Sucrose and Warmth for Analgesia in Healthy Newborns: An RCT

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abstract

BACKGROUND AND OBJECTIVE: Increasing data suggest that neonatal pain has long-term consequences. Nonpharmacologic techniques (sucrose taste, pacifier suckling, breastfeeding) are effective and now widely used to combat minor neonatal pain. This study examined the analgesic effect of sucrose combined with radiant warmth compared with the taste of sucrose alone during a painful procedure in healthy full-term newborns.

METHODS: A randomized, controlled trial included 29 healthy, full-term newborns born at the University of Chicago Hospital. Both groups of infants were given 1.0 mL of 25% sucrose solution 2 minutes before the vaccination, and 1 group additionally was given radiant warmth from an infant warmer before the vaccination. We assessed pain by comparing differences in cry, grimace, heart rate variability (ie, respiratory sinus arrhythmia), and heart rate between the groups.

RESULTS: The sucrose plus warmer group cried and grimaced for 50% less time after the vaccination than the sucrose alone group ($P < .05$, respectively). The sucrose plus warmer group had lower heart rate and heart rate variability (ie, respiratory sinus arrhythmia) responses compared with the sucrose alone group ($P < .01$), reflecting a greater ability to physiologically regulate in response to the painful vaccination.

CONCLUSIONS: The combination of sucrose and radiant warmth is an effective analgesic in newborns and reduces pain better than sucrose alone. The ready availability of this practical nonpharmacologic technique has the potential to reduce the burden of newborn pain.

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Dr Gray conceptualized and designed the study, participated in all phases of the study, and drafted the initial manuscript; Dr Garza carried out the initial analyses, coordinated data collection, and drafted the initial manuscript; Ms Zageris coordinated and assisted with the initial analyses; Dr Heilman edited and scored the heart rate data for reliability and conducted the statistical analyses for the final manuscript; Dr Porges participated in study design and data analysis and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Increasing data suggest that neonatal pain has long-term consequences. Pharmacologic interventions for minor pain are ineffective, and nonpharmacologic techniques (sucrose taste, pacifier suckling, breastfeeding) are effective and now widely used.

WHAT THIS STUDY ADDS: The taste of sucrose has been shown to be an effective and widely used analgesic for infants, and this study demonstrates that combining brief exposure to natural radiant warmth with the taste of sucrose improves the analgesic effect for the infant.

Healthy newborns undergo many minor painful procedures, such as heel lance for newborn screenings, blood draws, and immunizations. Newborns may not have the pain-modulating mechanisms that function in older children and adults, and they may be more sensitive to pain.[1] The short-term effects of painful procedures include crying or grimacing, disturbance in sleep or wakefulness state, increased oxygen consumption, ventilation–perfusion mismatch, and increased gastric acidity.[2–4] The long-term effects may be an exaggerated response to pain in later infancy[5] and the neurotoxicity of untreated pain in the developing brain.[6]

Strong pharmacologic interventions are rarely used during short, minor painful procedures in neonates because of the risk of adverse effects on the newborn's respiratory and central nervous systems. Studies evaluating pharmacologic agents such as morphine demonstrate reduced behavioral and hormonal stress responses during surgery in term infants[7–9]; morphine's analgesic effect on acute pain caused by minor procedures is less effective.[10] Topical anesthetics such as Eutectic Mixture of Local Anesthetics are available for minor pain procedures, but systematic review suggests topical anesthetics are less effective in infants and young children[11] and have not been recommended for minor pain caused by heel sticks in infants.[12]

