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Strategies for the Prevention and Management of Neonatal and Infant Pain

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Abstract Health care professionals caring for neonates (birth to 28 days of life) and infants up to 1 year of age have a professional and ethical responsibility to provide safe and effective pain management during painful procedures. Despite 14 years of research reports highlighting that sick infants are exposed to large numbers of painful procedures with minimal or no provision of pain management strategies, and generation of abundant evidence to support effectiveness of pain reduction strategies, insufficient practice changes have been made. As untreated pain in infancy has both immediate and longer-term negative consequences, such as increased sensitivity and responses to subsequent pain, it is imperative that widespread sustained practice changes are made to reduce the burden of pain. This review highlights recent advances within the past 2 to 3 years in pain management of acute procedural pain for neonates and infants, proposes recommendations for future research, and addresses practical implications and challenges for implementing best pain management practices.

Keywords Infant · Pain · Sucrose · Analgesic · Evidence-based

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Introduction

The past several decades have seen exponential growth in research on pain management in newborn and young infants. One of the factors stimulating this growth has been the evolution of the neonatal intensive care unit (NICU), which has resulted in increased survival rates for premature and sick infants [1]. This health care advancement has also resulted in increased numbers of infants exposed to major surgical procedures, minor painful procedures, and other painful stimuli during the course of their hospitalization. The often cited 1995 Barker and Rutter study [2] reported that 54 infants, over a 3-month period, underwent 3283 procedures, most of which were capillary blood sampling. Although the authors discussed available pain reduction methods, no pharmacological, physical, or psychological pain reduction strategies were documented during any procedures. Numerous subsequent reports and surveys similarly highlighted the exposure of sick infants to large numbers of painful procedures performed, mainly, with no or minimal strategies to reduce pain [3•, 4–6]. Adverse consequences of untreated pain in preterm and sick infants include both short- and long-term physiological, behavioral, and neurodevelopmental effects, including altered responses to subsequent pain and increased risk of adverse neurodevelopmental, behavioral, and cognitive outcomes [7, 8].

Since 2000, international and national evidence-based guidelines on the management of pain in infants have been published. Additionally, relevant systematic reviews, plus a review of systematic reviews on pain management strategies in hospitalized infants [9•], provide clinicians with high-quality synthesized evidence. Furthermore, the International Neonatal Pain Control Group, as part of the Newborn Drug Development Initiative, has addressed concerns relating to pain and sedation management and

has made a number of recommendations for practice and future research [10]. However, as highlighted by the continuing reports of untreated pain in sick infants, there has been less than optimal application of recommendations arising from such guidelines and reviews. The purpose of this article is therefore threefold: 1) to review current evidence and new advances concerning effective strategies for reducing acute procedural pain in newborn and young infants; 2) to provide clinicians with practical recommendations for translating knowledge into clinical practice; and 3) to make recommendations for further research. Although the focus of this review is limited to management of acute procedural pain, management of persistent or chronic pain and pain of longer duration in hospitalized infants is currently being explored [11]. Throughout the remainder of the article, infants in the neonatal period, as well as those up to 12 months of age, will both be referred to as infants. Furthermore, pain reduction strategies have been organized in terms of pain prevention, pharmacological interventions, and psychological interventions (strategies that exert their effect by behavioral, physical, or psychological means, or any combinations of these mechanisms).

Pain Prevention

Without doubt, the most effective method to reduce pain is preventing the occurrence of painful procedures. Reducing the occurrence or frequency of painful procedures is one of the key recommendations by the American Academy of Pediatrics and the Canadian Paediatric Society [12]. However, health care professionals (HCPs) seem to have made little headway in reducing sick infants' exposure to routinely performed painful procedures [3•]. Findings of numerous reports indicating large numbers of painful procedures performed in sick infants have not changed over the years, despite the move toward less invasive therapies (eg, the move to less invasive methods of assisted ventilation). Paradoxically, although associated with reduced respiratory-related painful procedures, such as suctioning of the airways, earlier weaning of invasive mechanical ventilation led to an increase in the number of heel lances performed for capillary blood sampling, thus exchanging—rather than preventing—painful events [13]. HCPs have a responsibility to balance the need for vigilant assessment, monitoring, and performing necessary care within the context of existing and novel therapies, with reducing pain exposure in sick infants.

