BMJ Open Ophthalmology

Non-pharmacological pain relief interventions in preterm neonates undergoing screening for retinopathy of prematurity: a systematic review

Iretiola Bamikeolu Fajolu ,[1] Iyabode Olabisi Florence Dedeke,[2] Beatrice Nkolika Ezenwa,[1] Veronica Chinyere Ezeaka[1]

To cite: Fajolu IB, Dedeke IOF, Ezenwa BN, *et al*. Non-pharmacological pain relief interventions in preterm neonates undergoing screening for retinopathy of prematurity: a systematic review. *BMJ Open Ophthalmology* 2023;**8**:e001271. doi:10.1136/bmjophth-2023-001271

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjophth-2023-001271).

Received 23 February 2023
Accepted 17 November 2023

[1]Paediatrics, University of Lagos College of Medicine, Idi-Araba, Lagos, Nigeria
[2]Paediatrics, Federal Medical Centre Abeokuta, Abeokuta, Ogun State, Nigeria

Correspondence to
Dr Iretiola Bamikeolu Fajolu; ifajolu@unilag.edu.ng

ABSTRACT

Objective The objective of this review was to determine the efficacy of non-pharmacological interventions for pain management during retinopathy of prematurity (ROP) screening.

Methods and analysis Electronic search of Ovid MEDLINE, PubMed, EMBASE, Cochrane Database of Systematic Reviews, Cumulative Index to Nursing and Allied Health Literature, Google Scholar and ClinicalTrials.gov (USA) was conducted. Search terms from the research question and inclusion criteria were used to select randomised control trials (RCT) published from January 2000 to May 2023. Relevant data were extracted, and risk of bias was assessed using the Cochrane Risk of Bias tool V.2. Critical appraisal and grading of the quality of evidence were done using the Critical Appraisal Skills Programme tool for RCTs and the Grading of Recommendations Assessment, Development and Evaluation, respectively.

Results Twenty-one RCTs were included; 14 used sweet taste, while 7 used modified developmental care, touch or positioning, multisensory stimulation, non-nutritive sucking or music. Six studies on sweet taste and all seven latter studies showed a difference in the pain scores in favour of the interventions. The quality of evidence was however judged low and moderate due to some concerns in the randomisation process, measurement of outcome assessment and selection of reported results domains.

Conclusion The use of gentle touch, nesting, positioning, music, multisensory stimulation and developmental care in reducing pain during ROP screening is promising, however, larger studies designed to eliminate the identified concerns are needed. More evidence is also needed before sweet taste interventions can be recommended in routine practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Retinopathy of prematurity screening is a painful procedure and topical anaesthesia which is recommended for pain management does not completely alleviate pain during the procedure, thereby exposing the neonates to the adverse short-term and long-term effects of pain.

WHAT THIS STUDY ADDS

⇒ Evidence from this review shows that non-pharmacological interventions such as modified developmental care, touch, positioning with or without non-nutritive sucking and music can help alleviate pain during retinopathy of prematurity (ROP) screening, although the quality of evidence was moderate-low. However, effectiveness of sweet taste interventions in reducing pain reduction during ROP screening appears to vary across studies and lacks consistency.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study shows that non-pharmacological interventions such as modified developmental care, music, touch or positioning alleviate pain during ROP screening and may be added as adjunct therapy to topical analgesia for pain management.
⇒ More robust studies with protocols reflecting the blinding of assessors and inclusion of precision estimates on these non-pharmacological interventions including sweet taste are needed to provide high-quality evidence to justify their inclusion in routine practice and policy.

INTRODUCTION

Retinopathy of prematurity (ROP) is a potentially blinding condition that affects preterm neonates. It may regress spontaneously or progress to retinal detachment and visual loss if not treated promptly.[1] Screening for ROP is recommended for preterm infants for early detection, monitoring and prompt treatment. However, the specific gestational ages and weights for screening may vary slightly depending on the country's guideline.[2–4]

Until recently, most extremely and early preterm neonates in low and middle-income countries did not survive the neonatal period, however, with improvement in neonatal care, more of these infants are surviving.[5] This, coupled with the high number of preterm births in Asia and sub-Saharan Africa,[6] has

increased the population exposed to risk factors such as supplemental oxygen without adequate monitoring, thus increasing those at risk of ROP.[7] Ophthalmologists and neonatologists caring for these infants are therefore encouraged to optimise care to reduce the risk factors, screen for ROP and treat when needed to avoid visual loss.[8]

The ROP screening procedure involves pupillary dilatation, inserting of a speculum to keep the eyes open and examining of the retina using indirect ophthalmoscopy. These are all distressing and painful to the neonate.[9 10] Follow-up eye examinations may be required depending on the retinal findings,[2] further exposing the preterm neonate to repeated pain during the eye examinations. The UK screening of retinopathy of prematurity guideline recommends topical anaesthesia and 'comfort care' for pain during ROP screening.[11] The American Academy of Pediatrics' policy statement on ROP screening also recommends topical anaesthesia and considers non-pharmacological interventions.[12]

Preterm infants with low birth weight and low gestational age, have the highest risk of ROP,[13] and are also prone to complications resulting in poor outcomes.[14–16] These neonates are usually sick and they undergo many painful procedures as part of their care during their neonatal intensive care unit (NICU) stay.[17] Repeated exposure to procedural pain in preterm neonates has been associated with short-term and long-term poor outcomes such as poor postnatal growth, poor cognitive and motor development and cortical changes.[18–21] It is therefore morally and ethically necessary to adequately manage pain in these neonates in keeping with the ethical principle of doing no harm (non-maleficence) in health research.[22]

A Cochrane review by Dempsey *et al*, concluded that topical anaesthesia, which is recommended for pain management during ROP screening, does not completely alleviate the pain.[23] Hence, it is important to study other interventions that may be beneficial and safe.

Pharmacological agents such as morphine have been associated with side effects such as hypotension and apnoea.[19 24] Many non-pharmacological interventions including oral sucrose, oral dextrose, non-nutritive sucking (NNS), swaddling and skin-to-skin position have been shown to be beneficial in pain management in neonates.[25–27] Non-pharmacological methods of pain relief are relatively easy to use, apparently safe, feasible and easy to learn and will be easy for universal implementation.[28] However, some of these methods such as skin-to-skin care may not be suitable for procedures requiring a particular position like ROP screening or in very sick neonates. On the other hand, the reverse kangaroo mother care position was reported to reduce stress in babies undergoing ROP in a pilot study.[29] Procedures such as acupuncture may not be readily acceptable due to concerns about infection, the inability of the infant to cooperate and the skill required for the procedure.[30]

It is important that the available evidence for or against these non-pharmacological interventions for pain relief during ROP screening should be critically appraised before the decision to apply these interventions to routine practice is made. Therefore, the objective of this systematic review was to determine the efficacy of non-pharmacological interventions for pain management during ROP screening.

MATERIALS AND METHODS

Study design

A literature search was conducted using a systematic review approach which ranks high on the hierarchy of evidence table,[31 32] to appraise and summarise available evidence from well-designed randomised studies on the efficacy of non-pharmacological pain relief interventions for ROP screening.

