A Cry for Comfort: Optimizing Postoperative Opioid Use in the NICU

Lucy Sherlock, PharmD
PGY2 Pediatric Pharmacy Resident
Advocate Lutheran General Hospital
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Disclosures

The planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Learning Objectives

At the end of this session, learners should be able to:

- Identify the consequences associated with inadequately addressing pain in neonates
- Choose the appropriate tool to assess pain in neonates
- Select an appropriate neonatal post operative pain regimen based on current literature
- Recognize the short and long-term consequences of opioid exposure in neonates

Abbreviation Key

- ADRs: Adverse Drug Reactions
- BP: Blood Pressure
- CDH: Congenital Diaphragmatic Hernia
- COX-1, COX-2: Cyclooxygenase 1,2
- HR: Heart Rate
- IM: Intramuscular
- IV: Intravenous
- NICU: Neonatal Intensive Care Unit
- NSAID: Nonsteroidal Anti-inflammatory Drugs
- PDA: Patent Ductus Arteriosus
- PICC: Peripherally Inserted Central Catheter
- PO: By Mouth
- PRN: As Needed
- SaO2: Oxygen Saturation
- SOC: Standard of Care
- SubQ: Subcutaneous

Background

Population

- Neonates: Defined as 0 days to 28 days old
- Gestational age (GA): Age from the time of conception to birth
  - Preterm: Born < 37 weeks
    - Late Preterm: 34 weeks to 36 6/7 weeks GA
    - Moderate-to-late preterm: 32 weeks to 33 6/7 weeks GA
    - Very preterm: 28 weeks < 32 weeks GA
    - Extremely preterm: < 28 weeks GA
  - Term: Born ≥ 37 weeks
- Patients admitted to the Neonatal Intensive Care Unit (NICU) can be older then 28 days depending on prematurity and severity of illness

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Ruggiero et al. *Drugs Context*. 2019

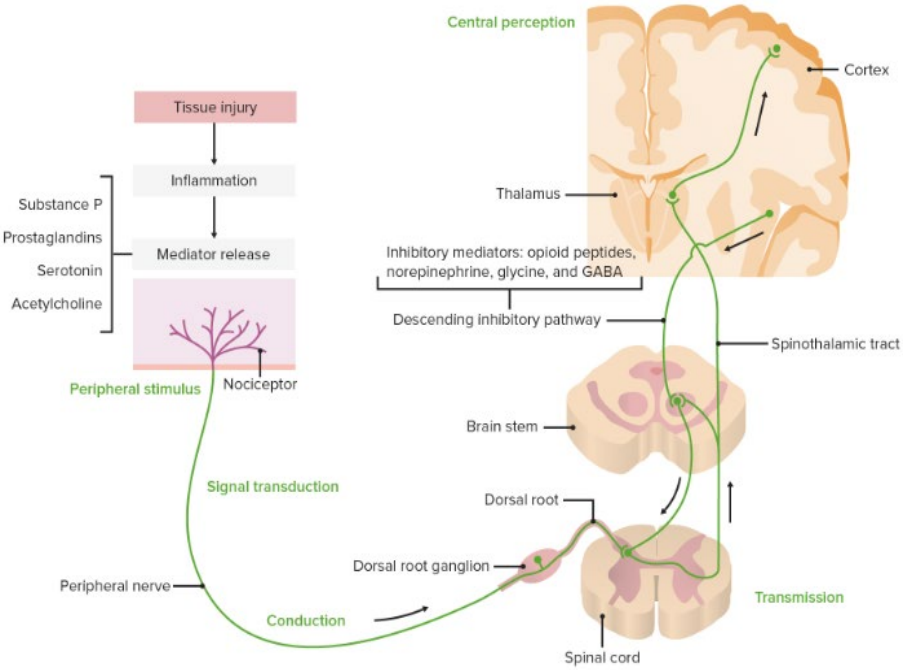
Pharmacokinetics

- Neonates are not considered "tiny adults"
- Differences in pharmacokinetics compared to adults
  - Absorption: Elevated pH and increased gastric emptying and motility
  - Distribution: Increased total-body water and volume of distribution (VD) for hydrophilic drugs and reduced circulating plasma proteins
  - Metabolism: Development of phase I and phase II enzymes
  - Elimination: Reduced glomerular filtration rate (GFR) in preterm neonates compared to term neonates

Ruggiero et al. *Drugs Context*. 2019
Kearns et al. *N Engl J Med*. 2003

Physiology

- Pain begins when specific nerve endings called nociceptors are stimulated
  - 3 main types that transmit noxious and painful stimuli
    - A beta fibers, A delta fibers, and C fibers
- Nociceptors transmit pain from the dorsal root to the dorsal horn
- Pain signals travel from the dorsal horn up to the thalamus along the spinothalamic tract



Pain: Types and pathways: Concise medical knowledge. Lecturio. May 17, 2024. Accessed September 11, 2025. https://www.lecturio.com/concepts/physiology-of-pain/.

