

Appendix 3

Table 1 Reasons for exclusion

No.	References	Reason for exclusion
1	Labban M, Menhem Z, Bandali T, et al. Pain control in neonatal male circumcision: A best evidence review. <i>Journal of Pediatric Urology</i> 2021;17:3-8.	Literature Review
2	Graf T, Duffey E, Spatz D. Development of an Interprofessional Policy on the Use of Human Milk and Breastfeeding for Pain Relief. <i>Advances in neonatal care</i> 2021;21:267-73.	Evidence summary
3	Çetinkaya B. Complementary and Alternative Therapies for Infantile Colic: A Systematic Review of the Literature. <i>Alternative therapies in health and medicine</i> 2021;27:42-47.	Non-hospitalized newborn
4	Tang XY. Oral Sweet Solution Reduces Infant Pain Caused by Invasive Care: a Meta-analysis. <i>World Latest Medicine Information (Electronic Version)</i> 2018;18:34-35.	No separate data for neonates
5	Suleiman N, Shamsudin SH, Rus RM, et al. The relevancy of paracetamol and breastfeeding post infant vaccination: A systematic review. <i>Pharmacy</i> 2018;6:27.	Non-hospitalized newborn
6	Miller MM, Meints SM, Hirsh AT. Catastrophizing, pain, and functional outcomes for children with chronic pain: a meta-analytic review. <i>Pain</i> 2018;159:2442-60.	Non-hospitalized newborn
7	Harrison D, Modanloo S, Desrosiers A, et al. A systematic review of YouTube videos on pain management during newborn blood tests. <i>Journal of Neonatal Nursing</i> 2018;24:325-30.	Not systematic review of clinical trials
8	Baird D, Bybel M. Effectiveness of Skin-to-Skin Care for Procedure-Related Pain in Newborns. <i>American family physician</i> 2018;97:170-71.	Synopses of syntheses
9	Huang RR. Systematic review of the effect of sweet solutions on venipuncture pain in neonates. <i>Diet Science</i> 2017;12:117-18.	Duplicate data
10	Matsuda E. Sucrose as Analgesia in Neonates Undergoing Painful Procedures. <i>AJN American Journal of Nursing</i> 2017;117:21-21.	Synopses of syntheses
11	Disher T, Benoit B, Johnston C, et al. Skin-to-skin contact for procedural pain in neonates: acceptability of novel systematic review synthesis methods and GRADEing of the evidence. <i>Journal of Advanced Nursing</i> 2017;73:504-19.	Updated Cochrane view available
12	van der Heijden MJE, Oliai Araghi S, Jeekel J, et al. Do Hospitalized Premature Infants Benefit from Music	The subject of the study was not

	Interventions? A Systematic Review of Randomized Controlled Trials. <i>PLOS ONE</i> 2016;11:e0161848.	pain
13	Gao HX. A systematic review of repeated sucrose for repeated procedural pain in neonates and a randomized controlled trial of combined sucrose and non-nutritive sucking for repeated pain relief in preterm infants [Doctorate]. Nanjing University of Chinese Medicine, 2016.	Duplicate data
14	da Silva Morais AP, de Abreu Façanha SM, Nogueira Rabelo S, et al. Non-pharmacological measures in the pain management in newborns: nursing care. <i>Rev Rene</i> 2016;17:435-42.	Literature review

Table 2 Characteristics of the included SRs

Study	Study design	No. of patients	Types of pain	Participants	Intervention	Comparator	Outcomes	Meta-analysis	Conclusion
Lian DM, 2021 ¹	5 RCTs; 1 NRS	432	Procedural pain: heel lance, venipuncture, endotracheal suction; arterial puncture	Preterm and term neonates	Maternal voice	Standard care	Pain score (NIPS, PIPP, PIPP-R, NIAPAS); comfort score; HR; SpO ₂	Yes	Maternal voice can reduce the pain scores and maintain the heart rates of neonates during and after the painful procedure, and improve comfort scores during the painful procedure.
Rossi S, 2021 ²	8 clinical studies*	1778	Postoperative pain: circumcision	Preterm and term neonates	anesthesia/analgesia/non-pharmacological interventions (sucrose, milk, non-nutritive sucking, dextrose, music)	Different types of anesthesia/analgesia/non-pharmacological interventions	Pain score (MBPS, PIPP, NIPS, N-PASS, FLACC, RIPS); physiological and behavioral indicators	No	Local anesthesia in combination with nonpharmacological interventions appears to be effective to relieve pain for newborn circumcision.
Francisco A, 2021 ³	15 RCTs; 5 NRS	907	Procedural pain: heel lance, diaper	Preterm and term neonates	Position	Pharmacological strategies, nonpharmacological	Pain score (PIPP, NFCS, ALPS-Neo, NIPS,	No	Positioning should be used to relieve procedural

