

# Effects of combined oral sucrose and nonnutritive sucking (NNS) on procedural pain of NICU newborns, 2001 to 2016

## A PRISMA-compliant systematic review and meta-analysis

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### Abstract

**Background:** Both oral sucrose (OS) and nonnutritive sucking (NNS) are effective nonpharmacological methods to alleviate procedural pain in neonatal intensive care unit (NICU) newborns when they were used alone, but the combined effect of OS+NNS remains controversial. So, we conducted this study to evaluate the efficiency of NNS combined with oral sucrose on pain relief in NICU newborns undergoing painful procedures.

**Methods:** We searched PubMed, Ovid (Medline), Embase (Medline), Cochrane Central Library, and other resources such as Google Scholar, bibliographies of included literatures for all available articles. Two reviewers screened literatures and extracted data independently. The fixed effects model was used to pool the results using Reviewer Manager (RevMan) 5.3. As each study included in our meta-analysis had been approved by Ethics Committee or institutional review board, thus our study did not need ethical approval.

**Results:** Seven randomized controlled trials, including 599 participants, were contained in our meta-analysis. The combination of oral sucrose and NNS is associated with reduced pain scores (mean difference [MD],  $-0.52$ ; 95% confidence interval [CI],  $-0.68$  to  $-0.36$ ); shortened crying time (MD,  $-0.92$ ; 95% CI,  $-1.39$  to  $-0.44$ ); but the 2 groups did not differ significantly in reducing bradycardia (MD,  $0.73$ ; 95% CI,  $0.32$ – $1.68$ ), tachycardia (MD,  $0.65$ ; 95% CI,  $0.38$ – $1.10$ ), or desaturations (MD,  $0.73$ ; 95% CI,  $0.32$ – $1.68$ ).

**Conclusion:** The pooled evidence indicates that the combination measures may serve as an evidence-based guideline for pain relief among patients having minor pain. Besides, it also indicates that OS combined with NNS can be an alternative for better prevention and management of procedure pain in NICU newborns. Nevertheless, the results may be limited due to incomplete data, and thus, more randomized controlled trials or well-designed studies are required to determine the effects of OS+NNS in the future.

**Abbreviations:** 95% CI = 95% confidence interval, MD = mean difference, NFCS = neonatal facial coding system scale, NICU = neonatal intensive care unit, NNS = nonnutritive sucking, N-PASS = neonatal pain, agitation and sedation scale, OS = oral sucrose, PICC = peripherally inserted central catheter, PIPP = premature infant pain profile scale, ROP = retinopathy of prematurity, RR = risk ratios, SMD = standard mean differences.

**Keywords:** NICU, nonnutritive sucking, oral sucrose, preterm, procedure pain

Editor: Maria Jose Carbonero Celis.

BL assisted YL and XH on formulating the research questions, designing the study and supervising the quality of this manuscript. This article and the data were screened and extracted by YL and XH, and were revised by BL. Our research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

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The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:6(e6108)

Received: 28 November 2016 / Received in final form: 16 January 2017 / Accepted: 20 January 2017

<http://dx.doi.org/10.1097/MD.00000000000006108>

## 1. Introduction

Neonates in neonatal intensive care unit (NICU) are generally exposed to a large number of diagnostic and therapeutic procedures,<sup>[1,2]</sup> such as heel stick for blood sampling, injection for immunizations, venipuncture for treatment, and eye examination for detecting retinopathy of prematurity (ROP).<sup>[3–5]</sup> In addition, peripherally inserted central catheter (PICC) puncture and endotracheal intubation are commonly painful surgical procedures in NICU.<sup>[6–8]</sup> Studies have shown that the premature and sick infants experienced 10 to 14 painful procedures per day,<sup>[9]</sup> with a mean of  $14 \pm 4$  per day in NICU.<sup>[10]</sup> Kyololo et al<sup>[11]</sup> also pointed out in a study conducted in Kenya that 95 neonates experienced a total of 404 painful procedures during 24 hours. Another study conducted by Stevens et al<sup>[8]</sup> confirmed that in NICU, 60% of pain procedures were associated with moderate-to-severe intensity. Besides, numerous studies suggested that repeated pain procedures can cause short-term and long-term consequences on the behavioral and neurological development of newborns.<sup>[12–15]</sup>