Research question

To keep the review focused, the main concepts of this research were identified to formulate a research question using the PICO (Population; Intervention; Comparison and Outcome) framework.[33] The research question was 'In preterm neonates undergoing ROP screening (Population), are non-pharmacological pain management interventions used alone or in combination with topical anaesthesia (Intervention) compared with placebo or topical analgesics (Comparison) efficacious for pain relief assessed by preterm pain scores (Outcome)?'.

Search strategy

A systematic electronic search of large databases Ovid MEDLINE, PubMed, EMBASE, Cochrane Database of systematic reviews, Cumulative Index to Nursing and Allied Health Literature, Google Scholar, Web of Science, and ClinicalTrials.gov (USA) (for completed clinical trials) was conducted to identify available studies on the topic. An initial quick search of the topic revealed two meta-analyses published in 2018,[34] and 2022,[35] respectively. The search for the studies included in the 2018 study ended in 2017, while the 2022 meta-analysis included only six studies. The search for this review was done from January 2000 to May 2023 to ensure all relevant available studies are included for a robust review.

The search terms derived from the research question, keywords (synonyms, abbreviations and truncations) used for the search were preterm (premature; prematurity); retinopathy of prematurity (ROP); screening; non-pharmacologic (breastmilk, breast milk, sucrose, glucose, 'non-nutritive sucking', swaddling, nesting, 'facilitated tucking', touch, 'developmental care'); 'pain management' ('pain relief', 'pain treatment', 'pain scores', reduc*; prevent*).

The search terms for the comparison, 'placebo OR topical anaesthetics' were excluded from the search.

Inclusion and exclusion criteria

The inclusion criteria were randomised controlled studies written in English and studies that used non-pharmacological interventions to treat or prevent pain during ROP screening. For objectivity of pain assessment and ease of comparison, only studies with objective outcome measures of pain scores using the premature infant pain profile (PIPP) or PIPP-revised which are the most frequently used and validated pain scales in preterm infants, were included.[36]

Exclusion criteria were articles on pharmacological interventions, pain management during ROP treatment and on interventions with the possibility of non-acceptance such as acupuncture and those where performing the eye examination may be difficult such as during breast feeding and skin-to-skin position. These may make the result not to be easily generalisable. Other exclusion criteria were non-English articles, non-peer-reviewed articles, abstracts and conference proceedings.

Study selection and analysis

The initial search was done by IBF and IOFD, BNE also performed an independent search for additional papers. The title/abstract screening, full-text screening and data abstraction were done using the Covidence tool independently by IBF and IOFD and consensus was agreed on by both authors. In case of disagreement, VCE acted as a tiebreaker. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram was used to describe the study selection process.[37] To determine how much value to place on the studies in clinical practice, the included randomised control trials (RCTs) were assessed for risk of bias using the Cochrane Risk of Bias tool V.2 (ROB 2).[38–41] The risk of bias was judged as 'high', 'low' or 'some concerns' for each of five domains (Randomisation process, Deviations from the intended interventions, Missing outcome data, Measurement of the outcome and Selection of the reported result). The ROB 2 for crossover studies had an additional domain (bias arising from period and carryover effects).[41] The data extracted from the articles were critically appraised using the Critical Appraisal Skills Programme (CASP) tool for RCTs to determine the reliability of the results of included studies.[42 43]

Trial registry databases (ClinicalTrials.gov, International Standard Randomised Controlled Trial Number and WHO International Clinical Trials Registry Platform) were also searched for registration of the protocols for these RCTs to improve the critical analysis and risk of bias assessment process.[44] Other aspects of the studies such as ethical consideration and reporting format were also appraised. The Grading of Recommendations Assessment, Development and Evaluation approach was also used to assess the overall quality of the evidence for the primary outcome.[45] The review was registered on PROSPERO (ID - CRD42023432500)

RESULTS

The search of databases identified 2152 references, after removing 693 duplicates and screening the abstracts for eligibility, 23 full articles were excluded for various reasons and 21 articles were finally included in the review as shown in figure 1. The details of the excluded studies are shown in online supplemental appendix A.

Study design and data extraction

All the included studies were prospective RCTs,[46–66] of these, two were crossover RCTs,[48 58] while the others were parallel-group RCTs. All the studies were done in Asia except three in North America,[46–48] and two in Europe.[49 50] The included studies were divided into two groups, A and B. Group A included the 14 studies utilising sweet taste (dextrose, sucrose, glucose and breast milk),[46–57 61 63] while the remaining 7 using touch, position, multisensory stimulation, environmental modification, music and NNS made up Group B.[58–60 62 64–66] A study which compared sucrose with pacifier was categorised under Group A,[49] while another compared multisensory stimulation with breast milk and was categorised in Group B.[64] The summary of the included studies in the two groups is shown in table 1.

Sample size and participants

The sample size was calculated in 12 studies to achieve the conventional alpha of 0.05 and power of 80–90%.[46 48–50 52 53 56–58 61 62 64] One study stated a power of 90% without the alpha level,[54] while five other studies used a power of 95 or 97%.[51 55 59 65 66] There was no information on the sample size power calculation in three studies,[47 60 63] however, Liao *et al*,[60] acknowledged the small sample size as a limitation. Eight of the studies enrolled infants who were undergoing their first ROP examination,[49 51 56 57 60 63–65] while others provided no information on this. Exclusion criteria varied among the studies, although the use of sedatives and analgesic drugs were common to most of the studies. The study by Liao *et al* did not state any exclusion criteria.[60]

A total of 1966 preterm infants were included in all the studies, 11 studies had sample size of 60 or more with a range of 60–120,[51 54–56 59 60 62–66] while the remaining had less than 60 with range of 14–45.[46–50 52 53 57 58 61]

Ethical considerations

All the included studies obtained ethical approval from their review boards, and informed consent from the parents of the infants. In addition to the study or control interventions, all the studies used topical anaesthesia, which is recommended for pain relief during ROP screening,[11 12] except Olsson and Eriksson.[50] One study gave no form of analgesia to the

