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Routine Sucrose Analgesia During the First Week of Life in Neonates Younger Than 31 Weeks' Postconceptional Age

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ABSTRACT. *Objective.* To determine the efficacy of sucrose analgesia for procedural pain during the first week of life in preterm neonates in neonatal intensive care units on enhancing later clinical outcomes.

Methods. A total of 107 preterm neonates who were born at <31 weeks' postconceptional age (PCA) entered this double-blind, randomized, controlled trial within 48 hours of birth at 3 level III university-affiliated neonatal intensive care units in Canada, and 103 completed the study. Sucrose (0.1 mL of 24%) or sterile water was administered orally up to 3 times, 2 minutes apart, for every invasive procedure during a 7-day period. Motor development and vigor, and alertness and orientation components of the Neurobehavioral Assessment of the Preterm Infant were measured at 32, 36, and 40 weeks' PCA; Score for Neonatal Acute Physiology was measured on the last day of intervention; and Neuro-Biological Risk Score (NBRS) was measured at 2 weeks of age and at discharge. Primary analyses of covariance were applied for each outcome to compare group differences followed by secondary analyses using standard linear regression within each group to determine predictors of outcomes.

Results. Although there were no differences between the groups on any outcomes, there were significant dose-related effects within each group. In the sucrose group only, higher number of doses of sucrose predicted lower scores on motor development and vigor, and alertness and orientation at 36 weeks', lower motor development and vigor at 40 weeks', and higher NBRS at 2 weeks' postnatal age. Higher number of invasive procedures was predictive of higher NBRS both times in the water group.

Conclusions. Repeated use of sucrose analgesia in infants <31 weeks' PCA may put infants at risk for poorer neurobehavioral development and physiologic outcomes. Additional study is needed to determine the most appropriate age and duration of sucrose analgesia in preterm infants. *Pediatrics* 2002;110:523–528; *neonate, preterm, pain, sucrose, analgesia.*

ABBREVIATIONS. NICU, neonatal intensive care unit; PCA, postconceptional age; NAPI, Neurobehavioral Assessment of the Preterm Infant; AO, alertness and orientation; MDV, motor development and vigor; SNAP, Score for Neonatal Acute Physiology; NBRS, Neuro-Biological Risk Score; CRIB, Clinical Risk Index for Infants.

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Sucrose has been reported to have analgesic properties in newborns, both animal and human.^{1–4} In a systematic review of sucrose analgesia, doses from 0.05 to 2 mL of 12% to 50% sucrose were reported to have analgesic effects in preterm or full-term neonates.⁵ The mechanism for the analgesic effect is thought to be via the release of endogenous opiates triggered by sweet taste,^{1,2,6} although the salience of a taste is immediately calming and distracting.⁷ Studies in which other saccharides were tested for analgesic properties provide support for the sweet taste hypothesis.^{8–10} Lactose and human milk seem not to have analgesic properties, but they are relatively less sweet than the other sugars studied.^{11,12} The data supporting the use of sucrose as an analgesic for “minor” painful procedures are sufficiently strong that the American and Canadian Pediatric Societies have recommended the use of sucrose for such procedures as heel lances, injections, and intravenous line insertions.¹³ This is particularly important for preterm or ill infants in the neonatal intensive care units (NICU) environment, where they undergo multiple invasive, tissue-damaging, and presumably painful procedures daily.^{14–16} Typically, more of these procedures occur during the first week of life with stabilization and diagnosis of the newborn. There is mounting evidence that untreated procedural pain in newborn preterm infants can alter subsequent behavior, specifically leading to less robust behavioral responses.^{17,18}

Although the data on the effect of sucrose for a single painful procedure are strongly supportive of the use of sucrose for management of minor procedural pain, the effects of routine use of sucrose analgesia in preterm infants have not been evaluated. Given emerging data on negative behavioral sequelae to untreated procedural pain in preterm neonates, it would be reasonable to hypothesize that if procedural pain were adequately managed in the first week of life in preterm neonates, then there might be positive long-term developmental effects. Therefore, the purpose of this study was to investigate the efficacy of routine sucrose analgesia for procedural pain in the first week of life in preterm infants born at <31 weeks' postconceptional age (PCA).

