

Analgesic Effects of Sweet-Tasting Solutions for Infants: Current State of Equipoise



WHAT'S KNOWN ON THIS SUBJECT: Evidence from RCTs and systematic reviews supports the use of sweet solutions for pain reduction during painful procedures for infants in medically stable condition. However, RCTs with placebo groups continue to be conducted.



WHAT THIS STUDY ADDS: A state of clinical equipoise regarding analgesic effects of small volumes of sweet-tasting solutions no longer exists. Therefore, there is no justification for conducting additional RCTs with placebo or no-treatment groups for infants in medically stable condition.

abstract

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OBJECTIVE: The goal was to review published studies of analgesic effects of sweet solutions, to ascertain areas with sufficient evidence of effectiveness and areas of uncertainty.

METHODS: Databases searched included Medline, Embase, the Cumulative Index to Nursing and Allied Health Literature database, and PsycINFO, using the terms pain*, infant*, neonat*, newborn*, sucrose, glucose, and alternative sugars. Publications were sorted according to type, year, painful procedure studied, placebo/no-treatment groups, population studied, and country of publication.

RESULTS: A total of 298 relevant unique publications involving human infants were identified; 125 (42%) were primary research studies, of which 116 (93%) were randomized controlled trials. Healthy preterm or term newborns were included in 82 studies (65%), and sick or very low birth weight infants were included in 22 (18%). Most studies included single episodes of painful procedures, with only 3 (2%) conducted over long periods. Procedures investigated most frequently were heel lance (49%), venipuncture (14%), and intramuscular injection (14%). Placebo or no-treatment groups were included in 111 studies (89%); in 103 (93%) of those studies, sweet solutions reduced behavioral responses, compared with placebo/ no treatment.

CONCLUSION: Clinical equipoise relating to analgesic effects of sweet solutions no longer exists for single episodes of procedures for healthy preterm and term newborn infants. Uncertainties include outcomes after prolonged use of sweet solutions, concomitant use of other analgesics, and effectiveness beyond the newborn period. Future research should focus on addressing these knowledge and research gaps. *Pediatrics* 2010;126:894–902

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KEY WORDS

infant, pain, sucrose, equipoise

ABBREVIATION

RCT—randomized controlled trial

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A substantive update of a systematic review of the use of sucrose for analgesia for newborn infants undergoing painful procedures was published recently.¹ The update included 44 randomized controlled trials (RCTs) and 3496 infants, which represented 23 more trials and 1880 more infants than the version published 6 years previously.² Key conclusions drawn in 2010 were the same as those drawn in 2004, that sucrose is safe and effective for reducing procedural pain from single events for newborn infants. Even before 2004, recommendations were made that there was sufficient evidence of analgesic benefits of sucrose to implement this intervention for single painful procedures for neonates.³ In 2001, the International Evidence-Based Group for Neonatal Pain published a consensus statement on the prevention and management of pain in newborns.⁴ Sucrose with nonnutritive sucking during painful procedures was 1 of 5 recommendations for practice, with 22 supporting references. Similarly, guidelines released by national and international groups near this time included recommendations to administer sucrose orally during acute painful procedures.^{5–7} Despite such high-quality, synthesized evidence, trials examining the efficacy of sucrose or other sweet solutions for infants during commonly performed painful procedures continue to be published.^{1,8} This continuation of conduct of trials including placebo or no-treatment groups potentially contravenes the principal of equipoise.⁹ Therefore, the aims of this study were to map the number and nature of publications relating to the use of sucrose or alternative sweet solutions for management of procedural pain in infants, to determine whether and where there is strong evidence, with no further justification for placebo/no treatment groups, and to ascertain where there are knowledge gaps or uncertainties

in the evidence. Findings should inform recommendations concerning the ethical basis for conducting additional studies of sweet solutions for procedural pain reduction management in infants.

METHODS

Electronic databases searched included the Cumulative Index to Nursing and Allied Health Literature database (1982–2009), Medline (1950–2009), Embase (1980–2009), PsycINFO (1967–2009), and all evidence-based medicine reviews. The search terms included newborn, infant, neonate, pain, sucrose, glucose, and other terms used to capture alternative sweet solutions, such as lactose, glucose, fructose, glycerine, dextrose, aspartame, polycose, saccharose, and saccharide. No language restrictions were imposed. Reference lists from retrieved articles and personal files also were searched for relevant trials. Articles were excluded if they were duplicates, were subanalyses, or involved animals only or if orally administered sweet solutions were not used. The search concluded as of December 31, 2009.

