Authors and Disclosures
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From Pain Management Nursing
Oral Sucrose and Pain Relief for Preterm Infants
Anita Mitchell, RN, PhD, Patricia A. Waltman, RNC, EdD, NNP

Abstract and Introduction

Abstract
The frequency of painful procedures performed on preterm infants in the neonatal intensive care unit (NICU) presents a challenge to nurses who are attempting to provide effective pain relief, and to the infants themselves who may suffer adverse consequences in response to repeated painful procedures. One new pain relief intervention under study is the administration of oral sucrose, which may activate endogenous opioid systems within the body. Studies with preterm infants that have examined the use of oral sucrose as an analgesic during heelsticks and venipunctures have shown that sucrose is effective in reducing pain. Sucrose may also be combined with nonnutritive sucking to provide significant pain relief. The use of oral sucrose is now recommended with a wide range of painful procedures in the NICU. Promising results have been observed in studies with both term and preterm infants, but less research has occurred with preterm infants. Additional research is warranted to determine the most effective approaches for the administration of sucrose, to examine the effectiveness of sucrose with additional types of painful procedures, and to examine the effects of long-term repeated use of sucrose.

Introduction
Preterm infants need effective pain management during and after the frequent painful procedures that are performed in neonatal intensive care units (NICUs). It is a challenge for nurses who work in these areas to provide comfort to infants and to prevent and relieve pain during diagnostic and therapeutic procedures. The American Academy of Pediatrics (2000) states that "despite the advances in pain assessment and management, prevention and treatment of unnecessary pain attributable to anticipated noxious stimuli remain limited" (p. 2).

In recent years, nurses have placed increasing emphasis on developmentally sensitive care for preterm infants, recognizing the unique needs of these infants who may have difficulty coping with extraterine life. Oral sucrose has been studied extensively in neonates and shows promise as a developmentally appropriate and effective means of relieving pain in preterm infants during procedures. The purpose of this article is to review the literature concerning the use of oral sucrose with preterm infants. This literature review will include physiologic mechanisms of sucrose action, current recommendations for sucrose use, and a critique of published studies involving the use of sucrose with preterm infants.

Physiologic Mechanisms and Background of Oral Sucrose

Studies support the theory that sucrose and pain relief are interrelated through the body's endogenous opioid system that provides natural analgesia (Barr et al., 1995; Nikfar, Abdollahi, Etemad, & Sharifzadeh, 1997). Sucrose as an analgesic was first studied using laboratory rats. In 1987, researchers demonstrated that rats receiving an oral infusion of 7.5% sucrose experienced a significant elevation in pain thresholds compared with groups of rats that received an oral infusion of water or no infusion (Blass, Fitzgerald, & Kehoe, 1987). The
The analgesic effect of sucrose is reversed with administration of naloxone, an opioid antagonist, suggesting that sucrose activates the central endogenous opioid system with an action similar to that of opioid analgesics (Barr et al., 1995; Blass et al., 1987). The analgesic action of sucrose may involve descending pain-modulating mechanisms, with inhibition of pain transmission at the spinal level. The presence of sucrose in the mouth also may stimulate the release of endorphins from the hypothalamus (Ren, Blass, Zhou, & Dubner, 1997).

Studies with infants indicate that the pain-reducing qualities of sucrose appear to be in its sweet taste, and do not rely on systemic absorption. In a double-blind crossover study of 30 preterm infants of 32 to 36 weeks' gestational age, sucrose effectively reduced pain when given by mouth but not when administered through a nasogastric tube (Ramenghi, Evans, & Levene, 1999). In another study that examined the action of sweet-tasting solutions, 60 full-term newborns were assigned randomly to four treatment groups. Each infant received one of the following: sterile water, 25% sucrose, 50% sucrose, or Calpol (a sweet-tasting solution). The artificially sweetened solution was as effective as both sucrose solutions in relieving pain, which suggests that the analgesic effect was due to sweet taste and not systemic absorption of sucrose products (Ramenghi, Griffith, Wood, & Levene, 1996). Similar results were found in a study that compared the effectiveness of the artificial sweetener aspartame with 24% sucrose (Barr, Pantel, Young, Wright, Hendricks, & Gravel, 1999). These authors described the analgesic action as a "sweetness effect" (p. 415).