Up to now, various nonpharmacological methods have been used to alleviate procedures pain in neonates, which include breastfeeding, oral sucrose, NNS, swaddling, facilitated tucking, kangaroo care, skin-to-skin contact, and music.<sup>[16–21]</sup> Many researches proved that oral sucrose is safe and effective for reducing pain from single and short-term procedures,<sup>[9,22,23]</sup> which has been suggested as the standard of pain care.<sup>[24,25]</sup> Simultaneously, there are also substantial evidences to suggest that NNS effectively reduced pain scores and pain behaviors in response to heel stick, needle insertions, and eye examination procedures;<sup>[3,26,27]</sup> and NNS was also recommended by international guidelines for neonatal pain management during procedures.<sup>[28]</sup> Administration of oral sucrose with or without NNS is the most frequently studied nonpharmacological intervention for procedural pain relief in neonates,<sup>[24]</sup> but evidence has been insufficient to support that oral sucrose combined with NNS had a better effect on pain relief among NICU newborns than oral sucrose or NNS alone. Therefore, we aimed to evaluate the efficiency of combined oral sucrose and NNS for pain relief in NICU newborns undergoing painful procedures.

## 2. Methods

### 2.1. Protocol and registration

We registered this systematic review at <http://www.crd.york.ac.uk/PROSPERO/>, with the registration number being CRD42016049032.

### 2.2. Eligibility criteria

1. The participants were newborns who were submitted to NICU (including preterm and term infants, gestation age of preterm  $\leq 37$  weeks and gestation age of term  $\leq 42$  weeks, birth weight of preterm  $\leq 2500$ g, and birth weight of term  $\leq 4000$ g at birth) and did not have congenital malformations, neurologic abnormalities, or severe medical conditions requiring treatment such as mechanical ventilation (excluding continuous positive airway pressure), analgesic drugs, and sedatives.
2. The types of exposure were oral sucrose combined with NNS in intervention group and single measure (oral sucrose/NNS) in control group. Sucrose was given orally with a syringe 2 minutes before procedures. NNS refers to placing a pacifier in the mouth of newborns during painful procedures to promote

sucking behavior without providing any breast milk or formula milk that can provide nutrition.

3. The main outcome was pain scores, which contains Premature Infant Pain Profile (PIPP) score,<sup>[9,29–32]</sup> Neonatal Facial Coding System (NFCS) score,<sup>[33]</sup> and Neonatal Pain, Agitation and Sedation Scale (N-PASS) score.<sup>[4]</sup> The secondary outcomes were heart rate (including bradycardia and tachycardia),  $SP_{O_2}$  ( $< 85\%$  for  $> 10$  seconds), and crying time.
4. The types of included studies were randomized controlled studies; review articles and commentaries were excluded; and non-English articles were restricted.

### 2.3. Information sources and search strategies

Our systematic review was designed and performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement<sup>[34]</sup> and Cochrane Handbook for Systematic Reviews of Interventions.<sup>[35]</sup> The included databases were Cochrane Central Library (<http://www.cochranelibrary.com/>), PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), Ovid (medline), Embase (medline), and some other resources such as Google Scholar and bibliographies of included literatures. All databases were searched from January 2001 to May 2016 and were updated in September 2016.

Our search strategy consisted of the Mesh terms, keywords, and truncation symbol mainly; and our search method was adjusted in accordance with each database. The flowing searched terms were used: “premature birth,” “infant, extremely premature,” “infant, premature,” “obstetric labor, premature,” “NICU,” “pacifiers,” nonnutritive sucking, oral sucrose, non-pharmacologic management, “pain management,” and procedural pain, etc. Details of our search strategy are provided in the online Supplementary material. References of eligible articles and previous reviews were manually searched for studies probably suitable for inclusion.

### 2.4. Study selection and data collection

Two reviewers (YL and XH) screened articles and extracted the data independently. They read the titles, abstracts, and reference lists of all relevant studies to identify original research articles, and reassessed the potentially eligible articles by retrieving and evaluating the full text. The data extracted included the author's name and country, year of publication, type of participants, number of participants, gestational of age, birth weight, definition of exposure, outcomes, and potential sources of bias (Table 1).

