Sweet Solutions to Reduce Procedural Pain in Neonates: A Meta-analysis

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abstract

CONTEXT: Abundant evidence of sweet taste analgesia in neonates exists, yet placebo-controlled trials continue to be conducted.

OBJECTIVE: To review all trials evaluating sweet solutions for analgesia in neonates and to conduct cumulative meta-analyses (CMAs) on behavioral pain outcomes.

DATA SOURCES: (1) Data from 2 systematic reviews of sweet solutions for newborns; (2) searches ending 2015 of CINAHL, Medline, Embase, and psychINFO.

DATA EXTRACTION AND ANALYSIS: Two authors screened studies for inclusion, conducted risk-of-bias ratings, and extracted behavioral outcome data for CMAs. CMA was performed using random effects meta-analysis.

RESULTS: One hundred and sixty-eight studies were included; 148 (88%) included placebo/no-treatment arms. CMA for crying time included 29 trials (1175 infants). From the fifth trial in 2002, there was a statistically significant reduction in mean cry time for sweet solutions compared with placebo (−27 seconds, 95% confidence interval [CI] −51 to −4). By the final trial, CMA was −23 seconds in favor of sweet solutions (95% CI −29 to −18). CMA for pain scores included 50 trials (3341 infants). Results were in favor of sweet solutions from the second trial (0.5, 95% CI −1 to −0.1). Final results showed a standardized mean difference of −0.9 (95% CI −1.1 to −0.7).

LIMITATIONS: We were unable to use or obtain data from many studies to include in the CMA.

CONCLUSIONS: Evidence of sweet taste analgesia in neonates has existed since the first published trials, yet placebo/no-treatment, controlled trials have continued to be conducted. Future neonatal pain studies need to select more ethically responsible control groups.

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Dr Harrison conceptualized all aspects of the study, was responsible for leading the study, supervising all aspects of the search strategy, screening, data extraction and data analysis, drafting and finalizing the manuscript; Ms Larocque was responsible, under the supervision of Dr Harrison, for working with the research team to compile all data, screening, conducting risk-of-bias assessments, data extraction, producing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram, working with Dr Hutton and Ms Turner on data analysis for the cumulative meta-analysis (CMA) and contributed to the writing of manuscript drafts; Dr Bueno, in collaboration with Dr Harrison supported the ongoing literature search and data organization, developing the study design, and contributed to all aspects of the writing of manuscript drafts and final submitted manuscript; Ms Stokes contributed to the compilation of all data, data screening, conducting risk-of-bias assessments, data extraction, and contributed to the writing of manuscript drafts; Ms Turner contributed to the conceptualization of the study, data analysis, data interpretation, production of the CMA figures, and all aspects of the writing of manuscript drafts and final submitted manuscript; Dr Hutton contributed to the data analysis, data interpretation, production of the CMA figures, and all aspects of the writing of manuscript drafts and final submitted manuscript; Dr Stevens contributed to the conceptualization of the study, data interpretation, and significantly contributed to the writing of manuscript drafts and final submitted manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

To cite: Harrison D, Larocque C, Bueno M, et al. Sweet Solutions to Reduce Procedural Pain in Neonates: A Meta-analysis. *Pediatrics.* 2017;139(1):e20160955

Sweet solutions for reducing acute procedural pain in newborn infants has been one of the most extensively studied interventions in health care. Two large systematic reviews, 1 of sucrose,[1] and 1 of glucose and other nonsucrose solutions,[2] collectively included 95 trials. Both reviews concluded that sweet solutions consistently reduced behavioral responses and composite pain scores during commonly performed painful procedures. However, due to study heterogeneity, in terms of the variability in painful procedures studied, pain outcomes, times when outcomes were measured, the type, volume, and concentration of sweet solutions and reporting metrics used, the maximum number of trials included in any meta-analysis was 4,[1] limiting the strength of the authors' arguments in both reviews. For example, in the sucrose systematic review, results were pooled for the outcome of the composite pain score Premature Infant Pain Profile (PIPP),[3] during the heel lance procedure. A total of 29 trials studied heel lance as the painful procedure and PIPP was used as an outcome measure in 13 trials, yet only 4 trials were included in the meta-analysis of PIPP scores. Although results showed a statistically significant and clinically relevant −1.76-point reduction in PIPP scores (95% confidence interval [CI] −2.54 to −0.97), the small numbers of included trials limits the strength of the argument supporting the analgesic effects of sucrose. Similarly, crying time was used as an outcome measure in 35 of the 57 included trials in the sucrose systematic review and 19 of the 38 included trials in the nonsucrose systematic review, yet only 2 trials were included in each respective meta-analysis on crying times.[1,2] The authors' explain the small numbers of included trials as an attempt to decrease heterogeneity, and thus including only studies that were similar in terms of type of painful procedures, timing of pain assessments, and volumes and concentrations of sweet solutions used. Given that the sweet taste induced endogenous opioid analgesic mechanism of any sweet solution in sufficient concentration is equivalent in reducing any acute procedural pain in infants,[4] a more inclusive and pragmatic systematic review and meta-analysis of all sweet solutions for procedural pain management in newborn infants is warranted. In addition, the authors previously argued that a state of equipoise had not existed for analgesic effects of sweet solutions since before the publication of the 2004 Cochrane systematic review of sucrose for pain relief in newborn infants.[5,6] No previous reviews, systematic reviews, or meta-analyses of sweet solutions for procedural pain management have included a cumulative meta-analysis (CMA). A CMA cumulatively combines studies chronologically to identify when a characteristic or statistically significant change first occurs.[7–9] CMAs of trials facilitate the determination of clinical efficacy and are considered helpful in tracking trials, planning future trials, and making clinical recommendations for treatment.[8]