Questions arose regarding the use of glucose, or breast milk as a substitute for sucrose. However, no studies have examined the use of alternate sweet liquids with preterm infants. A study with term newborn infants found that 30% glucose significantly reduced crying time (p < .01) and reduced increases in heart rate during heelsticks. The researchers concluded that 30% glucose was effective in relieving pain during procedures (Skogsdal, Eriksson, & Schollin, 1997). In a study that compared the effectiveness of breast milk with 25% sucrose as an analgesic during heelsticks in term newborns, sucrose was found to be effective in reducing crying time and heart rate, but breast milk did not make a significant difference in crying time or heart rate (Ors et al., 1999).

The peak response time for sucrose is compatible with the time needed to activate the endogenous opioid system. In a study that focused on response time, infants received oral sucrose followed by heelsticks at 30, 60, 90, 120, and 240 seconds. The maximum reduction in crying was noted in the 120-second heelstick group. This time delay is consistent with the time needed for the release of endogenous opioids by taste stimulation and the time needed to occupy opioid receptor sites (Blass & Shah, 1995).

At this time, there are no reports of side effects associated with the administration of single, small (< 2 ml) doses of 24% sucrose to term or preterm infants. Sucrose solution used in small doses for analgesia has not been shown to cause hyperglycemia in preterm infants (Bucher et al., 1995).

**Recommendations for Using Sucrose to Provide Pain Relief for Preterm Infants**

The International Evidence-Based Group for Neonatal Pain has published a consensus statement for the prevention and management of pain in the newborn. This interdisciplinary, international group was made up of infant pain experts from various practice settings. Faculty members reached a consensus and presented guidelines for the management of pain in infants after performing a thorough systematic literature review, analyzing and critiquing randomized controlled trials (RCTs), and performing meta-analyses. Evidence-based guidelines in this statement recommend interventions that prevent and manage pain for a wide variety of painful procedures performed on newborn infants (Anand, Phil, & the International Evidence-Based Group for Neonatal Pain, 2001).

(Anand and Phil (2001) recommend the use of a pacifier with 12% to 24% sucrose as a pain relief measure. The recommended dose of sucrose solution for the preterm infant is .1 to .4 ml, and the recommended dose for the term neonate is 2 ml. Guidelines in the consensus statement encourage the combination of a variety of behavioral and pharmacologic interventions during painful procedures to give an additive or synergistic effect. Therefore, offering an infant a pacifier with sucrose may be one of several interventions, combined with comfort measures such as swaddling and analgesic medications.
The Cochrane Collaboration is an international, interdisciplinary organization that performs systematic reviews and meta-analyses of RTCs, and provides evidence-based information for healthcare professionals who are making practice decisions. One systematic review provided by the Cochrane Collaboration examined the use of sucrose during painful procedures performed on preterm and term infants. This review recommended the use of oral sucrose to relieve pain in both term and preterm infants during single painful procedures such as heelsticks or venipunctures. Effective doses for preterm infants ranged from .012 g (.05 ml 24% solution) to .12 g (.5 ml 24% solution) sucrose given 2 minutes before heelsticks. It was also recommended that additional pain relief measures be used in combination with the sucrose (Stevens, Yamada, & Ohlsson, 2002). Sucrose is given two minutes before a painful procedure, and its action lasts approximately five minutes (Barr et al., 1995; Blass, 1994).

Ohlsson, Taddio, Jadad, & Stevens (2000) used a systematic review to make decisions on a variety of clinical practice questions pertaining to pain relief for infants. Using evidence-based guidelines, these researchers concluded that sucrose and alternative sweet liquids such as 30% glucose or Calpol (i.e., hydrogenated glucose) are effective in relieving pain during heelsticks.

A systematic review and meta-analysis of sucrose by Stevens, Taddio, Ohlsson, & Einarsen (1997) summarized and critically analyzed those sucrose studies that utilized varying concentrations and doses of sucrose for pain management studies with infants. According to this meta-analysis, the concentration of sucrose for use in infant pain management typically varies between 12% and 24%, and the volume varies from .05 ml for preterm infants to 2 ml for term infants. The sucrose may be administered to preterm infants by dipping a pacifier into the sucrose solution. The volume of sucrose on a dipped Wee Thumbe pacifier (Children's Medical Ventures, Norwell, Massachusetts) is approximately .1 ml (Stevens et al., 1999).