Data were plotted on a timeline to display graphically the total and cumulative numbers of publications per year from the year of the first identified publication. The method of study; population of participants; type, concentration, and volume of sweet solution used; use of placebo or no-treatment groups and alternative study arms; country where the study was conducted; journals where the study was published; and the language of publication were established.

RESULTS

Publications Identified

A total of 298 unique publications related to analgesic or calming effects of sweet-tasting solutions in human infants were identified. These 298 arti-

cles were published in 58 different journals. There were 125 primary efficacy or effectiveness studies (43%), 86 reviews (29%), and 16 systematic reviews (5%) (Table 1). The earliest publication identified, a review of stress-reducing effects of milk, sugars, and fats, was published in 1989.¹⁰ The first trial evaluating analgesic effects of sucrose for human infants during painful procedures was published in 1991 by one of the same authors.¹¹ From 1991, when this first trial was published, to the end of 1997, when the first systematic review of the use of sucrose for pain management in newborn infants was published,³ an average of 2.7 primary research studies were published each year. After the release of the consensus statement in 2001,⁴ the average number of published primary research studies of the use of sucrose or alternative sweet solutions increased to 10 per year. In the 5 years after publication of the 2004 systematic review of the use of sucrose,² 50 efficacy or effectiveness studies were published, accounting for 40% of the total studies. Of those 50 studies, 42 (84%) included a placebo or no-treatment group, and 30 (60%) of the painful procedures studied were heel lances or venipunctures. In 2008, 14 RCTs were published,

TABLE 1 Type of Publication (*N* = 298)

	<i>n</i> (%)
Primary efficacy/effectiveness studies	
Single-episode RCT or controlled clinical trial	94 (75)
RCT crossover	15 (12)
Cohort	9 (7)
Repeated-measures/longitudinal RCT	7 (6)
Total	125
Secondary publications	
Reviews	86 (29)
Commentaries or editorials	49 (16)
Systematic reviews	15 (5)
Surveys	14 (5)
Guidelines	5 (2)
Other	3 (1)
Review of systematic review	1 (0)
Total	173

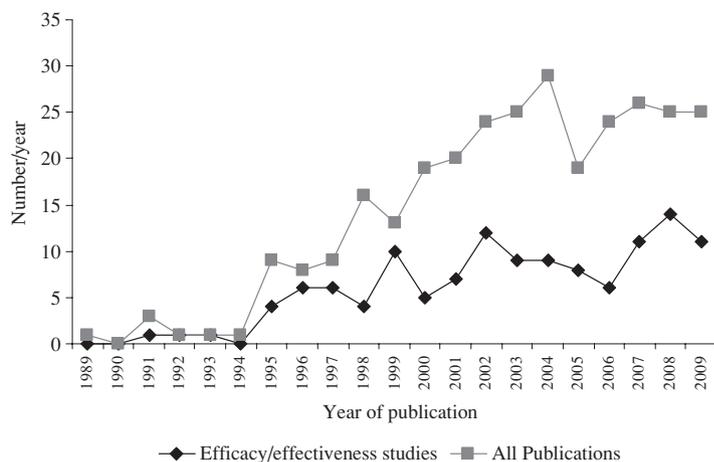


FIGURE 1 Total numbers of publications related to analgesic effects of sweet solutions each year.

which represented the largest number of studies published in a single year (Fig 1). The cumulative numbers of total publications and primary research studies published each year since 1989 are presented in Fig 2.