Practical Challenges/Implications for Practice

Reducing premature and sick infants' exposure to painful and noxious procedures requires commitment, planning, and coordination at many levels of an organization. This includes carefully evaluating the need for routine pathology testing, ensuring coordination of diagnostic and treatment modalities to reduce the need for multiple episodes of blood sampling, and judicious assessment of the need for routine procedures such as airway suctioning.

Recommendations for Research

At a local level, audit of data of painful procedures performed from medical records, followed by feedback to unit staff, together with educational outreach, is one of the suggested strategies that has the potential to raise awareness of clinical practices [14]. On a broader level, the inclusion of such data into existing large multicenter databases, such as the Canadian Neonatal Network [15], would permit benchmarking against other neonatal centers and provide valuable data on similarities and variations in neonatal pain practices.

Pharmacological and Psychological Pain Management Interventions

The pharmacological and psychological pain management interventions discussed in this review were rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [16] to assess the quality of evidence and strength of recommendations (Table 1). GRADE tool ratings were based on all available evidence on the pain management strategies included in this review. Agreement on the GRADE score was reached by consensus of two authors (DH and JY) (Table 2).

Pharmacological Interventions

Oral Sucrose

Sweet taste-induced analgesia to manage painful procedures has been one of the most frequently studied interventions in neonatal care. Currently, there are approximately 80 published randomized controlled trials (RCTs), plus reviews and systematic reviews, evaluating the use of either sucrose or glucose during painful procedures during the neonatal period (Yamada et al.: A systematic review and meta-analyses of non-sucrose sweet solutions sucrose for pain relief in neonates [unpublished data]; [17]). In addition, a search of the metaRegister of Controlled Trials, using the key words sucrose, glucose, and the Boolean term "*and*" pain, identified 22 relevant unpublished trials or trials in process; 15 including placebo or no treatment arms [18]. Sucrose was also one of the strategies included in a review of systematic reviews on pain interventions in

Table 1 GRADE score: quality of evidence and strength of recommendations

Level	Study design
High quality	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality	Any estimate of effect is very uncertain.

GRADE Grading of Recommendations Assessment, Development and Evaluation
(*Data from* Guyatt et al. [16])

hospitalized infants [9•]. The main analgesic effect of sweet taste is considered to be induced by an endogenous opioid mechanism, which is able to be blocked by opioid antagonists, and is ineffective for infants born to mothers on methadone. The effects have been shown to peak at 2 minutes following administration and are sustained for around 5 minutes [19].

Findings to date strongly support the use of sucrose or glucose as an effective strategy to reduce behavioral pain responses during commonly performed minor painful procedures (eg, heel lance) during the neonatal period. The use of sucrose to minimize procedural pain was initially recommended in 2001 by the International Evidence-Based Group for Neonatal Pain [20]. Despite this recommendation, recently published reports continue to highlight low rates of sucrose utilization. Although sucrose was given during 58% of painful procedures in a cohort of infants in one NICU in Australia [5], Carbajal et al. [3•], in a study of painful procedures and pain management in neonatal units in France, reported that sweet solutions were used during only 3.5% of procedures. In Canada, sucrose was only documented for 5% of hospitalized infants