			changing, suctioning, venipuncture, insertion of nasal CPAP prongs, eye examination			strategies (saccharose, glucose, breastfeeding, pacifier, KMC) and placebos	COMFORTneo, N-PASS); physiological and hormonal indicators; adverse effect (bradycardia, desaturation, apnea)		pain in neonates. Facilitated tucking by parents for 30 minutes was the best position for pain relief in preterm newborns.
Eissler A, 2021 ⁴	22 RCTs	1265	Procedural pain: heel lance, venipuncture, suction, eye examination, the vein blood sample	Preterm infants	Active parental involvement (Kangaroo/Skin-to-Skin Care, Facilitated Tucking, Breastfeeding)	Pain-reducing measures performed by health care professionals	Pain score (PIPP, NIPS, BIIP); NIRS; physiologic parameters; facial expressions	No	Active parental involvement in pain-reducing measures during painful procedures is beneficial for preterm infants.
Cañadas DC, 2021 ⁵	6 RCTs	371	Procedural pain: heel lance	Preterm infants	Nonpharmacological Interventions	A different treatment	Salivary cortisol reactivity	Yes	Prone-nest position, breast milk odor, kangaroo care, and twins co-bedding decreased the salivary cortisol levels.
Deng MQ, 2020 ⁶	12 RCTs	1363	Procedural pain	Preterm and term	Music therapy	Standard care, or other	Pain score (NIPS, PIPP, PIPP-R,	Yes	Music therapy could relieve

				neonates		nonpharmacological Interventions	N-PASS, NIAPAS); HR; respiratory rate; SpO ₂		procedural pain, and reduce the heart rate change in neonates.
Yasmeen I, 2020 ⁷	42 RCTs 3 NRS†	4106	Procedural pain: blood sampling (e.g., heel stick, heel lance), vaccination; injections	Preterm and term neonates	caregiver-facilitated pain management interventions: Activate, inform-activate-collaborate, inform-activate, activate-collaborate, or inform caregiver engagement strategies	Standard care or other pain management interventions	Pain score (NIPS, NFCS, DAN, MBPS); crying; HR change; pain knowledge; satisfaction; hospital length of stay, etc.	No	Caregiver-facilitated pain management interventions using an activate engagement strategy may be effective in reducing the pain of hospitalized neonates
Sezavar M, 2020 ⁸	3 clinical studies†	279	Procedural pain	Term infants	Lavender oil	Standard care, placebo, or other odors	Pain score (NIPS, DAN); Crying; HR, SpO ₂	No	Lavender was effective to relieve procedural pain in infants, though it did not affect the duration of crying
Norooziasl S, 2020 ⁹	4 RCTs	303	Procedural pain	Preterm infants	Aromatherapy through amniotic fluid, the mother's milk, vanilla and the mother's odor	Different treatment than the intervention group	Pain score (PIPP, DAN); Crying time; HR; salivary cortisol	No	The effects of amniotic fluid, breast milk, vanilla, and maternal odor on procedural pain in

									premature infants have not been determined
Neto MG, 2020 ¹⁰	15 RCTs	664	Procedural pain: heel stick, endotracheal suctioning	Preterm infants	facilitated tucking position	Different treatment than the intervention group	Pain score (PIPP, BPSN, NIPS, CRIES)	Yes	Facilitated tucking position may improve the pain during painful procedures
Guo WJ, 2020 ¹¹	8 RCTs	463	Repeated procedural pain: heel lance, venipuncture, finger/toe tip stick, other procedures	Preterm infants	combined nonpharmacological interventions	Different treatment than the intervention group	Pain score (PIPP, BPSN); crying; HR; oxygen saturation; cortisol; NBRS score; adverse events (suffocation, nausea, vomiting, tachycardia, bradycardia, rapid breathing, slow breathing, hypoxemia, hyperglycemia, et al)	No	Combined nonpharmacologic al treatments may be effective and safe for repeated procedural pain in preterm infants
De Clifford-Faugere G, 2020 ¹²	10 RCTs; 4 NRS	1028	Procedural pain: heel lance,	Preterm and term neonates	olfactive stimulation	Sterile water; standard care	Pain score (PIPP, DAN, NIPS, NFCS); crying	Yes	The effects of olfactive stimulation

			venipuncture, arterial puncture				duration; HR; oxygen saturation; salivary cortisol; adverse event		interventions on procedural pain in neonates have not been determined
Stadler J, 2019 ¹³	5 RCTs	265	Procedural pain: heel lance	Preterm and term neonates	Acupuncture	Different treatment than the intervention group	Pain score (PIPP, NIPS); HRV	Yes	Acupuncture may have a positive effect on pain-relieving in neonates.
Huang RR, 2019 ¹⁴	31 RCTs	4999	Procedural pain	Preterm and term neonates	Sweet solutions	Different treatment than the intervention group	Pain score (NIPS, INIPS, NFCS, PIPP, DAN); behavioral and physiological indicators; success rate of procedure; duration of procedure; adverse effects (coughing, choking, et al)	Yes	Small volumes of sweet solutions reduce acute procedural pain in neonates.
Hatfield LA, 2019 ¹⁵	14 RCTs	889	Procedural pain: heel lance, venipuncture,	Preterm infants	Behavioral and environmental interventions: swaddling, acupressure, incubator,	Different treatment than the intervention group	Pain score (PIPP, NIPS, BPSN); cry, grimace, limb extension	No	Facilitated tucking, oral sucrose, and kangaroo care

			endotracheal suctioning, laser treatment of ROP		kangaroo mother care, dextrose, etc.				significantly relieve biobehavioral responses associated with acutely painful procedures in preterm infants.
Zhang SY, 2018 ¹⁶	8 RCTs	453	Procedural pain: heel lance, venipuncture	Preterm and term neonates	Maternal milk odor	Placebo; other odors	Pain score (PIPP, DAN, NIPS); HR, HRV; oxygen saturation; crying duration; salivary cortisol	Yes	Maternal milk odor appears to play an analgesic role in newborns
Disher T, 2018 ¹⁷	29 RCTs	1487	Procedural pain: ROP examination	Preterm infants	Pharmacological, nonpharmacological, combined interventions	Different treatment than the intervention group	Pain score (PIPP); HR, oxygen saturation; crying time; adverse events (bradycardia, et al);	Yes	Topical anesthetic combined with sweet solutions and an adjunct intervention (e.g., non-nutritive sucking) is likely the optimal treatment for reducing pain resulting from eye examinations in preterm infants.
Lotto CR,	9 RCTs;	460	Procedural	Preterm	Skin-to-skin contact	Different treatment	Pain score	No	Skin-to-skin

