INTRAVENOUS ACETAMINOPHEN FOR POSTOPERATIVE PAIN IN NEONATES

INTRAVENOUS ACETAMINOPHEN FOR POSTOPERATIVE PAIN IN NEONATES: A MULTI-METHODS APPROACH

By VICTORIA A. ARCHER, BA (Hons.), BSc, MD

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Science

McMaster University Master of Science (2023) Hamilton, Ontario (Health Research Methodology)

Title: Intravenous acetaminophen for postoperative pain in neonates: a multi-methods approach

Author: Victoria A. Archer

BA (Hons.) (Acadia University, Wolfville, Nova Scotia, 2016)

BSc (Acadia University, Wolfville, Nova Scotia, 2016)

MD (McMaster University, Hamilton, Ontario, 2019)

Supervisors: Dr. Luis Braga, Dr. Mark Walton, Dr. Samira Samiee-Zafarghandy

Number of Pages: xiv, 130

LAY ABSTRACT

All patients experience some amount pain after major surgery. Babies who are born too early (i.e., preterm) may experience more pain than babies those who are born close to their due date. Opioid drugs such as Fentanyl are commonly used to manage pain after surgery, but they have side effects, such as slowing down breathing and causing problems with gut function. Using non-opioid drugs (such as acetaminophen) and opioid drugs together may reduce the amount of opioids needed. This combination may also help with pain control. We want to know if using intravenous (IV) acetaminophen will reduce the rate of side effects, decrease the amount of opioids given, and still control pain well. To answer this question, we completed three studies. The first study reviewed all the published data on IV acetaminophen in children who need surgery. In the second study, we surveyed pediatric surgeons, anesthesiologists, and neonatologists to see how they manage pain after surgery and what they thought about IV acetaminophen. The last study is the plan for our pilot trial, where we will see if giving IV acetaminophen and opioids together is better than opioids alone.

ABSTRACT

Background: Managing pain is challenging, especially in neonates. Uncontrolled pain and opioid exposure are associated with short- and long-term adverse events. Adequately controlling pain while reducing opioid exposure is paramount in the neonatal population. This thesis presents three studies, all aiming to determine if IV acetaminophen is an appropriate adjunct to current opioid-based postoperative pain regimens. The population of interest is neonates admitted to the neonatal intensive care unit (NICU) treated with major abdominal and thoracic surgery.

Chapter 1 provides the scientific framework underpinning this work and the rationale for performing the included studies.

Chapter 2 presents the results of a systematic review and meta-analysis assessing the effect of IV acetaminophen on postoperative pain in pediatric patients. This chapter further expands on gaps and opportunities for future research.

Chapter 3 reports the results of a national survey in which pediatric surgeons, anesthesiologists, and neonatologists reported their postoperative pain prescribing practices in the NICU and their perspectives on the use of IV acetaminophen.

Chapter 4 describes the protocol for a pilot randomized controlled trial (RCT). This study will assess the feasibility of a multicenter RCT to evaluate the effectiveness of IV acetaminophen for postoperative pain in neonates recovering from major abdominal and thoracic surgery.

Chapter 5 summarizes the results of the studies in context and details how the results of each study informed the others. It also discusses areas of future research.

ACKNOWLEDGEMENTS

This work would not have been possible without the support of my co-authors and collaborators. I am especially thankful to my thesis committee, which include Dr. Walton, Dr. Samiee-Zafarghandy and Dr. Braga. Thank-you for your mentorship, your patience, and your support.

To my friends and family who have heard so much about this work, you could likely recite this thesis from memory; thank you. Thank-you for listening, troubleshooting, proof-reading, and frequent reality checks.

My most important thank-you is to my (soon-to-be) husband, Ben. Any measure of success I have experienced is entirely due to your unwavering support and countless sacrifices. You (and Kit) are a constant reminder of what is truly important in life. Your faith in me defies all available evidence. I strive to be the person you think I am.

TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 2

CHAPTER 3

LIST OF FIGURES

CHAPTER 2

CHAPTER 4

APPENDIX 2

LIST OF ABBREVIATIONS

ALT: Alanine Transaminase

AST: Aspartate Aminotransferase

BiPAP: Bilevel Positive Airway Pressure

CDH: Congenital Diaphragmatic Hernia

CHEOPS: Children's Hospital of Eastern Ontario Pain Scale

CI: Confidence Interval

CPAP: Continuous Positive Airway Pressure

CROSS: Checklist for Reporting of Survey Studies

DSMB: Data Safety Monitoring Board

EHBA: Extrahepatic Biliary Atresia

FLACC: Face, Legs, Activity, Cry, Consolability Scale

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

HIREB: Hamilton Integrated Research Ethics Board

INR: International Normalized Ratio

IP: Internet Protocol

IQR: Interquartile Range

IV: Intravenous

MCH: McMaster Children's Hospital

MD: Mean Difference

MED: Morphine Equivalent Dosing

Mesh: Medical Subject Headings

N-PASS: Neonatal Pain Agitation and Sedation Scale

NEOPAIN: Neurological Outcomes and Pre-Emptive Analgesia In Neonates

NICU: Neonatal Intensive Care Unit

NIPS: Neonatal Infant Pain Scale

NR: Not Reported

OPS: Objective Pain Scale

PT: Prothrombin Time

RCT: Randomized Controlled Trial

REDCap: Research Electronic Data Capture

RoB: Risk of Bias

RR: Relative Risk

SD: Standard Deviation

SMD: Standard Mean Difference

SOF: Summary of Findings

SPSS: Statistical Package for Social Sciences

TOF: Tracheoesophageal Fistula

VAS: Visual Analogue Scale

DECLARATION OF ACADEMIC THESIS

I, Victoria A. Archer declare this thesis to be my own work. This thesis has been produced in the "sandwich" format, as two or more components of this thesis have been published or submitted for publication in peer reviewed journals. Victoria Archer is the primary author and contributed to all projects of this thesis in the following way: formulation of the research question, design of the study, attaining funding (if appliable), data collection, data analysis, interpretation, and manuscript presentation. Each chapter will detail the contributions of co-authors.

CHAPTER 1: INTRODUCTION

1.1 Background

The initial stimulus for this research was to determine how to reduce opioid use in neonates after surgery, since opioid exposure in neonates is associated with adverse events. There have been fewer studies focused on opioid reduction in neonates compared to older patients. Through discussions with stakeholders and examining the literature, it became clear that this was a multifaceted problem with numerous potential focus areas that needed to more fully explored. The following background information will introduce the scope of the problem and rationalize our approach. The projects presented in chapters two, three, and four were designed to help understand the scope of the problem, engage stakeholders, and develop a strategy to address this issue. These studies were performed sequentially, with the results of one study informing the design of the next. This multifaceted approach was purposefully selected to create the most clinically meaningful results.

The management of postoperative pain is subjective and primarily relies on the communication of the experience of pain by the patient. The reliance on verbal communication makes managing postoperative pain in neonates even more difficult as they cannot communicate. This challenge is further attenuated in neonates as there are more significant variations in their physiology, and there has been comparatively less research on the management of their pain relative to adults [1-5]. The historical management of neonatal pain further contributes to this challenge. Neonates were

historically not thought to experience pain, or that the pain they experienced was not meaningful. As such, intraoperative and postoperative pain in neonates was routinely not treated [6].

This practice began to change in 1987 and again in 1992 when Anand et al. first published that using agents such as halothane or fentanyl blunts the stress response and improve outcomes after surgery in neonates [7, 8]. Similar research established the short-term effects of unmanaged pain in neonates, confirming Anand et al.'s findings and demonstrating that unmanaged pain is associated with increased hemodynamic instability and muscle and protein catabolism [9, 10]. These findings spurred further research on pain in neonates. Researchers found that compared to their adult counterparts, neonates, particularly preterm neonates, have lower pain thresholds due to hyperinnervation of the skin, increased expression of neurotransmitters responsible for nociception, and increased excitability of the spinal cord [11, 12].

The response to pain is hypothesized to initiate stress responses, which contribute to intraventricular hemorrhage and leukomalacia [13]. Due to increased neurologic plasticity and development, unmanaged pain in infancy is correlated with long term long-term adverse effects [14]. In a series of studies evaluating the effect of neonatal circumcision on response to vaccinations, researchers found increased pain scores and crying time in infants who underwent circumcision without analgesia [15]. However, when infants had circumcision with local anesthetic, this difference was minimized [16]. The authors

hypothesized that pain may result in long-term effects on the perception of pain in infants by altering their developing nervous system. They further hypothesized that reducing nociceptive inputs via analgesia reduces the changes to their central nervous system, thus reducing heightened pain responses in the future [16]. These results were corroborated by Jeroen et al., who found that in infants who underwent major surgery, pain responses were not altered if treated with appropriate analgesia [17]. Responses to pain are multifactorial, with various biological and psychosocial confounding factors associated with hospitalized neonates, making it impossible to conclude that pain alone is responsible for changes in pain responses. However, researchers suggest that pain is likely an important factor [18]. Other animal and human studies have identified that painful procedures in neonates are correlated with long-term adverse neurodevelopmental and somatosensory outcomes in infancy, adolescence, and adulthood [18-23].

Pain management in neonates who undergo surgery is increasingly recognized as an important priority. has. Opioids are the most commonly used agents in this age group [24-26]. While opioids have resulted in better pain control, they are associated with short- and long-term adverse events. Acutely, they can cause respiratory depression, urinary retention, hypotension, tolerance, and delayed time to enteral feeds [27-30]. In the pilot and five-year follow-up of the Neurological Outcomes and Pre-Emptive Analgesia in Neonates (NEOPAIN) trial, authors found morphine exposure was linked with reduced intelligence, short-term memory, and increased parental concerns about social problems; however, in the eight to nine-year follow-up, this was not shown, suggesting that these

neuropsychologic may not be permanent [31-33]. Other smaller studies have been done, although they focus on neuroimaging, with little to no focus on behavioural outcomes. It is unclear whether these neuroimaging changes correlate with neurodevelopmental outcomes [34, 35]. There is a need for more studies with different cohorts of patients and prolonged follow-up to confirm these findings [36].

Although more research is required, the evidence suggests that neonatal exposure to opioids and pain may result in short- and long-term adverse events. Pain regimes should therefore aim to reduce both pain and the amount of opioids used. Multimodal pain regimens have been developed with this goal in mind. Pain is reduced by using multiple synergistic pharmacologic and non-pharmacologic techniques while minimizing opioid use [37]. These regimens have been widely adopted for use in adult and pediatric surgical patients [38-40]. Among neonatal patients, however, there is a paucity of data and lack of consensus. There are no studies which characterize specific postoperative pain management strategies in neonates. Although some studies described pain management practice patterns in the Neonatal Intensive Care Unit (NICU), they only involved neonatologists or nurses [24, 41-44]. Other critical stakeholders, such as pediatric surgeons and anesthesiologists, were not involved.

In chapter three of this thesis, we will describe the available literature and present the results of our national survey, which characterizes current strategies for the management of postoperative pain. This also aims to understand the perspectives on the utility of IV

acetaminophen for postoperative pain management in the NICU. In other developed countries, such as Europe and the United States, IV acetaminophen is used more commonly used for pain management [45]. At our institution, IV acetaminophen is not available for pain management in neonates, and the frequency of its use across Canada remains uncertain. Locally, there is ongoing interest in using IV acetaminophen as an adjunct to postoperative pain management. Despite its use in other regions, when we evaluated the evidence and spoke to neonatologists, surgeons, and anesthesiologists from across Canada, there seemed to be variable perceptions on its efficacy. We therefore elected to elicit the perspectives of surgeons, anesthesiologists, and neonatologists on IV acetaminophen for postoperative pain.

Chapter two of this thesis is a systematic review evaluating the efficacy of IV acetaminophen for postoperative pain in pediatric patients. This section describes patterns of use and perceived benefits and harms of IV acetaminophen in the NICU. In adults, acetaminophen has been shown to reduce pain and opioid consumption [46]. It has been further shown to reduce postoperative nausea and vomiting when given prophylactically in adults [47]. When oral and IV routes were compared in a systematic review in adults, a small but likely clinically insignificant reduction in pain (0.5 points on a scale of one to ten). There was also a small reduction in opioid requirements (a reduction in 5.56 oral morphine equivalents over 24 hours). In adults, economic analyses have suggested that IV formulations should only be considered in patients who cannot tolerate other routes of administration [48].

There has been comparatively less research on the use of acetaminophen in pediatric patients. Existing studies have shown that both rectal and oral acetaminophen is associated with reductions in postoperative pain, nausea and vomiting [49]. There is even less research regarding IV acetaminophen for postoperative pain in pediatric patients. Like adults, children have many restrictions in the immediate postoperative period, limiting the available routes of administration. Patients may not be able to have oral intake. In the case of rectal and pelvic surgery, they may not be able to take medications rectally either, necessitating IV administration. In neonates, there is significant variability in the maturity of their intestinal tracts and enterohepatic circulatory systems, with decreased motility, absorption, and circulation. As a result, the absorption of oral and rectal medications is less predictable compared to IV administration [50-53]. Using the IV route also avoids first-pass metabolism, resulting in up to 50% less accumulation in the liver and decreased production of hepatotoxic metabolites [54].

As will be detailed in the systematic review in chapter two, there is a paucity of literature regarding the efficacy of IV acetaminophen for postoperative pain control in pediatric populations. For non-abdominal and thoracic surgeries (including non-surgical pain), IV acetaminophen may reduce pain, opioid use, and opioid-related adverse events [55-58]. Evidence suggests that IV acetaminophen is safe and not associated with liver injury [59]. While the evidence demonstrates short-term safety in neonates, with ongoing research evaluating long-term effects, studies have yet to evaluate its utility for postoperative pain management in preterm neonates [60-64]. The unique physiology of preterm neonates and

the significant pain associated with major thoracic and abdominal surgery necessitates individual attention.

1.2 Research Question and Objectives

There are numerous possible solutions to optimizing the management of pain in neonates. The area we chose to focus on was multimodal therapy. Multimodal pain regimens, with the addition of multiple pain-controlling agents and techniques, offer the opportunity to reduce opioid exposure while adequately controlling pain. Multimodal pain regimens must be designed intentionally for specific populations to account for the unique physiology of different age groups and the types of pain being experienced. With the aforementioned differences in neonates' response to pain, special attention is required in developing appropriate strategies. This often starts with examining the efficacy of single agents and then studying their efficacy when used in combination.

The research question for this thesis is the following: “When used for postoperative pain management in patients admitted to the NICU, does IV acetaminophen reduce opioid use and effectively control pain?” With our understanding of the complexity of this problem, it was clear that no single study could effectively answer this question. We conducted three studies in a stepwise fashion, such that the results of each study could be incorporated into the design of subsequent work. This approach enabled us to introduce more nuance into each project, which will generate more clinically meaningful results.

We began with a systematic review and meta-analysis with the objective of assessing IV acetaminophen for postoperative pain management in pediatric patients, presented in chapter one. After identifying a lack of data on IV acetaminophen and on postoperative pain management strategies, we designed and implemented a survey that the goal of characterizing postoperative pain management in Canadian NICUs. In this study, we assessed the perspectives of surgeons, neonatologists, and anesthesiologists on the use of IV acetaminophen for postoperative pain management in neonates. The results appear in chapter three. Finally, in chapter four, we present the protocol for our pilot randomized controlled trial, which has the main objective of assessing the feasibility of a large-scale trial which will assess if the addition of IV acetaminophen to fentanyl-based postoperative pain management strategies is associated with a reduction in opioid use, adverse events, and pain scores. These three studies will provide novel evidence on this topic and will act as the foundation for future work in this field.

CHAPTER 2: INTRAVENOUS ACETAMINOPHEN FOR POSTOPERATIVE PAIN CONTROL AFTER OPEN ABDOMINAL AND THORACIC SURGERY IN PEDIATRIC PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Author names and affiliations:

Victoria Archer[1], Zacharie Cloutier[1], Lily Park[1], Daniel Briatico[2,3] J Mark Walton[2,3,4]
1. Division of General Surgery, Department of Surgery, McMaster University, Hamilton, Ontario, Canada
2. Division of Pediatric General Surgery, Department of Surgery, McMaster University, Hamilton, Ontario, Canada
3. McMaster Pediatric Surgery Research Collaborative, Hamilton, Ontario, Canada
4. McMaster Children's Hospital, Hamilton, Ontario, Canada

This paper has been previously published in Pediatric Surgery International November 28, 2022 and is available on the journal's website [65].

2.1 Abstract

Purpose: Pediatric opioid exposure increases short- and long-term adverse events (AE). The addition of Intravenous acetaminophen (IVA) to pediatric pain regimes to may reduce opioids but is not well studied postoperatively. Our objective was to quantify the impact of IVA on postoperative pain, opioid use, and AEs in pediatric patients after major abdominal and thoracic surgery.

Methods: Medline, Embase, CINAHL, Web of Science, and Cochrane Library were searched systematically for randomized controlled trials (RCTs) comparing IVA to other modalities.

Results: Five RCTs enrolling 443 patients with an average age of 2.12 years (±2.81) were included. Trials comparing IVA with opioids to opioids alone were meta-analyzed. Low to very low-quality evidence demonstrated equivalent pain scores between the groups (-0.23, 95% CI -0.88 to 0.40, p=0.47) and a reduction in opioid consumption (-1.95 morphine equivalents/kg/48h, 95% CI -3.95 to 0.05, p=0.06) and minor AEs (relative risk 0.39, 95% CI 0.11 to 1.43, p=0.15).

Conclusion: We conclude that the addition of IVA to opioid-based regimes in pediatric patients may reduce opioid use and minor AEs without increasing postoperative pain. Given the certainty of evidence, further research featuring patient-important outcomes and prolonged follow-up is necessary to confirm these findings.

2.2 Introduction

This chapter describes the rationale for conducting this systematic review. In the short-term, exposure to opioids in is associated with decreased respiratory drive, delayed intestinal motility, sedation, and increased length of stay (LOS) [66, 67]. Long-term adverse events are attenuated in pediatric patients as their state of rapid neurologic development places them at increased risk for long-term developmental delays when exposed to opioids, particularly in neonates [23, 68, 69]. At the same time, pain which is inadequately controlled can lead to as impaired ventilation, circulatory changes, intraventricular hemorrhage, and periventricular leukomalacia [68, 70-72].

A multimodal strategy provides the opportunity to balance pain control and medication-related adverse events; therefore, we have elected to evaluate one potential agent, IV acetaminophen. Patients may have restrictions in the immediate postoperative period, limiting the use of oral and rectal formulations and necessitating IV administration. Oral and rectal administration of pain medications in neonates may also be limited by their intestinal tracts and enterohepatic circulation. These systems are in varying stages of maturity, with decreased motility, absorption, and circulation. As such, the pharmacokinetics of oral and rectal medications become less predictable compared to IV [50-53]. IV administration also avoids first-pass metabolism, resulting in up to 50% less accumulation in the liver and decreased production of hepatotoxic metabolites [54].

We anticipated a lack of research focused on pain management in preterm and term neonates. We therefore elected to include studies which enrolled pediatric patients of any age, as this would allow us to understand the application of the drug broadly in pediatrics, and if data allowed, to perform subgroup analyses on neonates if possible. There has been research on the utility of IV acetaminophen for non-surgical pain in pediatric and neonatal populations, however, in keeping with our original research question, we elected to focus on pain following open abdominal and thoracic surgeries. Pain after surgery is physiologically unique from other procedures, such as venipuncture or nasogastric tube insertion. Further variation in pain is based on the type of surgery with open abdominal and thoracic surgeries resulting in a different physiologic response than other surgical procedures (i.e., laparoscopy, orthopedic interventions, sternotomies, etc.) [73-75].

As detailed in the first chapter of this thesis, we took a stepwise approach to understand if IV acetaminophen could reduce pain and opioid use in neonates. The available evidence had yet to be formally reviewed; thus, we felt it important to perform a systematic review and meta-analysis. This review not only assisted in quantifying the known effects of IV acetaminophen, but also identified the types of studies and outcome measures used previously, identified knowledge gaps, and revealed areas requiring further attention. These findings were crucial in the design of our randomized controlled trial (which is described in chapter four).

Objectives

This systematic review aimed to synthesize the best available evidence comparing IV acetaminophen to other pain medications in pediatric patients undergoing open abdominal and thoracic surgery. Specifically, the aim was to compare pain scores, opioid requirements, and adverse events.

2.3 Methods

Study design

This was a systematic review of IV acetaminophen for postoperative pain control in children undergoing open abdominal and thoracic surgeries. The primary outcome was postoperative pain scores, and the secondary outcomes included opioid requirements, analgesic complications, and length of stay (LOS). The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021274431).

Search strategy

A systematic search of Medline, Embase, CINAHL, Web of Science, and the Cochrane Library for randomized controlled trials (RCT) comparing IV acetaminophen to any other pain medication for pediatric patients after open abdominal and non-cardiac thoracic surgery was conducted. The search strategy was developed with a research librarian. Medical Subject Headings (MeSH) were used where applicable and included derivatives of acetaminophen, paracetamol, tylenol, orfirmev, intravenous, injection, parenteral, pain,

postoperative, procedural, and pediatric. A hand search of the reference lists of relevant studies was also conducted. Studies were restricted to those with full texts available in English. A sample search strategy is available in the supplemental files.

Study selection and data extraction

Studies were included if they involved patients under 18 years of age who underwent open abdominal or non-cardiac thoracic surgery, compared postoperative IV acetaminophen to any other pain medication, and were an RCT. Studies were excluded if they included other types of surgery, did not provide specific thoracic or abdominal surgery results, and if they only evaluated the effect of pre-or intraoperative IV acetaminophen. Title and abstract screening were completed independently and in duplicate by at least two reviewers (VA, LP, ZC). Discrepancies were automatically included in the full-text screening process and resolved at that time; a third reviewer adjudicated any unresolved discrepancies. This process was done using Covidence systematic review software [76].

Data were extracted by two independent reviewers (VA, LP, ZC). Any discrepancies were resolved by consensus. A third reviewer adjudicated any unresolved discrepancies. Study authors were contacted to obtain missing data.

Primary outcome

The primary outcome of this systematic review was postoperative pain scores (reported as standard mean difference (SMD) and back transformed to a numeric rating scale). This was extracted at 48 hours, as this was the only common time-period reported. Other time periods were reported descriptively.

Secondary outcomes

Prespecified secondary outcomes included opioid equivalents used, and adverse events (urinary retention, ileus, nausea and vomiting, sedation, and adverse drug reactions), LOS, time requiring mechanical ventilation, and time to first enteral feed. Opioid equivalents (reported as morphine equivalents/kg/48 hours) were extracted at 48 hours as this was the only common time-period reported. Adverse events were extracted up to 72 hours (the longest follow-up period reported). Outcomes not able to be meta-analyzed were reported descriptively.

