BMJ Open

Efficacy and safety of non-pharmacological interventions for neonatal pain: an overview of systematic reviews

Qiao Shen ,[1,2] Zixuan Huang,[1,2] Hongyao Leng,[1,2] Xufei Luo,[3] Xianlan Zheng[1,2]

To cite: Shen Q, Huang Z, Leng H, *et al*. Efficacy and safety of non-pharmacological interventions for neonatal pain: an overview of systematic reviews. *BMJ Open* 2022;**12**:e062296. doi:10.1136/bmjopen-2022-062296

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-062296).

Received 24 February 2022
Accepted 14 September 2022

[1]Department of Nursing, Children's Hospital of Chongqing Medical University, Chongqing, China
[2]National Clinical Research Center for Child Health and Diseases, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing Key Laboratory of Pediatrics, Chongqing, China
[3]School of Public Health, Lanzhou University, Lanzhou, Gansu, China

Correspondence to
Professor Xianlan Zheng;
zhengxianlan@vip.163.com

ABSTRACT

Objectives To synthesise current evidence from systematic reviews (SRs) regarding the efficacy and safety of non-pharmacological interventions to prevent and treat pain in newborn infants.

Design Overview of SRs.

Data sources We searched PubMed, Embase, Cochrane Library, Web of Science, CINAHL, Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Wanfang Database, Chinese Science and Technology Periodical Database (VIP) and Google Scholar to identify all relevant SRs published in the last 5 years.

Eligibility criteria for selecting studies We included SRs that evaluated the efficacy and safety of non-pharmacological interventions for neonatal pain.

Data extraction and synthesis Two reviewers independently extracted the data, assessed the methodological quality using a Measurement Tool to Assess Systematic Reviews (AMSTAR) 2 and graded the evidence quality with the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results A total of 29 SRs were included in this overview, of which 28 focused on procedural pain and only 1 focused on postoperative pain. Based on AMSTAR 2, seven reviews were found to be of 'high quality', eight of 'moderate quality', five of 'low quality' and nine of 'critically low quality'. The GRADE results suggested that facilitated tucking, kangaroo care, sweet solutions, familiar odour or combined non-pharmacological interventions, such as a combination of sucrose and non-nutritive sucking, were effective and safe in reducing pain from medical procedures in neonates. However, sucrose alone was less effective than local anaesthesia or a combination of the two during circumcision.

Conclusions Facilitated tucking, small volumes of sweet solutions, kangaroo care and familiar odour were recommended. Scientific implementation strategies should be developed to promote the clinical use of these effective non-pharmacological interventions. Meanwhile, further rigorous trials and SRs are needed to identify the best non-pharmacological approaches for pain from common surgery and illnesses in neonates.

PROSPERO registration number CRD42021292583.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This overview synthesised the latest evidence on non-pharmacological interventions for neonatal pain based on the findings of systematic reviews, which provided more extensive and direct evidence for clinical workers in neonatal intensive care units.
⇒ This overview was predesigned following the Cochrane Handbook, which reduced the risk of bias and increased the reliability of our overview.
⇒ Some information might have been missed since only English and Chinese studies were included in this overview.
⇒ As high-quality evidence emerges, the conclusions of this overview may be affected by newly published literature.

INTRODUCTION

Infants admitted to the neonatal intensive care unit (NICU) experience a high prevalence of painful stimuli. On average, the number of daily acute painful events for hospitalised neonates can reach up to 26,[1] and the cumulative time of persistent painful exposure is up to 57.61 hours.[2] It is confirmed that both preterm and term infants can recognise, process and respond to painful stimuli.[3] Neonatal pain exposure can induce a series of neurophysiological and behavioural changes, associated with adverse long-term effects, such as feeding difficulties, hyperalgesia, chronic metabolic diseases[2 4] and even poorer cognitive scores, motor ability, and behavioural control ability in childhood.[5]