The aims of this review were (1) to update the previously published descriptive overview of all sweet solutions for procedural pain management in infants,[5] and (2) to conduct a CMA of randomized controlled trials (RCTs) evaluating sweet solutions (sucrose or glucose) for newborn infant procedural pain reduction to statistically evaluate if convincing evidence of sweet solutions was evident at a particular point in time.

METHODS

All studies included in the 2 previously published systematic reviews of sweet solutions for analgesia in newborn infants[1,2] were screened for eligibility for inclusion in the systematic review and CMA. Additional trials, published since the 2 reviews, were identified as per the following search.

Study Eligibility

Studies were included if they were published randomized or quasi-randomized controlled trials, including term and/or preterm infants in the neonatal period, receiving sucrose, glucose, or other sweet solutions orally compared with no treatment, water, pacifier, swaddling/positioning, skin-to-skin care, formula feeding, expressed breast milk, breastfeeding, sensorial saturation, or topical anesthetics.

Eligibility criteria for inclusion in the CMA were studies that reported behavioral outcomes of crying duration, or composite pain scores. If these data were unable to be extracted, those studies were not included in the CMA. As physiologic responses to sweet solutions are varied and inconsistent,[1,2] and sweet solutions have been shown to cause an increase in heart rate in some studies, possibly due to an excitatory mechanism,[10] physiologic responses were not included as outcome measures in the CMA.

Reasons for study exclusion included trials including infants beyond the neonatal period, inability to extract data after contacting the corresponding author, and if translation of data in languages other than English was unable to occur. Authors of all studies listed as awaiting further results or clarification, in the previous systematic reviews,[1,2] were contacted to obtain required data.

Literature Search Strategy

To update the descriptive review, data from all trials in the 2 published systematic reviews of sucrose and glucose for procedural pain reduction in newborn infants[1,2] were included. To identify trials published since these 2 systematic reviews, the following databases were searched

from 2011 (the year the searches for Bueno et al[2] and Stevens et al[1] were completed): Medline, Embase, PsychINFO, and CINAHL up to the end of December 2015. The search was developed and conducted with the affiliated university librarian (Supplemental Information).

Two authors (C.L. and Y.S.) screened all studies for inclusion.

Data Collection and Extraction

For the additional studies identified that had not been included in the 2 published systematic reviews, risk of bias (RoB) was rated as per the methods used by the Cochrane collaboration, according to Higgins et al.[11] Two authors (C.L. and Y.S.) independently conducted RoB assessments of the additional studies not included in the published reviews.

For eligible studies, 2 authors (C.L. and Y.S.) extracted data for crying time (in seconds) and pain intensity scores. For studies published in languages other than English, native speakers of the languages were sought from the authors' affiliated institutions for assistance with data extraction. For studies with more than 2 arms, intervention and control data extracted for the CMA were the most comparable possible.

Data Analysis

CMA of mean differences for crying duration were performed by using a random effects model to generate summary measures with 95% CI. For pain scores, CMA using a random effects model to derive a summary standardized mean difference with 95% CI was conducted to include data from studies by using different scales. All analyses were conducted by using Stata Version 11 (Stata Corp, College Station, TX) and were verified by using CMA Version 2.2 (Biostat Inc, Englewood, NJ). Statistical heterogeneity was assessed by using the I^2 statistic. For crossover studies, data for the first condition studied were included.

