Sucrose for Procedural Pain Management in Infants

abstract

The use of oral sucrose has been the most extensively studied pain intervention in newborn care to date. More than 150 published studies relating to sweet-taste-induced calming and analgesia in human infants have been identified, of which 100 (65%) include sucrose. With only a few exceptions, sucrose, glucose, or other sweet solutions reduced pain responses during commonly performed painful procedures in diverse populations of infants up to 12 months of age. Sucrose has been widely recommended for routine use during painful procedures in newborn and young infants, yet these recommendations have not been translated into consistent use in clinical practice. One reason may be related to important knowledge and research gaps concerning analgesic effects of sucrose. Notably, the mechanism of sweet-taste-induced analgesia is still not precisely understood, which has implications for using research evidence in practice. The aim of this article is to review what is known about the mechanisms of sucrose-induced analgesia; highlight existing evidence, knowledge gaps, and current controversies; and provide directions for future research and practice. Pediatrics 2012;130:1–8

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KEY WORDS
pain, infant, neonate, sucrose, analgesia

ABBREVIATIONS
CNS—central nervous system
NNS—nonnutritive sucking
PIPP—Premature Infant Pain Profile
RCT—randomized controlled trial

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The use of oral sucrose has been the most extensively studied pain intervention in newborn care to date. More than 150 published studies relating to sweet-taste-induced calming and analgesia in human infants have been identified, of which 100 (65%) include sucrose. With only a few exceptions, sucrose, glucose, or other sweet solutions reduced pain responses during commonly performed painful procedures in diverse populations of infants up to 12 months of age.1-3 Sucrose has been widely recommended for routine use during painful procedures in newborn and young infants,4-10 yet these recommendations have not been translated into consistent use in clinical practice.11-15 One reason may be related to important knowledge and research gaps concerning analgesic effects of sucrose. Notably, the mechanism of sweet-taste-induced analgesia is still not precisely understood, which has implications for using research evidence in practice. The aim of this article is to review what is known about the mechanisms of sucrose-induced analgesia; highlight existing evidence, knowledge gaps, and current controversies; and provide directions for future research and practice.

HISTORICAL OVERVIEW

Oral sucrose has been the most extensively studied procedure-related pain reduction strategy in neonatal care.1,4 Although randomized controlled trials (RCTs) evaluating effects of sucrose in infants were not published until the late 1980s, there are historical references pertaining to the analgesic and calming benefits of sweet substances dating back to AD 632, when Prophet Mohammed recommended giving infants a well-chewed date.14 Sugar solutions, often mixed with a combination of alcohol and cocaine or opium, were widely promoted in the late 1840s and early 1900s as an effective intervention to calm crying infants, alleviate colic pain, and reduce pain during procedures in young children.15,16 Sugar mixed with wine or whisky was recommended for infant boys undergoing circumcision,17 and in 1938, recommendations were made that suggested anesthesia for infants during surgery was often not required and that “a sucker consisting of a sponge dipped in some sugar water will often suffice to calm a baby” (p. 2021).18 Language used to describe the effects of sucrose on infants from these early reports through to present-day studies varies from report to report. Terms such as “calming” and “analgesic” are frequently used interchangeably. Analgesia reduces behavioral and physiologic indicators of pain. Calming reduces observable behavioral indicators of pain and distress. The indicators for analgesia and calming are highly intertwined, making it difficult to discriminate between them. This is true as well for studies of sucrose using animal models. However, for the purposes of this article, the interpretation of these terms are as follows.

“Calm” was defined by Blass and Ciaramitaro in 1994 as an alert yet quiet state; “when infants cried less than 24 sec/min during the 10 min that preceded stimulation and were in an alert state as judged by eye opening and gross motor activity scores of approximately 0.5 or more” (p. 40).19 Calm is most commonly used to describe an alert and quiet, but not sedated state. “Analgesia” is defined by the International Association for the Study of Pain as the absence of pain in response to stimulation that would normally be painful20 and “pain” is defined as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Note: The inability to communicate verbally does not negate the possibility that an individual is experiencing pain and is in need of appropriate pain-relieving treatment. Pain is always subjective.”20 This use of the term analgesia, defined by the International Association for the Study of Pain, is particularly open to criticism when describing effects of most analgesic agents. “Absence of pain,” based on observational measures (behavioral indicators including facial expressions, crying, body movements) and composite measures (behavioral and physiologic indicators plus other indicators such as behavioral state, nurses perception of pain) is rarely achieved, yet the term is widely used in neonatal pain studies. This, highlights the subjective nature and selection of terms and the lack of clarity surrounding the term “pain” in infants among clinicians and researchers. In addition, the emotional component of pain in infants is not able to be interpreted. Despite many years of debate,21 this lack of clarity of the definition and meaning of these terms still has an impact on the interpretation of infants’ responses to sucrose, especially because the mechanisms of sucrose are not fully understood in either animals or humans.

