A Randomized, Controlled Trial of Sucrose Analgesia in Infants Younger Than 90 Days of Age Who Require Bladder Catheterization in the Pediatric Emergency Department

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Abstract

Objectives: To determine whether an oral sucrose solution improves pain response for infants undergoing bladder catheterization in an emergency department (ED) population.

Methods: A randomized, double-blinded study comparing the analgesic effects of a sucrose solution to placebo for infants ≤90 days of age and requiring bladder catheterization. Infants with prior bladder catheterization, previous painful procedures that day, or neurological or genital abnormalities were excluded. Infants were assigned baseline pain scores and then given 2 mL of sucrose or water 2 minutes before catheterization. Trained pediatric ED nurses rated the infants for pain, presence of cry, and time to return to baseline.

Results: Eighty-three patients were enrolled; 40 were randomized to sucrose, and 40, to placebo. Baseline pain scores were similar within each age group. Overall, sucrose did not produce a significant analgesic effect. In subgroup analysis, infants 1–30 days of age receiving sucrose showed a smaller change in pain scores (2.9 vs. 5.3, p = 0.035), were less likely to cry with catheterization (29% vs. 72%, p = 0.008), and returned to baseline more rapidly after catheter removal (10 seconds vs. 37 seconds, p = 0.04) compared with infants who received placebo. Infants older than 30 days of age who received sucrose did not show statistically significant differences in pain scores, crying, or time to return to baseline behavior.

Conclusions: There was no overall treatment effect when using an oral sucrose solution before bladder catheterization in infants younger than 90 days of age. However, infants younger than or equal to 30 days of age who received sucrose had smaller increases in pain scores, less crying, and returned to baseline more rapidly than infants receiving placebo. Older infants did not show an improved pain response with oral sucrose.

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The evaluation of infants in the emergency department (ED) frequently involves noxious stimuli. Infants are subjected to bladder catheterization, blood draws, intravenous lines, and lumbar punctures. Although pain long has been recognized in children, infant pain responses and their effects have only recently

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become better understood, and evidence suggests that infants may in fact be more susceptible to the effects of pain than older age groups.[1,2]

In February 2001, a Consensus Statement for the Prevention and Management of Pain in the Newborn was published.[3] This review recommends the use of various pain control methods for noxious procedures commonly performed on neonates, including the use of an oral 12%–24% sucrose solution.

The use of sucrose has been well studied for certain procedures in the neonatal intensive care unit and newborn nursery settings, particularly for venous blood draws, heel lance, and circumcision.[4,5,6] Infants receiving oral sucrose solutions before painful procedures cried less and had overall decreased behavioral pain responses compared with infants receiving placebo. Further, sucrose has been shown to be a safe intervention, with the few reported side effects generally consisting of minimal coughing with administration and no serious or life-threatening secondary effects reported from single-dose regimens.

Bladder catheterization is one of the most common procedures performed on acutely ill infants. Young patients presenting with fever or irritability are frequently catheterized to obtain a sterile urine specimen for both urinalysis and culture.[7] Bladder catheterization is an invasive, painful procedure and evokes crying and typical pain responses in infants. Analgesia for bladder catheterization in this age group rarely is administered.

Recently, guidelines for the use of sucrose in the ED have been published, drawing on data from studies performed in neonates and well infants undergoing immunization.[8] There has, however, yet to be a well-controlled study of sucrose for pain control in the ED setting. The ED patient population is qualitatively different than previously studied populations in that it represents a group of generally well children of all ages, with acute illness at time of presentation. These infants may react differently to painful stimuli than previously studied populations.

This study examines the use of an oral sucrose solution before bladder catheterization in infants presenting to the ED who are younger than or equal to 90 days of age. It seeks to determine whether sucrose is an effective pain intervention for this commonly performed procedure and, if so, whether there is an age range for the analgesic effect. We hypothesized that oral sucrose solution administered before bladder catheterization in the ED would have analgesic effects and could provide a simple analgesic option for infants requiring this procedure.