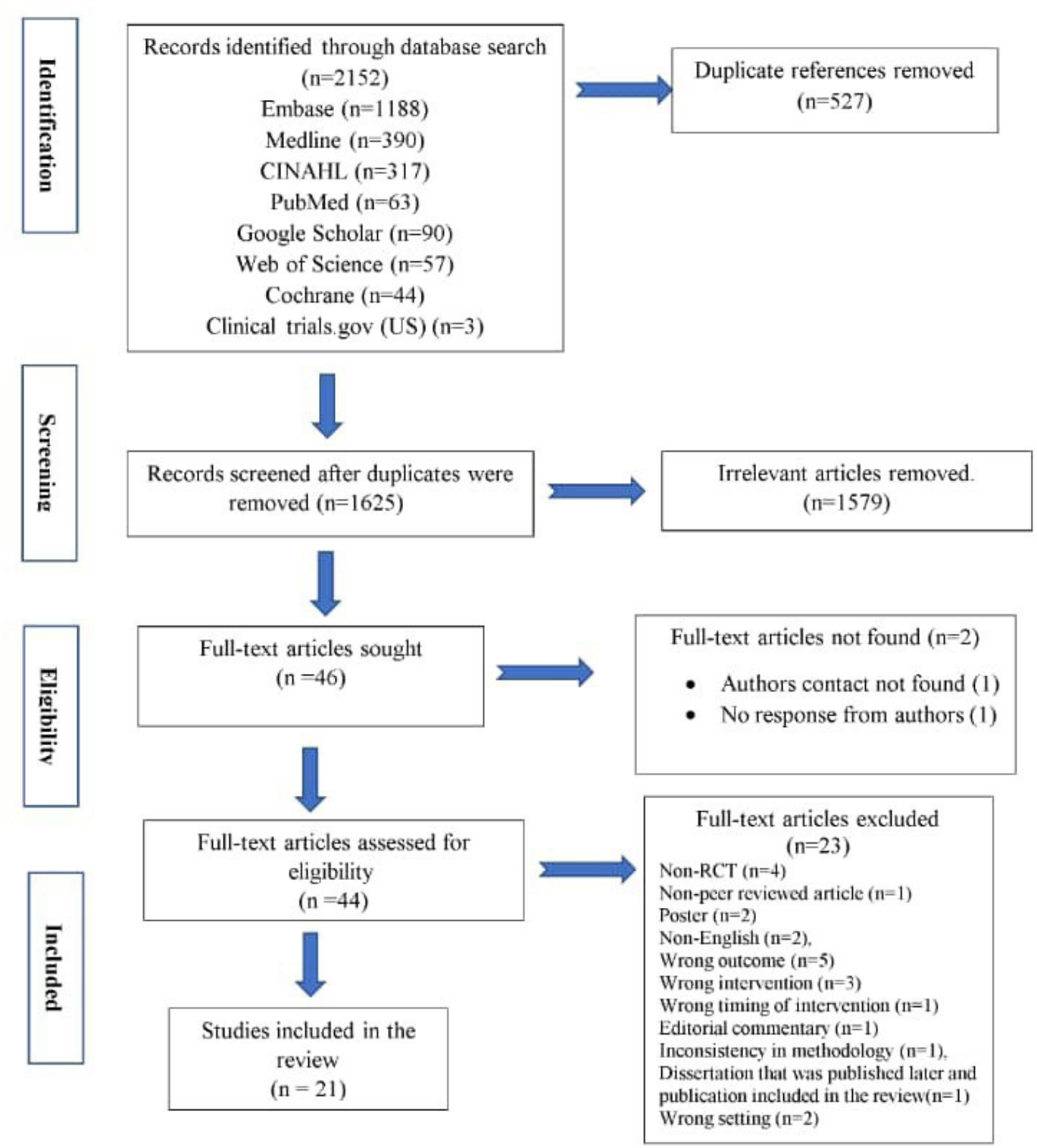

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the search. CINAHL, Cumulative Index to Nursing and Allied Health Literature, RCT, randomised control trial.

babies when they served as their own control during the second eye examination.[53]

Side effects

Only five studies monitored for adverse effects,[48 51–53 56] and all reported no adverse effects. The other studies did not report on adverse effects of the intervention used.

Statistical analysis

Six group A studies compared two non-pharmacological interventions; three compared sucrose with breast milk,[54 55 57] one compared dextrose and breast milk,[61] another one compared a single high dose with repeated low dose of 24% sucrose,[56] while the last compared pacifier and sucrose.[49] All the six studies had a control arm of distilled

Table 1 Summary of included studies

Authors/year/origin	Study design/randomisation	Sample size	Intervention	Comparison	Result of primary outcome measure
Studies on sweet taste					
Mitchell, *et al*/2004/ Level III NICU/ Canada[46]	Double-blind RCT. Randomised by using sealed envelopes.	30	Three doses of 0.1 mL 24% sucrose at 2 min interval+TA+swaddling.	Three doses of sterile water, at 2 min interval+TA+swaddling.	The mean PIPP scores was significantly lower for the sterile water compared with the sucrose group (11.4 vs 8.8, respectively, p=0.0077).
Grabska *et al*/2005/ Level III NICU/ USA[47]	Prospective RCT, blinded and placebo controlled.	32	24% sucrose 0.5–2 mL. TA+swaddling.	Sterile water+TA+swaddling.	No difference in PIPP scores between groups during examination.
Gal *et al*/2005/ NICU/ USA.[48]	Double-blind crossover RCT. Randomised by a group of 6, dice roll.	23	2 mL of 24% sucrose+TA+swaddling.	2 mL sterile water+TA+swaddling.	Lower pain scores at speculum insertion with sucrose compared with placebo (p=0.01).
Boyle *et al*/2006/UK[49]	A double-blind, 3-group RCT, 2 NNU. Randomised by sealed opaque envelopes.	40	1. Sucrose+TA. 2. Water+pacifier+TA. 3. Sucrose+pacifier+TA.	Water+TA.	The PIPP scores for the pacifier groups were lower than those without pacifiers (p=0.003). There was no difference between groups receiving sucrose and water (p=0.321). 95% CI, −4.23 to −6.96.
Olsson and Eriksson/2011/ Sweden[50]	Double-blind RCT. Randomised by sealed envelopes in groups of 4.	30	1 mL of 30% glucose.	1 mL sterile water.	There was no difference in PIPP scores between both groups.
Dilli *et al*/2014/ Turkey[51]	Double-blind RCT/ randomisation method not stated.	64	0.5 mL/kg 24% sucrose+TA+pacifier.	0.5 mL/kg distilled water+TA+pacifier.	The mean PIPP scores for intervention compared with the control group were significantly lower during examination (13.7±2.1 vs . 16.4±1.8, p=0.001).
Rosali *et al*/2015/ India[52]	Double-blind RCT. Randomisation was by computer generated random numbers in sealed opaque envelopes.	40	2 mL of EBM+nesting+swaddling+TA.	Nesting+swaddling+TA.	The mean PIPP scores for the EBM compared with the control groups were significantly lower during the procedure (12.7+1.69 vs 15.56+1.78, p<0.05). This effect persisted at 1and 5 min after the procedure.
Nesargi *et al* /2015/NICU/India[53]	A double-blind prospective RCT. Randomisation by random number table.	20	At first examination, group 1 received 2 mL of 25% dextrose orally. Group 2 received TA.	Infants served as their own control at second examination and received no form of analgesia.	There was no difference in mean PIPP scores between the two groups (p=0.165) and between the first and second examinations for the dextrose and topical anaesthesia groups (p=0.259, p=0.428), respectively.