We made efforts to contact authors for additional data if the articles were suitable for our meta-analysis. The authors were requested to provide mean values and standard deviations for outcomes of pain scores and crying time, and to provide numbers and constitute ratio for outcomes of HR and  $SPO_2$ . The study was excluded from the meta-analyses if the authors were unable to provide additional data. Finally, sufficient information of 1 study was obtained after correspondence with the author Zheng.<sup>[33]</sup>

### 2.5. Assessment of risk of bias

The Cochrane Risk of Bias Tool<sup>[35]</sup> was used to assess the methodological quality of included trials by 2 independent investigators (YL and XH). We performed the procedure based on the following 7 aspects: generation of randomization sequence, allocation concealment, blinding of participants and

**Table 1**

**The characteristics of the included studies.**

Study ID	Country	Objects	Exposure	No. of participants		Gestational age (I/C)	Birth weight (I/C)	Measures		Outcomes
				S+P/N	Control			Intervention	Control	
Boyle, 2006	Canada	Preterm	ROP	11	9	29 (24–31)	1210 (650–1910)	Topical anesthetics applied 30 s before examination	Topical anesthetics applied 30 s before examination	PPP scores
			Examination			30 (27–31)	1300 (820–1610)	One milliliter 33% sucrose was given by mouth with a syringe and a pacifier was put into the mouth 2 min before examination	One milliliter 33% sterile water was given by mouth with a syringe and a pacifier was put into the mouth 2 min before examination	PPP scores
Dilli, 2014	Turkey	Preterm	ROP	32	32	28.2 ± 2.7	1248 ± 392	Topical anesthetics applied 30 s before examination	Topical anesthetics applied 30 s before examination	HR, SPO <sub>2</sub>
			Examination			28.8 ± 2.9	1360 ± 530	0.5 mL/kg 24% sucrose was given by mouth with a syringe and a pacifier was put into the mouth 2 min before examination	0.5 mL/kg sterile water was given by mouth with a syringe and a pacifier was put into the mouth 2 min before examination	PPP scores
Elaeraty, 2009	USA	Preterm	Heel-stick	6	6	—	—	0.5 mL/kg 24% sucrose with a pacifier was held in the infant's mouth for 2 min before the procedure	0.5 mL/kg sterile water with pacifier was held in the infant's mouth for 2 min before the procedure	Crying time NFCS scores
Leng, 2016	China	Full-term	Venipuncture Procedure	167	176	—	—	Two milliliters 24% sucrose was given by mouth with a syringe 2 min before the procedure, then a pacifier was placed into the infant's mouth until the end of the process	Two milliliters 24% sucrose was given by mouth with a syringe 2 min before the procedure	HR, SPO <sub>2</sub> PPP scores
Mitchell, 2004	Canada	Preterm	Pain ROP	15	15	26.5 ± 1.6	970 ± 224	Topical anesthetics applied 30 sec before examination	Topical anesthetics applied 30 s before examination	N-PASS scores
			Examination			27.3 ± 2.3	982 ± 205	3 × 0.1 mL of 24% sucrose was given by mouth with a syringe at 2 min intervals before and during examination, then placed a pacifier	3 × 0.1 mL of sterile water was given by mouth with a syringe at 2 min intervals before and during examination, then placed a pacifier	HR, SPO <sub>2</sub> PPP scores
O sullivan, 2010	Ireland	Preterm	ROP	20	20	29.8 ± 2.4	1139 ± 200	Local anesthetics applied 30 s before examination	Local anesthetics applied 30 s before examination	HR, SPO <sub>2</sub> PPP scores
			Examination			29.5 ± 2.3	1140 ± 376	Infants were swaddled and received 0.2 mL 24% sucrose given by mouth with a syringe 2 min before examination and a soother	Infants were swaddled and received 0.2 mL sterile water given by mouth with a syringe 2 min before examination and a soother	N-PASS scores
Thakkar, 2016	India	Full-term	Heel-stick	45	45	—	—	Two milliliters 30% sucrose was given by mouth with a syringe 2 min before procedure and NNS was given (sterile gauze was held gently in neonate's mouth)	NNS (sterile gauze was held gently in neonate's mouth)	HR, SPO <sub>2</sub> Crying time

study personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other biases. Each aspect was classified as “low risk,” “high risk,” or “unclear risk,” according to the extracted data of eligible trials. If no obvious mistake was identified, the aspect(s) would be rated as low risk; by contrast, the aspect(s) would be identified as high risk as long as appropriate methods were not used; furthermore, the aspect(s) would be graded as unclear risk if information available was insufficient to grade the bias risk. Agreement on any aspect was reached based on consensus or consulting a third investigator (BL). In our meta-analysis, the bias risk of each trail is presented in Fig. 1.