Table 2 Recommended pain reduction strategies for neonates and infants

Pain management strategies	GRADE
Oral sucrose	
1. Single use of small (0.1–2 mL) volumes of sucrose, or glucose if sucrose is unavailable, prior to and during minor painful procedures; in infants up to 1 year of age (practical consideration: administer in aliquots every 2 minutes until the procedure is complete)	High
2. Sucrose remains effective for repeated use	Moderate
3. Conflicting evidence of sucrose efficacy beyond 12 months of age (practical consideration: administer in aliquots every 2 minutes until the procedure is complete)	Very low
Opioid analgesics	
Conflicting evidence exists concerning safety of opioids and effectiveness in reducing pain during acute painful procedures in premature infants	Low
Acetaminophen	
1. Despite ubiquitous use and part of standard care, minimal evidence of enterally administered acetaminophen effectiveness	Low
2. Growing evidence of efficacy, safety, and use of intravenously delivered acetaminophen in the postoperative period	Moderate
NSAIDs	
No evidence of efficacy or opioid sparing	Very low
Skin-to-skin contact/kangaroo care	
Effective during heel lance or venipuncture in preterm infants; the addition of sucrose or glucose further reduces pain outcomes during painful procedures; the addition of sucking, rocking, and maternal singing or talking did not further diminish pain response	High
Breast feeding	
1. Effective for healthy newborn infants during capillary blood sampling or venipuncture	High
2. Effective up to 12 months of age during immunization	Moderate
Music therapy	
Variable effects across studies; small number of studies, with small numbers of included infants	Very low

GRADE Grading of Recommendations Assessment, Development and Evaluation

younger than 12 months of age [21]. This low utilization of sucrose or glucose, as well as the ongoing conduct of RCTs with placebo or nontreatment arms, in the face of strong evidence and recommendations by multiple national and international groups is perplexing. Is this lack of adoption of sucrose or glucose as a pain-reducing strategy for neonates and infants related to lack of knowledge, unsuccessful knowledge translation efforts, or the complexities related to a practice/knowledge gap? The large majority of trials to date have studied the efficacy of single doses of sucrose or glucose during a single procedure (eg, heel lance); yet, it could be argued that the more clinically relevant and important research question concerns whether repeated administration of sweet solutions remain effective over weeks to months of use in hospitalized infants. Four published studies have addressed this evidence gap of effectiveness of multiple doses of oral sucrose administered over an extended period ranging from 7 days to an entire hospitalization (up to 5 months) [22•, 23–25]. Findings of these studies have highlighted ongoing effectiveness of sucrose in reducing procedural pain in preterm and term infants. Of particular note are the two most recent studies by Stevens et al. [25] and Harrison et al. [22•], which evaluated sucrose analgesia over an extended period. Stevens et al. [25], in a blinded RCT, reported ongoing effectiveness of sucrose, compared with placebo and standard care, in reducing pain during heel lance in preterm infants over a 4-week period. Of note, by day 28, a mean of 236 doses of sucrose had been given to infants in the sucrose group, providing new evidence to support ongoing analgesic effects of sucrose in the face of multiple previous doses. The longitudinal cohort study by Harrison et al. [22•] included infants born at, or near, term; most of whom required surgery, opioid analgesics, and sedatives during their hospitalization. Consistently low pain responses, as measured by facial expression scores and crying duration following sucrose administration during heel lancing, over the full course of a hospitalization ranging from 1 to 5 months were reported. Findings of these two studies add important evidence to support the effectiveness and safety of oral sucrose in the reduction of pain during repeated painful procedures over an extended period in diverse populations of sick and preterm hospitalized infants.

Another important clinical research question is the age at which sucrose becomes either less effective or ineffective. There is now a compelling body of evidence of analgesic effectiveness of oral sucrose or glucose during immunizations in infants up to 12 months of age (Harrison et al.: Efficacy of sweet solutions for analgesia in infants between one and 12 months of age: a systematic review [unpublished data]). However, the evidence for sucrose efficacy in infants older than 12 months of age is conflicting. Two studies evaluated analgesic effects of a low concentration of sucrose (12%), previously considered insufficiently sweet for the sweet taste–mediated analgesic effect [26, 27]. The earlier study, published in 1996, found the 12% sucrose solution to be ineffective beyond the neonatal period [26]. More recently, 12% sucrose was reported to be effective in reducing pain during immunizations in infants and children from 13 months to 4 years of age [27]. Such conflicting findings from a limited number of studies with small numbers of participants are problematic for clinicians endeavoring to provide evidence-based pain management practices.