ANIMAL MODEL STUDIES

Investigations into the cellular and molecular mechanisms underlying the effects of sucrose in animal models are relatively sparse and hampered by varying methodologies. However, there is compelling evidence that an endogenous opioid-sweet taste relationship exists.22-31 Calming and/or analgesic effects of sucrose that occur rapidly, last for several minutes, and can be blocked by systemic opioid receptor antagonists have been demonstrated in rats.29,32 The mechanism of effects suggest an increase in serum and cerebrospinal fluid beta-endorphin levels after orally ingested sucrose but not
intragastrically administered sucrose.\textsuperscript{31} However, as in human infants, the literature is confounded in part by the difficulty in distinguishing between a calming and pain-relieving effect\textsuperscript{33} (ie, separation of stress from noxious responses).

There are few firm conclusions to be drawn from the animal literature on the mechanism of sucrose. Variability in age of animals, modality of testing, sucrose dose, and timing of administration makes direct comparison between studies difficult. Using c-fos as a surrogate of neural activity combined with behavioral testing, Anseloni and colleagues showed an age-dependent analgesic action of sucrose in rat pups.\textsuperscript{32} Noxious activation of spinal c-fos, was significantly reduced with sucrose. Using reflex withdrawal thresholds to a noxious stimulus, Anseloni and colleagues demonstrated a postnatal window of efficacy of sucrose restricted to the first 2 or 3 weeks of life and also a clear rostrocaudal developmental gradient of this effect, with a delayed effect of sucrose on hind-paw responses compared with forepaw.

Considerable postnatal development occurs in central nervous system (CNS) structures involved in both nociception and opiate-receptor-dependent modulation of nociceptive input,\textsuperscript{34–36} which accounts for these changing sucrose responses in animals. In another study, to elucidate the central pathways that mediate the effects of sucrose, Anseloni and colleagues again used c-fos activity in CNS neurons and behavioral reflex responses to probe into higher centers of the CNS.\textsuperscript{57} Through the use of midcollicular lesions, they were able to isolate higher centers (eg, the forebrain), and show that sucrose persisted in attenuating the behavioral nociceptive responses in the rat pups, indicating that forebrain circuitry is not required for the activity of sucrose.

Furthermore, using c-fos expression, they were able to map sucrose-induced activity in the CNS and showed that the solitary tract in the brainstem was activated. Because this is the primary relay in the ascending gustatory pathway, it is not surprising that there is activity after intraoral sucrose in animals. However, they also found evidence of activity in brainstem areas associated with descending pain modulation, the periaqueductal gray, and raphe nucleus.\textsuperscript{37} The medullary raphe nucleus is a critical mediator of endogenous analgesia and modulates the analgesic actions of opioids.\textsuperscript{38} Furthermore, the ingestion of hedonic foodstuffs (eg, sucrose) is associated with analgesia.\textsuperscript{39} This effect has been proposed to be a consequence of suppressed reactions to distracting (ie, painful) stimuli mediated by the raphe nucleus.\textsuperscript{39} In the adult rat model, the brainstem-spinal cord projections are an important source of nociceptive processing in the spinal cord. In the neonate, however, the descending inhibitory influences are not fully mature,\textsuperscript{34,35} and descending inhibitory tone can only be detected after the third postnatal week in rats.\textsuperscript{35,36} As such, the influence of oral sucrose on these structures and central nociceptive processing is unclear and requires further elucidation.

Both the ascending gustatory and associated descending pathways are known to have an opioid-receptor-mediated modulated component, but where specifically within this pathway the antagonistic effects of opioid blockade on oral sucrose effects occurs is unclear.