Review of Studies Evaluating Sucrose for Pain Relief for Preterm Infants

The administration of oral sucrose as an analgesic for infants is a new approach in pain management, and it is important for nurses to examine the evidence that supports recommendations for sucrose use. Table 1 presents a summary of various randomized controlled trials that have examined the analgesic effect of sucrose during painful procedures in preterm infants. Selection of studies to be presented was based on inclusion in the Cochrane Database of Systematic Reviews (Stevens, et al., 2002). The following section presents a critique of studies that have examined the use of sucrose for pain relief in preterm infants. The studies are categorized according to the focus of the study or the specific questions addressed.

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**Effectiveness of Oral Sucrose as a Single Treatment Before Painful Procedures**

Only one study examined the effectiveness of oral sucrose to relieve pain during venipunctures in preterm infants (Abad, Diaz, Domenech, Robayna, & Rico, 1996). This double-blind RCT was carried out with a small sample of 28 infants who were younger than 37 weeks' gestational age. Infants were randomly assigned to receive 2 ml of spring water, 12% sucrose, or 24% sucrose through a syringe 2 minutes before venipunctures were performed for routine blood collection. Venipunctures were performed at least 1 hour after feeding or suctioning, and during a period when the infants were awake and quiet. Infants were monitored at baseline, throughout the venipuncture process, and 5 minutes after the venipuncture. No significant differences were found in oxygen saturation levels or respiratory rates among the groups, and heart rate was lowest in the group that received 12% sucrose. Significantly less crying occurred in the 24% sucrose group when compared with the water group or the 12% sucrose group (p < .05).

In a double-blind, crossover RCT to determine the effectiveness of a single treatment of oral sucrose to relieve pain during heelsticks, a sample of 15 infants with gestational ages ranging from 32 to 34 weeks were evaluated (Ramenghi, Wood, Griffith, & Levene, 1996). Each infant received, at separate times, 1 ml of sterile water and 1 ml of 25% sucrose solution. Random allocation determined which treatment would be given first and which would be given second to each individual infant. Treatments were given 2 minutes before heelsticks. Pain was measured partially by timing the duration of crying. Infants demonstrated significantly shorter duration of first cry (p = .004) and total percentage of crying time longer than 5 minutes (p = .018) after sucrose administration as compared with water administration. A pain score based on facial expressions (i.e., brow bulge, eye squeeze, nasolabial furrow, and open mouth) was assessed, but this score was not based upon an established, validated tool. Infants who received water demonstrated significantly higher facial pain scores at 1 minute (p = .01) and 3 minutes (p = .03) after heelstick. No significant differences in heart rate were found between the two treatments. A third double-blind, crossover RCT used 16 preterm infants with gestational ages of 33 to 36 weeks to examine the effectiveness of oral sucrose as an analgesic during heelsticks (Bucher et al., 1995). Each infant was assessed twice, and received either 2 ml of distilled water or 2 ml of 50% sucrose in random order before heelsticks. Pain was assessed by timing the duration of crying and by noting physiologic data. Infants who received sucrose cried for a significantly shorter period (p = .002) and experienced significantly smaller increases in heart rate (p = .005). Oxygen levels and cerebral blood volumes did not differ significantly between
treatments. Sucrose administration did not result in significantly increased blood glucose levels. Median glucose concentration after blood sampling with sucrose was 5.8 mmol/L and with water was 6 mmol/L.

All three of these studies reported that oral sucrose was effective in relieving pain. However, the results must be analyzed in light of the method used to measure pain, and these studies did not use valid tools designed to measure pain in preterm infants. All three studies evaluated pain response partially by timing the duration of crying. Crying may not be the most specific way to assess pain in preterm infants because these young infants do not consistently cry during painful procedures. The small and fragile preterm infant may not have the strength or energy to sustain an organized cry response in painful situations (Als, 1982; Stevens, Johnston, & Horton, 1994; Stevens, Johnston, Petryshen, & Taddio, 1996).

Facial activity is proposed to be the most sensitive measure of pain response in the preterm infant (Grunau & Craig, 1987; 1990; Lawrence, Alcock, McGrath, Kay, MacMurray, & Dulberg, 1993; Stevens et al., 1996). However, in two of these studies, facial expressions were not used as a measure of pain (Abad et al., 1996; Bucher et al., 1995). Changes in physiologic indicators, such as increased heart rate and decreased oxygen saturation, alert the caregiver that the infant may be experiencing pain (Craig, Whitfield, Grunau, Linton, & Hadjistavropoulos, 1993; Gonsalves & Mercer, 1993; Stevens & Johnston, 1994). All three of these studies used some form of valid physiologic measurements.