Based on the large body of high-quality evidence, sucrose, or glucose if sucrose is unavailable, can be recommended for the reduction of pain during minor painful procedures (eg, heel lance, venipuncture, immunization) in infants up to 12 months of age. HCPs therefore need to ensure sweet solutions are available for when painful procedures are performed on infants in any setting. Due to conflicting and insufficient evidence, similar recommendations cannot be made beyond this age group. For prolonged and more painful or stressful procedures (eg, circumcision, eye examination, bladder catheterization), sucrose given in aliquots over the duration of the procedure, and the use of additional pain reduction strategies (swaddling, non-nutritive sucking, topical anesthetic agents, and dorsal penile nerve block and topical anesthetic agents during circumcision) are recommended.

Practical Challenges/Implications for Practice

Availability and accessibility of sucrose or glucose in sufficient concentrations for the sweet taste–mediated effect to be effective (24% sucrose or 25%–50% glucose) where infants undergo painful procedures is vital for the successful adoption of sweet solutions for reduction of pain. This includes community settings where scheduled childhood immunizations take place, outpatient settings where pathology testing and diagnostic procedures occur, and inpatient settings including pediatric hospitals and pediatric wards within general hospitals. Sucrose use may be facilitated by clearly written and easy to follow clinical practice guidelines (CPGs), which have been approved by all relevant stakeholders. Sucrose CPGs are publicly available online for use, such as those provided by the Royal Children's Hospital (Melbourne, Australia) [28]. Guidelines should highlight how to achieve optimal effectiveness of sweet solutions over the course of prolonged procedures. Only very small volumes are required. Sucrose or glucose should be administered 2 minutes prior to commencement of procedures and, for procedures lasting more than a few seconds, immediately prior to and throughout prolonged procedures, in small aliquots at around 2-minute intervals until completion [29]. Sucrose use is only appropriate in the context of acute procedural pain reduction for short-lived procedures. It is not appropriate or effective for reducing pain of ongoing nature or for extended periods of crying.

Recommendations for Research

A large body of high-quality evidence supports the efficacy of sucrose and glucose in the first month of life during commonly performed painful procedures; therefore, it can be argued that a state of equipoise no longer exists. Further placebo-controlled sucrose or glucose trials in this population of infants during procedures such as heel lance, venipuncture, and intramuscular injections should, therefore, be considered unethical. However, there remains a dearth of evidence of the effectiveness of sucrose in sick infants receiving opioid or equivalent analgesics, necessitating further research in this population. In addition, there is conflicting and insufficient evidence of effective sweet taste–induced analgesia in infants beyond 12 months of age [29], warranting further well-conducted studies in this population across settings and during painful procedures of both short and longer duration.

In summary, based on abundant evidence of benefits of sucrose or glucose during single painful procedures in infants up to 12 months of age, a GRADE score of *High quality* (further research is very unlikely to change our confidence in the estimate of effect) was assigned (Tables 1 and 2). As there are currently only two studies that have systematically evaluated the effectiveness of prolonged use of sucrose over time, a GRADE rating of *Moderate* (Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate) was allocated. The strength of recommendation for using sweet solutions to reduce pain in infants beyond 12 months of age has been rated as *Very low quality* (Any estimate of effect is very uncertain) (Tables 1 and 2).