Neonatal caregivers should fulfil the obligation to provide newborns with analgesic treatment, given the well-established harmful impact of painful experiences in early life.[6] Although both non-pharmacological and pharmacological methods can be used to alleviate pain and suffering in neonates, non-pharmacological approaches are recommended as the first-line treatment according to guidelines of neonatal pain management.[7 8] Non-pharmacological analgesia is preferred not only because it is ethical but also because of its high benefit–risk ratio. Non-pharmacological therapies,[9] comprising more than a dozen strategies such as non-nutritive sucking (NNS), sweet solutions,

breast feeding, kangaroo care (KC) and music therapy, can reduce neonatal pain directly by blocking the transmission of nociception or activating descending inhibitory pathways, and indirectly by reducing the total amount of nociceptive stimuli to which infants are exposed.[10] Furthermore, they also show greater advantages on account of their low risk and lack of side effects, ease of implementation, low cost, and nurse-friendliness.

Systematic reviews (SRs), considered as high-quality evidence, have been increasingly developed to investigate the efficacy and safety of non-pharmacological interventions for neonatal pain. However, a large amount of information can make it difficult for clinicians in NICUs to make decisions across various analgesic interventions rapidly.[11] It is also unlikely to assess the efficacy of all non-pharmacological strategies for various painful stimuli in only one systematic review owing to time and resource limitations. For example, a Cochrane SR has comprehensively evaluated the efficacy of multiple non-pharmacological interventions for acute procedural pain in neonates.[12] However, it still does not include all types of non-pharmacological treatments, such as KC and music therapy, or all types of pain, such as postoperative pain and persistent pain. Furthermore, when conducting SRs, the reliability of their findings is susceptible to various risks of bias.[13] The decision-makers would thus be misled if SRs were recommended for clinical practice without rigorous quality evaluation. Therefore, it is necessary to assess the quality of SRs and aggregate high-quality evidence to provide direct guidance for pain management practices in NICUs.

An overview is a comprehensive approach to summarise evidence from multiple SRs for a particular health condition in one document through a systematic literature search and strict quality assessment.[14] Therefore, we conducted an overview to present comprehensive evidence on the efficacy and safety of non-pharmacological interventions for neonatal pain, which can aid evidence-based clinical decision-making and highlight current gaps in knowledge.

METHODS AND ANALYSIS

This overview was conducted and reported following the Cochrane Handbook for Systematic Reviews of Interventions[15] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[16] separately (for the PRISMA checklist, see online supplemental appendix 1). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/prospero/). We developed this overview by following a predetermined protocol. Significantly, we reported pain assessment and non-pharmacological and pharmacological treatments separately. This study provides an overview of the efficacy and safety of non-pharmacological interventions for neonatal pain, while the other two reports are currently under review.

Inclusion and exclusion criteria

The inclusion criteria were (1) types of participants: preterm or term neonates who underwent one or more painful stimuli during their hospital stay in the NICU; (2) types of interventions for pain relief: non-pharmacological therapies, including but not limited to sucrose, glucose, breast feeding, NNS, KC, swaddling, music therapy and touch.[9] Actually, whether sucrose and glucose are non-pharmacological or pharmacological analgesics is still controversial. We included sucrose and glucose as non-pharmacological treatments in this study according to the recommendations of the guidelines[17]; (3) types of outcomes: pain scores measured by a validated scale and incidence of adverse reactions were primary outcomes[18]; physiological, biochemical or behavioural indicators (eg, heart rate, respiratory rate, a saturation of peripheral oxygen in the blood, cortisol levels, cry duration and the proportion of time crying) were secondary outcomes; (4) types of reviews: SRs or meta-analyses in English or Chinese in which at least one randomised controlled trial (RCT) or non-randomised controlled studies were included accordingly. The exclusion criteria were as follows: SRs whose neonates' data could not be extracted, duplicated publications, protocols of overviews, review comments, and conference abstracts.

Search strategy

An electronic literature search was conducted via PubMed, Embase, Cochrane Library, Web of Science, CINAHL, Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), Wanfang Database and Chinese Science and Technology Periodical Database (VIP). The search strategies were developed in collaboration with a librarian specialising in medical literature retrieval. The details of the search strategies with free-text words and subject headings are presented in online supplemental appendix 2. The reference lists of included studies and Google Scholar were screened for additional relevant SRs. The WHO Handbook for Guideline Development pointed out that guideline recommendations need to be based on the best available evidence.[19] Moreover, evidence from high-quality SRs would be obsolete 3–5 years after publication.[20] Thus, we limited the search period to the last 5 years, from November 2016 to November 2021.