METHODS

Study Design

A convenience sample of infants presenting to the ED and requiring bladder catheterization was recruited from June 2003 to November 2004. Consent was obtained from a parent or legal guardian according to a protocol that received review and approval from the Emory University Institutional Review Board.

Study Setting and Population

All infants were enrolled from a single tertiary-care dedicated pediatric ED. The pediatric ED is staffed with a combination of board-certified or board-eligible pediatric emergency physicians as well as with general pediatricians and a site-specific nursing staff.

Eligible infants were those younger than or equal to 90 days of age, born at at least 34 weeks' gestational age, for whom the attending pediatrician determined that a bladder catheterization was required for diagnostic evaluation. Infants were excluded if they needed immediate critical intervention, had undergone invasive or painful procedures within the prior 24 hours, had any prior bladder catheterizations, or were known to have neurological or urologic abnormalities. Eligible infants were enrolled by six pediatric-ED registered nurses who had undergone prior training to participate in the study. Infants were not enrolled if a study nurse was unavailable to evaluate the infant. Enrollment occurred seven days a week, with a mix of days, nights, and weekends. Pain was assessed by the study nurses by using the previously validated Douleur Aigue du Nouveau-né (DAN) scale, as well as for the presence of cry and time to return to behavioral baseline after catheter withdrawal[9] (Table 1).

Sample size was calculated to detect a 20% mean change in DAN score with catheterization, SD of ±2.5, and $p < 0.05$. This was based on previous studies using the DAN scale and sucrose analgesia and was determined to be a clinically significant outcome.[10] A total of 26 patients in each group would yield a power of 80% to detect a difference.

Study Protocol

Enrolled infants were randomized to receive either sterile water or a 24% sucrose solution. For this study, a dose of 2 mL of a 24% oral sucrose solution was selected.

Table 1
DAN Scoring System

Measure	Finding	Points
Facial expression	Calm	0
	Snivels and alternates gentle eye opening and closing	1
	Intensity mild and intermittent with return to calm	2
	Intensity moderate	3
	Intensity very pronounced, continuous	4
Limb movements	Calm or gentle movements	0
	Intensity mild and intermittent with return to calm	1
	Intensity moderate	2
	Intensity very pronounced, continuous	3
Vocal expression	No complaints	0
	Moans briefly	1
	Intermittent crying	2
	Long-lasting crying, continuous howl	3

The Douleur Aigue du Nouveau-né (DAN) is an acute-pain rating score for neonates that is based on observation of behavior. The score range is 0–10 (10 is maximum painful response). Facial expression intensity is based on one or more of the following: eye squeeze, brow bulge, or naso-labial furrow; limb movement intensity is based on one or more of the following: pedals feet, toes spread, legs tensed and pulled up, agitation of arms, withdrawal reaction.

Although sucrose solutions from 12% to >50% have been studied in neonates, we selected the 24% solution because it is the only commercially available sucrose solution available in the United States (Sweet-Ease; Children's Medical Ventures, Norwell, MA). The dose of 2 mL was selected because it had been shown previously to be effective in full-term infants.[11]

Randomization was performed by a research pharmacist using a random-numbers table, with all other study personnel blinded to the randomization tables. The study drug or placebo was preloaded into coded syringes by the pharmacy, and it was not possible to distinguish sucrose solution from placebo by color, smell, or viscosity. Syringes and codes were changed every 25 patients to maintain blinding and maintain drug stability.

After enrollment, basic demographic information was obtained. Pain responses were assigned by using the DAN scoring system, a 10-point scale using cry, facial expression, and limb movements to quantify infant behavioral responses to pain, with 10 representing maximal pain response. This validated behavioral scale has been used in previous studies of sucrose analgesia on term infants.[10] All participating study nurses received standardized DAN score training before study implementation via prerecorded video tape.