Characteristics of Research Studies

Of the 125 primary research studies evaluating analgesic effects of sweet solutions, 116 (93%) were controlled clinical trials (CCT) or RCTs and 9 (7%) were cohort studies (Table 1). A placebo arm or “standard care,” no-treatment group was included in 111

studies (89%). Reduced pain, as measured on the basis of various behavioral responses and/or composite pain assessment tools, was reported for the sweet solution groups, compared with the placebo or control groups, in 103 studies (93%). In 1 study, no painful procedure was performed but heart rate increases after administration of sucrose, compared with placebo, in resting newborns were evaluated.¹² Of the 7 studies in which sucrose did not result in analgesic effects during painful procedures, 3 involved eye examinations,^{13–15} 1 cir-

cumcisions,¹⁶ 1 heel lances with the use of a weak 7.5% sucrose solution,¹⁷ 1 stroking of the heel with a blunt instrument,¹⁸ and 1 immunizations for infants 3 to 5 months of age with the use of a 12% sucrose solution.¹⁹ In another 4 studies that included infants beyond the newborn period, sucrose was effective only for the youngest groups of infants.^{20–23}

Procedures Studied

One-half of the painful procedures studied were heel lances ($n = 65$ [50%]), followed by venipunctures ($n = 19$ [14%]) and intramuscular injections ($n = 19$ [14%]) (Table 2). Nine studies (7%) did not include painful procedures; 4 were conducted with crying infants to evaluate the calming effects of sucrose,^{23–26} 1 was to ascertain the effects of orally administered glucose on heart rate increases,¹² 1 was to measure the effects of orally administered sucrose on β -endorphin levels in preterm infants,²⁷ and 3 were to evaluate the analgesic/calming effects of sucrose for infants with colic.^{28–30} In these 3 latter studies, sucrose in concentrations of 12% (2 studies) or 48% resulted in improvements in colic symptoms, on the basis of crying time.

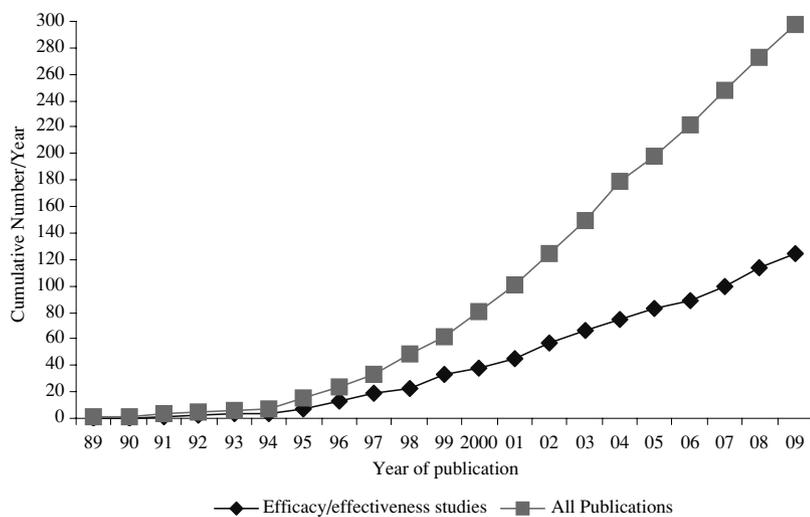


FIGURE 2 Cumulative numbers of publications per year.

TABLE 2 Procedures Studied ($N = 132$)

	<i>n</i> (%)
Heel lance	65 (49)
Venipuncture	19 (14)
Intramuscular injection	18 (14)
Circumcision	8 (6)
No procedure (5 with crying infants, 1 at rest)	6 (5)
Eye examination	5 (4)
Colic	3 (2)
Heel stroke/blunt poke	2 (2)
Subcutaneous injection	2 (2)
Bladder catheterization	1 (1)
Finger prick	1 (1)
Nasogastric tube insertion	1 (1)
Pharyngeal suction	1 (1)

Numbers add up to >125 because 6 studies included >1 procedure.

Solutions Used

In 74 trials (59%) that used a single sweet solution, sucrose was used, in concentrations ranging from 5.8% to 75%. Glucose, in concentrations ranging from 10% to 50%, was used in 35 studies (28%), and >1 sweet solution was used in 14 studies (11%). Comparative sweet solutions included alternative concentrations of sucrose or glucose, glycine, fructose, lactose, breast milk, formula milk, and nonsucrose sweetener.