**HUMAN MODEL STUDIES**

While the role of sucrose in reducing pain and stress in animal models was being studied, effects in human infants were also being evaluated. In 1989, Blass and colleagues first reported that sucrose was extraordinarily calming with effects persisting well beyond the initial sucrose dose.\textsuperscript{40} Numerous subsequent studies reported the same findings.\textsuperscript{41–47} Calming effects were clearly nonsedating, with infants remaining alert after sucrose administration.\textsuperscript{19} In addition, effects were observed to be sweet-taste dependent, sucrose was more effective than glucose, and the least sweet sugar, lactose, was no more effective than water in reducing crying. To further test the endogenous opioid basis of sweet-taste-induced calming, the response of sucrose in infants born to mothers on methadone was evaluated.\textsuperscript{19} Because infants exposed to antenatal methadone have a poorly functioning endogenous opioid system, it was hypothesized that the sweet-taste-mediated analgesic mechanism would not function in these infants.\textsuperscript{19} Findings supported the hypothesis; sucrose was ineffective in calming methadone exposed infants suffering from withdrawal symptoms, adding evidence to the association among sweet taste, an intact endogenous opioid system, and analgesia. Until recently, this was the only study examining effects of sucrose in infants with antenatal opioid exposure.

From these studies demonstrating calming effects of sucrose on crying infants, the research questions turned to whether sucrose reduced pain if given before painful procedures. In the first published report of a placebo-controlled RCT of sucrose for procedural pain in newborn infants, sucrose significantly reduced crying during a heel lance and resulted in a more rapid return to a calm state compared to water.\textsuperscript{46} Additionally, the combination of 24% sucrose solution and non-nutritive sucking (NNS) significantly reduced crying duration during circumcision, compared with no treatment or NNS with water.\textsuperscript{48} The compelling evidence from these early studies demonstrating profound
effects of oral sucrose in inducing and maintaining a calm yet awake state in newborn infants and reducing behavioral responses during painful procedures compared with water and less sweet solutions, set the stage for an abundance of subsequent studies, reviews, and systematic reviews. A systematic review and meta-analysis of 44 RCTs showed that sucrose consistently reduced behavioral responses (cry duration, facial actions, and composite pain scores (consisting of behavioral and physiologic indicators) to tissue-damaging noxious procedures compared with placebo, no treatment, or less sweet solutions including breast milk. An exception to these findings was when sucrose had minimal effects compared with water when given within hours of birth before intramuscular injection of vitamin K. This finding concurred with an animal model study in which sucrose had no effect in reducing responses to thermal stimuli in newborn rats on the first day of life. One explanation proposed for this more modest effect of sweet taste in the first 12 hours of birth may be due to high circulating serum β-endorphins negating further increase in response to sweet taste.

Sucrose has also been shown to be less effective when used for prolonged and/or more intensely painful procedures. Although results of a meta-analysis of 4 studies conducted during eye examination showed sucrose significantly reduced Premature Infant Pain Profile (PIPP) scores, the effects were small and inconsistent between individual studies. In addition, a 50% glucose solution was no more effective than water during circumcision, and a single dose of sucrose failed to significantly reduce crying in older infants undergoing urethral catheterization and venepuncture. The reduced effectiveness of sweet solutions in these more invasive procedures of relatively long duration may be due to the short-lasting effects of a single dose given 2 minutes before the procedures. Effects may not be sustained over prolonged procedures, especially in infants beyond the newborn period. Although the duration of sucrose for ≥5 minutes in healthy newborn infants has been demonstrated, and in one study, a prolonged effect time up to 45 minutes in healthy newborns was reported, a short effect time of only 1 minute was demonstrated in infants aged 5 to 7 weeks.

Based on these observations, administering sucrose in small aliquots throughout the duration of painful procedures of prolonged duration may ensure a more sustained analgesic effect.

Despite the strong evidential base of analgesic effects of sucrose in newborn and young infants for single painful procedures, there remain knowledge gaps concerning the following:

- Opioid pathways involved in mechanism of effect, especially in the developing infant
- Effectiveness when administered with concomitant opioid analgesics
- Effectiveness when administered concurrently with other pain management strategies such as skin-to-skin care
- Use, safety, and effectiveness when used repeatedly for extended periods in extremely low birth weight infants and sick infants requiring prolonged hospitalization

Despite the extensive work conducted in animal laboratories from the 1980s onward, the mechanisms of analgesic effects of sweet solutions in human infants remain poorly understood. On the basis of animal studies, the key mechanism is believed to be sweet-taste-induced β-endorphin release.