Continued

Table 1 Continued

Authors/year/origin	Study design/randomisation	Sample size	Intervention	Comparison	Result of primary outcome measure
Dolgun and Bozlak/2017/Level III NICU/Turkey[54]	A double-blind prospective RCT. Randomisation by computer generated numbers in sealed envelopes.	87	1. Swaddling+24% oral sucrose (0.2 mL) +TA. 2. Swaddling+0.2 mL breast milk+TA.	Swaddling+0.2 mL oral distilled water+TA.	There was no difference in mean PIPP score across the sucrose, BM and DW groups, respectively, during (9.10+1.82 vs 8.45+1.38 vs 8.38+1.24, p=0.134) or after the first eye examination (4.59+1.64 vs 4.86+1.27 vs 5.28 2.0, p=0.288),
Taplak and Erdem/2017/Turkey[55]	Double blind RCT, how randomisation was done was not stated.	60.	1. 1 mL BM+TA, 2. 1 mL 33% sucrose+TA,	1 mL distilled water+TA,	There was no difference in PIPP scores for BM and sucrose groups during examination (p>0.05). The PIPP scores were significantly higher for the control compared with the BM and sucrose groups after examination (p<0.001).
Benzer *et al*/ 2017/ NICU/Turkey[56]	A double-blind, placebo controlled, prospective RCT. Randomisation by computer numbers in sealed envelopes.	64	1. 24% sucrose (0.6 mL) before examination+TA. 2. 24% sucrose, 0.2 mL before and repeated at 2 min intervals during and after examination+TA.	Distilled water (0.2 mL) + TA.	Pain score 30 s after speculum insertion into the first eye were higher in the control compared with the repeated low and single high dose dextrose, respectively (9.0 (9) vs 7.5 (11) vs 8.0 (12) p=0.015).
Jang *et al*/2019/ Level III NICU/South Korea[57]	A double-blind, RCT. Randomised by random digit table numbers kept in sealed envelopes.	45	1. Pacifier dipped in breast milk+TA. 2. Pacifier dipped in 24% sucrose+TA.	Pacifier dipped in distilled water+TA.	There was no significant difference in the generalised equation estimates when distilled water was compared with human milk and sucrose were −0.44, p=0.517 and 0.98, p=0.132, respectively.
Nayak *et al*/2020/ India[61]	A double-blind RCT. Randomised by computer generated numbers in sealed envelopes.	45	1. Breast milk+TA+NNS. 2. 10% dextrose water+TA+NNS.	Sterile water+NNS+TA.	The mean pain scores were 11.8±2.8 vs 9.8±3.3 vs 10.2±2.9, p=0.18 for breast milk, 10% dextrose and sterile water, respectively.
Sagheb *et al*/2020/ NICU/Iran[63]	Three-group Double blind. prospective RCT. Randomisation method not stated.	60	1. 1 mL oral 25% glucose+TA. 2. TA.	1 mL distilled water+TA.	The mean PIPP score was significantly lower during the procedure for the sucrose (13.8±1.39) compared with the TA and distilled water groups (15.95±1.27 and 15.10±1.19, p=0.001). The positive effects persisted for 5 min after the procedure (7.6±1.26), (p=0.034).

Continued

Table 1 Continued

Authors/year/origin	Study design/randomisation	Sample size	Intervention	Comparison	Result of primary outcome measure
Studies on position, touch non-nutritive-sucking, music and multisensory interventions.					
Chuang *et al*/2018/ NICU/Taiwan[58]	A crossover prospective RCT. Randomisation by sealed envelopes in blocks of two.	14	Modified developmental care+TA.	Standard care+TA.	There were differences in the care type comparison of the pain scores, p=0.003 and p=0.03 at speculum insertion and 1 min after examination, respectively.
Metres *et al*/2019/ NICU/Turkey[59]	A prospective RCT with no blinding or allocation concealment. Randomisation by computer software.	70	ROP position+pacifier+TA.	Pacifier+TA.	Mean pain scores at speculum insertion into first eye (6.51+1.84 vs 10.69+2.99, p=0.001) and at removal from the second eye (5.34+1.85 vs 8.97±2.83, p=0.001) were lower in intervention compared with control arm.
Liao *et al*/2019/China[60]	A prospective RCT with no blinding. Computer-based randomisation using sealed opaque envelopes.	120	TA+NNS+nesting.	Routine nursing (not described in the paper) + TA.	Pain scores were lower in the experimental compared with control group during the examination of the first eye (12.9+2.0 vs 16.5+2.0, p<0.001).
Sun *et al*/2020/NICU/ China[62]	A prospective RCT with no blinding. Randomisation by table of random number.	82	Gentle human touch protocol+swaddling+TA.	Swaddling+TA.	The PIPP score during the examination was higher for controls compared with intervention group (14.82±3.22 vs. 9.29±2.89, respectively; p<0.05).
Dehghani *et al*/2021/ NICU/Iran[64]	A three-limb RCT. Randomised by sealed envelopes of 3.	90,	1. Multisensory stimulation. 2. Mother's breast milk.	TA+standard care (NIDCAP).	Both intervention groups had significantly lower pain scores at than control, p=<0.05.
Ozkan *et al*/2022/ Turkey[65]	A prospective RCT with no blinding. Randomised by randomisation programme.	60	Non-nutritive sucking with gloved finger+TA.	TA.	The PIPP score were significantly lower during (14.16 (0.91) vs 15.43 (0.97), p=0.000) and after (5.93 (0.90) vs 6.73 (0.63)), p=0.000 examinations for the NNS group compared with control group.

Continued

Table 1 Continued

Authors/year/origin	Study design/randomisation	Sample size	Intervention	Comparison	Result of primary outcome measure
Dur *et al*/2023/NICU/ Turkey[66]	A prospective RCT. Randomised by web-based programme.	90	1. White noise/ swaddling+TA. 2. Classical music+swaddling+TA.	Swaddling+TA.	The mean PIPP scores in the control group during and after (12.27±1.70; 9.70±3.02) the examination) were significantly higher than those for white noise (7.00±1.68; 3.60±2.11) and classical music, (11.2±2.28 and 3.77±1.83) (p<0.001)

BM, breast milk; DW, distilled water; EBM, expressed breast milk; NICU, neonatal intensive care unit; NIDCAP, Newborn Individualized Care Assessment Program; NNS, non-nutritive sucking; PIPP, premature infant pain profile; RCT, randomised control trial; TA, topical anaesthesia.

water or sterile water. Only four of these studies analysed the data comparing each arm with the control group,[49 55–57] while the remaining two did a global analysis of all the three arms together with no multiplicity adjustment.[54 61] Two of the group B studies also had three arms comparing two non-pharmacological interventions with a control arm, both compared the two interventions with each other as well as with the control arm separately.[64 66] All the included studies reported only the p values except Boyle *et al*[49] and Chuang *et al*,[58] that reported 95% CI. This limits the precision and strength of evidence that can be attached to the results of studies without precision estimates.

Outcome

All the studies included in this review used the premature infant pain profile or the revised premature infant pain profile pain scoring tools as the measure of primary outcome, both tools have been validated in preterm infants.[67–69] The PIPP demonstrated good construct validity and excellent inter-rater and intra-rater reliability coefficients of 0.93–0.96 and 0.94–0.98, respectively.[69] This is similar to the >0.09 intraclass correlation coefficient for the level of agreement,[59] and 0.90–1.00 inter-observer consistency in this review.[62] Another primary outcome assessed was behavioural score (colour, respiration and alertness).[58]

Benzer *et al* studied two different doses of sucrose, 0.2 mL repeated three times and a single dose of 0.6 mL with a single dose of distilled water.[56] Pain scores were recorded at baseline, 30 s, 60 s and 2 min after insertion of the speculum into each eye and at 4 min after insertion of speculum into the eye that was examined last. They reported lower median pain scores in both intervention groups compared with control (p=0.015), 30 min after examination of the first eye. The crying duration and severity were also reduced in the intervention groups compared with the control (p=0.028 and p=0.009 respectively) also after the first eye examination. All the other measurements were similar between the groups (p>0.05).

All group B studies, reported lower mean pain scores in the experimental groups compared with the control groups and these differences were statistically significant.[58–60 62 64–66] The outcome assessors were not blinded in five of the studies,[58–60 62 65] however, there were at least two assessors to reduce bias in outcome measurements.