Populations of Infants Studied

More than two-thirds ($n = 83$ [66%]) of the studies included healthy term or preterm infants. Very low birth weight infants or sick infants in the NICU were included in 22 studies (18%). Nineteen studies (15%) included infants beyond the neonatal period, of which 14 studies were conducted during scheduled childhood immunizations.^{19,20,31–42} Analgesic effects of sweet solutions, on the basis of reduced behavioral responses to pain, were reported for 12 (86%) of 14 of those studies; the only 2 with negative results were those in which a 12% sucrose solution was used.^{19,20} Of the remaining 5 studies that included infants beyond the neonatal period, 3 included infants with colic^{28–30} and 2 included infants in the emergency department undergoing venipuncture²¹ or urethral catheterization.²² Negative results were obtained for the latter 2 studies, which indicates that administration of a single dose of a sweet solution, 2 minutes before the commencement of painful or distressing procedures, to infants beyond the neonatal period may be insufficient to reduce pain significantly.

Repeated Doses of Sucrose

Ten studies (8%) evaluated the effectiveness of multiple repeated doses of sweet solutions for repeated painful procedures. Seven of those 10 studies

were placebo-controlled RCTs,^{31,33,43–47} and 3 were cohort studies with no placebo groups.^{48–50} The duration of those studies varied from 2 or 3 painful episodes^{31,33,43,50} to 1 week⁴⁴ or up to 1 month or longer.^{45,46,49} Results of the 3 studies that examined consistent sucrose use over 1 month or longer were that sucrose continued to reduce pain during heel lances^{46,49} and subcutaneous injections.⁴⁵

Countries Where Studies Were Conducted

Twenty-four countries produced the 125 primary research studies. Twenty-five studies (20%) were conducted in the United States, 18 (14%) in Canada, and 11 (9%) in Sweden (Table 3). Six

TABLE 3 Country of Origin and Language of Published Studies ($N = 125$)

	<i>n</i> (%)
Country where published	
United States	25 (20)
Canada	18 (14)
Sweden	11 (9)
Turkey ^a	9 (7)
Italy	9 (7)
United Kingdom	8 (6)
Spain	6 (5)
Iran ^a	5 (4)
France	5 (4)
India ^a	4 (3)
Australia	3 (2)
Brazil ^a	3 (2)
Finland	3 (2)
Norway	3 (2)
Switzerland	3 (2)
Denmark	2 (2)
Argentina ^a	1 (1)
Germany	1 (1)
Israel	1 (1)
Malaysia ^a	1 (1)
Japan	1 (1)
Korea	1 (1)
Russia	1 (1)
Saudi Arabia	1 (1)
Language	
English	112 (89.6)
Spanish	5 (4)
Finnish	2 (1.6)
French	2 (1.6)
Danish	1 (0.8)
Russian	1 (0.8)
Italian	1 (0.8)
Korean	1 (0.8)

^a Developing country, as defined by the World Trade Organization.⁵¹

countries were classified as developing,⁵¹ and those 6 countries produced 23 studies (18%). Most publications were in English ($n = 112$ [89.6%]), but 5 were in Spanish, 2 in Finnish, 2 in French, and 1 each in Danish, Italian, Korean, and Russian.

Additional Interventions Studied

In addition to either sucrose or glucose, >1 intervention was evaluated in 74 studies (59%), with most of those ($n = 66$ [90%]) including a placebo/no-treatment group. The number of additional intervention arms ranged from 2 to 9 and included alternative types, concentrations, doses, or delivery methods of sweet solutions; breast or formula milk; eutectic mixture of topical anesthetic; opioid analgesics; breastfeeding; physical interventions such as nonnutritive sucking, facilitated tucking, holding, or kangaroo care; various combinations of interventions; and different methods of either blood collection or circumcision. In the majority of studies, sucrose or glucose was more effective than small volumes of breast or formula milk or other less-sweet solutions.^{52–57} Kangaroo care^{58,59} and breastfeeding^{60–64} were more or equally effective, compared with sucrose alone, in most studies, with few exceptions.^{65–67} Sucrose or glucose was equal to or more effective than eutectic mixture of topical anesthetics during heel lances,⁶⁸ finger pricks,⁶⁹ venipunctures,^{70–72} circumcisions,^{73,74} subcutaneous injections,⁴⁵ and immunizations.³² Higher concentrations of sweet solutions were more effective than less-sweet solutions.^{25,39,52,55,57,69,75–87} Two studies compared opioid analgesics with sweet solutions, and conflicting results were obtained.^{69,88} Axelin et al⁸⁸ reported that oral administration of a 24% glucose solution resulted in lower pain scores during heel lancing and pharyngeal suctioning, compared with oxycodone, but Idam-Siuriun et al⁶⁹ re-

ported that intravenously administered fentanyl and promodol resulted in lower pain scores than did a 20% glucose solution during finger pricks for infants in the postoperative period.