2018 ¹⁸	1 case study; 1 cross study; 1 DEC		pain: calcaneal puncture, venous puncture, removal of adhesive tape, tracheal or nasal aspiration	infants		than the intervention group: breastfeeding, standard care	(NFCS, PIPP, ABSS); HR; oxygen saturation; NIRS		contact was effective to relieve procedural pain in preterm infants. The time staying in the Kangaroo position that was more effective for pain relief was 30 minutes before the painful procedure in NICU.
Liu LX, 2017 ¹⁹	5 RCTs	422	Procedural pain: heel lance	Preterm and term neonates	Kangaroo care	Standard care; swaddling	Pain score (PIPP, NFCS); HR; oxygen saturation; crying time	Yes	Kangaroo care compared with standard care may stabilize heart rate, ease the decline of oxyhemoglobin saturation, shorten the crying time, and alleviate pain score in neonates during heel blood sampling.
Li YB, 2017 ²⁰	9 RCTs	402	Procedural pain: ROP	Preterm infants	Sweet solutions: glucose, sucrose	Different treatment than the intervention	Pain score (PIPP); adverse event	Yes	The single oral sweet solution

			examination			group: placebo, standard care, blank control, pacifier	(tachycardia, bradycardia, et al)		may not be effective to relieve pain during screenings for ROP, but it is effective for pain relief and has no obvious adverse reactions when combined with a pacifier
Pagni AM, 2017 ²¹	20 clinical studies	1035	Procedural pain: heel lance, blood sampling, diaper change, other invasive procedures	Preterm infants	Kangaroo care	Different treatment than the intervention group	Pain score (PIPP, NFCS); HR; HRV; cortisol; cry time; muscle extension	No	Preterm infants greatly benefit from the implementation of Kangaroo Care for procedural pain control.
Liu Y, 2017 ²²	7 RCTs	599	Procedural pain: ROP examination, heel lance, venipuncture,	Preterm and term neonates	Combined oral sucrose and nonnutritive sucking	Single measure (oral sucrose/NNS)	Pain score (PIPP, NFCS, N-PASS); HR, SPO ₂ ; crying time; adverse effect (tachycardia, bradycardia, desaturations)	Yes	Oral sucrose combined with nonnutritive sucking can be an alternative for better preventing and managing procedural pain in newborns.

Johnston C, 2017 ²³	25 RCTs	2001	Procedural pain: heel lance, venipuncture, intramuscular injection, vaccination, tape removal	Preterm and term neonates	Skin-to-skin care	Different treatment than the intervention group	Pain score (PIPP, NIPS); HR, HRV, oxygen saturation; cry duration; adverse events	Yes	Skin-to-skin care appears to be effective as measured by composite pain indicators with both physiological and behavioral indicators and, independently, using heart rate and crying time; and safe for a single painful procedure
Harrison D, 2017 ²⁴	168 randomized or quasi-randomized controlled trials	—	Procedural pain: heel lance, venipuncture, eye examination, circumcision, intramuscular injection, naso/orogastric tube insertion, a compilation	Preterm and term neonates	Sweet solutions: sucrose, glucose, other sweet solutions orally	No treatment, water, pacifier, swaddling/positioning, skin-to-skincare, formula feeding, expressed breast milk, breastfeeding, sensorial saturation, or topical anesthetics	Pain score (PIPP, NIPS, NFCS, DAN); cry duration; HR, oxygen saturation, respiratory rate; cortisol; NIRS, EEG	Yes	Sucrose or glucose can reduce behavioral responses to commonly performed painful procedures in neonates.

			of painful procedures						
Chen SL, 2017 ²⁵	6 RCTs	441	Procedural pain: gastric tube insertion	Preterm and term neonates	Nonpharmacological treatments: glucose, sucrose, pacifier	No treatment, placebo, pacifier, standard care	Pain score (PIPP, NFCS); crying; HRV/SpO ₂ ; adverse event (apnoea, self-limiting bradycardia); difficult insertion	Yes	Small volumes of oral sweet solutions relieve pain during gastric tube insertion in neonates.
Benoit B, 2017 ²⁶	20 RCTs; 1 NRS	2336	Procedural pain: heel lance, intramuscular injections, venipuncture	Preterm and term neonates	Nonpharmacological treatments: breastfeeding or expressed breast milk	Music therapy; topical anesthetics and cooling sprays; sweet taste; simple holding; skin-to-skin contact; nonnutritive sucking;	Pain score (PIPP, NIPS, revised NFCS, DAN); NIRS; HR; oxygen saturation; facial actions; cry duration; cortisol	No	Direct breastfeeding was more effective than maternal holding, maternal skin-to-skin contact, topical anesthetics, and music therapy, and was as or more effective than sweet solutions in full-term infants.
Stevens B, 2016 ²⁷	74 RCTs	7049	Procedural pain: heel lance, venipuncture,	Preterm and term neonates	sucrose via oral syringe, dropper or in addition to a pacifier	Breastfeeding; breast milk or milk formula; water; local anesthetics; pacifier;	Pain score (PIPP, PIPP-R, NIPS, DAN, NFCS, COMFORTneo,	Yes	Sucrose is effective for reducing single procedural pain in