However, elevated serum levels of β-endorphin in response to oral sucrose has not been identified in human infants to date. In addition, other central mechanisms of sucrose including dopamine and acetylcholine have been postulated. Additional research is required to elucidate their role in pain reducing effects of sucrose.

The limited understanding of sucrose mechanisms has also had an impact on the interpretation of nonbehavioral responses that are not attenuated by sucrose solutions. As highlighted in the systematic review of sucrose for analgesia in newborn infants undergoing painful procedures, sucrose reduced behavioral responses and various composite pain measures during single episodes of short, sharp, painful procedures compared with no treatment, water, NNS, and small volumes of breast or formula milk. However, when examined in isolation, responses other than behavioral were less consistently attenuated by sucrose. Oxygen saturation during heel lance or venipuncture was not influenced by oral sucrose, and sucrose reduced heart rate changes from baseline in only half of the studies. Similarly, cortical activity, as measured by EEG responses are inconsistent with behavioral responses.

No differences in EEG responses during heel lance between sucrose and water (measured <1 second after heel lance) or glucose and water (averaged over 2 minutes after heel lance) were demonstrated despite significant reduction in PIPP scores. In addition, hormonal responses as measured by salivary cortisol were not affected by sucrose administration during heel lance, circumcision, or all painful procedures during the first week of life in a NICU. These studies highlight important questions about the mechanisms of sweet-taste-mediated pain reducing responses, in particular, the inconsistency among behavioral, physiologic, hormonal, and cortical responses. In infants, the correlation between physiologic and
behavioral responses to pain is reported to be only 0.3. The dissociation, direction, and degree of responses is common among all types of pain indicators across all ages, illustrating the complexity of the responses to nociceptive stimuli and the subjective phenomenon of pain. Given this complexity and weak correlation among various types of indicators, the ongoing, fundamental question remains whether there is an optimal indicator(s) of pain and what it might be in infants. The dissociation among behavioral, physiologic, and cortical responses illustrates that 1 pain outcome or 1 indicator of pain does not sufficiently capture the complete picture of pain.

Another key unanswered question is to what extent the sweet-taste-mediated endogenous opioid effects occur in the context of exogenous opioid delivery. Whether sucrose reduces pain when given with concomitant opioid analgesics is an important question because the effectiveness of opioid analgesics alone in reducing pain in sick infants during acute painful procedures is questionable.65–69 Sucrose given with exogenous opioid analgesics has only been evaluated in 2 studies. Harrison et al reported no statistically significant differences in behavioral responses during heel lance when infants were receiving opioid analgesics and sucrose compared with receiving sucrose alone. However the number of observations when infants were receiving opioid analgesics (n = 79) may have been underpowered to detect a difference. Second, Marceau et al evaluated 24% sucrose during heel lance in newborn infants born to mothers on antenatal methadone, compared with non-methadone exposed infants. Eight of the 26 methadone-exposed infants were receiving morphine at the time of study for management of opioid withdrawal. No group differences in PIPP scores, heart rate, or oxygen saturation were reported. In fact, PIPP scores across all infants were all low, suggesting efficacy of sucrose even in the context of methadone exposure and withdrawal. The study had a number of limitations due to unblinding, and the small sample size of infants receiving morphine (n = 8 infants). Given the inconsistency of results with the only previous study evaluating sucrose for methadone exposed infants, more research in this area is warranted.