For studies comparing different concentrations of sweet solutions, data for 24% sucrose, or the most comparable sweet solution and concentration, compared with water or no treatment were used in the CMA, as 24% sucrose is the most commonly studied sweet

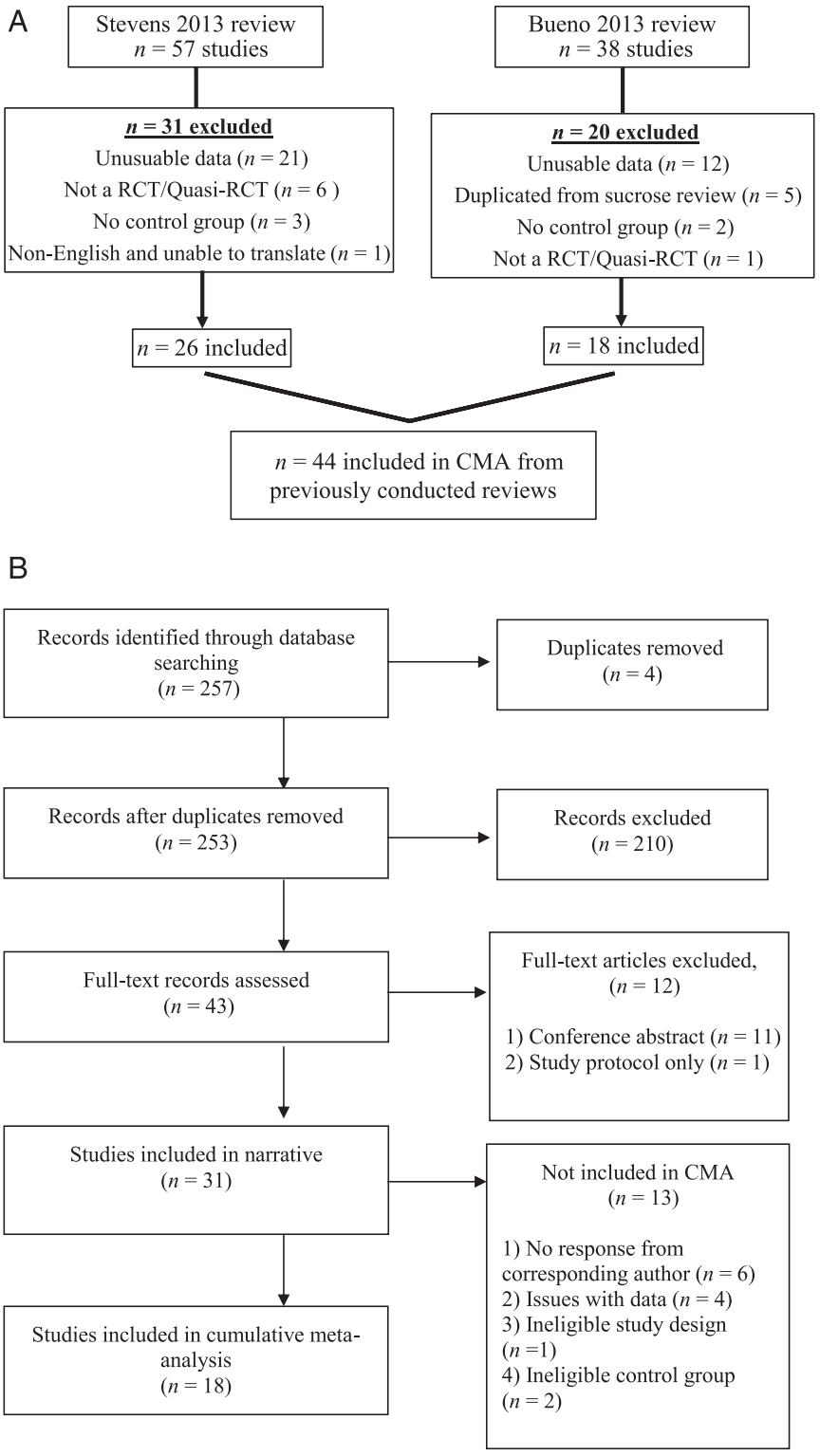

FIGURE 1
CMA PRISMA studies included in previous systematic reviews. B, PRISMA studies published 2011 to 2015.

solution in research,[1] and the most recommended for clinical care in most neonatal and infant pain guidelines.[12] For studies that included heel lance as well as additional painful procedures, data for the heel lance group only were included, because it is the most commonly studied painful procedure.[1,2]

RESULTS

Extent of Literature Identified

A total of 168 primary published studies of sweet solutions for pain reduction or for calming in human neonates was identified. Thirty-one additional trials to those included in the systematic reviews of sucrose[1] and glucose[2] were identified.[13–43] See Fig 1 for illustration of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagrams. Fig 1A illustrates data included in the CMA from the 2 previously published systematic reviews, whereas Fig 1B illustrates findings from the literature search update for 2011 to end 2015.