Demographics

Reviewers also extracted study characteristics (year and country of study), participant characteristics (age, gender, indication for surgery, type of surgery performed, pain scale used, and outcomes reported).

Risk of bias and certainty of evidence

The Cochrane Risk of Bias (RoB) 2.0 Tool for Randomized Control Trials was used to evaluate the risk of bias of the included studies. Score of low, high, or unclear were assigned to each of the following domains: randomization, deviation from the intended intervention, missing data, measurement of outcomes, and selection of outcomes [77]. Scoring was performed independently and in duplicate (ZC, LP), with conflicts resolved by a third reviewer (VA).

Each meta-analyzed outcome was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool. The quality of evidence for each outcome was scored as high, moderate, low or very low based on six pre-specified categories (limitations in study design/ROB, inconsistency of results, directness of evidence, imprecision, publication bias, and other) [78]. This was done to characterize the quality of evidence of the research, which contributed to this meta-analysis. The results were collated in a single summary of findings (SOF) table, highlighting the magnitude of effect and overall grading of evidence for each outcome, as recommended by the Cochrane Collaborative [78]. GradePro software was used to create the SOF table [79].

Statistical analysis

Given the heterogeneous nature of the included studies (in terms of measurement and reporting), only a limited number of data could be pooled. The results included in the meta-analysis were SMD in pain scores, cumulative opioid use both at 48 hours (both for

trials comparing IV acetaminophen to opioids), and proportions for minor adverse events. Statistical analysis was done using the Cochrane Review Manager 5.3 with an alpha of < 0.05 [80]. A pairwise meta-analysis was performed with a Dersimonian and Laird random-effects model to estimate the effect size for each outcome if more than two studies reported the result.

SMD with 95% confidence intervals (CI) were calculated for pain scores to account for the variability between studies. To interpret the SMD, Cohen's effect size (d) was used, where an SMD 0-0.19 is a trivial effect, 0.20-0.49 is a small effect, 0.50-0.79 is a medium effect, and 0.80 is a large effect [81]. To ease the interpretation, SMDs were back-transformed into the numeric rating scale-11 (NRS-11), allowing the result to be displayed on a scale of 0 to 10. This was done using the standard deviation from Ceelie et al.'s trial, which was felt to be the most representative [82].

Using standard conversions, cumulative opioid doses were converted into morphine equivalent doses (MED). In studies where the median and interquartile range were reported, Wan et al.'s standard deviation estimation method was used [83]. For dichotomous outcomes, where one arm had no events, a value of 0.4 was used instead of zero, which allowed for calculating the relative risk (RR). For each pooled outcome, heterogeneity was assessed using Higgin's I^2 statistic with the following prespecified classifications: 0-40% might not be important, 30-60% moderate heterogeneity, 50-90% substantial heterogeneity, and 75-100% considerable heterogeneity [84]. Subgroup

analyses were planned for age and type of surgery but were not feasible due to a lack of data. For trials where full texts unavailable or with unreported data, the study authors were contacted to obtain this data. If the number of patients analyzed was not specifically displayed for each outcome, it was assumed to be the number of patients in each group at baseline.

2.4 Results

Search results

The search identified 896 citations. After removing duplicates, 805 studies were screened by title and abstract. Title and abstract screening removed 779 irrelevant studies. There was moderate agreement between the reviewers during this phase (95.6% agreement, κ =0.49). 25 articles underwent full-text screening. Studies were excluded during full-text screening due to an incorrect study design (5), full text not being available (3), incorrect population (1), duplicate (1), and incorrect intervention (10). 5 studies were included in the final analysis. Study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is illustrated in Figure 1.

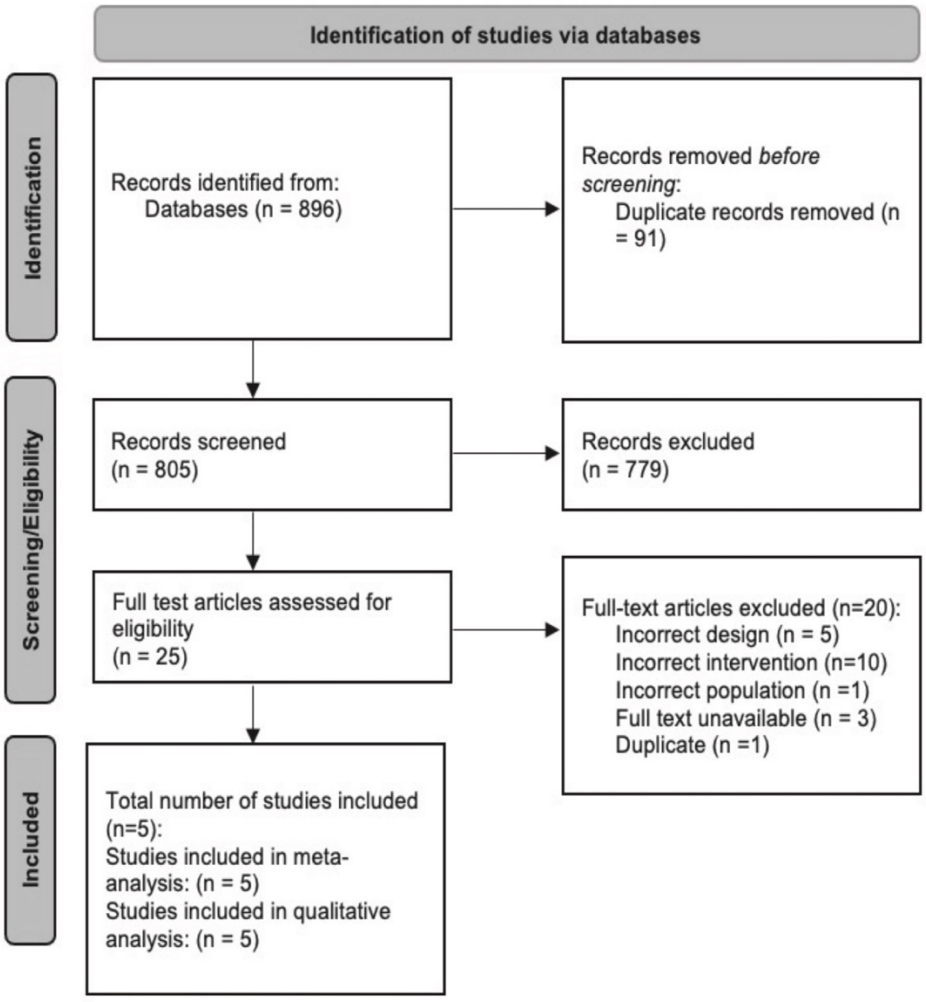


Figure 1. Study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Excluded studies

Several studies initially appeared to meet the inclusion criteria but were excluded. The first was a study by Arora et al. which was an abstract only with no available author contact information [85]. The second was a trial by Majeed et al. where they performed appendectomies, but it was not clear whether this was an open or laparoscopic procedure.

The study author was contacted with no response [86]. Given the year of publication (2020), the study team felt there was a high chance that these procedures were performed laparoscopically, therefore the study was excluded. The third study was a trial by Rugyte et al., in which they reported data from orthopedic and abdominal surgeries [87]. The authors were contacted to provide data only for abdominal surgery, but no response was received, therefore it was also excluded.

Characteristics of included studies

5 RCTs enrolling a total of 443 patients were included. The pooled mean age of participants was 2.12 years (SD 2.81). The median number of patients enrolled per study was 66 (range 60-183). The median follow-up time was 48 hours (range 6-72). Three studies compared IV acetaminophen to opioids [82, 88, 89]. One of these studies (Ceelie et al.) compared acetaminophen as a primary agent to morphine as a primary agent; however, 66.77% of patients received morphine in the acetaminophen group [82]. As most patients in this trial received a combination of opioids and acetaminophen, it was included with the other two trials comparing IV acetaminophen and opioids to opioids alone. For trials not comparing IV acetaminophen to opioids, one compared acetaminophen to its prodrug form (propacetamol), and one compared it to a bupivacaine-based epidural [90, 91]. Two studies evaluated only open abdominal surgery [90, 92]. The others evaluated open abdominal and non-cardiac thoracic surgery. Two studies used the visual analogue scale (VAS); otherwise, no common pain scale was used [89, 90]. Overall, there was heterogeneity with comparator pain modalities, outcome

measurements, pain scales, and data reporting. A summary of included studies can be found in Table 1.

Table 1. Characteristics of included studies

	Ceelie	**Dehghan**	**Hong**	**Murat**	**Solanki**
Year	2013	2019	2010	2005	2017
Sample Size	71	66	63	183	60
Age					
Control	20 days (IQR 1.8-87.5)	16.79 days (SD 15.57)	17.8 months (SD 10.4)	4.3 years (SD 2.6)	40.12 days (SD 45.4)
Acetaminophen	5 days (IQR 1.5-64.5)	16.67 days (SD 15.77)	16.9 (SD 8.3)	4.8 years (SD 2.5)	42.96 days (SD 68.49)
% Male					
Control	68.4%	NR	NR	76.1%	56.6%
Acetaminophen	54.5%	NR	NR	73.7%	66.67%
Type of surgery	Non-Cardiac Thoracic (22.5%) and Abdominal (77.46%)	Abdominal and thoracic surgery (esophageal atresia, CDH, gastroschisis, duodenal atresia, omphalocele and intestinal obstruction)	Open ureteroneocystostomy	Open inguinal hernia repair	Major thoracic or abdominal (TOF, Thoracotomy, Colostomy, Laparotomy, CDH, EHBA)
Follow up (hours)	48	48	72	6	48
Comparison	IV Morphine	IV Fentanyl	IV Fentanyl PCA	Propacetamol	Bupivacaine epidural
Pain Scale	NRS 11 and COMFORT-B	NIPS	CHEOPS	VAS (OPS if child unable to do VAS)	FLACC
Opioid Use Recorded	Yes	Yes	Yes	No	No
Secondary Outcomes	Urinary retention, bradycardia, apnea, reintubation	Duration of intubation	Nausea and vomiting, pruritus, poor oral feeding, sedation, desaturations	Nausea, vomiting, injection site pain, hypotonia,	Sedation, bradycardia, vomiting, delayed

, time on ventilator Other medications required	abdominal pain/reaction, fever, other medications required	recover, cardiac arrest

Abbreviations
IQR: Interquartile Range
SD: Standard Deviation
NR: Not Reported
NIPS: Neonatal Infant Pain Scale
CHEOPS: Children's Hospital of Eastern Ontario Pain Scale
VAS: Visual Analogue Scale
OPS: Objective Pain Scale
FLACC: Face, Legs, Activity, Cry, Consolability Scale
TOF: Tracheoesophageal fistula
CDH: Congenital Diaphragmatic Hernia
EHBA: Extrahepatic biliary atresia

Risk of bias

The results of the risk of bias (ROB) assessment for each meta-analyzed outcome are displayed in Table 2. There was at least some concern for ROB for each outcome due to inconsistent reporting of randomization and allocation concealment techniques and measurement of outcomes. Our comprehensive search identified only one unpublished manuscript; therefore, the risk of publication bias was not suspected. Funnel plots could not be constructed to further evaluate publication bias as fewer than 10 studies were included [84].

Table 2. Cochrane risk of bias assessment 2.0 for meta-analyzed outcomes

	Randomization	Deviation from intended intervention	Missing outcome data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Postoperative pain scores						
Ceelie 2013	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Dehghan 2019	**Some concern**	**Low**	**Low**	**High**	**Low**	**High**
Hong 2010	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Opioid consumption at 48 hours						
Ceelie 2013	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Dehghan 2019	**Some concern**	**Low**	**Low**	**Low**	**Low**	**Some concern**
Hong 2010	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Minor adverse events						
Ceelie 2013	**Low**	**Low**	**Low**	**Some concern**	**Low**	**Some concern**
Dehghan 2019	**Some concern**	**Low**	**Low**	**High**	**Some concern**	**High**
Hong 2010	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**

Primary outcome: postoperative pain scores (IV acetaminophen compared to opioids)

Given the inconsistent comparisons, it was only possible to pool studies comparing IV acetaminophen to opioids. We calculated a pooled SMD of -0.20, which represents a small decrease in postoperative pain (-0.20, 95% CI -0.76 to 0.35, p=0.47). The 95% CI encompasses both a decrease and increase in pain scores. On the NRS-11 scale, this translates to a decrease of 0.23 points (95% CI -0.88 to 0.40) on a scale of 0 to 10 (with 0 being no pain and 10 being the worst pain). The certainty of the evidence is downgraded due to heterogeneity (I^2, 74%), ROB, imprecision, and inconsistency. Therefore, the addition of IV acetaminophen to opioid-based pain regimes may result in little to no

difference in postoperative pain scores, but the evidence is very uncertain. The forest plot of this data can be seen in Figure 2.

Due to a lack of data and variation in recording times, pain scores for time periods before and after 48 hours could not be meta-analyzed. Both Dehghan and Hong recorded pain scores up to 48 hours; Ceelie et al. only reported pain scores at 48 hours [82, 89, 92]. Hong and Dehghan did not identify a statistically significant difference in pain scores at up to 48 hours [89, 92]. After 48 hours, only Hong et al. recorded pain scores (60 and 72 hours) which were non-significantly different [92].

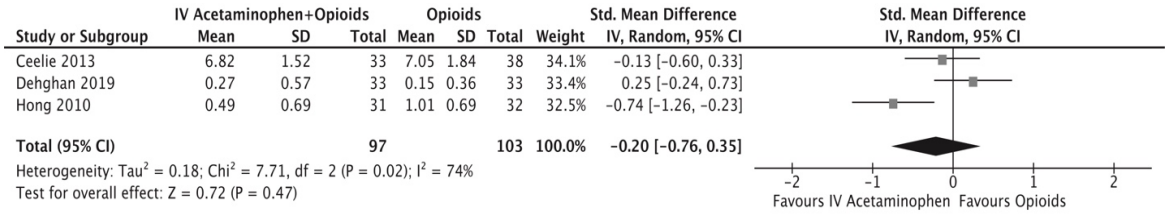


Figure 2. Random-effects meta-analysis comparing IV acetaminophen and opioids to opioids alone presented as standard mean difference in postoperative pain scores

Primary outcome: postoperative pain scores (IV acetaminophen compared to non-opioids)

Using the Face, Legs, Activity, Cry, Consolability (FLACC) Scale (range 0-10), Solanki et al. found that pain scores were statistically significantly lower in patients treated with bupivacaine epidural compared to IV acetaminophen/ This occurred at multiple time points. When comparing IV paracetamol to propacetamol, Murat et al. used a 10-point

visual analogue scale (VAS) to assess pain difference and pain relief and found no difference in their 6-hour follow up.

Secondary outcome: opioid consumption

Ceelie, Dehghan and Hong et al. recorded cumulative opioid use [82, 89, 92]. A mean difference (MD) of -1.95 oral MED/kg/48 hours (-3.95 to 0.05, p=0.06) was found when pooled. Using conservative dosing guidelines of 0.08 MED/kg/dose every four hours or the more liberal 0.1 MED/kg/dose every 3 hours resulted in a clinical decrease of 1.62 to 2.03 doses of oral morphine equivalents per day. Based on a target minimally clinically important difference of a 30% decrease (as used in the sample size calculations by Ceelie and Hong et al.), this is a clinically significant difference. However, the certainty of the evidence is downgraded due to inconsistency (I^2, 99%) and imprecision (due to the small sample size). Ultimately, low-quality evidence suggests that IV acetaminophen in conjunction with opioids may reduce opioid use. The forest plot demonstrating this data is available in Figure 3.

Only Hong et al. examined cumulative opioid use beyond 48 hours [92]. They found that from 48 to 72 hours, there was a difference in 6.1 mcg/kg/24 hours of fentanyl use, but this difference was not significant (p=0.357).

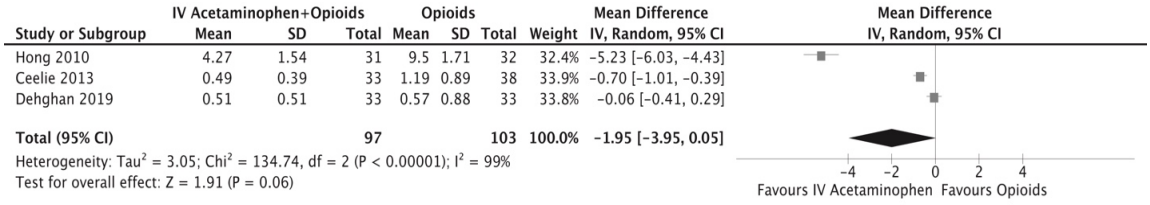


Figure 3. Random-effects meta-analysis comparing IV acetaminophen and opioids to opioids alone for opioid consumption presented in morphine equivalent doses/kg/48 hours

Secondary outcome: minor adverse events (IV acetaminophen compared to opioids)

Due to the heterogeneity in the comparators of the included trials, it was felt not to be methodologically feasible to pool the data from all studies together. Therefore, minor adverse events from the studies comparing IVA to opioids were aggregated. Minor adverse events included nausea, vomiting, apnea (with and without naloxone administration), and urinary retention. Pooling demonstrated a reduction in minor adverse events (RR 0.39, 95% CI 0.11 to 1.43, p=0.15), with an absolute reduction of 207 fewer per 1000 (95% CI from 302 fewer to 146 more). The I^2 of 0% indicates low levels of heterogeneity. The quality of evidence was downgraded due to ROB, inconsistency, and imprecision and was upgraded due to the large effect size. Therefore, there is low-quality evidence suggesting that the addition of IV acetaminophen may reduce minor adverse events. The results of this analysis represented as a forest plot can be seen in Figure 4.

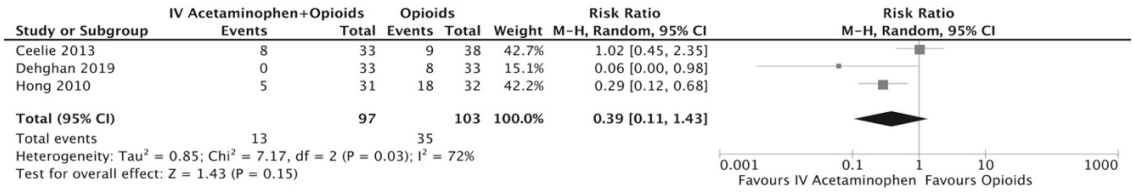


Figure 4. Random-effects meta-analysis comparing IV acetaminophen and opioids to opioids alone for minor adverse events (nausea, vomiting, urinary retention, apnea)

Secondary outcome: other adverse events (IV acetaminophen compared to non-opioids)

When Solanki et al. compared IV acetaminophen to a bupivacaine epidural, there were significantly higher sedation scores at multiple time points in the IV acetaminophen group compared to the epidural group [91]. Solanki et al. also found more bradycardia in the epidural group (5/30 vs. 0/30, $p<0.05$). They reported that all bradycardia was asymptomatic and successfully managed with anticholinergics [91]. Murat et al. found IV paracetamol to have less injection site pain (14/95 vs. 29/88, $p=0.005$) than propacetamol, but otherwise did not find a difference with any other adverse events [93].

Secondary outcome: other adverse events (IV acetaminophen compared to opioids)

Ceelie et al. found no difference in adverse events (9/33 vs. 11/38, $p=0.875$). Specifically, they did not find a difference in reintubation rates (1/33 vs. 2/38, $p=0.444$) or bradycardia (6/33 vs 7/38, $p=0.979$) [82]. Dehghan et al. found no difference in duration of intubation between the acetaminophen and fentanyl groups (6.76 ± 10.34 vs 7.82 ± 14.48 hours, p 0.733) [89]. Hong et al. found significantly less sedation in the IV acetaminophen arm

compared to the fentanyl arm (3/31 vs. 15/32, p=0.019). They found no difference in pruritus (2/31 vs. 3/32, p=0.515) or poor oral feeding (0/31 vs. 4/32, p=0.060) [92].

Unreported outcomes

Additional outcomes selected a priori for analysis, including LOS, ileus, and time to enteral feeds, were not reported in any of the included studies.

2.5 Summary of Findings

The GRADE SOF table summarizing the results of the meta-analysis can be found in Table 3. Footnotes are included to indicate the rationale for down or upgrading the certainty of evidence.

Table 3. Summary of findings for IV acetaminophen and opioids compared to opioids alone for postoperative pain management

Patient or population: Pediatric patients after open abdominal or thoracic surgery
Setting: Inpatients
Intervention: IV acetaminophen and opioids
Comparison: Opioids alone

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Opioids Alone	Risk difference with IV Acetaminophen and Opioids
Standard Mean Difference in Postoperative Pain Score at 48 Hours Presented on NRS-11 Scale of 0-10	200 (3 RCTs)	⊕◯◯◯ Very low[a,b,c]	-		MD **0.23 lower** (0.88 lower to 0.40 higher)
Opioid Consumption (MED/kg/48 hours)	200 (3 RCTs)	⊕⊕◯◯ Low[d,e]	-	The mean opioid was **3.75** MED/kg/48 hours	MD **1.95 MED/kg lower** (3.95 lower to 0.05 higher)
Minor Adverse Events follow-up: 48 to 72 hours	200 (3 RCTs)	⊕⊕◯◯ Low[f,g,h]	**RR 0.39** (0.11 to 1.43)	340 per 1,000	**207 fewer per 1,000** (302 fewer to 146 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
NRS-11: Numeric rating scale 11 **MED:** Morphine equivalent doses **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Concerns with allocation concealment and appropriateness of the scale used to measure pain (NIPS) lead to an overall high risk of bias for Dehghan et al.
b. Variability in point estimates, with minimal overlap of confidence intervals. I^2 statistic of 74%, with p-value of 0.02. Heterogeneity in populations (ages and procedures) and co-interventions may account for some of this heterogeneity.
c. SMD of 0.2 was selected for the minimal clinically important difference (MCID) based on Cohen's delta. Using this MCID, optimal information size criteria is not met, and effect estimate with confidence interval demonstrates appreciable benefit or harm.
d. Wide variance between point estimates, with minimal overlap of confidence intervals. I^2 statistic of 99%, with a p-value of <0.001. Heterogeneity in populations (ages, procedures) and based on local prescribing practices may account for this heterogeneity.
e. Using the threshold of a 30% reduction in MED/kg/48h used by Ceelie et al. and Hong et al in their sample size calculation, the difference identified in this meta-analysis is a clinically significant reduction, however; the optimal information size criterion is not met.
f. Concerns for bias in lack of consistent definition of outcome measures and reporting and lack of clear allocation concealment in Dehghan et al.
g. There is some variation in point estimates (notably Dehghan et al), however confidence intervals overlap. I^2 of 72% (p 0.03) indicates substantial heterogeneity.
h. Optimal information size criteria is not met. Using a threshold of a 13% reduction (based on other trials adverse events), the difference identified is clinically significant, with the confidence intervals encompassing potential benefit and no difference and excluding potential harm.