Recent systematic reviews indicate that sweet taste is effective for reducing behavioral indicators of pain in infants ≤1 year of age during common minor procedures including heel lance, venipuncture, bladder catheterizations, circumcision, retinopathy of prematurity examinations, nasogastric tube insertion, and subcutaneous injections.[13–16] Despite sucrose's wide use, there is concern about repeated use of sucrose in this population.[3,17,18] Asmerom et al[2] reported that a single dose of sucrose for heel lance in preterm infants decreases the behavioral indicators of pain but increases physiologic markers of oxidative stress and heart rate. Although using sucrose use is safe,[19–23] it does not prevent later exaggerated pain response,[24,25] and its mechanism of action is not fully understood.[26,27] Finally, the evidence is inconclusive on whether multiple doses of sucrose may alter later development. Preterm infants (<31 weeks' estimated gestational age) who received sucrose for all painful procedures during their first 7 days had lower neurodevelopmental scores at term,[18] particularly if they received >10 doses per day.[28] However, a similar detrimental neurodevelopmental effect was not found in preterm infants (<30 weeks' estimated gestational age) who had sucrose for all painful procedures during their first 28 days of life.[29]

In the hospital setting, nonpharmacologic interventions have become increasingly popular for minor painful procedures. Breastfeeding reduces pain response in neonates during minor painful procedures[30–34] and is the preferred natural analgesic technique.[35,36] Incorporating breastfeeding into hospital protocols for painful procedures has been difficult.[37] Several obstacles have been identified for incorporating nonpharmacologic techniques into hospital pain protocols, including the organizational challenges of coordinating a mother–baby–phlebotomist blood draw, attitudes and lack of knowledge about infant pain, and the hospital culture's high resistance to change.[37–39] Sucrose's advantage is that it can be prescribed like a medication, ordered on preprinted or standard nursery forms, and made immediately available to babies when mothers cannot breastfeed. Recent survey data suggest that in younger high-risk populations, >60% of newborn babies are not breastfed.[40]

We have previously used natural warmth as an analgesic agent in newborn pain studies, transmitted through skin-to-skin contact,[41] during breastfeeding,[30] and by use of a radiant warmer,[42] to overcome these obstacles in providing pain relief to newborns. The current study aimed to determine whether the combination of sucrose and radiant warmth would decrease behavioral and physiologic indicators of pain in newborns undergoing a hepatitis B vaccination more effectively than sucrose alone.

METHODS

Subjects

Participants were 29 healthy, full-term newborns born at the University of Chicago Hospital between July and August 2008. Per hospital protocol, consent for the hepatitis B vaccination was obtained in the delivery room. The hospital's preprinted newborn nursery orders included sucrose taste as an analgesic. Mothers in the general care nursery who had previously consented for the vaccination were asked to participate. Consistent with the hospital policy, mothers could request to breastfeed as analgesic for the procedure, but none did. Exclusion criteria included preterm birth (<37 weeks' completed gestation), birth weight <2 kg, any Apgar score <6, congenital abnormalities, medical complications, or drug exposure. Infants with previous oxygen administration, ventilatory support, or NICU admission were also excluded. Based on our previous study,[34] we calculated that a sample size of 15 infants per group was necessary to achieve a statistically reliable reduction in grimacing and crying, with a power of 80% and a $P < .05$. Table 1 shows demographic data. The

TABLE 1 Subject Characteristics

Characteristic	*n*	Mean (%)	SD
Gestational age (wk)		39	0.6
Maternal age (y)		27	5.99
Gender			
Male	17	59	
Female	12	41	
Ethnicity			
African American	18	62	
White	4	14	
Hispanic	2	7	
Asian	1	3	
Other	4	14	
Mode of delivery			
Spontaneous vaginal	24	83	
Cesarean	5	17	
Birth wt (g)		3202	316.9

University of Chicago institutional review board approved this study, and informed consent was obtained from the parents of each infant.

Procedure

We randomly assigned each infant in the study to sucrose alone or sucrose plus warmer groups by using a sealed envelope randomization system. All hepatitis B vaccinations were given in the general care nursery by a single physician (L.G.) to minimize variability. Infants in the warmer plus sucrose group were placed under the Ohmeda Ohio Infant Warmer (Model No. 3000; GE Healthcare, Fairfield, CT), and their clothing was removed, except for a diaper. As a precaution against overheating or overcooling, infants were connected to the warmer's servo control and temperature monitoring system at all times. Infants in the sucrose alone group rested quietly in their bassinets, clothed in a diaper and shirt and unswaddled for the duration of the study. All infants had 3 neonatal electrocardiographic (ECG) electrodes placed for heart rate monitoring and intrascapular, abdominal, and rectal temperature probes for safety temperature monitoring.