**2.6. Synthesis of results**

All extracted data were entered into RevMan 5.3 (The Cochrane Collaboration) for statistical analysis. Standard mean differences (SMD) with 95% confidence interval (CI) for continuous outcomes and risk ratios (RR) with 95% CI for dichotomous outcomes were selected to estimate the pooled effect size. Heterogeneity among the studies in effective measures was assessed using both the  $\chi^2$  test ( $P \geq 0.05$ ;  $\chi^2$  test) and the  $I^2$  statistic. We also conducted sensitivity analysis and subgroup analysis to identify the source of heterogeneity.

**3. Results study selection and characteristics**

The flow diagram of literature retrieval and selection is outlined in Fig. 2. No difference was found in mean gestational age at birth or mean birth weight between 2 groups. A total of 392 articles were captured by search strategy, and 6 articles were identified additionally by assessing the references of the captured articles and other sources. A total of 215 duplicate articles were removed

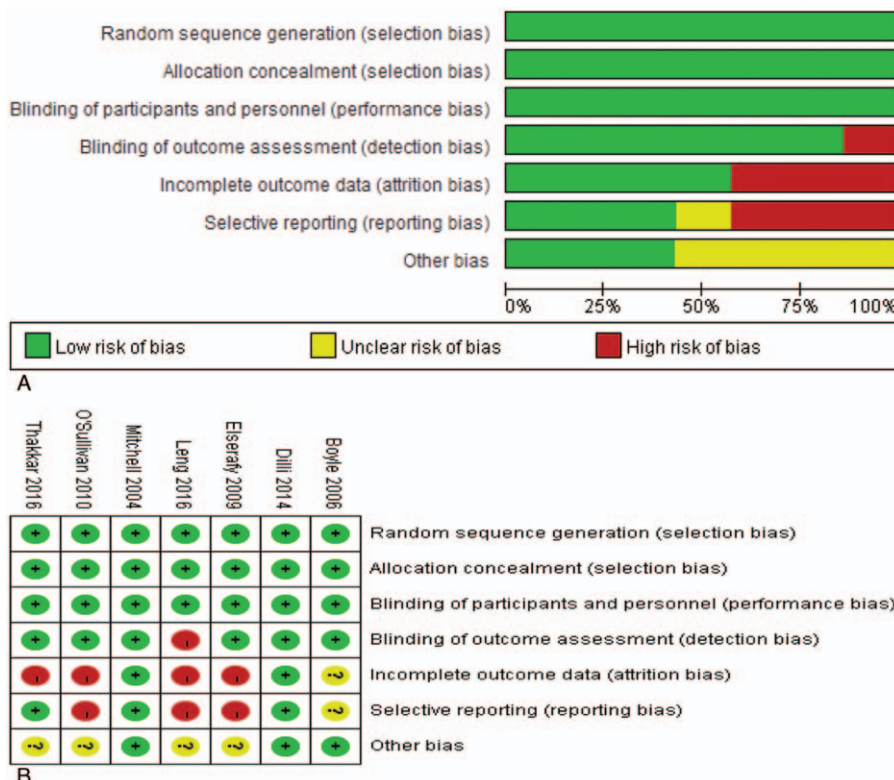
by references management software (EndNote X7). After reviewing the titles and abstracts, the 2 reviewers considered 17 articles relevant; and after reading the full texts of these papers, they identified 7 studies as eligible for inclusion in this meta-analysis. Ten studies were excluded if: the articles included oral sucrose or nonnutritive sucking separately,<sup>[18,26,36–38]</sup> the primary outcomes were not reported,<sup>[9,39]</sup> article type was review,<sup>[40,41]</sup> or the study was conference publication and had no full-text.<sup>[27]</sup>

Altogether, 7 studies were included in this systematic review<sup>[4,9,29–33]</sup> (Table 1). We tried to contact the authors of 1 study because data were incomplete for meta-analysis.<sup>[33]</sup> The first author replied and provided additional information. The main tool used to evaluate pain degree was PIPP score,<sup>[9,29–32]</sup> and other tools of NFCS score<sup>[33]</sup> and N-PASS score<sup>[4]</sup> were also used. For infants who were under ROP examination, only screening of the first eye was video-recorded for pain score by the same investigator who had received network training. Outcomes were measured during examination for infants who were under other minor procedures. In our meta-analysis, 6 studies were stated double-blinded while only 1 study reported no blinding of outcome assessors;<sup>[33]</sup> 6 studies explained the randomization method while only 1 study did not report the randomization sequence generation;<sup>[32]</sup> all studies used allocation concealment. The detailed exposure measures between intervention group and control group are summarized in Table 1.

