Reduced Infant Response to a Routine Care Procedure After Sucrose Analgesia

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

**What’s Known on This Subject**

Sucrose reduces infant responses during painful procedures. It is not known if it affects responses during caregiving procedures performed after the painful procedure, beyond the presumed duration of action of sucrose (ie, 10 minutes).

**What This Study Adds**

This study demonstrates that when sucrose is used for pain, it also reduces infant responses to caregiving procedures performed afterward.

**ABSTRACT**

**OBJECTIVES.** Sucrose has analgesic and calming effects in newborns. To date, it is not known whether the beneficial effects extend to caregiving procedures that are performed after painful procedures. Our objective was to determine the effect of sucrose analgesia for procedural pain on infant pain responses during a subsequent caregiving procedure.

**PATIENTS AND METHODS.** We conducted a double-blind, randomized, controlled trial. Healthy neonates within 2 strata (normal infants and infants of diabetic mothers) were randomly assigned to a sucrose or placebo water group before all needle procedures after birth. Pain response during a diaper change performed after venipuncture for the newborn screening test was determined by using a validated multidimensional measure, the Premature Infant Pain Profile.

**RESULTS.** The study was conducted between September 15, 2003, and July 27, 2004. Altogether, 412 parents were approached; 263 consented. Twenty-three infants were not assigned, leaving 240 for participation (n = 120 per group), with an equal number in each infant strata. Of those, 186 (78%) completed the study. There were no significant differences in birth characteristics between groups. During diaper change, sucrose-treated infants had lower pain scores than placebo-treated infants. The relative risk of having pain, defined as a Premature Infant Pain Profile score of $\geq 6$, was 0.64 with sucrose compared with placebo.

**CONCLUSIONS.** This study demonstrates that when used to manage pain, sucrose reduces the pain response to a subsequent routine caregiving procedure. Therefore, the benefits of sucrose analgesia extend beyond the painful event to other aversive and potentially painful procedures. *Pediatrics* 2009;123:e425–e429

SUCROSE (TABLE SUGAR) is a naturally occurring sugar with analgesic and calming effects in young infants. In 2 systematic reviews, sucrose reduced pain during needle procedures in preterm and term infants.\textsuperscript{1,2} In separate well-designed studies, it also reduced spontaneous crying in term infants.\textsuperscript{3–5} The observations of both the analgesic and calming effects of sucrose led us to hypothesize that sucrose could reduce infant responses during routine caregiving procedures such as diaper changes. Diaper changes trigger infant reactions akin to pain, but of a lower magnitude.\textsuperscript{6–8}

There is the possibility, however, that in using sucrose for every caregiving procedure as well for painful procedures, the cumulative number of daily doses of sucrose will exceed the recommended limit and induce hyperglycemia or other adverse effects. Hospitals currently limit the number of doses of sucrose for painful procedures because of concerns about safety.\textsuperscript{9} Therefore, it is reasonable to anticipate that if sucrose is effective for both needle procedures and caregiving procedures, and the number of doses that can be given is limited, its administration would be reserved for needle procedures because they are more aversive than caregiving procedures. Although currently demonstrated to be beneficial for procedures lasting up to ~10 minutes,\textsuperscript{10} the effect of sucrose on procedures performed thereafter has not been determined. If the effect of sucrose persists beyond 10 minutes, then infants undergoing subsequent procedures could benefit without the need for additional doses. With these issues in mind, we designed a study to evaluate the residual analgesic and/or calming effects of sucrose analgesia on
caring procedures performed shortly after painful procedures. Our specific objective was to determine if administration of sucrose before venipuncture for the newborn screening test would result in reduced pain response during a subsequent diaper change.

PATIENTS AND METHODS

We studied newborn infants \( \geq 36 \) weeks’ gestational age at birth who were enrolled in a double-blind, randomized, controlled trial of the effectiveness of sucrose analgesia administered before every needle procedure performed after birth.\(^{11}\) To ensure inclusion of infants administered a wide range of procedures, we included normal newborn infants (born to women with uneventful pregnancies) and infants of diabetic mothers (DMs). We excluded infants who were admitted to the NICU, were scheduled to undergo circumcision during the study period, had a major congenital or neurologic anomaly, had a clinical diagnosis of birth asphyxia\(^{12}\) or seizures, or were receiving analgesics or sedatives.