METHODS

Sample

Three level III university-affiliated NICUs in Canada were the sites for the study, and each site provided ethics approval by a

constituted review board. The sites were similar in level of acuity of the infants and teaching programs. There were differences in level of developmental care: 1 site had completely implemented it, and the other 2 had some components (eg, unit darkened except for morning rounds). One unit treated with indomethacin more than the other units. Infants who were born between 25 and 31 completed weeks' PCA, were expected to live according to the opinion of the attending neonatologist, were above the fifth percentile weight for gestational age, had intraventricular hemorrhage less than grade 3 and no periventricular leukomalacia, were free of major congenital anomalies, and did not require surgery and whose parents consented within 48 hours of birth were included in the study. Sample size estimates based on the primary outcomes of Neurobehavioral Assessment of the Preterm Infant (NAPI¹⁹; see below) were 35 per group for a power of 0.8 with statistical significance set at .05.

Intervention

Enrolled infants were randomly assigned to the sucrose or water group from a computer-generated schedule for each site. Only the project nurses in each site knew the group assignment; treating clinicians were blind to group assignment. Solutions of 0.1 mL of 24% sucrose or water were drawn up into sterile syringes and placed in the unit medicine refrigerator. Every time the infant was to undergo an invasive (eg, heel lance, intravenous cannulation, arterial puncture, injection) or noninvasive but presumably uncomfortable procedure (eg, endotracheal tube suctioning, tape/lead removal, gavage insertion for feeding), the solution in the syringe was administered into the infant's mouth, at the beginning of the procedure, 2 minutes into the procedure, and another 2 minutes into the procedure. If the procedure was to last >15 minutes, up to another 3 0.1 doses were to be given 2 minutes apart.

In 1 site, there was videotaping of 1 infant at any point in time for the duration of the study week. A small wide-angle lens camera rested on top of the isolette and was connected to a mat on the floor next to the isolette such that stepping on the mat triggered 5-minute recording. The person who approached the infant was to identify his or her role (eg, nurse, mother) and the purpose of his or her approach (eg, suctioning, visiting). In this way, facial actions could be recorded during painful procedures to verify whether there was an immediate analgesic effect of the sucrose. Coding of faces was conducted in the laboratory according to the upper facial components of the Neonatal Facial Coding System.²⁰ Only the upper facial components were coded because many of the infants were intubated and these components have been shown to be specific to pain response in preterm infants.²¹

Outcomes

The primary outcome was neurobehavioral development assessed by the subscales of alertness and orientation (AO) and motor development and vigor (MDV) of the NAPI developed by Korner and colleagues.^{19,22-24} The NAPI is appropriate for infants between 32 weeks' PCA and term. It assesses the relative maturity of functioning of preterm infants, with higher scores reflecting higher maturity, and can differentiate 2 weeks' PCA. Much of the examination consists of observational items, and the remainder rates the infant's response to stimuli. This assessment takes approximately 30 minutes to administer and includes 7 clusters of

single-item neurobehavioral dimensions: MDV, scarf sign, popliteal angle, AO, irritability, vigor of crying, and percentage asleep ratings. Test-retest reliability over 2 consecutive days ranged from 0.59 to 0.90. Original interobserver reliability ranged from 0.64 to 0.93.²³ The observers in this study were either occupational therapists (L.S., C.L.) or a psychologist (H.C.) with doctoral training and experience with this population. After the viewing of a detailed training tape provided with the NAPI kit, the interrater reliability using the intraclass correlation coefficient was >0.9. The clinical validity and sensitivity of the NAPI were established using an index of medical complications based on a 1 to 5 classification range of degrees of complications.²⁵ Functions that required strength and vigor were significantly related to medical complications, whereas items that assessed AO were not.^{25,26} Assessments were conducted at 32, 36, and 40 weeks' PCA if respirations were unassisted and the infant was available for assessment.