2.6 Discussion

Due to the limited number of studies and significant heterogeneity in outcomes, it is impossible to draw firm conclusions about the role of IV acetaminophen in postoperative pain control in pediatric patients. When studies compared IV acetaminophen to opioids, the analyses suggested there may be little to no difference in pain scores but a decrease in opioid consumption and minor adverse events. In isolation, that lack of change in postoperative pain scores with the addition of IV acetaminophen may appear to provide evidence against its use. However, when viewed in concert with its ability to reduce opioid use and adverse events without sacrificing pain management, it can be viewed as

an important adjunct to postoperative pain management. When IV paracetamol was compared to propacetamol, it demonstrated no difference in pain scores, but paracetamol was associated with less injection site pain. When IV acetaminophen was compared to bupivacaine epidural, the data demonstrated decreased pain scores with epidural use with no change in adverse events aside from bradycardia.

Each trial included or allowed additional rescue medication for pain, making it difficult to assess if IV acetaminophen is suitable as a single agent. Notably, Ceelie et al. reported that 66.77% of patients assigned IV acetaminophen alone required rescue opioids, indicating it is likely inadequate as a single agent for major surgery [82]. However, the rates of rescue morphine for the morphine group were not significantly different at 60.5% (p 0.59), which provides a more nuanced analysis that no single agent is suitable for postoperative pain control after major surgery in infants. This observation supports the notion of multi-modal pain control in these populations.

Adverse events, including urinary retention, duration of intubation, reintubation, apnea, and bradycardia, were reported infrequently and could not be individually pooled. In addition, other relevant outcomes such as LOS, time to first enteral feed, and time to first bowel movement were not reported in any of the included studies.

Limitations of the evidence and of the review

There are multiple limitations associated with this meta-analysis that must be considered. The methodologic decision to include only RCTs resulted in a smaller sample size. It is unclear how this may have affected the results; however, the risk of bias associated with including low-level evidence was felt to be significant enough to warrant excluding them so as not to bias results. Similarly, a decision was made to focus this review on open non-cardiac-thoracic and abdominal procedures due to the different physiology and management compared to other types of pain and surgery. This revealed that most literature on IV acetaminophen was done in non-surgical settings or during minor procedures, demonstrating a need for further research. Another methodologic limitation was the choice to include multiple pain control comparators (opioids, pro-drugs, and epidural medications), which made pooling difficult due to inconsistency.

Not only were there a limited number of trials included, but each trial included a limited number of participants, with the largest sample being 180 [90]. Small sample sizes lead to more uncertainty surrounding point estimates and greater uncertainty in the results of this meta-analysis [94]. The I^2 statistics for the meta-analysis of pain and opioid use were quite high, particularly for opioid use (99%); these results must be interpreted cautiously. Large, adequately powered studies are required. There was significant heterogeneity in the age of participants, pain scales used, pain modalities assessed, and secondary outcomes. This heterogeneity limited conducting meta-analyses that included all trials or other important secondary outcomes. There were also concerns about the high ROB of the included studies, limiting the analysis due to bias. Finally, only one trial assessed children

over 24 months in age, meaning that the results of this review may not apply to older children. Due to the limited sample size and variability in the available data, it was impossible to perform the pre-planned subgroup analyses to evaluate the impact of IV acetaminophen based on age and type of surgery.

Pain reporting is subjective by nature, which represents another limitation. This subjectivity is compounded in children, where many patients are not developmentally capable of reporting their pain, and a guardian or clinician reports their experience of pain. The bias associated with pain scores in pediatrics cannot be wholly avoided. However, it can be mitigated by using validated scales appropriate for the age and setting, including objective components (such as vital signs), blinded outcome assessors, and multiple scales and assessors to ensure inter-test reliability and inter-rater reliability [95-97].

Future directions

This field requires more large-scale RCTs to increase the sample size and thus precision. A uniform lack of patient-centric designs limits the existing data. Many patient-important outcomes related to the use of opioids in patients undergoing abdominal and thoracic surgery and opioids were sparsely reported. These included gastrointestinal function, urinary retention, and oxygen/ventilatory support requirements. These variables are important contributors to LOS, are patient-important, and require further attention. Furthermore, the longest follow-up period was 72 hours; however, after major surgery,

pain persists beyond 48-72 hours and does not capture the entire recovery period. Including longer follow-up would help clarify when IV acetaminophen could be most effectively used during the recovery period. This topic requires specific analysis in pediatric patients of various ages to understand best how it may uniquely benefit different age groups. Specifically, there were no studies which evaluated infants less than 36 weeks post conceptual age or less than 1500 grams. The unique physiology of preterm neonates highlighted in chapter one of this thesis demonstrates the need for dedicated research on this population. Finally, more work is required comparing IV acetaminophen to non-opioid medications.

Conclusions

There is mounting evidence of the short- and long-term consequences of opioid exposure in pediatrics. Therefore, research evaluating how to reduce this exposure is paramount [98, 99]. The available evidence suggests that in children less than 24-months, when IV acetaminophen is added to opioid-based postoperative pain regimes, there may be no difference in postoperative pain scores, but a possible decrease in opioid consumption and minor adverse events. However, the quality of evidence for these outcomes is very low to low. There is insufficient evidence to conclude how IV acetaminophen compares to other modalities or its effects in children older than 24 months or less than 36 weeks corrected gestational age. More high-quality, patient-centric research is required to confirm these results.

2.7 Author's Contributions

All authors contributed to the study conception and design. V.A completed the literature search. V.A., Z.C., and L.P performed data collection and analysis. Conceptualization, methodology, and supervision were performed by J.M.W. and D.B. The original draft of the manuscript was written by V.A. All authors participated in review and editing.

CHAPTER THREE: POSTOPERATIVE PAIN PRESCRIBING PRACTICES AND PERSPECTIVES ON INTRAVENOUS ACETAMINOPHEN IN CANADIAN NICUS: A NATIONAL SURVEY

Authors: Archer, Victoria A[1]., Samiee-Zafarghandy, S[2]., Braga, L[4], Walton, J.M.[5]

Affiliations:

1. Division of General Surgery, Department of Surgery, McMaster University, Hamilton, ON, Canada
2. Division of Neonatology, Department of Pediatrics, McMaster University, Hamilton, ON, Canada
3. Division of Urology, McMaster University, Hamilton, ON
5. Division of Pediatric General Surgery, Department of Surgery, McMaster University, Hamilton, ON, Canada

3.1 Abstract

Introduction: Pain management in neonates admitted to the neonatal intensive care unit (NICU) remains an area of active research with variable practice patterns. No study has described practice patterns nationally or has included surgeons or anesthesiologists. This research aimed to ascertain postoperative pain practice patterns of physicians involved in perioperative care in Canadian NICUs.

Methods: Canadian pediatric surgeons, anesthesiologists, and neonatologists who care for neonates admitted to the NICU during and after surgery were invited to participate in this mixed-methods online survey.

Results: 109 participants from 16 centers responded (34 neonatologists, 41 anesthesiologists, and 34 surgeons). Neonatologists most often manage postoperative pain (96.87%, n=31). 20.51% (n=8) of surgeons and 22.58% (n=7) of anesthesiologists report routinely managing postoperative pain. Opioids were the most common first line agent (60.87%, n=28) for postoperative pain, followed by acetaminophen (32.61%, n=15). Overall, 86.96% (n=40) reported always or usually prescribing opioids in some capacity postoperatively. Most respondents (82.61%, n=38) felt pain was always or usually well-controlled postoperatively. Qualitative results demonstrated support for multidisciplinary practice styles and multimodal pain control.

Conclusions: Opioids remain the most common agent for postoperative pain in the NICU; however, over a third of respondents use a non-opioid as a first line agent for postoperative pain. Neonatologists are the primary managers of postoperative pain; however, over 20% of surgeons and anesthesiologists report being involved. Qualitative data demonstrate room for increased multidisciplinary care and multimodal pain management. Future multi-center chart reviews, policy reviews, and in-depth qualitative interviews will provide depth to these findings.

3.2 Introduction

The data presented in chapter one identified evidence suggesting that IV acetaminophen may be efficacious, although there was a paucity of evidence, and it was of low quality. Most of the studies that were included focused on patients under two years of age. No studies included patients less than 35 weeks gestational age. This gap in the literature prompted us to investigate the reported patterns of use of IV acetaminophen in preterm neonates. As we explored the literature, we also became interested more broadly in postoperative pain management practices in the NICU both on institutional and individual levels.

Fernandez et al. first attempted to characterize pain management in Canadian NICUs in 1994. The authors surveyed head nurses of 30 Canadian NICUs to determine their perception of the frequency of use of various pain management modalities. Their results demonstrated that charge nurses reported opioids to be used postoperatively always or

often by 88% of Canadian NICUs after major non-cardiac surgery. They found that local anesthesia was routinely used for emergency chest tube placement in only 16% of NICUs and 48% for elective ones. From this work, they concluded that postoperative pain management was still frequently undertreated [43].

In 1997, Johnston et al. performed a weeklong chart review across 14 Canadian NICUs to characterize their general pain management patterns. The charts of 239 patients were reviewed, revealing that 6.8% of patients undergoing a "tissue damaging procedure" received analgesia. For more invasive procedures, 60% of chest tube insertions were found to involve analgesia. They did not specifically assess postoperative pain. They found that only six centers had developed pain protocols but did not find a difference in the frequency of analgesia delivery between sites with and without pain protocols [24].

Johnston et al. replicated this study in 2011. The same 14 institutions were included, and data were collected prospectively for one week. Again, they did not specifically evaluate postoperative pain but found a significant increase in analgesia rates for "tissue-damaging procedures," which had increased from 6.8% to 54%. They found that 43% of patients receiving chest tubes received analgesia, a slight decrease from 1997. They found an increase in the number of NICUs with pain protocols, with ten centers reporting their use, but again found no difference in the frequency of administration of analgesia. Although there was an increase in protocols and local guidelines, inconsistencies were identified between sites, with 25-90% of patients who underwent tissue-damaging procedures

receiving analgesia. Overall, there appeared to be an improvement in the use of analgesia, but this was limited to less invasive procedures, as demonstrated by the decrease in analgesia provided for chest tube insertions. Ultimately, these sparse data demonstrate that there is still a significant gap in the understanding of pain management in neonates [100].

Similar work was performed in Italy in 2005 [101]. The authors distributed a survey to the head physicians of all 102 Italian NICUs and received 90 responses. They found that 67% of chest tube insertions were reported to be performed with analgesia. They reported that for postoperative pain, 88% of NICUs report using opioids alone, with only a small (unreported) number using paracetamol. The authors concluded that there are still gaps in care and that neonatal pain is likely underestimated and inadequately managed. In a study from France in 2002, Debillon et al. distributed a similar survey to the head physicians of their 143 level II or III NICUs [42]. One hundred sixteen sites responded. 65% of sites had pain protocols, and 70% used pain scores to assess neonatal pain. They did not assess pain management for invasive or surgical procedures.

In a survey of neonatal nurses in the United States in 2009, the authors found that only 45% of nurses felt pain was well-controlled in their unit. The nurses reported inconsistencies in individual physician prescribing practices as a barrier to pain management. They also identified a lack of evidence-based pain management protocols, staff members' resistance to change in practice, pain assessment tools and inadequate

training as other critical barriers to effective pain management [44]. No further work has been repeated in Canada to establish practice patterns, nor has there been work to interrogate the management of postoperative pain specifically. No studies have attempted to ascertain the perspectives of clinicians to determine their reasoning for their use of analgesia.

These studies demonstrate the significant change that can occur over time, demonstrating a need to re-evaluate pain management practices. The studies broadly group all painful procedures, providing a good overview of general pain practices, but less nuanced information on the management of especially painful procedures. Surgeries often result in severe pain acutely and require more comprehensive management than needed for heel lances, arterial sampling, or lumbar punctures [75]. Further attention is needed for the management of postoperative pain. Since these studies were conducted, research has demonstrated the importance of multidisciplinary approaches to pain management [102, 103]. Surgeons, anesthesiologists, and neonatologists all have crucial roles in managing postoperative pain in neonates, but the unique roles they play, practices, and perspectives are largely unstudied. While chart reviews provide valuable insights into which drugs were prescribed in which context, the rationale for these practices, perceived barriers to multimodal pain management, and variations based on role in the health care team cannot be demonstrated through these methodologies.

Opioids are the most common agents used for pain management in the NICU [24, 25]. While opioids effectively manage pain, they are associated with long-term developmental delays, as well as acute adverse events, such as apnea, increased duration of mechanical ventilation, increased length of stay, hypotension, ileus, and necrotizing enterocolitis [23, 104]. Multimodal pain control offers the opportunity to manage pain while reducing short- and long-term opioid-related adverse events. Intravenous (IV) acetaminophen may be a good addition to neonatal postoperative pain management. IV administration of acetaminophen, with its direct entry into the circulatory system, results in a more predictable response in neonates compared to oral and rectal formulations [50, 51, 53]. Primarily due to cost, IV acetaminophen is not available in all NICUs. However, there is some evidence supporting its use in the postoperative setting. Understanding current prescribing practices, physicians' views on its efficacy, safety, and barriers to implementation are crucial to determining if there is a role for IV acetaminophen in routine care.

Aims

Our study has three main objectives. The first is to understand the landscape of postoperative pain practices in Canadian NICUs. We will determine which physicians manage pain after surgery at each institution, if there are order sets or guidelines available, and if specific pain or multidisciplinary teams are available to manage pain. Our second objective is to determine the practice patterns of postoperative pain management on an individual level. We will determine which pharmacologic and non-

pharmacologic therapies physicians use most frequently and their perspectives on the efficacy of postoperative pain management. Our third objective is to determine the availability of IV acetaminophen in Canadian NICUs, determine physicians' clinical experiences with IV acetaminophen, and assess perspectives on barriers to implementation.

3.3 Methods

This mixed-methods, cross-sectional survey has been reported in accordance with the Consensus-Based Checklist for Reporting of Survey Studies (CROSS) guidelines [105].

Study Design

This is a mixed-methods, cross-sectional web-based survey. It was hosted on SurveyMonkey and comprised of 5 sections with a total of 35 questions [106]. Using page logic, participants were only required to answer questions that specifically applied to them. Table 4 below displays the sections of the survey. The complete questionnaire can be found in Appendix 3.

Question types include Likert scales, single-answer multiple choice question, “select all that apply” multiple choice questions, and open-ended (i.e., free text) questions. Likert scales were created on a 5-point scale using the following anchors: always, usually, sometimes, rarely, and never. A 5-point scale was selected instead of a 4-point to allow respondents to express a neutral opinion, reducing positive or negative biases [107]. The

analysis of open-ended questions is described below. These question types were selected as much of this data is novel; therefore, providing preselected responses may not have captured the full extent of perspectives [108].

This survey did not make use of pre-existing questionnaire instruments. Instead, the survey was internally piloted by eight pediatric surgeons, pediatric anesthesiologists, and neonatologists who met our inclusion criteria.

The survey was initially distributed on November 29, 2022, and was closed on February 21, 2023. We initially planned to leave it open for six weeks (until January 10, 2023); however, we elected to extend the recruitment period to account for low response volumes over the holiday period. This also allowed time for national groups to review and distribute the survey. After initial distribution, two reminder e-mails were sent. SurveyMonkey limited responses to one per internet protocol (IP) address to ensure individuals did not participate multiple times. IP addresses were not recorded.

Table 4. Survey Sections

Section 1: Practice demographics (4 questions)
Section 2: NICU demographics (9 questions)
Section 3: Postoperative pain prescribing practices (9 questions)
Section 4: Perspectives on Intravenous Acetaminophen (9 questions)
Section 5: Demographics (4 questions)

Population

The eligible population included pediatric surgeons (of all subspecialty disciplines), pediatric anesthesiologists, and neonatologists who currently practice in Canada and routinely care for patients in the NICU after surgery. Physicians who are not fellowship-trained in their current practice area were eligible as long as the other criteria were met. We excluded non-physicians, trainees, and physicians not practicing in Canada.

Estimating the actual population size was challenging. There are no maintained lists of physicians who meet our inclusion criteria. Only some pediatric surgical subspecialists routinely interact with NICU patients, only some neonatologists work in a facility with surgical capabilities, and only some pediatric anesthesiologists work in centers with NICUs. Using a combination of faculty directories, national specialty group membership, and workforce publications, we estimated the population size to be 500. The predicted distribution of subspecialists is 42% neonatologists, 24% surgeons, and 34% anesthesiologists [109-111].

Sample Size

Given the relatively small population and the ability to reach them through national organizations and hospital departments, we used the entire population as our sampling frame. We used voluntary responses and snowballing methods to access the population [112]. Individuals were contacted via e-mail distributed by their department heads, e-mail from national specialty groups, and e-mails sent to individual addresses. Participants were

sent the initial survey invitation with two subsequent follow-up reminder messages. Participants were encouraged to distribute the survey link to colleagues who they felt met the inclusion criteria.

Our minimal acceptable sample size to provide an accurate representation of this population was calculated using Cochran's formula with an alpha of 0.05, a margin of error of 5.0% and a population proportion of 50% (which is suggested when the true population proportion is unknown) is 218 respondents [113].

Ethical Considerations

This survey was designed in keeping with Helsinki and Good Clinical Practice declarations and was approved by the Hamilton Integrated Research Ethics Board (HIREB) [114, 115]. Participants' names, phone numbers, e-mail addresses, and other personal identifying information were not collected. As described above, IP addresses were used by SurveyMonkey to reduce the risk of multiple responses, but IP addresses were not recorded. There are relatively few pediatric subspecialists in Canada, making identification a concern. To mitigate this specific concern, only aggregate data was presented, and no direct quotes were used.

Quantitative Analysis

Demographic data were reported as means or medians for continuous variables and proportions for categorical variables. To assess if variables were related to one another,

the chi-square test of independence was used. The chi-square goodness of fit test was used to assess if the distribution of responses of categorical variables were significantly different. When appropriate, Fisher's exact test was used [116]. Data were analyzed using Statistics Package for Social Sciences (SPSS) [117]. Subgroup analysis was conducted based on specialty using this same analysis plan. All analyses used an alpha of 0.05 and a beta of 0.80. Differences were considered significant if $p<0.05$. Post hoc testing was done for chi-square tests of independence with more than two comparators to determine which comparators were statistically significant. Beasley and Shumacker's standardized residual method were used for post hoc testing. Standardized residuals and p-values were calculated for each cell to determine which cell significantly contributes to the significant omnibus chi-square statistic[118]. All p-values for post hoc testing were adjusted using the Bonferroni correction to account for multiplicity [118, 119].

For ease of interpretation, Likert scales were recoded from five-point to three-point scales (never and rarely, sometimes, and often and always). No weighting methods or propensity scores were used to adjust the data. Sensitivity analyses were not conducted.

Qualitative Analysis

Charmaz's grounded theory was used to analyze qualitative data generated in the survey's open-ended questions [120]. Grounded theory diverges from traditional hypothesis-first methodologies, which are standard in quantitative research. This methodology involves systematic and iterative analysis of qualitative data allowing for themes to emerge

independently from the data, reducing the reliance on pre-existing frameworks of knowledge which could bias the analysis. Qualitative data will be coded line by line for key and recurring concepts. These concepts will be broadly grouped into categories which will be used to generate theories. The small population size paired increased the risk for identification with the use of direct quotes. To reduce the risk of identification direct quotes were not used in the manuscript.

Missing Data and Non-Response Error

Within the survey, various questions do not apply to all participants; as such, we anticipated different denominators for many of the variables. A response was coded as missing data if a participant if was eligible to answer a question but did not provide an answer. This survey design is challenging for multiple imputation methods, as some of the missing data would be appropriate, as the participant may not have been eligible to answer a particular question. In this context, imputation methods may introduce more bias than deletion methods. Case-wise deletion was employed for non-respondents (when more than 50% of eligible questions were not answered or if specialty information was not provided) or respondents that provided inappropriate answers (when inappropriate answers were provided for more than 50% of eligible responses). Pairwise deletion was used for all other missing data [121].

In our design, we utilized techniques such as prolonged recruitment periods, follow-up e-mails, multiple points of contact, and creating a short survey to reduce the risk of non-

response error [122]. However, given that the total population size was not well established, it was difficult to accurately estimate the degree of non-response error. We, therefore, elected not to perform weighting or imputation techniques and have presented the raw data [123].

3.4 Quantitative Results

The survey was accessed by 119 participants. Four responses were removed for failing to meet the inclusion criteria (not practicing in Canada) and six were removed for non-responses. This left a working sample size of 109 participants. This represented 34 pediatric surgeons (31%), 41 pediatric anesthesiologists (38%) and 34 neonatologists (31%).

The mean age was 47.9 (± 11.4) years old. The average years in practice was 14.7 (± 9.6) years. Individuals from 16 of the 22 centers that offer pediatric surgical services in Canada were represented. Table 5 displays the demographic results of our sample.

Table 5. Survey demographic results

	Neonatologists	Pediatric Anesthesiologists	Pediatric Surgeons	Total
Sample Size	34	41	34	109
Mean age, n (SD)	46.0 (15.7)	46.21 (8.2)	50.73 (9.3)	47.62 (11.4)
Mean years in practice, n (SD)	13.22 (8.5)	13.74 (8.1)	16.68 (11.9)	14.53 (9.7)
Female, n (%)	15 (44.2)	12 (29.3)	15 (41.7)	42 (38.5)

SD: Standard Deviation

Primary managers of pain

Individuals at 15 out of 16 institutions reported that neonatologists are primarily responsible for postoperative pain management at their center. At one site, responses were split between anesthesia and neonatology.

96.9% of neonatologists, 20.5% of pediatric anesthesiologists, and 22.6% of pediatric surgeons reported that managing postoperative in the NICU is part of their usual practice. The relationship between specialty and managing postoperative pain was statistically significant, (X^2 (4) =47.72, p<0.001), with neonatologists being more likely to report managing postoperative pain than surgeons or anesthesiologists (p<0.001). These results are displayed in Table 6.

Table 6. Number of respondents who report to routinely managing postoperative pain in the NICU as part of their practice

	Neonatologists n=32	Pediatric Anesthesiologists n=39	Pediatric Surgeons n=31
n (%)	31 (96.9) *	8 (20.5)	7 (22.6)

X^2 (4) =47.72, p<0.001
* p<0.001

Frequency of Opioids, Non-Opioids, and Non-Pharmacologic Adjuncts

Participants were asked how often they prescribe opioids for postoperative pain management in the NICU. Most respondents (87.0%) reported always or usually prescribing opioids. 8.7% of respondents rarely or never prescribe them, and 4.3%

sometimes do. This distribution was statistically significant (X^2 (2) =59.65, p<0.001) and is displayed in Table 7.