Study selection and data collection

The reviewer (QS) conducted a comprehensive search according to a predeveloped standardised search strategy. After removing duplicate records with EndNote V.X9 (Beijing, China; Clarivate), two reviewers (QS and ZH) independently screened for candidates according to the prespecified selection criteria by reading the titles and abstracts. Full texts were retrieved for further screening. Finally, bibliographical references of the included studies were reviewed to identify possible SRs. Any disagreements after cross-checking were resolved by discussion or

Shen Q, *et al*. *BMJ Open* 2022;**12**:e062296. doi:10.1136/bmjopen-2022-062296

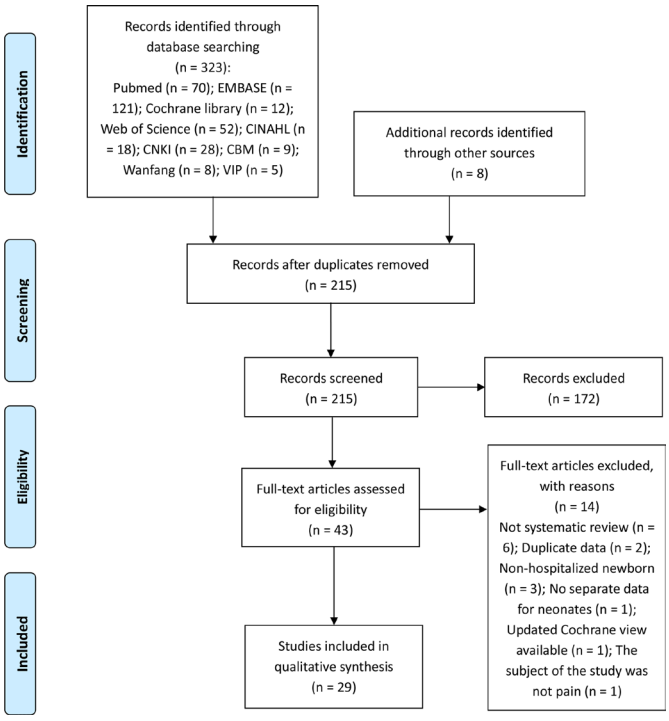

Figure 1 Flowchart of the selection process of included systematic reviews.

consultation with a third reviewer (HL) if consensus was not reached among the designated two reviewers.

Data were independently extracted by two reviewers (QS and ZH) using a predefined spreadsheet in Microsoft Excel 2019, including authors, review title, year of publication, number of studies included, analgesic interventions, outcomes, quality evaluation method and conclusion. The extracted data were cross-checked by two reviewers (QS and ZH) to eliminate input errors. Differences were resolved through mutual discussion and consensus.

Quality assessment and strength of evidence

Two qualified reviewers (QS and ZH) trained in the Fudan University Center for Evidence-based Nursing (A JBI Centre of Excellence) independently evaluated the methodological quality of the included SRs using a Measurement Tool to Assess Systematic Reviews (AMSTAR) 2.[13] Then, the results were cross-checked, and disagreements were resolved by group discussion or were arbitrated by a third reviewer (XL). The checklist consisted of 16 items, 6 of which were identified as critical domains (Item 4, 7, 9, 11, 13 and 15) based on the AMSTAR 2 guideline and group discussions.[13] Each item was evaluated as 'yes', 'partial yes', 'no' and 'no meta-analysis conducted' according to compliance with the standard. The methodological quality of SRs was determined by weaknesses in the critical domains instead of generating an overall score. The overall quality was categorised as 'high (no or one non-critical weakness)', 'moderate (more than one non-critical weakness)', 'low (one critical flaw with or without non-critical weaknesses)' and 'critically low (more than one critical flaw with or without non-critical weaknesses)'. Systematic reviews of moderate or high quality can provide an accurate and comprehensive summary of available studies.