Tucker et al. *Semin Fetal Neonatal Med*. 2023
Perry et al. *Crit Care Nurs Clin North Am*. 2018

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Do Neonates Experience Pain?

- Up until the late 1980s it was widely believed that neonates do not experience pain
  - Thoughts of incomplete development of pain pathways in this population
- This was found to be false
  - At 20 weeks gestation the peripheral nervous system is functional
  - Number and type of nociceptors are the same in adults at 20 weeks
    - Greater density of nociceptors per smaller surface area in neonates leads to a higher sensitivity of pain

Tucker et al. *Semin Fetal Neonatal Med*. 2023
Perry et al. *Crit Care Nurs Clin North Am*. 2018
Marchant. *Bioscience Horizons*. 2014
Selvanathan et al. *Semin Perinatol*. 2024
R. Whit et al. *Neoreviews*. 2005

Pain Felt in the NICU

- On average, neonates can experience 7-15 painful procedures per day in the NICU
- Painful procedures can range from diagnostic, therapeutic or surgical interventions
  - Diagnostic: Heel stick, retinopathy of prematurity
  - Therapeutic: Dressing change, tracheal suctioning
  - Surgical: G-Tube insertion, Patent Ductus Arteriosus (PDA) ligation, Congenital Diaphragmatic Hernia (CDH) repair
- Due to repetitive noxious stimuli felt daily, adequate pain control is very important in this population

Cruz et al. *Eur J Pain*. 2016
Carbajal et al. *JAMA*. 2008
Selvanathan et al. *Semin Perinatol*. 2024
Tucker et al. *Semin Fetal Neonatal Med*. 2023
Williams et al. *Front Pediatr*. 2020

Inadequate Pain Control

- Prolonged repetitive pain can lead to short and long-term consequences if not adequately treated
- Consequences of inadequate pain control
  - Low pain threshold
    - More sensitive to pain (hyperalgesia)
  - Longer lasting pain
  - Altered brain development
    - Reduction in gray and white matter
    - Reduction in brain size at the frontal and parietal regions
  - Increased somatization later in life

Grunau et al. *Clin Perinatol*. 2002
McPherson et al. *Pediatr Res*. 2020
Perry et al. *Crit Care Nurs Clin North Am*. 2018
Anand et al. *Lancet*. 2004

Assessment Question #1

All of the following are consequences to inadequate pain control in the NICU EXCEPT for?

A. Hyperalgesia
B. Effects on brain development
C. Longer lasting pain
D. Shorter length of hospital stay

Pain Assessment

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Barriers to Pain Assessment

Non-verbal communication

- Assessment relies on healthcare provider interpretation
- Observation is prone to subjectivity and bias

Differences in gestational age and types of pain

Schenk et al. *BMC Pediatr*. 2019
Olsson et al. *Pain*. 2021
Färnqvist et al. *Cochrane Database Syst Rev*. 2025

Principles of Pain Assessment

- Pain assessment tools should account for all indicators of pain
  - Behavioral: Crying, facial expressions
  - Physiologic: Heart rate, respiratory rate
  - Contextual: Gestational age, previous painful experiences
- Assessment tools should be specific and sensitive to age and type of pain
- Assessments should occur every 4-6 hours
- Repeat assessment should occur within 1 hour of a clinical intervention

Anand et al. *Arch Pediatr Adolesc Med*. 2001
Schenk et al. *BMC Pediatr*. 2019

Pain Assessment Scales

Pain Scale	Age Range	Type of pain assessed	Indicators used
Neonatal Pain, Agitation and Sedation Scale **(N-PASS)**	23 to 40 weeks gestation	Procedural Postoperative Mechanical ventilation	Behavioral Physiological
Premature Infant Pain Profile – Revised **(PIPP-R)**	Premature to term neonates	Procedural Postoperative	Behavioral Physiological
Neonatal Facial Coding System **(NFCS)**	24 to 40 weeks gestation	Acute Postoperative	Physiological
COMFORT-Behavior **(COMFORT-B)**	Neonate to 3 years old	Acute intensive care Postoperative	Behavioral Physiological
Neonatal Infant Pain Scale **(NIPS)**	Premature to term infants < 1 year old	Acute Postoperative	Behavioral Physiological

Selvanathan et al. *Semin Perinatol*. 2024
Smith et al. *Pediatr Crit Care Med*. 2022
Manworren et al. *Semin Pediatr Neurol*. 2016
Pediatrics. 2016

Neonatal Pain Assessment: Do we have the right tools?

- Objective: To assess and compare previous research on available pain assessment tools used in the NICU
- Methods: Systemic review of literature published between 2016 and 2021
  - 13 studies were found evaluating neonatal pain scales
  - Pain scales were evaluated using 8 categories of measurement
    - Behavior, physiologic, continuous pain, acute pain, chronic pain, high inter-rater reliability, ability to distinguish between stress and pain, provider usability

Llerena et al. *Front Pediatr*. 2023

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Neonatal Pain Assessment: Do we have the right tools?