All enrolled infants had the bladder catheterization as their first noxious procedure of their visit, if more than one procedure was to be performed. After undressing the infant, but before sterile preparation and catheterization, baseline DAN scores were recorded. Infants then were orally administered 2 mL of the study drug. After a 2-minute wait, the infant's urethra was catheterized in standard sterile fashion by a staff member (nurse or technician) who was not responsible for the study observations. No other specific comfort measures were used as part of the study. Pacifiers were given to infants as per parental request. To minimize interobserver variation, DAN scores and presence of cry were recorded at maximum catheter insertion. Time needed for the infant to return to behavioral baseline was recorded. If after 3 minutes the infant had not returned to baseline, a new DAN score was assigned. The amount of time needed to complete the catheterization, as well as results from urinalysis, and all culture data were followed to identify possible confounders. The observing nurses also were instructed to watch for potential adverse reactions, such as choking or cyanosis, and to report these to the study team.

Data Analysis

The primary outcomes of interest were the change in DAN (pain) score (from baseline to maximal insertion), crying during the procedure, and the time to return to baseline (in seconds). Although the pain score is the most specific measure of the outcome of interest, the crying and time variables were slightly more objective and should indicate similar trends to indicate a possible analgesic effect of sucrose. In addition, we performed post hoc subgroup analyses that attempted to determine the age range at which the use of sucrose might no longer be effective. Infants were grouped by age (1–30 days, 31–60 days, and 61–90 days) for analysis. This breakdown was chosen both for clinical applicability and to coincide with age-related guidelines for evaluation of young infants, which often use one-month cutoffs.[12]

Comparison of treatment groups (sucrose, placebo) were performed by using t-tests for the change in DAN score, which was treated as a continuous measure, and chi-square tests of independence for the crying outcome. Because the time to return to baseline was considerably skewed, we used the Mann-Whitney test of medians to compare treatment groups. In addition, we tested possible confounding variables (e.g., pacifier use, previous analgesic) for associations with any outcome to determine whether the analyses for the treatment effects might need to be adjusted.

Further analyses involving the age group factor used analysis of variance (ANOVA) to determine whether there was an age group by treatment group interaction in the change in DAN score or time to return to baseline. We also tested the odds ratios for crying in the treatment versus the placebo group for a possible difference across age groups by using the Breslow-Day (BD) test for homogeneity.

RESULTS

From June 2003 to November 2004, 99 patients were approached for enrollment. Of these, 83 were enrolled and randomized. The parents of 16 patients refused participation, and 3 patients were withdrawn after randomization as a result of inappropriate enrollment or withdrawal of consent. The ages of enrolled infants ranged from 3 to 90 days. Of the remaining 80 patients, 40 were randomized into each group (Figure 1). We elected to enroll more than our initial power calculation to compensate for possible interrater differences inherent in our study design. The randomization was successful in that patient characteristics were in general similar across groups. The only difference noted was that the placebo group had a higher incidence of previous hospitalizations (Table 2).

The placebo group did not differ in DAN score increase (5.0 [±3.1] vs. 4.0 [±3.0]) from the sucrose group ($t = 1.42$, $df = 70$, $p = 0.161$). This remained the case even after analysis of covariance was used to adjust for the gender difference ($F_{1,69} = 1.48$, $p = 0.228$). Although the overall percentage of subjects crying at maximal insertion was higher in the placebo group (68.4% vs. 54.1%), this also was not statistically significant ($\chi^2 = 1.63$, $df = 1$, $p = 0.201$). The median time to return to baseline also was not significantly different in the treatment groups ($Z = -0.962$, $p = 0.336$) but was slightly longer in the placebo group (37 vs. 30 seconds). There were no adverse effects noted in the study population.