Opioid Analgesics

A series of studies first published in the mid-1980s provided extensive evidence of the effectiveness of intravenous (IV) opioid analgesics in significantly reducing stress responses in infants occurring as a result of surgery, reducing postoperative complications, and improving clinical outcomes [30]. Opioid analgesics remain the mainstay of postoperative pain management and optimization of physiological stability during major procedures such as endotracheal tube insertion, management of sedation, and management of ventilator-induced distress [31, 32]. However, there is conflicting evidence on the effectiveness of background infusions of opioid analgesics in reducing pain during acute minor painful procedures during the course of a critical illness. Studies conducted in the 1990s reported that continuous morphine administration was associated with reduced pain responses during minor painful procedures [33]; yet, findings from more recent studies suggest that morphine has negligible analgesic effects during acute minor painful procedures [32]. In addition, safety concerns arose following a large multicenter blinded RCT of IV morphine compared with placebo in preterm infants [34, 35]. Longer duration of assisted ventilation was found in newborn infants randomly assigned to receive continuous morphine. Further, a higher risk of severe intraventricular hemorrhage was found in infants in both treatment and placebo groups, who received additional analgesia (intermittent doses of morphine), compared with infants who did not receive open-label morphine. These findings of negligible acute pain-reducing benefits and serious safety concerns are extremely concerning and confusing for clinicians striving to provide safe and effective pain management to sick infants. There remains little information regarding safety and effectiveness, as well as utilization, of prolonged use of continuous opioid analgesics for procedural and disease-related pain in infants with complex medical and surgical conditions [36].

Practical Challenges/Implications for Practice

Conflicting and limited evidence on opioid analgesics to reduce pain and distress during periods of assisted ventilation highlights the complex issues faced by HCPs when making decisions about strategies to reduce pain and stress in sick infants. The imperative to ensure optimal comfort during periods of assisted ventilation and associated management and to reduce adverse consequences of untreated pain, yet balance optimal comfort against the risks of opioid analgesics in the context of a limited evidential base relating to long-term effectiveness and safety of opioid analgesics, is one of today's key challenges facing HCPs caring for sick infants.

Recommendations for Research

In a review of pharmacological analgesic agents used in neonates, fentanyl and morphine were considered the highest priority for future research [37]. Further studies that systematically evaluate effectiveness of continuous infusions of opioid administration, with concomitant oral sucrose and psychological strategies with known effectiveness during acute minor painful procedures, are warranted. As per Table 2, a GRADE rating of *Low quality* (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) has been allocated for the use of IV opioid analgesics in the reduction of acute minor procedural pain in infants.

Acetaminophen

Acetaminophen (paracetamol) is a mild analgesic and often the analgesic of choice for infants, children, and adults [38]. Ubiquitous use of acetaminophen for postoperative pain, nonspecific use, and minor procedural pain reduction in

infants has been widely reported [36, 38–40], and is probably the most commonly used medication in the Western world. Yet, there is a paucity of research relating to the benefits of orally and rectally administered acetaminophen in neonates and infants. Findings from the few studies including newborn or young infants have generally shown little analgesic benefits [41–44]. Well-conducted studies of enterally administered acetaminophen, given alone or in combination with other analgesics, are required to address this knowledge gap. In contrast, effectiveness of IV formulations of acetaminophen are increasingly being studied in preterm and term newborn infants, older infants, and children in the postoperative period [45–47]. Advantages of the IV route over oral and rectal routes include smaller required doses for effective postoperative pain management, predictable bioavailability, and more rapid and predictable onset of action, particularly compared with the rectal route. Furthermore, IV administration of acetaminophen has been shown to reduce opioid requirements in infants and children in the early postoperative period [46, 47].

Practical Challenges/Implications for Practice

Issues relating to the use of acetaminophen in infants need to be considered independently for hospitalized infants and infants in the community receiving acetaminophen for pain related to immunization. One of the key recommendations for clinical practice in the inpatient hospital setting is to systematically evaluate and document effectiveness of acetaminophen, a practice that is rarely observed [39]. An additional clinical challenge is to ensure the prescribed and administered doses are appropriate for the route of administration. Due to variable rectal absorption of acetaminophen in neonates and children, larger doses are required to achieve optimal analgesia [47]. Despite such different dose recommendations, equivalent acetaminophen doses were administered to infants in one NICU regardless of whether the route of administration was rectal, oral, or not specified [36]. Documentation by HCPs of the route of administration and analgesic response will permit systematic evaluation of the effectiveness of this commonly used analgesic in hospitalized infants.