			injection, arterial puncture, circumcision, bladder catheterization, gastric tube insertion, ROP examination			positioning/containing; facilitated tucking; warmth; no treatment; various concentrations of glucose.	BPSN, revised NFCS, VAS, N-PASS); HR; respiratory rate; oxygen saturation; NIRS; EEG; crying time; plasma cortisol; long-term neurodevelopmental outcomes		neonates without serious side effects or harm. Sucrose in combination with non-nutritive sucking is more effective than sucrose alone
Gao HX, 2016 ²⁸	8 RCTs	782	Repeated procedural pain: intramuscular injection, venipuncture, heel lance	Preterm and term neonates	Repeated oral sucrose	Blank Control; water; facilitated tucking; breastfeeding; skin to skin contact; music; touch; sucking	pain scores (NFCS, PIPP, NIPS, BPSN); cry; facial actions; HR; respiratory rate; SpO ₂ ; TcpO ₂ ; TcpCO ₂ ; cortisol; clinical outcomes; neurobehavioral development; adverse events	No	The efficacy and safety of repeated sucrose on repeated procedural pain in neonates have not been determined.
Boundy EO, 2016 ²⁹	16 clinical studies‡	—	procedural pain: heel prick, intramuscular injection,	Preterm and term neonates	Kangaroo mother care	Different treatment than the intervention group	Pain score (NIPS, NFCS, PIPP); crying duration; HR	Yes	Kangaroo mother care can lower mean respiratory rate and pain scores, and higher

nasal suctioning, tape removal	oxygen saturation.
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* Only data related to non-pharmacological interventions were included.

† Only neonatal-related data were included.

‡ Only pain-related data were included.

Note: *ALPS-Neo*: Astrid Lindgren Children's Hospital Pain Scale Neonates; *ABSS*: Anderson Behavioral State Scoring System; *BPSN*: Bernese Pain Scale for Neonates; *BIIP*: Behavioral Indicators of Infant Pain; *CRIES*: Cries, Requires Oxygen, Increased Vital Signs, Expression, Sleeplessness; *DAN*: Douleur Aiguë du Nouveau-né; *DEC*: descriptive, exploratory, and correlational Study; *EEG*: electroencephalogram; *FLACC*: The Face, Legs, Activity, Cry, and Consolability; *HR*: heart rate; *INIPS*: Improved Neonatal Infant Pain Scale; *MBPS*: Modified Behavioral Pain Scale; *NIPS*: Neonatal Infant Pain Scale; *NFCS*: Neonatal Facial Coding System; *N-PASS*: Neonatal Pain Agitation and Sedation Scale; *NIAPAS*: Neonatal Infant Acute Pain Assessment Scale; *NIRS*: near-infrared spectroscopy; *NRS*: non-randomized controlled studies; *PIPP*: Premature Infant Pain Profile; *PIPP-R*: PIPP-Revised; *RIPS*: Riley Infant Pain Scale; *RCT*: randomized controlled trial; *ROP*: retinopathy of prematurity; *VAS*: visual analogue scale

Table 3 Methodological quality of included SRs using the AMSTAR 2

Review	Criteria*																Quality level
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Lian DM, 2021 ¹	Y	N	Y	Y	Y	Y	PY	Y	Y	N	Y	N	Y	Y	N	N	Low
Rossi S, 2021 ²	Y	N	N	Y	Y	Y	Y	N	N	N	NM	NM	N	Y	NM	Y	Critically low
Francisco A, 2021 ³	Y	Y	N	PY	Y	Y	PY	Y	Y	N	NM	NM	Y	Y	NM	Y	Moderate
Eissler A, 2021 ⁴	Y	N	Y	Y	Y	Y	PY	Y	Y	N	NM	NM	Y	Y	NM	Y	Moderate
Cañadas DC, 2021 ⁵	Y	N	N	Y	Y	Y	PY	Y	Y	N	N	Y	Y	Y	Y	N	Low
Deng MQ, 2020 ⁶	Y	N	Y	PY	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	N	Critically low
Yasmeen I, 2020 ⁷	Y	Y	N	Y	Y	Y	PY	Y	Y	N	NM	NM	Y	Y	NM	Y	Moderate
Sezavar M, 2020 ⁸	Y	N	Y	N	Y	Y	PY	PY	Y	N	NM	NM	N	N	NM	Y	Critically low
Norooziasl S, 2020 ⁹	Y	N	N	N	Y	Y	PY	N	Y	N	NM	NM	N	N	NM	Y	Critically low
Neto MG, 2020 ¹⁰	Y	PY	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	High
Guo WJ, 2020 ¹¹	Y	PY	Y	Y	Y	Y	PY	Y	Y	N	NM	NM	Y	Y	NM	Y	High
De Clifford-Faugere G, 2020 ¹²	Y	Y	N	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Moderate
Stadler J, 2019 ¹³	Y	PY	N	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Moderate
Huang RR, 2019 ¹⁴	Y	PY	Y	PY	Y	Y	PY	Y	Y	N	Y	Y	N	N	N	Y	Critically low
Hatfield LA, 2019 ¹⁵	Y	N	Y	PY	Y	Y	PY	PY	N	N	NM	NM	Y	Y	NM	Y	Low
Zhang SY, 2018 ¹⁶	Y	N	Y	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	N	Y	Low
Disher T, 2018 ¹⁷	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	High
Lotto CR, 2018 ¹⁸	N	N	N	PY	Y	Y	PY	Y	N	N	NM	NM	N	N	NM	N	Critically low
Liu LX, 2017 ¹⁹	Y	N	N	N	Y	N	PY	N	Y	N	Y	Y	N	N	Y	N	Critically low
Li YB, 2017 ²⁰	N	N	Y	PY	N	Y	N	N	N	N	Y	Y	Y	Y	Y	N	Critically low