**4. Synthesis of results**

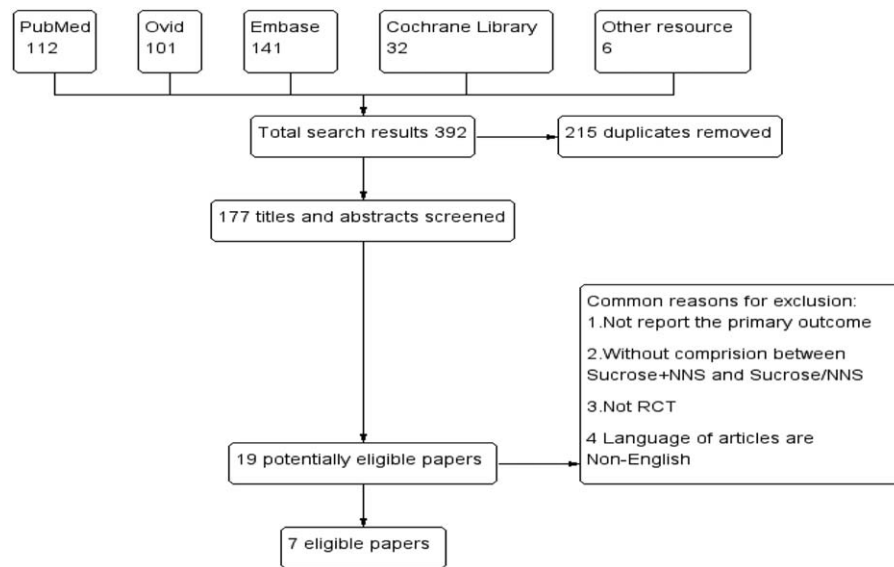
**4.1. Meta-analysis on pain score**

All trials involving 599 newborns reported the pain score. Heterogeneity was identified from the included studies ( $P = 0.03$ ;



**Figure 1.** Assessment of risk of bias: (A) risk of bias graph and (B) risk of bias summary. Quality of each study was evaluated from 7 aspects and was classified as “low risk” (green), “high risk” (red), or “unclear risk” (yellow).





**Figure 2.** The flow diagram of literature retrieval and selection. A total of 392 articles were captured by search strategy. After review, 7 studies were identified eligible for inclusion in this meta-analysis finally.

$I^2 = 57%$ ), and a fixed-effects model was performed to summarize mean effect size of pain score, with the mean difference being  $-0.52$  (95% CI,  $-0.68$  to  $-0.36$ ) (Fig. 3). To detect the source of heterogeneity among included trials, we made the sensitivity analysis based on different pooled models to test the robustness of pooled results. We found that when removing the study of Dill et al,<sup>[31]</sup> pooled results of fixed-effects model indicated a more robust summary effect size with the mean difference being  $-0.44$  (95% CI,  $-0.61$  to  $-0.26$ ). The meta-analysis suggested that pain scores were significantly lower in the S+NNS group than in the control group. Besides, 4 trials of all studies reported the benefits of S+NNS on ROP screening. However, no statistic differences were detected with the mean difference being  $-0.67$  (95% CI,  $-1.34$  to  $0.01$ ).

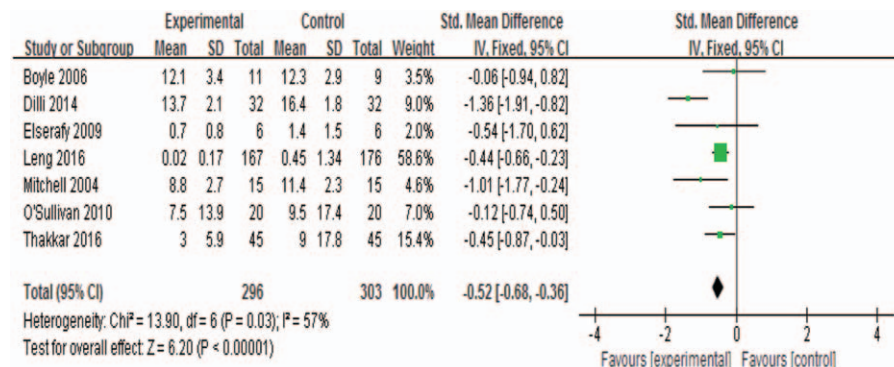
**4.2. Meta-analysis on crying time**

Three trials, which included 166 participants, were enrolled in the meta-analysis for calculating the crying time. We assessed