Use of acetaminophen in community settings for infants undergoing scheduled childhood immunization poses different clinical challenges. Despite widespread use by clinicians, often as a result of parental request [40], there is little evidence that acetaminophen given either prophylactically or following immunization reduces acute needle-related pain. Additionally, although recommendations have been made to advise parents to use acetaminophen only for management of fever or local inflammation following immunization [40], a recent study showed that although acetaminophen did effectively reduce fever following immunizations, antibody responses were reduced [48]. A recommendation from this recent study was that *prophylactic* acetaminophen should not be routinely recommended to reduce fever following immunization, but should be used *therapeutically* as necessary if fever and local inflammation surrounding the injection site develop.

Recommendations for Research

Although there are a growing number of studies evaluating the IV formulation of acetaminophen in reducing postoperative pain in infants [46, 47], the conduct of further placebo-controlled RCTs of enterally administered acetaminophen in the postoperative period are warranted. However, due to widely accepted current prescribing and administration practices, to be ethically acceptable, studies would need to include an open-label administration of "standard care" acetaminophen pending assessment of pain. Such a study, with a protocol allowing additional open-label acetaminophen, with systematic documentation of pain scores following administration, would provide high-quality evidence and significantly contribute to the current dearth of evidence in this area.

As per Table 2, quality of evidence for the use of enterally administered acetaminophen in the reduction of acute procedural pain was rated as *Low quality*. However, due to the growing evidence of efficacy and safety, a GRADE score of *Moderate quality* was assigned for the quality of recommendations for IV acetaminophen in the postoperative period.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Minimal published data exist on the efficacy and safety of NSAIDs in infants. A recently published study examined two cohorts of infants younger than 6 months of age following cardiothoracic surgery [49]. Nineteen infants who received IV ketorolac were compared with 19 infants matched for age (control). Although there were no differences between the two cohorts in relation to safety of NSAIDs, as measured by renal function and hematologic effects, there were also no differences in postoperative opioid or acetaminophen requirement. To date, there have been no studies identified showing that NSAIDs used in the postoperative period in young infants are efficacious in reducing pain. As shown in Table 2, quality of evidence for the use of NSAIDs in infants in the reduction of postoperative pain was rated as *Very low*.

Psychological Pain Management Strategies

Kangaroo Care

An important recent advance in pain management in preterm infants has been the study of kangaroo care (KC).

There are increasing numbers of RCTs evaluating the efficacy of KC, or skin-to-skin contact, in reducing pain during minor painful procedures [50–53•, 54–56]. In all studies, reduced pain responses during heel lance or intramuscular injections were found in KC groups compared with control groups. Two of the studies also compared KC with sweet solutions (eg, sucrose [56] and glucose [51]) during heel lancing. Both studies reported a greater pain reduction effect in the KC group compared with the sweet solution group, although sweet solutions given concomitantly to KC may provide additional analgesia [52]. Site differences in pain scores in a multicenter study of KC during heel lance found that study infants in the only site that used sucrose as standard care had lower pain scores during KC compared with the two sites that did not have sucrose as standard care [52]. A further important finding in this study was that an "enhanced" KC condition, in which the mother sat in a rocking chair, sang or talked to the baby, and offered her finger or pacifier to the baby for sucking, did not result in additional pain-reducing benefits. This lack of further pain-reducing benefits by offering additional psychological strategies to KC is important information for HCPs considering implementing KC in their clinical setting.