The secondary outcomes were measures of severity of illness during the course of the intervention and at discharge. These were assessed during the week of study by the Score for Neonatal Acute Physiology (SNAP)^{27,28} for each 24-hour period and by the Neuro-Biological Risk Score (NBRS)²⁹ at 2 weeks' postnatal age and at discharge. Background information, including PCA at birth (determined by ultrasound), birth weight, and Apgar, was obtained from the medical record, and the Clinical Risk Index for Infants (CRIB),³⁰⁻³² an index of severity of illness at birth, was calculated from information in the medical record. Serum glucose levels during the study time were obtained from the medical record when ordered clinically (not for purposes of the study).

RESULTS

Sample

Over the course of 27 months, 281 infants were admitted within the age category. Eighty-one (29.2%) were not evaluated for eligibility for the following reasons: mother too ill to consent within 48 hours, compassionate reasons (twin or triplet sibling had died), or unit difficulties when recruitment was temporarily stopped (Y2K problems, understaffing during holidays or ice storm). Thirty-two (16.3%) did not meet the selection criteria (died within 48 hours, deemed too ill by staff). Of the 168 remaining infants, 107 (63.7%) parents gave consent for the infant to participate. The reasons for the 63 refusals were as follows: the parents thought that the infant was too ill (5), were too stressed to consider study (4), did not want their infant to be in any research (10) or to receive sugar (4), or gave no reason (38). There were no significant differences between excluded infants, infants whose parents refused, and participating infants in the distribution of PCA or weight (Table 1).

Two infants were withdrawn from the study during the week of intervention. Two other infants died: 1 of grade 4 intraventricular hemorrhage and periventricular leukomalacia on the first day of the

TABLE 1. Demographic Characteristics of Final Sample

	N	Age (Weeks)	Birth Weight (Grams)	CRIB
Participants versus nonparticipants				
Participants	107	28.15 (1.72)	1134.14 (277.26)	
Nonparticipants	63	27.94 (1.62)	1101.43 (299.68)	
Site				
1	20	28.7 (2.33)	1160.75 (342.61)	1.85 (2.32)
2	69	27.9 (1.83)	1084.14 (279.79)	2.54 (2.77)
3	14	28.34 (1.35)	1263.93 (238.18)	1.36 (1.55)
Total	103	28.11 (1.89)	1123.46 (292.08)	2.24 (2.58)
Condition				
Sucrose	51	28.18 (1.72)	1130.78 (287.71)	2.00 (2.33)
Water (control)	52	28.05 (2.06)	1116.27 (298.93)	2.48 (2.80)
Total	103	28.11 (1.89)	1123.46 (292.08)	2.24 (2.58)

study after receiving 1 dose of water and the other infant of cardiac failure associated with patent ductus arteriosus at age 29 days. One infant was withdrawn on study day 4 for hyperglycemia after receiving 10, 6, and 12 doses of sucrose and serum glucose levels of 3.5, 16, and 12 on the respective study days. The infant became septic 48 hours after withdrawal from the study, which may be an alternative explanation for the glucose instability. The second infant was withdrawn from the study for suspected necrotizing enterocolitis. The infant did not develop necrotizing enterocolitis but did have *Escherichia coli* sepsis. At baseline, there were no group differences in birth PCA, birth weight, or CRIB score (see Table 1), and there were no differences between sites on age, CRIB score, or birth weight (see Table 1). There were differences in amount of indomethacin given to infants at 1 site.

Solutions

The total number of study doses given per infant during the week ranged from 24 to 125 with a mean of 58 in the water group and 63 in the sucrose group. An estimate of compliance in administering solutions was determined by dividing the number of procedures by the number of doses, which was an underestimate because an infant could potentially receive up to 3 doses per intervention. Overall, this estimate was only 69%, ranging widely between 27% and 185%, and was the same for both groups. One site accounted for the lack of compliance that became evident after the first 6 months of study, and this noncompliance persisted despite holding sessions with the nursing staff on the importance of adhering to the protocol. Serum glucose levels ranged from 1.8 to 13.5, but there were no group differences and there was no relationship between the number of solutions and the serum glucose level in either group.

