CE 2.3 HOURS Continuing Education

# The Analgesic Properties of Intraoral Sucrose

## *An Integrative Review*

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**ABSTRACT**

The treatment of pain is an essential component of the clinical and ethical care of infants. Despite evidence-based practice consensus statements recommending that infants receive analgesia during minor painful procedures, numerous studies have shown that procedural pain remains poorly managed in this population. Oral sucrose administration has been associated with calming effects and reductions in observed pain behaviors with preterm and term infants aged up to 1 year. The objective of this integrative review is to synthesize findings from published randomized controlled trials evaluating the efficacy and safety of oral sucrose as a preprocedural intervention for mild to moderate procedural pain in infants. Overall, studies indicate that oral sucrose is an effective, safe, convenient, and immediate-acting analgesic for reducing crying time and significantly decreases biobehavioral pain response following painful procedures with infants.

**KEY WORDS:** infant, neonate, oral sucrose, pain, randomized controlled trial

Although significant progress has occurred in the control of surgical pain during infancy, newborns undergoing procedure-related pain, which occurs during routine diagnostic and treatment interventions, do not routinely receive interventions to relieve their pain.[1,2] Mounting evidence suggests that even brief periods of severe pain experienced early in life may be a causative factor for prolonged sensory disturbances and altered pain responses lasting into adolescence and adulthood.[3] Despite strong evidence supporting the analgesic properties of oral sucrose and the American Academy of Pediatrics and the Canadian Paediatric Society recommendation for the use of oral sucrose as a preprocedural analgesic for newborn painful procedures,[4] sucrose analgesia is not universally employed as a standard of care for procedural pain in hospitals and pediatric clinics.

Substantial evidence confirms that preterm and term infants have the anatomic and functional capacity for mounting a response to noxious stimulus at birth.[5-9] In newborn infants, the increased density of peripheral nerves and immature descending pathway expose the infants to greater pain intensity during the first 8 weeks of life compared with adults exposed to the same stimulus.[5,10-13] Yet, infants often receive subtherapeutic levels of analgesia and suboptimal pain control for procedures that are typically treated more aggressively in adults.[14] This exposure to undermanaged pain is significant because frequent or severe pain early in life may be a potentially causative factor for adverse neurodevelopmental outcomes persisting into adolescence and adulthood.[12,13,15,16]

Knowledge of interventions to prevent pain in infants has not translated into a decrease in prevalence or intensity of painful experiences. The administration of oral sucrose is the most frequently