Practical Challenges/Implications for Practice

Integrating KC into the NICU routine poses important practical challenges. A setting and policy that fully supports KC, 1) during all nonemergency painful procedures (eg, blood tests, IV line placements, injections), and 2) which dictates such nonemergency procedures are only performed when mothers (or fathers or other family members) are available for KC, would facilitate the utilization of this effective pain reduction strategy. Implementation of KC during painful procedures requires commitment and support from all HCPs, members of phlebotomy teams, and parents of infants. Other factors identified by nurses that influence implementation of KC include physiologic stability of the infant, staffing, maternal readiness, and support from unit management for use of this method of pain management [57].

Recommendations for Research

Studies evaluating the feasibility of KC during painful procedures, as well as rates of utilization of KC during procedures, will help to inform practice. In addition, research on the effectiveness and feasibility of KC during procedures in sick hospitalized term newborn and older infants is warranted. A GRADE score of *High quality* was assigned for quality of recommendations to use KC for preterm and term infants, when feasible, during minor painful procedures (Table 2).

Breastfeeding

In a systematic review of five trials, breastfeeding medically stable, term, newborn infants prior to, or during painful procedures was shown to effectively reduce physiological and behavioral responses to pain during heel lancing or venipuncture [58]. Three studies published since this systematic review evaluated the efficacy of breastfeeding in infants up to 12 months of age during immunization [27, 59, 60•]. Dilli et al. [27] included 158 infants up to 6 months of age; Efe and Ozer [59] included 66 infants at 2 to 4 months of age; and Abdel Razek and Az El-Dein [60•] included 120 infants from 1 to 12 months of age. All three studies reported significantly reduced pain during immunizations as assessed by behavioral responses, including incidence and duration of cry and composite behavioral pain scores (Facial Pain Rating Scale and Neonatal Infant Pain Scale). Mechanisms contributing to the analgesic effects are thought to be multifactorial, involving maternal contact [61], skin-to-skin contact, sucking, pleasant taste [62], and intake of naturally occurring endorphins present in the breast milk [63–65]. Although breastfeeding has been efficacious in reducing procedural pain, small volumes of breast milk are no more effective than water [58]. This discrepancy is in all likelihood due to the contribution of multiple factors at play during breastfeeding other than taste alone. The sugar in breast milk is primarily lactose, the least sweet of the sugars (sucrose > fructose > glucose > lactose) [66], thereby likely contributing little to analgesia in isolation (eg, delivered by oral syringe or via pacifier).

As early childhood immunization is a significant cause of pain and distress for both infants and their parents [40, 67, 68], breastfeeding (when possible) during immunizations has the potential to significantly reduce pain and distress for infants, improve the immunization experience for infants and mothers, and optimize adherence to early immunization schedules.

Practical Challenges/Implications for Practice

Promoting the practice of breastfeeding healthy newborn infants, medically stable hospitalized infants, or infants beyond the newborn period up to 12 months of age, when feasible, during painful procedures, requires clinicians to strongly advocate for this method of pain management. An environment that fully supports mothers of hospitalized infants to breastfeed during all nonemergency blood tests, IV catheter placements, or injections, and which dictates such procedures are only performed when mothers are available and prepared to breastfeed, is required for breastfeeding to be adopted into routine pain management practices. Allowing and promoting breastfeeding during early childhood immunization in community practice

settings may be more feasible to implement, and an approach that can be integrated into standard immunization practices [59].

Recommendations for Research

Studies to date have included only healthy term infants; therefore, the feasibility of breastfeeding infants during procedures irrefutably remains in the realm of medically stable infants. Research should focus on barriers and facilitators to breastfeeding infants during painful procedures in diverse perinatal, pediatric, and community settings from both parent and HCP perspectives. The identification of barriers and facilitators, as well as rates of utilization of breastfeeding during procedures, will contribute to knowledge relating to feasibility, acceptability, and adoption of this pain reduction strategy into clinical practice.