Pagni AM, 2017 ²¹	Y	N	N	PY	N	N	N	PY	N	N	NM	NM	N	N	NM	N	Critically low
Liu Y, 2017 ²²	Y	Y	Y	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	High
Johnston C, 2017 ²³	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Harrison D, 2017 ²⁴	Y	N	Y	PY	Y	Y	PY	Y	Y	N	Y	Y	Y	N	Y	Y	Moderate
Chen SL, 2017 ²⁵	Y	PY	N	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	N	Y	Low
Benoit B, 2017 ²⁶	Y	N	Y	PY	Y	N	PY	Y	Y	N	NM	NM	Y	N	NM	Y	Moderate
Stevens B, 2016 ²⁷	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
Gao HX, 2016 ²⁸	Y	PY	N	Y	Y	Y	PY	Y	Y	Y	NM	NM	Y	Y	NM	Y	High
Boundy EO, 2016 ²⁹	Y	N	Y	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Moderate

* Y: Yes; N: No; PY: Partial yes; NM: No meta-analysis conducted;

¹Did the research questions and inclusion criteria for the review include the components of PICO? ²Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? ³Did the review authors explain their selection of the study designs for inclusion in the review? ⁴Did the review authors use a comprehensive literature search strategy? ⁵Did the review authors perform study selection in duplicate? ⁶Did the review authors perform data extraction in duplicate? ⁷Did the review authors provide a list of excluded studies and justify the exclusions? ⁸Did the review authors describe the included studies in adequate detail? ⁹Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? ¹⁰Did the review authors report on the sources of funding for the studies included in the review? ¹¹If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? ¹²If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? ¹³Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? ¹⁴Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? ¹⁵If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? ¹⁶Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Table 4 Evidence quality of the primary outcomes in included meta-analyses

Review	Comparison *	Participants **	Outcomes ***	No. of studies	Effect (95% CI) ****	Certainty Assessment (GRADE)					
						Risk of bias	Inconsistency	Indirectness	Imprecision	Other bias	Certainty
Neto MG, 2020	FT position VS routine care	Preterm infants during heel stick	Pain scores	3 RCTs (188)	MD 4.14 lower (6.96 lower to 1.31 lower)	not serious	serious ¹	not serious	serious ²	none	⊕⊕○○ Low
		preterm infants during endotracheal suctioning	Pain scores	4 RCTs (216)	MD 1.02 lower (1.66 lower to 0.37 lower)	not serious	Serious ¹	not serious	Serious ²	none	⊕⊕○○ Low
	FT position VS oral glucose	Preterm infants during heel stick	Pain scores	2 RCTs (88)	MD 0.34 lower (2.05 lower to 1.36 higher)	not serious	Serious ¹	not serious	Serious ^{2,3}	none	⊕⊕○○ Low
	FT position VS opioid	Preterm infants during heel stick	Pain scores	2 RCTs (140)	MD 0.22 higher (1.38 lower to 1.81 higher)	not serious	Serious ¹	not serious	serious ^{2,3}	none	⊕⊕○○ Low
De Clifford-Faugere G, 2020	Familiar odor VS routine care	Neonates during painful procedures	Pain reactivity	5 RCTs (390)	SMD 0.69 SD lower (0.93 lower to 0.44 lower)	Serious ⁴	not serious	not serious	Serious ⁵	none	⊕⊕○○ Low
			Pain regulation	4 RCTs (310)	SMD 0.4 SD lower (0.66 lower to 0.14 lower)	Serious ⁴	not serious	not serious	Serious ⁵	none	⊕⊕○○ Low
	Familiar odor VS artificial odor without habituation	Neonates during painful procedures	Pain reactivity	2 RCTs (128)	SMD 0.28 SD lower (1.39 lower to 0.83 higher)	Serious ⁴	Serious ¹	not serious	very serious ⁶	none	⊕○○○ Very low
			Pain regulation	1 RCT (78)	SMD 0.17 SD lower (0.63 lower to 0.29 higher)	Serious ⁴	not serious	not serious	very serious ⁶	none	⊕○○○ Very low
	Artificial odor with habituation VS routine care	Neonates during painful procedures	Pain reactivity	2 RCTs (148)	SMD 0.67 SD lower (1.01 lower to 0.33 lower)	Serious ⁴	not serious	not serious	Serious ²	none	⊕⊕○○ Low