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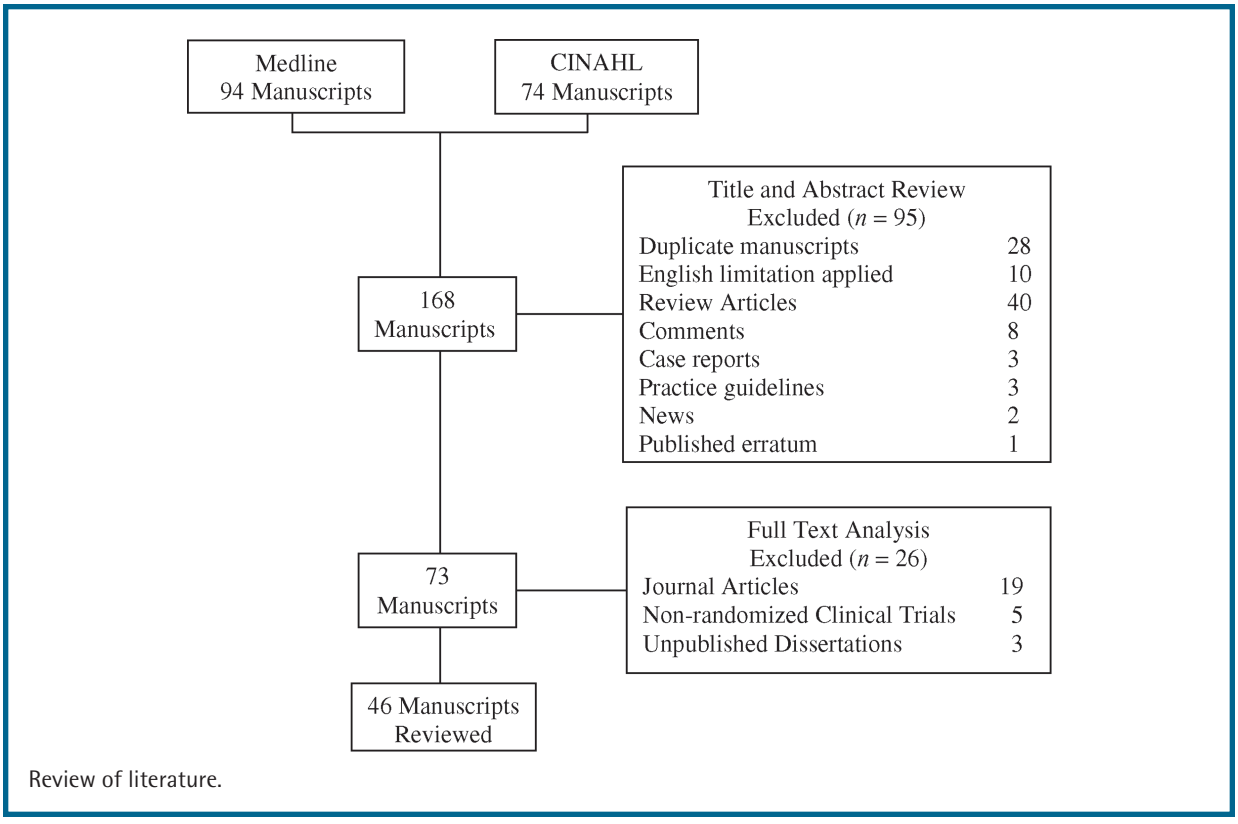
studied behavioral and environmental intervention for the relief of procedural pain in newborns,[17] but limited randomized clinical trials (RCTs) and contradictory reports in the published literature hamper the ability to draw definitive conclusions regarding its efficacy.

Oral sucrose administration has been associated with calming effects and reductions in observed pain behaviors in preterm, term, and postnatal infants.[18-20] The mechanisms underlying the efficacy of sucrose as an analgesic are advanced through indirect evidence for endogenous opioid mediation that has been primarily derived from studies using animal models.[21-23] Rats given naloxone, an opioid antagonist, 30 minutes prior to intraoral sucrose showed earlier times to paw withdrawal indicating a lower threshold when exposed to noxious stimuli compared with those in rats not receiving the opioid reversal agent.[21,23] It is hypothesized that the sweet taste of sucrose promotes the activation of endogenous opioids that attenuate nociception or processing of noxious information at the level of the dorsal horn,[24] demonstrating strong support for endorphin release.

The purpose of this integrated review is to synthesize findings from published RCTs examining the efficacy and safety of oral sucrose as a preprocedural analgesic in preterm and term infants. Specifically, studies are examined in the context of variability in samples, study methods, procedures, and outcome measures. Areas of controversy and gaps in our knowledge of this problem are highlighted. Finally, an evidence-based/best practice clinical practice guideline and an agenda for future research are proposed.

## Methods

Randomized clinical trials examining the utilization of oral sucrose as a preprocedural intervention for mild to moderate procedural pain in infants were identified from electronic databases: MEDLINE, January 1996 to June 2009, and CINAHL, January 1982 to June 2009. Medical subject headings terms were analgesia, infant, neonatal, newborn, nociception, pain, sucrose, and randomized controlled trial. Database searches used the explode function for the following key terms: sucrose, infant, and pain. English language restrictions were imposed. The literature review recognized 168 articles. Review articles (40), duplicate manuscripts (28), journal articles without original data (19), English language restriction (10), comments (8), nonrandomized clinical trials (5), case reports (3), practice guidelines (3), unpublished dissertations (3), literature categorized as news (2), and published erratum (1) were discarded. The remaining RCTs (46) were critically reviewed (Figure 1). Table 1 summarizes the most recent RCTs from the past 5 years.




Review of literature.