Results		
Pain Scale	Strengths	Limitations
NPASS	- Provides adequate assessment of acute, chronic and continuous pain - Distinguishes between stress and pain	- Found to require more training compared to other tools - More inter-rater inconsistencies
PIPP-R	- Provides adequate assessment of acute, chronic and continuous pain - Distinguishes between stress and pain	- Found to lack inter-rater reliability
NFCS	- Distinguishes between stress and pain - High inter-rater reliability	- Lacks usability - Not designed to measure chronic pain
COMFORT-B	- Adequate assessment of behavioral and physiological parameters	- Lacks usability and functionality
NIPS	- Distinguishes between stress and pain	- Does not assess for chronic or continuous pain

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Llerena et al. *Front Pediatr*. 2023

Which One is the Best?

- No pain assessment tool is considered the "gold standard" in this population
- Based on the strengths and limitations of each one, use is dependent on age, type of pain, and the provider utilizing the tool
- No studies have been conducted comparing one tool against another

Llerena et al. *Front Pediatr*. 2023
Giordano et al. *JAMA Pediatr*. 2019

Assessment Question #2

Which of the following is true regarding pain assessment in neonates?

A. Pain assessments should occur every 8 to 12 hours
B. Assessments should account for behavioral, physiological and contextual indicators of pain
C. Assessment tools are not specific for age and type of pain
D. NPASS scoring is considered the "gold standard" in neonates

Current Literature For Postoperative Pain Management in the NICU

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Guidelines on the Management of Postoperative Pain

Clinical Practice Guideline from the American Pain Society

- Recommendations:
  - Multimodal analgesia should be used for the treatment of postoperative pain in children and adults
    - Multimodal analgesia: the use of various analgesic agents that target different mechanisms in the central nervous system (CNS)
      - Most commonly in addition to systemic opioids
  - Acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) should be provided as part of a multimodal approach to postoperative pain management in children and adults

Chou et al. *J Pain*. 2016

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Guidelines for Perioperative Care in Neonatal Intestinal Surgery

Enhanced Recovery After Surgery (ERAS®) Society Recommendations:

- Postoperative care
  - Multimodal, opioid sparing analgesia
    - Scheduled acetaminophen (intravenous or rectal)
    - Addition of morphine for breakthrough pain (lowest dose and shortest duration possible)
    - Lingual sucrose/dextrose for minor procedures (heel lance, venipuncture)
- No postoperative guidelines in the NICU that encompasses all surgical procedures

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Brindle et al. World J Surg. 2020

Limited Research

- Lack of robust data regarding preferred postoperative pain management regimens in the NICU
  - Currently no guidelines available specifically targeted to neonates
- Without a consensus on postoperative pain management, it is difficult to determine the most effective regimen for adequate pain control

Kinoshita et al. *Cochrane Database Syst Rev*. 2023

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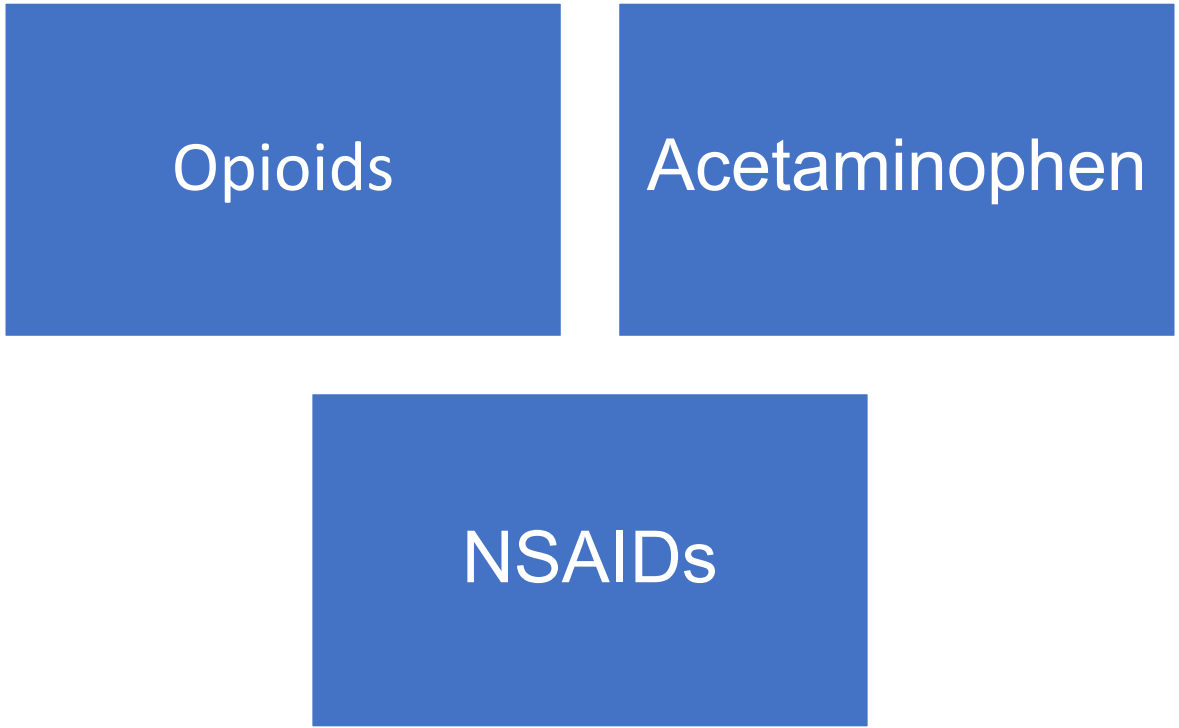
Postoperative Pain Medications