			Pain regulation	1 RCT (68)	SMD 0.24 SD lower (0.75 lower to 0.26 higher)	Serious ⁴	not serious	not serious	Serious ^{2,3}	none	⊕⊕○○ Low
	Mother milk VS routine care	Neonates during painful procedures	Pain reactivity	4 RCTs (171)	SMD 0.82 SD lower (1.26 lower to 0.39 lower)	Serious ⁴	not serious	not serious	Serious ²	none	⊕⊕○○ Low
			Pain regulation	4 RCTs (171)	SMD 0.43 SD lower (0.89 lower to 0.04 higher)	Serious ⁴	Serious ¹	not serious	Serious ^{2,3}	none	⊕○○○ Very low
	Amniotic fluid VS routine care	Neonates during painful procedures	Pain reactivity	2 RCTs (71)	SMD 0.38 SD lower (0.88 lower to 0.12 higher)	Serious ⁴	not serious	not serious	Serious ^{2,3}	none	⊕⊕○○ Low
			Pain regulation	2 RCTs (71)	SMD 0.4 SD lower (0.9 lower to 0.1 higher)	Serious ⁴	not serious	not serious	Serious ^{2,3}	none	⊕⊕○○ Low
	Stadler J, 2019	Invasive and non-invasive acupuncture techniques	Neonates during painful procedures	Pain scores	4 RCTs (144)	MD 0.74 lower (2.26 lower to 0.79 higher)	not serious	Serious ⁸	not serious	Serious ^{2,3}	none
Disher T, 2018	sweet taste multisensory and TA VS TA	Preterm infants during ROP examination	Pain reactivity (PIPP)	16 RCTs (966)	MD 3.67 lower (5.86 lower to 1.47 lower)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High
			Pain regulation (PIPP)	12 RCTs (963)	MD 5.53 lower (10.28 lower to 0.86 lower)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High
Liu Y, 2017	Combined oral sucrose and NNS VS oral sucrose or NNS only	Neonates during painful procedures	Pain scores	7 RCTs (599)	SMD 0.52 SD lower (0.68 lower to 0.36 lower)	not serious	Serious ¹	not serious	not serious	none	⊕⊕⊕○ Moderate
Johnston C, 2017	Skin-to-skin care VS no treatment or swaddled control	Neonates during heel lance	Pain scores (PIPP) 30 s after heel lance	5 RCTs (267)	MD 3.21 lower (3.94 lower to 2.47 lower)	not serious	Serious ¹	not serious	not serious	none	⊕⊕⊕○ Moderate
	Skin-to-skin care VS no treatment or	Neonates during IM injection	Pain scores (NIPS)- infants in	2 RCTs (380)	RD 0.35 (0.26 to 0.44)	not serious	Serious ¹	not serious	not serious	none	⊕⊕⊕○ Moderate

	swaddled control		no pain during recovery								
Harrison D, 2017	Sweet solutions VS placebo	Neonates during painful procedures	Pain scores	50 RCTs (3341)	SMD 0.90 lower (1.09 lower to 0.70 lower)	not serious	Serious ⁸	not serious	not serious	none	⊕⊕⊕○ Moderate
Stevens B, 2016	Sucrose (20% to 33%) VS water	Neonates during heel lance	Pain scores (PIPP) at 30 s after heel lance	2 RCTs (105)	MD 1.42 lower (2.86 lower to 0.01 higher)	not serious	Serious ¹	not serious	Serious ³	none	⊕⊕○○ Low
		Preterm infants during heel lance	Pain scores (PIPP) at 60 s after heel lance	1 RCT (31)	MD 1.80 lower (3.81 lower to 0.21 higher)	Serious ⁹	not serious	not serious	Serious ⁷	none	⊕⊕○○ Low
		Neonates during heel lance	Pain scores (PIPP) during heel lance	1 RCT (107)	MD 0.00 lower (1.52 lower to 1.52 higher)	not serious	not serious	not serious	Serious ²	none	⊕⊕⊕○ Moderate
		Term infants during heel lance	Pain scores (DAN) at 30 s after heel lance	1 RCT (32)	MD 1.90 lower (8.58 lower to 4.78 higher)	Serious ¹⁰	not serious	not serious	Serious ²	none	⊕⊕○○ Low
		Term infants during heel lance	Pain scores (NIPS) during heel lance	1 RCT (56)	MD 2.00 lower (2.42 lower to 1.58 lower)	not serious	not serious	not serious	Serious ²	none	⊕⊕⊕○ Moderate
	Sucrose (24%) VS breastfeeding	Preterm infants during heel lance	Pain scores (PIPP)	1 RCT (47)	MD 1.75 lower (2.22 lower to 1.28 lower)	Serious ¹⁰	not serious	not serious	Serious ²	none	⊕⊕○○ Low
	Sucrose (24%) + NNS VS water + NNS	Term infants during heel lance	Pain scores (NFCS)	1 RCT (100)	MD 0.60 lower (1.47 lower to 0.47 higher)	Serious ¹⁰	not serious	not serious	Serious ²	none	⊕⊕○○ Low
		Neonates during heel lance	Pain scores (PIPP) at 30 s after heel lance	3 RCTs (278)	MD 1.70 lower (2.13 lower to 1.26 lower)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High
		Neonates during heel lance	Pain scores (PIPP) at 60 s after heel lance	2 RCTs (164)	MD 2.14 lower (3.34 lower to 0.94 lower)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High
Sucrose (24%) +	Neonates during	Pain scores (PIPP)	1 RCT	MD 1.75 lower	Serious ¹⁰	not serious	not serious	Serious ²	none	⊕⊕○○	

