Published in final edited form as:
Pediatrics. 2010 May ; 125(5): 1042–1047. doi:10.1542/peds.2009-2445.

Considerations for Using Sucrose to Reduce Procedural Pain in Preterm Infants

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Abstract

Preterm and critically ill newborns admitted to a NICU undergo repeated skin-breaking procedures that are necessary for their survival. Sucrose is rapidly becoming the accepted clinical standard nonpharmacologic intervention for managing acute procedural pain for these infants. Although shown to be safe in single doses, only 4 studies have evaluated the effects of repeated doses of sucrose over relatively short periods of time. None has examined the use of sucrose throughout the NICU stay, and only 1 study evaluated the neurodevelopmental outcomes after repeated doses of sucrose. In that study, infants born at <31 weeks' gestational age and exposed to >10 doses per day in the first week of life were more likely to show poorer attention and motor development in the early months after discharge from the NICU. Results of studies in animal models have suggested that the mechanism of action of sucrose is through opioid pathways; however, in human infants, little has been done to examine the physiologic mechanisms involved, and the findings reported thus far have been ambiguous. Drawing from the growing animal literature of research that has examined the effects of chronic sugar exposure, we describe alternative amine and hormone pathways that are common to the processing of sucrose, attention, and motor development. In addition, are view of the latest research to examine the effects of repeated sucrose on pain processing is presented. These 2 literatures each can inform the other and can provide an impetus to initiate research to examine not only the mechanisms involved in the calming mechanisms of sucrose but also in the long-term neurodevelopmental effects of repeated sucrose in those infants born extremely preterm or critically ill.

Keywords

premature; infant; pain; sucrose; dopamine

Providing adequate pain management for procedure-related pain remains complex for infants in the Neonatal Intensive Care Unit (NICU). Although research has been conducted to find ways to manage pain, effective treatments that are free from adverse effects are elusive. Indeed, in a joint statement by the American Academy of Pediatrics and the Canadian Paediatric Society, the committees reported that major gaps remain in our knowledge regarding the most effective ways to prevent and relieve pain in neonates.[1]

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

Currently, for preterm infants, severe pain, such as postoperative pain, is controlled with pharmacologic agents.[2,3] However, sweet solutions, primarily sucrose, have been recommended extensively for minor procedural pain relief in term and preterm infants.[4] A host of individual studies and a recent Cochrane review revealed that single doses of sucrose administered orally reduce crying, facial grimacing, motor activity, and, in some cases, heart rate in term, preterm, and older infants during minor painful procedures.[5–9]

Those in many NICUs consider the use of sucrose the clinical standard for managing acute procedure-related pain. In fact, across Canada, 64% of the nurseries have protocols for administering sucrose for procedural pain management; nevertheless, extensive variability in specific dosing guidelines between units is evident.[10] Another group conducted an extensive chart review of critically ill infants hospitalized for >28 days and found that, over the course of their NICU stay, sucrose was administered 40% of the time, and an additional 17% of the time sucrose was used in combination with morphine.[11] Of concern here is the use of sucrose in combination with opioids when empirical evidence for efficacy and/or safety is absent.

It is important to note that preterm or critically ill term-born infants undergo repeated skin-breaking events. The average number of painful procedures can be as high as 15 per day in the first few weeks of life.12,13 If sucrose were administered for each procedure, the tiniest and sickest infants could be exposed to relatively high volumes of sugar during a period of rapid brain development.[14] To give this level of exposure some perspective, if an infant who weighs 1000 g has even 10 painful procedures per day, and for each procedure 0.5 to 1.0 mL of 24% sucrose is given, we would be administering the same quantity as if we were giving a 10-kg1-year-old a half can of Coke Classic per day, the concentration of sugar in a Coke Classic being ~11% (42 g/355 mL). Although we recognize that our example is of a liquid that has additional constituents that may add to its negative effects (eg, caffeine), our intent is to provide an example understood by a wide audience and one to which adults themselves could easily relate.

To date, 4 studies have examined the effects of repeated doses of sucrose over specific time periods. In the first study, infants born at <31 weeks' gestation were given either sterile water or 0.1 mL of 24% sucrose during the first week of life.15 Infant development was assessed at 32, 36, and 40 weeks of age. At ages 36 and 40 weeks, greater exposure to sucrose (>10 doses in 24 hours) was associated with poorer motor and attentional developmental outcomes. In another study, infants born between 27 and 30 weeks' gestational age were given 0.1 mL of 24% sucrose before all painful procedures until 28 days of life or discharge.[16] The average cumulative number of procedures over the 28 days in which sucrose was administered was 248, with 71 of these procedures occurring in the first week of life. Early clinical outcomes and safety were evaluated. A very low incidence of adverse events was reported, and the incidence of hyperglycemia, oral infections, necrotizing enterocolitis, intraventricular hemorrhage (grades III or IV), or death did not differ between treatment and control groups. However, developmental outcomes were not assessed. Next, either sterile water or lower volumes (0.5 mL/kg) of 25% sucrose were given to infants born at 25 to 33 weeks' gestational age for each procedure over 3 days.17 No immediate adverse effects were found, and pain responsiveness remained constant; however, once again, developmental effects were not assessed. Finally, in the most recent study, sucrose did not prevent the development of hyperalgesia in term-born infants of diabetic mothers given sucrose for all needle procedures in the first 24 hours.18 In summary, although it seems that in the short-term sucrose is safe,9 only 1 study has evaluated later neurodevelopment.15 Of critical importance is the fact that the existing studies addressed effects of sucrose administered in preterm infants over a brief period of only 3 days,[17] the first week of life,[15] or the first 28 days[16] and in term infants in the first day.[18] However, for

infants born very preterm, sucrose is used over longer periods, and the relatively high cumulative amount of sucrose during the entire NICU stay has yet to be evaluated.