We tested the following dichotomous variables for association with the change in DAN score, crying at maximal insertion, and time to return to baseline: prior analgesic, use of pacifier, prior hospitalizations, gender, number of catheterization attempts, hematuria, and pathology evident in the urine culture. The only significant association indicated that there was a greater increase in pain in the male subjects compared with in females (5.0 [±2.8] vs. 3.5 [±3.3], $p = 0.056$), with circumcision status having no appreciable effect.

Given that all three measures of interest showed a trend toward an analgesic effect of sucrose and that the

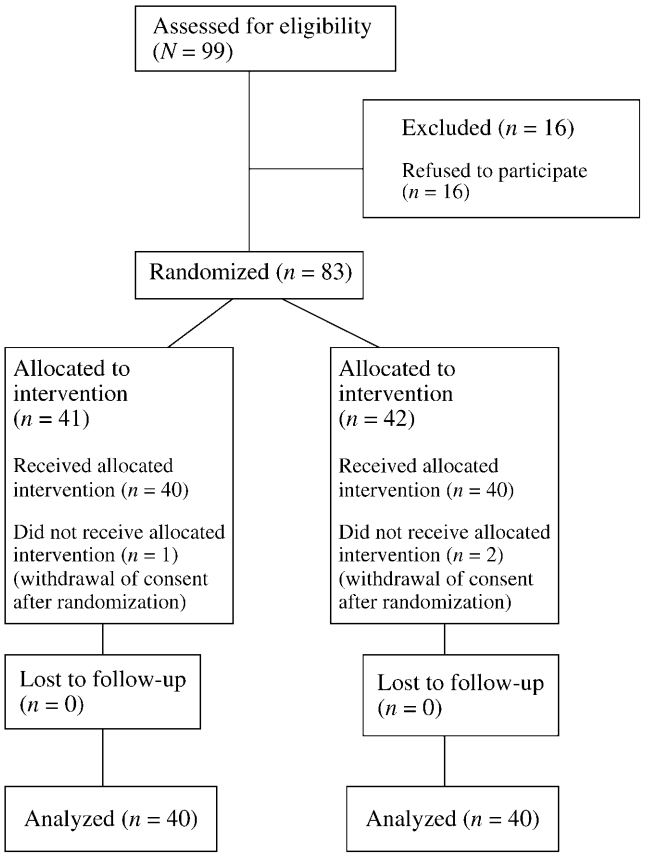

Figure 1. Recruitment flowchart.

majority of prior studies have focused on younger infants, we grouped the data by patient age (1–30 days, 31–60 days, and 61–90 days) and performed post hoc tests to determine whether the treatment effect was moderated by age. The treatment group by age group interaction was not significant for the change in DAN score ($F_{2,66} = 1.64$, p = 0.20). However, the test for homogeneity of the odds ratio for crying across age groups was rejected (B-D$\chi^2 = 6.85$, df = 2, p = 0.032), and an ANOVA on the ranks for time to return to baseline indicated a trend toward a significant interaction effect ($F_{2,66} = 2.45$, p = 0.094). We therefore analyzed the age-divided subgroups for treatment effect for each of the outcome variables. In the youngest subgroup of patients (1–30 days), infants receiving sucrose showed a smaller mean change in DAN score (2.86 vs. 5.29, p = 0.035), less crying at maximal catheter insertion (28.6% vs. 78.6%, p = 0.008), and a faster return to baseline behavior after catheter withdrawal (10 vs. 37 seconds, p = 0.04). The two older groups showed no significant differences in pain response between the sucrose and placebo groups (Table 3).

