will be blinded to the intervention to avoid any influence on the results. A statistical analysis plan will be developed before the initiation of the study to avoid data-driven analyses that can introduce bias.
- Reporting Bias: A standardized protocol for intervention, data collection, and outcome assessments will be developed to reduce variability and minimize bias. The primary and secondary outcomes will be clearly defined. The protocol will be registered in a public registry before enrollment to prevent selective reporting of outcomes.
- Publication Bias: Prior to initiating this trial, we will register this protocol on https://clinicaltrials.gov, a well-known publicly available trial registry. The trial's findings will be reported regardless of whether the results are statistically significant. Any conflict of interest among researchers will be disclosed to the public when publishing the results.

2.2.13 Data collection, handling and security

After ensuring, that consent has been obtained for each participating infant, data collection will be done by trained research personnel. Unique participant numbers will be used to identify study subjects. A standardized data collection form will be developed, including baseline demographic data and information on the intervention and the outcomes. The forms will contain no patient identification information. Data will be securely organized and stored in a password-protected institutional computer to ensure confidentiality. Data entry will be conducted by trained personnel to minimize errors. Only research members will have access to the participant's data. All study members will be educated about the study protocol. The trial committee will monitor the data collection process regularly for accuracy and completeness. The study records will be retained for 5 years from the date of publication of a report on the project research and then destroyed according to the institutional policy and procedure for destroying/disposing of sensitive data.

2.2.14 Follow-up plan

All participants will have a follow-up appointment at 18-24 months (corrected for prematurity) at the neonatal follow-up clinic. Certified psychologists and psychometrists will administer the Fourth edition of the BSID (Bayley-4; Bayley & Aylward, 2019), a commonly used psychometric test in this age group. Results of the neuromotor function assessment (Gross Motor Function Classification System, Palisano 1997), vision, and hearing tests will be collected. A dedicated follow-up team will be responsible for managing long-term follow-up assessments and maintaining regular contact with participants to address any questions or concerns.

2.2.15 When and how to withdraw subjects

At the time of consent parents or guardians will be informed about the voluntary participation in the trial and allowed to choose to withdraw at any point with no consequences. In addition, the research team can choose to withdraw participants for the following reasons: (a) If participation in the trial is no longer in the best interest of the patient, as when the patient becomes critically ill and requires aggressive support. (b) If, there are serious adverse effects related to the medication that is intolerable to the

patient. (c) If the patient continues to experience recurrent significant apneas. In the last scenario, the team can choose to either give an additional loading dose of study medication and continue the patient in the study arm or withdraw the participant from the allocated treatment and start open-label caffeine treatment. If the clinical team chooses to terminate the participation of an individual in the trial, it should document objectively the reasons for its decision.

2.2.16 Risk and Benefits

Overall, the benefit-risk balance of this trial appears to be favourable. Caffeine therapy carries a risk of adverse reactions, although they are generally considered to be mild. Possible side effects may include irritability, tachycardia, gastrointestinal disturbances, and transient hypertension. The healthcare team will carefully monitor and manage these risks throughout the trial. Also, there is a potential risk of medication errors or incorrect dosing during the administration of caffeine therapy. To mitigate this risk, strict adherence to standardized dosing protocols will be followed. Finally, the participants in this trial may undergo various procedures, such as respiratory monitoring, and neurodevelopmental assessments. While these are generally considered safe, there may be temporary discomfort from these assessments. The trial team will respond appropriately to minimize any potential discomfort and ensure the well-being of the participants. The likely benefits could be better outcomes for infants who are MLPT such as better respiratory outcomes, a shorter hospital stay, and potential advantages for neurodevelopment. In this patient population, the risk of caffeine therapy is generally well-known and seen as manageable.

2.2.17 Strengths and limitations

This trial has several strengths such as:

- Randomized control design: This is the gold standard in clinical research that helps to reduce bias and provides a rigorous tool to examine cause-effect relationships between caffeine therapy and the suggested outcomes.
- Double-blinding: This helps to minimize detection and performance bias and enhance the integrity of the trial.

- Representative population: This guarantees the validity and generalizability of the study results to the population at large.
- Standardized protocol for providing trial interventions and cointerventions, and for measuring outcomes. This helps to reduce variability and ensure consistency in the administration of care and data collection.
- Adequate sample size: This guarantees statistically significant results.
- Study outcomes: The trial has primary and secondary outcomes that are, reproducible, assess the impact of the intervention, and are relevant to the target population.
- Long-term neurodevelopmental outcome: This provides valuable insights into the sustained effects of caffeine and its impact on infant development and health.

On the other hand, the trial also faces some limitations related to the following:

- Generalizability: Due to study site characteristics and variability among practitioners on when to consider respiratory support. To minimize that, the trial will have stratified-blocked randomization and standardized protocols to ensure consistency and reduce variations.
- Confounding variables: Premature infants are at high risk of multiple comorbidities that could impact the outcome. The study design ensures that participants are allocated to the caffeine therapy and placebo groups in a balanced and unbiased manner. However, despite the randomization, if the groups are still unbalanced on certain predefined variables known to be confounders, we will perform additional analyses to adjust for those confounding variables.
- Ethical concerns: May arise when infants are randomized to receive a placebo rather than caffeine, which could affect recruitment or parents' willingness to take part.
- Long-term follow-up: This could be challenging and could lead to incomplete data for the secondary outcome of neurodevelopmental outcome with potential attrition. To address that, the research team will ensure the engagement of the caregivers through education, and clear communication, and offer to provide flexible scheduling for those appointments.

2.2.18 Safety and adverse events

An adverse event is defined as an unwanted medical occurrence in a patient administered a therapeutic product, whether the occurrence is related to or considered to have a causal relationship with the treatment (28). A systematic approach to monitoring and recording adverse events will be implemented to ensure participant safety. A data safety monitoring committee (DSMC) will review results monthly to inform whether it is ethical to continue the trial or terminate it prematurely. An adverse event reporting form will be developed. The form will contain details about the event's date, description, severity, and any subsequent actions. The safety committee will be responsible for tracking and reporting events. The adverse events will be reported as soon as they are identified.

2.2.19 Statistical methods

All randomized participants will be included in the analysis using the intention-to-treat principle, regardless of how much they adhered to the prescribed course of therapy or any potential protocol deviations. For the primary endpoint assessing the duration of respiratory support between the caffeine therapy group and the placebo group, we will use appropriate statistical tests based on the distribution of the outcome data. If the duration of respiratory support follows a normal distribution, we will use a general linear model to compare the means between the two groups. The adjustment model will include terms for the stratification variables (site and GA), in addition to other relevant variables (i.e., sex of the infant, maternal education, antenatal administration of steroids for fetal lung maturity, multiple births, and intubation at randomization). Results for both unadjusted and adjusted analyses will be presented. On the other hand, if the data is non-normally distributed, a non-parametric test will be used (e.g., ordinary least squares regression).

For our key secondary endpoint of interest, we will use a survival analysis approach, the Kaplan-Meier method, to estimate survival probability for the outcome of time-to-event data, that is the time until weaning from breathing support to room air/low-flow oxygen.

Additionally, for the other secondary endpoints, the continuous variables (number of significant apneas per day, PMA at successful weaning, PMA at discharge home, length

of hospital stay, and Bayley scores) will be analyzed using either the independent t-test or Mann-Whitney U test, depending on the data distribution. The categorical variables (proportion needing mechanical ventilation, proportion needing hospital readmission, and proportion of death) will be analyzed using the Chi-Square test to compare proportions between the two groups.