## TABLE 1. Table of Randomized Controlled Trials 2004-2009

| Author | Sample | Stimulus | Intervention | Measure | Outcome |
|---|---|---|---|---|---|
| Elserafy et al[83] | 36 preterm infants 27 to 36 weeks' gestational age | Venipuncture | Sterile water with or without pacifier. Sucrose with or without pacifier. Pacifier alone, no treatment | PIPP | There was a statistically significant difference in pain scores between treatment groups. Lowest pain scores occurred with the use of 24% oral sucrose solution and pacifier. |
| Hatfield[26] | 40 infants, 2- and 4-months-old | Immunizations | 24% sucrose or sterile water by pacifier | UWCH | Infants receiving sucrose returned to baseline 90% faster than infants receiving sterile water. No significant differences in analgesia response were detected at 2 or 4 months of age. |
| Hatfield et al[19] | 100 infants, 2- and 4- months-old | Immunizations | 24% sucrose or sterile water by pacifier | UWCH | Infants receiving sucrose had a 78% reduction in behavioral pain response scores and returned to baseline faster than infants receiving sterile water. |
| Efe and Ozer[40] | 66 term infants | Venipuncture | 25% sucrose by pacifier, breastfeeding, or standard care (control) | NIPS, cry | Significant difference in analgesia found between sucrose and breastfeeding and control. No significant difference was observed for analgesia between sucrose and breastfeeding. |
| Curtis et al[71] | 84 infants 0-6 months | Venipuncture | 44% sucrose or sterile water with and without pacifier | FLACC, cry, HR | Sucrose and pacifier had a significant effect on crying in infants younger than 3 months. Sucrose did not significantly reduce FLACC, crying time, or HR in older infants. |
| Rogers et al[84] | 83 infants younger than 90 days | Bladder catheterization | 24% sucrose or sterile water orally | DAN Pain Scale, cry | Sucrose showed a small but nonsignificant change in pain scores and crying time in infants younger than 30 days. No significant effect of sucrose occurred in infants older than 30 days. |
| Boyle et al[65] | 40 infants younger than 32 weeks | ROP examination | 33% sucrose or sterile water with and without pacifier | PIPP | Infants randomized to pacifier displayed lower pain score than those without pacifiers. No difference detected between groups receiving sucrose and sterile water. |
| Stevens et al[57] | 66 preterm infants older than 26 weeks' and younger than 30 weeks' gestation | All painful procedures | 24% sucrose or sterile water with pacifier, positioning and swaddling | PIPP | A significant effect between sucrose and pacifier and positioning and swaddling was found. |
| Ogawa et al[43] | 100 full-term infants | Venipuncture heel lance | 50% sucrose or sterile water orally | NFCS, cry | Sucrose significantly reduced NFCS scores in the heel lance group compared to the venipuncture group. |
| Gal et al[68] | 23 infants ≤30 weeks' gestation | ROP examination | 24% sucrose or sterile water orally | PIPP | Sucrose significantly reduced the pain in 3 of the 5 defined pain responses during speculum insertion. |

(*continues*)

TABLE 1. Table of Randomized Controlled Trials 2004–2009 (*Continued*)

| Author | Sample | Stimulus | Intervention | Measure | Outcome |
|---|---|---|---|---|---|
| Grabska et al[66] | 32 infants 28 weeks' gestation | ROP examination | 24% sucrose or sterile water orally | PIPP | Infants receiving sucrose displayed a small but significant drop in $O_2$ saturation. Both groups showed significant increase in HR, BP, and PIPP. All infants cried for a significant amount of time crying during the examination. |
| Mitchell et al[67] | 30 preterm infants | ROP examination | 24% sucrose or sterile water orally | PIPP | Significant differences in mean PIPP scores were found between sucrose and sterile water during left eye examination. |
| Boyer et al[25] | younger than 31 weeks' gestation | Every painful procedure | 24% sucrose or sterile water orally | Salivary cortisol, HR | No significant difference in cortisol response to painful stimulus or HR variability between groups. |
| Acharya et al[44] | 39 infants younger than 37 weeks' gestation | Venipuncture | 25% sucrose or sterile water orally | NFCS, cry | HR and behavioral responses to pain were significantly reduced with sucrose. |

Abbreviations: BP, blood pressure; DAN, Douleur Aiguë Nouveau-né pain scale; FLACC, Faces Legs Activity Crying and Consolability; HR: heart rate; NFCS, Neonatal Facial Coding System; NIPS, Neonatal Infant Pain Score; PIPP, Premature Infant Pain Profile; UWCH, University of Wisconsin Children's Pain Scale.