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Opioids

- Mechanism of Action (MOA): Binding to receptors in the CNS leads to inhibition of the ascending pain pathways altering the perception and response to pain
- Types of opioids used for postoperative pain in the NICU
  - Morphine
  - Fentanyl
- Dosing:
  - Morphine:
    - Intermittent: 0.05-0.1 mg/kg every 4-8hr
    - Continuous: 0.01-0.05 mg/kg/hr
  - Fentanyl:
    - Intermittent: 1-3 mcg/kg every 2-4hr
    - Continuous: 0.5-1 mcg/kg/hr

Opioids for Postoperative Pain

- Although opioids are widely used in neonates among various indications, there is limited evidence supporting the use postoperatively
  - Especially in extremely preterm neonates
- Available literature focuses on administration techniques in relation to pain score outcomes
- Majority of literature focuses on morphine use compared to other opioids

Intravenous Morphine in Postoperative Infants: Intermittent Bolus Dosing Versus Targeted Continuous Infusions

- Objective: To determine the analgesic effect of continuous and intermittent morphine infusions and the risk of ventilatory depression
- Methods:
  - Infants ≥ 36 weeks old scheduled for non-cardiac surgery were included
  - Randomized into 2 groups:
    - Intermittent: 0.05 mg/kg every 1-2h PRN
    - Continuous: Dose targeted to a serum morphine concentration not to exceed 20 ng/mL
  - Modified infant pain scores were assessed every 4h and prior to morphine doses

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Lynn et al. *Pain*. 2000

Intravenous Morphine in Postoperative Infants: Intermittent Bolus Dosing Versus Targeted Continuous Infusions

Results: 83 patients were included

- Percent of pain scores indicating adequate pain control was 77% in the continuous group compared to 60% in the intermittent group ($p<0.0001$)
- Average number of supplemental morphine doses needed was 3.2 in the continuous infusion group and 5.6 in the intermittent bolus group ($p=0.01$)
- Percent time with room air saturations <90% were similar between both groups
- Instance of ventilatory depression did not differ significantly between both groups

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Lynn et al. *Pain*. 2000

Efficacy of Continuous Versus Intermittent Morphine Administration After Major Surgery in 0-3-Year-Old Infants

- Objective: To compare the efficacy of morphine continuous infusion with intermittent morphine after major abdominal or thoracic surgery
- Methods: Randomized, double-blind trial
  - Patients 0 to 3 years old were included
  - COMFORT and visual analogue scales (VAS) were used to assess pain
  - Patients randomized into 2 groups:
    - Continuous morphine (CM): 0.01 mg/kg/h IV
    - Intermittent morphine (IM): 0.03 mg/kg IV every 3h
  - Loading dose of 0.1 mg/kg morphine was given to each patient following surgery
  - Additional morphine doses given if VAS ≥ 4
    - 0.05 mg/kg IV

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Van Dijk et al. Pain. 2002

Efficacy of Continuous Versus Intermittent Morphine Administration After Major Surgery in 0-3-Year-Old Infants

- Results: 181 patients were included (65 were neonates)
  - Max VAS and comfort median scores were similar between both CM and IM
    - VAS: 4.9 and 4.6 (P=0.25)
    - COMFORT: 14.3 and 14.2 (p=0.97)
  - In the CM group 29% of patients were without pain compared to 39% in the IM group (P=0.26)

Van Dijk et al. *Pain*. 2002

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Efficacy of Morphine

	Bouwmeester et al 2003a	Bouwmeester et al 2003b
Objective	To determine the impact of clinical variables and route of administration on morphine requirements and morphine pharmacokinetics	To determine the age-related differences in morphine requirements and metabolism in full-term neonates
Methods	-Double-blind, randomized clinical trial -Children 0-3 yo following non-cardiac thoracic and abdominal surgery -4 age groups I: 0-4 wks II: 4-26 wks III: 26-52 wks IV: 1-3 yo -Pain was assessed using COMFORT and VAS -Plasma morphine concentrations were collected at 6, 12 and 24h	-Double-blind, randomized clinical trial -Group I from Bouwmeester et al 2003a was split into 2 groups: Age 0-7 days Age 8-28 days -Pain was assessed using COMFORT and VAS -Plasma morphine concentrations were collected at 6, 12 and 24h
Interventions	-Continuous morphine (CM): 0.01 mg/kg/h IV -Intermittent morphine (IM): 0.03 mg/kg IV Q3h -Additional analgesia was given indicated by VAS score >4	
Results	-% of patients requiring extra morphine was higher in group II, III and IV compared to group I -Plasma concentrations were significantly higher in group I compared to all other groups	-Neonates 0-7 days old required fewer additional doses of morphine and maintained higher plasma morphine levels compared to the older group -Pain scores did not differ significantly between both groups