The study began once the infant achieved a calm and drowsy state. We controlled for behavioral state by initiating the protocol after each infant spontaneously reached 1 of 3 quiet behavioral states as defined by Prechtl (State 1: eyes closed, regular respiration, no movements; State 2: eyes closed, irregular respiration, small movements; or State 3: eyes open, no movements).[43] The protocol consisted of a baseline period (5 minutes), intervention (2 minutes), followed by the vaccination (10 seconds), and a recovery period (5 minutes). During the baseline period, the infant's face was videotaped and the infant's heart rate was continuously recorded. After 5 minutes, the intervention period began. During the 2-minute intervention period, infants in the sucrose alone group were given 0.24 g of sucrose (1.0 mL of 24% sucrose solution, Sweet-Ease; Philips Children's Medical Ventures, Monroeville, PA). Infants in the sucrose plus warmer group were given 0.24 g of sucrose with the infant warmer increased to create a 0.5°C temperature gradient between the baby and the radiant warmth control temperature. The infant warmer's power is preset to create a 0.5°C temperature difference (100% power) and has an automatic safety shutoff at 12 minutes, well past this study's 2-minute timed radiant heat exposure.[45] Each infant received the recommended 1 mL sucrose dose in accordance with the Cochrane Systematic Review recommendations of 0.2 to 0.5 mL/kg for full-term infants for a single procedure.[3,19] After the 2-minute intervention period, the infant's lateral thigh was swabbed with alcohol, the intramuscular hepatitis B immunization (Recombivax HB; Merck & Co Inc, Whitehouse Station, NJ) was administered via a 1-mL Kendall Syringe with Safety Needle (Covidien, Mansfield, MA), and an adhesive bandage was applied. After the vaccination, the radiant warmer was returned to the automatic or servo control setting. Heart rate, temperature, and video recording continued for 5 minutes after the immunization.

Data Analysis

We assessed pain by using both behavioral and physiologic indices. The infant's face was videotaped for offline coding of grimace and cry. Two research assistants not associated with data collection were trained (by L.G.) to record grimace as brow bulge, eye squeeze, and nasolabial furrowing, and they independently coded each video. Both cry and grimace were coded after the vaccination was completed and adhesive bandage applied. Facial grimacing was scored continuously from the video portion of the tape, and crying was scored independently from the audio portion with video blank. Crying was scored continuously as the presence of an audible crying sound independent of quality. Facial grimacing was scored when brow bulging, eye squeezing, and nasolabial furrowing occurred simultaneously. These facial actions have been reported in 99% of neonates within 6 s of heel stick and are believed to be very sensitive indices of infant pain.[45,46] Because sleep state was controlled for at the onset of the study, this allowed us to focus on facial action as the most sensitive behavioral indicator of infant pain.[47] Scorers were uninformed as to experimental condition when scoring cry from the auditory portion of the tape. For grimacing, the video camera was focused on the infant's face to record facial actions only and prevent accidental unblinding of subjects during coding. The total amount of time each infant spent grimacing or crying throughout the study was quantified. The level of grimacing and crying was low in each group, and the correlations between the coders was high (r = 0.999 for grimace; r = 0.998 for cry). Therefore, we averaged the data from each coder into a "master average" for all analyses.