2.2.20 Sample size

Based on the available literature, the median duration of mechanical ventilation and non-invasive respiratory support is 2 days with a range of 1 to 26 for the study population (29). To estimate the mean and standard deviation from the median and range, we used the following formulas (30):

Mean = (The minimum + 2*Median + The maximum)/4

Standard Deviation= Range / 6

Therefore, the estimated mean duration of respiratory support in the control group is 7.75 days with a standard deviation of 4.2. To detect a 25% reduction in the primary outcome (intervention mean = 5.82) with 90% power we will need 98 infants in each arm with a two-sided alpha of 0.05 (31). Considering a drop-out rate of 10%, the total sample size will be 218. A power of 90% is used to increase the sensitivity of the trial in detecting a true effect and enhance precision as well as increase power available for secondary endpoints. The drop-out rate is estimated based on the fact that caffeine is a non-invasive and well-tolerated therapy that is commonly used in NICU and the minimal drop-out rate that was observed in the CAP trial (18).

The table below shows the sample size estimation for a reduction in the primary outcome of 20%, 25% and 30% for a study power of 80% or 90%.

		Reduction		
		20%	25%	30%
Power	90%	310	196	136
	80%	232	146	102

2.2.21 Feasibility

The proposed study is feasible given the experienced study team, prior success in similar trials and available research resources. In addition, the study is in line with the standard clinical practice and can be carried out within neonatal care units without the need for major changes in the current standard of care. Caffeine is a commonly used medication and is relatively cheap, affordable and safe. There is an adequate number of MLPT infants admitted per year to the study sittings to achieve the sample size, with an average of 137 infants per unit per year (32). It is estimated that 20-30% of the study population may require respiratory support (28, 33). Therefore, the sample size is expected to be achieved within 2 years of recruitment. Also, the study protocol addresses ethical concerns and meets ethical standards. Finally, the challenges that are related to long-term follow-up are addressed through caregiver engagement, education, and flexible appointments.

2.3 Discussion

MLPT infants have a higher risk of short-term respiratory illness and long-term neurodevelopmental delay than term infants. In this RCT, we sought to assess the efficiency of caffeine therapy in reducing respiratory disease in this vulnerable population, with the duration of respiratory support being the primary outcome.

For years, caffeine has been used to help premature infants breathe easier and lower their risk of developing AOP. However, its effect on respiratory disease in MLPT infants is still of interest. Caffeine has several beneficial effects that can improve respiratory function and reduce the duration of respiratory support in MLPT infants. It improves lung compliance, stimulates the central nervous system, improves diaphragmatic contractility and reduces the incidence of AOP. Our findings will indicate whether caffeine therapy could significantly reduce the duration of respiratory support compared to placebo. The earlier respiratory stability could be translated into shorter time to establish enteral feeding, shorter hospital stays, and lower costs to the health system. To evaluate the potential effect of caffeine on neurodevelopment, a follow-up assessment will be conducted at 18 to 24 months of corrected age. The assessment will use standardized

developmental assessment tools to estimate cognitive, motor, language, and social-emotional development.

The potential effect of caffeine therapy on long-term neurodevelopmental outcomes in the study population is an important aspect to consider in this trial. While caffeine may improve short-term respiratory outcomes and reduce the duration of respiratory support, its impact on neurodevelopmental outcomes requires further exploration. Caffeine has neuroprotective properties that could help protect the brain from damage caused by inflammation and oxidative stress.

In this trial, we will also observe factors that may influence the primary outcome, besides the intervention itself. GA, BW, history of maternal diabetes, exposure to antenatal steroids, and severity of respiratory distress were identified as critical determinants of the duration of respiratory support. Infants with lower GAs and BW may require more extended respiratory support due to their immature lungs and increased respiratory instability. Antenatal steroids and the severity of respiratory distress at birth may also correlate with the duration of support needed. Such findings highlight the importance of considering these variables when interpreting the impact of caffeine therapy on the primary outcome.

Furthermore, the trial will evaluate the impact of caffeine therapy on healthcare resource utilization, including the frequency and duration of hospital admissions, length of stay in the hospital, and utilization of respiratory support interventions.

Overall, our study may provide valuable insights into the use of caffeine therapy in managing MLPT infants on respiratory support and will inform practitioners whether it should be integrated into routine neonatal care protocols for this population.

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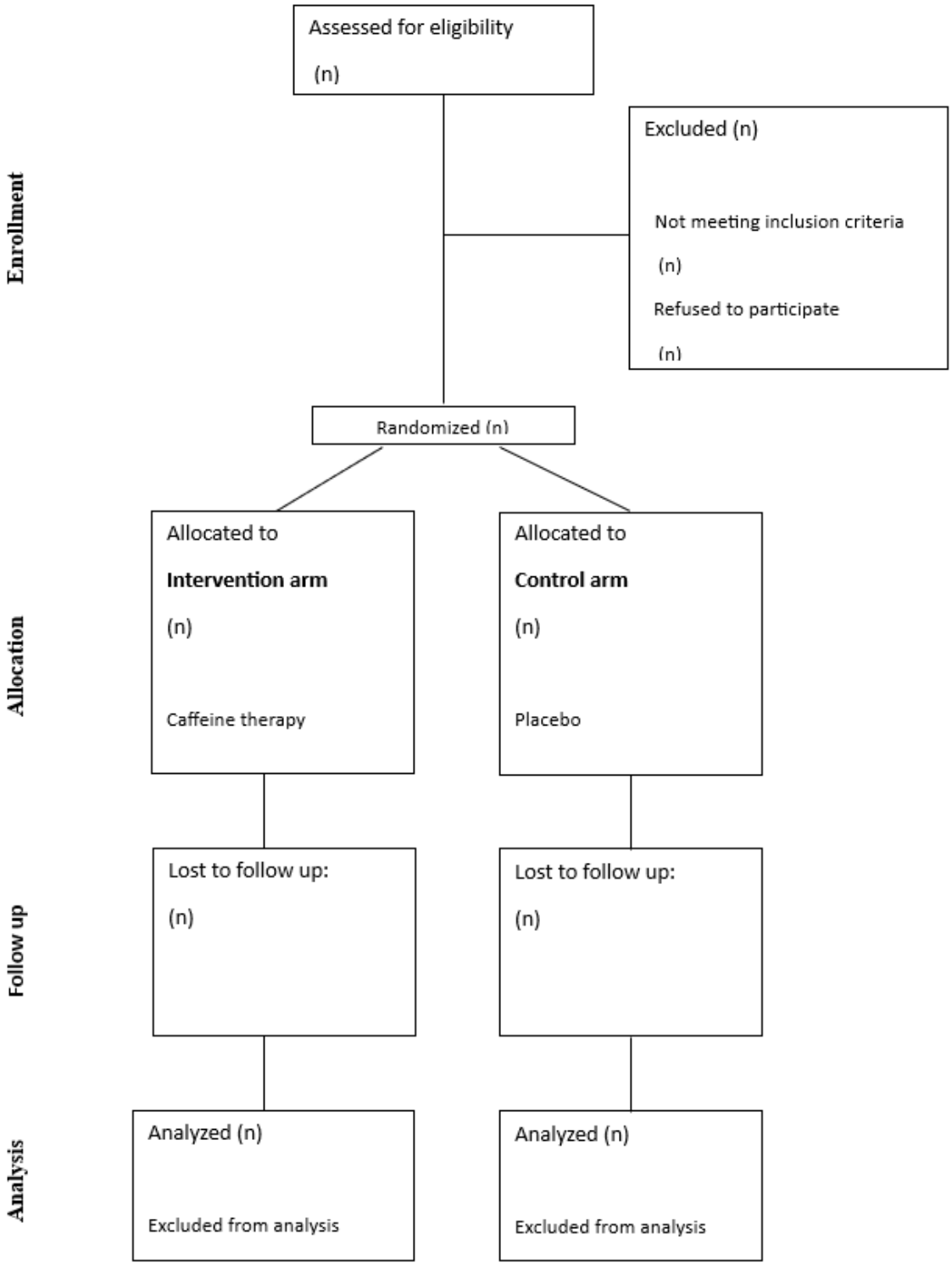
2.5 Tables