The strength of evidence for all outcomes was assessed by the reviewer (QS) based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[21] Then, the evaluation results were reviewed for correctness by another qualified reviewer (XL) who was trained in the Lanzhou University GRADE Center (China). If the GRADE system was applied in a systematic review, it was also graded by the authors. The overall quality of evidence was rated as follows: 'high', 'moderate', 'low' and 'very low'. Evidence based on RCTs began as high quality and otherwise began with low quality. The evidence quality was downgraded one level for serious or two levels for very serious limitations if there was: risk of bias, inconsistency across studies, indirectness of evidence, imprecision of estimates and publication bias.[22] A web version of the GRADE profiler Guideline Development Tool (GRADEpro GDT, https://www.gradepro.org/) was used to create a summary of findings to report the quality of the evidence.

Data synthesis

A descriptive analysis was performed to synthesise evidence on the efficacy and safety of non-pharmacological treatments for neonatal pain and to clarify the gaps between existing evidence and the clinical practice of pain management in neonates.

Patient and public involvement

No patient or the public was directly involved in the development of this overview of SRs.

RESULTS

Literature search

This review retrieved 331 records in total. After removing 116 duplicates, the titles and abstracts of 215 papers were reviewed for eligibility. A total of 172 articles were excluded, leaving 43 full-text screening of which 29 articles met the inclusion criteria and were included in this overview.[23–51] Online supplemental appendix 3 table 1 lists the reasons for the exclusion of 14 studies. Figure 1 shows a PRISMA diagram of the literature selection.

Characteristics of the included SRs

The characteristics of the included SRs are shown in online supplemental appendix 3 table 2. The number of trials in the SRs ranged from 3 to 168. Eighteen SRs included RCTs only,[26–28 31–33 35–39 41 42 44 45 47 49 50] while the other reviews included non-RCTs, case studies and descriptive studies. Regarding the participants, 10 SRs were specific to preterm infants,[26 27 31–33 37 39 40 42 43] 1 SR was directed at term neonates[30] and the other 18 SRs included both term and preterm neonates.[23–25 28 29 34–36 38 41 44–51] The types of pain involved in the included SRs consisted of postoperative pain (3.4%), single procedural pain

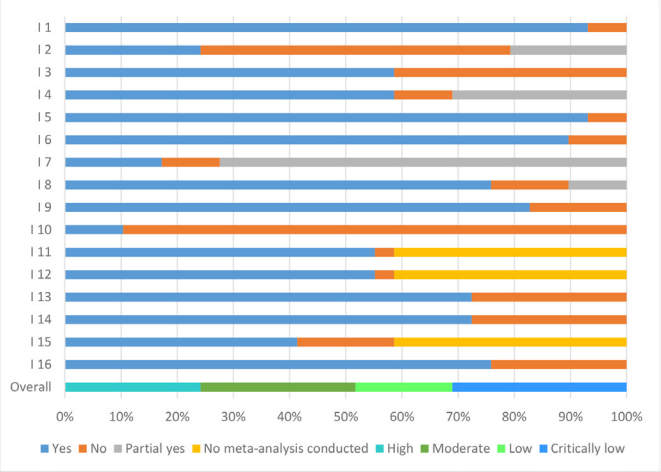

Figure 2 Graphical representation of the methodological quality of included systematic reviews. Note: (1) Did the research questions and inclusion criteria for the review include the components of PICO (population, intervention, control group and outcome)? (2) Did the report of the review contain an 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? (3) Did the review authors explain their selection of the study designs for inclusion in the review? (4) Did the review authors use a comprehensive literature search strategy? (5) Did the review authors perform study selection in duplicate? (6) Did the review authors perform data extraction in duplicate? (7) Did the review authors provide a list of excluded studies and justify the exclusions? (8) Did the review authors describe the included studies in adequate detail? (9) Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (10) Did the review authors report on the sources of funding for the studies included in the review? (11) If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? (12) If 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? (13) Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? (14) Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (15) If 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? (16) Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