ECG data were digitized, and time series of R–R intervals (time between successive R-waves of the ECG) were processed to quantify the amplitude of respiratory sinus arrhythmia (RSA) by Porges' method.[48,49] We derived RSA from the edited R–R intervals by using CardioBatch software (Brain–Body Center, University of Illinois, Chicago, IL). CardioBatch applies a moving polynomial filter[50–52] and quantifies the amplitude of RSA with age-specific parameters, sensitive to the maturational shifts in the frequency of spontaneous breathing (0.3–1.3 Hz for the neonate).[52,53] Average heart rate and the amplitude of RSA were calculated in sequential 30-s epochs in each condition (baseline, intervention, and recovery). Data were truncated to ensure that the last 6 30-s epochs before vaccination were used for baseline, the first 6 30-s epochs after vaccination were use for the vaccination condition, and the subsequent 8 30-s epochs were used for the recovery condition. The means of the within-condition epochs (baseline, vaccination, and recovery) were used as a repeated measure for heart rate and RSA. ECG data with minimal recording artifact, sufficient for data analyses, were available from 27 neonates (12 in the sucrose plus warmer group and 15 in the sucrose only group).

We analyzed data by using SPSS 16.0 (IBM SPSS Statistics, IBM Corporation). Pillai's trace multivariate tests were used for univariate repeated-measures analyses of variance to evaluate heart rate, RSA, and temperature during the 3 conditions of the experiment (baseline, intervention, and recovery). The multivariate analyses provide a robust estimate of effects when the repeated measures are autocorrelated, as is the case with heart rate, RSA, and temperature. Because the distributions of both cry and grimace deviated from normal, nonparametric Kruskal–Wallis 1-way analysis of variance by ranks was used to compare group differences. Interrater reliability for ranks approached 1.0, and the average rank for each participant was used in the Kruskal–Wallis analyses.

RESULTS

The sucrose plus warmer group cried and grimaced for 50% less time after the vaccination than the sucrose alone group ($P < .05$, respectively). Infants in the sucrose plus warmer group ($n = 14$) cried and grimaced on average 12.8 and 14.9 seconds, respectively. Infants who received sucrose alone ($n = 15$) cried and grimaced on average for 28.0 and 31.1 seconds, respectively. Figure 1 illustrates the cry and grimace durations for each group. Cry and grimace durations were significantly shorter in the sucrose plus warmer group than in the sucrose alone group ($P < .05$, Kruskal–Wallis test). The standard deviations for each variable within each group were noticeably greater in the sucrose group for cry (eg, 6.9 seconds vs 2.2 seconds) and grimace (eg, 7.2 seconds vs 2.4 seconds). The correlation between the latencies of the 2 variables approached unity (ie, >0.975).

Elevation of heart rate and suppression of RSA were used as physiologic indicators of pain. Heart rate and RSA data across the 3 conditions (baseline, vaccination, and recovery) were available for 15 neonates in the sucrose-only group and 12 neonates in the sucrose plus warmer group. Analyses of variance contrasted the mean heart rate and RSA between the groups during the 3 conditions of the experiment. Analyses of variance documented significant condition effects for both heart rate ($P < .001$) and RSA ($P < .001$) and a significant group × condition interaction for RSA ($P < .02$). As illustrated in Figs 2 and 3, heart rate increased and RSA decreased in response to the vaccination. Focusing on the reactivity to the vaccination, group by repeated measure analyses of variance were conducted on the baseline and vaccination conditions. These analyses indicated that the sucrose only group reacted to the vaccination with significantly greater increases in heart rate ($P < .02$) and greater decreases in RSA ($P < .03$). Heart rate increased approximately 20 beats per minute for the sucrose-only group and about 11 beats per minute for the sucrose plus warmer group. Similarly, RSA decreased approximately 1.83 (natural log units) for the sucrose only group and