Table 2.5.1. Schedule of enrolment, interventions, and assessments

	STUDY PERIOD								
	Enrolment	**Allocation**	**Post-allocation**						**Close-out**
TIMEPOINT	***Antenatally***	**Birth**	***First 72 hrs***	***Wk 1***	***Wk 2***	***Wk 3***	***Wk 4***	***D/C***	***18-24 mon***
ENROLMENT:									
Eligibility screen	X	X	X						
Informed consent	X	X	X						
Allocation		X	X						
INTERVENTIONS:									
[Caffeine therapy]			----------	----------	----------	----------	----------		
[Placebo]			----------	----------	----------	----------	----------		
ASSESSMENTS:									
[Baseline variables]								X	
[Outcome variables]								X	X
[other data variables]								X	X

2.6 Figures

Figure 2.6.1. CONSORT Diagram



Chapter 3: Acetaminophen versus Indomethacin for Patent Ductus Arteriosus Management in Premature Infants: Systematic Review and Meta-Analysis of Randomized Controlled Trials

3.1 Introduction

Premature infants with PDA have a high rate of morbidity and mortality (1) Approximately three-quarters of extremely premature infants demonstrate symptoms of hemodynamically significant PDA (HsPDA) (2) The ideal management for HsPDA in this vulnerable group of patients remains uncertain (3,4). Available pharmacological agents which are used to promote ductal closure act on the PGs pathway, with indomethacin probably the most studied agent. Evidence shows that indomethacin is effective in closing the duct (5); however, its use is associated with numerous side effects related to its vasoconstrictive effects on renal, cerebral, and mesenteric circulation (6-8). Recently, acetaminophen (also known as paracetamol) has gained interest in the neonatal community for the indication of ductal closure due to its fewer side effects. Similar to indomethacin, it blocks the arachidonic acid pathway; however, it acts on a different enzyme (peroxidase) in the pathway. Acetaminophen could be an alternative to indomethacin if it has a similar efficacy for ductal closure.

We conducted a systematic review of RCTs enrolling preterm infants with HsPDA that compared acetaminophen with indomethacin, for the primary outcome of PDA closure.

3.2 Methods

This systematic review of RCTs was designed as per the methodology provided in the Cochrane Handbook for Systematic Reviews (9) and is being reported as per the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) statement (10).

3.2.1 Search Strategy

A search was executed by an expert librarian (SC) on the following databases: PROSPERO, OVID Medline, OVID EMBASE, Wiley Cochrane Library (CDSR and Central), EBSCO, CINAHL, and SCOPUS using a controlled vocabulary (e.g.: MeSH, Emtree, etc) and keywords representing the concepts "preterm neonates" and "acetaminophen" and "indomethacin". Variations of the randomized controlled trial filter

by Lefebvre, et al were used to limit each search (9). Animal studies were excluded. No language restrictions were applied. Databases were searched from inception to June 15, 2021. Results were exported to COVIDENCE review management software, where duplicates were removed. Detailed search strategies are available in Appendix 1. In addition, the bibliography of the identified trials was searched for other potentially relevant studies.

3.2.2 Study selection

Two members (EB, AH) independently assessed the study eligibility for inclusion according to the pre-established criteria. Disagreements between the two reviewers were resolved through discussion with the third reviewer (MK). The studies were identified for inclusion if they satisfied the following criteria: randomized control trial, enrolling preterm infants with HsPDA, for treatment with acetaminophen (enteral or intravenous) or indomethacin (enteral or intravenous) for the outcome of PDA closure (defined as evidence of ductal closure or change to non- hemodynamically significant duct on an echocardiogram conducted within one week of the treatment completion). We recorded the following secondary outcomes: need for surgical closure of PDA, death, pulmonary hemorrhage, intraventricular hemorrhage (IVH), gastrointestinal bleeding, necrotizing enterocolitis (NEC), sepsis, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and laboratory markers of liver or renal toxicity and platelet counts.

3.2.3 Risk of bias assessment

Cochrane risk-of-bias (RoB) tool for randomized trials was used to assess the risk of bias in the included studies (11). Two reviewers (EB, MK) evaluated each study for RoB and the disagreements were resolved through discussion among the review team. The included studies were assessed for RoB for the following domains: Selection bias, performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias, reporting bias, and other biases.

3.2.4 Data extraction

Two authors (EB, AH) independently extracted the data from the included articles. Data were extracted for demographic characteristics (e.g., GA, BW, sex), clinical

characteristics (e.g., diagnostic criteria, therapy courses, route of delivery), study characteristics (e.g., year of publication, setting, study design, sample size, comparison group and blinding), reported efficacy and safety outcomes, and authors' conclusions, using a standardized form.

3.2.5 Strategy for data synthesis

Data were analyzed with the help of Review Manager (RevMan) Version 5.3. [Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014]. We conducted meta-analyses using a random-effects model (9). We selected risk ratios as the effect measure for all our binary outcomes and the mean difference for the continuous outcomes. Results are presented as summary estimates along with 95% confidence intervals. Sensitivity analyses were planned by including studies assessed as low risk of bias for the main outcome of treatment efficacy. Statistical heterogeneity was measured using I^2 statistic and if substantial heterogeneity was noted (I^2 >50%), additional sensitivity analyses were planned.

3.3 Results

3.3.1 Study selection and characteristics

We identified a total of 270 references that were exported to Covidence, a web-based software platform (Figure 3.8.1). Two researchers (EB, AH) independently screened the studies for eligibility based on pre-established inclusion and exclusion criteria. Four studies met the criteria and were included in the analysis (12-15). Table 3.7.1 represents the characteristics of the included studies. Mean GA ranged from 25 to 32 weeks across studies. PDA was diagnosed using echocardiography in all studies. Protocol for acetaminophen administration ranged from 15 mg/kg/dose four times daily for 3 days (3 studies) to 7 days (1 study). Indomethacin protocol involved the administration of 3 doses at 0.2 mg/kg/dose (2 studies), 0.1-0.2 mg/kg/dose (1 study) and 0.2-0.25 mg/kg/dose (1 study).

3.3.2 Risk of bias

The risk of bias for the four studies is reported in Figure 3.8.2. Cochrane Risk of bias assessment shows a range of low to high degrees of bias. The risk of performance bias was judged high for all studies, as none of the studies had undertaken blinding of participants and healthcare providers. Reporting bias was considered high for two studies (13,14) as they did not provide data for important clinical outcomes such as mortality and BPD. One trial (15) was assessed as high RoB in the domain of other biases as it was stopped early with < 50% of the targeted sample size enrolled.

3.3.3 Primary outcome

The pooled estimates for the outcome of PDA closure show that the closure rates were similar for acetaminophen and indomethacin groups following a single course of treatment [4 studies; 380 subjects; RR 1.04 (95% CIs: 0.84, 1.29); I^2 = 69%] (Figure 3.8.3) or after two courses of treatment [2 studies; 270 subjects; RR 1.01 (95% CIs: 0.92, 1.12); I^2 = 0%] (Figure 3.8.4). We observed significant heterogeneity with the pooled estimate of treatment effect following a single course of intervention (I^2 = 69%) which resulted from the extreme results noted in a small study (15). This study was assessed as at a high risk of bias. In sensitivity analysis, we excluded the results of this study and noted the resolution of significant heterogeneity, with no significant change in the pooled effect estimate [3 studies; 343 patients; RR 1.05 (95% CIs: 0.92, 1.19); I^2 = 44%].

There was no difference in PDA ligation rates noted between the two groups [3 studies; 310 subjects; RR 1.56 (95% CIs: 0.48, 5.12)); p-value 0.46] (Figure 3.8.5).