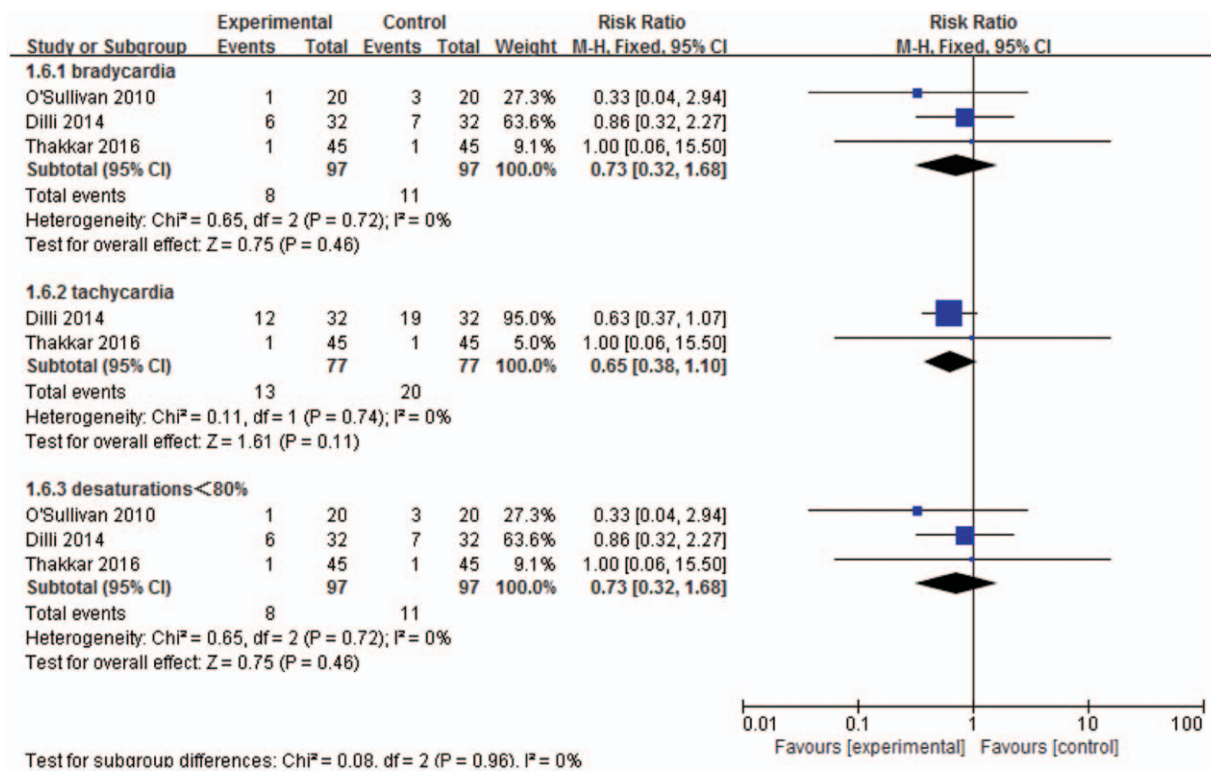
homogeneity in the 3 studies ( $P = 0.49$ ,  $I^2 = 0%$ ), and a fixed-effects model was performed to calculate mean effect size. The meta-analysis revealed that S+NNS shortened the crying time of NICU newborns significantly (MD,  $-0.92$ ; 95% CI,  $-1.39$  to  $-0.44$ ) (Fig. 4).

**4.3. Meta-analysis on physiological index**

Three trials involving 194 participants reported bradycardia ( $<100$  bpm); 2 trials involving 154 participants reported tachycardia ( $>180$  bpm); and 3 trials involving 194 participants reported desaturation ( $<85%$  for  $>10$  seconds), with the homogeneity being ( $P = 0.72$ ,  $I^2 = 0%$ ), ( $P = 0.74$ ,  $I^2 = 0%$ ), and ( $P = 0.72$ ,  $I^2 = 0%$ ), respectively. Therefore, the fixed-effects model was used in each synthesis. No statistic deference was observed in the risk of happening bradycardia (RR, 0.73; 95% CI, 0.32–1.68), tachycardia (RR, 0.65; 95% CI, 0.38–1.10), or desaturations (RR, 0.73; 95% CI, 0.32–1.68) between 2 groups (Fig. 5).



**Figure 3.** Meta-analysis on pain score. The outcome suggested that the pain scores were significantly lower in the S+NNS group when compared with the control group (MD,  $-0.52$ ; 95% CI,  $-0.68$  to  $-0.36$ ). MD = mean difference, NNS = nonnutritive sucking.