## Results

### Samples

All studies used convenience samples. Of RCTs conducted in the past 5 years (2004-2009), 3 studies performed a power analysis.[19,25,26] Infants aged 27 weeks' gestation to 6 months were included in the analysis. With the exception of Blass and Miller,[27] who utilized a quasi-random distribution, all RCTs were double-blind, placebo-controlled trials. Studies that provided demographic data found sex to be statistically nonsignificant in predicting responses to sucrose.[26]

### Measures

Studies involving the administration of oral sucrose in preterm and term infants do not always provide clarity around the concept of pain. Few studies define pain conceptually or provide a scientific rationale for linking pain to the outcomes of interest. From reported outcomes, it can be assumed that investigators considered proportion, percentage, or duration of crying to be the most valid indicator of pain in infants.[28-32] Few investigators used a composite pain assessment or multidimensional approach to pain measurement that represents a more comprehensive conceptualization of pain. Although research on infant cry has delineated certain cry characteristics such as pitch, intensity, melody, and harmonics as being acceptable indicators of pain,[33] these characteristics were not routinely assessed within studies of oral sucrose administration. Cry duration may provide some indication of distress; however, alone, it does not necessarily confirm or deny the presence of infant pain.[34,35] Research suggests that a multivariable approach or composite pain score including physiological, behavioral, and contextual indices is a more valid measure of pain in infants.[34-36]

#### *Pain Measurement*

Various behavioral response scales were selected for 18 studies. Twelve studies used the Premature Infant Pain Profile, a composite instrument, which incorporates behavioral, physiological, and contextual components and has established reliability and validity.[37,38] Two studies utilized the University of Wisconsin Children's Pain Scale, which consists of 4 behavioral parameters that demonstrate content validity for measuring pain.[39] The Neonatal Infant Pain Score,[40] Douleur Aiguë Nouveau-né pain scale,[41] and the Faces Legs Activity Crying and Consolability were each used once.[42] Two studies[43,44] utilized a pain concatenation scale in addition to crying to capture signs of acute pain in both preterm and full-term infants. Pain concatenation scales, such as the Neonatal Facial Coding System,[45] measure the simultaneous occurrence of facial or body movements, which are characteristic but not specific for pain during painful procedures.[46]

### *Behavioral and Physiological Indicators*

The majority of the studies (n = 20) utilized cry, cortisol levels, and physiological indicators such as heart rate and oxygen saturation as indicators of infant pain. Although these measures may be present during pain, their presence does not confirm or refute infant pain.[17] Increased heart rate and decreased oxygen saturation were common outcome measures for evaluating the pain in infants, but the studies failed to show how these indicators were related to pain.

A double-blind, placebo-controlled RCT was utilized to estimate the physiologic effects of repeated doses of 24% sucrose on pulse rate variability and salivary cortisol levels in infants born at less than 30 weeks' gestation.[25] Boyer et al[25] reported measures of central tendency did not differ among groups for heart rate or cortisol levels; however, a significant correlation between the standard deviation of heart rate and number of doses of only sucrose in the group receiving high doses of sucrose indicated greater variance in response measures. Findings from this study suggest that treating procedural pain with repeated doses of sucrose may not affect physiological parameters. Whereas vagal tone index and norepinephrine are considered sensitive indicators of physiological stability,[47] pulse rate variability and salivary cortisol levels may not be sensitive enough to measure physiological stability in preterm infants. Repeated handling or immobilization can significantly increase the physiologic response to subsequent painful stimuli. Although Boyer et al[25] found no significant difference in heart rate variability, Acharya et al[44] reported oral sucrose attenuated heart rate. This conflicting observation may be the infant's response to the stress of the procedure and does not confirm the presence of pain. Measurements of cortisol can vary based on the immature hypothalamic-pituitary axis in preterm infants and their ability to adapt to prolonged stress leading to unpredictable stress responses and cortisol levels.