The study was approved by the research ethics boards of Mount Sinai Hospital, the Hospital for Sick Children, York University, and Health Canada, and took place in the Mother and Baby Unit of Mount Sinai Hospital.

Study Procedures

The procedures have been described in detail in our clinical trial.\(^{11}\) Briefly, all infants were randomly assigned to receive either 2 mL of 24\% sucrose\(^{1}\) (weight/volume) or 2 mL of sterile water (placebo), in a double-blind manner, by mouth 2 minutes before all needle procedures performed from birth until the newborn screening test, \( \sim 24 \) hours later.

Infant pain response was recorded during a diaper change performed after a venipuncture for the newborn screening test. All data were collected prospectively by using a standardized method.\(^{11}\) Before the diaper change, a portable pulse oximeter (Datex-Ohmeda 3900P [Missisauga, Ontario, Canada]) was applied to the infant’s foot and a digital camera (Sony DCRTRV25 [Sony, Toronto, Ontario, Canada]) and tripod were positioned \( \sim 1 \) meter from the infant’s body. The infant’s face was videotaped and physiologic (heart rate and oxygen saturation) responses were continuously recorded during the diaper change. All diaper changes were conducted by certified nurse(s) per standard clinical practice.

The a priori primary outcome measure was infant response during diaper change, as assessed by the Pre-mature Infant Pain Profile (PIPP).\(^{13}\) The PIPP was developed from pain responses observed in preterm infants and subsequently validated in preterm and term infants. It incorporates 7 indices of pain that are scored individually on a 4-point scale from 0 to 3 and then summed together for an overall score. In term infants, PIPP scores can vary from 0 (no pain) to 18 (maximum pain). The PIPP contains 3 behavioral (facial actions; brow bulge, eyes squeezed shut, naso-labial furrow), 2 physiologic (heart rate, oxygen saturation), and 2 contextual (gestational age, infant state) indicators of pain. A research assistant who was blinded to treatment allocation, study hypotheses, and infant strata scored infant pain from videotapes by using the PIPP. Data on behavioral state was obtained during the baseline phase immediately before the diaper change. Each facial action was scored as present or absent in 2-second intervals for the first 20 seconds of the procedure. The percentage of the total time that each facial action was observed was calculated and used to assign a score of 0 to 3. For physiologic data, heart rate and oxygen saturation change from baseline was recorded over the same time frame and used to assign a score of 0 to 3. An overall PIPP score was computed for the procedure by summing the scores of the 7 indicators, and was used in the analysis.

Sample-Size Calculation and Statistical Analysis

The sample-size calculation, described in our main trial,\(^{11}\) was based on the primary outcome in the clinical trial (ie, analgesic efficacy of sucrose during venipuncture for the newborn screening test), and was set at 120 infants per group \((N = 240)\).

The a priori primary analysis in the present study compared PIPP scores during diaper change between treatment groups (sucrose and placebo) with a 1-way analysis of covariance (ANCOVA), where covariates included the infant’s pain response to the preceding venipuncture, the elapsed time between the venipuncture and diaper change, and the total number of painful needle procedures before venipuncture. The analysis was then repeated by using a 2-way ANCOVA, with treatment (sucrose and placebo) and infant strata (normal infant and infant of DMs) included as fixed factors. A posthoc power analysis was performed by using data from the trial. In addition, the proportion of infants with PIPP scores of \( \geq 6 \) (indicative of pain)\(^{13}\) were compared between groups by using a \( \chi^2 \) test, and the relative risk (95\% confidence interval [CI]) was calculated. The number needed to treat to prevent 1 infant from having a PIPP score of \( \geq 6 \) (indicative of pain)\(^{13}\) was calculated. Demographic data were analyzed by using a \( \chi^2 \) test, \( t \) test, or Mann-Whitney \( U \) test, as appropriate. An intent-to-treat approach was used that included all infants where outcome data were obtained. A \( P \) value of \( \leq 0.05 \) was considered significant. Data were analyzed by using SPSS 16.0 (SPSS Inc, Chicago, IL).