The number of infants whose videotapes were able to be coded throughout the week was small (14) but indicated that the sucrose was effective as an analgesic during the immediate 60 seconds of initiation of the painful procedure, even on day 7.

NAPI

The NAPI was administered to infants who no longer required ventilatory assistance and were not discharged back to distant referring centers. At 32 weeks, 75 infants could be tested, 87 at 36 weeks, and 67 at 40 weeks, with only 53 infants having data at all 3 times. There were, however, at least 35 infants/group at each time, thus meeting the original sample size estimates. Multivariate analysis of covariance was therefore conducted at each age, to maintain the sample size estimates that would not have been met with repeated measures analyses, with covariates of PCA and number of invasive procedures on the 2 components of the NAPI that were tested, MDV and AO. No significant differences were found between the sucrose and water groups (MDV: sucrose at 32, 36, 40 weeks = 20.4, 48.6, 66.1; water at 32, 36, 40 weeks = 21.7, 49.7, 63.9; $F(1,52) = 0.223$, $P = .64$; AO: sucrose at 32, 36, 40 weeks = 16.0, 40.7, 54.3; water at

weeks 32, 36, 40 = 19.5, 42.2, 55.5; $F(1,52) = 2.016$, $P = .162$).

Because compliance with administering solutions was generally low and there was a wide range of compliance, we were interested in determining whether number of doses of sucrose was related to outcomes while accounting for other factors that might be correlated with number of doses. Secondary analyses using standard multiple regressions were conducted by group on each of the NAPI components at each age to determine whether there were background factors, specifically age at birth, CRIB, or other factors related to the NICU experience, such as days on certain medications (sedatives, analgesics, caffeine, indomethacin), number of invasive procedures, or number of doses of sucrose that might have had an effect on the NAPI scores. So few infants received sedatives (4) or analgesics (3) that these medications were not able to be included in the analysis. After analyses of Pearson correlation coefficients, which fell below 0.5, thus satisfying lack of multicollinearity, the predictor variables for the 2 sets of standard regression analyses (ie, a set for sucrose group and a set for water group) on each NAPI outcome, were 1) age at birth, 2) CRIB, 3) days on caffeine, 4) days on indomethacin, 5) number of painful procedures, and 6) number of doses of sucrose or water. At 32 weeks, there were no significant predictive factors on the NAPI. Significant predictors were identified for only the sucrose group, with no factors reaching significance in the water group (Table 2). At 36 weeks, more developed MDV and more developed AO were predicted for the sucrose group by fewer days on indomethacin and fewer doses of sucrose. At 40 weeks, fewer doses of sucrose predicted more developed MDV and fewer days on indomethacin predicted more AO (Table 2). The only site differences were accounted for by days on indomethacin.

SNAP and NBRs

There were no group differences or factors associated with SNAP over each day, with day 7 being of interest because it was calculated on the final 24 hours of the intervention and would be most reflective of cumulative physiologic effects of the intervention (sucrose = 3.72 [3.33], water = 4.10 [3.18]; $F(1,101) = 0.093$, $P = .761$). On the basis of analysis of covariance with PCA at birth and number of invasive procedures as covariates, there were no group differences on any of the secondary outcomes of NBRs scores at 2 weeks' postnatal age (sucrose = 1.42 [1.32], water = 1.68 [1.58]; $F(1,101) = 0.640$, $P = .426$) or at discharge (sucrose = 2.29 [2.68], water = 2.31 [2.47]; $F(1,100) = 0.002$, $P = .965$).