DISCUSSION

Conclusive evidence from abundant RCTs exists for analgesic effects of sweet solutions, compared with placebo or no treatment, for healthy term and preterm infants in the first month of life during single episodes of heel lancing, venipuncture, or intramuscular injection. Therefore, there is a lack of equipoise, with no ethical justification for conducting additional trials with placebo/no-treatment arms in this population for these frequently performed procedures. As shown by the large number of studies with multiple intervention arms, many investigators are comparing the efficacy of different sweet solutions with other interventions but placebo groups continue to be included. This highlights the fact that, despite the strong body of evidence, sucrose/glucose is not considered standard care.

One explanation for the ongoing conduct of such studies could be the lag time between the commencement of studies and final publication. In the 5 years after publication of the 2004 systematic review of data on the use of sucrose for newborn infants, in which evidence of analgesic effects of sucrose during single episodes of heel lancing or venipuncture was highlighted,² 50 additional studies were published. Of those, 42 (84%) included a placebo or no-treatment group and 30 (60%) of the painful procedures studied were heel lances or venipunctures, which highlights a continuation of publication of placebo-controlled trials in the presence of lack of equipoise. However, an average delay of 4 to 5 years to publish trials with positive results and 6 to 8 years to publish trials with neg-

ative results⁸⁹ means that the majority of studies published since 2004 had commenced before the publication of the systematic review, when the analgesic effects of sweet solutions might still have been considered by some to be uncertain. Over the next few years, there should be a reduction in the publication of replicated trials, at least from countries with easy access to health care journals and published synthesized evidence. However, clinicians and researchers in developing countries might have limited access to the same journals and synthesized evidence, which might make it difficult for investigators in such countries to undertake a comprehensive review of the literature.⁹⁰ Replication of trials where there is no longer a state of equipoise is therefore a risk. As shown in Table 3, however, 6 countries classified as developing produced 23 studies (18%), and only 12 (24%) of the 50 studies published in 2005–2009 originated from those countries. This does not indicate that developing countries are overrepresented in replication of trials since the 2004 systematic review. Identifying effective ways to disseminate key health research findings globally, in a timely manner, is important for health care researchers in resource-rich countries. Although resource-rich countries theoretically have the benefit of easy availability of high-quality synthesized evidence, this does not necessarily equate to implementation of such research.⁹¹ Although most literature concerning problems with translating research into practice focused on clinicians, the same things may be said for researchers themselves, because researchers may not necessarily use existing evidence when planning and conducting their own research. This highlights the fact that effective means of translating existing research into clinical practice are vital for both clinicians and researchers.

There do remain important knowledge gaps concerning analgesic effects of sweet solutions, and investigators are advised to concentrate on these knowledge gaps in future studies. Such gaps include the efficacy and safety of sweet solutions for extremely preterm infants, the effectiveness of multiple and repeated doses of sweet solutions for sick and preterm infants hospitalized for long periods, the long-term consequences of prolonged use of sweet solutions for management of procedural pain, the effectiveness of sweet solutions for infants receiving concomitant opioid or other strong analgesics, use for procedures of longer duration (such as eye examinations, lumbar punctures, and arterial punctures), and the effectiveness of sweet solutions for infants >12 months of age.