These three studies assigned infants randomly to treatment groups, included only healthy preterm infants, carried out blinding of the intervention and outcome measurement, and standardized all aspects of the procedure including the provision of a consistent health care provider to perform the heelstick or venipuncture. These studies did not include an examination of the frequency and timing of additional painful procedures experienced by the infants. An examination of these contextual factors is important because if the infant has undergone frequent or recent painful procedures, this may diminish the behavioral response to pain (Johnston & Stevens, 1996; Johnston, Stevens, et al., 1999; Stevens et al., 1994).

Questions Concerning Single Versus Repeated Doses of Sucrose

In clinical studies with human infants, researchers have typically given a single dose of sucrose before a procedure. The analgesic effect of sucrose lasts approximately 3 to 5 minutes (Blass et al., 1987), with the peak effect in 2 minutes (Blass & Shah, 1995). One double-blind RCT examined whether there was a difference between administration of a single dose of sucrose and administration of repeated doses of sucrose on preterm infant pain as measured by the Premature Infant Pain Profile (PIPP). The sample consisted of 48 infants between 25 and 34 weeks’ gestational age. Three comparison groups were used during heelsticks as follows: three doses of 24% sucrose given by syringe 2 minutes before heelstick and every 2 minutes thereafter, one dose of 24% sucrose and two doses of sterile water given as above, and three doses of sterile water. All doses of sucrose and water were limited to a volume of .05 ml. The repeated sucrose group showed significant reductions in pain scores compared with the single sucrose group (p < .05) only in the last block of time measured (120 to 150 seconds). Background data were collected concerning each infant’s medical history and severity of illness (Johnston, Stremler, Horton, & Friedman, 1999).

This study was the first to examine the effectiveness of repeated doses of sucrose to relieve pain for preterm infants during procedures. It would be important to extend the data collection time longer to determine the effectiveness of repeated doses in helping an infant to return to a baseline state, and to determine the need for repeated doses in painful procedures that last longer than a heelstick. A replication of the study using a larger sample size would also be helpful.

The Combination of Sucrose and Rocking

Johnston, Stremler, Stevens, and Horton (1997) determined the effectiveness of oral sucrose and rocking to relieve procedural pain in preterm infants. Eighty-five infants between 25 and 34 weeks of age were randomly assigned to one of four treatment groups: 24% sucrose alone, rocking alone, combined 24% sucrose and rocking, and a control group that was given sterile water without rocking. The sucrose dose was .05 ml. Both the sucrose and water were given by syringe. Pain responses were measured using increase in heart rate and the
Neonatal Facial Coding System (NFCS). The NFCS was originally designed to assess pain in full-term neonates and was based on findings that facial activity is a sensitive indicator of pain (Grunau & Craig, 1987; 1990).

The administration of sucrose alone or in combination with rocking resulted in a significant reduction of facial expression of pain ($p < .02$). No significant difference in facial expression was found between sucrose alone and sucrose in combination with rocking. Similarly, no significant difference in facial expression was found between rocking alone and the control group. No significant differences in heart rates were found among the four groups ($p = .566$) (Johnston et al., 1997).

One limitation to this study is that the treatment groups contained varying numbers of infants resulting from early termination of the study. The study was stopped when it became evident that sucrose provided significant pain relief and the rocking did not. The group that received sucrose in combination with rocking was smaller in number than the other groups.

The Combination of Sucrose and Nonnutritive Sucking

Some researchers have used oral syringes to administer sucrose, and some have given sucrose accompanied by nonnutritive sucking with a pacifier. A pacifier soothes an infant and may help to relieve the infant’s pain (Campos, 1989; 1994; Corbo et al., 2000; Field, 1999; Field & Goldson, 1984). However, few studies have been carried out to determine whether a pacifier accompanied by sucrose is significantly more effective in relieving pain than a pacifier given alone or accompanied by sterile water.