In the regression analysis to determine background and clinical factors that might have predicted higher (worse) physiologically based illness scores, multiple factors were identified (Table 3). Younger age was predictive of higher SNAP scores on study day 7 for the water group only. At 2 weeks' postnatal age, younger PCA, fewer days on caffeine, and greater number of invasive procedures were predictive of higher NBRs for the water group, and fewer

TABLE 2. Significant Results of Standardized Multiple Regression by Group on Primary Neurobehavioral Development Outcomes

Variable		β	CI	P
MDV at 36 wk*	Water			
	Sucrose	Days on indomethacin Doses of sucrose	-6.098 -2.158	-10.444, -1.752 -4.244, -0.072
AO at 36 wk*	Water			
	Sucrose	Days on indomethacin Doses of sucrose	-8.724 -3.819	-15.114, -2.334 -6.804, -0.834
MDV at 40 wk†	Water			
	Sucrose	Doses of sucrose	-2.737	-5.203, -0.272
AO at 40 wk‡	Water			
	Sucrose	Days on indomethacin	-6.801	-12.768, -0.834

CI indicates confidence interval.

* Nonsignificant variables entered in the equation included age at birth, CRIB, days on caffeine, and number of invasive procedures.

† Nonsignificant variables entered in the equation included age at birth, CRIB, days on caffeine, days on indomethacin, and number of invasive procedures.

‡ Nonsignificant variables entered in the equation included age at birth, CRIB, days on caffeine, doses of sucrose, and number of invasive procedures.

days on caffeine and greater number of doses of sucrose were predictive of higher NBRS for the sucrose group. For the NBRS at discharge, younger age, fewer days on caffeine, and greater number of invasive procedures were predictive of higher NBRS for the water group. However, fewer days on caffeine was predictive of higher NBRS at discharge for the sucrose group.

DISCUSSION

There were no differences on either neurobehavioral developmental outcomes or severity of illness outcomes between infants who received sucrose for painful procedures in the first week of life and those who received water. Because compliance was often low, number of doses of study solution that the infants received was examined for influencing outcomes.

Surprisingly, the effect of number of doses of sucrose was related in the opposite direction than predicted on the neurobehavioral outcomes at 2 of the 3 test ages and on 1 severity of illness outcome before discharge. The number of doses was significant only

in the sucrose group. Because the number of study solution doses was not different between the sucrose and water groups, the effect of the procedure to administer a solution in the infant's mouth in association with a painful procedure can be dismissed.

Tolerance to the sucrose was considered as a possible explanation for the relationship between total doses of sucrose and the outcomes. In this study, the few infants for whom facial expressions of pain could be coded showed a decrease in facial actions for those in the sucrose group compared with those in the water group late in the intervention (days 6–7), as well as in the initial period of the intervention, so sucrose seemed to be analgesic even after several days of receiving it. Thus, sucrose seemed to remain effective in decreasing pain during the study period and there were no signs of tolerance to its analgesic effect. A methodological explanation is that the sample size was inadequate. Sample size was calculated on univariate analyses for each outcome. Thus, when some factors appear as significant for some outcomes but not for others, this could be a result of a sample size that was inadequate in terms of the relative

TABLE 3. Significant Results of Standardized Multiple Regression by Group on Secondary Physiologically Based Illness Outcomes

Variable		β	CI	P	
SNAP at day 7	Water				
	Sucrose	Age	-0.674	-1.151, -0.196	.007
NBRS1†	Water	Age	-0.432	-0.664, -0.200	.000
		Invasive procedures	0.072	0.021, -124	.006
	Sucrose	Days on caffeine	-0.147	-0.256, -0.038	.009
		Doses of sucrose	0.212	0.034, 0.390	.021
NBRS2‡	Water	Days on caffeine	-0.125	-0.241, -0.008	.037
		Age	-0.691	-1.001, -0.380	.000
	Sucrose	Invasive procedures	0.084	0.015, 0.153	.018
		Days on caffeine	-0.144	-0.029, -0.002	.05
		Days on caffeine	-0.240	-0.465, -0.015	.037

* Nonsignificant variables entered into the equation included CRIB, days on caffeine, days on indomethacin, doses of sucrose, and number of invasive procedures.

† NBRS at 2 weeks' postnatal age, 1 week after intervention. Nonsignificant variables entered into the equation included CRIB and days on indomethacin.