**Figure 4.** Meta-analysis on physiological index. No statistical difference was found in the risk of bradycardia (RR, 0.73; 95% CI, 0.32–1.68), tachycardia (RR, 0.65; 95% CI, 0.38–1.10), and desaturations incidence (RR, 0.73; 95% CI, 0.32–1.68) between 2 groups. CI = confidence interval, RR = risk ratios.

**4.4. Publication bias**

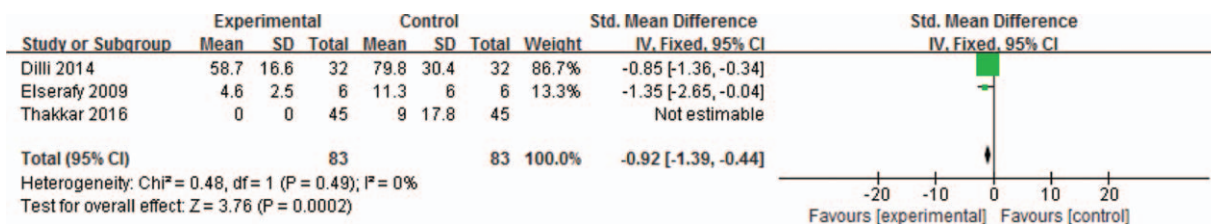
A funnel plot was performed to assess the publication bias in the 6 included studies. The symmetrical outcome of our analysis showed that no publication bias possibly exists among included studies (Fig. 6).

**5. Discussion**

Because newborns are actually very sensitive to pain,<sup>[9]</sup> pain management has been stated as a significant part of health care in newborns. In 2001, the American Academy of Pediatrics proposed guidelines for prevention and treatment of neonatal pain, in which nonpharmacological interventions, such as sucrose, NNS, and skin-to-skin contact were recommended in minor painful procedures.<sup>[42]</sup>

An increasing number of studies have revealed that both oral sucrose and NNS are effective for reducing pain from procedural events in newborns.<sup>[24]</sup> However, data on the combination of

NNS and sucrose for analgesia in neonates were limited, and the combined efficiency remained unclear. To explore the efficiency of sucrose combined with NNS, we performed this meta-analysis and confirmed that such combination can significantly reduce the pain score in full-term and preterm neonates undergoing painful procedures. Our findings accord with previous findings that showed that combined intervention is more effective in providing analgesia than a single one.<sup>[9,43]</sup> On one hand, the analgesic mechanism of NNS may be attributed to the fact that it can activate the tactile receptors and reduce pain through gait control mechanism of pain inhibition;<sup>[9]</sup> on the other hand, sucrose is thought to stimulate the gustatory receptors and reduce the pain perception by releasing endogenous opioids in the central nervous system.<sup>[9,44,45]</sup> When sucrose is combined with NNS, nonopioid mechanisms are also activated.<sup>[31,46]</sup> For this reason, we infer that the combination of sucrose and NNS activates both the opioid and nonopioid mechanisms at the same time and enhances the analgesic effect finally.



**Figure 5.** Meta-analysis on crying time. The outcome revealed that S+NNS shortened the crying time of NICU newborns effectively (MD, -0.92; 95% CI, -1.39 to -0.44). CI = confidence interval, MD = mean difference, NICU = neonatal intensive care unit, NNS = nonnutritive sucking.