3.3.4 Secondary outcomes

Two studies reported on the outcome of neonatal mortality (12,15) showing no difference among the intervention groups for the risk of death [RR 0.90 (95% CIs: 0.40, 2.02); p-value 0.79]. Incidence of NEC was reported in 3 studies (347 infants) (12-14) and was noted to be significantly lower in the acetaminophen group as compared to

indomethacin [RR 0.37 (95% CIs: 0.14, 0.95); p-value 0.04] [Absolute risk difference -0.06 (95% CIs: -0.11, -0.01)].

There was no difference noted between the two groups for the outcomes of pulmonary hemorrhage [3 studies; RR 0.92 (95% CIs: 0.14, 6.00); p-value 0.93], IVH [2 studies; RR 0.80 (95% CIs: 0.34, 1.84); p-value 0.59], gastrointestinal bleeding [3 studies; 0.43 (95% CIs: 0.06, 3.40); p-value 0.43], sepsis [3 studies; RR 1.02 (95% CIs: 0.58, 1.79); p-value 0.95], BPD [2 studies; RR 1.22 (95% CIs: 0.85, 1.76); p-value 0.28], ROP [2 studies; RR 0.71 (95% CIs: 0.27, 1.86); p-value 0.49] or ROP requiring treatment [2 studies; RR 1.35 (95% CIs: 0.60, 3.06); p-value 0.47] (Table 3.7.2).

Two studies reported on the results of the laboratory investigations that were conducted as part of the trial to assess for renal, hepatic, and hematological toxicity associated with the treatments (13, 14). Indomethacin treatment was associated with a significant elevation of blood urea and serum creatinine levels as compared to the acetaminophen treatment. However, the studies did not provide data for a number of participants with acute kidney injury. There was no evidence of increased liver toxicity or thrombocytopenia noted with either of the treatments.

3.4 Discussion

We have presented here an updated systematic review and meta-analyses of the available RCTs that compared acetaminophen with indomethacin for the management of HsPDA in preterm infants. The results reveal that treatment of HsPDA with acetaminophen is as effective as indomethacin for the outcome of ductus closure, with a better safety profile in terms of a lesser risk of NEC and post-treatment azotemia. There was no difference between the two interventions for the outcomes of death and other

major neonatal morbidities. The duration of the acetaminophen treatment varied between 3 to 7 days in the included studies. A summary of findings table developed as per GRADE methodology (GRADEpro Guideline Development Tool [Software]. Available from gradepro.org) revealed low certainty of evidence for the majority of salient clinical outcomes (Table 3.7.3).

Our results compare with the results of an existing Cochrane review that showed that acetaminophen was as effective as indomethacin and ibuprofen for the outcome of PDA closure in premature infants (16). However, we are able to provide more precise estimates of the pooled effect size of all the clinical outcomes as we included two more RCTs that were published following the publication of the Cochrane review (14,15). As such, we are able to show that treatment of HsPDA with acetaminophen is associated with a lesser risk of NEC [RR 0.37 (0.14, 0.95); p-value 0.04], an important clinical side-effect that was not identified in the Cochrane review. A few previous studies have suggested a possible link between indomethacin use and NEC (17, 18). Indomethacin use has been shown to diminish splanchnic circulation with resultant mucosal hypoxia and increased risk for gastrointestinal perforations (17). On the other hand, acetaminophen acts at a more distal level in the PGs synthesis pathway (peroxidase inhibition) and apparently, unlike cyclooxygenase inhibitors, its use in amounts needed for PDA closure doesn't result in significant vasoconstriction and local hypoxia in other organs (19). Also, post-treatment azotemia is a well-known side-effect of indomethacin resulting from the reduction of PGs syntheses (due to suppression of cyclooxygenase pathway in the kidneys) leading to a reduction in renal perfusion (20). However, the long-term effect of indomethacin on renal function remains uncertain.

Another systematic review, (21) that compared the use of oral acetaminophen with oral ibuprofen for the management of PDA showed similar efficacy of the two agents for the outcome of PDA closure. However, the authors showed that acetaminophen use was associated with a lesser incidence of renal dysfunction (OR 0.27 [0.10, 0.77]) and gastrointestinal bleeding (OR 0.31 [0.11, 0.88]), as compared to ibuprofen. The incidence of NEC was not different between the two agents.

Until now, the predominant use of acetaminophen in neonatal practice has been for the management of HsPDA following treatment with one to two courses of indomethacin or ibuprofen. Based on the results of this systematic review, clinicians could consider using acetaminophen as the first-line drug for the management of HsPDA in preterm infants for its better safety profile as compared to indomethacin. Although, the included trials enrolled ELBW infants and extremely low GA infants (mean GA $\leq$ 28 weeks in 3 out of 4 included trials), but they did not separately provide data for this population. This subgroup is at higher risk of developing NEC and acute renal failure with the treatment of HsPDA with NSAIDs and is thus likely to benefit more from the use of acetaminophen as the first-line drug for the treatment of HsPDA.

There is an urgent need for methodologically rigorous trials that test the efficacy and safety profile of acetaminophen against other NSAIDs for the management of HsPDA in extremely preterm infants. Such a trial should avoid the pitfalls observed in the existing RCTs, especially the lack of masking of the trial interventions. Future research should also focus on the optimal duration of the acetaminophen treatment. In a systematic review that included several observational studies, it was noted that a 6-day course of

acetaminophen was more efficacious, as compared to a 3-day course, for closure of PDA (22).

Our systematic review has a few limitations. First, we were able to include only four small to moderate-size RCTs in this review, as such the majority of pooled effect estimates of our secondary outcomes have low certainty of evidence with wide 95% confidence intervals. On the other hand, all the included studies were conducted within the last 5-10 years and reflect the current understanding of the PDA approach and management. Second, all the included trials did not employ masking of interventions to reduce the risk of bias. In addition, we assessed a high risk of bias for selective reporting in two of the included RCTs and extreme results were noted in another RCT that was terminated early. As such, we are unable to make strong recommendations in favour of acetaminophen, despite the observed results of this systematic review. Lastly, we were unable to perform a test for publication bias in view of the small number of included studies in this review. However, it is unlikely that we missed any existing trial for inclusion, as our search strategy, undertaken with the help of an experienced research librarian, was exhaustive and included several electronic databases.

3.5 Conclusion

This systematic review of the small to moderate-sized RCTs shows that acetaminophen has comparable efficacy to indomethacin for the clinical outcome of HsPDA closure, with lesser rates of NEC and post-treatment azotemia. Based on the data presented here, clinicians could consider using acetaminophen as the first-line drug for the management of HsPDA in preterm infants. However, a few of the included trials were assessed at high risk of bias and the treatment estimates of effect size for several

secondary outcomes were imprecise. There is a need for a larger methodologically rigorous trial to confirm a better risk-benefit profile of acetaminophen as compared to the NSAID agents in the sub-population of extremely preterm infants.