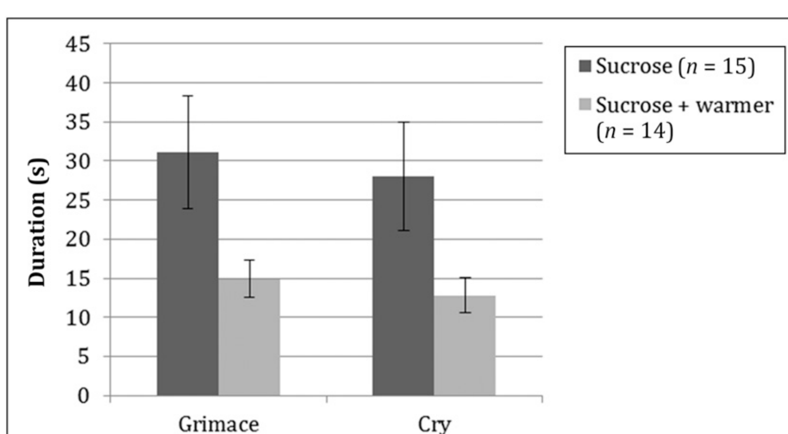

FIGURE 1
Cry and grimace durations. Durations were coded after completion of the vaccination. Infants in the sucrose plus warmer group cried for significantly less time ($P < .05$, Kruskal–Wallis test) and grimaced significantly less than infants in the sucrose alone group ($P < .05$, Kruskal–Wallis test).

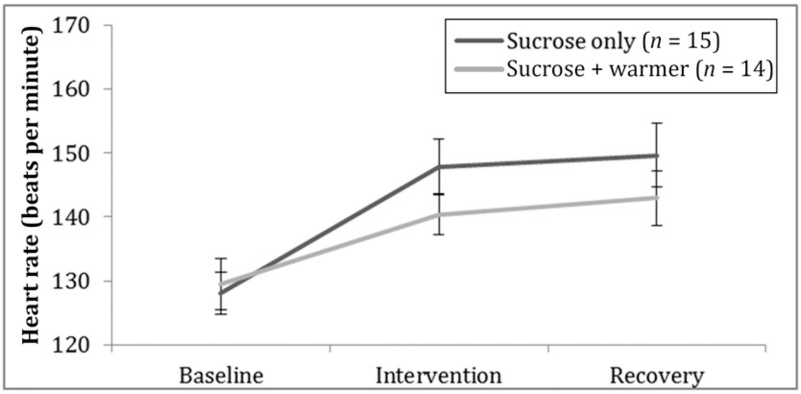

FIGURE 2
Heart rate during protocol. The sucrose plus warmer group had dampened heart rate acceleration to the vaccination, $F(1, 25) = 6.1$, $P < .02$.

about 0.65 (natural log units) for the sucrose plus warmer group. The behavioral and autonomic indices of reactivity to the vaccination were moderately correlated. Across both groups, the duration of grimacing was significantly correlated with increases in heart rate ($r = 0.531$, $P < .004$) and decreases in RSA ($r = -0.454$, $P < .017$). Similarly, across groups, the duration of crying was significantly correlated with increases in heart rate ($r = 0.529$, $P < .005$) and decreases in RSA (-0.437, $P < .02$).

Rectal temperatures did not differ between the groups throughout the study period. Mean rectal temperature ± SEM was 36.6 ± 0.09°C for the sucrose and warmer group and 36.5 ± 0.08°C for the sucrose alone group, $P = .44$.

DISCUSSION

Sucrose is widely used in pain relief for newborns during minor painful procedures. Based on our previous work,[30,41] including data on thermal analgesia,[42] we have demonstrated that the transmission of warmth is 1 component of breastfeeding that protects the infant during a painful experience. In this study, we showed that the combination of sucrose and radiant warmth before a hepatitis B vaccination reduced both physiologic and behavioral indicators of pain in newborns better than sucrose alone. The sucrose plus warmer group had consistently lower mean crying and grimace times after the vaccination compared with infants in the sucrose alone group. As illustrated in Figs 2 and 3, the sucrose plus warmer group also reacted with a dampened autonomic reaction (eg, less heart rate acceleration and RSA reduction) from baseline to the vaccination than the sucrose alone group. The differences in both behavioral and physiologic indices of pain indicate that radiant warmth enhanced the analgesic effects of sucrose.