The secondary outcomes assessed varied between the studies. The crying time was shorter in the intervention compared with the control groups (p=0.028, 0.01 and 0.001),[56 59 60] and the crying severity was also lower in the sucrose group compared with placebo (p=0.009).[56] The mean recovery time was shorter for the developmental compared with the standard care group (8.6±11.5 min vs 25.5±20.8 min, p=0.003).[58] The reduction in regional cerebral oxygen saturation measured with near-infrared spectrophotometer from baseline for controls (−9.94+8.98) was greater than (−4.61±5.23) for the experimental group.[62]

Critical appraisal

The ROB 2,[40] was used to assess the risk of bias for the parallel-group RCTs,[46 47 49–57 59–66] while the ROB 2 for cross-over studies,[41] was used for the two crossover studies.[48 58] Three group A studies,[51 53 63] had some concerns with the randomisation process and or allocation concealment, while all the others had a low risk of bias. There was also a low risk of bias in the deviation from intended interventions, missing outcome data and selection of reported results domains in the parallel-group RCTs in group B.[59 60 62 64–66] The four parallel group RCTs in group B that used interventions in which blinding of outcome assessors was difficult, had 'some concerns' in the measurement of outcome domain.[59 60 62 65] However, there were at least two outcome assessors with good interobserver reliability. The group A crossover RCT also had some concerns about the selection of reported results.[48] The group B crossover study, had some concerns regarding risk of bias in the randomisation process, measurement of outcome and selection of reported results domain.[58] The information provided was not detailed enough to show whether the results of both periods or only those of the first period were analysed.

Only four of the studies had their protocols registered in the trial registries that were searched, though the details were scanty.[56 62 64 65] This was considered when assessing the risk of selective reporting to answer the question on whether the statistical analysis methods used were decided before the unblinded outcome results (where applicable), were made available. This domain was however judged as low-risk for all the parallel-group RCTs as the answers to the other questions did not suggest a problem with reporting bias. The result for the risk of bias for the parallel-group RCTs is shown in figure 2.

The included studies were further critically appraised for quality using the CASP checklist,[42] as summarised in table 2.

The quality of evidence from an RCT in the hierarchy of evidence is high,[31] however, some issues with risk of bias/limitations, inconsistency, indirectness, imprecision or publication bias may require that the level of evidence of the RCT be downgraded.[70] The quality for two of the group A studies was downgraded from high to low,[51 63] while the remaining were downgraded from high to moderate. All the parallel group RCTs where there was no blinding of outcome assessors except the study by Chuang *et al*,[58] were downgraded from high to low on account of concerns with risk of bias and imprecision (table 3).

Discussion

The objective of this review paper was to identify and judge the quality of available evidence to support the routine use of non-pharmacological interventions for pain relief during ROP screening. The evidence identified from this review shows that non-pharmacological interventions using position and environmental modification, multisensory stimulation, NNS and music are beneficial in reducing pain in neonates undergoing ROP screening. All the group B studies showed significant differences in pain scores in favour of the interventions,[58–60 62 64–66] however, only one reported the effect estimates which provide information on the strength and direction of the effect.[58] Therefore, the strength of the evidence could not be weighted, in addition, a forest plot could not be done to summarise and compare the weight of the results obtained from these studies.

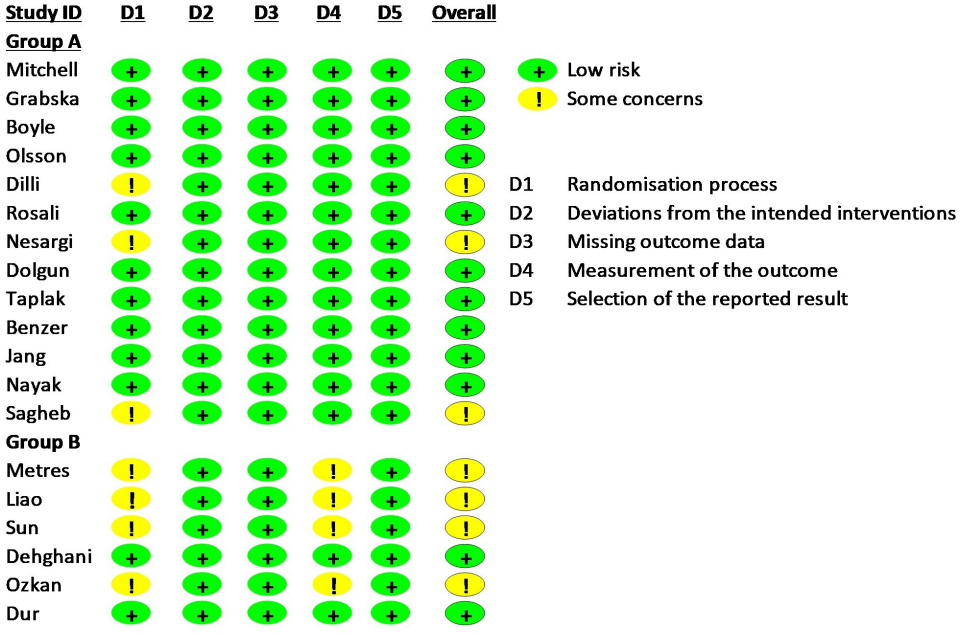

Figure 2 Risk of bias judgement for included parallel-group randomised control trials using Cochrane Risk of Bias tool V.2.

Table 2 Summary of the critical appraisal of the included studies using the Critical Appraisal Skills Programmes (CASP) for randomised control trials checklist

Study	Is the basic study design valid for a randomised control trial?	Was the study methodologically sound?	What are the results?	Will the results help locally?
Grabska *et al* (2005), Olsson *et al* (2011), Nesargi *et al* (2015), Dolgun and Bozlak (2017), Benzer *et al* (2017), Jang *et al* (2019), Nayak *et al* (2020).[47 50 53 54 56 57 61]	Yes	Yes	No difference between interventions with sweet taste and control groups.	No, there is no evidence for the benefit of the interventions.
Mitchell *et al* (2004), Gal *et al* (2005), Rosali *et al* (2015), Taplak *et al* (2017).[46 48 52 55]	Yes	Yes	Significantly lower pain scores in intervention group.	Yes, however, there is need for continued monitoring for possible side effects
Dilli *et al* (2014), Sagheb *et al* (2020).[51 63]	Probably yes, though there was no information on randomisation and allocation concealment, the baseline characteristics of both groups were similar.	Yes	Significantly lower pain scores in the intervention group.	Yes, however, there is need for continued monitoring for possible side effects
Chuang *et al* (2018).[58]	Yes, however, using sealed envelopes in blocks of 2 increased the risk of selection bias.	Yes, however, non-blinding of outcome assessors creates a risk of bias.	Significantly lower pain scores in intervention group.	Possibly yes, though, the cost for training in the absence of a high-quality evidence, may be a challenge.
Metres *et al* (2019).[59]	Probably yes, however, there was no allocation concealment and baseline characteristics of the groups differed.	Yes, however, the authors did not state the exclusion criteria, and outcome assessors were not blinded.	Significantly lower pain scores in intervention group, however, no precision estimate reported.	Possibly yes, however, the cost for training in the absence of a high-quality evidence, will may be a challenge.
Boyle *et al* (2006), Liao *et al* (2019), Ozkan *et al* (2022).[49 60 65]	Probably yes, though there was no information on allocation concealment, the baseline characteristics of both groups were similar.	Yes, however, non-blinding of outcome assessors.	Significantly lower pain scores in intervention group, however, no precision estimate reported.	Yes, nesting, and non-nutritive sucking maybe introduced to practice with no added cost, while better designed studies to confirm the efficacy are needful.
Sun *et al* (2020).[62]	Probably yes, though there was no information on allocation concealment, the baseline characteristics of both groups were similar.	Yes, however, the outcome assessors were not blinded. More neonates were withdrawn from the experimental compared with control group increasing the risk of attrition bias.	Significantly lower pain scores in intervention group, however, no precision estimate reported.	Possibly yes, the intervention can be conducted among a larger group of infants and users trained to standardise the gentle touch method.
Dehghani *et al* (2021), Dur *et al* (2023).[64 66]	Yes	Yes	Significantly lower pain scores in intervention group, however, no precision estimates were reported.	Possibly yes, however, may require evidence from more studies before routine use. In addition, initial funds for the music gadgets will be required.