The first trial was published in 1991, and for the next 3 years, 1 study was published each year. From 1995 until 2015, an average of 7.8 studies were published each year, peaking at 13 studies published in 2009 and 2013 (Fig 2). RoB bias was overall low for most studies, with most being well-blinded RCTs (Table 1, RoB). No studies were excluded based on RoB.

Trials were conducted in 35 different countries (Table 2), with most conducted in the United States (n = 23, 13.7%), Canada (n = 21, 12.5%), Italy and Turkey (n = 14, 8%, respectively), and Sweden and India (n = 13, 6%, respectively). English was the language of publication in 154 (91.7%) studies. Other languages were Spanish (n = 5, 3%), 2 studies were published in Italian, French, Finnish, and Korean, respectively, and 1 study was published in Russian.

Study Characteristics

Most trials included a placebo or no-treatment group (n = 148, 88%).

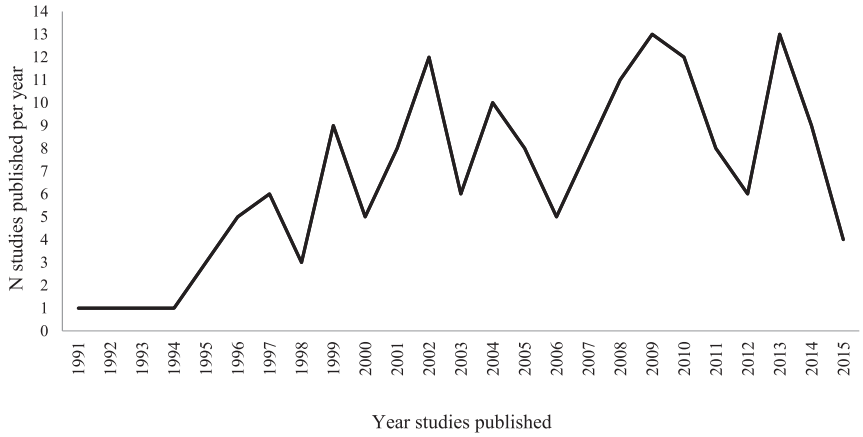

FIGURE 2
Number of studies of sweet solutions for analgesia in newborns published per year.

TABLE 1 Risk of Bias

Author Name and Year	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other
	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Sources of Bias
Cignacco E et al 2012[13]	Low	Low	High	High	Low	Low	Low
Da Costa MC et al 2013[14]	Low	Low	High	Low	Low	Low	Low
Marin-Gabriel MA et al 2013[15]	Low	Low	High	High	High	Low	Low
Mekkaoui N et al 2012[16]	Unclear	Unclear	High	High	Unclear	Unclear	Low
Nimbalkar S et al 2013[17]	Low	Low	Low	Low	Low	Unclear	Low
Pandey M et al 2013[18]	Low	Low	Low	Low	Low	Low	Low
Sahoo JP et al 2013[19]	Low	Low	Unclear	Low	Low	Low	Low
Scaramuzzo RT et al 2013[20]	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear
Ravishankar et al 2014[21]	Low	Low	Low	Low	Low	Low	Low
Dilli D et al 2014[22]	Unclear	Unclear	Low	Unclear	Unclear	Low	Low
Suhrabi Z et al 2014[23]	Low	Unclear	High	Unclear	Low	Unclear	Unclear
Al Qahtani R et al 2014[24]	Low	Low	Unclear	Low	Low	Unclear	Low
Bueno M et al 2012[25]	Low	Low	Low	Low	Low	Low	Low
Kataria M et al 2015[26]	Low	Low	High	Low	Low	Unclear	Low
Ou-Yang M et al 2012[27]	Low	Low	Low	Low	Low	Low	Low
Tutag Lehr V et al 2015[28]	Low	Low	High	High	Low	Unclear	Low
Uzelli D and Yapucu GU 2015[29]	Low	Unclear	High	High	Low	Unclear	High
Vezyroglou K et al 2014[30]	Low	Low	Low	Low	Low	Low	Low

For studies not included in previous published systematic reviews (Bueno et al 2013[2]; Stevens et al 2013[1]).

Sweet solutions used were mostly sucrose (*n* = 102, 60.7%) or glucose (*n* = 58, 34.5.9%). Both sucrose and glucose were studied in 4 trials, 2 trials used nonsucrose sweetener, 1 used honey, and 1 study compared glucose with fructose. As summarized in Table 2, the most frequently studied procedures were heel lance (*n* = 79, 47%), venipuncture (*n* = 24, 14.3%), eye examination (*n* = 11, 6.6%), and intramuscular injection (*n* = 11, 6.6%). More than half the studies focused on a population of term newborn infants (*n* = 97, 57.7%), 52 studies (30.1%) included preterm infants, and 19 (11.3%) studies included both term and preterm infants. Of the studies that included preterm infants, only 3 studies included infants younger than 30 weeks' gestational age.