We believe that the dampened heart rate and behavioral reactivity to the vaccination observed in the sucrose plus warmer group has clinical significance. The sucrose plus warmer group showed almost no reduction in RSA in response to the pain procedure, compared with the large drop observed in the sucrose alone group. The observed drop in RSA represents a significant decrease in the vagal regulation of the heart. Vagal efferent pathways regulate heart rate by acting as a “brake” on the sinoatrial node. In response to an environmental challenge, cardiac vagal tone decreases to increase cardiac output to respond to the painful challenge.[48] Infants in the sucrose plus warmer group were able to maintain a higher RSA during the vaccination. Higher RSA in the sucrose plus warmer group reflects a more optimal ability to physiologically self-regulate during the stressful parts of vaccination.[54] In contrast, the sucrose alone group had a marked decrease in RSA during the stressful parts of the study. This, we believe, was evidence of poor physiologic self-regulation during the stress of vaccination.

One limitation of this study is the choice of our pain assessment tool. With >30 different pain scales available and none demonstrating clear superiority, we decided to focus on the most sensitive behavioral and physiologic indicators of infant pain by using crying, facial grimacing, and changes in heart rate. In fact, a recent comparison of pain assessment tools indicates that these behavioral and physiologic features

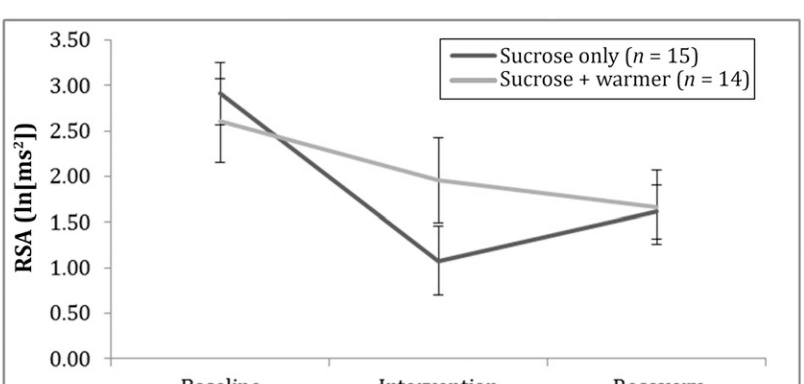

FIGURE 3
RSA. The sucrose plus warmer group had a dampened suppression of RSA in response to the vaccination, $F(2, 50) = 4.12$, $P < .02$.

are more sensitive in identifying infant pain than a multidimensional pain assessment tool.[55] Our data support this decision: Both groups of infants showed significant correlations between their behavioral indicators of pain (duration of crying and grimacing) with their physiologic response to the pain (increases in heart rate). Second, in this study we collected safety temperature monitoring with rectal temperature probes. Here, as in our previous study,[42] a 2-minute exposure to increased natural warmth did not alter the infant's core temperature. These data support the use of warmers for short periods without ongoing monitoring of rectal temperatures. However, these data do not indicate the optimal temperature gradient for analgesic effectiveness or the time period that may affect core temperatures. Finally, our small sample size may have introduced the risk of a type 1 error.

This study adds to the growing literature on natural calming techniques to combat infant pain. The use of sucrose as an analgesic for newborns undergoing routine, minor painful procedures is part of many hospitals' existing pain protocols. This study demonstrates that adding natural warmth to this widely used technique confers additional pain-relieving benefits to the infant while adding little or no additional cost or effort. Ultimately, knowledge gained from this study may allow health care providers to examine their current practice and incorporate more or all of the components of maternal breastfeeding into their minor procedure pain management strategies for the newborn. Encouraging breastfeeding in the newborn nursery and keeping the mother and healthy infant together is an increasingly important priority for the health care provider. When breastfeeding is not possible, however, this study adds another natural nonpharmacologic analgesic technique for health care providers to protect the newborn from the pain of a routine immunization needle stick. Additional studies examining the use of this practical and nonpharmacologic technique in combination with nonsucrose natural analgesic techniques, such as pacifier suckling, and with different populations of newborn infants are needed.

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