Furthermore, five of the studies had some concerns regarding outcome measurement bias due to the non-blinding of the assessors which is attributed to the nature of the interventions being tested,[58–60 62 65] and these could affect the results and internal validity of the studies.[71] However, the use of pain scales and the dual or triple assessors for outcome assessment in these studies, could reduce this bias in outcome.

The result of the studies using sweet taste in this review are inconsistent. Only 6 of the 14 studies on sweet taste

Table 3 Assessment of quality of evidence of included RCTs using the GRADE approach

Study ID	No. of patients	Limitation	Inconsistency	Indirectness	Imprecision	Publication bias	Rating
Sweet taste compared with placebo							
Mitchell	30	Not serious*	Not relevant	Not serious	Serious†	Unlikely	↓
Gal	23	Not serious*	Not relevant	Not serious	Unlikely	Unlikely	↓
Grabska	32	Not serious	Not relevant	Not serious	Serious†	Unlikely	↓
Boyle	40	Not serious*	Not relevant	Not serious	Serious†	Unlikely	↓
Dilli	64	Serious‡,§	Not relevant	Not serious	Serious†	Unlikely	↓↓
Dolgun	87	Not serious*	Not relevant	Not serious	Serious†	Unlikely	↓
Benzer	64	Not serious*	Not relevant	Not serious	Serious†	Unlikely	↓
Jang	45	Not serious*	Not relevant	Not serious	Serious†	Unlikely	↓
Nesargi	20	Not serious*,§	Not relevant	Not serious	Serious†	Unlikely	↓
Taplak	60	Not serious*	Not relevant	Not serious	Serious†	Unlikely	↓
Rosali	40	Not serious*	Not relevant	Not serious	Serious†	Unlikely	↓
Olsson	30	Not serious*	Not relevant	Not serious	Serious†	Unlikely	↓
Nayak	45	Not serious*	Not relevant	Not serious	Serious†	Unlikely	↓
Sagheb	60	Serious‡,§	Not relevant	Not serious	Serious†	Unlikely	↓↓
Environmental modification/touch/position compared with routine care							
Chuang	14	Serious¶	Not relevant	Not serious	Unlikely	Unlikely	↓
Metres	70	Serious¶	Not relevant	Not serious	Serious†	Unlikely	↓↓
Liao	120	Serious¶	Not relevant	Not serious	Serious†	Unlikely	↓↓
Sun	82	Serious¶	Not relevant	Not serious	Serious†	Unlikely	↓↓
Dehghani	90	Not serious	Not relevant	Not serious	Serious†	Unlikely	↓
Ozkan	60	Serious¶	Not relevant	Not serious	Serious†	Unlikely	↓↓
Dur	90	Not serious	Not relevant	Not serious	Serious†	Unlikely	↓

↓Downgraded once from high to moderate; ↓↓ Downgraded twice from high to low.
*Possible analysis bias as the authors did not provide information on whether analysis plan decided and documented prior to unblinded outcome result.
†No precision estimates were reported, only p values were reported.
‡No information on randomisation process.
§Possible lack of concealment of allocation.
¶Unblinded outcome assessment.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCTs, randomised control trials.

were favourable for the intervention,[46 48 51 52 55 63] while the remaining 8 showed no significant changes in the pain scores between the intervention and the control arms in the group. Contrary to the findings in this current review, the two recent meta-analyses earlier identified,[34 35] reported that sweet taste was beneficial. Disher *et al* reported that sweet taste combined with topical anaesthesia and an adjunct intervention such as non-nutritive sucking had the highest probability of being the optimal intervention for pain management during ROP screening. The pain score difference was −3.67 (95% CI −5.86 to −1.47) and surface under the curve was 0.86.[34] The reason for the difference between these studies and the current one is however not clear.

There were some variations in the patient population regarding the number of ROP examinations, the timing of the pain score assessment and when the study ended. Some studies recruited preterm infants undergoing their first ROP examination,[49 51 56 57 60 63–65] while others did not add this in their inclusion criteria. This could influence the results as repeated pain has been shown to modulate pain response in preterm infants.[72] Therefore, infants having their second or third ROP examination may show reduced pain compared with those having their first examination.[72 73] The timing of pain scores assessment varied across studies, some assessed before, during and after the eye examination, some had specific timing such as 30 s after insertion of speculum, some were at insertion of speculum, while others were not specific.[54 62] The study ended after examination of the first eye in some of the studies,[46 49 51 60 61] some ended after examination of the second eye,[47 48 54 56 57 59 62 64 66] while others were not specific.[50 52 53 55 58 63 65] These variations could be sources of type 1 errors and may affect the internal validity of the studies.

Implementation of findings

The interventions that consistently showed reduction in pain scores in this review appear to be low-cost as no equipment or drug were involved in their use. However, interventions like ROP position, gentle touch and developmental care require training and additional personnel which all come with added costs and expertise. Interventions such as developmental care programme are also time consuming and may overstretch the already overworked staff in NICUs in low-resource countries. This may reduce the widespread use of these interventions even when there is high-level of evidence in support of their use.

Another challenge to implementation is the fact that preterm infants with the exclusion criteria in the included studies such as presence of stage 3 or 4 intraventricular haemorrhage, use of mechanical ventilator and asphyxia are also at risk of ROP, thus, the reproducibility of the findings of these studies in these excluded populations is not certain.

Strengths and limitations

The rigorous process for conducting systematic reviews which was employed in this review is a major strength for this study. The limitations of this study include the exclusion of non-English publications which could create bias during the study selection, data extraction and analysis process. Performing a meta-analysis may have improved precision and quality of evidence of this review,[74] however, the heterogeneity within the studies was a major constraint.

CONCLUSION

Non-pharmacological pain management interventions during ROP screening using touch, position, multisensory interventions, music, NNS and environmental modification appear to be beneficial, however, the quality of the level of evidence for these studies is low to moderate. Considering the negative consequences of untreated pain in preterm neonates, interventions such as music, nesting and NNS, which are easy to administer and require little or no funds may be added as adjunct to topical anaesthesia for pain management during ROP screening. Larger and better-designed studies with a low-risk of bias (outcome assessment and selection reporting bias), that consider the feasibility of these interventions in more settings are needed before these interventions can be recommended for routine use.

