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Enhanced Recovery After Surgery (ERAS) consensus recommendations for opioid-minimising pharmacological neonatal pain management

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ABSTRACT

Objective Enhanced recovery after surgery (ERAS) guidelines have been successfully applied to children and neonates. There is a need to provide evidence-based consensus recommendations to manage neonatal pain perioperatively to ensure adequate analgesia while minimising harmful side effects.

Methods Following a stakeholder needs assessment, an international guideline development committee (GDC) was established. A modified Delphi consensus iteratively defined the scope of patient and procedure inclusion, topic selection and recommendation content regarding the pharmacologic management of neonatal pain. Critical appraisal tools assessed the relevance and quality of full-text studies. Each recommendation underwent a formal Grades of Recommendation, Assessment, Development and Evaluation (GRADE) assessment of the quality of evidence and expert consensus was used to determine the strength of recommendations.

Results The GDC included paediatric anaesthesiologists, surgeons, and ERAS methodology experts. The population was defined as neonates at >32 weeks gestational age within 30 days of life undergoing surgery or painful procedures associated with surgery. Topic selection targeted pharmacologic opioid-minimising strategies. A total of 4249 abstracts were screened for non-opioid analgesia and 738 abstracts for the use of locoregional analgesia. Full-text review of 18 and 9 articles, respectively, resulted in two final recommendations with a moderate quality of evidence to use regular acetaminophen and to consider the use of locoregional analgesia. There was inadequate evidence to guide the use of other non-opioid adjuncts in this population.

Conclusions Evidence-based, ERAS-driven consensus recommendations were developed to minimise opioid usage in neonates. Further research is required in this population to optimize multimodal strategies for pain control.

INTRODUCTION

Neonates admitted to a neonatal intensive care unit (NICU) undergo multiple interventions during their hospitalisation, many of which are painful.[1 2] Although once believed insensate to pain by virtue of an underdeveloped nervous system, it is now widely accepted that neonates perceive pain.[3] As there are short- and long-term effects of exposure to painful stimuli during infancy,[4] it is important that practitioners recognise, quantify and treat pain in neonates.

Providing analgesia to neonates is a delicate balance between achieving adequate pain relief and minimising side effects. While opioids are effective analgesics, they are associated with a myriad of short- and long-term side effects in neonates.[5 6] The use of non-opioid adjuncts and multimodal analgesia is a well-supported practice in the adult literature that balances pain control without overreliance on opioids.[7]

The Enhanced Recovery After Surgery (ERAS) Society guidelines for most specialties and procedures include recommendations regarding multimodal opioid-sparing analgesic strategies.[8] Similar evidence-based recommendations are needed for paediatric and neonatal patients. Many providers understand the benefits of opioid mitigation strategies but would benefit from specific evidence-based recommendations to facilitate multimodal analgesia in neonates alongside other ERAS recommendations. The guideline development committee (GDC) sought to create critical and actionable evidence-based recommendations concerning the pharmacologic management of pain in neonates that can be introduced into existing and future care pathways and ERAS guidelines.[9]

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METHODS

The detailed methodology regarding the GDC and consensus process is previously described and follows the approach outlined by the ERAS society's standards for guidelines.[10] Patient and public involvement included a stakeholder needs assessment that included parent and caregiver focus groups conducted to understand the priorities of ERAS implementation in the NICU including the management of neonatal pain.[11] Following this, a GDC was assembled with experts from paediatric anaesthesiology (n=7), paediatric surgery (n=4) and ERAS methodology experts (n=7). Topics were selected using a modified Delphi consensus of all GDC members, and five topics were selected for development of a search strategy: (1) parent and staff education, (2) pain assessment, (3) non-opioid pharmacological agents, (4) local and regional analgesia and (5) non-pharmacological agents and interventions. Working groups were created for each of these topic areas with relevant expertise. This study describes the results of the topics related to the pharmacologic management of pain (Topics 3 and 4). The study population was defined as neonates at >32 weeks gestational age (GA) within 30 days of life undergoing surgery or painful procedures associated with surgery. Through consensus, this GA was felt to be an appropriate threshold as physiology is relatively comparable to term neonates, and recommendations are still applicable. Inclusion criteria were a comparative study design (any primary original research including experimental and/or observational studies involving humans), >32 weeks GA within 30 days of life.