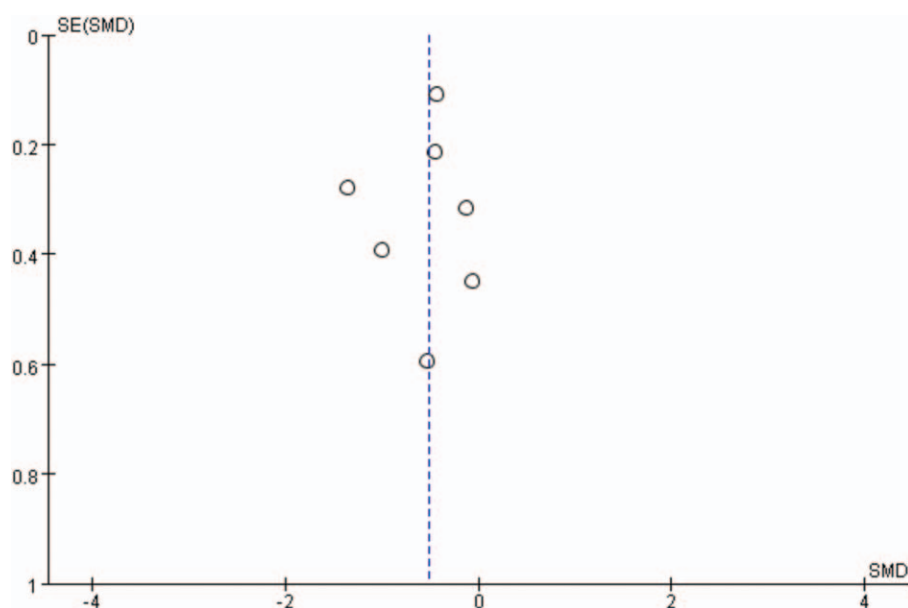


Figure 6. Funnel plot of publication bias. No publication bias possibly exists among included studies.

Nevertheless, sucrose combined with NNS did not reduce pain scores significantly for ROP examinations. The benefits of sucrose in ROP screening have been controversial.<sup>[32,38,47-49]</sup> On one hand, Ucar pointed out that NNS may be more effective in reducing pain score during screening examinations for ROP,<sup>[27]</sup> providing a longer effect in analgesia than sucrose.<sup>[50]</sup> On the other hand, however, ROP examination is a distressful and painful procedure for a newborn. The pain stimulation is stronger than some other minor procedures, such as heel stick and venipuncture.<sup>[24]</sup> This means that the efficacy of the combined intervention is limited and that pharmacological interventions may be needed in the procedure of ROP scanning.

Although studies have shown that the combination of sucrose and NNS lowered O<sub>2</sub> saturation fluctuations and HR when compared with oral sucrose alone,<sup>[33]</sup> our meta-analysis found that the combined measures did not differ significantly in lowering the risk of bradycardia, tachycardia, and desaturations incidence between the 2 groups. This may be because both sucrose and NNS could mitigate pain by activating the mechanoreceptors that modulate the transmission of nociception,<sup>[26]</sup> but the stimulation lingered and physical effects did not diminish too much, which in turn resulted in the nonsignificant difference. Besides, our meta-analysis showed that NNS combined with oral sucrose shortened the crying time effectively. When the pain perceived by the newborn was relieved, crying time was shortened for certain. Because the direct cause of crying during the procedures is the pain stimulation.

## 6. Limitations

Our study has 3 limitations. First, the methods of pain evaluation were not unified. Three methods were used in all captured studies in our meta-analysis. Among them, PIPP score was the most widely used. It was developed at the Universities of Toronto and McGill in Canada and was recommended in both term and preterm neonates.<sup>[51,52]</sup> Besides, the NFCS score and N-PASS

score are also reliable and valid for assessing pain. Studies have reported a strong correlation among the 3 tools.<sup>[53,54]</sup> Nevertheless, differences in the assessment details among the 3 methods may cause bias to our pooled effects.

Second, the dosage and concentration of oral sucrose were not unified within included studies. The recommended standard of sucrose is 0.1 to 0.4 mL of 12% to 24% for preterm infants and 2 mL of 24% to 33% for term infants,<sup>[4]</sup> and as little as 0.05 to 0.5 mL of 24% sucrose is effective in heel lance or venipuncture.<sup>[25]</sup> Furthermore, a review further concluded that the use of repeated dosages may be more beneficial than a single dosage.<sup>[4,55]</sup> Nevertheless, Johnston et al<sup>[56]</sup> observed worse neurodevelopmental outcomes in infants who had received repeated dosages. In our meta-analysis, newborns in different studies were exposed to different procedures. Ideally, standards of sucrose usage should accord with the procedure because the stimulation of ROP examination is stronger than other minor procedures and it may require a higher dosage of sucrose to produce analgesia. Therefore, additional work is needed to quantify the optimal dosages.

Third, we only searched the PubMed, the Cochrane Library Embase (medline), Ovid (medline), and some other resources, but did not search the Web of Science, Springer Link, and some other relevant electronic databases. This may result in a risk of incomplete retrieval. In addition, only articles published in English were included in our meta-analysis, which may lead to selection bias and thus influence the pooled results finally.

## 7. Conclusion

Our meta-analysis confirmed the efficacy of sucrose combined with NNS. Such a combination significantly reduced the composite pain score and total crying time. More effective than single intervention as the combination is, it should be considered as an evidence-based guideline for the prevention and management of pain in NICU newborns.

## Acknowledgments

The authors are grateful to Professor Zheng et al for their additional information on the results of their studies. The authors also thank Dong-tao Lin from College of Foreign Languages and Cultures of Sichuan University for editing the manuscript.

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