The previously established evidence regarding the ability of opioid antagonists to block analgesic effects of sweet solutions has also been called into question. Although in animal models, naloxone blocked analgesic effects of sucrose, this same effect was not demonstrated in human newborn infants when naloxone was injected intravenously. In fact, the opposite effect occurred; analgesic effects of naloxone were demonstrated. Such analgesic effects of opioid antagonists when given in low doses have been reported previously. However, such conflicting results emphasize uncertainties as to the mechanism of sucrose analgesia, the opioid pathways responsible, as well as the differences between animal and human infant mechanisms precluding consistent application of bench to bedside findings. Although there is a plethora of published studies evaluating sucrose during single episodes of painful procedures, knowledge gaps concerning the effectiveness and safety of multiple doses given during varying frequencies over the course of an infant’s hospitalization remain. Prolonged use of sucrose for periods of >1 weeks’ duration, during repeated painful events has been reported in only 3 studies: 2 RCTs in preterm infants and a longitudinal cohort study of infants hospitalized between 1 and 5 months, all of whom received sucrose during heel lance. Both RCTs showed that sucrose was more effective than NNS alone or standard care, and sucrose alone was more effective than NNS and topical anesthetic during repeated subcutaneous injections, although the combination of all 3 interventions had the largest effect. Harrison et al reported that behavioral indicators of pain remained persistently low with no increase in these parameters over the full course of infants’ hospitalization. In addition, changes in physiologic parameters in response to heel lance remained stable over the course of hospitalization. To date, these are the only studies examining prolonged use of sweet solutions for procedural pain management.

Prolonged use of sucrose raises important questions related to effectiveness and safety, although there is a paucity of data relating to long-term outcomes. Johnston et al reported that preterm infants <31 weeks’ gestational age who received >10 doses of sucrose per 24 hours in the first week of life had poorer neurologic outcomes compared with infants who received fewer sucrose doses. No differences in any safety outcomes after consistent use of sucrose for pre-term infants over the first month of life were reported in another study. These are the only studies that have reported on longer-term outcomes in infants after repeated sucrose use.

**Practice and Research Implications**

The complexities in interpreting such a diverse body of evidence relating to the role of sucrose in inducing calm and reducing pain responses, the prevailing deficiencies in understanding mechanisms involved in sucrose analgesia, and the dearth of evidence relating to extended and repeated use of sucrose in preterm and sick infants have
resulted in debates and controversy over whether sucrose should be considered standard care.1,6,16 The same argument applies to glucose, because many studies have shown that glucose, if sufficiently concentrated, also reduces pain in infants.1,78,79 However, although basic science and clinical researchers and clinicians continue to address the knowledge and research gaps relating to analgesic effects and mechanisms of sucrose, we need to remain cognizant that untreated or poorly treated pain in fragile infants has well-documented short-term adverse consequences and potential longer-term negative effects.4 Clinicians therefore have an ethical responsibility to minimize pain exposure; use sucrose appropriately for single painful procedures, along with other evidence-based strategies including NNS, kangaroo care, and breastfeeding.80 and monitor use and effectiveness of these strategies over short- and long-term periods. Importantly, clinicians’ decisions must be based on the best evidence available and not swayed by single studies or pervasive myths.81 Clinicians and researchers would, however, benefit from clear guidelines including recommended volumes and dosing regimens of sucrose. Although the authors of the Cochrane systematic review of sucrose analgesia in newborn infants could not establish an optimal sucrose dose,3 only small volumes are required, such as 0.1 to 1 mL or ~0.2 to 0.5 mL/kg. Researchers and clinicians should take into account tailoring doses based on context in which sucrose is to be used, including gestational and postnatal age of the infant, severity of illness, and the painful procedure being performed. Finally, a consensus on the definition of “pain” in infants may greatly assist pain researchers to use consistent terms and to use consistent outcome measurements in future studies. Remaining knowledge and research gaps concern the mechanism of the effects of sucrose, determination of the best indicator or combination of indicators for assessing pain in infants, effectiveness and safety for repeated use in extremely preterm infants and critically ill infants, effectiveness for infants exposed to antenatal methadone or receiving postnatal opioid analgesics, and best dosing regimes.

CONCLUSIONS

Prolific research concerning pain-reducing properties of sucrose has been conducted over the past 25 years, with indisputable evidence that small volumes significantly reduce behavioral responses and composite pain scores to painful procedures in newborn and young infants. Recommendations for practice include using small volumes of sucrose for painful procedures only; avoiding use for calming irritable infants who are not undergoing procedures; giving solutions in aliquots over the duration of the procedure for prolonged procedures; avoiding use of >10 doses per 24 hours, especially during the first week of life; and using other effective strategies during painful procedures when feasible. Future research needs to address remaining areas of uncertainty with the ultimate aim of ensuring that no infant suffers unnecessary pain during painful procedures.

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