The search strategy was prospectively registered on PROSPERO (ID#: CRD42021265273). A research librarian assisted in creating the search strategy which spanned from 1 January 2011 to 2 March 2021 with limits to human subjects and English language. These initial search strategies were intended to provide a scoping literature base from which the working groups were encouraged to perform additional snowball sampling (see attached Search Strategies and PRISMA diagrams (online supplemental appendix A-C)). Some articles were relevant to more than one topic, and some articles were identified during snowballing that were deemed relevant to the working group discussion, even if they did not meet strict inclusion criteria. All articles underwent abstract screening by at least one working group member. Full-text data extraction was performed by at least one member of the GDC, and the data were extracted and provided back to each relevant working group. Every full text included in the study underwent a quality assessment using the JBI Critical Appraisal Tools most relevant to the study design.[12] Following the creation of recommendations by the working group, consensus was sought from the entire GDC. Once consensus on the scope and content of each recommendation was reached, the overall quality of evidence was determined using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodology.[13] The quality of evidence affected final wording of recommendations (eg, weaker evidence leading to a 'may consider' vs stronger evidence leading to a 'should consider' recommendation). The strength of recommendation was reached through consensus of the GDC based on the balance between desirable and undesirable consequences.[13] The guideline was reported using the AGREE Reporting Checklist (online supplemental file 1). Institutional IRB approval was not sought for this guideline creation.

RESULTS

Two topic areas were selected by the GDC regarding the pharmacologic management of neonatal pain in the perioperative setting: (1) the use of non-opioid pharmacologic agents and (2) the use of local and regional analgesia. The GDC framed both recommendations as important aspects of opioid-minimising strategies and elected not to create a specific recommendation regarding opioid use. These recommendations are intended to inform clinical decisions of healthcare providers caring for neonates perioperatively (eg, neonatologists, anesthesiologists, neonatal nurses, etc.).

A total of 4249 records were screened for non-opioid analgesia, of which 18 full-text papers underwent data extraction (online supplemental appendix B). From these, one recommendation was made concerning the use of acetaminophen (figure 1). The GDC felt there was inadequate evidence to supply a recommendation about non-steriodal anti-inflammatory drugs, dexmedetomidine, clonidine or gabapentin at this time as is detailed in the discussion.

A total of 738 abstracts were identified and screened regarding the use of local and regional analgesia techniques in neonates. After the screening process, nine full-text papers underwent data extraction (online supplemental appendix C), from which one recommendation resulted (figure 2).

Recommendation	Quality of Evidence	Strength of Recommendation
Unless contraindicated, regularly scheduled acetaminophen (oral, intravenous, rectal) should be administered in the early postoperative period to manage pain and minimize opioid use in neonates.	Moderate	Strong

Figure 1 Acetaminophen recommendation.

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Recommendation	Quality of Evidence	Strength of Recommendation
Consider the use of regional analgesia (e.g., caudal, epidural, spinal, peripheral nerve block) ideally with ultrasound guidance, when appropriate and not contraindicated, as part of an opioid-minimizing analgesia strategy.	Moderate	Weak

Figure 2 Locoregional analgesia recommendation.

DISCUSSION

It is well-recognised that untreated and undertreated pain can have short- and long-term negative consequences in neonates.[3 4] Surgical neonates are at particular risk of repeated noxious exposures due to surgical pain, as well as the resultant postoperative care (venipuncture, nasogastric tube exchange, etc).[2 14] It is important to have targeted evidence-based analgesic strategies to guide practitioners in managing minor, moderate and severe perioperative pain. These Neonatal ERAS Analgesia guidelines provide evidence-based recommendations regarding the pharmacologic management of pain in the perioperative setting. These recommendations should be used in conjunction with other non-pharmacologic strategies where appropriate.