	NNS + NIDCAP VS breastfeeding	heel lance		(47)	(4.03 lower to 0.53 higher)						Low
	Sucrose (24%) + NNS + NIDCAP VS breast milk (by syringe)	Neonates during heel lance	Pain scores (PIPP)	1 RCT (47)	MD 0.13 lower (2.41 lower to 2.15 higher)	Serious ¹⁰	not serious	not serious	Serious ²	none	⊕⊕○○ Low
	Sucrose (24%) VS laser acupuncture	Term infants during heel lance	Pain score (NIPS)	1 RCT (42)	MD 0.86 lower (1.43 lower to 0.29 lower)	Serious ¹¹	not serious	not serious	Serious ²	none	⊕⊕○○ Low
	Sucrose (24%) VS sucrose (24%) + NNS	Neonates during heel lance	Pain score (Revised NFCS)	1 RCT (343)	MD 0.43 higher (0.23 higher to 0.63 higher)	Serious ¹⁰	not serious	not serious	not serious	none	⊕⊕⊕○ Moderate
	Sucrose (24%) VS sucrose (24%) + swaddling	Neonates during heel lance	Pain score (Revised NFCS)	1 RCT (343)	MD 0.40 higher (0.19 higher to 0.61 higher)	Serious ¹⁰	not serious	not serious	not serious	none	⊕⊕⊕○ Moderate
	Sucrose (24%) VS sucrose (24%) + NNS + swaddling	Neonates during heel lance	Pain score (Revised NFCS)	1 RCT (337)	MD 0.43 higher (0.23 higher to 0.63 higher)	Serious ¹⁰	not serious	not serious	not serious	none	⊕⊕⊕○ Moderate
	Sucrose (20%) VS facilitated tucking	Neonates during repeated heel lances	Pain score (BPSN) during heel lance	1 RCT (48)	MD 2.27 lower (4.66 lower to 0.12 higher)	not serious	not serious	not serious	Serious ⁷	none	⊕⊕⊕○ Moderate
Pain score (BPSN) during recovery			1 RCT (48)	MD 0.31 lower (1.72 lower to 1.10 higher)	not serious	not serious	not serious	Serious ⁷	none	⊕⊕⊕○ Moderate	
	Sucrose (20%) VS facilitated tucking and sucrose (20%)	Preterm infants during repeated heel lances	Pain score (BPSN) during heel lance	1 RCT (47)	MD 0.05 lower (2.16 lower to 2.06 higher)	not serious	not serious	not serious	Serious ⁷	none	⊕⊕⊕○ Moderate
Pain score (BPSN) during recovery			1 RCT (47)	MD 0.64 higher (0.73 lower to 2.01 higher)	not serious	not serious	not serious	Serious ⁷	none	⊕⊕⊕○ Moderate	
	Sucrose (12%) VS water	Neonates during venipuncture	Pain score (NIPS)	1 RCT (111)	MD 0.90 lower (0.81 lower to 0.01 higher)	Serious ¹²	not serious	not serious	not serious	none	⊕⊕⊕○ Moderate

	Sucrose (24% to 30%) VS sterile water or no treatment	Neonates during venipuncture	Pain score (PIPP)	2 RCTs (213)	MD 2.79 lower (3.76 lower to 1.83 lower)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High
	Sucrose (24% to 30%) VS sucrose (24% to 30%) + EMLA/liposomal lidocaine cream	Preterm infants during venipuncture	Pain score (PIPP)	1 RCT (76)	MD 1.30 higher (0.12 lower to 2.72 higher)	not serious	not serious	not serious	Serious ^{2,3}	none	⊕⊕⊕○ Moderate
			Pain score (PIPP) during post-injection period	1 RCT (76)	MD 0.60 higher (0.73 lower to 1.93 higher)	not serious	not serious	not serious	Serious ^{2,3}	none	⊕⊕⊕○ Moderate
			Pain score (DAN) during venipuncture	1 RCT (76)	MD 1.30 higher (0.26 higher to 2.34 higher)	not serious	not serious	not serious	Serious ^{2,3}	none	⊕⊕⊕○ Moderate
			Pain score (DAN) during post-injection period	1 RCT (76)	MD 1.40 higher (0.03 higher to 2.77 higher)	not serious	not serious	not serious	Serious ^{2,3}	none	⊕⊕⊕○ Moderate
	Sucrose (20% to 25%) VS water or no intervention	Term infants during intramuscular injection	Pain score (NIPS)	1 RCT (60)	MD 2.30 lower (2.93 lower to 1.67 lower)	Serious ¹³	not serious	not serious	Serious ^{2,3}	none	⊕⊕○○ Low
			Pain score (PIPP)	2 RCTs (232)	MD 1.05 lower (1.98 lower to 0.12 lower)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High
	Sucrose (25%) VS glucose (25%)	Term infants during intramuscular injection	Pain score (NIPS)	1 RCT (60)	MD 0.10 lower (0.89 lower to 0.69 higher)	Serious ¹³	not serious	not serious	Serious ^{2,3}	none	⊕⊕○○ Low
	Sucrose (24%) VS sterile water	Neonates during bladder catheterization	Pain score (DAN)	1 RCT (33)	MD 2.43 lower (4.50 lower to 0.36 lower)	not serious	not serious	not serious	Serious ^{2,3}	none	⊕⊕⊕○ Moderate
	Sucrose (24%) VS distilled water	Preterm infants during orogastric	Pain score (PIPP) intra procedure	1 RCT (105)	MD 0.30 lower (1.33 lower to 0.73 higher)	not serious	not serious	not serious	Serious ³	none	⊕⊕⊕○ Moderate