Fernandez et al[48] examined electroencephalographic (EEG) activity, heart rate activity, and infants' facial behaviors before and after a noxious, but noninvasive, heel stroke procedure. Thirty-four newborns in an RCT were administered 2 mL of water or sucrose solution before the heel stroke. Frontal EEG asymmetry scores and power in the 3 to 6 Hz frequency band were analyzed. Infants who received water showed a pattern that typifies negative effect, increased relative right frontal EEG activation from baseline to the postheel stroke. The EEG of infants in the sucrose group remained unchanged. Heart rate increased in both groups during the heel stroke phase; however, after the heel stroke, the heart rate of infants who tasted water remained elevated, whereas the heart rate of infants who received sucrose returned to baseline. During the heel stroke, the infants in the water group exhibited twice the duration of crying and grimacing compared with those in the sucrose group. Because cry duration was measured in this study, it is difficult to conclude that sucrose decreased pain; however, it appears that oral sucrose demonstrated reductions in newborns' adverse physiological and behavioral responses to noxious stimuli.

## Interventions

### *Dose and Concentration*

In addition to the variety of sucrose concentrations (7.5%, 12%, 24%, or 50%), there is a wide variation in dose, ranging from 0.012 g[49] to 1 g,[50,51] with 0.12 g[49,52,53] and 0.24 g[17,27,34,35,54,55] being the most common dosage. Stevens et al[17] found that 2 mL of 12% to 24% sucrose, in the range of 0.24 g or 0.50 g, is effective in reducing pain responses in preterm and term infants. Despite the evidence supporting a reduction in crying time with greater concentrations of oral sucrose,[50] the literature does not support increased pain relief with doses greater than 0.5g.[17,34-36]

Small doses of sucrose (0.12 g) reduce composite pain scores (heart rate, respiratory rate, and facial expressions) in neonates with the gestational age of less than 34 weeks.[49,53,56,57] Johnston et al[49] found that repeated doses of oral sucrose efficacy during painful procedures in preterm infants (mean gestational age of 31 weeks) over 7 days demonstrated diminishing efficacy. The analgesic effect was diminished 4 minutes after the initial dose and 2 minutes after the second dose. It is possible that the infants develop a tolerance to the analgesic effects of sucrose with repeated dosing. More research is necessary to explore the dose tolerance relationship of sucrose.

Hatfield, in 2 separate studies,[19,26] reported that 0.6 mL/kg of a 24% oral sucrose solution was effective in decreasing behavioral pain response score during routine immunizations in healthy infants aged 2 and 4 months. Although the analgesic effect of oral sucrose was significant during a single immunization,[19] during serial immunizations, the greatest effect of oral sucrose appeared to be during the recovery phase of the procedure.[26] These findings suggest that sucrose analgesia cannot mitigate the severe amount of pain that infants experience during the injection phase of routine serial immunizations. Consequently, it will be important to investigate other interventions, alone or in combination, that can contribute to decreasing pain during routine procedures.

### *Timing*

Time delays between oral sucrose intake and the initiation of painful procedures ranged from 2 minutes to immediately before the procedure.[36,58,59] Blass and Ciaramitero[60] found that oral sucrose calmed neonates as early as 9 hours after birth, and the infants remained calm for 5 to 10 minutes after a painful stimulus. The investigators concluded that peak effect of the sucrose (measured as reduction in

crying time) occurs 2 minutes after administration to the tongue.

When duration of cry is used as an indicator of pain in term infants, 0.24 g (2 mL of 12% weight/volume sucrose) is efficacious for heel lances[49,56,61] and venipunctures.[62] In preterm neonates, 0.24 g administered 2 minutes before the painful procedure (2 mL of 12% weight/volume sucrose) has demonstrated efficacy for heel lances,[63,64] retinopathy of prematurity examinations,[65-68] and intramuscular injections.[28,30-32] Although the validity of findings is limited by the utilization of cry as the outcome measure, recent studies,[19,26] and the utilization of valid and reliable multidimensional behavioral pain scales, offer some indication as to the onset and duration of analgesia and timing of peak effects of sucrose.[19] The pharmacokinetic and pharmacodynamic properties of oral sucrose have not been adequately described.