(89.7%) and repeated procedural pain (6.9%). The most frequently performed procedures were heel lance (26.9%), venipuncture (16.7%), injection (11.5%), eye examination (9.0%) and suction (9.0%). A meta-analysis was performed in 17 SRs (58.6%). The outcomes of SRs included validated pain scores; physiological, behavioural and hormonal indicators; and adverse events. Eleven pain scores were included as primary outcome measures for analgesic efficacy, and the most commonly used scales were Premature Infant Pain Profile (27.1%), Neonatal Infant Pain Scale (19.8%), Neonatal Facial Coding System (13.5%), Douleur Aiguë du Nouveau-né (9.4%), Bernese Pain Scale for Neonates (5.2%) and Neonatal Pain Agitation and Sedation Scale (5.2%). Furthermore, the incidence of adverse events, such as bradycardia, tachycardia, desaturation, apnoea, nausea, vomiting and hyperglycaemia, was the main indicator for evaluating the safety of non-pharmacological therapies. Non-pharmacological interventions that were demonstrated to be effective and safe for reducing procedural pain in neonates included sweet solutions, NNS, breast feeding, KC, positioning (facilitated tucking or swaddling), maternal voice, music therapy, aromatherapy, acupuncture or a combination of these. Whereas, for the single study of postoperative pain, non-pharmacological interventions alone were shown to be insufficiently analgesic, and pharmacological strategies in addition are required.

The methodological quality of included SRs

Details of the methodological quality of the included SRs are presented in online supplemental appendix 3 table 3. Seven reviews (24.2%) were found to be of 'high quality',[32 33 39 44 45 49 50] eight reviews (27.6%) of 'moderate quality',[25 26 29 34 35 46 48 51] five reviews (17.2%) of 'low quality'[23 27 37 38 47] and nine reviews (31.0%) of 'critically low quality'.[22 28 30 31 36 40–43] Only two SRs met all criteria of AMSTAR 2.[45 49] Most of the remaining SRs did a good job on Items 1, 3–6, 8, 9, 11–14 and 16, especially did well in clearly describing the PICO (population, intervention, control group and outcome) questions, performing study selection and data extraction in duplicate, presenting the included studies in adequate detail, assessing the risk of bias (ROB) with a satisfactory technique and discussing the likely impact of ROB on the results, providing a satisfactory explanation and discussion of any heterogeneity observed in the SRs, and reporting potential sources of conflict of interest. However, most studies showed shortcomings in explicitly stating that the reviews were conducted following a well-developed protocol and reported any significant deviations from the protocol, providing a list of excluded studies with justification, reporting the funding sources for the studies included in the reviews, and investigating publication bias. A graphical representation of the methodological quality of the included SRs is presented in figure 2.

Quality of evidence in included SRs

The evidence quality of the primary outcomes extracted from included nine meta-analyses[32 34 35 39 42 45 46 49 51] of moderate-to-high methodological quality is displayed with downgrading justification in online supplemental appendix 3 table 4. The results of the GRADE system showed that 6 outcomes (9.1%) were rated as high quality, 27 (40.9%) as moderate quality, 30 (45.5%) as low quality and the other 3 (4.5%) as very low quality. The evidence quality was downgraded mainly because of