Opioid-minimising strategies

According to a recent Cochrane review, the overall risks and benefits of opioid use in neonates exposed to painful procedures are unclear.[5] Kinonshita *et al* caution that there may be increased apneic events with opioid administration, while data regarding the impact on pain scores, bradycardia and hypotension remain uncertain. The landmark NEOPAIN randomised controlled trial (RCT) demonstrated that preterm infants who received open-label morphine boluses had higher rates of a composite outcome of death, severe intraventricular haemorrhage and periventricular leukoplakia. Additionally, pre-emptive treatment of mechanically ventilated infants with morphine did not reduce the incidence of the composite outcome.[15] While this study focused on premature infants, who are not the intended population for this guideline, its impact on NICU opioid administration is acknowledged. With regard to concerns that neonatal opioid use may impact future opioid sensitivity and pain thresholds, some studies have shown these concerns about long-term effects may be overstated with equivalent pain detection thresholds and incidence of chronic pain following low-dose opioid infusions in the neonatal period.[16] Opioids will likely continue to play a role in acute pain management in some neonates, but recommendations were developed for adjunctive methods to manage pain with an opioid-minimising strategy. Safety and efficacy data were considered when determining the strength of recommendations by the GDC, particularly as there is often limited safety data in the neonatal population.

Non-opioid adjuncts: acetaminophen

Non-opioid adjuncts are frequently used to help minimise the dose of opioids required to achieve adequate pain control. The GDC recommends the use of early postoperative acetaminophen to minimise opioids. Two high-quality studies in cardiac and non-cardiac surgery demonstrated decreased narcotic requirements with equivalent pain scores for neonates following acetaminophen administration.[17 18] Ochsenreither *et al* demonstrated that infants who received rectal acetaminophen following open heart surgery required less opioid with equivalent pain scores.[17] In an RCT, infants (0–10 days) who received IV paracetamol had a 49% lower cumulative morphine dose compared with neonates who received a continuous morphine infusion with equivalent pain scores.[18] When administered as a loading dose (20 mg/kg) followed by 10 mg/kg of IV acetaminophen every 6 hours, infants with mild to moderate pain were shown to have a trend of lower pain scores within 30 min.[19] Acetaminophen in appropriate doses is well tolerated in neonates without elevation of liver enzymes or hepatotoxicity[20]; however, it is noted that no studies have specifically assessed the long-term safety of acetaminophen for pain. The GDC strongly recommended the use of acetaminophen given the potential benefits with a low side-effect profile.

Non-opioid adjuncts: NSAIDs

There is limited evidence in the neonatal population to guide the use of NSAIDs. A few small studies have shown ketorolac to be an effective adjunct or primary analgesic in neonates[21–23]; however, there are also conflicting data that suggest it did not decrease opioid use.[24] Furthermore, there may be safety concerns with the use of NSAIDs in postsurgical neonates. One case series of 57 postsurgical patients who received ketorolac demonstrated that 17.2% had a bleeding event.[25] The majority of patients who bled were less than 14 days old, and the authors cautioned against the use of ketorolac in patients younger than 21 days or less than 37 weeks corrected gestational age (cGA). Others have identified that it may contribute to renal morbidity in neonates.[26] As such, the GDC did not feel there was strong enough evidence to make a recommendation for or against the use of NSAIDs in neonatal surgical patients at this time.

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Non-opioid adjuncts: clonidine

There is some limited evidence to suggest that clonidine may reduce the doses of opioid required to achieve adequate sedation and analgesia in ventilated newborns[27]; however, there is inadequate data regarding its use as an analgesic.