Table 7. Overall frequency of prescription of opioids for postoperative pain in the NICU

	Frequency n=46 n, (%)
Always or usually	40 (87.0)
Sometimes	2 (4.3)
Rarely or never	4 (8.7)
X^2 (2) =59.65, p<0.001	

The relationship between speciality and frequency of prescription of opioids for postoperative pain was statistically significant (X^2 (4) =9.95, p=0.014). When post hoc testing was done, neonatologists were found to report rarely or never prescribing opioids for postoperative pain, statistically significantly less than expected (p=0.03). This is displayed in Table 8.

Table 8. Frequency of prescription of opioids for postoperative pain in the NICU by specialty

	Neonatologists n=30 n, (%)	Pediatric Anesthesiologists n=9 n, (%)	Pediatric Surgeons n=7 n, (%)
Always or usually	29 (96.7)	6 (66.7)	5 (71.4)
Sometimes	1 (3.3)	1 (11.1)	-
Rarely or never	- *	2 (22.2)	2 (28.6)
X^2 (4) =9.95, p=0.014			
* p=0.03			

71.7% of respondents stated they always or usually prescribe non-opioid medications for postoperative pain in the NICU, 19.6% sometimes do, and 8.7% rarely or never do. This distribution is statistically significant (X^2 (2) =31.35, p<0.001). These data are displayed in Table 9.

Table 9. Frequency of prescription of non-opioids for postoperative pain in the NICU

	Frequency n=46 n, (%)
Always or usually	33 (71.7)
Sometimes	9 (19.6)
Rarely or never	4 (8.7)
X^2 (2) =31.35, p<0.001	

The relationship between the frequency of prescription of non-opioids for postoperative pain and specialty was statistically significant (X^2 (4) =10.24, p=0.048). The significance of the omnibus chi-square test is due to pediatric anesthesiologists reporting to sometimes prescribe non-opioids for postoperative pain more than expected (p=0.024). These data are displayed in Table 10.

Table 10. Frequency of prescription of non-opioids for postoperative pain in the NICU by specialty

	Neonatologists n=30 n, (%)	Pediatric Anesthesiologists n=9 n, (%)	Pediatric Surgeons n=7 n, (%)
Always or usually	23 (76.7)	4 (44.4)	6 (85.7)
Sometimes	4 (13.3)	5 (55.5) *	-
Rarely or never	3 (10.0)	-	1 (14.3)

X^2 (4) =10.24, p=0.048
* p=0.024

When asked how frequently they order non-pharmacologic adjuncts for postoperative pain, half of the respondents (50.0%) reported always or usually ordering them. 21.7% reported sometimes, and 28.3% rarely or never ordering them. These findings were statistically significant (X^2 (2) =6.043, p=0.048). When compared by specialty, there was no statistically significant difference (X^2 (4) =5.39, p=0.243). These results are displayed in Table 11.

Table 11. Frequency of prescription of non-pharmacologic therapy for postoperative pain in the NICU

	Frequency n=46 n, (%)
Always or usually	23 (50.0)
Sometimes	10 (21.7)
Rarely or never	13 (28.3)
X^2 (2) =6.043, p=0.048	

First- and second line agents

To reduce the survey length and complexity (in order to retain participants), we focused on classes of drugs and excluded routes. The following results therefore do not include routes of administration. In physicians who reported routinely managing postoperative pain (n=46), opioids were the most common first-line agent (60.9%), followed by acetaminophen (32.6%) Three respondents reported that their choice of first-line agent was variable depending on the clinical situation. There did not appear to be any differences in response between specialities (X^2 (4) =8.20 p=0.07).

The choice of second-line agent was also statistically significant (X^2 (5) =20.83 p<0.001). The most common second-line agent was acetaminophen, followed by opioids. When compared by specialty, there was no statistically significant difference in the choice of second-line agent (X^2 (10) =15.80 p<0.108). Table 12 displays the overall frequency of first- and second-line agents. We calculated the frequency of various first- and second-line combinations; we found that the most common combination was an opioid and acetaminophen (39.1%), followed by acetaminophen and opioids (19.6%).

Table 12. Overall frequency of first- and second-line agents

	First line n=46 n, (%)	Second line n=46 n, (%)
Opioids	28 (60.9)	10 (21.7)
Acetaminophen	15 (32.6)	19 (41.3)
NSAIDs	-	6 (13.0)
Regional anesthesia	-	2 (4.3)
Primarily use a single agent	-	1 (2.2)
Other	3 (6.5)	8 (17.4)
First line: (X^2 (2) =20.39 p<0.001). Second line: X^2 (5) =20.83, p<0.001		

When asked about the most common opioid they prescribe for postoperative pain, over half of participants (54.3%) reported fentanyl. Morphine was the next most common (32.6%). 10.9% of respondents use morphine or fentanyl, one reported hydromorphone, and one reported morphine or ketamine. These results were statistically significant (X^2 (4) =46.17 p<0.001). The choice of opioid did not differ based on specialty (X^2 (8) =13.77 p=0.141). Table 13 displays these results.

Table 13. Overall frequency of use of specific opioid agents

	Frequency n=46 n, (%)
Fentanyl	25 (54.3)
Morphine	14 (32.6)
Morphine or fentanyl	5 (10.9)
Hydromorphone	1 (2.2)
Morphine or ketamine	1 (2.2)
X^2 (4) =46.17, p<0.001	

Participants were also asked about the most common non-opioid they prescribe. Acetaminophen was the most common, with 82.6% of participants reporting it as their most common non-opioid. Ketamine, dexmedetomidine, acetaminophen or dexmedetomidine, midazolam, ibuprofen, and oral sucrose were selected by one or two respondents as their most used non-opioid. This distribution was statistically significant (X^2 (6) =175.56 p<0.001). The choice of non-opioid did not differ based on specialty (X^2 (12) =12.96 p=0.565). These results are displayed in Table 14.

Table 14. Overall frequency of use of specific non-opioid agents

	Frequency n=46 n, (%)
Acetaminophen	38 (82.6)
Ketamine	2 (4.3)
Dexmedetomidine	2 (4.3)
Acetaminophen or dexmedetomidine	1 (2.2)
Midazolam	1 (2.2)
Ibuprofen	1 (2.2)
Oral sucrose	1 (2.2)
X^2 (6) =175.56, p<0.001	

Institutional practices

A consensus was not reached on the availability of postoperative pain order sets at each site. Only one site had most individuals report that postoperative pain order sets were available. Five of the sixteen represented sites had no individual report that order sets were available. The remaining sites each had participants reporting that order sets were or were not available or that they were unsure.

At eleven of the sixteen sites, most participants did report that pharmacists are involved in postoperative pain management. At the remaining sites, most participants were unsure of their involvement.

Frequency of Use and Perceptions of IV Acetaminophen

At six of the sixteen sites, most individuals reported that IV acetaminophen was available for postoperative pain management. At six sites, most individuals reported that it was unavailable; at the remaining four sites, most were unsure if it was available.

Over half of the individuals (53.9%) have not used IV acetaminophen for postoperative pain. 44.12% have reported using it, and 2.0% were unsure. This distribution was statistically significant (X^2 (2) =46.65 p<0.001). These results are shown in Table 15. No statistically significant relationship existed between specialty and reported use of IV acetaminophen (X^2 (4) =5.07 p=0.450).

Table 15. Overall frequency of use of IV acetaminophen for postoperative pain in the NICU

	Frequency n=102 n, (%)
Yes	45 (44.1)
No	55 (53.9)
Unsure	2 (2.0)
X^2 (2) =46.65, p<0.001	

Participants were asked separately if they had noted clinical harm or clinical benefit with IV acetaminophen for postoperative pain. Of the 44 participants who reported using IV acetaminophen in this context, 35 reported observing clinical benefit, and nine were unsure if they had witnessed benefit (X^2 (1) =11.25, p<0.001). None reported observing clinical harm and three were unsure of harm (X^2 (1) =33.80, p<0.001). These data are shown below in Tables 16 and 17.

Table 16. Reported observation of clinical benefits with IV acetaminophen for postoperative pain in the NICU

	Frequency n=48 n, (%)
Observed benefits	35 (74.5)
Not observed benefits	1 (2.1)
Unsure if observed benefits	12 (25.0)
X^2 (1) =37.62, p<0.001	

Table 17. Reported observation of clinical harms with IV acetaminophen for postoperative pain in the NICU

	Frequency n=46 n, (%)
Observed harm	-
Not observed harm	43 (93.5)
Unsure if observed harm	3 (6.5)
X^2 (1) =34.78, p<0.001	

Pain control

Individuals were asked to rate how frequently they felt pain was adequately controlled after surgery. Most participants (82.6%) reported that pain was always or usually well-controlled. 13.0% felt it was sometimes well controlled, and 4.3% felt it was never or rarely well controlled. The distribution of responses was statistically significant (X^2 (2) =50.74, p<0.001). These data are displayed in Table 12. There was no relationship between perception of pain control and specialty (X^2 (4) =2.87, p=0.772). These data are displayed in Table 18.

Table 18. Reported frequency of adequate postoperative pain control in NICU patients

	Frequency n=46 n, (%)
Always or usually	38 (82.6)
Sometimes	6 (13.0)
Rarely or never	2 (4.3)
X^2 (2) =50.74, p<0.001	

3.5 Qualitative Results

Participants were given the opportunity to describe practices at their institution, comment on their approach to postoperative pain management in neonates, and to discuss the harms, benefits, and barriers to using IV acetaminophen. Due to the limited size of the population and the potential for identification, direct quotes were not reported.

Institutional characteristics

The most prevalent positive themes that emerged were the availability of specific pain services and collaboration, order sets, multimodal pain control, and opioid use.

Pain services and collaboration

Nine participants from five separate sites spoke about the availability of specific pain services. These pain teams ranged from the anesthesia-based acute pain service managing patients with regional anesthesia and being available for complex cases to multidisciplinary teams involving neonatology, surgery, and anesthesia, and palliative and symptom management teams.

Four participants from four separate institutions spoke specifically about collaboration in their NICU. One individual highlighted close collaboration with pediatric surgery regarding postoperative pain management. The remaining respondents discussed formal multidisciplinary teams. One team was a quality improvement team involving surgery, neonatology, and anesthesia with aims of improving multiple aspects of perioperative care. The other teams were pain focused. The most comprehensive model included a pre-

operative huddle including anesthesia, surgery, and neonatology in which the operative and pain management plan was discussed and a postoperative huddle in which the plan was reviewed and modified as needed. This model was paired with a multi-modal order set.

Three participants from two different centers highlighted lack of collaboration as a negative aspect. The participants all cited a perceived lack of involvement of the anesthesia team in managing pain or providing regional anesthesia.

Order sets

The availability of specific postoperative pain order sets was another common theme. Six participants from four centers described order sets at their site. Four participants spoke explicitly about the nuanced nature of these order sets. The described order sets involved pathways based on predicted levels of pain (mild, moderate, and severe). Two respondents specifically discussed how surgery, neonatology, and anesthesiology collaboratively decided the level of perceived pain based on the pathology, the procedure, and the use of regional anesthesia to determine the appropriate pathway in the order sets.

Multimodal pain management

Seven participants from five centers discussed multimodal pain control and opioid-sparing techniques. Three individuals from three sites referenced the use of regional techniques. The remaining individuals referenced using non-opioid drugs in their postoperative pain order sets.

Opioid use

Three participants from two centers spoke about patterns of opioid use. Two participants compared their experience to other centers where they have worked, both noting an increased dose and duration of opioid use in the NICU. The other participant described a general culture of opioid reliance.

Individual approaches to postoperative pain

Individual responses to postoperative pain management practices were more heterogeneous. However, the most common themes that emerged were individual approaches to pain control and multimodal and opioid-sparing approaches.

The four participants (representing three sites) each emphasized the nuanced nature of managing postoperative pain in this population. While general approaches can be taken, each patient is unique. Participants discussed considering the surgical procedure, the patients clinical state, the use of regional anesthesia, and input from their colleagues.

Individual multimodal and opioid sparing approaches

Nine participants from seven centers discussed multimodal or opioid-sparing approaches in their responses. Three participants from four centers discussed using IV acetaminophen specifically for postoperative pain. Two participants from two centers specifically discuss now using IV acetaminophen as a first-line agent for postoperative pain. One participant stated their desire for more non-opioid options. Five participants from five different centers referenced the regular use of regional anesthetic techniques in their patients.

One participant noted at their site that pain control seems to be improved with multimodal techniques, but they felt that this may be contributing to polypharmacy.

Observed harms and benefits of IV acetaminophen

Participants were given the opportunity to describe the harms and benefits they observed with the use of IV acetaminophen for postoperative pain in NICU patients. No participants identified harm.

Three themes emerged when participants were asked to report the benefits, they observed with IV acetaminophen use. The first being a reduction in opioid requirements. Twenty-two participants reported that they felt it was associated with opioid reduction. Some noted that the general need for opioids was less, that weaning from opioids was faster or easier, and that fewer breakthrough doses were needed.

The next most common theme was decreased postoperative pain, with 12 participants citing a reduction in postoperative pain with IV acetaminophen.

The final theme was logistics. Four participants noted that IV acetaminophen is beneficial as they can provide it to patients who cannot take medication orally.

Barriers to the use of IV acetaminophen

Whether or not participants had experience prescribing IV acetaminophen, they were asked to comment on what they perceived as barriers to its more widespread use. The most common responses were cost, availability, culture, lack of awareness and lack of research.

The most common barrier identified was cost, with 37 respondents identifying this in their responses. The next most common theme was logistic barriers, which was identified by 17 participants.

Eleven participants cited the general lack of availability and five noted administrative barriers as restricting access. Two respondents noted that it was available at their hospital, but only certain groups were allowed to prescribe it.

Ten participants reported a lack of awareness regarding the use of IV acetaminophen. They believed that other clinicians were not aware that IV acetaminophen can be used for analgesia in neonates, or do not know it might be beneficial.

The culture of the institution was identified as a barrier to the use of IV acetaminophen by nine participants. They cited a hesitancy to change practice and a culture of opioid dependence. Two participants felt strict pain control parameters also contributed. Both

cited the culture and pressure of having pain scores of zero as leading to an overreliance on opioids.

The last theme was a lack of research or guidelines, which was reported by seven participants. They highlighted a general lack of research, a lack of strong evidence supporting its efficacy, a lack of evidence that it is superior to rectal or oral acetaminophen, no clear guidelines, and that IV acetaminophen is not approved by Health Canada for analgesia in this age group.

3.6 Discussion

Many of the results described above confirm commonly held beliefs about postoperative pain management in neonates, while some challenge these beliefs. These results provide a more concrete picture of what is happening in NICUs in Canada and act as a baseline for future work.

The results reveal that neonatologists are primarily responsible for managing postoperative pain. What may be more surprising is the degree to which many surgeons and anesthesiologists are involved in postoperative pain management. Neonatologists, as the primary physicians caring for these patients, are certainly well-suited for this role; however, the unique perspectives, training, and skills of surgeons and anesthesiologists make them important collaborators. There was variation at each center regarding who is involved in postoperative pain management, with some centers utilizing order sets and

multidisciplinary teams. Others reported less collaboration. Each center is unique, and it would be inappropriate to suggest that one model of care could be universally applied. Moving forward, centers should involve key stakeholders in determining which models of care may be the most appropriate at their site.

Another important finding is the high frequency of opioid use, with most participants using it as a first-line agent and the majority of participants reporting that they use it in some capacity for almost all postoperative patients. Although it is technically off-label in patients less than 2 years of age, fentanyl was reported to be the most common opioid used. A result that challenges the perception of opioid reliance in the NICU is that almost one-third of physicians reported using a non-opioid as a first-line agent (specifically acetaminophen) for postoperative pain. Multimodal pain control is occurring in Canadian NICUs, with only one respondent reporting using a single agent for postoperative pain control and many participants reported the use of opioids, non-opioids, and regional techniques to manage pain in neonates. While most physicians surveyed feel that pain is always or usually well controlled in these patients, 17% felt that it was not.

Most centers and the majority of physicians surveyed have not used IV acetaminophen for analgesia in neonates. At the same time, six centers reported having access to this medication for post-operative pain control and more than 44% of physicians reported using it in this context. Many physicians who use it have witnessed benefits and none reported experiencing harm. The benefits were primarily improved pain control and

decreased need for opioids. Participants identified barriers to use, with cost being the largest driver. This concern is supported by available literature suggesting that the price ratio of oral liquid to IV formulations of acetaminophen is as high as 1:84 [124]. A cost-benefit analysis in this context has yet to be performed and will be crucial in determining if the use of this drug is economically feasible. Other deterrents, such as logistics and administrative barriers, were identified, which are likely driven by cost as well. A lack of knowledge about the drug and a lack of research was also reported, which demonstrates the need for further research in this area.

Limitations

The most significant limitation of this survey is the sample size. To achieve a margin of error of 5%, 218 responses were required. We achieved 109 complete responses, which means this survey is powered to a margin of error of 8%. Therefore, this survey may be underpowered to detect differences and may suffer from non-response bias. We employed strategies to increase the response rate, including designing a short survey, adjusting the administration period to account for holidays, and using multiple points of contact and multiple follow-up reminders via e-mail [123]. However, we still were not able to achieve the target sample size. Low response rates in surveys of healthcare workers are well documented, with response rates for physicians ranging from 20% to more than 50% [125-127]. Using financial incentives has been shown to increase response rates in this population [126, 128]. Incentives were not utilized in this survey but should be considered in future iterations to increase the sample size.

Another limitation is the lack of objective data and recall bias inherent to surveys. The practice patterns and institutional practices reported here are all self-reported and have not been validated through chart or policy reviews. This raises the concern that individuals' subjective perceptions may impact these data. While this is a limitation, it must be weighed against the opportunity to gain unique individual perspectives on these topics, which other methodologies do not provide. Completing chart reviews and performing reviews of policies in the future would help validate and enrich the results of this survey.

Our methodologic decision to omit direct quotations was beneficial to participants in that it decreased the risk of identification. Although the quotes were available to the authors for analysis and interpretation, we were unable to fully present the nuanced perspectives of individual participants. The qualitative responses were also limited in that they were text-based responses. This does not allow for further exploration or explanation of themes through interview-style techniques. Using semi-structured qualitative interviews or Delphi method interviews would provide additional context and depth to the qualitative results.

Future directions

As highlighted above, repeating this survey in the future with the use of financial incentives may improve response rates and provide more accurate data. If time has elapsed to allow institutions to enact changes in their postoperative pain management strategies, this will also allow progress to be measured.

There are multiple related studies which will function to strengthen the results. In addition, performing chart reviews, policy reviews, and completed in-depth qualitative interviews will provide novel insights and depth to the results presented here.

There are other non-physician stakeholders whose perspectives should be considered. The inclusion of opinions of nurses and pharmacists would add additional depth to these findings. Due to the nature of care provided by NICU nurses, they may have nuanced insights into the effectiveness and limitations of IV acetaminophen. Pharmacists may also be able to provide insight into the pharmacokinetics of this medication in the neonatal population.

Many participants of this survey highlighted the need for more research to determine if IV acetaminophen is effective for postoperative pain control in neonates, especially given the high cost. Therefore, prospective, randomized data is required. This will be explored in chapter four.

3.7 Author's contributions

V.A. designed the survey, obtained ethics approval, distributed the survey, performed data analysis, and wrote the manuscript. J.M.W., L.B., and S.S. revised the survey, assisted in ethics approval, and revised the manuscript.

CHAPTER 4: IVA POP: INTRAVENOUS ACETAMINOPHEN FOR POSTOPERATIVE PAIN IN THE NEONATAL INTENSIVE CARE UNIT: A PROTOCOL FOR A PILOT RANDOMIZED CONTROLLED TRIAL

Authors: Archer, Victoria A[1]., Samiee-Zafarghandy, S[2]., Farrokyhar, F[3]., Briatico, D[4]., Braga, L[5], Walton, J.M.[4]

Affiliations:

1. Division of General Surgery, Department of Surgery, McMaster University, Hamilton, ON, Canada
2. Division of Neonatology, Department of Pediatrics, McMaster University, Hamilton, ON, Canada
3. Department of Surgery, McMaster University, Hamilton, ON
4. Division of Pediatric General Surgery, Department of Surgery, McMaster University, Hamilton, ON, Canada
5. Division of Urology, McMaster University, Hamilton, ON

This protocol has been created in accordance with the requirements for publication by Pilot and Feasibility Studies and was submitted for publication April 24, 2023.

4.1 Abstract

Background: Uncontrolled pain and opioid exposure are correlated with short- and long-term adverse events in neonates. Multimodal pain control offers the opportunity to manage pain while reducing opioid-related adverse events. IV acetaminophen may represent an appropriate adjunct, but no trials have assessed this medication in patients less than 36 weeks post-conceptual age or weighing less than 1500 grams.

Objective: The proposed study aims to determine the feasibility of conducting a randomized control trial to compare the efficacy of IV acetaminophen and fentanyl compared to fentanyl alone for patients admitted to the neonatal intensive care unit (NICU) undergoing major abdominal or thoracic surgery.

Methods and Design: This protocol is for a single-centre, external pilot randomized controlled trial (RCT), which aims to assess the feasibility of a superiority, parallel-design, multicentre RCT. Infants in the NICU who have undergone major thoracic or abdominal surgery will be enrolled. Sixty participants will undergo 1:1 randomization to receive IV acetaminophen and fentanyl or saline placebo and fentanyl. After surgery, IV acetaminophen or placebo will be given routinely for eight days (192 hours). Appropriate dosing will be determined based on the participant's gestational age. Patients will be followed for eight days after surgery and will undergo a chart review at 90 days. Primarily feasibility outcomes include recruitment rate, follow-up rate, compliance, and blinding index.

Conclusion: This external pilot RCT will assess the feasibility of performing a multicenter RCT assessing the efficacy of IV acetaminophen and fentanyl, compared to

fentanyl and placebo in neonatal patients following major abdominal and thoracic surgery. This will be the first trial to evaluate this medication in for pain control in preterm neonates. The results will inform the final design of a multicenter RCT, which will have the appropriate power to determine the efficacy of this treatment.

Trial Registration

ClinicalTrials.gov NCT05678244

4.2 Introduction

Pain management in neonates is of significant clinical and ethical importance. Pain in the neonate began to garner academic interest in the 1980s when Anand et al. demonstrated that unmanaged pain is associated with hemodynamic instability, muscle and protein catabolism, intraventricular hemorrhage, and leukomalacia [9-12]. Furthermore, researchers determined that due to their rapid state of neurodevelopment, uncontrolled pain may lead to long-term neurodevelopmental changes and chronic pain [14, 129] [18-23].

.