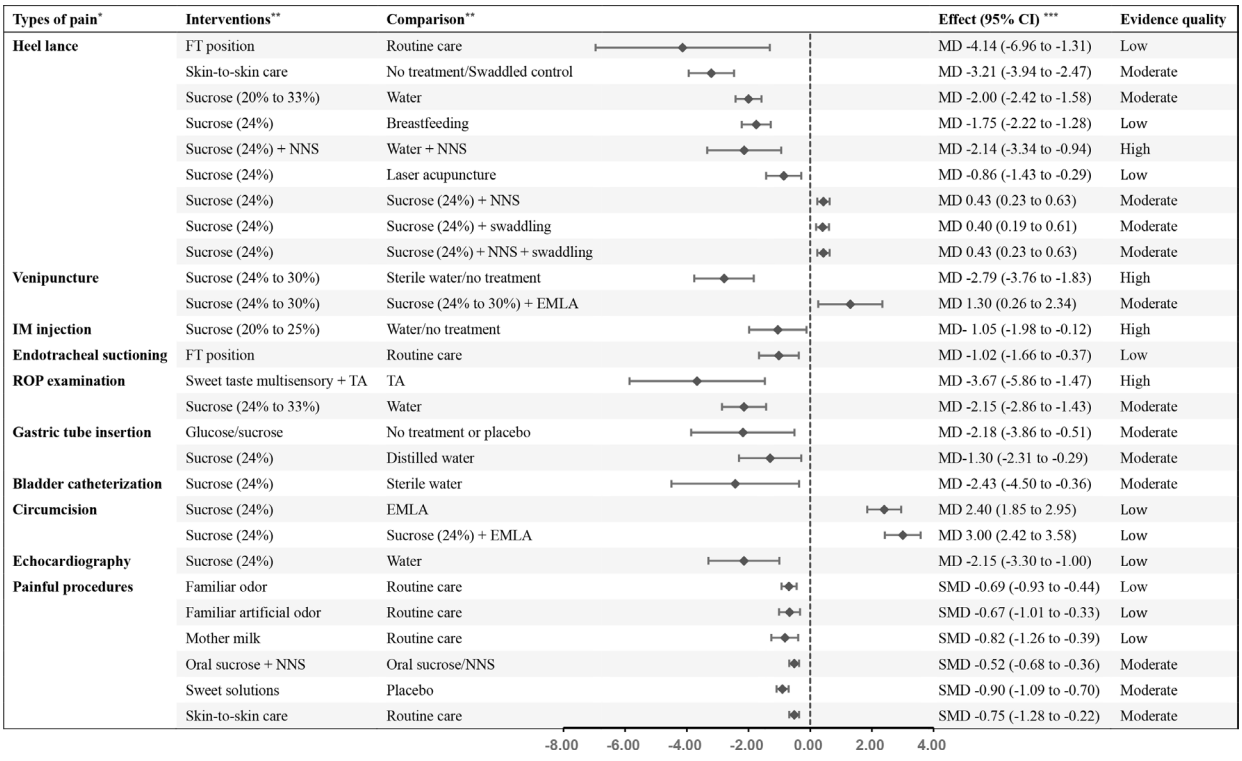

Figure 3 Evidence for effective non-pharmacological interventions on pain scores in neonates. Note: *IM injection, intramuscular injection; ROP, retinopathy of prematurity; **FT, facilitated tucking; NNS, non-nutritive sucking; TA, topical anaesthetic; EMLA, eutectic mixture of local anaesthetics; ***MD, mean difference; SMD, standardised mean difference.

methodological limitations, significant heterogeneity and a small sample size failing to meet the optimal information size.

Efficacy of non-pharmacological interventions for neonatal pain

We summarised the effective non-pharmacological interventions for reducing neonatal pain from the included meta-analyses with relatively high quality and presented them in figure 3. These analgesic interventions were mainly used to reduce pain from heel lance, venipuncture, intramuscular (IM) injection, endotracheal suctioning, retinopathy of prematurity (ROP) examination, gastric tube insertion, bladder catheterisation, circumcision and echocardiography.

Regarding heel lance, there was low-to-high quality evidence that showed a significant reduction in pain scores for neonates in the facilitated tucking (FT),[32] skin-to-skin care (SSC)/KC[45] or sucrose (20%–33%)[49] group compared with routine care or no-treatment control. Sucrose (24%) was superior to breast feeding or laser acupuncture during heel stick.[49] The moderate-to-high quality evidence indicated that sucrose (24%–30%), sucrose (24%–33%) and sucrose (20%–25%) were separately effective in reducing pain during venipuncture, ROP examination and IM injection.[49] Based on low-to-moderate quality of evidence, FT position could result in statistically significant decreases in pain during endotracheal suctioning,[32] while sucrose (24%)[49] showed benefits in improving pain scores during gastric tube insertion, bladder catheterisation and echocardiography; combined non-pharmacological interventions, such as sucrose combined with NNS, were more beneficial than either method alone. In addition, SSC, sweet solutions and familiar natural and artificial odours appeared to reduce pain from non-specific painful procedures.[34 46 51] The low-quality evidence suggested that sucrose (24%) alone was less effective than an eutectic mixture of local anaesthetics cream or a combination of those two during circumcision.