Bouwmeester et al. *Br J Anaesth*. 2003
Bouwmeester et al. *Intensive Care Med*. 2003

Comparison of Continuous Infusion of Fentanyl to Bolus Dosing in Neonates After Surgery

- Objective: To determine whether continuous infusion fentanyl is associated with less respiratory depression compared to intermittent bolus dosing
- Methods: Double-blind randomized control trial
  - Patients 36-52 weeks postmenstrual age (PMA) who underwent a surgical procedure were included
  - Patients were randomized into 2 groups:
    - Continuous infusion (group C): Fentanyl 1 mcg/kg/h initial
    - Bolus dosing (group B): Fentanyl 2 mcg/kg every 2h
  - Pain scores and saliva cortisol concentration were obtained at 2, 6, and 24h following treatment start

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Vaughn et al. *J Pediatr Surg*. 1996

Comparison of Continuous Infusion of Fentanyl to Bolus Dosing in Neonates After Surgery

- Results: 16 patients were enrolled
  - 56% of patients experienced apnea
    - 8 out of 9 in group B and 1 out of 7 in group C (p=0.009)
  - Fentanyl dosing was similar between both groups.
  - Bolus dosing was discontinued prior to the end of the trial due to the high rates of apnea
- A second phase was conducted looking only at the association of continuous fentanyl and apnea
  - 20 patients enrolled and given continuous infusion fentanyl
  - 25% of this study group had apnea events (p=0.005 when compared to 89% in previous group B)
- No differences found in pain scores or salivary cortisol between group C and B

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Vaughn et al. J Pediatr Surg. 1996

Summary of Opioid Literature			
Study	Age Studied	Opioid Used	Doses used
Lynn et al.	0 to 365 days old (17% neonates) GA ≥ 36 weeks	Morphine	Intermittent: 0.05 mg/kg IV Q1-2h PRN Continuous: 0.05 to 0.25 mg/kg/h IV
Van Dijk et al.	0 to 3 years old (36% neonates) GA 35 weeks	Morphine	Load: 0.1 mg/kg IV Intermittent: 0.03 mg/kg IV Q3h Continuous: 0.01 mg/kg/h IV
Bouwmeester et al. 2003a	0 to 3 years old (31% neonates) GA 37 to 38 weeks	Morphine	Load: 0.1 mg/kg IV Intermittent: 0.03 mg/kg IV Q3h Continuous: 0.01 mg/kg/h IV
Bouwmeester et al. 2003b	Neonates GA 35 to 42 weeks	Morphine	Load: 0.1 mg/kg IV Intermittent: 0.03 mg/kg IV Q3h Continuous: 0.01 mg/kg/h IV
Vaughn et al.	36 to 56 PMA	Fentanyl	Intermittent: 2 mcg/kg Q2h Continuous: 1 mcg/kg/h

Summary of Opioid Literature

- Morphine is the most commonly used opioid during the postoperative period
- Neonates comprised a small proportion of the populations used in the studies
  - Youngest GA studied was 35 weeks
  - No trial included very preterm or extremely preterm neonates
- Although the majority of the studies observed continuous versus intermittent opioids, the evidence was mixed
  - Lynn et al found better pain control with the continuous infusion
  - Van Dijk found no differences in pain control between continuous and intermittent dosing
- Overall, the evidence for postoperative opioid use in the NICU is minimal

Consequences of Opioids

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Short Term Consequences

- Respiratory depression
- Histamine release
  - Can induce pruritus
  - Hypotension (higher risk with morphine)
- Gastrointestinal effects (nausea and constipation)
  - Feeding intolerance
- Chest wall rigidity
  - Associated with rapid administrations of fentanyl
  - Can lead to impaired ventilation

Kinoshita et al. *Cochrane Database Syst Rev*. 2023
Morphine. *Lexidrug.* 2025
Fentanyl. *Lexidrug.* 2025
Shah et al. *Am J Health Syst Pharm*. 2019

Long Term Consequences

- Various studies have been conducted to determine the association of opioids with neurodevelopment
- Exposure in neonates have been associated with reduced brain volume and development
  - Can lead to poor motor, cognitive and developmental outcomes
    - Impaired learning abilities
    - Reduced motivation
    - Behavior
- Effects can persist into school age

Selvanathan et al. *Semin Perinatol*. 2024
Puia-Dumitrescu et al. *JAMA*. 2021
Fong et al. *Neoreviews*. 2024

Effects of Morphine Analgesia in Ventilated Preterm Neonates (NEOPAIN)

- Objective: To determine the effects of pre-emptive morphine analgesia in ventilated preterm neonates
- Methods:
  - Included infants born at 23-32 weeks gestation who were ventilated for at least 8H prior to time of enrollment
  - 898 patients were included and randomized into 2 groups
    - Masked placebo (n=449)
    - Morphine load followed by continuous infusion (n=449)
    - Open label morphine available for both groups
- Results did not show a significant increase in short term effects from morphine
- Cohort was used 5-7 years later to evaluate the long-term effects of opioids