Acknowledgements This was originally an MSc dissertation by IBF and was later expanded and contributed to by other authors. We appreciate Dr Michael Hall and Susan Smith of the Faculty of Health Sciences, University of Southampton, and Rami Subhi of University of Melbourne for their immense and valuable contributions to shaping this work.

Contributors Conception or design of the study: IBF. Acquisition of data: IBF, IOFD and BNE. Analysis and interpretation of data: IBF, IOFD and VCE. Drafting the manuscript: IBF. Revising it critically for important intellectual content: IOFD, BNE and VCE. Final approval of the version to be published: IBF, IOFD, BNE and VCE. Agreement to be accountable for all aspects of the work: IBF, IOFD, BNE and VCE. Guarantor: IBF.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iD

Iretiola Bamikeolu Fajolu http://orcid.org/0000-0003-3045-9616

REFERENCES

1 Hellström A, Smith LEH, Dammann O. Retinopathy of prematurity. *Lancet* 2013;382:1445–57.
2 Fierson WM, American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, *et al*. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2018;142:e20183061.
3 Wilkinson AR, Haines L, Head K, *et al*. UK retinopathy of prematurity guideline. *Early Hum Dev* 2008;84:71–4.
4 Jefferies AL, Lacaze-Masmonteil T, Newhook LA. Retinopathy of prematurity: an update on screening and management. *Paediatr Child Health* 2016;21:101–8.
5 Gilbert C, Malik ANJ, Nahar N, *et al*. Epidemiology of ROP update – Africa is the new frontier. *Semin Perinatol* 2019;43:317–22.
6 Chawanpaiboon S, Vogel JP, Moller A-B, *et al*. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019;7:e37–46.
7 Gilbert C, Blencowe H. Retinopathy of prematurity: it is time to take action. *Community Eye Health* 2017;30:45–8.
8 Edwards EM, Horbar JD. Retinopathy of prematurity prevention, screening and treatment programmes: the role of neonatal networks. *Semin Perinatol* 2019;43:341–3.
9 Moral-Pumarega MT, Caserío-Carbonero S, De-La-Cruz-Bértolo J, *et al*. Pain and stress assessment after retinopathy of prematurity screening examination: indirect ophthalmoscopy versus digital retinal imaging. *BMC Pediatr* 2012;12:132.
10 Belda S, Pallás CR, De la Cruz J, *et al*. Screening for retinopathy of prematurity: is it painful? *Biol Neonate* 2004;86:195–200.
11 Royal College of Paediatrics and Child Health. UK screening of retinopathy of prematurity guideline; 2022.
12 Fierson WM, American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, *et al*. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 2013;131:189–95.
13 Schaffer DB, Palmer EA, Plotsky DF, *et al*. Prognostic factors in the natural course of retinopathy of prematurity. *Ophthalmology* 1993;100:230–7.
14 Quinn GE, Ying G-S, Bell EF, *et al*. Incidence and early course of retinopathy of prematurity: secondary analysis of the postnatal growth and retinopathy of prematurity (G-ROP) study. *JAMA Ophthalmol* 2018;136:1383–9.
15 Adams GGW, Bunce C, Xing W, *et al*. Treatment trends for retinopathy of prematurity in the UK: active surveillance study of infants at risk. *BMJ Open* 2017;7:e013366.
16 Adams-Chapman I, Heyne RJ, DeMauro SB, *et al*. Neurodevelopmental impairment among extremely preterm infants in the neonatal research network. *Pediatrics* 2018;141:e20173091.