As evidence highlighted the need to control pain in neonates adequately, the use of opioids in NICUs increased [130]. For the management of both operative and non-operative pain, opioids, especially fentanyl, remain the most common medication used [131, 132]. There is limited data about the frequency of use of opioids after surgery in the NICU. Authors have reported that between 88-93% of NICUs predominantly use opioids for the management of postoperative pain [43, 101]. In a retrospective chart review in

1997, Johnston et al. found that all 13 postoperative patients in their cohort received opioids for postoperative pain, most commonly via a continuous infusion [24]. Opioids can provide analgesia but are associated with adverse events. Acutely, they are associated with respiratory depression, urinary retention, hypotension and tolerance [27-30, 36, 104]. Similar to neonates' response to uncontrolled pain, their state of neurodevelopment may make them susceptible to long-term adverse events, although more research is needed. The small-scale studies completed previously have identified that opioid exposure may be linked the reduced intelligence, memory, and social problems; however, it is unclear if these changes are reversible and persist into adolescence and adulthood [31-33].

The mounting evidence demonstrating the need to adequately manage pain while also reducing opioid use in neonates has led to an interest in the development of multimodal pain regimes [133]. These regimes are commonplace in managing postoperative pain in adults and older children [37] [38-40]. These regimes, however, cannot simply be applied to the neonatal population. The unique physiology of neonates, particularly pre-term neonates, necessitates specific attention, including evaluating the efficacy of individual medications [134, 135].

Rationale

One of the most promising non-opioid analgesics is IV acetaminophen. This medication is beneficial postoperatively as many patients cannot take medications orally or rectally, and it has more predictable responses in neonates than other routes [50]. We recently

conducted a systematic review on IV acetaminophen for postoperative pain in pediatric patients recovering from abdominal and thoracic surgery. We found that when it is added to opioid-based pain regimes, there is a reduction in opioid use and minor adverse events without sacrificing pain control. However, we identified no trials that evaluated IV acetaminophen for postoperative pain in patients under 36 weeks gestational age or birth weight under 1500 grams. In pre-term neonates, slight differences in gestational age may significantly impact physiology. Therefore, the data from older children and neonates cannot be applied to this population. Furthermore, all available trials suffer from short follow-up periods, with the median follow-up time being 48 hours. Recovery after major surgery extends well beyond this time; prolonged follow-up times are needed to capture the entire postoperative period. [65]. While there may be clinical benefits, IV acetaminophen is expensive. It is reported to be 20 times more expensive than rectal formulations and 84 times more expensive than oral liquid formulations [124].

IV acetaminophen has not been studied in pre-term infants; therefore, its clinical efficacy remains unknown. The research question of this study is: “Does the addition of IV acetaminophen to fentanyl-based postoperative pain regimes (compared to placebo) reduce opioid use and adverse events without sacrificing pain scores?” In order to determine whether its clinical effect is worth the significant cost, its efficacy must first be established. We therefore developed a study protocol to answer this question. This trial will be the first to examine the efficacy of IV acetaminophen for postoperative pain in pre-term neonates. It will also be the first to use a prolonged follow-up period. Our study

will build on existing data and may uncover novel insights into the care of pre-term neonates in the extended perioperative period.

4.3 Methods

Study design and objectives

This study is a single-center, blinded, parallel-arm, placebo-controlled, superiority, external feasibility randomized controlled trial. The primary objective of this pilot study is to determine the feasibility and cost of conducting a RCT to assess the effect of IV acetaminophen on postoperative pain in preterm neonates in the neonatal intensive care unit.

Setting and timeline

This study will occur in the NICU at McMaster Children's Hospital (MCH) in Hamilton, Ontario, Canada. This NICU has 72 beds and admits more than 1,500 infants annually. Using Canadian Neonatal Network data from 2018-2020 and local internal case recording, an estimated 41 eligible cases will occur each year. Assuming a recruitment rate of 60%, our estimated recruitment period will be approximately 2 years [136].

Participants

The participants of this study will include neonates admitted to the NICU at MCH who have undergone major open abdominal or thoracic surgery (as defined by the Canadian Neonatal Network, Appendix 1 Table 26) [136]. Neonates of all corrected gestational ages

will be eligible up until 12 months corrected gestational age. Patients who have or develop hepatic or renal dysfunction, as described in Table 19, will be excluded [137-142]. Neonates who received acetaminophen administration within 24 hours of the end of surgery (which includes intraoperative administration) will be excluded to prevent contamination groups. Neonates who have nerve blocks or epidurals will also be excluded. The medical team will be asked for approval of the patient to enter the study; if they have any clinical concerns (such as a duct-dependent cardiac lesion), the patient will be excluded. Patients can be enrolled up to 12 hours after surgery, including emergent overnight cases if the research team cannot obtain consent. If a patient is discharged from the McMaster NICU within the study period (including transfer to another institution, discharge home, or death), the patient will be prematurely withdrawn from the study, but data up to that point will be included. If a participant undergoes multiple surgeries during the recruitment period, they will only be eligible for inclusion once (i.e., if a patient was already enrolled, they may not be enrolled again for a second surgery).

Table 19. Inclusion and exclusion criteria for the IVA POP trial

Inclusion Criteria	Exclusion Criteria
Neonates, admitted to McMaster Children's Hospital NICU	Hepatic dysfunction - Aspartate aminotransferase (AST), Alanine transaminase (ALT) or Bilirubin > 3x upper limit of normal - International Normalized Ratio (INR) ≥ 3.0 or Prothrombin Time (PT) greater than 20s regardless of vitamin K administration
Has had major open, thoracic or abdominal surgery (see Appendix 1 Table 26).	Renal dysfunction - Increase in serum creatinine ≥ 2x baseline (baseline: lowest value in first 5 days of hospitalization) - Urine output < 0.5 mL/kg/h for ≥ 12h
Informed consent obtained from guardians	Allergy or intolerance to acetaminophen or fentanyl Acetaminophen administration within 24 hours of the end of surgery Nerve blocks or epidurals Refusal or withdrawal of consent Enrolment in another competing trial More than 12 hours after the end of surgery 12 months post conceptual age or greater in age Birthweight greater or equal to 2,500g. Discharged from the McMaster NICU Concern from medical team

Interventions

Participants will be randomized in a 1:1 fashion to the treatment or control group. To maintain a pragmatic trial design and ensure that analgesia is provided when clinically indicated, all subjects in the treatment and control arms will receive fentanyl as per the

standard of care and discretion of the NICU team. As in the NICU of MCH, a continuous fentanyl infusion is the drug of choice for postoperative pain management for all patients receiving major thoracic or abdominal surgery, with intermittent bolus dosing used at the discretion of the primary care team to optimize pain management. The specific dosing instructions for fentanyl (i.e., infusion or bolus, rate, frequency, the timing of escalation or de-escalation) for all the subjects in our study's control or intervention arm will be directed by the NICU team. Dosing guidelines for infusions and boluses can be seen below in the fentanyl formulation section. We will maintain an accurate record of each subject's fentanyl dosing in mcg/kg/day.

Subjects randomized to the treatment arm (acetaminophen and fentanyl) will receive the indicated dose of IV acetaminophen (including the age-appropriate loading dose if indicated) seen below in Table 20. Subjects randomized to the control (fentanyl) group will receive a saline placebo at the same time interval and volume as whichever dose of acetaminophen they would have received. The acetaminophen treatment dosing guidelines were developed in consultation with the neonatal pharmacists and neonatologists at MCH. The guidelines used at MCH are based on validated dosing guideline [143-147]. Should patients change age categories throughout the trial, their dose will be adjusted accordingly. The McMaster research pharmacy has calculated a maximum daily volume of administration (using the maximum gestational age and a weight of 3 kg) of 12 mL per day, and a maximum loading dose of 6 mL, meaning the maximum daily volume requirement would be 18 mL. Regardless of treatment

assignment, this additional fluid will be accounted for in the patient's total fluid intake to ensure they maintain an appropriate total fluid intake.

Table 20. IV Acetaminophen dosing guidelines for the IVA POP trial

Current Gestational Age	Intravenous dose	Maximum daily dose
32+6 weeks and under	10 mg/kg IV q12h	22.5 mg/kg/day IV
33-36 weeks	Loading dose: 20 mg/kg IV x 1, then 10 mg/kg IV q8h	30 mg/kg/day IV
37+ weeks and less than ten days old 37+ weeks and at least ten days old	Loading dose: 20 mg/kg IV x 1, then 10 mg/kg IV q6h	40 mg/kg/day IV
Pediatric dosing (44+ weeks and 28+ days old)	Loading dose: 20 mg/kg IV x 1, then 10 mg/kg IV q6h	60 mg/kg/day IV

The intervention will begin once the patient is returned to the NICU from the operating room or at the time of completion of the procedure if performed at the bedside. The fentanyl infusion will be assessed to be increased or decreased on an ongoing basis by the primary care team in keeping with current standard practice. Rescue doses of fentanyl will be provided in both groups at the discretion of the primary care team. Each dose will be recorded. Any additional analgesics provided by the primary care team will also be recorded.

Blood work (AST, ALT, Bilirubin, INR, PT, and creatinine) will be tested preoperatively and at least twice during the 192-hour follow-up period. Using data from the Hamilton

Regional Laboratory Medicine Program, the volume of blood required for these tests is 2.6 mL. It will be done twice during the follow-up period (postoperative days 3 and 7) for a total of 5.2 mL. Liver and renal function tests are commonly required postoperatively. These tests will be done in a coordinated fashion with other required blood work to reduce the frequency and volume of blood draws. A meta-analysis of neonatal venous sampling concluded there is minimal risk with single blood draws of less than 5% blood volume and less than 10% over eight weeks [148]. A preterm neonate has a blood volume of approximately 100 mL/kg, so the volume of blood draws within this study complies with these suggestions, even in neonates weighing as little as 500 grams [149, 150]. Patients will be withdrawn from the study if there is evidence of hepatic or renal failure (as described in Table 19).

Acetaminophen formulation

Avir Pharma brand IV acetaminophen will be used in this study. It will arrive from the supplier in 1000 mg/100 mL (10 mg/mL) IV bags. The appropriate amount of medication will be drawn from the bag using sterile technique and into a separate syringe; it does not require further dilution. It will be administered over 15 minutes. The research pharmacy will generate an appropriate label.

Placebo formulation

Normal saline infusion will be used as the placebo. Like IV acetaminophen, it is clear and colourless, maintaining blinding. The research pharmacist will prepare a syringe with a volume corresponding to the IV acetaminophen dosing guidelines with an identical label to maintain blinding. It will also be administered over 15 minutes.

Fentanyl formulation

Sandoz and Sterimax brand fentanyl will be used to prepare 20 mcg/mL, 5 mcg/mL and 1 mcg/mL (diluted in D5W, normal saline, or D10W) syringes to be used in infusion pumps as is standard practice in the MCH pharmacy and NICU. The pharmacist will select the concentration based on the ordered dose of the medication. Please see Table 27 in Appendix 1 for more details.

To prepare the drug, the pharmacy will send the raw syringes or vials of Sandoz or Sterimax brand fentanyl (50 mcg/mL). Using standard technique, the solution will be diluted and prepared to the final target concentration based on the patient's required dose, as determined by the neonatologist. The solution will then be mixed, capped, and appropriately labelled. Infusion dosing (including escalation, de-escalation, and discontinuation) will be at the discretion of the NICU physician, with a usual dose ranging between 0-3 mcg/kg/h; however, some patients may require up to 5 mcg/kg/h [151]. The NICU physician will be eligible to provide bolus doses as needed. The dosing range for bolus fentanyl, as described by the International Evidence-Based Group for

Neonatal Pain, is a slow IV push of 0.5 to 3 mcg/kg/dose every 2 for 4 hours, titrated to effectiveness [152]. The NICU physician will ultimately determine specific dosing on a case-by-case basis.

Trial flow and follow-up

Patients will receive the intervention from postoperative day zero to postoperative day seven for a total of eight days or 192 hours. Their postoperative day will be determined based on the time from the surgery's end, as shown in Table 21. Data on opioid use, pain scores, and other clinical outcomes will be collected daily during these seven postoperative days. At the end of the week, cumulative opioid consumption and clinical outcomes will be calculated. At 90 days, a chart review will be done to assess the total length of assisted ventilation, length of stay, and mortality. Figure 5 demonstrates the flow of patients through the trial from identification to completion.

Table 21. Time parameters for postoperative day designation for the IVA POP trial

Post-Operative Day	Time From Surgery
Day 0	0-23 hours
Day 1	24-47 hours
Day 2	48-71 hours
Day 3	72-95 hours
Day 4	96-119 hours
Day 5	120-143 hours
Day 6	144-167 hours
Day 7	168-192 hours

\

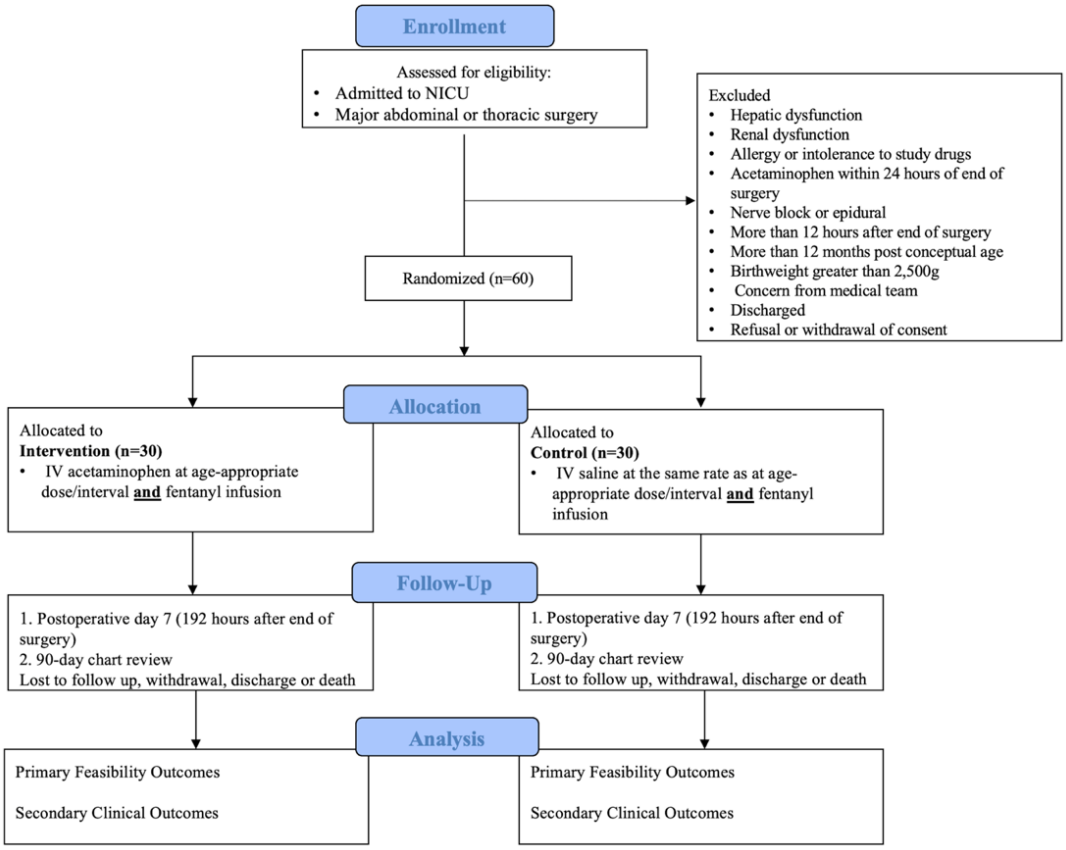


Figure 5. Flow of patients through the IVA POP trial

Sequence Generation, Randomization, and Allocation Concealment

Sequence generation and randomization will be done using Research Electronic Data Capture (REDCap), a secure, web-based software platform designed for study design and data capturing [153]. The allocation tables will be generated within REDCap by an unblinded, uninvolved research assistant. Patients will be randomized in a 1:1 fashion between the treatment and control groups. The sequence will be generated in randomly permuted blocks of four or six to ensure equal group sizes. Due to the small sample size, stratification will not be done; however, the balance of demographic features between

groups will be evaluated as a feasibility outcome. The allocation tables will be provided in advance to the unblinded research pharmacists. Each participant will be assigned a study number. Using a linking key, the research pharmacy will be able to determine which arm the patient is randomized to. Medication will be prepared and dispensed by a trained research pharmacist. Only the research pharmacists, the unblinded research assistant and the data safety monitoring board members will have access to the randomization key. None of these parties are involved with data collection or analysis.

Blinding and Unblinding

Guardians, investigators, statisticians, nurses, allied health professionals and physicians will be blinded to treatment allocation. The research and clinical pharmacists will not be blinded as they will be involved in study drug preparation. They will not be blinded but will play no role in outcome assessment or analysis. Saline will be used for the placebo. Saline and IV acetaminophen are indistinguishable when prepared in solution. To ensure the protocol was followed, the key will be checked against the treatments provided at the end of the study. The patient's chart will not mention which arm of the study the patient was enrolled in, therefore ensuring blinding at the 90-day chart review. The statistician will be provided with blinded data. The groups will not be revealed until after analysis.

If a safety concern is raised by the patient's physician, member of the research team, the DSMB, the ethics committee, or Health Canada, the unblinded research assistant will be

contacted with the patient's name and participant number, and they will then provide their allocation. If unblinding occurs, the patient will be discontinued from the study.

4.4 Outcomes

Outcomes are displayed below in Tables 22-27. When needed, additional elaboration is provided for key outcomes. Table 22 displays demographic variables to be collected.

Table 22. Demographic variables for IVA POP trial

Sex
Race
Gestational age
Birth weight
Age at surgery
Preoperative diagnosis
Procedure
Length of OR
Preoperative opioid use (administered opioids within 7 days prior to surgery)
Intubated preoperatively
Maternal opioid use (use of opioids on more than two separate days during pregnancy)

Feasibility outcomes

The primary outcomes of recruitment rate, follow-up rate, medication compliance, and blinding index have all been pre-selected to determine the success of the pilot RCT. The primary outcomes and the predetermined definition of success are displayed below in Table 23. We will also include other outcomes to assess feasibility. Below in Table 24, we have described the secondary feasibility outcomes and their rationale and measurement.

Table 23. Primary Outcomes for the IVA POP trial

Outcome	Definition	Success
1. Monthly recruitment rate	Mean number of patients randomized per month	Average of 2 patients per month
2. Follow up rate	Number of patients followed in completion from postoperative day 0 to 7	90% of patients followed completely
3. Medication compliance	Number of patients who received at least 80% of doses of study drugs at the correct dose and interval	80%
4. Blinding index [154].	Responses of nurse's, medical staff, and research assistant's guess of group assignment (control vs treatment) compared to actual group assignment	Less than 0.20

Table 24. Secondary Feasibility Outcomes for the IVA POP trial

Outcome	**Definition**	**Rationale**
Time from randomization to start of surgery	Number of hours, positive hours indicate randomized prior to surgery, negative hours indicate randomized after surgery	This will help determine the average number of hours until surgery, to help determine how much lead time pharmacy must prepare and administrate medications.
Recruitment rate	Total number of patients randomized/number of eligible patients	Will help estimate recruitment time in the largescale trial
Number and type of protocol violations	-	Assess feasibility of adhering to the current protocol
Cost	Canadian dollars per patient recruited	Will help more accurately estimate the cost of a largescale RCT.
Amount of additional analgesics administered at each pain score in each arm.	Number of patients receiving rescue doses and doses administered (per weight) of additional analgesics for each pain score for pain scores above 6	Ensure that NICU physicians use of additional analgesics is balanced between the groups.
Number of study related adverse events		Ensure that the trial is not associated with an unacceptably high number of adverse events

Secondary clinical outcomes

As this study is a pilot, it will not be adequately powered to assess these clinical outcomes fully; however, collecting these data will indicate the feasibility of data collection and

may provide important preliminary data. The rationale and measurement for key secondary clinical outcomes are described below and displayed in Table 25.

Pain scores

The primary outcome of the multicenter trial will be postoperative pain scores. Postoperative pain will be assessed using the pain component of the Neonatal Pain Agitation and Sedation Scale (N-PASS). N-PASS has two scorable components, sedation and pain. For this study we will only utilize the pain component of this score. Pain is scored on a scale of 0 to 13. It includes subjective assessments of behaviour and objective assessments of vital signs [155, 156]. The N-PASS pain score is validated in term and preterm neonates and for assessment of prolonged and postoperative pain. It is recommended by the Neonatal Pain-Control Group [155, 157, 158]. It has been independently validated and is reliable with high clinical utility [159, 160]. The N-PASS pain score is the measurement scale currently used in the MCH NICU. The bedside nurses, who will be responsible for measuring pain, are comfortable using this instrument, increasing the validity of the measurements. Furthermore, documenting this pain score regularly is part of their daily workflow. As this is already required documentation, the risk of missing data is reduced. It will reduce the burden of documentation required by the nurses.

Initial pain score will be recorded when the patient returns from the operating room. Pain scales will then be done just before the patient's dose of acetaminophen or placebo (every

4 or 6 hours), as recommended by the Neonatal Pain-Control Group [158]. The neonatologists will have access to the patient's N-PASS score to aid in clinical decision-making. Although staff members on this unit are comfortable with using and interpreting this instrument, an infographic will be available to the physicians and nurses to aid in interpreting N-PASS scores and includes suggested interventions; this is available Appendix 2 Figure 6.

Table 25. Secondary clinical outcomes for the IVA POP trial

Outcome	Definition
Postoperative Pain	N-PASS pain score every four or six hours, filled out by nurse
Fentanyl consumption	Cumulative over 24/hour periods, over entire study period, and duration of fentanyl infusion
Consumption of other analgesics	Cumulative over 24/hour periods and over entire study period
Invasive ventilation	Length of time requiring intubation
Non-invasive ventilation	Length of time requiring Continuous Positive Airway Pressure (CPAP,) Bilevel Positive Airway Pressure (BiPAP), or supplemental oxygen
Enteral feeds	Time to first enteral feeds and time to full enteral feeds (using NICU's calculated goal feed)
Bowel movement	Time to first bowel movement
Glycerin suppository use	Number of patients requiring one or more glycerin suppositories

Length of stay	At 90-day chart review (with discharge destination)
Vomiting	Number of patients with ≥ 1 episode of vomiting documented
NG/Vygon	Number of patients, mean duration
Reintubation	Number of patients
Apnea	Number of patients with a documented oxygen saturation less than 94% or respiratory less than 20 breaths/min
Naloxone administration	Number of patients
Bradycardia	Number of patients with a documented heart rate less than 100
Hypotension	Number of patients with documented systolic blood pressure less than 60, or requiring vasoactive medication
Foley catheterization	Number of patients, mean duration
Feeding intolerance	Number of patients: feeds stopped or decreased due to vomit/increased gastric output, or if diagnosed by the treating team
Hepatic injury	Number of patients
Mortality	All-cause mortality at 90 days

4.5 Statistical Analysis

As this is a feasibility study, all comparative analyses on clinical outcomes are for exploratory purposes, and no inferences will be made from these analyses. Demographics will be reported as means or medians for continuous variables and frequencies and proportions for categorical variables. Feasibility outcomes (recruitment rate, completion rate, rate of patients discharged at 90 days, success of randomization, study related

adverse events, and protocol violations) will be reported as proportions. Blinding success will be reported with the calculated blinding index, as described by James et al. [154]. Cost will be reported in Canadian dollars for the total cost and cost per participant randomized. Secondary clinical outcomes (pain scales, cumulative consumption of fentanyl and other drugs, number of rescue doses, length of time requiring fentanyl infusion, length of time requiring non-invasive (intubation, CPAP, BiPAP, supplemental oxygen), time to enteral fees, time to first bowel movement, and length of stay) will be reported as means or medians with standard deviation (SD) and interquartile ranges, respectively. As this study is not adequately powered to detect differences hypothesis testing will not be conducted. Statistics Package for the Social Sciences (SPSS) will be used for data analysis [117].