A composite pain assessment score was used in 129 (76.8%) studies. The most commonly used composite pain scales were the PIPP (*n* = 51, 30.3%), the Neonatal Infant Pain Scale (*n* = 27, 16%), the Neonatal Facial Coding System (*n* = 26, 15.5%), and the Douleur Aiguë du Nouveau-né (*n* = 13, 7.7%). Cry duration was measured in more than half of the studies (*n* = 98, 58.3%). Physiologic parameters were included as outcome measures in 104 (61.9%) studies. Heart rate was most frequently measured, and was reported in 96 (57.1%) studies, and oxygen saturation in 61 (36.3%) studies. Less frequently measured parameters were respiratory rate (*n* = 17, 10.2%), hormonal levels such as cortisol or β-endorphins (*n* = 8, 4.7%), and cortical responses such as near infrared spectroscopy or EEG (*n* = 6, 3.6%).

Findings From CMA

Of the 168 studies included in this review, 62 were eligible for inclusion in the CMAs performed (Fig 1). From the 2 previously published reviews, 26 trials from the sucrose systematic review by Stevens et al[1] and 18 from the nonsucrose systematic review by Bueno et al[2] were retained for inclusion in the meta-analysis. Eighteen additional studies were identified through the earlier described search.[13–30]

Supplemental Table 3 summarizes the characteristics of the 62 studies included in the CMA.

For meta-analysis of cry duration data, 29 trials (totals of 888 and 887 infants randomized to the treatment and control groups, respectively) were included in the CMA. One study was included twice,[44] by using different data, as data for 2 different treatment arms were included. As shown in Fig 3, by the fifth trial included in the CMA, there was a statistically significant reduction in mean cry time for sweet solutions compared with placebo of nearly 30 seconds (−27.42 seconds, 95% CI −51.35 to −3.49). By the final trial included in the CMA, the mean difference in crying time was −23.18 seconds in favor of sweet solutions (95% CI −28.89 to −17.47). Heterogeneity was high (85.4%).

For meta-analysis of composite pain intensity scores, 50 trials (enrolling 1686 and 1655 infants randomized to the intervention and control groups, respectively) were included

TABLE 2 Demographic Characteristics of Trials (*n* = 168)

	n (%)
Country of origin	
United States	23 (13.7)
Canada	21 (12.5)
Italy, Turkey (respectively)	14 (8.3)
Sweden, India (respectively)	10 (6.0)
United Kingdom	9 (5.4)
Brazil	8 (4.8)
France	7 (4.2)
Spain, Iran (respectively)	6 (3.6)
Norway	5 (3.0)
Switzerland, Finland (respectively)	4 (2.4)
Australia, South Korea	3 (1.8)
China, Germany (respectively)	2 (1.2)
One trial was published from: Argentina, Belgium, Colombia, Denmark, Ireland, Israel, Japan, Malaysia, Morocco, Nepal, Netherlands, Nigeria, Russia, Saudi Arabia, Serbia, Taiwan, Ukraine	
Age of infants	
Term newborns	97 (57.7)
Preterm infants (gestational age not specified)	29 (17.3)
Preterm <34 wk	20 (11.9)
Combination term and preterm newborns	19 (11.3)
Preterm <30 wk	3 (1.8)
Painful procedure	
Heel lance	79 (47)
Venipuncture	24 (14.3)
Eye examination	11 (6.5)
No painful procedure (colic, handling, routine care)	8 (4.8)
Circumcision	8 (4.8)
Intramuscular injection	7 (4.2)
Naso/orogastric tube insertion	5 (3.0)
Compilation of painful procedures	4 (2.4)
Airway suctioning (nasopharyngeal and unspecified),	4 (2.4)
Heel lance + venipuncture & Heel lance + pharyngeal suction (respectively)	3 (1.8)
Subcutaneous injection; peripherally inserted central catheter insertion; arterial puncture; echocardiogram (respectively)	2 (1.2)
Heel lance + circumcision; finger prick (respectively)	1 (0,6)
Outcome measurements	
Composite pain score	129 (76.8)
Cry duration	98 (58.3)
Physiologic parameters	104 (61.2)