### Method of Delivery

Oral sucrose has been delivered by a syringe,[19,26] with a pacifier,[69] or through a nasogastric tube.[70] When oral sucrose was given by syringe, the duration of delivery ranged from 30 seconds to 2 minutes.[26,71] For sucrose delivery by pacifier, there were inconsistencies in the number of times the pacifier was dipped into the sucrose solution. The absence of a universal method, dose exposure, and timing of sucrose administration across studies hampers the ability to draw definitive conclusions that would support best practices with oral sucrose administration. Considerable variations in the behavioral state of infants prior to intervention, preparation for procedures, and soothing interventions that occur randomly were not always controlled by investigators, and these may act synergistically to promote analgesia.[29,72] Failure to account for these cointerventions confounds the ability to make an appropriate clinical judgment about the isolated effects of oral sucrose as an analgesic.

### *Safety*

Systematic reviews and meta-analyses have provided the strongest level of evidence to support the safety and efficacy of a single dose of oral sucrose in infants.[34,35,73] Although no adverse effects of sucrose were reported in many of the studies examined in this review, it is not clear whether the study investigators monitored adverse effects or if they did, for how long. One study[74] hypothesized that a 20% sucrose concentration could predispose preterm infants to necrotizing enterocolitis (NEC). Small concentrations of 20% oral sucrose were mixed with calcium lactate and delivered directly into the stomach 8 to 12 times a day. These investigators suggested that the hyperosmolarity of the sucrose resulted in local trauma to the upper gut wall, which initiated the pathological process for NEC. This study failed to consider alternative pathogenic mechanisms. The highest incidence of NEC occurs during the winter months. It is possible that the increased occurrences of NEC during July through October could be attributed to a novel pathogen occurring during the study period.

Johnston et al[75] examined the effects of repeated doses of oral sucrose analgesia on neurobehavioral development during the first week of life in neonates younger than 31 weeks' gestation. Infants were randomly assigned to a sucrose or sterile water group. Although there were no differences between the groups on either neurobehavioral developmental outcomes or severity of illness outcomes, there were significant dose-related effects within each group. For the sucrose group, higher doses of sucrose predicted lower scores on motor development, vigor, alertness, and orientation at 36 weeks' gestation and lower motor development and vigor at 40 weeks' gestation. Although the sample size was inadequate (n = 107) in terms of the relative colinearity of the variables of interest, this study raises concerns that repeated doses of oral sucrose in infants younger than 31 weeks' gestation may place infants at risk for poorer neurobehavioral development and physiological outcomes. Several factors may have contributed to this outcome. First, the investigators gave the sucrose solution for 1 week and then withdrew the intervention. This may have increased the sensitivity to subsequent painful experiences. Second, by giving the preterm infant sucrose in the first week of life, the infants may have delayed the utilization of self-modulating behaviors, relying instead on external mediators (sucrose). When sucrose was removed, they were slower in development of self-modulating behaviors and it resulted in neurobehavioral and physiologic consequences in the subsequent few weeks.

In the previously mentioned RCT conducted by Hatfield,[26] 13% of the full-term infants (5 of the 40) experienced an adverse event. All adverse events occurred during the administration of the solution: 3 events in the 2-month groups and 2 events in the 4-month group. Coughing (n = 4) occurred with infants in the sucrose groups, and gagging (n = 1) occurred in the sterile water group. All infants recovered spontaneously within 10 seconds. Gibbins[53] reported minor adverse effects in 6 infants of the 190 infants who were randomized to a sucrose and nonnutritive sucking (NNS) group, sucrose alone, or sterile water and NNS. Desaturation occurred in both the sucrose alone and in the water and NNS group during the study period, and 1 neonate in the water and pacifier group choked when administering water but stabilized within 10 seconds. None of the infants required medical intervention. Because of the small number of adverse events, only frequencies and percentages for these were reported.

## Discussion

This integrated review, based on an exhaustive search of medical and nursing literature, highlights