3.6 Tables

Table 3.6.1. Characteristics of the included studies

	Dash 2015	El Mashad 2017	Meena 2020	Davidson 2021
Country	India	Egypt	India	USA
Funding source	None	None	None	None
Inclusion criteria	BW ≤1500 g & Echo in <= 48 hrs of birth showing HsPDA	GA< 28 wks or BW< 1500 g & HsPDA diagnosed on basis of Echo and Clinical exam within <2wks of birth	GA <37 wks & HsPDA diagnosed clinically and confirmed by Echo in first 28 postnatal days of life	GA between 22- 32 wks & BW < 1500 g at ≤21 days of age with HsPDA diagnosed clinically and confirmed by Echo
HsPDA Echo criteria	PDA ≥1.5 mm with Left -to- right shunt, and LA:AO ratio > 1.5:1	LA dilatation (LA:AO >1.6), diastolic turbulence (backflow) on Doppler in the pulmonary artery, internal diameter of duct >1.5 mm, and reverse end diastolic flow in the descending aorta/mesenteric artery	Internal diameter of the duct >1.5 mm, left atrial dilatation (LA/Ao >1.4), diastolic turbulence (backflow) on Doppler in the pulmonary artery, and reversed end-diastolic flow in the descending aorta/mesenteric artery	Left -to- right ductal flow and 2 of the 3 following: ductal size ≥1.5 mm at smallest diameter, reversal of flow in descending aorta or LA:AO ratio ≥ 1.5
INTERVENTION 1	PO acetaminophen at 15 mg/kg/dose four times daily for 7 days	IV acetaminophen at 15 mg/kg/dose four times daily for 3 days	IV acetaminophen at 15 mg/kg/dose four times daily for 3 days	IV acetaminophen at 15 mg/kg/dose four times daily for 3 days
INTERVENTION 2	IV indomethacin at 0.2 mg/kg/dose once daily for 3 days	IV indomethacin at 0.2 mg/kg/dose twice daily for 3 doses	PO indomethacin twice daily for 3 doses at: Starting dose: 0.2 mg/kg following doses: * Infants <2 days: 0.1 mg/kg * Infants 2–7 days: 0.2 mg/kg * infants >7 days: 0.25 mg/kg	IV indomethacin twice daily for 3 doses at: * Infants 2–7 days: 0.2 mg/kg for all doses * Infants >7 days: 0.2 mg/kg for 1st dose and 0.25 mg/kg for subsequent doses
Sample size **PCM vs Indo**	38 vs 39	100 vs 100	35 vs 35	17 vs 21
Loss to follow-up for primary outcome	4/77 (5.2%)	None	None	1/38 (2.6%)

GA mean (SD) **PCM vs Indo**	28.5 (2.7) vs 28.9 (2.6)	26 (1.9) vs 26 (2.1)	32.14 (2.01) vs 31.77(2.26)	25.7 (1.4) vs 25.3 (1.8)
BW mean (SD) **PCM vs Indo**	989 (299) vs 1027 (262)	1100 (130) vs 1100 (140)	1440 (340) vs 1410 (320)	785 (203) vs 756 (241)
Male **PCM vs Indo**	36.9% vs 33.3%	60% vs 60%	51.4% vs 42.9	53% vs 40%
PDA size (mm) **mean (SD)** **PCM vs Indo**	2.02 (0.42) vs 2.11 (0.53)	2.7 (0.6) vs 2.7 (0.7)	1.85 (0.43) vs 1.82 (0.28)	2.7 (0.7) vs 2.9 (0.7)
Postnatal age for diagnosis or Rx **PCM vs Indo**	Mean (SD) (hours) 14.7 (8.4) vs 15.9 (11.8)	Mean (SD) (days) 2.7 (4.4) vs 3.1 (5.1)	Mean (SD) (days) 9.02 (3.43) vs 10.85 (4.25)	Median (IQR) (days) 8 (7,11) vs 6.5 (4,9.3)
Primary outcome	PDA closure	PDA closure	PDA closure	Successful PDA treatment (No longer HsPDA)

AO: aortic root; BW: birth weight; g: gram; GA: gestational age; hr: hour; HsPDA: hemodynamically significant patent ductus arteriosus; Indo: indomethacin; IV: intravenous; LA: left atrial; PCM: paracetamol (acetaminophen); PDA: patent ductus arteriosus; PO: per oral; Rx: treatment

Table 3.6.2. Summary of results of the secondary outcomes: Acetaminophen vs Indomethacin

Outcome	Studies	Participants	Statistical Method	Effect Estimate RR [95% CIs:]	p-value
GI Bleed	3	347	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.06, 3.40]	0.43
Pulmonary haemorrhage	3	347	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.14, 6.00]	0.93
NEC	3	347	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.14, 0.95]	0.04
ROP	2	259	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.27, 1.86]	0.49
ROP needing treatment	2	91	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.60, 3.06]	0.47
Sepsis	3	314	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.58, 1.79]	0.95
IVH	2	275	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.34, 1.84]	0.59
BPD	2	94	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.85, 1.76]	0.28
Death	2	114	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.40, 2.02]	0.79

BPD: bronchopulmonary dysplasia; GI: gastrointestinal; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity

Table 3.6.3. Summary of findings table as per GRADE methodology

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with [Indomethacin]	**Risk with [Acetaminophen]**			
PDA closure after single course	703 per 1,000	**731 per 1,000** (591 to 907)	**RR 1.04** (0.84 to 1.29)	380 (4 RCTs)	⊕⊕◯◯ Low[a,b]
PDA closure after two courses	822 per 1,000	**830 per 1,000** (756 to 921)	**RR 1.01** (0.92 to 1.12)	270 (2 RCTs)	⊕⊕⊕◯ Moderate[a]
PDA ligation	102 per 1,000	**159 per 1,000** (49 to 522)	**RR 1.56** (0.48 to 5.12)	310 (3 RCTs)	⊕⊕◯◯ Low[a,c]
NEC	86 per 1,000	**32 per 1,000** (12 to 82)	**RR 0.37** (0.14 to 0.95)	347 (3 RCTs)	⊕⊕◯◯ Low[a,c]
IVH	123 per 1,000	**99 per 1,000** (42 to 227)	**RR 0.80** (0.34 to 1.84)	275 (2 RCTs)	⊕⊕◯◯ Low[a,c]
BPD	380 per 1,000	**464 per 1,000** (323 to 669)	**RR 1.22** (0.85 to 1.76)	94 (2 RCTs)	⊕⊕◯◯ Low[a,c]
Death	186 per 1,000	**168 per 1,000** (75 to 377)	**RR 0.90** (0.40 to 2.02)	114 (2 RCTs)	⊕⊕◯◯ Low[a,c]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with [Indomethacin]	**Risk with [Acetaminophen]**			
ROP needing treatment	160 per 1,000	**216 per 1,000** (96 to 490)	**RR 1.35** (0.60 to 3.06)	91 (2 RCTs)	⨁⨁◯◯ Low[a,c]

Explanations

a. Blinding of participants and healthcare providers was not done

b. High heterogeneity (I-square: 69%, P=0.02)