Sample size

A sample size of 30 participants per group (a total of 60) will be used. This decision is based on methodologic guidelines, suggesting that 30 participants is ideal for assessing feasibility and assisting in calculating future sample sizes [161-163].

Subgroup Analysis

In the full RCT sub-group analysis is planned for the following demographic variables: gestational age (<32 weeks, ≥32 weeks), location of operation (thorax or abdomen), preoperative opioid use, and sex. Aside from sex, these have all been identified as predictors of postoperative pain [164-167]. Gestational age was selected rather than birth

weight, as it is a better measure of the infant's development and a more accurate predictor of physiologic response to pain [168].

4.6 Ethics and Safety

This study was approved by the Hamilton Integrated Research Ethics Board (14887), the Neonatal Research Committee at McMaster Children's Hospital, and Health Canada (268629). Parents or legal guardians will provide written and informed consent prior to enrollment.

A data safety monitoring board (DSMB) will be formed, including at least one neonatologist and one pediatric surgeon. They will meet when five patients have been enrolled and every six months after that. They will be provided with the study key to unblind data. They will meet within fifteen days after a possible study-related adverse event (non-life-threatening/non-fatal) and within 48 hours after a study-related life-threatening or fatal adverse event. The DSMB will create a summary report for the steering committee to categorize adverse events based on severity and relatedness to the study drug. The DSMB cannot recommend stopping early for benefit but may recommend stopping for harm if they observe significant safety concerns.

4.7 Discussion

Anticipated pitfalls

Due to the types of surgical conditions that affect neonates in the NICU, we anticipate several pitfalls that may affect recruitment and follow-up. Many neonates who require surgery are treated on an emergent basis, which can occur overnight or on weekends. There is also minimal lead time with high-acuity emergency surgery. These factors represent a challenge for enrollment as we may be unable to capture all after-hours cases due to financial and logistic restraints. The research team will be in close contact with the surgical and NICU teams to attempt to be aware of any potential cases as soon as possible to reduce this risk.

Again, the emergent nature of many neonatal surgical conditions (e.g., necrotizing enterocolitis) may affect recruitment. Renal and hepatic dysfunction are both exclusion and withdrawal criteria for this trial. In preterm infants, immaturity of the renal system and nephrotoxic events (i.e., congenital abnormalities, sepsis, hypovolemia, aminoglycoside antibiotics) put patients admitted to the NICU at risk for acute renal failure. The precise incidence is unknown, but studies have demonstrated rates between 6% and 24% [169-171]. In preterm infants, rates of cholestasis have been reported to be up to 24%. There will also be infants with non-cholestatic hepatic dysfunction. Factors such as lack of enteral feeds, prolonged parenteral nutrition, sepsis, and hepatoxic medications, which are more common in surgical populations, have been shown to increase this risk of hepatic dysfunction [172, 173]. The relatively high incidences of

these conditions may impact recruitment. For recruited patients, whether their renal or hepatic dysfunction is related to IV acetaminophen administration, they will have to be prematurely withdrawn from the study.

The measurement of pain Is Ir potential pitfall. The measurement of pain In Itself is subjective [174]. This is attenuated in neonates who are unable to communicate verbally. This has the potential to inject subjectivity not only into the results of the pain scores themselves but also into the amount of opioids prescribed, as the administration of opioids depends on the clinician's interpretation of the patient's pain score. While this subjectivity is not wholly avoidable, we have employed strategies to mitigate it. Firstly, we have selected a pain score validated for this clinical situation. And already used on this unit, meaning that staff are already comfortable with its administration and interpretation. Secondly, proper randomization should help balance variation in pain assessment and medication administration between groups.

Mortality is another potential limitation. The overall mortality rate after surgery for preterm infants is 16.8%. This rate increases as gestational age decreases with a postoperative mortality rate of 31% in patients less than 24 weeks gestational age [175] Patients may die at any point along the study pathway, impacting recruitment and post-randomization withdrawal rates.

Loss to follow-up is unlikely as study participants will be monitored closely in the NICU and will not be discharged or transferred to another institution within eight days of major surgery. To enhance recruitment, we will continue proactively screening all potential participants. To reduce the frequency of post-randomization withdrawals, we will collect all data up until the point of withdrawal.

Anticipated strengths

There are several methodologic features of this study which are anticipated strengths. First, the pragmatic design, which allows neonatologist control over other analgesics means the results of this RCT will be readily applicable to clinical practice. Furthermore, we purposely designed the trial to not significantly add to the workflow of the clinical team, which will reduce missing or incomplete data. The extended follow-up period is another strength of this trial. The primary 192-hour (eight-day) and secondary (90-day) follow-up periods will provide novel data on the extended perioperative period and may offer insights into the ideal duration of treatment and the longer-term ramifications of this intervention. This will be the first trial on this topic to have a follow-up period beyond 72 hours. This will also be the first trial to include pre-term neonates, which will offer new insights into the effect of this drug on this population [65]. Using James et al.'s blinding index as a feasibility outcome is another strength [154]. This measure was selected because we were concerned the efficacy of IV acetaminophen for pain control may lead to inadvertent unblinding of the clinical team at clinical team, and that bedside nurses in

particular may be able to ascertain treatment assignment. This information will be essential in designing the multicenter RCT.

Conclusion

There are no data evaluating the efficacy of IV acetaminophen for postoperative pain in preterm infants following major abdominal and thoracic surgery. This external pilot study will allow us to assess the feasibility of a superiority, multi-centred, placebo-controlled, parallel-design, randomized controlled trial. When completed, the multicentre study will be powered to determine if the addition of IV acetaminophen to fentanyl-based postoperative pain regimes reduces opioid exposure and adverse events without sacrificing pain scores.

Trial status

Enrollment is scheduled to begin on March 20, 2023, and is anticipated to be completed in September 2024.

4.8 Authors' contributions

VA designed the protocol, obtained funding, and completed the neonatal research committee, ethics, and Health Canada reviews and is assisting in trial management. JMW, SS, and LB assisted with the study conception and literature review. SS, JMW, LB, DB and FF all assisted with funding applications and ethics and regulatory applications. SS,

JMW, LB, and FF revised the study protocol. VA wrote the manuscript, and all authors participated in revisions. All authors have read and approved the final manuscript.

CHAPTER 5: CONCLUSION

5.1 Main Findings

The results of the studies presented within this thesis must not be viewed in isolation. Understanding these results in context provides more nuanced insights into this field. The main finding of the systematic review presented in chapter two demonstrates that adding IV acetaminophen to opioid-based regimes may reduce opioid use and minor adverse events without sacrificing pain scores in pediatric patients up to two years of age. It also demonstrated that IV acetaminophen still needed to be studied in neonates less than 36 weeks post-conceptual age; therefore, its effects in this population remained unknown. Finally, none of the studies in the systematic review had a follow-up period that exceeded 72 hours, likely not capturing the entire recovery period for major abdominal and thoracic surgeries. These findings were instrumental in the design of the pilot RCT presented in chapter four. We specifically designed our population to include pre-term neonates. We also featured a prolonged follow-up period which will allow us to better understand the effect of this medication on the entire recovery period and 90-day outcomes. This may provide new insights into the optimal duration of therapy and the long-term effects of this medication. Without our systematic review, the need to specifically interrogate these areas would not have been known, and these novel insights would have remained unstudied. Our review also demonstrated that the quality of evidence was very low and that more high-quality, randomized data are necessary. This lack of high-quality evidence demonstrated that clinical equipoise remains regarding the use of IV acetaminophen in

this setting. This reinforced that an RCT was necessary but also prompted us to survey key stakeholders to understand their perspectives and experiences with this medication.

The national survey presented in the third chapter of this thesis focused on two themes: postoperative pain prescribing practices and perspectives on IV acetaminophen. The results of our systematic review moved us to formally survey neonatologists, surgeons, and anesthesiologists about their practices and perspectives. However, in our preliminary research for the systematic review and the pilot RCT, we became aware of the lack of consensus and the lack of data on postoperative pain management trends in Canadian NICUs.

Our survey demonstrated that while neonatologists are the primary managers of postoperative pain, approximately 20% of surgeons and 20% of anesthesiologists are involved in postoperative pain management. Our findings confirmed that opioids, specifically fentanyl, remain the most common agent for postoperative pain in Canadian NICUs. However, we found that almost all participants use some degree of multimodal pain control. Almost a third of physicians use a non-opioid medication as a first-line agent for postoperative pain control. We further described the use of IV acetaminophen nationally. We found that almost half of the physicians have experience with its use, and those who use it noted many benefits. Importantly, cost and a lack of supporting research were identified as barriers to more widespread use. Physicians' positive experiences, support for the use of IV acetaminophen, and their desire for more research reinforced the

need for high-quality prospective data. Future work will be important in determining if IV acetaminophen is efficacious and cost-effective, which was another cited barrier.

As demonstrated throughout this thesis, the design of the pilot RCT presented in chapter four is based on the prior studies, which will create clinically meaningful and relevant results. Like the other studies, its results will be used to design future studies in this domain. As it is a pilot study, the results will inform the design and implementation of a high-quality, multicentered randomized trial, providing more accurate results regarding the utility of IV acetaminophen in neonates after major abdominal and thoracic surgery. This trial has just begun recruiting, and data has yet to become available.

5.2 Future Directions

Throughout this thesis, areas for future research were identified. This future work aims to fill identified knowledge gaps and address limitations in the research conducted to this point. The most pertinent work necessary to answer our original research question is performing a high-quality multi-center RCT. The results of the pilot study will be critical in ensuring that the large-scale RCT is designed and implemented in such a way as to answer our research question. As highlighted several times, this RCT will be the first to study this drug in pre-term infants and the first with a follow-up period beyond 72 hours. The results will undoubtedly generate further questions. Future work may involve understanding if and when IV acetaminophen can be used as a single agent for

postoperative pain, investigating other pharmacologic agents and regional anesthesia, and studying the effects of using these medications in a bundled fashion.

Nonrandomized data is also incredibly valuable in this domain. As highlighted in chapter three, performing a retrospective review of prescribing practices for postoperative NICU patients would help quantify the frequency and dosage of medications used and confirm the specialty of the prescribing physicians. These data would provide additional context to our survey and potentially validate our results. Non-physician perspectives are also crucial in the acceptance of this drug and in understanding postoperative pain practices more broadly. Performing surveys that aim to understand nurses' perspectives is necessary as they have unique perspectives due to the nature of the direct hands-on care they provide. Surveying family members is essential to understanding their expectations and experiences with their child's postoperative pain. This would aid in the design of educational material, support parental engagement, and identify areas for improvement or further research in this field.

5.3 Conclusion

We began this work by asking, "when used for postoperative pain management in patients admitted to the NICU, does IV acetaminophen reduce opioid use and effectively control pain?" We demonstrated through a meta-analysis and survey of physicians that IV acetaminophen may be an effective adjunct in postoperative pain management in neonates after major abdominal and thoracic surgery. Both studies, however, identified the need for

more research, specifically in the pre-term population. This thesis represents the incremental and cumulative work required to answer these clinical questions. The results act as an essential foundation for future research. These studies have allowed us to understand the true scope of this question and identify multiple areas requiring further research. They have provided us with potential hypotheses about the answer to this question and, importantly, have allowed us to design a trial in an informed fashion.

APPENDICES

Appendix 1: Supplemental Tables

Table 26. Major abdominal and thoracic operations as defined by the Canadian Neonatal Network

Major Abdominal Operations	Major Thoracic
Repair or closure of omphalocele	Atrial septal defect closure
Repair of aneurysm in internal iliac artery	Blalock-Taussig Shunt (BTS) for tricuspid atresia
Closure of bladder rupture	Coarctation repair
Bowel resection	Correction of cystic adenomatoid malformation
Correction of Atresia	Cystic hygroma
Colostomy	Esophageal atresia (thoracic approach)
Revision of prolapsing colostomy	Lobectomy
Esophageal atresia (abdominal approach)	Lung biopsy (open)
Release of corkscrew duodenum	Pacemaker insertion (open)
Removal of dermoid cyst (abdominal)	Removal of dermoid cyst (thoracic)
Diaphragmatic hernia repair (abdominal approach)	Diaphragmatic hernia repair (thoracic approach)
Duodenojejunostomy	Pneumonectomy
Fundoplication	Pulmonary artery banding (open)
Enterotomy (for removal of meconium)	Pulmonary artery plasty
Epispadias repair	Tracheoesophageal (TEF) repair
Closure of gastroschisis defect	Vascular ring operation
Ileostomy or mucus fistula reversal	Exploratory thoracotomy
Ileostomy or mucus fistula creation	
Laparotomy for necrotizing enterocolitis (NEC)	
Nephrectomy	
Omphalomesenteric duct fistula repair	
Orchidectomy	
Pyloromyotomy (open)	
Pyloroplasty	
Vesicostomy closure/revision	
Repair of volvulus	
Exploratory laparotomy	

Table 27. Summary of acceptable formulations and concentrations of fentanyl for use in this trial

Brands	Prepared syringe concentrations
SteriMax Fentanyl (fentanyl citrate injection) 100 mcg/2 mL Ampule (Concentration: 50 mcg/mL) DIN 02496143	Fentanyl 1000 mcg/50 mL of D5W (or normal saline or D10W) syringe (concentration: 20 mcg/mL)
SteriMax Fentanyl (fentanyl citrate injection) 250 mcg/5 mL Vial (Concentration: 50 mcg/mL) DIN 02496151	Fentanyl 250 mcg/50 mL D5W (or normal saline or D10W) syringe (concentration: 5 mcg/mL)
Sandoz Fentanyl (fentanyl citrate injection) 100 mcg/2 mL Ampule & 250 mcg/5 mL vial (Concentration: 50 mcg/mL) DIN 02240434 Sandoz Fentanyl (fentanyl citrate injection) 100 mcg/2 mL Ampule (Concentration: 50 mcg/mL) DIN 02384124	Fentanyl 50 mcg/50 mL D5W (or normal saline or D10W) syringe (concentration: 1 mcg/mL)

Appendix 2: Supplemental Figures

N-PASS:
Neonatal Pain, Agitation, & Sedation Scale

Pat Hummel, MA, RNC, NNP, PNP & Mary Puchalski, MS, RNC

Assessment Criteria	Sedation		Normal	Pain / Agitation	
	-2	-1	0	1	2
Crying Irritability	No cry with painful stimuli	Moans or cries minimally with painful stimuli	Appropriate crying Not irritable	Irritable or crying at intervals Consolable	High-pitched or silent-continuous cry Inconsolable
Behavior State	No arousal to any stimuli No spontaneous movement	Arouses minimally to stimuli Little spontaneous movement	Appropriate for gestational age	Restless, squirming Awakens frequently	Arching, kicking Constantly awake or Arouses minimally / no movement (not sedated)
Facial Expression	Mouth is lax No expression	Minimal expression with stimuli	Relaxed Appropriate	Any pain expression intermittent	Any pain expression continual
Extremities Tone	No grasp reflex Flaccid tone	Weak grasp reflex ↓ muscle tone	Relaxed hands and feet Normal tone	Intermittent clenched toes, fists or finger splay Body is not tense	Continual clenched toes, fists, or finger splay Body is tense
Vital Signs HR, RR, BP, SaO_2	No variability with stimuli Hypoventilation or apnea	< 10% variability from baseline with stimuli	Within baseline or normal for gestational age	↑ 10-20% from baseline SaO_2 76-85% with stimulation – quick ↑	↑ > 20% from baseline $SaO_2 \leq 75\%$ with stimulation – slow ↑ Out of sync with vent

Premature Pain Assessment

+ 3 if < 28 weeks gestation / corrected age
+ 2 if 28-31 weeks gestation / corrected age
+ 1 if 32-35 weeks gestation / corrected age

Assessment of Sedation

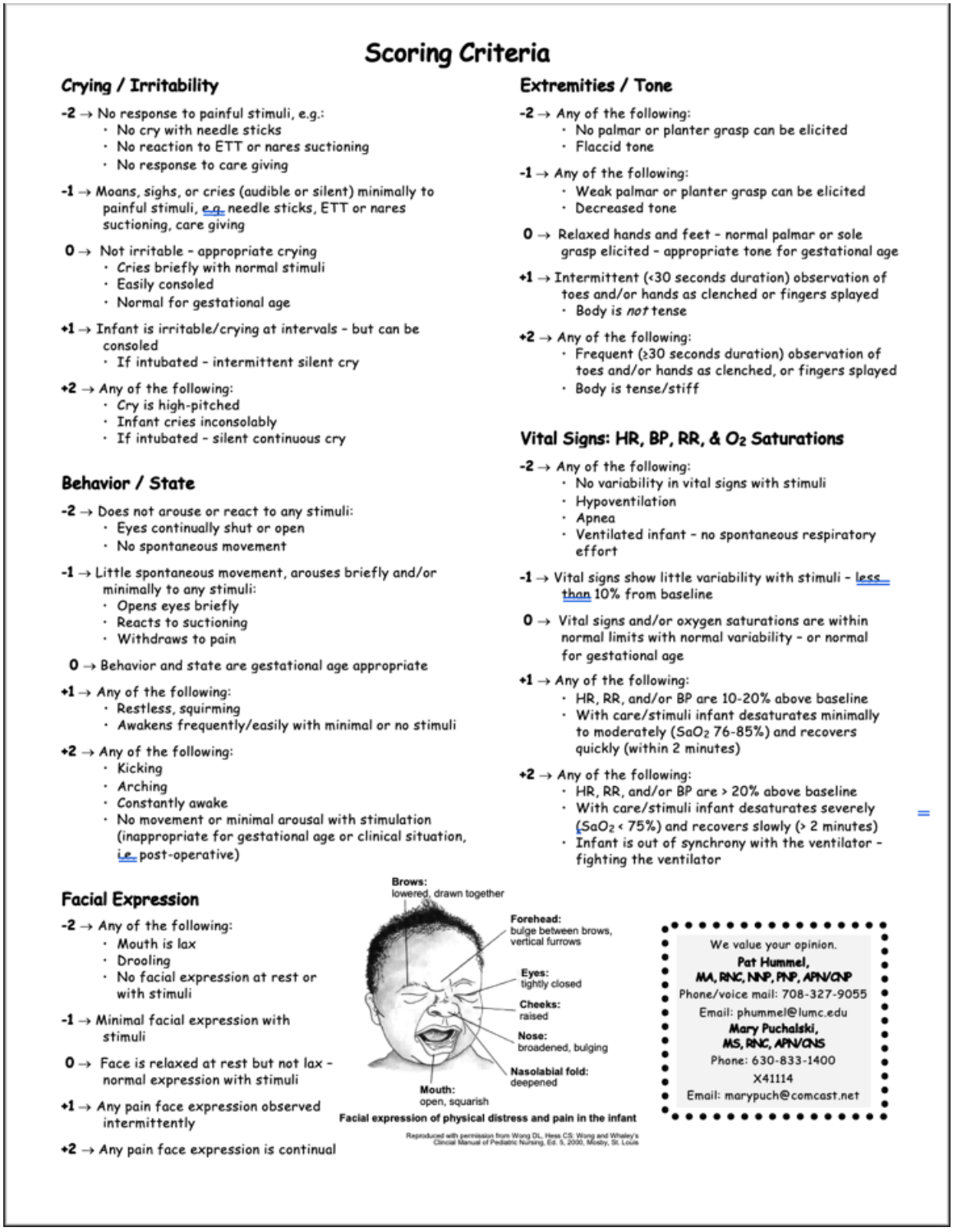
- Sedation is scored in addition to pain for each behavioral and physiological criteria to assess the infant's response to stimuli
- Sedation does not need to be assessed/scored with every pain assessment/score
- Sedation is scored from 0 → -2 for each behavioral and physiological criteria, then summed and noted as a negative score (0 → -10)
  - A score of 0 is given if the infant's response to stimuli is normal for their gestational age
- Desired levels of sedation vary according to the situation
  - "Deep sedation" → score of -10 to -5 as goal
  - "Light sedation" → score of -5 to -2 as goal
  - Deep sedation is not recommended unless an infant is receiving ventilatory support, related to the high potential for apnea and hypoventilation
- A negative score without the administration of opioids/ sedatives may indicate:
  - The premature infant's response to prolonged or persistent pain/stress
  - Neurologic depression, sepsis, or other pathology

Assessment of Pain/Agitation

- Pain assessment is the fifth vital sign – assessment for pain should be included in every vital sign assessment
- Pain is scored from 0 → +2 for each behavioral and physiological criteria, then summed
  - Points are added to the premature infant's pain score based on their gestational age to compensate for their limited ability to behaviorally or physiologically communicate pain
  - Total pain score is documented as a positive number (0 → +10)
- Treatment/interventions are indicated for scores > 3
  - Interventions for known pain/painful stimuli are indicated before the score reaches 3
- The goal of pain treatment/intervention is a score ≤ 3
- More frequent pain assessment indications:
  - Indwelling tubes or lines which may cause pain, especially with movement (e.g. chest tubes) → at least every 2-4 hours
  - Receiving analgesics and/or sedatives → at least every 2-4 hours
  - 30-60 minutes after an analgesic is given for pain behaviors to assess response to medication
  - Post-operative → at least every 2 hours for 24-48 hours, then every 4 hours until off medications

Pavulon/Paralysis

- It is impossible to behaviorally evaluate a paralyzed infant for pain
- Increases in heart rate and blood pressure may be the only indicator of a need for more analgesia
- Analgesics should be administered continuously by drip or around-the-clock dosing
  - Higher, more frequent doses may be required if the infant is post-op, has a chest tube, or other pathology (such as NEC) that would normally cause pain
  - Opioid doses should be increased by 10% every 3-5 days as tolerance will occur without symptoms of inadequate pain relief



Scoring Criteria

Crying / Irritability

-2 → No response to painful stimuli, e.g.:
- No cry with needle sticks
- No reaction to ETT or nares suctioning
- No response to care giving

-1 → Moans, sighs, or cries (audible or silent) minimally to painful stimuli, e.g. needle sticks, ETT or nares suctioning, care giving