RESULTS

The study was conducted between September 15, 2003 and July 27, 2004. Altogether, 412 parents were approached. Of those, 263 consented. Twenty-three infants were not randomized because of the following reasons: 6 were unstable at birth and were withdrawn from the study and the remainder was missed after delivery by study personnel. Two hundred forty infants \((n = 120 \) per group) participated, with an equal number in the sucrose and placebo groups.\(^{11}\) Of the 240 infants enrolled in the main trial,\(^{11}\) 186 (78\%) infants were included in the analysis of diaper change responses (Fig 1).

Demographic characteristics of participating infants are shown in Table 1. There were no statistically significant differences between groups. Ninety-five percent of
infants had a diaper change performed within 1 hour of the venipuncture. The mean (SD) time difference between the venipuncture and diaper change was 37 minutes (14) for the sucrose group versus 45 minutes (15) for the placebo group (P = .74). Removal of outliers (>2 SDs from the mean), however, reduced the values to 13.1 (16.4) and 14.8 (28.8) minutes, respectively (P = .62). The number of previous painful procedures was 3.2 (2.5) vs 3.7 (2.9), for sucrose-treated and placebo-treated infants, respectively (P = .17).

The ANCOVA demonstrated significant effects of treatment group on infant PIPP scores during diaper change; sucrose-treated infants had significantly lower pain scores than water-treated infants (mean difference: −1.4 [95% CI: −2.4 to −0.4]; P = .008; n = 186) (Table 2). The posthoc power calculation revealed a value of 0.766. There was no significant influence on diaper change pain responses for the following: pain during preceding venipuncture (P = .167); elapsed time between the venipuncture and diaper change (P = .313); or the total number of painful needle procedures (P = .374) before venipuncture. Results were not changed by the addition of infant strata (infants of DMs and infants of non-DMs) in the analysis (P = .694 for infant strata; P = .009 for treatment group).

The percentage of infants with PIPP scores of ≥6 (indicative of pain) was 40% versus 62% for the sucrose and placebo groups, respectively (P = .002). The relative risk of having pain was 0.64 (95% CI: 0.47–0.85) with sucrose compared with placebo. The number needed to treat to prevent 1 infant from having pain was 4.3.11

There were no adverse effects observed in any infant during the trial.

DISCUSSION
The present study demonstrated that sucrose analgesia used to manage pain during venipuncture for the newborn screening test reduced infant pain responses during a subsequent diaper change. The magnitude of reduction in pain response was 22%, which is considered clinically significant.14 Furthermore, the number of infants needed to treat to prevent 1 infant from having a PIPP score of ≥6 was 4.

To our knowledge, this is the first study to determine the effects of sucrose analgesia on routine care procedures performed after painful procedures. Our results are consistent with previous research demonstrating a prolonged calming effect of sucrose in infants with colic.15 In that study, twice-daily sucrose administration resulted in a statistically significant diminution in the total number of hours spent crying per day from 5.7 to 3.9 hours when compared with no intervention.15

The underlying mechanism responsible for the sus-

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**TABLE 1** Characteristics of Participating Neonates

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sucrose (N = 120)</th>
<th>Placebo (N = 120)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, d</td>
<td>273 (8)</td>
<td>273 (8)</td>
<td>.62</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.4 (0.5)</td>
<td>3.4 (0.5)</td>
<td>.63</td>
</tr>
<tr>
<td>No. (%) of male infants</td>
<td>64 (53)</td>
<td>58 (48)</td>
<td>.44</td>
</tr>
<tr>
<td>No. (%) of vaginal deliveries</td>
<td>49 (41)</td>
<td>56 (47)</td>
<td>.36</td>
</tr>
<tr>
<td>5-min Apgar score</td>
<td>9.0 (0.2)</td>
<td>9.0 (0.2)</td>
<td>.76</td>
</tr>
</tbody>
</table>

Values shown are mean (SD), or frequency (%).