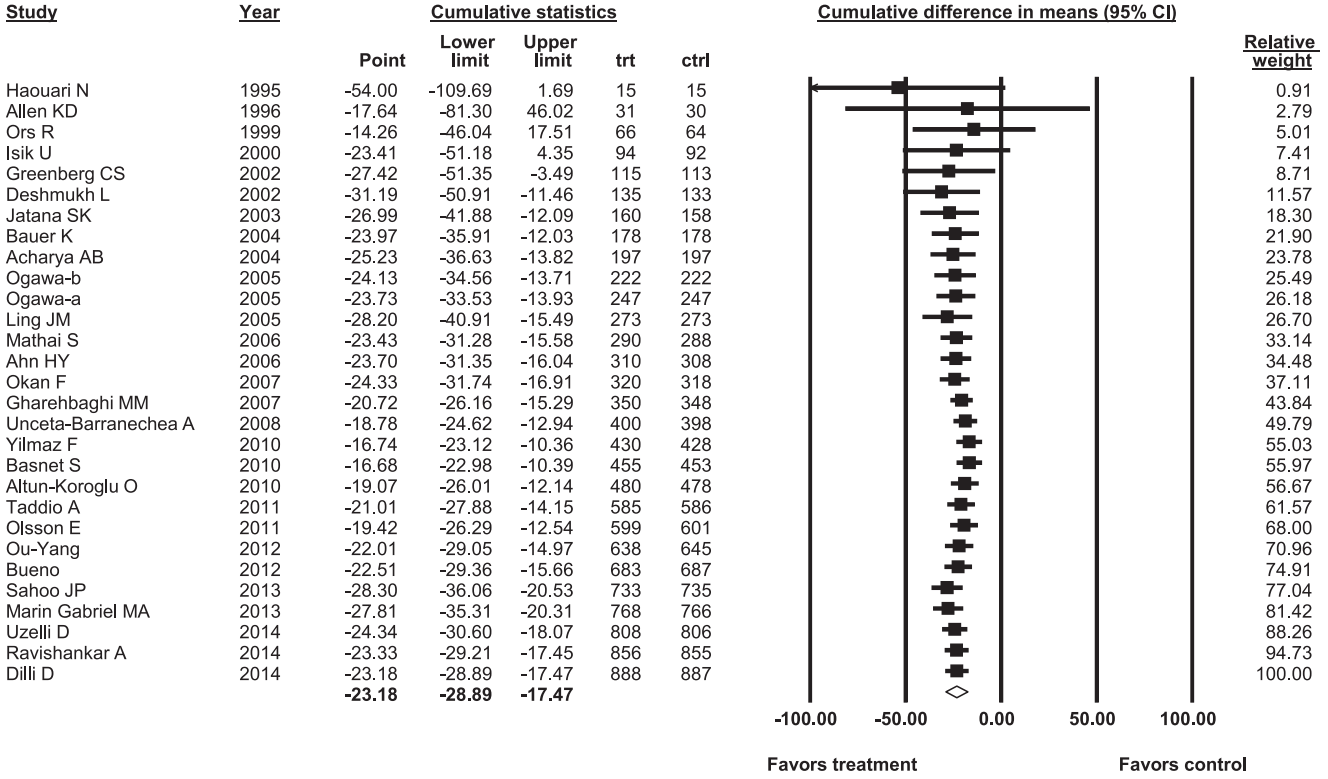

FIGURE 3
CMA mean difference crying time.

in the analysis. Two studies, with 2 separate data sets each for 2 different comparisons with the control group, was included twice.[44,45] As shown in Fig 4, a statistically significant reduction in standardized pain scores was evident by the second trial (−0.53, 95% CI −1.00 to −0.07). The final cumulative result showed a standardized mean difference of −0.90 in favor of the sweet solutions over control or placebo (95% CI −1.09 to −0.70). Heterogeneity was high, at 85.5%.

DISCUSSION

This systematic review included 168 studies, which is 43 more than the previous overview of studies of sweet solutions for analgesia in infants.[5] Data were able to be pooled for 62 of these studies for inclusion in CMA. To our knowledge, this is the first CMA concerning analgesic effects of sweet solutions for pain management in infants. Conducting a CMA of trials allows for the study of trends in efficacy and facilitates the determination of the point at which clinical efficacy is established and clinical recommendations for treatment and future research can be made.[7,8] Results of this CMA clearly demonstrated that since the first few trials were published, there was sufficient evidence to show that sweet solutions reduce behavioral responses of crying time and composite pain intensity scores compared with no treatment or placebo. Further studies since this time have served to add to the already known evidence by narrowing the CIs and increasing the certainty of effect.