**TABLE 2. Sucrose Clinical Practice Guidelines**

- Indication for use[34, 35, 73]
  - Relief of mild to moderate procedural pain such as heel lance, venipuncture, intravenous insertion, arterial punctures, subcutaneous/intramuscular injections, dressing changes, tape removal, eye examinations, wound care, suctioning, nasogastric insertion, bladder catheterization
  - As part of multimodal therapy during chest tube insertion, lumbar puncture, percutaneous line insertion, PIA insertion, circumcision
- Exclusion criteria
  - Infants who are sedated or paralyzed
  - Infants younger than 31 weeks and those with cardiorespiratory instability[49,75]
  - Infants with active GI concerns
  - Infants with unstable glucose
  - Infants with seizures or altered neurological status
- Age
  - Infants 31 weeks or older[49,75]
  - Infants aged up to 6 months[26]
  - Older infants should be evaluated for analgesic effectiveness
- Administration
  - Administer solution at room temperature
  - Administer with a pacifier or syringe, not effective if administered NG[70]
- Pacifier
  - Administer 2 minutes before painful procedure[34, 35, 73]
  - Dip pacifier in sucrose; if Sweetease (Children's Medical Ventures, LLC, Norwell, MA) is used, each dip approximately 0.2 mL (per manufacturer)
  - Repeat as needed for pain relief. Limited evidence exists to establish safety and efficacy limits
- *Oral syringe*
- Oral syringe use is preferred for safety. Apply directly on tongue
- Calculate solution administration by either weight OR gestational age
  - Weight guidelines: 0.6 mL/kg[19,26]
  - Gestational age guidelines for upper limits per administration
    - 0.5 mL for infants aged 27-31 weeks
    - 1 mL for infants aged 32-36 weeks
    - 2 mL for infants older than 37 weeks
- Deliver slowly over 1 minute
- Dose limits (mL/d)
  - No published limits

(*continues*)

**TABLE 2. Sucrose Clinical Practice Guidelines (*Continued*)**

  - Assess infant's pain regularly (time interval determined by infant's condition)
  - Administer appropriate volume to mitigate pain
  - If part of multimodal therapy, assess the effectiveness of other analgesia
- Alert intubated infants[85]
  - Assess infants ability to swallow
  - Assess tolerance, avoid gagging or choking
  - Document any adverse effects (gagging choking, etc)
- Adverse effects
  - With 24% sucrose solution, documented chocking, coughing, gagging. All self-resolved.[26,53]
- Documentation
  - Oral sucrose use should be considered a medication.
  - Oral sucrose may be ordered in a protocol for pain management.
  - Transcribe the sucrose as "as needed" pain medication.
  - Documentation of doses administered and effect of treatment related to pain should be charted.
  - Chart as pacifier dips or as a volume if given by syringe.
  - Caution: If a syringe is used, label the syringe so it is not mistaken for an intravenous medication.

Abbreviations: NG, nasogastric tube; PIA, peripherally inserted arterial line

Adapted from Lefrak Let al.[81]

the research supporting oral sucrose as preprocedural analgesic for management of mild to moderate procedural pain in infants. Findings from this review demonstrate the high prevalence of infant procedural pain in hospitals and pediatric clinics, the frequent lack of preprocedural analgesia, the efficacy of oral sucrose analgesia with biobehavioral approaches, and the avoidance of pharmacological interventions. The studies stress the importance of managing pediatric pain early in life to avoid possible long-term neurological sequela.

Emerging data on the long-term effects of undermanaged procedural pain in preterm neonates suggest that if procedural pain were adequately managed in the first week of life in preterm neonates, there might be positive long-term developmental effects.[1,12,13,15,16] Walco[76] contends that failure to treat procedural pain and distress has 2 major negative effects on infants. Painful procedures without adequate analgesia inflict unnecessarily pain and suffering. Repeated exposures to painful procedures at an early age are thought to be "remembered," and for newborns, sensitization to pain can persist into childhood and possibly over a lifetime.[77,78] This sensitization is thought to occur more

frequently from exposure to pain at a younger age[76] and even from one single painful event such as circumcision.[16] Moreover, sensitivity to pain can be expressed in terms of both physiological alterations, increased sensibility in the central nervous system to painful stimuli, and behavioral manifestations, which can include more pronounced aversive responses to potential or actual painful encounters. Walco[76] states that it is ethically unjustifiable and unacceptable to trivialize early exposures to pain that are left untreated or undertreated. With a physiological association between undermanaged acute pain and the potential development of chronic pain,[79] the importance of mitigating painful stimuli in infants cannot be overemphasized.

There have been nearly 2 decades of research on the management of pediatric pain; yet, little progress has been made to resolve the controversy surrounding pharmacological and behavioral interventions for procedural pain in infants.