c. Wide 95% confidence intervals

3.7 Figures

Figure 3.7.1. Study flow diagram

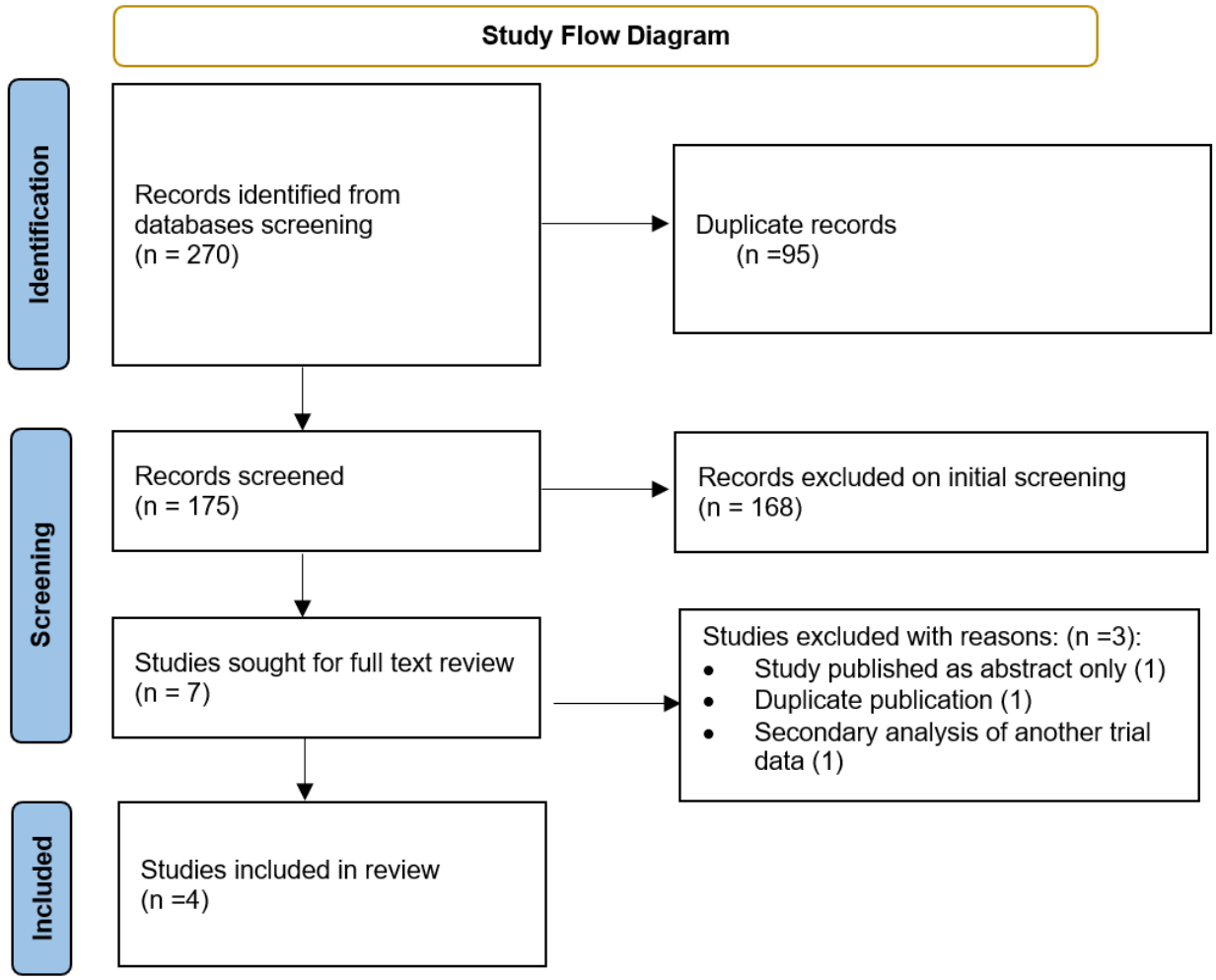


Figure 3.7.2. Risk of bias assessments of the included studies

Figure 3.7.3. Acetaminophen vs Indomethacin: PDA closure rate after a single course of treatment.

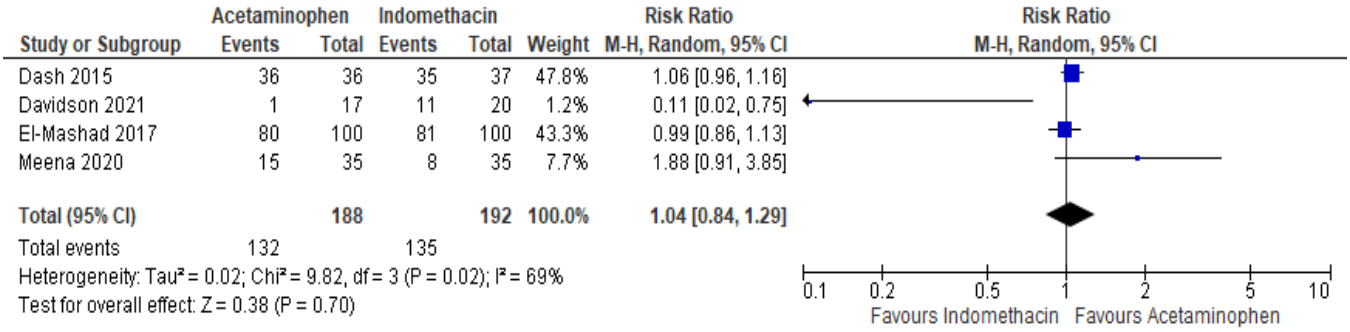


Figure 3.7.4. Acetaminophen vs Indomethacin: PDA closure rates after two courses of treatment.

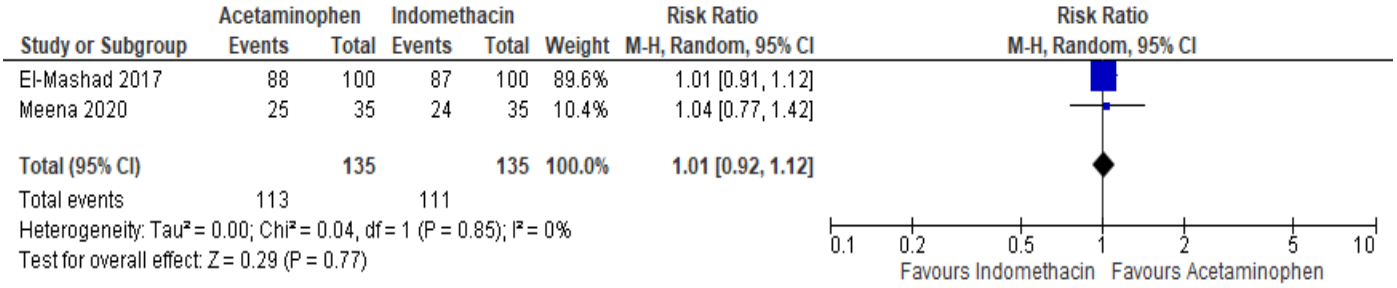
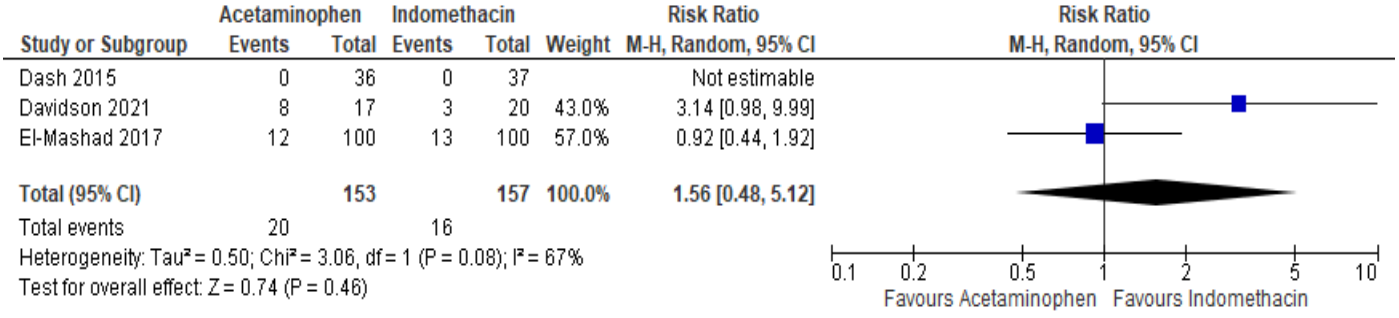


Figure 3.7.5. Acetaminophen vs Indomethacin: PDA ligation rates with each intervention.