Safety of non-pharmacological interventions for neonatal pain

Eleven of the included 29 SRs mentioned the adverse events of non-pharmacological interventions in treating neonatal pain.[25 33 34 36 39 42 44 45 47 49 50] Most studies on non-pharmacological therapies (eg, facilitated tucking, KC, breast feeding, aromatherapy, acupuncture, sweet solutions or a combination of those) for neonatal pain reported no or minimal adverse effects. Meanwhile, the number of minor adverse events was similar across the groups, suggesting no contribution to adverse events of non-pharmacological interventions.

DISCUSSION

This overview of SRs aimed to provide comprehensive evidence of non-pharmacological treatments for neonatal pain. Through a systematic search, it was found that the current SRs for non-pharmacological analgesia focused on procedural pain (28 SRs), and rarely

on postoperative pain (only 1 SR). Based on AMSTAR 2, 13 out of the 29 SRs were rated as moderate or high quality. The results of the GRADE suggested that facilitated tucking, KC, sweet solutions, familiar odour or combined non-pharmacological interventions, such as a combination of sucrose and NNS, were effective and safe in reducing pain from medical procedures in neonates. Although there is no evidence that non-pharmacological interventions are recommended alone for postoperative pain, we do know that sucrose in combination with local anaesthesia appears to be effective in reducing pain for newborn circumcision. There is sufficient evidence of altered brain development and increased pain sensitivity following repeated exposure to painful procedures during the newborn period.[52] Leaving neonates suffering from painful stimuli without intervention is inappropriate, and further placebo-controlled trials are considered unethical.[46] Hence, the following non-pharmacological methods were recommended for clinical use and control treatment in clinical trials based on the results of this study.

FT is described as the method where neonates are placed in a flexed position in either lateral, supine or prone positions with parents' or professionals' hands on the baby's hands and feet to control the entire body and provide support.[53] It was mentioned in a systematic review that facilitated tucking by parents (FTP) was the best position for procedural pain relief in preterm infants.[25] The authors recommended that FTP in side-lying be administered from 15 min before the beginning of the painful procedures to 15 min after the painful stimuli.[25] One advantage of FT is that parents or health professionals can easily learn and perform it because of its minimal technical challenges.[54] Another advantage is that it is effective for extremely or very premature infants without requiring any other abilities, such as mature sucking ability.[55] Moreover, it can be used when newborns are unable to be transferred from the incubator or bed.[26]

SSC, also known as KC, refers to the way the mother holds a diaper-clad infant upright on her breast at approximately 60°, providing maximum skin-to-skin contact between the baby and mother.[45] Studies have shown that KC can not only reduce pain and stabilise the physiological and behavioural responses of the neonates, but it also strengthens the mother–infant bonding.[56 57] Furthermore, no significant difference in pain scores was found between the mother and other providers (father and another woman).[45] If mothers could not participate in KC, fathers or other women can serve as alternatives. As for the number of minutes in KC, no analyses were conducted to identify its effect on neonatal pain response. The duration of KC before painful procedures varied from 2 min to 3 hours. The most commonly used scheme was 15 or 30 min of KC before and throughout the painful stimuli.[45] There was one limitation, however, to be noted for KC. Contextual challenges such as heavy workload and parental anxiety have restrained its utilisation in NICUs.[58]

One of the most commonly studied interventions is administering sucrose via syringe, dropper, pacifier or any other way for pain relief in neonates.[59] The dose and concentration of sucrose, administration time and the method of delivery varied among studies. The optimal timing and volume for sucrose intervention for pain relief in preterm and term neonates have not yet been determined. A Cochrane SR that included 74 trials with 7049 infants recommended that 24% sucrose solution could be used approximately 2 min before the painful stimulus.[49] The minimally effective dose of 24% sucrose during a single painful procedure in neonates was found to be 0.1 mL in a multicentre randomised controlled study.[60]