In the following section we highlight research that has examined mechanisms of action, including studies of neurochemical alterations after chronic sugar exposure found in animal models.

POTENTIAL MECHANISMS OF ACTION OF SUCROSE AND IMPACT ON DEVELOPMENT

Results of rodent studies have suggested that sweet solutions modulate pain through opioid mechanisms.[19–21] Only 3 studies have examined potential mechanisms of action of sucrose in human infants, and the evidence is less clear. First, in a study of term infants born to mothers who used methadone during pregnancy, sucrose did not provide calming. Methadone would competitively block opioid receptors and make sucrose ineffective; thus, the results of this study are consistent with the opioid-mediated hypothesis for sucrose effects.[22] On the other hand, in a small sample of preterm infants, changes in plasma β endorphin did not increase after treatment with sucrose, β endorphin being an endogenous opioid peptide neurotransmitter that acts as an opioid agonist and that has been used to evaluate the efficacy of analgesics.[23] Although in this study peripheral circulating β-endorphin levels were not increased, changes could have occurred at a central level but could not be measured. Finally, in term infants, naloxone hydrochloride, a morphine antagonist given before glucose administration, did not decrease the effects of glucose during heel lance.[24] Results of these last 2 studies suggest that mechanisms other than those mediated by opioid pathways may be involved in the effects of sucrose. Increased awareness of the multiple physiologic processes is important for understanding how repeated sucrose might affect both attention/orientation and motor development in preterm infants.[15]

Dopamine

Multiple pathways interact to transmit pain signals to the brain and to dampen the effects of pain.25 Common links between the central processing of sugar, pain modulation, attention, and motor development lie in the mesolimbic dopaminergic and cholinergic systems. Dopamine plays a primary role in the descending modulation of pain.26,[27] During phasic (acute) pain, dopamine is released in sufficient quantities to stimulate postsynaptic receptors, which results in rapid responses to a stimulus.[28] Indeed, in a rodent model, acute stress in the form of a mild foot shock not strong enough to elicit pain response induced an increase in extracellular dopamine in the nucleus accumbens.29 More recent reports on both animals and humans also demonstrated the supraspinal pain-modulating effects of dopamine and dopamine receptors.30,31 Furthermore, inputs from the brainstem pedunculopontine and laterodorsal tegmentum activate the acute firing of neurons in mesolimbic pathways. Acting through D2-like receptors in the spinal cord, dopamine activates potassium channels in the substantia gelatinosa and induces analgesia.[32] In addition, dopamine can activate noradrenalin, serotonin, somatostatin, enkephalins, or neuropeptides, all of which modulate pain.[33]

Acetylcholine

Acetylcholine has a critical role in a wide variety of physiologic processes. Specific to pain modulation, acting through muscarinic receptors in the spinal cord and supraspinally through the nicotinic receptors in the periaqueductal gray area of the thalamus, increases in acetylcholine have been shown to reduce the release of glutamate (excitatory amino acid) and to increase the release of γ-aminobutyric acid (inhibitory amino acid), which

concomitantly acts to reduce glutamate release.[34–38] In addition, acetylcholine release in the dentate gyrus of the hippocampus modulates pain processing.[39]

THE EFFECTS OF SUCROSE ON DOPAMINE AND ACETYLCHOLINE REGULATION

A growing body of research has examined the effects of sugar on neural systems. Emerging evidence shows the effects of sucrose/carbohydrates on regulation of the hypothalamic-pituitary-adrenal axis in rodents (for a review see Walker[40] [2005]). In addition, research examining the parallel physiologic actions that sucrose exposure has with other substances, such as cocaine, is now more prevalent. Although the concentration of sucrose administered to the rodents being studied is often lower than that used in preterm infants (in animals, the concentration is typically ~10% but can goashighas32%), the mechanisms of action have implications for how sucrose could be processed by developing neonates.