Anand et al. *Lancet*. 2004
Fong et al. *Neoreviews*. 2024

A Pilot Study of Preemptive Morphine Analgesia in Preterm Neonates: Effects on Head Circumference, Social Behavior, and Response Latencies in Early Childhood

- Trial was conducted using the patients from NEOPAIN 5-7 years following the initial trial
- Objective: Effects of preemptive morphine analgesia on neurodevelopment in early childhood
- Methods: Parent-completed questionnaires, physical exams neuropsychological assessments, and operant tests
- Results
  - Patients in the morphine treated group found to have lower body weight and head circumference, more impaired social interactions and prolonged response latency compared to the placebo group

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Ferguson et al. *Neurotoxicol Teratol*. 2011

Assessment Question #3

Opioids are commonly used for pain management in all ages. What is one reason as to why exposure should be limited in neonates?

A. There is an increased risk for long term neurodevelopmental effects
B. Cost
C. Limited dosage forms available
D. Opioids are safe to use in neonates and there are no side effects associated with exposure

Consequences of Opioids

Although opioids are effective analgesics, they come with a risk.

There are both short- and long-term consequences associated with opioid exposure in this population.

Multimodal Based Pain Management

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Protocol Based Approach

- Creating a standardized multimodal pathway has been shown to be beneficial in postoperative neonates
- Guidance on
  - How often pain should be assessed
  - Comfort measures
  - Medication selection based on pain assessment
  - Medication and dose escalation/de-escalation based on changes in pain scores
- Goals
  - Utilize adjunctive analgesics to help reduce the amount of opioids needed
    - Acetaminophen
    - NSAIDs
  - Maintain adequate pain control

Sprecher et al. *Adv Neonatal Care*. 2025
Kinoshita et al. *Cochrane Database Syst Rev*. 2023

Acetaminophen

- MOA: Activation of descending serotonergic inhibitory pathways in the CNS are believed to cause analgesic properties
- Dosing: 7.5 to 15 mg/kg/dose every 6 hours
- Route: oral, rectal, IV

Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants

- Objective: To determine if IV acetaminophen would reduce morphine requirements in neonates and infants after major surgery
- Methods: Single-center, randomized, double-blind study
  - Neonates and infants aged 36 weeks to <1 year old weighing >1500g undergoing thoracic (noncardiac) or abdominal surgery
  - Patients were randomized to two groups
    - IV acetaminophen 30 mg/kg/day in 4 doses
    - Morphine continuous infusion based on age and weight
      - Ex: 10kg (0.016 mg/kg/hr); 5kg (0.011 mg/kg/hr); 3 kg and >10 days old (0.009 mg/kg/hr); 3 kg and ≤10 days old (0.004 mg/kg/hr)
  - Rescue morphine was available for both groups based on NRS and COMFORT scores
    - 0.01-0.015 mg/kg/dose IV

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Ceelie et al. *JAMA*. 2013

Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants

- Results
  - Median cumulative morphine dose was 1.21 mg/kg over 48h in the IV acetaminophen group which was 66% lower than the morphine group at 3.75 mg/kg ($P < 0.0001$)
  - No significant differences were found in pain scores and ADRs between both groups

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Ceelie et al. *JAMA*. 2013

Intravenous acetaminophen for postoperative pain in the neonatal intensive care unit (IVA POP)

- Objective: To determine the ability of conducting a trial comparing IV acetaminophen to fentanyl for postoperative care in the NICU
- Methods: Single center randomized controlled trial
  - Patients in the NICU were included if they underwent a major thoracic or abdominal surgery
    - All corrected gestational ages up to 12 months are included
  - Randomized into 2 groups
    - Treatment group: IV acetaminophen dosed based on age
    - Control group: Saline boluses
    - Both groups received a continuous fentanyl infusion
  - Pain assessed via NPASS prior to each intervention dosing

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Archer et al. *PLoS One*. 2023

IVA POP Trial

Acetaminophen Dosing		
GA	IV Dose	Max Daily Dose
<33 weeks	10 mg/kg IV q12H	22.5 mg/kg/day IV
33–36 weeks	Loading dose: 20 mg/kg IV x 1 Maintenance: 10 mg/kg IV q8H	30 mg/kg/day IV
≥ 37 weeks	Loading dose: 20 mg/kg IV x 1 Maintenance: 10 mg/kg IV q6H	40 mg/kg/day IV
≥44 weeks and ≥28 days old	Loading dose: 20 mg/kg IV x 1 Maintenance: 10 mg/kg IV q6H	60 mg/kg/day IV

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Archer et al. *PLoS One*. 2023

IVA POP Trial

- Clinical outcomes
  - Postoperative pain scores
  - Cumulative analgesic dose over 24H
  - Ventilation requirements
  - Signs of opioid ADRs (constipation, hypotension, bradycardia and apnea)
  - Length of stay
- This is an ongoing trial (results not yet posted)