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3.9 Appendix

Appendix 3.9.1

Ovid MEDLINE(R) ALL <1946 to June 14, 2021>

#	Search Statement	Results
1	exp Acetaminophen/	18891
2	(362o9itl9d or apap or acamol or acephen or acetaco or acetamidophenol or acetaminophen or acetominophen or algotropyl or "anacin 3" or anacin-3 or anacin3 or datril or hydroxyacetanilide or "n-(4-hydroxyphenyl) acetanilideor n-acetyl-p-aminophenol" or panadol or paracetamol or tylenol or p-acetamidophenol or p-hydroxyacetanilide).mp. or "103-90-2".rn.	30831
3	1 or 2	30831
4	exp Indomethacin/	30459
5	(amuno or indocid or "indocin indomet 140" or indometacin or indomethacin or "indomethacin hydrochloride" or metindol or osmosin or "xxe1cet956").mp.	43478
6	"53-86-1".rn.	0
7	4 or 5 or 6	45562
8	3 and 7	852
9	("early birth*" or prematur* or "pre matur*" or preterm or "pre term" or "very low birthweight" or VLBW).mp.	250777
10	Infant, Premature/ or exp Infant, Premature, Diseases/	86001
11	9 or 10	260758
12	8 and 11	83
13	((randomized controlled trial or controlled clinical trial).pt. or (Randomized or placebo or randomly or trial or groups).ab. or drug therapy.fs.) not (exp animals/ not exp humans/)	4372839
14	12 and 13	55

Embase <1974 to 2021 June 11>

#	Search Statement	Results
1	exp Paracetamol/	96479
2	(362o9itl9d or apap or acamol or acephen or acetaco or acetamidophenol or algotropyl or anacin-3 or anacin3 or datril or hydroxyacetanilide or "n-(4-hydroxyphenyl) acetanilide" or "n-acetyl-p-aminophenol" or panadol or paracetamol or tylenol or p-acetamidophenol or p-	312844

	hydroxyacetanilide or "4 acetamidophenol" or "acetaminophenol" or "4 acetylaminophenol" or "4 hydroxyacetanilide" or "4' hydroxyacetanilide" or "a-mol" or abenol or acamol or "acamoli forte" or acenol or acephen or "acet suppositories" or acetalgin or "acetamino phenol" or "acetaminophen" or acetaminophene or acetaminophenol or acetamol or acetomenophen or acetylaminophenol or adorem or afebrin algiafin or algocit or algotropyl or alphagesic or alvedon or amadil or amadol or "anacin 3" or anadin or anaflon or analgiser apamide or apap apirex or apotel or arthralgen or atamel or "ben-u-ron" or benuron or biogesic or bodrex or calapol or calodol or calonal or calpol or causalon or cemol or christamol or claradol or clocephen or cp 500 or cp500 or dafalgan or daga or "acetylsalicylic acid" or depon or depyretin or dirox or dismifen or disprol or dolal or dolex or "dolex 500" or doliprane or dolitabs or dolofen or dolomol or dolorol or dolotec or dolotemp or dolprone or doltem or drilan or "dristan af" or duorol or dymadon or efferalgan or "efferalgan 500" or Efferalganodis or Efferelgan or enelfa or eneril or eraldor or "eu med" or exopon or expandol or febrilix or fendon or fervex or fibrinol or fortolin or gelocatil or "geluprane 500" or Gunaceta or hedex or helporal or infants feverall or injectapap or janupap or kamolas or kyofen or lekadol or lemgrip or letamol or liquiprin or lotemp or lyteca or malidens or medamol or meforagesic or metagesic or metalid or mexalen or "milidon 500" or Minopan or Mypara or "n acetyl 4 aminophenol" or "n acetyl para aminophenol" or "n-acetyl-p-aminophenol" or Nalgesik or Napamol or Napap or Naprex or Nebs or "nektol 500" or neocitran or neodalmin or neopap or nevral or nilapur or nobedon or nysacetol or ofirmev or pacemol or pacimol or pamal or pamol or panadol or panamax or panasorb or panodil or "para acetylaminophenol" or "para hydroxyacetanilide" or "para suppo" or Paracet or Paracetaminophenol or "paracetamol ester" or Paracetamole or parafusiv or parageniol or paragon or paralen or paralief or paramax or paramidol or parapaed or paratabs or parvid or pasolind or paximol or pedipan or perfalgan or phenaphen or pinex or polarfen or predimol or puernol or pyrigesic or raperon or rapidol or relaphen or remedol or revanin or "rhinapen elixir" or rhodapap or roxamol or salzone or serimol or setamol or sinaspril or sinebriv or sinedol or sinpro or supofen or tabalgin or tachipirin or tachipirina or taganopain or tapar or tempra or tempte or temzzard or termofren or tralgon or "tralgon elixir" or Tramil or Treuphadol or turpan or tylex or valadol or wegmal or winadol or winasorb or xebramol or zolben or zydinol or "RN= 103-90-2").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	
3	1 or 2	312844
4	exp Indomethacin/	78637
5	(amuno or indocid or "indocin indomet 140" or indometacin or indomethacin or "indomethacin hydrochloride" or metindol or osmosin or "xxe1cet956").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	84561
6	"53-86-1".rn.	76042
7	4 or 5 or 6	84564
8	3 and 7	16906
9	("early birth*" or prematur* or "pre matur*" or preterm or "pre term" or "very low birthweight" or VLBW).mp.	333135

10	Infant, Premature/ or exp Infant, Premature, Diseases/	108926
11	9 or 10	333135
12	8 and 11	391
13	(Randomized controlled trial/ or Controlled clinical study/ or random*.ti,ab. or randomization/ or intermethod comparison/ or placebo.ti,ab. or (compare or compared or comparison).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. or (open adj label).ti,ab. or ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. or double blind procedure/ or parallel group*1.ti,ab. or (crossover or cross over).ti,ab. or ((assign* or match or matched or allocation) adj5 (alternate or group*1 or intervention*1 or patient*1 or subject*1 or participant*1)).ti,ab. or (assigned or allocated).ti,ab. or (controlled adj7 (study or design or trial)).ti,ab. or (volunteer or volunteers).ti,ab. or human experiment/ or trial.ti.) not (((random* adj sampl* adj7 ("cross section*" or questionnaire*1 or survey* or database*1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)) or (Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group*1.ti,ab.)) or (((case adj control*) and random*) not randomi?ed controlled).ti,ab. or (Systematic review not (trial or study)).ti. or (nonrandom* not random*).ti,ab. or "Random field*".ti,ab. or (random cluster adj3 sampl*).ti,ab. or ((review.ab. and review.pt.) not trial.ti.) or ("we searched".ab. and (review.ti. or review.pt.)) or "update review".ab. or (databases adj4 searched).ab. or ((rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset*1).ti. and animal experiment/) or (Animal experiment/ not (human experiment/ or human/)))	4814104
14	12 and 13	70

CINAHL Plus with Full Text

Expanders - Apply equivalent subjects

Search modes - Find all my search terms

#	Query	Results
S1	acetaminophen	7,551
S2	(362o9itl9d or apap or acamol or acephen or acetaco or acetamidophenol or acetaminophen or acetominophen or algotropyl or "anacin 3" or anacin-3 or anacin3 or datril or hydroxyacetanilide or "n-(4-hydroxyphenyl) acetanilideor n-acetyl-p-aminophenol" or panadol or paracetamol or tylenol or p-acetamidophenol or p-hydroxyacetanilide)	8,749

S3	S1 OR S2	8,749
S4	(MH "Indomethacin")	1,561
S5	(amuno or indocid or "indocin indomet 140" or indometacin or indomethacin or "indomethacin hydrochloride" or metindol or osmosin or "xxe1cet956")	2,599
S6	S4 OR S5	2,599
S7	(MH "Infant, Very Low Birth Weight") OR (MH "Infant, Premature") OR (MH "Infant, Premature, Diseases+")	33,266
S8	("early birth*" or prematur* or "pre matur*" or preterm or "pre term" or "very low birthweight" or VLBW)	74,344
S9	S7 OR S8	78,506
S10	(MH (randomized controlled trials OR double-blind studies OR single-blind studies OR random assignment OR pretest-posttest design OR cluster sample) OR TI (randomised OR randomized) OR AB random* OR TI trial OR ((MH (sample size) AND AB (assigned OR allocated OR control))) OR MH (placebos OR crossover design OR comparative studies) OR AB ((control W5 group) OR (cluster W3 RCT) OR PT (randomized controlled trial))) NOT ((MH animals+ OR MH (animal studies) OR TI (animal model*)) NOT MH (human))	818,358
S11	((MH (randomized controlled trials OR double-blind studies OR single-blind studies OR random assignment OR pretest-posttest design OR cluster sample) OR TI (randomised OR randomized) OR AB random* OR TI trial OR ((MH (sample size) AND AB (assigned OR allocated OR control))) OR MH (placebos OR crossover design OR comparative studies) OR AB ((control W5 group) OR (cluster W3 RCT) OR PT (randomized controlled trial))) NOT ((MH animals+ OR MH (animal studies) OR TI (animal model*)) NOT MH (human))) AND (S3 AND S6 AND S9 AND S10)	10