A number of foods stimulate dopamine release in the nucleus accumbens, including sugar.[41–43] In animals that have adequate food intake, this release decreases when the animals have access repeatedly; on the other hand, for animals that are food deprived, dopamine increase continues (as reviewed by Avena et al[44] [2008]). It is important to note that dopamine release is proportional to sucrose concentration, not to the volume ingested.[43] In addition, excessive sugar intake increases not only μ-1 receptors but also D1 receptors.[41] Chronic exposure to sucrose alters dopamine and opioid messenger RNA levels similar to those seen in morphine-addicted rats.[45] It is interesting that in animals, whereas dopamine release is influenced by nutrition levels at the time of ingestion, 10% sucrose administration stimulates extra-cellular acetylcholine each time it is ingested independent of nutritional status.[46]

SUCROSE ADMINISTRATION, ATTENTION, AND MOTOR DEVELOPMENT IN PRETERM INFANTS

In the only study to examine neurodevelopment, preterm infants exposed to greater numbers of doses of sucrose during the first week of their NICU stay performed less well on attention/orientation and motor tasks.[15] Among many other functions, dopamine and acetylcholine play a significant role in both attention and motor movement.[47–51] First, as suggested by the authors, the effects observed may have been the result of stopping the sucrose suddenly after 1 week of administration. Although they did not comment further on this result, one might speculate that the infants were in some way exhibiting a “withdrawal” to the sucrose. In rodent models, animals that experienced long-term exposure to 25% glucose (28 days for 30 minutes/day) showed a “deprivation effect” that lasted the 2 weeks of the study period.[52] Depressed behavior after the removal of sucrose has also been observed.[44] However, sucrose in the Johnston et al[15] study was given for 1 week, and the assessments occurred 5 to 9 weeks after the treatment; in the animal studies, the effects on dopamine depended on the percentage of sucrose rather than the volume.

Another plausible explanation might be that the neural system has been programmed in a more permanent way. Indeed, environmental regulation of dopamine systems has been examined in developing rodents (reviewed by Meaney et al[53]). Early life stress, such as maternal separation, was associated with upregulation of the system, and the rats showed increased behavioral and dopamine responses later in life. Thus, with early repeated doses of sucrose, acute reduction or ongoing administration could prime the system. Once the sucrose is stopped, the system has an overabundance of receptors with reduced hormone substrate. As has been shown in other systems, the reduction in substrate then causes a rapid pruning

of the central receptors and resultant lowering of levels of transmitted dopamine and acetylcholine later.

INSULIN

The role of insulin in motor and cognitive function may be another mechanism through which sucrose has effects. Very little is known about the central actions of insulin. Newly emerging research has shown that high-concentration insulin receptors in the brain are found in the hypothalamus and the thalamus, among other regions.[54] Central insulin plays a role in food intake, motor activity, and memory.[55] Insulin crosses the blood-brain barrier, and the uptake of insulin into the brain is separate from its peripheral effects on blood glucose. In mice, although central insulin had no effect on pain, it had sedative effects on locomotion and exploratory behaviors in a dose-specific manner.[54] This fact is important, because in the Stevens et al study,[16] increased risk of hyperglycemia was not found in infants who were given repeated doses of sucrose; however, insulin levels were not measured directly. Indeed, to the best of our knowledge, no studies have evaluated insulin levels after sucrose/glucose administration in this population. Nevertheless, if central nervous system effects are independent of peripheral levels, increased insulin uptake could still take place and have an effect at a central level. Levels high enough to induce peripheral hyperglycemia may not be required for changes at a central level. On the other hand, even if insulin levels are modestly elevated, it is not clear that increased transport through the blood-brain barrier would occur. Insulin transport into the brain may exhibit lower sensitivity than peripheral sensitivity. However, this suggestion is speculative, because at the present time, no evidence exists to show differing levels of sensitivity between peripheral and central effects.

CONCLUSIONS

Our aim is to suggest multiple potential mechanisms by which sucrose might alter attention and motor development in preterm infants. Despite recommendations that infants receive no more than 10 doses per day, the most recent national review of use of sucrose for pain management revealed that although the average daily dose was 6 (mode), the maximum number of doses ranged up to 24.[10] Furthermore, with or without sucking, pain reduction with sucrose ranges between 16% and 28% on pain-assessment scales.16,56 These effects are equivalent to the level of pain reduction when using other nonpharmacologic interventions such as facilitated tucking and kangaroo care.57–60 More effective pain reduction has been found by using breastfeeding.[61–63] Moreover, sucrose has variable effects on physiologic pain indices.[64] Reducing behavioral responses without concordant reduction in physiologic responses may leave preterm infants vulnerable to adverse effects of pain on stress hormone systems.[65–68] It is important to note that Fitzgerald[69] suggested that sucrose may act as a sedative rather than an analgesic. If this is the case, then we are likely not ameliorating potential early negative programming that repeated early pain may have on these infants.

Although it may seem that we are giving low volumes of sugar during NICU care, research on the potential negative long-term effects of early dietary exposure to sugar is an emerging field.[70] Thus, before clinicians lose their equipoise on the repeated use of sucrose for pain management in pre-term infants, much more study is needed, particularly of long-term developmental effects, because the mechanisms of action of sucrose in human infants are not well understood. In the meantime, we urge clinicians to use sucrose cautiously and to use other nonpharmacologic comfort measures.

Acknowledgments

Funded by the National Institutes of Health (NIH).

Dr Holsti's research is funded by the SickKids Foundation, the Canadian Institutes of Health Research, and the Faculty of Medicine, University of British Columbia. Dr Grunau's research is funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Canadian Institutes of Health Research, and she received salary support from the Child & Family Research Institute and the Human Early Learning Partnership.

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