0 → Not irritable – appropriate crying
- Cries briefly with normal stimuli
- Easily consoled
- Normal for gestational age

+1 → Infant is irritable/crying at intervals – but can be consoled
- If intubated – intermittent silent cry

+2 → Any of the following:
- Cry is high-pitched
- Infant cries inconsolably
- If intubated – silent continuous cry

Behavior / State

-2 → Does not arouse or react to any stimuli:
- Eyes continually shut or open
- No spontaneous movement

-1 → Little spontaneous movement, arouses briefly and/or minimally to any stimuli:
- Opens eyes briefly
- Reacts to suctioning
- Withdraws to pain

0 → Behavior and state are gestational age appropriate

+1 → Any of the following:
- Restless, squirming
- Awakens frequently/easily with minimal or no stimuli

+2 → Any of the following:
- Kicking
- Arching
- Constantly awake
- No movement or minimal arousal with stimulation (inappropriate for gestational age or clinical situation, i.e. post-operative)

Facial Expression

-2 → Any of the following:
- Mouth is lax
- Drooling
- No facial expression at rest or with stimuli

-1 → Minimal facial expression with stimuli

0 → Face is relaxed at rest but not lax – normal expression with stimuli

+1 → Any pain face expression observed intermittently

+2 → Any pain face expression is continual

Extremities / Tone

-2 → Any of the following:
- No palmar or planter grasp can be elicited
- Flaccid tone

-1 → Any of the following:
- Weak palmar or planter grasp can be elicited
- Decreased tone

0 → Relaxed hands and feet – normal palmar or sole grasp elicited – appropriate tone for gestational age

+1 → Intermittent (<30 seconds duration) observation of toes and/or hands as clenched or fingers splayed
- Body is *not* tense

+2 → Any of the following:
- Frequent (≥30 seconds duration) observation of toes and/or hands as clenched, or fingers splayed
- Body is tense/stiff

Vital Signs: HR, BP, RR, & O_2 Saturations

-2 → Any of the following:
- No variability in vital signs with stimuli
- Hypoventilation
- Apnea
- Ventilated infant – no spontaneous respiratory effort

-1 → Vital signs show little variability with stimuli – less than 10% from baseline

0 → Vital signs and/or oxygen saturations are within normal limits with normal variability – or normal for gestational age

+1 → Any of the following:
- HR, RR, and/or BP are 10-20% above baseline
- With care/stimuli infant desaturates minimally to moderately (SaO_2 76-85%) and recovers quickly (within 2 minutes)

+2 → Any of the following:
- HR, RR, and/or BP are > 20% above baseline
- With care/stimuli infant desaturates severely (SaO_2 < 75%) and recovers slowly (> 2 minutes)
- Infant is out of synchrony with the ventilator – fighting the ventilator

Facial expression of physical distress and pain in the infant

Reproduced with permission from Wong DL, Hess CS: Wong and Whaley's Clinical Manual of Pediatric Nursing, Ed. 5, 2000, Mosby, St. Louis

We value your opinion.
Pat Hummel,
MA, RNC, NNP, PNP, APN/CNP
Phone/voice mail: 708-327-9055
Email: phummel@lumc.edu
Mary Puchalski,
MS, RNC, APN/CNS
Phone: 630-833-1400
X41114
Email: marypuch@comcast.net

Figure 6. N-PASS scoring sheet and interpretation instructions

Appendix 3: Survey

Postoperative Pain Prescribing Practices in Canadian NICU's: A National Survey

Investigators:

Staff Principal Investigator:
Dr. J. Mark Walton
Division of Pediatric General Surgery, McMaster University (905) 525-9140 ext.75244
waltonj@mcmaster.ca

Resident Principal Investigator:
Dr. Victoria Archer
Division of General Surgery,
McMaster University (506)-721-9285
vicki.archer@medportal.ca

Introduction
You are invited to participate in a survey about postoperative pain management in Canadian Neonatal Intensive Care Units (NICUs). The current practice patterns for the management of postoperative pain in patients in NICUs in Canada are unknown; last studied in 1997 and 2011. Significant advancements in postoperative pain management have been made. One such advancement has been the use of intravenous acetaminophen. Furthermore, the unique perspectives of surgeons and anesthesiologists have yet to be studied. We hope to capture the general prescribing practices of neonatologists, surgeons, and anesthesiologists and understand the perceived benefits and barriers to using intravenous acetaminophen for postoperative pain.

Participation
Participation in this study is voluntary. You may refuse to take part in the research or exit the survey at any time without penalty. You are free to decline to answer any question. If you consent, you will complete a 5-10 minute online survey.

Benefits
There are no direct benefits anticipated by participating in this survey, nor is there financial compensation. However, it will help us better understand national postoperative pain prescribing practices, specifically understanding perceptions of the utility of intravenous acetaminophen. We plan to publish and present our findings.

Risks
While the investigators will make all efforts to keep your information confidential, there

is still a chance of a data breach. We will minimize these risks by not collecting your name, phone number, email address, IP address or other personal information. Although there are a limited number of neonatologists, pediatric surgeons, and pediatric anesthesiologists in Canada, increasing the chance of identification, we will only present aggregate data. After collection, survey responses will be encrypted using industry-standard techniques and stored on a password and firewall-protected survey software. It will be encrypted and stored on McMaster Universities cloud-based OneDrive platform. It will only be accessed by members of the research team. It will be securely destroyed after the study has been completed. For the purposes of ensuring proper monitoring of the research study, it is possible that representatives of the Hamilton Integrated REB (HiREB), this institution, and affiliated sites or regulatory authorities may consult your original research data to check that the information collected for the study is correct and follows proper laws and guidelines. By participating in this study, you authorize such access.

Conflict of Interest
The Investigators have not received funding or other financial compensation, nor are there conflicts of interest to declare.

Contact
If you have any questions about this study, please contact the investigators with the contact information listed above. This study has been reviewed by the Hamilton Integrated Research Ethics Board (HIREB). The HIREB is responsible for ensuring that participants are informed of the risks associated with the research and that participants are free to decide if participation is right for them. If you have any questions about your rights as a research participant, please call the Office of the Chair, Hamilton Integrated Research Ethics Board, at 905.521.2100 x 42013.

Consent
By completing this survey, you are providing consent to participate in this study. By participating in this study, you do not waive any rights to which you may be entitled under the law.

Postoperative Pain Prescribing Practices in Canadian NICU's: A National Survey

Practice Demographics

The following questions are designed to collect information on your training and current practice.

1. *In which subspeciality do you currently practice? (This includes adult and pediatric mixed practices)*

Neonatology

Pediatric

Anesthesiology

Pediatric Cardiac

Surgery

Pediatric

Otolaryngology

Pediatric General Surgery

Pediatric Neurosurgery

Pediatric Ophthalmology

Pediatric Plastic Surgery

Pediatric

Urology

Pediatric

Vascular

Surgery

Other (please specify):

2. How many years have you been in practice (excluding residency and fellowship)?

3. At which hospital did you complete your fellowship training?

4. At which hospital do you currently practice?

NICU Demographics

This section is designed to capture information on the NICU you currently work in.

5. What level(s) of NICU care does your hospital currently provide? (Select all that apply)

Level 1: basic newborn care, healthy term babies

Level 2: advanced newborn care, moderately ill infants

Level 3: subspecialty newborn care, critically ill infants requiring the highest level of care

6. Which surgical services are available at your institution? (Select all that apply)

Pediatric Cardiac Surgery

Pediatric Otolaryngology

Pediatric General Surgery Pediatric

Neurosurgery Pediatric

Ophthalmology Pediatric Plastic

Surgery

Pediatric Urology Pediatric

Vascular Surgery

7. *How often do you work with residents and/or fellows?*

Always

Usually

Sometimes

Rarely

Never

8. In your NICU which service is primarily responsible for managing postoperative pain (i.e. assessing the patient's pain and writing the primary orders for pain management outside of the intraoperative and immediate postoperative phase of care)?

Anesthesia/Acute

Pain Service

Neonatology

Surgery

Other (please specify)

9. Does your NICU have any standardized postoperative pain order sets?

Yes

No

Unsure

10. Does your NICU involve pharmacists in postoperative pain management (i.e. attending and providing input on bedside or multidisciplinary rounds, providing input on pain medication regimes)?

Yes

No

Unsure

13. *How are the pharmacists in your NICU involved in postoperative pain management? (Select all that apply)*

Attending bedside rounds

Attending multidisciplinary rounds

Reviewing medication orders and providing suggestions

Unsure

Other (please specify)

13. If applicable, please provide any specific comments about unique or notable practices in your NICU as it relates to postoperative pain management (i.e. order sets, multidisciplinary teams, drug availability).

Prescribing Practices

The following questions are designed to capture the general prescribing practices for postoperative pain in Canadian NICUs. If you do not routinely manage postoperative pain in the NICU you will automatically be redirected to the next section.

13. In your current practice, do you routinely manage postoperative pain (i.e. are you assessing the patient's pain and writing the primary orders for pain management outside of the intraoperative and immediate postoperative phase of care)?

Yes

No

Unsure

The following questions will collect information on your approach to postoperative pain in the NICU.

14. In your current practice, what is your most frequent **first-line** agent for postoperative pain in NICU patients?

Opioids

Non-steroidal anti-inflammatory drugs (NSAIDs)

Acetaminophen

Antidepressants

Topical anesthetics

Muscle relaxants

Non-pharmacologic therapies

Regional anesthesia (i.e. epidurals)

Other (please specify)

14. In your current practice, what is your most frequent **second-line** agent for postoperative pain in NICU patients?

Opioids

Non-steroidal anti-inflammatory drugs (NSAIDs)

Acetaminophen

Antidepressants

Topical anesthetics

Muscle relaxants

Non-pharmacologic therapies

Regional anesthesia (i.e. epidurals)

I primarily use a single agent to manage pain

Other (please specify)

15. In your current practice, how often do you prescribe **opioids** for postoperative pain management for NICU patients?

Always

Usually

Sometimes

Rarely

Never

16. *What is the most common **opioid** you prescribe for postoperative pain management in the NICU?*

17. *In your current practice, how often do you prescribe **non-opioids** for postoperative pain management for NICU patients?*

    Always

    Usually

    Sometimes

    Rarely

    Never

18. *What is the most common **non-opioid** you prescribe for postoperative pain management in the NICU?*

19. *In your current practice, how often do you prescribe **non-pharmacologic** therapies for postoperative pain in NICU patients?*

    Always

    Usually

    Sometimes

    Rarely

    Never

20. *What is the most common **non-pharmacologic adjunct** you utilize for postoperative pain management in the NICU?*

21. *In NICU patients you have cared for who have had surgery, how often do you feel that their pain is adequately controlled?*

    Always

    Usually

    Sometimes

    Rarely

    Never

22. If applicable, please provide any specific comments about unique or notable practices in your approach to managing postoperative pain in NICU patients (i.e. pharmacologic regimes, medication titration, non-pharmacologic adjuncts).

Perspectives on Intravenous Acetaminophen

The following questions are designed to gain an understanding of your perspective on the utility of intravenous acetaminophen for postoperative pain in the NICU population. If you have not used intravenous acetaminophen for postoperative pain, you will be automatically redirected to the following section.

23. Does your current NICU have intravenous acetaminophen available for postoperative pain?

    Yes

    No

    Unsure

24. How long has your NICU had intravenous acetaminophen available for postoperative pain?

    Less than 1 year

    1-3 years

    3-5 years

    5-10 years

    More than 10 years

    Unsure

25. Have you ever used intravenous acetaminophen for postoperative pain in NICU patients?

    Yes

    No

    Unsure

26. Have you noted clinical benefits with the use of intravenous acetaminophen for postoperative pain in NICU patients?

    Yes

    No

    Unsure

27. Please describe the benefit(s) you have identified in NICU patients.

28. Have you noted clinical harm associated with the use of intravenous

acetaminophen for postoperative pain in NICU patients?

Yes

No

Unsure

29. Please describe the harm(s) you have identified in NICU patients.

30. What do you perceive as barriers to the more widespread use of intravenous acetaminophen in NICU patients?

31. If applicable, please provide any additional comments regarding the use of IV acetaminophen in the NICU for postoperative pain not yet addressed by this survey.

Demographics

These questions are designed to understand the demographics of our respondents.

32. What is your age?

33. How do you identify your gender or gender expression? (Select all that apply)

Gender Fluid

Gender Nonconforming

Genderqueer

Man

Nonbinary

Trans Woman

Trans Man

Two-Spirit

Woman

Unsure or questioning

Prefer not to answer

My identity is not listed, or I would prefer to self-identify

References

1. Yaster, M., P.P. McNaull, and P.J. Davis, *The opioid epidemic in pediatrics: a 2020 update.* Current Opinion in Anesthesiology, 2020. **33**(3): p. 327-334.
2. Winstanley, E.L. and A.N. Stover, *The Impact of the Opioid Epidemic on Children and Adolescents.* Clinical Therapeutics, 2019. **41**(9): p. 1655-1662.
3. Daley, D.C., et al., *Forgotten but not gone: The impact of the opioid epidemic and other substance use disorders on families and children.* Commonwealth, 2018. **20**(2-3).
4. Mak, W.Y., et al., *Pharmacotherapy for acute pain in children: current practice and recent advances.* Expert opinion on pharmacotherapy, 2011. **12**(6): p. 865-881.
5. Chiaretti, A., et al., *Current practice and recent advances in pediatric pain management.* Eur Rev Med Pharmacol Sci, 2013. **17**(Suppl 1): p. 112-126.
6. Rodkey, E.N. and R.P. Riddell, *The infancy of infant pain research: the experimental origins of infant pain denial.* The Journal of Pain, 2013. **14**(4): p. 338-350.
7. Anand, K.J.S., W.G. Sippell, and A.A. Green, *RANDOMISED TRIAL OF FENTANYL ANAESTHESIA IN PRETERM BABIES UNDERGOING SURGERY: EFFECTS ON THE STRESS RESPONSE.* The Lancet, 1987. **329**(8527): p. 243-248.
8. Anand, K.J. and P.R. Hickey, *Halothane-morphine compared with high-dose sufentanil for anesthesia and postoperative analgesia in neonatal cardiac surgery.* N Engl J Med, 1992. **326**(1): p. 1-9.
9. Obara, H., et al., *Plasma cortisol levels in paediatric anaesthesia.* Canadian Anaesthetists' Society Journal, 1984. **31**(1): p. 24-27.
10. Anand, K., *Hormonal and metabolic functions of neonates and infants undergoing surgery.* Current Opinion in Cardiology, 1986. **1**(5): p. 681-689.
11. De Lima, J., et al., *Sensory hyperinnervation after neonatal skin wounding: effect of bupivacaine sciatic nerve block.* British journal of anaesthesia, 1999. **83**(4): p. 662-664.
12. Anand, K.J.S., *Clinical Importance of Pain and Stress in Preterm Neonates.* Neonatology, 1998. **73**(1): p. 1-9.
13. Bouza, H., *The impact of pain in the immature brain.* J Matern Fetal Neonatal Med, 2009. **22**(9): p. 722-32.
14. Eckstein Grunau, R., *Early pain in preterm infants: A model of long-term effects.* Clinics in Perinatology, 2002. **29**(3): p. 373-394.
15. Taddio, A., et al., *Effect of neonatal circumcision on pain responses during vaccination in boys.* The Lancet, 1995. **345**(8945): p. 291-292.
16. Taddio, A., et al., *Effect of neonatal circumcision on pain response during subsequent routine vaccination.* The Lancet, 1997. **349**(9052): p. 599-603.

17. Peters, J.W.B., et al., *Major Surgery Within the First 3 Months of Life and Subsequent Biobehavioral Pain Responses to Immunization at Later Age: A Case Comparison Study.* Pediatrics, 2003. **111**(1): p. 129-135.
18. Walker, S.M. *Long-term effects of neonatal pain*. in *Seminars in Fetal and Neonatal Medicine*. 2019. Elsevier.
19. Valeri, B.O., L. Holsti, and M.B. Linhares, *Neonatal pain and developmental outcomes in children born preterm: a systematic review.* The Clinical journal of pain, 2015. **31**(4): p. 355-362.
20. Vinall, J., et al., *Invasive Procedures in Preterm Children: Brain and Cognitive Development at School Age.* Pediatrics, 2014. **133**(3): p. 412-421.
21. Hunt, R.W., et al., *Early surgery and neurodevelopmental outcomes of children born extremely preterm.* Archives of Disease in Childhood - Fetal and Neonatal Edition, 2018. **103**(3): p. F227.
22. Walker, S.M., et al., *Somatosensory function and pain in extremely preterm young adults from the UK EPICure cohort: sex-dependent differences and impact of neonatal surgery.* British Journal of Anaesthesia, 2018. **121**(3): p. 623-635.
23. Puia-Dumitrescu, M., et al., *Assessment of 2-Year Neurodevelopmental Outcomes in Extremely Preterm Infants Receiving Opioids and Benzodiazepines.* JAMA Network Open, 2021. **4**(7): p. e2115998-e2115998.
24. Johnston, C.C., et al., *A cross-sectional survey of pain and pharmacological analgesia in Canadian neonatal intensive care units.* Clin J Pain, 1997. **13**(4): p. 308-12.
25. Hall, R.W. and K.J.S. Anand, *Pain management in newborns.* Clinics in perinatology, 2014. **41**(4): p. 895-924.
26. Hall, R.W. and K.J. Anand, *Pain management in newborns.* Clin Perinatol, 2014. **41**(4): p. 895-924.
27. Menon, G., et al., *Morphine analgesia and gastrointestinal morbidity in preterm infants: secondary results from the NEOPAIN trial.* Archives of Disease in Childhood - Fetal and Neonatal Edition, 2008. **93**(5): p. F362.
28. Simons, S.H.P. and K.J.S. Anand, *Pain control: Opioid dosing, population kinetics and side-effects.* Seminars in Fetal and Neonatal Medicine, 2006. **11**(4): p. 260-267.
29. Anand, K.J.S. and a.t.I.E.-B.G.f.N. Pain, *Consensus Statement for the Prevention and Management of Pain in the Newborn.* Archives of Pediatrics & Adolescent Medicine, 2001. **155**(2): p. 173-180.
30. Visoiu, M. *Evolving approaches in neonatal postoperative pain management*. in *Seminars in Pediatric Surgery*. 2022. Elsevier.
31. De Graaf, J., et al., *Long-term effects of routine morphine infusion in mechanically ventilated neonates on children's functioning: five-year follow-up of a randomized controlled trial.* Pain, 2011. **152**(6): p. 1391-1397.
32. De Graaf, J., et al., *Does neonatal morphine use affect neuropsychological outcomes at 8 to 9 years of age?* PAIN®, 2013. **154**(3): p. 449-458.

33. Ferguson, S.A., et al., *A pilot study of preemptive morphine analgesia in preterm neonates: Effects on head circumference, social behavior, and response latencies in early childhood.* Neurotoxicology and Teratology, 2012. **34**(1): p. 47-55.
34. Zwicker, J.G., et al., *Smaller Cerebellar Growth and Poorer Neurodevelopmental Outcomes in Very Preterm Infants Exposed to Neonatal Morphine.* The Journal of Pediatrics, 2016. **172**: p. 81-87.e2.
35. van den Bosch, G.E., et al., *Prematurity, opioid exposure and neonatal pain: do they affect the developing brain?* Neonatology, 2015. **108**(1): p. 8-15.
36. Anand, K.J., et al., *Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial.* Lancet, 2004. **363**(9422): p. 1673-82.
37. Joseph, J.M., et al., *Gaps in standardized postoperative pain management quality measures: A systematic review.* Surgery, 2021.
38. Horlocker, T.T.M.D., *Pain Management in Total Joint Arthroplasty: A Historical Review.* Orthopedics (Online), 2010. **33**(9): p. 14-19.
39. Zernikow, B. and T. Hechler, *Pain therapy in children and adolescents.* Dtsch Arztebl Int, 2008. **105**(28-29): p. 511-21; quiz 521-2.
40. Boric, K., et al., *Interventions for postoperative pain in children: An overview of systematic reviews.* Paediatric Anaesthesia, 2017. **27**(9): p. 893-904.
41. Johnston, C., et al., *Pain in Canadian NICUs: Have We Improved Over the Past 12 Years?* The Clinical Journal of Pain, 2011. **27**(3): p. 225-232.
42. Debillon, T., et al., *Pain management in French neonatal intensive care units.* Acta Paediatr, 2002. **91**(7): p. 822-6.
43. Fernandez, C.V. and E.P. Rees, *Pain management in Canadian level 3 neonatal intensive care units.* CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 1994. **150**(4): p. 499-504.
44. Byrd, P.J., I. Gonzales, and V. Parsons, *Exploring Barriers to Pain Management in Newborn Intensive Care Units: A Pilot Survey of NICU Nurses.* Advances in Neonatal Care, 2009. **9**(6).
45. ten Barge, J.A., et al., *Current pain management practices for preterm infants with necrotizing enterocolitis: a European survey.* Pediatric Research, 2023.
46. Macario, A. and M.A. Royal, *A Literature Review of Randomized Clinical Trials of Intravenous Acetaminophen (Paracetamol) for Acute Postoperative Pain.* Pain Practice, 2011. **11**(3): p. 290-296.
47. Apfel, C.C., et al., *Intravenous acetaminophen reduces postoperative nausea and vomiting: a systematic review and meta-analysis.* Pain®, 2013. **154**(5): p. 677-689.
48. Yeh, Y.-C. and P. Reddy, *Clinical and Economic Evidence for Intravenous Acetaminophen.* Pharmacotherapy, 2012. **32**(6): p. 559-579.
49. Korpela, R., P. Korvenoja, and O.A. Meretoja, *Morphine-sparing effect of acetaminophen in pediatric day-case surgery.* Anesthesiology, 1999. **91**(2): p. 442-447.
50. Arana, A., N.S. Morton, and T.G. Hansen, *Treatment with paracetamol in infants.* Acta Anaesthesiologica Scandinavica, 2001. **45**(1): p. 20-29.