Archer et al. *PLoS One*. 2023

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Postoperative NSAIDs

- Closure of patent ductus arteriosus (PDA) is the main indication for NSAIDs in neonates
  - Ibuprofen and indomethacin
- Although NSAIDs widely used in pediatric postop, very limited evidence for use in neonates
  - Safety concerns: gastrointestinal, renal and hematologic complications
- Recently a systemic review was completed of ketorolac use in postoperative neonates and infants

Persad et al. *Cochrane Database Syst Rev*. 2023
Aranda et al. *J Matern Fetal Neonatal Med*. 2009
Aranda et al. *Pediatr Clin North Am*. 2017

Ketorolac in Postoperative Neonates and Infants: A Systematic Review

- Objective: To evaluate PK, safety and efficacy of ketorolac for postoperative pain in pediatrics < 6 months old
- Study Design: 8 studies included
- Results
  - Results from the studies were mixed
    - Majority showed ketorolac having effective analgesic properties in this population, however, reduction in opioid use varied
  - One study found patients <21 days old and <37 weeks post conceptual age were at a higher risk for ketorolac associated bleeding
- Authors' Conclusions: There are limited studies regarding ketorolac use in this population
  - Although efficacy has been noted, there may be safety concerns in preterm neonates <21 days old

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Stone et al. *J Pediatr Pharmacol Ther*. 2021

Quality Improvement Intervention to Reduce Postoperative Opiate Use in Neonates

- Objective: To reduce the use of opiates in neonates undergoing nonemergent GI surgery following multimodal protocol implementation
- Study design: Neonates admitted to the NICU requiring surgery were included (all ages and weights)
  - ≤ 28 days old (minimum 32 wks GA):
    - 12.5 mg/kg of IV acetaminophen Q6H x 8 doses (max 50 mg/kg/day)
  - > 28 days old
    - 15 mg/kg of IV acetaminophen Q6H x 9 doses (max 60 mg/kg/day)
  - Rescue fentanyl was available PRN based on protocol and pain scores
- Outcomes: Preintervention vs postintervention
  - Cumulative postoperative opioid use over the first 48h postop
  - Individual pain scores over the first 48h postop
- Results: 77 neonates included (mean GA of 34 weeks with age range of 4.5-94 days old)
  - Median postoperative morphine equivalent doses were reduced from 7.96 mg/kg to 0.095 mg/kg over 48h postop following implementation ($P < 0.0001$)
  - N-PASS scores were equivalent in both groups across the study period

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Grabski et al. *Pediatrics*. 2020

Reduction of Post-operative Opioid Use in Neonates Following Open Congenital Diaphragmatic Hernia Repairs

- Objective: To reduce the use of opiates in neonates undergoing congenital diaphragmatic hernia (CDH) repairs following multimodal protocol implementation
- Study design: Neonates admitted to the NICU requiring open CDH repair were included
  - < 28 days old (minimum 32 wks GA)
    - 12.5 mg/kg of IV acetaminophen Q6H x 8 doses (max 50 mg/kg/day)
  - Rescue fentanyl was available PRN based on protocol and pain scores
- Outcomes
  - Cumulative postoperative opioid use over the first 48h postop
  - Individual pain scores over the first 48h postop
- Results: 45 neonates included (mean GA of 38 weeks with age range of 3-16 days old)
  - Cumulative postoperative morphine equivalent doses were reduced from 82.2 mg/kg to 2.9 mg/kg over 48h postop following implementation ($P < 0.0001$)
  - N-PASS scores were equivalent in both groups across the study period

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Grabski et al. *J Pediatr Surg*. 2022

A NICU Postoperative Pain Management Improvement Project to Reduce Uncontrolled Pain

- Objective: To improve postoperative pain control in neonates following protocol implementation while reducing variability
- Study Design: 811 infants from the NICU included (breakdown of age was not reported)
  - Data was collected pre-implementation, during implementation and post implementation
  - Majority of procedures recorded: G-Tube placement and exploratory laparotomy
- Outcomes
  - Uncontrolled post operative pain within the first 24H post-surgery
    - Uncontrolled postoperative pain: 2 consecutive pain scores above the N-PASS treatment threshold of 3
- Results
  - Uncontrolled postoperative pain decreased from 26% pre-implementation to 18% post implementation
  - Opioid exposure (morphine equivalents) decreased from 1.8 mg/kg to 0.9 mg/kg for 24H postop following implementation of the protocol