‡ NBRS at discharge. Nonsignificant variables entered into the equation included CRIB, days on indomethacin, and doses of sucrose.

colinearity of the variables of interest. There may be other factors that did not seem to be significant because the sample size was inadequate to detect them.

Nevertheless, the results of this study should not be ignored. The number of doses of sucrose, as opposed to water, was related to several outcome variables in a way that suggests that for infants <32 weeks' PCA, receiving more doses of sucrose during the first week of life may have questionable long-term effects, despite immediate beneficial effects. The underlying mechanism for sucrose analgesia is understood to be attributable to the release of endogenous opiates as a result of sweet taste.^{1,2,33} By giving the sucrose analgesia for 1 week only and then withdrawing it, we may have increased the sensitivity to subsequent pain. This is based on an animal study in which it was found that exposure to morphine at birth resulted in increased morphine threshold in adulthood.³⁴ Related to this possibility is that the infants may have failed to adopt appropriate self-modulating behaviors, relying instead on external mediators (sucrose). When this external mediating resource was removed, they were slower in developing self-modulating behaviors, which resulted in neurobehavioral and physiologic consequences in the subsequent few weeks. The outcome measures, with the exception of the SNAP on day 7, were at least 1 week beyond the cessation of the intervention, so they may have had heightened pain experience in the intervening time.

Although there is not a clear age delineation, there are indications from animal models that the endogenous opiate system does not become functional until the third trimester or 32 weeks' PCA.³⁵ The infants in this study were born at <31 weeks' PCA and received sucrose analgesia (or water) at <32 weeks 2 days. Although we and others have shown an analgesic effect of sucrose in infants <32 weeks for a single painful event,³⁶⁻³⁹ other studies on preterm infants were with infants 32 weeks or older.^{40,41} Perhaps in infants <32 weeks' PCA, the repeated stimulation of an immature endogenous opiate system by routine use of sucrose "stresses" the system or interferes with the normal developmental functioning and maturation of this system. For example, a possible explanation for the negative neurobehavioral outcomes could be cross-sensitization between dopamine and endogenous opiates. It is possible that chronic opioid release (as activated by routine sucrose administration) would repeatedly stimulate dopaminergic neurons that are implicated in locomotor activity and arousal.⁴²⁻⁴⁵ The projecting areas of these neurons may not be mature enough to demonstrate motor sensitization and in fact could even be inhibitory at this age. This may then explain the higher alertness scores as well as higher motor development scores being predicted by fewer sucrose doses.

The first week of life was selected for this study because that is typically the time of the highest number of invasive procedures^{14,15} and, as well, the younger the infant, the greater the number of interventions because the infant requires more external support for stabilization.⁴⁶ Replication of this study

is strongly urged but with a larger sample or a less varied sample, with assurance of greater compliance, and inclusion of ongoing physiologic data for all infants. We did have physiologic data on some infants, but there were no group differences and there were too few infants with complete physiologic monitoring to conduct the same regression analyses as in this report.

Other significant results have not been reported. Although Grunau et al¹⁷ reported that dexamethasone exposure may have detrimental long-term outcomes despite its immediate benefit, this was not found for indomethacin. The administration of caffeine seems to be associated with long-term beneficial effects in this study. This has not been reported previously, although a Cochrane review on caffeine for the treatment of apnea of prematurity suggested that it is the preferred treatment for apnea of prematurity and recommended additional study on later effects.⁴⁷

Although it could be argued that the clinical magnitude of our findings were not worrisome, we cannot recommend that sucrose analgesia be used routinely for every painful event in infants <32 weeks' PCA despite much evidence of its immediate beneficial effect. It could be that older infants, >32 weeks, would benefit from the routine use of sucrose analgesia or that it should be continued beyond 1 week. Because of the recent recommendation of the use of sucrose routinely¹³ and the increasing numbers of NICUs that are recommending its use routinely, it is particularly important that selection criteria for the appropriate population be established.

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