SCOPUS Searched June 15, 2021 Results =99

(TITLE-ABS-KEY (362o9itl9d OR apap OR acamol OR acephen OR acetaco OR acetaminophen OR acetamidophenol OR algotropyl OR anacin-3 OR anacin3 OR datril OR hydroxyacetanilide OR "n-(4-hydroxyphenyl) acetanilide" OR "n-acetyl-p-aminophenol" OR panadol OR paracetamol OR tylenol OR p-acetamidophenol OR p-hydroxyacetanilide OR "4 acetamidophenol" OR

"acetaminophenol" OR "4 acetylaminophenol" OR "4 hydroxyacetanilide" OR "4' hydroxyacetanilide" OR "a-mol" OR abenol OR acamol OR "acamoli forte" OR acenol OR acephen OR "acet suppositories" OR acetalgin OR "acetamino phenol" OR "acetaminophen" OR acetaminophene OR acetaminophenol OR acetamol OR acetomenophen OR acetylaminophenol OR adorem OR "afebrin algiafin" OR algocit OR algotropyl OR alphagesic OR alvedon OR amadil OR amadol OR "anacin 3" OR anadin OR anaflon OR "analgiser apamide" OR "apap apirex" OR apotel OR arthralgen OR atamel OR "ben-u-ron" OR benuron OR biogesic OR bodrex OR calapol OR calodol OR calonal OR calpol OR causalon OR cemol OR christamol OR claradol OR clocephen OR cp 500 OR cp500 OR dafalgan OR daga OR "acetylsalicylic acid" OR depon OR depyretin OR dirox OR dismifen OR disprol OR dolal OR dolex OR "dolex 500" OR doliprane OR dolitabs OR dolofen OR dolomol OR dolorol OR dolotec OR dolotemp OR dolprone OR doltem OR drilan OR "dristan af" OR duorol OR dymadon OR efferalgan OR "efferalgan 500" OR efferalganodis OR efferelgan OR enelfa OR eneril OR eraldor OR "eu med" OR exopon OR expandol OR febrilix OR fendon OR fervex OR fibrinol OR fortolin OR gelocatil OR "geluprane 500" OR gunaceta OR hedex OR helporal OR "infants feverall" OR injectapap OR janupap OR kamolas OR kyofen OR lekadol OR lemgrip OR letamol OR liquiprin OR lotemp OR lyteca OR malidens OR medamol OR meforagesic OR metagesic OR metalid OR mexalen OR "milidon 500" OR minopan OR mypara OR "n acetyl 4 aminophenol" OR "n acetyl para aminophenol" OR "n-acetyl-p-aminophenol" OR nalgesik OR napamol OR napap OR naprex OR nebs OR "nektol 500" OR neocitran OR neodalmin OR neopap OR nevral OR nilapur OR nobedon OR nysacetol OR ofirmev OR pacemol OR pacimol OR pamal OR pamol OR panadol OR panamax OR panasorb OR panodil OR "para acetylaminophenol" OR "para hydroxyacetanilide" OR "para suppo" OR paracet OR paracetaminophenol OR "paracetamol" OR paracetamole OR parafusiv OR parageniol OR paragon OR paralen OR paralief OR paramax OR paramidol OR parapaed OR paratabs OR parvid OR pasolind OR paximol OR pedipan OR perfalgan OR phenaphen OR pinex OR polarfen OR predimol OR puernol OR pyrigesic OR raperon OR rapidol OR relaphen OR remedol OR revanin OR "rhinapen elixir" OR rhodapap OR roxamol OR salzone OR serimol OR setamol OR sinaspril OR sinebriv OR sinedol OR sinpro OR supofen OR tabalgin OR tachipirin OR tachipirina OR taganopain OR tapar OR tempra OR tempte OR temzzard OR termofren OR tralgon OR "tralgon elixir" OR tramil OR treuphadol OR turpan OR tylex OR valadol OR wegmal OR winadol OR winasorb OR xebramol OR zolben OR zydinol)) AND (TITLE-ABS-KEY ("early birth*" OR prematur* OR "pre matur*" OR preterm OR "pre term" OR "very low birthweight" OR vlbw)) AND (TITLE-ABS-KEY ({Clinical-trial} OR {controlled-trial} OR randomi* OR randomly OR (random W/4 (allocat* OR distribut* OR assign*)) OR {placebo} OR {trial} OR {groups} OR {subgroups}) OR TITLE (rct)) AND (TITLE-ABS-KEY (amuno OR indocid OR "indocin indomet 140" OR indometacin OR indomethacin OR "indomethacin hydrochloride" OR metindol OR osmosin OR "xxe1cet956"))

Cochrane Library (CDSR and Central Register of Controlled Trials)

ID	Search	Hits
#1	MeSH descriptor: [Acetaminophen] explode all trees	3330
#2	(362o9itl9d or apap or acamol or acephen or acetaco or acetamidophenol or acetaminophen or acetominophen or algotropyl or "anacin 3" or anacin-3 or anacin3 or datril or hydroxyacetanilide or "n-(4-hydroxyphenyl) acetanilideor n-acetyl-p-aminophenol" or panadol or paracetamol or tylenol or p-acetamidophenol or p-hydroxyacetanilide):ti,ab,kw	11295

#3	#1 or #2	11295
#4	MeSH descriptor: [Indomethacin] explode all trees	2669
#5	(amuno or indocid or "indocin indomet 140" or indometacin or indomethacin or "indomethacin hydrochloride" or metindol or osmosin or "xxe1cet956"):ti,ab,kw	3243
#6	#4 or #5	4341
#7	MeSH descriptor: [Infant, Premature] explode all trees	3891
#8	MeSH descriptor: [Infant, Extremely Premature] explode all trees	210
#9	MeSH descriptor: [Infant, Premature, Diseases] explode all trees	3401
#10	(("early birth*" or prematur* or "pre matur*" or preterm or "pre term" or "very low birthweight" or VLBW)):ti,ab,kw	29664
#11	#7 or #8 or #9 or #10	30368
#12	((randomized controlled trial or controlled clinical trial)):pt	597062
#13	((Randomized or placebo or randomly or trial or groups)):ab	1106024
#14	MeSH descriptor: [Drug Therapy] explode all trees	143069
#15	#12 or #13 or #14	1233074
#16	MeSH descriptor: [Animals] explode all trees	607044
#17	MeSH descriptor: [Humans] explode all trees	606985
#18	#15 not (#16 not #17)	1233041
#19	#3 and #6 and #11 and #18	23

PROSPERO Searched June 15, 2021

Line	Search for	Hits
#1	("early birth*" OR prematur* OR "pre matur*" OR preterm OR "pre term" OR "very low birthweight" OR vlbw)	3952
#2	(amuno OR indocid OR "indocin indomet 140" OR indometacin OR indomethacin OR "indomethacin hydrochloride" OR metindol OR osmosin OR "xxe1cet956")	73
#3	acetaminophen or acetominophen or paracetamol or panadol or anacin	3371
#4	"clinical register" or "controlled trial*" or random* or placebo or trial or group* or subgroup* or rct	110097
#5	#1 AND #2 AND #3 AND #4	13