A GRADE score of *High quality* was assigned for the quality of recommendations for breastfeeding healthy term newborn infants prior to, and during, capillary sampling or venipuncture; a score of *Moderate quality* was assigned for recommending breastfeeding in infants up to 12 months of age prior to, and during, scheduled childhood immunization (Table 2).

Music Therapy

The use of music therapy to reduce pain during procedures in infants is not a new area of study. However, until recently, there were no systematic reviews of music during acute painful procedures in infants, although four studies involving infants were included in a larger systematic review of music for pain relief in all populations [69]. A recently published systematic review, specifically relating to preterm and term newborn infants in the first month of life, included six studies on the efficacy of music during painful procedures [70]. Three of these studies were conducted during circumcision and three during heel lance. The authors highlighted major methodological flaws in these studies, including small sample sizes (n=11–31 infants), unclear concealment of allocation, and lack of blinding. Overall effects of music compared with control conditions during painful procedures were reported to be small and inconclusive.

Practical Challenges/Implications for Practice

Numerous studies of psychological strategies aimed at reducing procedural pain in preterm and term infants highlight the ongoing search by researchers and HCPs to seek diverse effective methods to reduce pain. Although there is insufficient evidence of the benefits of music therapy during painful procedures, an environment that supports parents of sick infants to individualize their infant's bed area and to play their choice of music throughout the infant's stay is one of many ways that may assist families and infants during their hospitalization. Promoting a supportive environment for parents, which also optimizes growth and development of preterm and sick infants, requires commitment and close family collaborations at all levels of health care organizations.

Recommendations for Research

Hartling et al. [70] recommended further methodologically sound, well-powered RCTs to further elucidate the benefits of music for infants during painful procedures. Researchers designing such studies need to ensure that the "standard" care group receives current best pain management practices, such as KC, breastfeeding, or sweet solutions with non-nutritive sucking if feasible. Due to the limited studies with small numbers of included infants, and variable effects of music therapy during painful procedures across studies, a GRADE score of *Very low quality* (any estimate of effect is very uncertain) was assigned (Table 2).

Future Directions for All Pain Management Studies

Further studies are needed that target feasibility, clinical utility, effectiveness, and safety of long-term use of the numerous pharmacological, physical, and psychological pain management strategies. Studies on the adoption and sustainability of new pain management strategies in the clinical area are also warranted. Unit, hospital, or nationwide CPGs may assist in promoting a consistent approach to pain management and guiding practice. However, such guidelines alone are not sufficient to change practice [71]. Attention to strategic and wide dissemination of guidelines, integrated with active knowledge translation strategies in partnership with key professional organizations through decision-maker partners, is essential to facilitate sustainable changes in practice [72].

Consistent documentation of pain assessment scores using validated and age-appropriate pain assessment tools are encouraged to assist in the systematic evaluation of the multiple pain management strategies available and utilized for neonates and infants during painful procedures [73, 74]. Such studies are challenging, especially in the area of critical care in which polypharmacy abounds, and a mix of opioid analgesics, sedatives, acetaminophen, and sucrose may be given concomitantly to psychological interventions [36]. Such studies require careful prospective research designs, with support from clinical staff to optimize accurate and comprehensive data collection. These challenges are not insurmountable, and such studies will

significantly contribute to the body of knowledge on utilization and effectiveness of both pharmacological and psychological interventions to reduce pain in neonates and infants in diverse clinical settings.

Conclusions

HCPs caring for sick and healthy infants undergoing painful procedures have a responsibility to reduce the number and frequency of painful procedures, to consistently implement pain reduction strategies with known pain-reducing effects, and to evaluate the effectiveness of pain-reducing interventions during painful procedures. HCPs need to advocate for infants and their parents and facilitate family participation in reducing infant pain. Collaboration with clinicians, managers, and organizational leaders at all levels is an important component to optimize translation of findings and recommendations into the clinical area.

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