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**TABLE 2** PIPP Scores During Diaper Change (N = 186)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose (n = 96)</td>
<td>5.1</td>
<td>0.3</td>
<td>4.4–5.7</td>
</tr>
<tr>
<td>Placebo (n = 90)</td>
<td>6.5</td>
<td>0.4</td>
<td>5.8–7.2</td>
</tr>
</tbody>
</table>

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FIGURE 1
Participant flow diagram. Data-collection errors include missing data for calculation of PIPP scores (n = 5) and diaper changes performed before venipuncture for newborn screening test (n = 23).
tained benefit of sucrose after venipuncture is not currently known. Previous studies have postulated a preabsorptive (taste-induced) activation of the endogenous opioid pathway as a mechanism for the analgesic and calming effects, because of a rapid onset (1 minute) and short duration (10 minutes) of action, together with opioid-antagonist reversal of the effects.\(^\text{16}\) This mechanism, however, does not explain the benefits of sucrose during diaper change, as the diaper change occurred >10 minutes after sucrose administration. Alternatively, the benefit of sucrose during diaper change may involve a postabsorptive (ingestion-induced) mechanism. In support of this hypothesis are data in animals demonstrating a reduction in morphine-induced analgesia that is determined by the duration of exposure to sucrose.\(^\text{17}\)

In our study, the prolonged effect of sucrose during diaper change was found even after statistically controlling for venipuncture pain, ruling out the possibility that the present results reflect a carry over of sucrose analgesic efficacy during venipuncture. Clearly, additional studies are needed to elucidate the underlying mechanisms responsible for the analgesic and calming actions of sucrose.

Our results have important implications for clinical practice. Not only does sucrose reduce pain in newborns undergoing venipuncture,\(^\text{11}\) it also reduces responsiveness during subsequent routine care procedures. For ill and preterm infants, the implications of these findings are clinically significant, because handling procedures such as diaper changes are associated with greater pain responses, including behavioral and physiologic instability, and significant increases in energy expenditure.\(^\text{6,7,18,19}\)

It is important to note that the PIPP is intended to measure pain, and we do not know if diaper changes are painful for infants. However, infants often respond to stressful and painful stimuli using a similar repertoire of behaviors and physiologic responses. We decided to use the PIPP because all of these responses are included in a single measure. That the PIPP demonstrated an effect of sucrose suggests that it may be used for procedures that may be “stressful” as well as “painful.” In addition, we only assessed the first 20 seconds of the infants’ response. This short observation period may have led to an overall PIPP score that failed to take into account the inherent lag time between changes in physiologic responses and changes in reading in our instrument. It is unknown if differences between groups would have been even larger had we included a longer observation period. We determined our method of analysis a priori, however, this is clearly an area that is worthy of future investigation.

There are several strengths of our study including: double-blind, randomized design minimizing bias; inclusion of healthy term newborn infants, which reduced the confounding effects of an underlying medical condition or development on assessments of pain;\(^\text{20}\) inclusion of a varied infant population that included normal infants as well as infants of DMs; and lack of strict control over timing of diaper changes, which together improve the generalizability of the results.

CONCLUSIONS

We demonstrated that the use of sucrose to manage procedural pain reduces infant pain response during a subsequent routine care procedure. Based on these results, sucrose may be recommended for postprocedural caregiving procedures that follow painful procedures. The results also further support the use of sucrose to manage procedural pain in newborn infants.

ACKNOWLEDGMENTS

This study was funded by Canadian Institutes of Health Research grant MCT 63143. Dr Taddio was supported by a New Investigator Award by the Canadian Institutes of Health Research. Dr Katz was supported by a Canada Research Chair in Health Psychology at York University. The study supplies (sucrose and placebo) were provided by Respironics Inc (Monroeville, PA).

We thank the staff at Mount Sinai Hospital and parents of participating infants for allowing their infants to participate.

REFERENCES