Twenty years ago, it was argued that meta-analyses of related published trials should be performed during the planning of a new trial to ascertain whether such a new trial is needed at all, or needed in its planned form.[9] It is not evident that such meta-analyses were conducted before the conduct of most of the published trials included in this review. This would have been especially relevant for all trials planned and conducted since the early 2000s, when, based on crying duration, the evidence for analgesic effects of sweet solutions was already clearly established. The evidence based on standardized composite pain scores had already been established since 1999. High-quality systematic reviews of sucrose for analgesia in newborn infants had already been conducted by 2001,[46] and recommendations from an international consensus statement on newborn pain treatment, also published in 2001, included using sucrose for painful procedures.[47] Yet from 2002 onward, 125 of the total 168 studies included in this review were published. The questions we must ask are (1) what is the point at which study replication is sufficient, and (2) when are no further studies

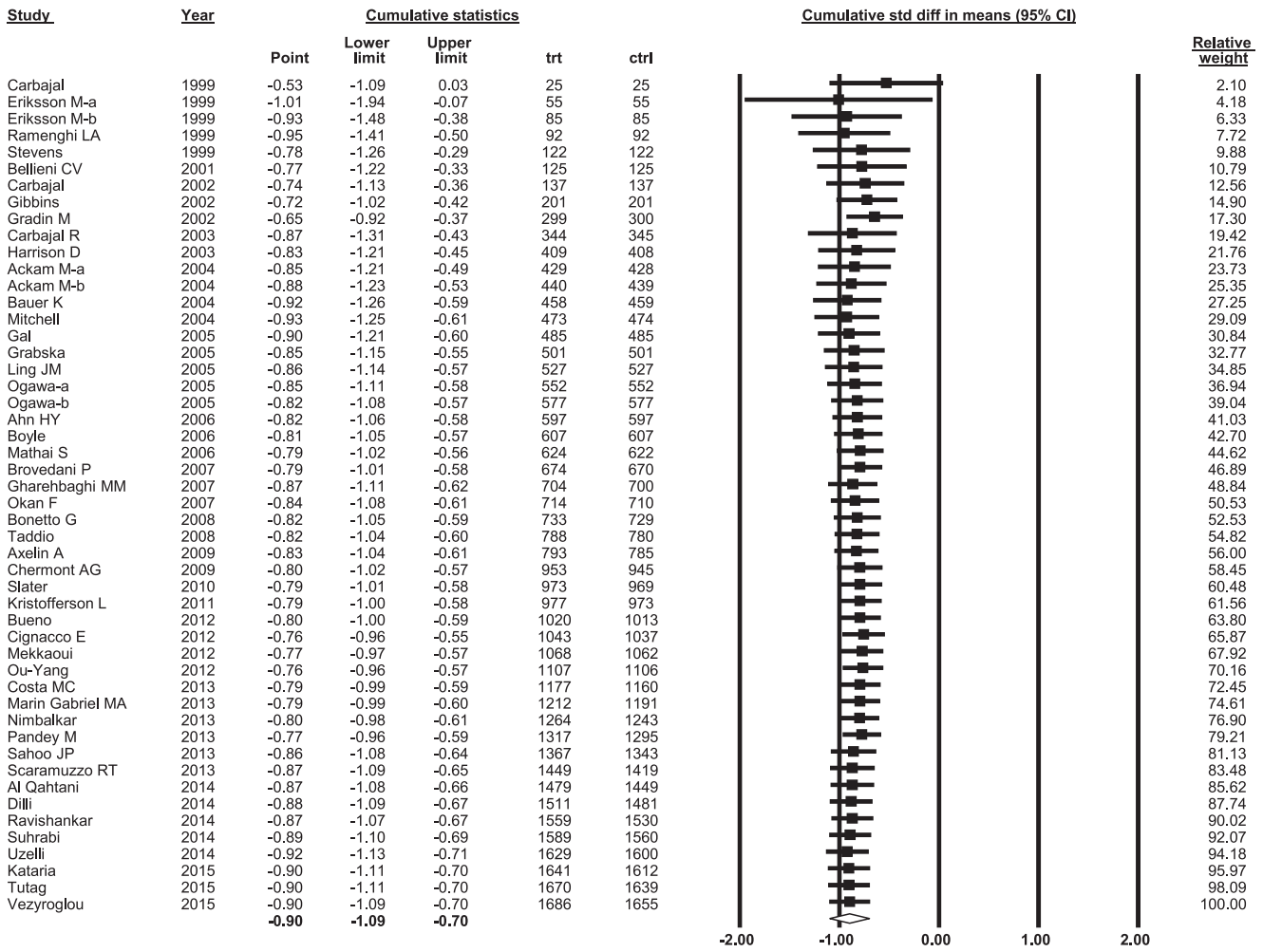

FIGURE 4
CMA standardized mean difference pain scores.

required to confirm results? The ethics of conducting further placebo-controlled trials of analgesic effects of sweet solutions has already been questioned.[5,48–50] Six years ago, an argument was put forth that there was a lack of equipoise and further placebo or no-treatment RCTs were considered unethical. This current article adds strength to that argument, as it is clearly seen from the first few trials published that sweet solutions significantly reduced behavioral pain responses of cry time and composite pain scores during painful procedures in newborn infants, and a lack of uncertainty of the analgesic effects of sweet solutions has been evident for more than a decade.