Table 2
Patient Characteristics

Group	Sucrose, *n* (%) (*n* = 40)	Placebo, *n* (%) (*n* = 40)	p-value*
Age group (d)			
1–30	15 (37)	18 (45)	0.670
31–60	15 (37)	15 (37)	
61–90	10 (25)	7 (18)	
Race			
African American	22 (56)	20 (50)	0.121
Caucasian	16 (41)	12 (32)	
Hispanic	1 (3)	6 (16)	
Male (total) by days of age	24 (60)	27 (68)	0.485
1–30	10 (67)	11 (61)	0.741
31–60	8 (53)	10 (67)	0.465
61–90	6 (60)	6 (60)	0.252
Circumcised males by days of age	21 (87)	20 (74)	0.823
1–30	10 (100)	8 (73)	0.074
31–60	6 (75)	8 (80)	0.8
61–90	5 (83)	4 (67)	0.505
Fever on presentation by days of age	28 (70)	26 (65)	0.633
1–30	9 (60)	10 (56)	0.8
31–60	13 (87)	11 (73)	0.361
61–90	6 (60)	5 (71)	0.627
Use of pacifier by days of age	20 (50)	18 (46)	0.491
1–30	6 (40)	7 (41)	0.946
31–60	9 (75)	8 (53)	0.247
61–90	5 (50)	3 (43)	0.772
Prior analgesic by days of age	8 (22)	8 (22)	0.952
1–30	2 (14)	2 (13)	0.886
31–60	3 (20)	3 (20)	1.0
61–90	3 (33)	3 (50)	0.519
Prior hospitalization by days of age	2 (5)	10 (25)	0.012
1–30	0	3 (17)	0.097
31–60	2 (13)	4 (27)	0.361
61–90	0	3 (27)	0.022

* Chi-square test of proportions.

DISCUSSION

This study examined the effectiveness of a 24% oral sucrose solution on the behavioral response to bladder catheterization in infants younger than 90 days of age who were presenting to the ED. To our knowledge, this is the first study of oral sucrose in the ED setting and the first to evaluate sucrose for bladder catheterization. The results did not demonstrate a reliable analgesic effect across the age spectrum of 1–90 days of age. A post hoc subgroup analysis did reveal a decreased behavioral pain response to bladder catheterization for infants younger than one month of age.

For infants in the 1- to 30-day age group, statistically significant differences in pain response were observed by using the primary outcome of the DAN score, as well as cry at maximal catheter insertion, and time to return to baseline. There were no consistent trends in cry or pain scores for infants in the two- or three-month age range. This suggests that for bladder catheterization, oral sucrose may only be reliably effective in children 30 days of age or younger.

Other studies have found that oral sucrose, when combined with other interventions, decreased pain response in older infants. In 1997, Lewindon et al. described a decrease in distress when sucrose was given before immunizations in two-, four-, and six-month infants.[13] The sucrose administration was combined with a nursing

Table 3
Age Group–specific Analyses

Age Group (d) by Measure	Sucrose	Placebo	Group-difference p-value
Change in DAN, mean (±SD)*			
1–30	2.86 (2.93) (*n* = 15)	5.29 (3.14) (*n* = 18)	0.035
31–60	4.31 (2.90) (*n* = 15)	4.85 (2.91) (*n* = 15)	0.641
61–90	5.33 (2.83) (*n* = 10)	4.50 (3.27) (*n* = 7)	0.608
Crying at maximal catheter insertion (%)†			
1–30	28.6	78.6	0.008
31–60	69.2	71.4	0.901
61–90	70.0	42.9	0.263
Time (s) to return to baseline‡			
1–30	10	37	0.04
31–60	60	60	0.887
61–90	60	23	0.601

DAN = Douleur Aigue du Nouveau-né.
* Student's t-test of means.
† Chi-square test of proportions.
‡ Mann-Whitney test of medians.

intervention to soothe the infant, and the results were not analyzed by age. More recently, Reis et al. showed that oral sucrose, when combined with oral tactile stimulation and parent contact, reduced crying in two-month infants receiving multiple injections.[14] Neither of these studies isolated the sucrose effect from the co-interventions. This difference in results with our study might be a result of a number of factors. First, our study tested sucrose solution as the only intervention. Pacifiers were allowed per parental preference but did not make an impact on the pain scores. The positioning and length of procedure are very different for bladder catheterization compared with immunizations, and the duration of painful stimulus may alter or mask the effect of sucrose. Finally, with the smaller numbers in the older age groups, there may not have been enough power to detect a difference, although trends were not suggestive of an analgesic effect.