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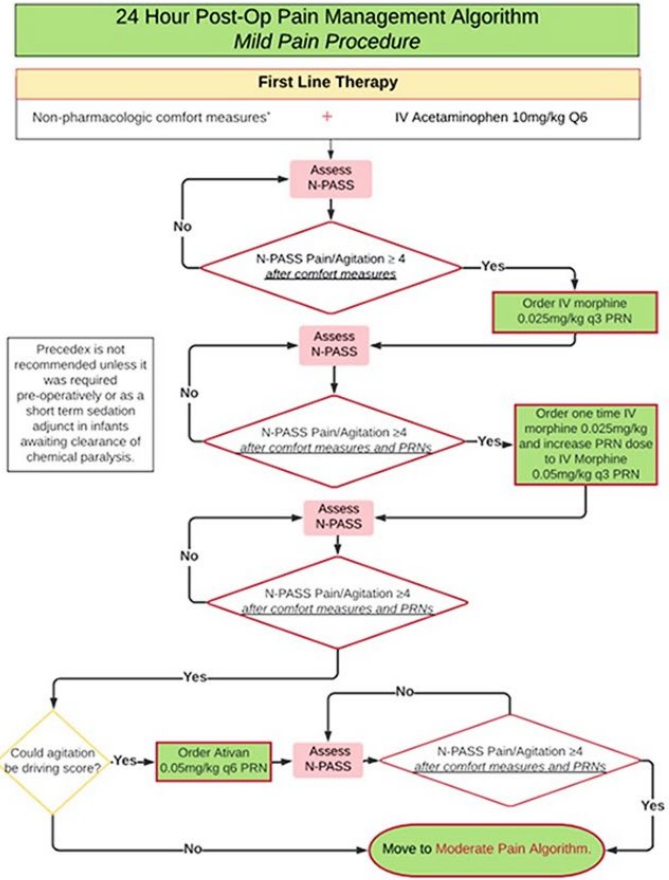
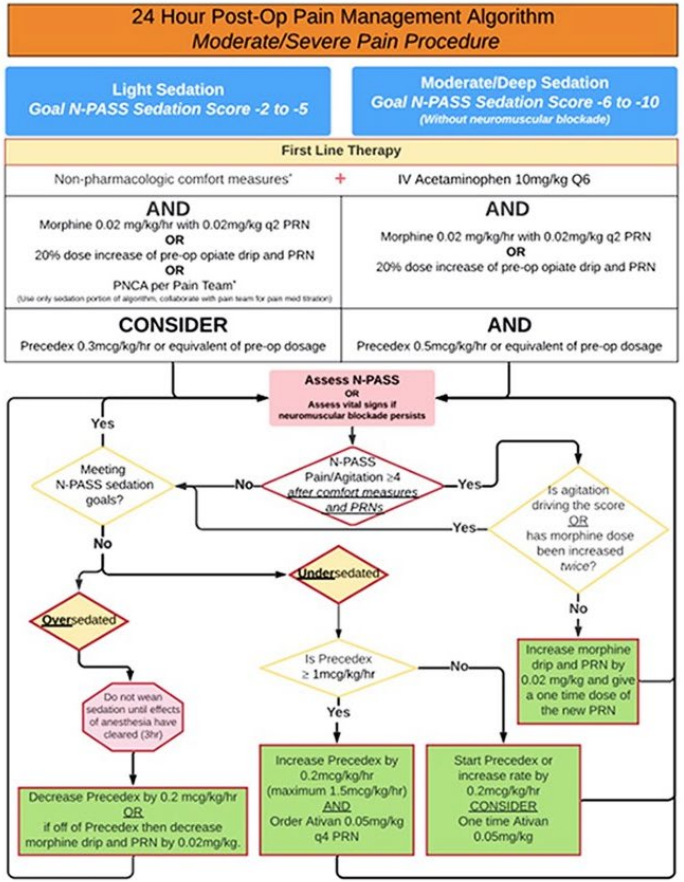
Sprecher et al. *Adv Neonatal Care*. 2025





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Multimodal Protocols

All three studies used a multimodal protocol for postoperative pain management

All protocols used IV acetaminophen as the initial analgesic agent. PRN and/or continuous morphine were added based on protocol and severity of procedure.

Results of these studies showed a reduction in opioid requirements without an increase in pain scores.

This suggests effective pain control can be achieved with lower opioid exposure

- Potentially reducing the risk of both short- and long-term adverse effects commonly associated with opioids.

Grabski et al. Pediatrics. 2020
Grabski et al. J Pediatr Surg. 2022
Sprecher et al. Adv Neonatal Care. 2025

Assessment Question #4

Baby Girl KS was born at 30 weeks gestation. At 7 days of life, she underwent a CDH repair. She is expected to require pain management for at least the next 48H. Based on current literature, which regimen is the most appropriate to start initially?

A. Ibuprofen 10 mg/kg PO Q6H
B. Non-pharmacologic comfort measures only
C. Continuous morphine at 0.02 mg/kg/hr IV with PRN boluses
D. Acetaminophen 10 mg/kg IV Q6H with Morphine 0.025 mg/kg IV Q3H PRN

Key Takeaways

- Although opioids are widely used in the NICU, there is minimal evidence regarding the use in postoperative patients
  - Therefore, it is difficult to determine the most appropriate regimen
- Overall, the goal with postoperative pain management in this population is to adequately treat pain while reducing the use of opioids.
- Multimodal regimens have been shown to be effective in providing adequate pain control while reducing the doses of opioids needed

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Questions?

Lucy.Sherlock@aah.org