The ideal preprocedural analgesic for infants must be effective, safe, short-acting, practical, and easy to use. It should be cost-effective and provide significantly greater analgesia than the current standard of care. A recent systematic review and meta-analysis confirms that oral sucrose has an important role in mitigating procedural pain in infants.[80]

Definitive conclusions from studies about the efficacy of oral sucrose is hindered by confounding study variables that were not controlled or addressed. Few

**TABLE 3. A Research Agenda for the Administration and Dosing of Sucrose Analgesia in Infants**

| |
|---|
| **Outcome Measures** |
| Gestational age and severity of illness may confound sucrose response. |
| What are appropriate outcome measures for extremely premature infants? |
| What are the valid and reliable outcome measures for the analgesic properties of sucrose? (eg, behavioral responses may show significant differences, physiologic responses may not) |
| Dosing |
| What are the upper and lower limits of volume and concentration that can be safely administered during a single procedure? |
| Is there a dose-response curve or threshold effect? |
| Does severe pain during procedures require higher doses or concentrations compared with mild or moderate pain during procedures? |
| Are the analgesic properties of sucrose affected by chronological age? |
| What is the upper limit of age or development at which sucrose analgesia remains effective? |
| Etiology/risk factors |
| What is the upper limit of sucrose administration over a 24-hour period without adverse short or long-term effects? |
| What is the safe and effective duration of sucrose analgesic therapy? |
| Can sucrose be safely administered to infants experiencing adverse metabolic effects as hyperglycemia and metabolic acidosis? |
| Are the analgesic properties of sucrose affected by adverse metabolic effects as hyperglycemia and metabolic acidosis? |
| What neonatal or infant populations are at risk for developing long-term adverse neurobehavioral effects? |
| What are the long-term clinical, behavioral, and neurodevelopmental consequences of sucrose therapy? |
| Pharmacodynamics/pharmacokinetics |
| What other factors influence the mechanism of action of oral sucrose? |
| Does sucrose have a synergistic or antagonistic effect with other analgesics? |
| Does sucrose alter the pharmacodynamics or pharmacokinetics of other medications? |
| Do other medications alter the analgesic properties of sucrose? |
| Are there synergistic or antagonistic interactions between sucrose therapy and behavioral or environmental measures, such as nonnutritive sucking, rocking, or music therapy? |
| Is sucrose metabolism and effectiveness altered during severe illness or extreme prematurity? |
| Is opioid responsiveness altered in children who are exposed to sucrose in the neonatal period? |

Adapted from Anand KJ et al.[82]

studies evaluated the interaction of behavioral or environmental conditions occurring during the interventions such as soothing, swaddling, comforting, reassuring, or distracting infants on infant pain. Diversity of samples and settings limits the generalizability of findings across populations and clinical areas.

Future research must focus on quantifying the overall treatment effect, determining the age at which sucrose is ineffective, establishing concentration and dosing schedules, and examining the relationship between sucrose and coanalgesic interventions that are commonly used to alleviate infant pain.

## Implications for Practice and Research

Evidence supporting the use of oral sucrose as a preprocedural analgesic guides health care providers in determining the appropriate population for this therapy, optimal concentrations and timing for administration, measures for determining a desired response, and identifying analgesic success with types of painful procedures. In clinical practice, oral sucrose administration may challenge the current standard of care by becoming an integral component of a pediatric multimodal pain protocol. Table 2 suggests an evidence-based/best practice clinical practice guideline for the administration of oral sucrose in hospitals and pediatric clinics.[81]

A research agenda to defining critical issues associated with sucrose analgesia is proposed in Table 3. Researchers do face challenges when conducting analgesic trials with infants and young children. The biggest challenge is the concern for the safety of infants participating in studies. Amazingly, there are limited numbers of pain research and controversies that exist over infants' ability to respond to various analgesics. The rigidity or variability in the interpretation of infant pain management guidelines makes it difficult to identify or establish standards of care.[82] This paucity of evidence and the lack of neonatal expertise on local institutional review boards delay approval of many pain management studies. Sometimes parents are reluctant to enroll their infant in a study because they misunderstand the randomization process and study procedures fearing that their child may not receive adequate pain relief.[82] Given these limitations, research demonstrates the value of oral sucrose in treating procedure-related pain. Importantly, advances in pain science justify the need for adequate pain control for infants.

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