Another unknown is the ideal dose of sucrose to produce an analgesic effect. This study used 2 mL of a 24% sucrose solution on all infants randomized into the sucrose group. This is consistent with the doses used in other studies. It is possible that older infants, who on average received a smaller dose (in milligrams per kilogram), were in fact underdosed and therefore did not show an analgesic response.

The mechanism of sucrose analgesia in infants has been thought to be mediated by the release of endogenous opioids and has been shown to be suppressible with opioid antagonists in animal models.[15] However, umbilical line blood sample from preterm infants given oral sucrose have not shown increases in systemic beta-endorphin concentrations.[16] More recently, Gradin and Schollin demonstrated that administration of naloxone before giving a sweet solution did not alter its analgesic effect.[17]

A 2004 Cochrane Systematic Review by Stevens et al. looked at 21 studies of oral sucrose solution for analgesia in the neonate.[18] In their meta-analysis, sucrose in a variety of dosages was found to decrease physiologic (heart rate) and behavioral (the mean percentage time crying, total cry duration, duration of first cry, and facial action) pain responses and composite pain scores in neonates undergoing heel stick or venipuncture. None of the studies referenced evaluated sucrose for use with bladder catheterization.

Despite the publication of recommendations regarding the use of oral sucrose in the emergency setting, there have been no published studies representing an ED population.[8] Infants in the ED represent a different population than do those that previously have shown benefit with sucrose. Emergency department infants generally have an acute illness but have been healthy enough to be at home before presentation. The ED probably also is less baby-friendly than both nursery or outpatient pediatric offices, and interventions such as nurse soothing or kangaroo care can be inconsistently applied in a busy ED setting. Therefore, it is important to have data on the effectiveness of pain interventions such as oral sucrose, which is gaining popularity because of relatively low cost and perceived safety.

This study was not powered to evaluate the safety of oral sucrose analgesia. Although some studies have shown brief periods of choking or gagging with sucrose administration, none have reported serious side effects from single-dose administration, and there were no adverse effects found during this study. One study did report poorer neurobehavioral development in preterm infants who had received multiple doses of sucrose compared with a placebo.[19] Sucrose also is inexpensive and either can be compounded by a hospital pharmacy or purchased in a sterile 11-mL package as a 24% solution.

LIMITATIONS

This study had a number of limitations. First, the observations and pain scoring were performed by six different nurses working in a single pediatric ED. Observers underwent standardized training with video footage to learn the DAN scoring system and study protocol. The use of multiple observers allowed us to capture a range of patients presenting both days and evenings, as well as weekdays and weekends. The use of multiple observers potentially added scatter into the data but should not have led to systematic bias that would skew the results toward a particular outcome. Because the observations were performed by nurses physically present in the department (not videotaped) and study nurses were chosen to provide maximum coverage, and therefore had minimal schedule overlap, interrater reliability cannot be reported for this study.

The number of infants enrolled in the individual subgroups were not separately randomized and, particularly in the oldest group, were relatively small. This makes it difficult to make conclusions regarding the effectiveness of sucrose in the older subgroups, and the study was not powered to demonstrate a conclusive negative effect within the subgroups.

CONCLUSIONS

In summary, oral administration of a sucrose solution to infants younger than or equal to 90 days of age did not show a convincing analgesic effect. In subgroup analysis, however, infants younger than or equal to 30 days of age who received sucrose did demonstrate decreased behavioral pain response to bladder catheterization, with lower pain scores, less crying, and faster return to baseline behavior than infants receiving placebo. Oral sucrose appears to provide some analgesia in very young infants ($\leq$30 days of age). However, although sucrose analgesia has been recommended for infants undergoing painful procedures in the ED, providers should be aware that convincing data for its efficacy, particularly in older infants, is lacking.

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