51. Bartelink, I.H., et al., *Guidelines on Paediatric Dosing on the Basis of Developmental Physiology and Pharmacokinetic Considerations.* Clinical Pharmacokinetics, 2006. **45**(11): p. 1077-1097.
52. Holmer Pettersson, P., J. Jakobsson, and A. Owall, *Plasma concentrations following repeated rectal or intravenous administration of paracetamol after heart surgery.* Acta Anaesthesiologica Scandinavica, 2006. **50**(6): p. 673-7.
53. Holmer Pettersson, P., A. Owall, and J. Jakobsson, *Early bioavailability of paracetamol after oral or intravenous administration.* Acta Anaesthesiologica Scandinavica, 2004. **48**(7): p. 867-70.
54. Shastri, N., *Intravenous Acetaminophen Use in Pediatrics.* Pediatric Emergency Care, 2015. **31**(6): p. 444-448.
55. Nour, C., et al., *Analgesic effectiveness of acetaminophen for primary cleft palate repair in young children: a randomized placebo controlled trial.* Pediatric Anesthesia, 2014. **24**(6): p. 574-581.
56. Alhashemi, J.A. and M.E. Daghistani, *Effect of intraoperative intravenous acetaminophen vs. intramuscular meperidine on pain and discharge time after paediatric dental restoration.* European Journal of Anaesthesiology, 2007. **24**(2): p. 128-133.
57. Ohlsson, A. and P.S. Shah, *Paracetamol (acetaminophen) for prevention or treatment of pain in newborns.* Cochrane Database of Systematic Reviews, 2020. **1**: p. CD011219.
58. Zhu, A., H.A. Benzon, and T.A. Anderson, *Evidence for the Efficacy of Systemic Opioid-Sparing Analgesics in Pediatric Surgical Populations: A Systematic Review.* Anesthesia and Analgesia, 2017. **125**(5): p. 1569-1587.
59. Lavonas, E.J., K.M. Reynolds, and R.C. Dart, *Therapeutic Acetaminophen Is Not Associated With Liver Injury in Children: A Systematic Review.* Pediatrics, 2010. **126**(6): p. E1430-E1444.
60. Allegaert, K., *A Critical Review on the Relevance of Paracetamol for Procedural Pain Management in Neonates.* Frontiers in Pediatrics, 2020. **8**.
61. Allegaert, K., et al., *The pharmacokinetics of a high intravenous dose of paracetamol after caesarean delivery: the effect of gestational age.* European Journal of Anaesthesiology, 2012. **29**(10): p. 484-8.
62. Allegaert, K. and G. Naulaers, *Haemodynamics of intravenous paracetamol in neonates.* European Journal of Clinical Pharmacology, 2010. **66**(9): p. 855-858.
63. Allegaert, K., et al., *The paracetamol concentration-effect relation in neonates.* Pediatric Anesthesia, 2013. **23**(1): p. 45-50.
64. Allegaert, K., et al., *Systematic evaluation of pain in neonates: effect on the number of intravenous analgesics prescribed.* European Journal of Clinical Pharmacology, 2003. **59**(2): p. 87-90.
65. Archer, V., et al., *Intravenous acetaminophen for postoperative pain control after open abdominal and thoracic surgery in pediatric patients: a systematic review and meta-analysis.* Pediatric Surgery International, 2022. **39**(1): p. 7.
66. Swegle, J.M. and C.D. Logemann, *Management of common opioid-induced adverse effects.* American family physician, 2006. **74**(8): p. 1347-1354.

67. Pizzi, L.T., et al., *Relationship between potential Opioid-Related adverse effects and hospital length of stay in patients receiving opioids after orthopedic surgery.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2012. **32**(6): p. 502-514.
68. Attarian, S., et al., *The Neurodevelopmental Impact of Neonatal Morphine Administration.* Brain Sciences, 2014. **4**(2): p. 321-334.
69. Grunau, R.E., L. Holsti, and J.W. Peters. *Long-term consequences of pain in human neonates*. in *Seminars in Fetal and Neonatal Medicine*. 2006. Elsevier.
70. Bosenberg, A. and R.P. Flick, *Regional anesthesia in neonates and infants.* Clinics in perinatology, 2013. **40**(3): p. 525-538.
71. Fitzgerald, M. and S. Beggs, *Book Review: The neurobiology of pain: Developmental aspects.* The Neuroscientist, 2001. **7**(3): p. 246-257.
72. Maxwell, L.G., C.P. Malavolta, and M.V. Fraga, *Assessment of pain in the neonate.* Clinics in perinatology, 2013. **40**(3): p. 457-469.
73. Minami, K., et al., *Association Between Sternotomy Versus Thoracotomy and the Prevalence and Severity of Chronic Postsurgical Pain After Mitral Valve Repair: An Observational Cohort Study.* Journal of Cardiothoracic and Vascular Anesthesia, 2021. **35**(10): p. 2937-2944.
74. Allvin, R., et al., *Open versus laparoscopic surgery: does the surgical technique influence pain outcome? Results from an international registry.* Pain research and treatment, 2016. **2016**.
75. Rawal, N., *Current issues in postoperative pain management.* European Journal of Anaesthesiology | EJA, 2016. **33**(3): p. 160-171.
76. Veritas Health Innovation, *Covidence Systematic Review Software*. 2021: Melbourne, Australia.
77. Eldridge, S., et al., *Revised Cochrane risk of bias tool for randomized trials (RoB 2.0): additional considerations for cluster-randomized trials.* 2016.
78. Boutron, I., et al. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3*. Chapter 7: Considering bias and conflicts of interest among the included studies 2022 February 2022 [cited 2022 March 2022]; Available from: https://training.cochrane.org/handbook/current/chapter-07.
79. McMaster University and Evidence Prime, *GRADEpro GDT: Gradepro Guideline Development Tool.* 2021.
80. The Cochrane Collaboration, *Review Manager (RevMan)*. 2020, The Cochrane Collaboration,.
81. Cohen, J., *Statistical power analysis for the behavioral sciences*. 2013: Routledge.
82. Ceelie, I., et al., *Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial.* JAMA, 2013. **309**(2): p. 149-154.
83. Wan, X., et al., *Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range.* BMC Medical Research Methodology, 2014. **14**(1): p. 135.
84. Deeks, J., J. Higgins, and D. Altman. *Chapter 9: Summarizing study characteristics and preparing for synthesis*. Cochrane Handbook for Systematic

Reviews of Intervention 2021 [cited 2021 January]; Available from: https://training.cochrane.org/handbook/current/chapter-09.
85. Arora, M., et al., *Comparison of two doses of iv paracetamol as adjunct to caudal ropivacaine in children undergoing lower abdominal surgery: A prospective, randomized, controlled, double blind trial.* Regional Anesthesia and Pain Medicine, 2013. **38**(5): p. E144-E145.
86. Majeed, M.N.A. and Z.M. Anwer, *Comparing the efficacy of paracetamol, diclofenac, and ketorolac on post-appendectomy outcomes in children and adolescents.* Iraqi journal of pharmaceutical sciences, 2020. **29**(1): p. 123-133.
87. Rugyte, D. and J. Gudaityte, *Intravenous Paracetamol in Adjunct to Intravenous Ketoprofen for Postoperative Pain in Children Undergoing General Surgery: A Double-Blinded Randomized Study.* Medicina-Lithuania, 2019. **55**(4).
88. Hong, J.Y., et al., *Fentanyl sparing effects of combined ketorolac and acetaminophen for outpatient inguinal hernia repair in children.* Journal of Urology, 2010. **183**(4): p. 1551-5.
89. Dehghan, K., et al., *The Comparison of the Analgesic Effect of Intravenous Acetaminophen with Fentanyl in Thoracic and Abdominal Surgeries of Newborns.* International Journal of Pediatrics-Mashhad, 2019. **7**(7): p. 9773-9781.
90. Murat, I., et al., *Tolerance and analgesic efficacy of a new i.v. paracetamol solution in children after inguinal hernia repair.* Pediatric Anesthesia, 2005. **15**(8): p. 663-670.
91. Solanki, N., S. Engineer, and P. Vecham, *Comparison of epidural versus systemic analgesia for major surgeries in neonates and infants.* Journal of clinical neonatology, 2017. **6**(1): p. 23-28.
92. Hong, J.-Y., et al., *Fentanyl-sparing Effect of Acetaminophen as a Mixture of Fentanyl in Intravenous Parent-/Nurse-controlled Analgesia after Pediatric Ureteroneocystostomy.* Anesthesiology, 2010. **113**(3): p. 672-677.
93. Murat, I., et al., *Tolerance and analgesic efficacy of a new i.v. paracetamol solution in children after inguinal hernia repair.* Paediatric anaesthesia, 2005. **15**(8): p. 663-670.
94. Pagano, M. and K. Gauvreau, *Principles of biostatistics*. 2018: CRC Press.
95. Rosier, E.M., M.J. Iadarola, and R.C. Coghill, *Reproducibility of pain measurement and pain perception.* Pain, 2002. **98**(1): p. 205-216.
96. Cohen, L.L., et al., *Evidence-based assessment of pediatric pain.* Journal of pediatric psychology, 2008. **33**(9): p. 939-957.
97. Giordano, V., et al., *Pain and sedation scales for neonatal and pediatric patients in a preverbal stage of development: a systematic review.* JAMA pediatrics, 2019. **173**(12): p. 1186-1197.
98. Harder, H.J. and A.Z. Murphy, *Early life opioid exposure and potential long-term effects.* Neurobiology of Stress, 2019. **10**: p. 100156.
99. Chung, C.P., et al., *Outpatient opioid prescriptions for children and opioid-related adverse events.* Pediatrics, 2018. **142**(2).
100. Johnston, C., et al., *Pain in Canadian NICUs: Have We Improved Over the Past 12 Years?* The Clinical Journal of Pain, 2011. **27**(3).

101. LAGO, P., et al., *Pain management in the neonatal intensive care unit: a national survey in Italy.* Pediatric Anesthesia, 2005. **15**(11): p. 925-931.
102. Wren, A.A., et al., *Multidisciplinary pain management for pediatric patients with acute and chronic pain: a foundational treatment approach when prescribing opioids.* Children, 2019. **6**(2): p. 33.
103. Odell, S. and D.E. Logan, *Pediatric pain management: the multidisciplinary approach.* Journal of pain research, 2013. **6**: p. 785.
104. Hällström, M., et al., *Frequency of and risk factors for necrotizing enterocolitis in infants born before 33 weeks of gestation.* Acta Paediatrica, 2003. **92**(1): p. 111-113.
105. Sharma, A., et al., *A Consensus-Based Checklist for Reporting of Survey Studies (CROSS).* J Gen Intern Med, 2021. **36**(10): p. 3179-3187.
106. Momentive, *SurveyMonkey*. 2022: United Sates of America.
107. Chyung, S.Y., et al., *Evidence-Based Survey Design: The Use of a Midpoint on the Likert Scale.* Performance Improvement, 2017. **56**(10): p. 15-23.
108. Singer, E. and M.P. Couper, *Some methodological uses of responses to open questions and other verbatim comments in quantitative surveys.* Methods, data, analyses: a journal for quantitative methods and survey methodology (mda), 2017. **11**(2): p. 115-134.
109. Emil, S., et al., *The Canadian pediatric surgery workforce: A 5-year prospective study.* Journal of Pediatric Surgery, 2019. **54**(5): p. 1009-1012.
110. Rosen, H.D., D. Mervitz, and J.P. Cravero, *Pediatric emergence delirium: Canadian Pediatric Anesthesiologists' experience.* Pediatric Anesthesia, 2016. **26**(2): p. 207-212.
111. Canadian Neonatal Network. *Network Report 2017*. 2017 [cited 2022 October]; Available from: https://www.canadianneonatalnetwork.org/portal/Portals/0/Annual%20Reports/CNN%20Report_2012%20to%202017.pdf.
112. Hibberts, M., R. Burke Johnson, and K. Hudson, *Common survey sampling techniques*, in *Handbook of survey methodology for the social sciences*. 2012, Springer. p. 53-74.
113. Cochran, W.G., *Sampling techniques*. 1977: John Wiley & Sons.
114. Association, G.A.o.t.W.M., *World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.* The Journal of the American College of Dentists, 2014. **81**(3): p. 14-18.
115. Guideline, I.H.T., *Guideline for good clinical practice.* J Postgrad Med, 2001. **47**(3): p. 199-203.
116. Rao, J.N. and A.J. Scott, *The analysis of categorical data from complex sample surveys: chi-squared tests for goodness of fit and independence in two-way tables.* Journal of the American statistical association, 1981. **76**(374): p. 221-230.
117. IBM®, *SPSS® Statistics*. 2019.
118. Beasley, T.M. and R.E. Schumacker, *Multiple regression approach to analyzing contingency tables: Post hoc and planned comparison procedures.* The Journal of Experimental Education, 1995. **64**(1): p. 79-93.

119. Armstrong, R.A., *When to use the B onferroni correction.* Ophthalmic and Physiological Optics, 2014. **34**(5): p. 502-508.
120. Charmaz, K., *Constructing grounded theory: A practical guide through qualitative analysis*. 2006: sage.
121. Brick, J.M. and G. Kalton, *Handling missing data in survey research.* Statistical methods in medical research, 1996. **5**(3): p. 215-238.
122. Peytchev, A., R.K. Baxter, and L.R. Carley-Baxter, *Not All Survey Effort is Equal: Reduction of Nonresponse Bias and Nonresponse Error.* Public Opinion Quarterly, 2009. **73**(4): p. 785-806.
123. Toepoel, V. and M. Schonlau, *Dealing with nonresponse: Strategies to increase participation and methods for postsurvey adjustments.* Mathematical Population Studies, 2017. **24**(2): p. 79-83.
124. Bourgeois, F.T., et al., *Cost implications of escalating intravenous acetaminophen use in children.* JAMA pediatrics, 2019. **173**(5): p. 489-491.
125. Cunningham, C.T., et al., *Exploring physician specialist response rates to web-based surveys.* BMC Medical Research Methodology, 2015. **15**(1): p. 32.
126. VanGeest, J.B., T.P. Johnson, and V.L. Welch, *Methodologies for improving response rates in surveys of physicians: a systematic review.* Evaluation & the health professions, 2007. **30**(4): p. 303-321.
127. Cook, J.V., H.O. Dickinson, and M.P. Eccles, *Response rates in postal surveys of healthcare professionals between 1996 and 2005: An observational study.* BMC Health Services Research, 2009. **9**(1): p. 160.
128. James, K.M., et al., *Getting Physicians to Respond: The Impact of Incentive Type and Timing on Physician Survey Response Rates.* Health Services Research, 2011. **46**(1p1): p. 232-242.
129. Fitzgerald, M., C. Millard, and N. McIntosh, *Cutaneous hypersensitivity following peripheral tissue damage in newborn infants and its reversal with topical anaesthesia.* PAIN, 1989. **39**(1).
130. Allegaert, K., S. Simons, and J. Van Den Anker, *Research on medication use in the neonatal intensive care unit.* Expert review of clinical pharmacology, 2019. **12**(4): p. 343-353.
131. Stevens, B., S. Gibbins, and L.S. Franck, *TREATMENT OF PAIN IN THE NEONATAL INTENSIVE CARE UNIT.* Pediatric Clinics of North America, 2000. **47**(3): p. 633-650.
132. Committee On, F., et al., *Prevention and Management of Procedural Pain in the Neonate: An Update.* Pediatrics, 2016. **137**(2): p. e20154271.
133. Allegaert, K., F. Veyckemans, and D. Tibboel, *Clinical practice: analgesia in neonates.* European Journal of Pediatrics, 2009. **168**(7): p. 765-770.
134. Yu, G., Q.-S. Zheng, and G.-F. Li, *Similarities and Differences in Gastrointestinal Physiology Between Neonates and Adults: a Physiologically Based Pharmacokinetic Modeling Perspective.* The AAPS Journal, 2014. **16**(6): p. 1162-1166.
135. Johnston, C.C.l. and B.J. Stevens, *Experience in a Neonatal Intensive Care Unit Affects Pain Response.* Pediatrics, 1996. **98**(5): p. 925-930.

136. Network, C.N. *The Canadian Neonatal Network Abstractor's Guide*. 2015 [cited 2022 February 10]; 2.2:[Available from: http://www.canadianneonatalnetwork.org/portal/Portals/0/CNN%20Manuals/CNN%20Manual_20150814.pdf.
137. Davidson, J.M., et al., *A randomized trial of intravenous acetaminophen versus indomethacin for treatment of hemodynamically significant PDAs in VLBW infants.* Journal of Perinatology, 2021. **41**(1): p. 93-99.
138. Palmer, G.M., et al., *I.V. acetaminophen pharmacokinetics in neonates after multiple doses.* British Journal of Anaesthesia, 2008. **101**(4): p. 523-530.
139. Squires, R.H., et al., *Acute liver failure in children: The first 348 patients in the pediatric acute liver failure study group.* The Journal of Pediatrics, 2006. **148**(5): p. 652-658.e2.
140. Taylor, S.A. and P.F. Whitington, *Neonatal acute liver failure.* Liver Transpl, 2016. **22**(5): p. 677-85.
141. Ciocca, M. and F. Álvarez, *Neonatal acute liver failure: a diagnosis challenge.* Arch Argent Pediatr, 2017. **115**(2): p. 175-180.
142. Palevsky, P.M., et al., *KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury.* American Journal of Kidney Diseases, 2013. **61**(5): p. 649-672.
143. Pacifici, G.M. and K. Allegaert, *Clinical pharmacology of paracetamol in neonates: a review.* Current therapeutic research, clinical and experimental, 2014. **77**: p. 24-30.
144. Allegaert, K., I. Murat, and B.J. Anderson, *Not all intravenous paracetamol formulations are created equal.* Paediatr Anaesth, 2007. **17**(8): p. 811-2.
145. Allegaert, K., G.M. Palmer, and B.J. Anderson, *The pharmacokinetics of intravenous paracetamol in neonates: size matters most.* Arch Dis Child, 2011. **96**(6): p. 575-80.
146. Bartocci, M. and S. Lundeberg, *Intravenous paracetamol: the 'Stockholm protocol' for postoperative analgesia of term and preterm neonates.* Paediatric Anaesthesia, 2007. **17**(11): p. 1120-1.
147. Lexicomp Inc. *Acetaminophen (paracetamol): Pediatric drug information*. 2022 2022 [cited 2022 June]; Available from: https://www.uptodate.com/contents/acetaminophen-paracetamol-pediatric-drug-information?search=acetaminophen-paracetamol-drug-&topicRef=9242&source=see_link.
148. Howie, S.R., *Blood sample volumes in child health research: review of safe limits.* Bull World Health Organ, 2011. **89**(1): p. 46-53.
149. Sisson, T.R.C., L.E. Whalen, and A. Telek, *The blood volume of infants: II. The premature infant during the first year of life.* The Journal of Pediatrics, 1959. **55**(4): p. 430-446.
150. Lau, W. *Chapter 13 Neonatal and Pediatric Transfusions*. Canadian Blood Services Tranfusion Clinical Guide 2017 August 2 2017 [cited 2022; Available from: https://professionaleducation.blood.ca/en/transfusion/clinical-guide/neonatal-and-pediatric-transfusion.

151. World Health Organization, *WHO Guidelines Approved by the Guidelines Review Committee*, in *WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses*. 2012, World Health Organization: Geneva.
152. Anand, K.J., *Consensus statement for the prevention and management of pain in the newborn.* Arch Pediatr Adolesc Med, 2001. **155**(2): p. 173-80.
153. Harris, P.A., et al., *The REDCap consortium: Building an international community of software platform partners.* Journal of Biomedical Informatics, 2019. **95**: p. 103208.
154. James, K.E., et al., *An index for assessing blindness in a multi-centre clinical trial: disulfiram for alcohol cessation--a VA cooperative study.* Stat Med, 1996. **15**(13): p. 1421-34.
155. Hummel, P., et al., *Clinical reliability and validity of the N-PASS: neonatal pain, agitation and sedation scale with prolonged pain.* J Perinatol, 2008. **28**(1): p. 55-60.
156. Lyngstad, L.T., S. Steinnes, and F. Le Marechal, *Improving pain management in a neonatal intensive care unit with single-family room—A quality improvement project.* Paediatric and Neonatal Pain, 2022. **4**(2): p. 69-77.
157. Hummel, P., P. Lawlor-Klean, and M.G. Weiss, *Validity and reliability of the N-PASS assessment tool with acute pain.* J Perinatol, 2010. **30**(7): p. 474-8.
158. Anand, K.J.S., et al., *Summary Proceedings From the Neonatal Pain-Control Group.* Pediatrics, 2006. **117**(Supplement_1): p. S9-S22.
159. Desai, A., et al., *Comparing N-PASS and NIPS: improving pain measurement in the neonate.* Advances in Neonatal Care, 2018. **18**(4): p. 260-266.
160. Benbrook, K., et al., *Agreement of the Neonatal Pain, Agitation, and Sedation Scale (N-PASS) With NICU Nurses' Assessments.* Advances in Neonatal Care, 2022: p. 10.1097.
161. Billingham, S.A., A.L. Whitehead, and S.A. Julious, *An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database.* BMC Med Res Methodol, 2013. **13**: p. 104.
162. Browne, R.H., *On the use of a pilot sample for sample size determination.* Stat Med, 1995. **14**(17): p. 1933-40.
163. Thabane, L., et al., *A tutorial on pilot studies: the what, why and how.* BMC Medical Research Methodology, 2010. **10**(1): p. 1.
164. Kalkman, C.J., et al., *Preoperative prediction of severe postoperative pain.* Pain, 2003. **105**(3): p. 415-423.
165. Mekonnen, Z.A., et al., *Prevalence and Contributing Factors Associated With Postoperative Pain in Pediatric Patients: A Cross-Sectional Follow-up Study.* Perioperative Care and Operating Room Management, 2021. **23**: p. 100159.
166. Ancora, G., et al., *Influence of gestational age on the EDIN score: an observational study.* Archives of Disease in Childhood - Fetal and Neonatal Edition, 2009. **94**(1): p. F35-F38.

167. Caljouw, M.A.A., et al., *Measurement of pain in premature infants with a gestational age between 28 to 37 weeks: Validation of the adapted COMFORT scale.* Journal of Neonatal Nursing, 2007. **13**(1): p. 13-18.
168. Wilcox, A.J., *On the importance—and the unimportance— of birthweight.* International Journal of Epidemiology, 2001. **30**(6): p. 1233-1241.
169. Bueva, A. and J. Guignard, *Renal function in preterm neonates.* Pediatric research, 1994. **36**(5): p. 572-577.
170. Stapleton, F.B., D.P. Jones, and R.S. Green, *Acute renal failure in neonates: incidence, etiology and outcome.* Pediatric Nephrology, 1987. **1**: p. 314-320.
171. Andreoli, S.P., *Acute Renal Failure in the Newborn.* Seminars in Perinatology, 2004. **28**(2): p. 112-123.
172. Satrom, K. and G. Gourley, *Cholestasis in preterm infants.* Clinics in perinatology, 2016. **43**(2): p. 355-373.
173. Beath, S.V., *Hepatic function and physiology in the newborn.* Seminars in Neonatology, 2003. **8**(5): p. 337-346.
174. Birnie, K.A., P.J. McGrath, and C.T. Chambers, *When does pain matter? Acknowledging the subjectivity of clinical significance.* PAIN®, 2012. **153**(12): p. 2311-2314.
175. Cairo, S.B., et al., *Mortality after emergency abdominal operations in premature infants.* Journal of Pediatric Surgery, 2018. **53**(11): p. 2105-2111.