A recent double-blind, randomized, crossover study compared the efficacy of nonnutritive sucking, sucrose, and prone positioning with standard care in relieving procedural pain in premature infants (Stevens, et al., 1999). Standard care consisted of no pacifier, no sucrose, and a supine or side-lying position. The sample consisted of 128 infants with gestational ages ranging from 27 to 31 weeks. The effect of the number of painful procedures experienced by the infants was controlled for using an analysis of covariance (ANCOVA). Every infant in the study received each of the following interventions in random order during a heelstick: prone positioning in a Snuggle Up; a pacifier dipped in sterile water given 5 minutes before the heelstick and redipped 2 minutes before the heelstick; a pacifier dipped in 24% sucrose given 5 minutes before the heelstick and redipped 2 minutes before the heelstick; and standard care. Pain response was measured using the PIPP (Stevens et al., 1996). The PIPP is a valid and reliable tool for evaluating pain in preterm infants.

Both the pacifier with sterile water ($p = .003$) and the pacifier with sucrose ($p < .0001$) were significantly more effective than standard care in relieving pain during a heelstick. However, there was a definite trend but no statistically significant difference between a pacifier with sterile water and a pacifier with sucrose ($p = .059$). A significant difference between these two interventions might be found with a larger sample. No differences in pain relief were found with prone positioning versus supine or side-lying positioning (Stevens et al., 1999).

(Gibbins et al. 2002) studied the effects of oral sucrose and nonnutritive sucking in 190 preterm and full-term infants. In this RCT, 3 treatment groups received sucrose with nonnutritive sucking, water with nonnutritive sucking, or sucrose alone. A single dose (.5 ml) of sucrose or water was administered 2 minutes before a heel lance, and in 2 of the groups, a pacifier was held in the mouth throughout the duration of the heel lance. Pain scores were measured by the PIPP at 30 seconds and 60 seconds following initiation of the heel lance. Statistical analysis with repeated measures analysis of variance (RM ANOVA) found a significant main effect of intervention ($F = 22.49, p < .001$). There were significantly lower PIPP scores in the sucrose and pacifier group compared with sucrose alone ($p < .002$), and significantly lower PIPP scores in the sucrose and pacifier group compared with the water and pacifier group ($p < .001$). There was not a statistically significant difference between PIPP scores in the sucrose-alone group and PIPP scores in the water with pacifier group ($p = .57$). This study indicates that the combination of sucrose and pacifier is important for effective pain relief.

Summary of Research and Need for Continued Research

Several RCTs have provided evidence that oral sucrose does give significant pain relief in preterm infants during heelsticks and venipunctures. The seven oral sucrose studies presented in Table 1 have all used random
assignment of infants to treatment groups, blinding of the intervention, blinding of outcome measurement, and standardization of the data collection processes. Some studies have been limited by possibly invalid pain measurement and insufficient attention to contextual factors. Future research must address these issues, and continue to ensure rigor in the methodology. Overall, there is sufficient evidence to recommend the use of oral sucrose during procedures, but there is also a need for continued research in this area.

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Questions remain concerning comparisons of the effectiveness of sucrose with alternative interventions, and combinations of sucrose with additional behavioral or pharmacologic interventions. Research is also needed to investigate clinical outcomes of using sucrose for pain management over the course of an entire hospital stay, and to determine whether any adverse effects occur as a result of repeated doses of sucrose.
Based on a study that examined neurological functioning of preterm infants who received repeated doses of sucrose during the first week of life, (Johnston et al. 2002) do not recommend the repeated use of sucrose for infants less than 32 weeks of age. Higher doses of sucrose for infants who were less than 31 weeks' gestational age were predictive of lower scores on the Neurobehavioral Assessment of the Premature Infant (NAPI) test, and higher scores on the Neuro-Biological Risk Score. More research is needed in this area.

An important area for future research will be to examine the effectiveness of oral sucrose for procedures other than heelsticks and venipunctures. Currently, all published studies address the effectiveness of sucrose only during heelsticks and venipunctures. Preterm infants undergo a variety of painful procedures on a daily basis, and the effectiveness of oral sucrose during more complex or prolonged procedures needs to be examined.

Conclusion

Studies have demonstrated that the administration of oral sucrose is effective as a simple and safe method of pain relief for infants during painful procedures. Oral sucrose may be combined with additional measures such as swaddling and offering a pacifier. A critical review of all published research in this relatively new area of nursing research is essential as we address the problem of frequent painful procedures in preterm infants, and evaluate the beneficial effects of sucrose. Oral sucrose has the potential to be a comfort to infants who are undergoing painful procedures, and a useful tool for nurses who are attempting to provide developmentally sensitive care.(Ramenghi et al 1996, Stevens and Johnston 1994)

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References


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