		tube insertion			higher)						
			Pain score (PIPP) 30 s post procedure	1 RCT (105)	MD 1.30 lower (2.31 lower to 0.29 lower)	not serious	not serious	not serious	Serious ²	none	⊕⊕⊕○ Moderate
			Pain score (PIPP) 1 min post procedure	1 RCT (105)	MD 0.50 lower (1.40 lower to 0.40 higher)	not serious	not serious	not serious	Serious ³	none	⊕⊕⊕○ Moderate
	Sucrose (24%) by syringe + swaddled + pacifier VS water by syringe + swaddled + pacifier	Neonates during ROP examination	Pain score (PIPP)	1 RCT (32)	MD 0.00 lower (2.08 lower to 2.08 higher)	Serious ¹⁴	not serious	not serious	Serious ^{2,3}	none	⊕⊕○○ Low
	Sucrose (24% to 33%) (sucrose or sucrose + NNS) VS water (or water + NNS)	Neonates during ROP examination	Pain score (PIPP)	3 RCTs (134)	MD 2.15 lower (2.86 lower to 1.43 lower)	Serious ¹⁴	not serious	not serious	not serious	none	⊕⊕⊕○ Moderate
	Sucrose (24%) compared with EMLA	Neonates during circumcision	Pain score (N-PASS) during circumcision	1 RCT (60)	MD 2.40 higher (1.85 higher to 2.95 higher)	Serious ¹³	not serious	not serious	Serious ^{2,3}	none	⊕⊕○○ Low
			Pain score (N-PASS) after 5 min	1 RCT (60)	MD 1.40 higher (0.74 higher to 2.06 higher)	Serious ¹³	not serious	not serious	Serious ^{2,3}	none	⊕⊕○○ Low
	Sucrose (24%) VS EMLA + sucrose (24%)	Neonates during circumcision	Pain score (N-PASS) during circumcision	1 RCT (60)	MD 3.00 higher (2.42 higher to 3.58 higher)	Serious ¹³	not serious	not serious	Serious ^{2,3}	none	⊕⊕○○ Low
			Pain score (N-PASS) after 5 min	1 RCT (60)	MD 1.20 higher (0.49 higher to 1.91 higher)	Serious ¹³	not serious	not serious	Serious ^{2,3}	none	⊕⊕○○ Low
	Sucrose (24%) VS water	Neonates during echocardiography	Pain score (PIPP)	1 RCT (104)	MD 2.15 lower (3.30 lower to 1.00 lower)	Serious ⁹	not serious	not serious	Serious ^{2,3}	none	⊕⊕○○ Low

	Sucrose (24%) VS water	Neonates during potentially painful procedures for a period of seven days	'Motor development and vigor' (MDV) domain of NAPI tool	1 RCT (93)	MD 1.83 lower (8.59 lower to 4.93 higher)	not serious	not serious	not serious	Serious ³	none	⊕⊕⊕○ Moderate
			'Alertness and orientation' (AO) domain of NAPI	1 RCT (93)	MD 3.09 higher (6.49 lower to 12.67 higher)	not serious	not serious	not serious	Serious ³	none	⊕⊕⊕○ Moderate
Boundy EO, 2016	Kangaroo mother care VS controls	Neonates during painful procedures	Pain score (PIPP)	5 RCTs (344)	MD 0.98 lower (1.83 lower to 0.13 lower)	not serious	Serious ⁸	not serious	Serious ²	none	⊕⊕○○ Low
			Pain score (NIPS)	2 RCTs (694)	MD 1.21 lower (2.88 lower to 0.45 lower)	not serious	Serious ⁸	not serious	not serious	none	⊕⊕⊕○ Moderate
			Pain score (NFCS)	2 RCTs (699)	MD 1.40 lower (3.08 lower to 0.28 higher)	not serious	Serious ⁸	not serious	Serious ³	none	⊕⊕○○ Low
			Pain score	8 RCTs (1097)	SMD 0.75 lower (1.28 lower to 0.22 lower)	not serious	Serious ⁸	not serious	not serious	none	⊕⊕⊕○ Moderate

* FT: Facilitated tucking; NNS: nonnutritive sucking; TA: Topical anesthetic; NIDCAP: Newborn Individualized Developmental Care and Assessment Program;

** NGT: nasogastric tube; OGT: orogastric tube

*** Pain reactivity: pain scores at the beginning of the procedure; Pain reactivity: pain scores immediately after the procedure; PIPP: Premature Infant Pain Profile; DAN: Douleur Aiguë du Nouveau-né Scale; NIPS: Neonatal Infant Pain Scale; NFCS: Neonatal Facial Coding System; BPSN: Bernese Pain Scale for Neonates; N-PASS: Neonatal Pain Agitation and Sedation Scale

**** CI: confidence interval; MD: mean difference; SMD: standardized mean difference; SD: standard deviation; RR: risk ratio; RD: Risk Difference

1. $I^2 > 50\%$; 2. small sample size; 3. a wide 95% CI; 4. the majority of risk of bias judgements was rated as "unclear" or "high"; 5. the total number of participants is less than the threshold for continuous outcomes (<400); 6. the total number of participants is less than the threshold for imprecision (<150); 7. only one study with small size; 8. $I^2 > 75\%$; 9. There were concerns about allocation concealment and performance bias in this single study; 10. concerns about blinding of performance and detection bias; 11. There was high risk of selection bias and performance bias in this study; 12. It is uncertain if outcome assessors were blinded; 13. concerns about bias for random sequence generation, allocation concealment and lack of blinding for performance and detection; 14. the authors did not describe how the random sequence was generated, nor did they describe how allocation concealment was achieved; 15. There were some concerns about risk of bias in these studies for random sequence generation and allocation concealment.

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