Non-opioid adjuncts: dexmedetomidine

There were no studies that met the inclusion criteria addressing the use of dexmedetomidine for pain in neonates, so the GDC is unable to make a recommendation regarding its use at this time.

Non-opioid adjuncts: Gabapentin

There were no studies that met the inclusion criteria addressing the use of gabapentin for pain in neonates, so the GDC is unable to make a recommendation regarding its use at this time.

Regional analgesia

The consideration of regional analgesia is recommended. Many healthcare professionals have advocated for the use of regional analgesia in neonates to help minimise opioids and their subsequent side effects.[28] The recommendation to consider its use is weak as the GDC recognises that not all providers and/or facilities may be equipped to safely administer and deliver all forms of regional analgesia. There is a potential added benefit of reducing chronic pain, as has been demonstrated in adult patients treated with regional analgesia.[29] There is moderate to high level of evidence to support the use of a variety of blocks in surgical neonates although some inconsistency in the literature regarding efficacy remains. A small case series demonstrated that the use of ultrasound guided ilio-inguinal nerve blocks with bupivacaine obviated the need for opioids in all patients undergoing inguinal hernia repair.[30] A small prospective RCT was unable to show any impact on fentanyl requirements of neonates who underwent laparotomy with surgeon-administered infiltration of bupivacaine in the incision.[31] There are paediatric data suggesting that regional anaesthetic techniques provide improved postoperative analgesia and reduced morphine requirements when compared with local infiltration.[32] Further research examining the effectiveness of different regional anaesthetic techniques for various neonatal surgeries are needed. It is unclear whether the use of image guidance adds significant benefit during nerve block for neonates, but the GDC does recommend the use of ultrasound to guide peripheral nerve blocks when there is adequate local expertise in keeping with evidence from the broader field of paediatric anaesthesia.[33]

The use of neuraxial analgesia with a caudal, epidural and/or spinal has also been studied in neonates. Bilgen *et al* demonstrated that a caudal approach provided adequate analgesia for neonatal circumcision without requiring additional adjunctive pain medications.[34] In 47 patients with biliary atresia, those who underwent an epidural catheter placement had lower pain scores, decreased need for systemic opioids and were more likely to be extubated in the OR than patients managed without an epidural.[35] A large multicentre safety analysis of the use of neuraxial catheters in neonates has shown a low risk of serious complications (0.3%) with catheter malfunction, contamination and vascular puncture being the most common adverse events.[36] In addition to reduction in opioid exposure, neonates who underwent a combined spinal-epidural anaesthesia (CSEA) were shown to have fewer respiratory and cardiovascular adverse events than those who underwent general anaesthesia.[37] Those who had CSEA were also shown to have a faster return of intestinal function with less abdominal distension than those who underwent general anaesthesia following intestinal surgery.[38] Structured programme development can help introduce the routine use of regional anaesthesia in neonatal patients as part of an opioid-minimising analgesia strategy.[39] Despite moderate-quality evidence, this is a weak recommendation based on the balance of benefits given that not all providers and facilities currently have the expertise to manage regional analgesia in neonates.

Guideline implementation

The current recommendations are based on available evidence and expert consensus. The recommendations should be considered in parallel with non-pharmacologic pain management particularly for less painful procedures. The current guideline was reviewed for feedback and feasibility by several stakeholders, and their suggestions contributed to the final product. These guidelines can be implemented individually or within a broader ERAS approach.[940] Users are encouraged to monitor adherence and implementation using both process and outcome metrics (eg, neonatal pain scores, opioid utilisation and provider satisfaction). These guidelines do not provide specific dosing recommendations. Future studies will focus on implementation and will inform guideline updates. The GDC plans to review updated evidence and implementation trials to develop a practice guideline update in 5 years.

CONCLUSIONS

Pain management for neonates is a complex balance of ensuring adequacy of analgesia with the minimisation of side effects. The regular administration of acetaminophen together with the use of regional analgesia can help spare opioids and facilitate recovery for surgical neonates as part of an ERAS protocol.

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