Although the efficacy and safety of sweet solutions for preterm infants have been well established, only a few studies have included extremely preterm infants at postnatal ages of <27 weeks.^{13,15,43,46,92–94} Because infants at such low gestational ages are exposed to numerous painful procedures over months of hospitalization, the consequences of both pain exposure and interventions to reduce pain need to be studied carefully. Only 4 of the 125 studies evaluated repeated doses of sucrose over more than a few days.^{44–46,49} Ongoing analgesic effects of sucrose were reported in all 4 studies; however, Johnston et al^{44,95} reported worrying findings of poorer neurodevelopmental outcomes for preterm infants who received ≥ 10 doses of sucrose in the first week of life. Although this finding was not supported in the only other study that evaluated neurodevelopmental outcomes after sucrose use for preterm infants over a longer duration of 1 month,⁴⁶ it highlights the dearth of evidence in relation to outcomes other than immediate behavioral and physi-

ologic responses after the use of sweet solutions for acute pain.

Another important knowledge gap concerns the effectiveness of sweet solutions in comparison with and given in conjunction with opioid analgesics. Two studies compared glucose with opioid analgesics during a painful procedure^{69,88} and reported conflicting findings; however, the 2 studies were dissimilar in many respects. Axelin et al⁸⁸ included preterm infants and Idam-Siuriun et al⁶⁹ included term infants in the postoperative period. There also were differences in the choices and doses of opioids used, additional intervention arms, painful procedures, and pain outcomes. These 2 studies highlight uncertainties concerning analgesic effects of sweet solutions for sick infants receiving opioid analgesics. Because current evidence suggests that background infusions of opioid analgesics are ineffective in reducing pain during acute, minor, painful procedures,⁹⁶ additional research evaluating effective interventions that can be administered in conjunction with opioid analgesics is warranted.

There is conflicting and insufficient evidence related to analgesic effects of sweet solutions during longer procedures such as eye examinations and urethral catheterizations. Negative findings regarding analgesic effects of sucrose during such procedures might be explained by a lack of sustained effect of a single dose given 2 minutes before commencement of these longer procedures.⁹⁷

Although there is now sufficient evidence of benefits of sweet solutions during immunization for infants up to 12 months of age,⁹⁷ there is conflicting evidence beyond this age group.^{20,32} Only 2 studies evaluated analgesic effects of sweet solutions for infants >12 months of age. Both studies were

performed during immunizations, and both used the same low concentration of 12% sucrose. Dilli et al³² reported analgesic effects of sucrose even for children up to 4 years of age, whereas Allen et al²⁰ reported negative results for infants at 18 months of age. Reasons for the conflicting results are not known, which emphasizes that more studies are warranted to ascertain effective interventions for acute, minor, painful procedures for infants beyond 12 months of age.

Responsibility for ensuring that placebo/no-treatment controlled trials are conducted only when there is no evidence of benefit of existing treatments lies with clinicians and researchers at all levels, along with their research mentors and supervisors. Efforts to translate knowledge of research findings into clinical care need to be considered as much a part of the research project as conducting the actual studies. Local ethics committees have a responsibility to ensure that only ethically appropriate studies are conducted. Responsibility also lies with editors of peer-reviewed journals and peer reviewers, who often are senior and respected researchers in their own fields, to ensure that ethically sound studies are published and to question the need for replication of studies when a state of equipoise no longer exists.

The strengths of this article lie in the rigorous historical and current overview of all studies relating to analgesic effects of sweet solutions. This has permitted strong recommendations regarding the lack of need for additional research in areas where there is substantial evidence base and has highlighted areas where additional research would contribute considerably with respect to current gaps in knowledge. This review was limited to studies of sweet solutions, but evaluations

of many other pain management interventions and observational studies of pain responses are being conducted with infants during minor painful procedures. The use of sucrose or glucose as standard care in such studies is not known.

CONCLUSIONS

A state of equipoise relating to analgesic benefits of sucrose or glucose in healthy term and preterm infants during single episodes of heel lancing, venipuncture, or intramuscular injection no longer exists. Therefore, it is unethical to conduct additional placebo-controlled or no-treatment trials in this population, and sucrose or glucose should be considered standard care for these procedures in future studies. Uncertainties remain with respect to outcomes after long-term use of sucrose during painful procedures for very preterm and sick infants, effectiveness of concomitantly administered sweet solutions and opioid analgesics, effectiveness during longer procedures, and effectiveness for infants >12 months of age. Future investigations should focus on addressing these important research gaps regarding sucrose analgesia for our youngest patients.

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Noted by WVR, MD

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