Since the conduct of this systematic review and CMA, an update of the Cochrane systematic review of sucrose for procedural pain in newborn infants was published.[51] This update by Stevens et al (2016) included 74 studies enrolling 7049 infants; 17 more studies and 2319 more infants than their previous review. Overall, their conclusions were similar to their previous review, that sucrose reduces pain from single, and to a lesser extent, repeated heel lances, as well as venipuncture and intramuscular injection.

The evidence is continually mounting for consistent use of effective pain treatment during commonly occurring painful procedures in healthy and sick infants. There is growing evidence of a positive association between the number of painful procedures and an increased risk of poor neurodevelopmental outcomes in preterm infants,[52–54] behooving health care providers to partner with parents to minimize pain and distress[55] and to consistently use effective pain treatments during painful procedures. Although we still have much to learn from research on pain in infants,[56] we must remain cognizant of using current evidence to reduce pain while we continue to advance the science of pain management in sick and healthy preterm and term infants. Implementation of evidence in the

clinical setting, including sweet solutions, or, when appropriate and feasible, breastfeeding and skin-to-skin care, during painful procedures is the clinical priority.[55,57] Research priorities include addressing remaining knowledge gaps, for example, the exact mechanisms of sweet-taste–induced analgesia.[4] Future research focusing on this knowledge gap, as well as other knowledge gaps including use of sweet solutions in critically ill and extremely low birth weight infants is warranted.

This large, unique CMA highlights the need to inform clinicians, researchers, parents of infants, and research ethics boards, as well as funders of research, about their decisions to continue to conduct placebo-controlled trials after decades of research. Had such a CMA analysis been conducted earlier, uptake of sucrose or glucose for procedural pain management may have occurred sooner, thereby reducing exposure of infants around the world to unnecessary procedural pain, and reducing wasted resources resulting from unjustified research.

Some limitations of this review should be mentioned. The CMA focused only on crying time and composite infant pain intensity scores. However, the effect of sweet solutions on physiologic responses to pain are far less consistent and sweet solutions actually result in an increase in heart rate in some instances. Behavioral responses are considered to be most specific to acute procedural pain in newborn infants,[58–60] and are most commonly included as outcome measures in RCTs.[57] Therefore, crying time and composite pain scores were considered most relevant for this CMA.

An additional limitation to this systematic review and CMA is that only traditionally used databases were searched, which does not include searches of databases in other languages. For example, Chinese databases, such as Chinese Biomedical Literature Database, China National Knowledge Infrastructure, and WANFANG, were not included. There is a rapidly increasing production of biomedical research within China,[61] yet fewer than 6% of journals indexed in Chinese databases are indexed for Medline.[61] This gap highlights the need to collaborate internationally and include such databases in addition to English databases conventionally used for future systematic reviews to ensure all eligible studies on a topic are included.

CONCLUSIONS

Sweet solutions, primarily sucrose or glucose, have been extensively shown over the past 2 decades to consistently reduce behavioral responses to acute procedural pain during single episodes of commonly performed painful procedures in newborn infants. There has not been a state of equipoise regarding the effectiveness of sweet solutions for reducing procedural pain for newborn infants for well over a decade, and it is our position that it is unethical to continue to conduct placebo or no-treatment controlled trials in infants. Future research needs to focus on knowledge translation of effective procedural pain treatment of infants, and to address remaining knowledge gaps.

ACKNOWLEDGMENTS

Ruirui Huang, Yanni Lui, and Li Tian participated in the study examining the Chinese literature. These data were not included in this review, and are being prepared for publication elsewhere. Shanthi Sembacuttiaratchy assisted in the organization of the data and Amanda Bowman and Lindsay MacNaughton participated in the organization of results for publication.

ABBREVIATIONS

CI: confidence interval
CMA: cumulative meta-analysis
PIPP: Premature Infant Pain Profile
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial
RoB: risk of bias

DOI: 10.1542/peds.2016-0955

Accepted for publication Oct 10, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics 2017;139;
DOI: 10.1542/peds.2016-0955 originally published online December 16, 2016;

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