17 Cruz MD, Fernandes AM, Oliveira CR. Epidemiology of painful procedures performed in neonates: a systematic review of observational studies. *Eur J Pain* 2016;20:489–98.
18 Ranger M, Chau CMY, Garg A, *et al*. Neonatal pain-related stress predicts cortical thickness at age 7 years in children born very preterm. *PLoS One* 2013;8:e76702.
19 McPherson C, Miller SP, El-Dib M, *et al*. The influence of pain, agitation, and their management on the immature brain. *Pediatr Res* 2020;88:168–75.
20 Vinall J, Grunau RE. Impact of repeated procedural pain-related stress in infants born very preterm. *Pediatr Res* 2014;75:584–7.
21 Valeri BO, Holsti L, Linhares MBM. Neonatal pain and developmental outcomes in children born preterm: a systematic review. *Clin J Pain* 2015;31:355–62.
22 Scott PA. Ethical principles in Healthcare research. In: Scott P, ed. *Key Concepts and Issues in Nursing Ethics*. Cham: Springer, 2017: 191–205.
23 Dempsey E, McCreery K. Local anaesthetic eye drops for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity. *Cochrane Database Syst Rev* 2011;7:CD007645.
24 Hartley C, Moultrie F, Hoskin A, *et al*. Analgesic efficacy and safety of morphine in the procedural pain in premature infants (Poppi) study: randomised placebo-controlled trial. *Lancet* 2018;392:2595–605.
25 Stevens B, Yamada J, Ohlsson A, *et al*. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev* 2016;7:CD001069.
26 Harrison D, Reszel J, Bueno M, *et al*. Breastfeeding for procedural pain in infants beyond the neonatal period. *Cochrane Database Syst Rev* 2016;10:CD011248.
27 American Academy of Pediatrics Committtee on Fetus, Newborn and Section on Anesthesiology and Pain Medicine. Prevention and management of procedural pain in the neonate: an update. *Pediatrics* 2016;137:e20154271.
28 Mangat AK, Oei J-L, Chen K, *et al*. A review of non-pharmacological treatments for pain management in newborn infants. *Children (Basel)* 2018;5:130.
29 Padhi TR, Sareen D, Pradhan L, *et al*. Evaluation of retinopathy of prematurity screening in reverse kangaroo mother care: a pilot study. *Eye (Lond)* 2015;29:505–8.
30 Raith W, Urlesberger B, Schmölzer GM. Efficacy and safety of acupuncture in preterm and term infants. *Evid Based Complement Alternat Med* 2013;2013:739414.
31 Howick J, Chalmers I, Glasziou P, *et al*. The Oxford 2011 levels of evidence. Oxford Centre for Evidence-Based Medicine; 2011. Available: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence
32 Sackett DL, Rosenberg WM, Gray JA, *et al*. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;312:71–2.
33 Schardt C, Adams MB, Owens T, *et al*. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;7:16.
34 Disher T, Cameron C, Mitra S, *et al*. Pain-relieving interventions for retinopathy of prematurity: a meta-analysis. *Pediatrics* 2018;142:e20180401.
35 Erçelik ZE, Yilmaz D. Nonpharmacological applications during the retinopathy of prematurity examination and their effects on pain control: a systematic review and meta-analysis. *J Perinat Neonatal Nurs* 2022;36:297–304.
36 Olsson E, Ahl H, Bengtsson K, *et al*. The use and reporting of neonatal pain scales: a systematic review of randomized trials. *Pain* 2021;162:353–60.
37 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
38 Higgins JPT, Savović J, Page MJ, *et al*. Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.4*. Cochrane, 2023.
39 Higgins JP, Eldridge S, Li T, *et al*. Including variants on randomized trials. In: Higgins JPT, Thomas J, J C, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.4*. Cochrane, 2023.
40 Risk of Bias Tools. Current version of rob 2. 2019 Available: https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2
41 Risk of Bias Tools. Risk of bias tools - rob 2 for crossover trials. 2021 Available: https://www.riskofbias.info/welcome/rob-2-0-tool/rob-2-for-crossover-trials
42 Critical Appraisal Skills Programme. CASP (randomized controlled trials) checklist. 2019. Available: https://casp-uk.net/casp-tools-checklists/
43 Fineout-Overholt E, Melnyk BM, Stillwell SB, *et al*. Evidence-based practice step by step: critical appraisal of the evidence: part I. *Am J Nurs* 2010;110:47–52.
44 Boutron I, Page M, Higgins J, *et al*. Considering bias and conflicts of interest among the included studies. In: Higgins J, Thomas J, Chandle J, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.4*. Cochrane, 2023.
45 Zhang Y, Akl EA, Schünemann HJ. Using systematic reviews in guideline development: the GRADE approach. *Res Synth Methods* 2018;10:312–29.
46 Mitchell A, Stevens B, Mungan N, *et al*. Analgesic effects of oral sucrose and pacifier during eye examinations for retinopathy of prematurity. *Pain Manag Nurs* 2004;5:160–8.
47 Grabska J, Walden P, Lerer T, *et al*. Can oral sucrose reduce the pain and distress associated with screening for retinopathy of prematurity? *J Perinatol* 2005;25:33–5.
48 Gal P, Kissling GE, Young WO, *et al*. Efficacy of sucrose to reduce pain in premature infants during eye examinations for retinopathy of prematurity. *Ann Pharmacother* 2005;39:1029–33.
49 Boyle EM, Freer Y, Khan-Orakzai Z, *et al*. Sucrose and non-nutritive sucking for the relief of pain in screening for retinopathy of prematurity: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F166–8.
50 Olsson E, Eriksson M. Oral glucose for pain relief during eye examinations for retinopathy of prematurity. *J Clin Nurs* 2011;20:1054–9.
51 Dilli D, İlarslan NEÇ, Kabataş EU, *et al*. Oral sucrose and non-nutritive sucking goes some way to reducing pain during retinopathy of prematurity eye examinations. *Acta Paediatr* 2014;103:e76–9.
52 Rosali L, Nesargi S, Mathew S, *et al*. Efficacy of expressed breast milk in reducing pain during ROP screening-a randomized controlled trial. *J Trop Pediatr* 2015;61:135–8.
53 Nesargi SV, Nithyanandam S, Rao S, *et al*. Topical anesthesia or oral dextrose for the relief of pain in screening for retinopathy of prematurity: a randomized controlled double-blinded trial. *J Trop Pediatr* 2015;61:20–4.
54 Bozlak Ş, Dolgun G. Effect of nonpharmacologic pain control during examination for retinopathy of prematurity. *J Obstet Gynecol Neonatal Nurs* 2017;46:709–15.
55 Şener Taplak A, Erdem E. A comparison of breast milk and sucrose in reducing neonatal pain during eye exam for retinopathy of prematurity. Breastfeed Med 2017;12:305–10.
56 Benzer D, Pehlevan O, Guler K, *et al*. The effect of sucrose on the control of pain secondary to retinopathy of prematurity screening: randomised controlled trial. *Hong Kong J Paediatr* 2017;22:151–8.
57 Jang EK, Lee H, Jo KS, *et al*. Comparison of the pain-relieving effects of human milk, sucrose, and distilled water during examinations for retinopathy of prematurity: a randomized controlled trial. *Child Health Nurs Res* 2019;25:255–61.
58 Chuang L-J, Wang S-H, Ma M-C, *et al*. A modified developmental care bundle reduces pain and stress in preterm infants undergoing examinations for retinopathy of prematurity: a randomised controlled trial. *J Clin Nurs* 2019;28:545–59.
59 Metreş Ö, Yıldız S. Pain management with ROP position in Turkish preterm infants during eye examinations: a randomized controlled trial. *J Pediatr Nurs* 2019;49:e81–9.
60 Liao W, Xu H, Zhou X, *et al*. Non-nutritive sucking and nesting greatly reduces pain during retinopathy screening in premature infants. *Hong Kong J Paediatr* 2019;24:135–9.
61 Nayak R, Nagaraj KN, Gururaj G. Prevention of pain during screening for retinopathy of prematurity: a randomized control trial comparing breast milk, 10% dextrose and sterile water. *Indian J Pediatr* 2020;87:353–8.
62 Sun Y, Zhang J, Chen X, *et al*. Effectiveness of gentle human touch for pain control during examination for retinopathy of pre-maturity: a randomized controlled trial. *Front Pediatr* 2020;8:608378.
63 Sagheb S, Mosayebi Z, Karimi N, *et al*. Efficacy of 25% glucose in pain alleviation during retinopathy of prematurity (ROP) screening: a randomized controlled trial. *ACTA* 2020;58:621–4.
64 Dehghani K, Mobasherizadeh K, Manaviat MR, *et al*. The comparative effect of multisensory stimulation and breast milk on intensity of pain in premature infants during retinopathy screening examination. *Int J Pediatr (Mashhad)* 2021;9:13325–37.
65 Özkan TK, Yüksel ED, Akar S. Effect of non-nutritive sucking on pain during the examination of retinopathy of prematurity. J Neonatal Nurs 2022;28:155–8.
66 Dur Ş, Çevik SG, Ustabaş Yıldız N. The effect of white noise and classical music on pain and physiologic parameters in preterm infants during retinopathy of prematurity examinations: a randomized controlled trial. Early Child Dev Care 2023;193:60–71.

67 Giordano V, Edobor J, Deindl P, *et al*. Pain and sedation scales for neonatal and pediatric patients in a preverbal stage of development: a systematic review. *JAMA Pediatr* 2019;173:1186–97.
68 Gibbins S, Stevens BJ, Yamada J, *et al*. Validation of the premature infant pain profile-revised (PIPP-R). *Early Hum Dev* 2014;90:189–93.
69 Ballantyne M, Stevens B, McAllister M, *et al*. Validation of the premature infant pain profile in the clinical setting. *Clin J Pain* 1999;15:297–303.
70 Granholm A, Alhazzani W, Møller MH. Use of the GRADE approach in systematic reviews and guidelines. *Br J Anaesth* 2019;123:554–9.
71 Sil A, Kumar P, Kumar R, *et al*. Selection of control, randomization, blinding, and allocation concealment. *Indian Dermatol Online J* 2019;10:601–5.
72 Donia AES, Tolba OA. Effect of early procedural pain experience on subsequent pain responses among premature infants. Egypt Paediatr Assoc Gaz 2016;64:74–80.
73 Holsti L, Grunau RE, Oberlander TF, *et al*. Prior pain induces heightened motor responses during clustered care in Preterm infants in the NICU. *Early Hum Dev* 2005;81:293–302.
74 Deeks JJ, Higgins JPT, Altman DG, *et al*. Analysing data and undertaking meta-analyses |Cochrane training. In: Higgins JPT, Thomas J, Chandler J, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.4*. Cochrane, 2023.