Olfactive stimulation interventions using a familiar odour refer to exposing infants to either natural odour or artificial odour with habituation during painful procedures.[34] The natural odour consists of maternal odour, breast milk odour of a newborn's mother or other mothers and amniotic fluid odour.[61] On the other hand, the artificial odour comprises formula milk, lavender odour and vanilla odour.[62 63] The habitation of artificial odour refers to the preliminary exposure to an odour for a while before the painful procedure to improve the effectiveness of the artificial odour.[34] And the habitation time spans between 8 and 18 hours.[34] Compared with other non-pharmacological treatments, the advantage of olfactive stimulation is that it can be easily implemented anytime during hospitalisation with little preparation or cost and without requiring parental presence. Meanwhile, it can be easily applied with other effective methods, thus demonstrating an enhanced effect.[64] The results of SRs included in this study recommended that a pad with maternal breast milk or an artificial odour with a previous period of habituation could be used during painful procedures.[34] However, concerning the intervention, the best artificial odours, the method of releasing the odour, the time required for odour habituation and the distance from the odour position to the neonate's nose are inconclusive.

In addition, this review identified the following critical clinical questions that need to be explored further: (1) What are the effective and safe non-pharmacological interventions for common postoperative pain, and prolonged pain in neonates? Neonatal pain is often classified as acute pain, prolonged pain and particular types of pain such as postoperative pain and mechanical ventilation pain.[18] Although acute pain from minor medical procedures such as heel lance is most common during neonatal hospitalisation,[65] other types of pain from major procedures, surgery, medical illness and even painful stimulation like postoperative mechanical ventilation also deserve attention. Yet the available evidence is scant on the latter.[66] (2) How to adjust non-pharmacological strategies based on pain scores? The guideline or expert consensus for neonatal pain management recommends a stepped analgesic approach based on pain assessment results with prevention as the premise and non-drug treatment as the mainstay.[7 8] However, current evidence focuses on

preventive interventions for specific painful procedures. The use of pain scores to guide the clinical selection of appropriate non-pharmacological interventions is still lacking. More research is urgently needed to identify the best non-pharmacological methods for various painful stimuli and to establish a stepped strategy. Finally, scientific implementation strategies are required to effectively translate research evidence on non-pharmacological interventions into practice.

The results of this overview could serve as guidance for clinicians and researchers in the selection of suitable non-pharmacological interventions for neonatal pain. However, there are several limitations to be noted in this study. First, there might be some missing information because only studies in English and Chinese were included in this overview. Second, because this overview was primarily based on published studies, its conclusions may be influenced as new evidence emerges.

CONCLUSION

This was the first overview to comprehensively assess published SRs to investigate the efficacy and safety of non-pharmacological interventions for neonatal pain. It was concluded that small volumes of sweet solutions, facilitated tucking, KC, familiar odour or combined non-pharmacological interventions, such as a combination of sucrose and NNS were superior in reducing pain from medical procedures in hospitalised neonates. However, sucrose alone was less effective than local anaesthesia or a combination of the two during circumcision. Next, we need to explore scientific implementation strategies to promote the clinical application of these effective non-pharmacological interventions. Moreover, further rigorous trials and SRs are needed to identify the best non-pharmacological approaches for various types of pain, especially pain from common surgery and medical illnesses in neonates. Meanwhile, a stepped non-pharmacological intervention strategy based on pain scores should be explored and established accordingly.

Acknowledgements We would like to thank Professor Rong Ou and Professor Xiaorong Hou from the College of Medical Informatics, Chongqing Medical University (Chongqing, China) for peer-reviewing the retrieval strategies; Shan He, Yuting Yao, Songlin Ke, Yating Zhou and Lin Wang for article selection. Many thanks to Editage for helping to improve the quality of the English throughout our manuscript.

Contributors QS was the major researcher and involved in the design, implementation, analysis and reporting of this work. XZ served as the study guarantor supervising all study activities. QS, ZH, HL and XL selected articles, extracted data, performed the assessment of bias and graded the evidence. QS drafted the manuscript. All authors critically reviewed and revised the manuscript and approved the final manuscript.

Funding This study was supported by grants from the National Natural Science Foundation of China (No. 72074038) and the Chongqing Science and Technology Commission (No. cstc2019jscx-msxmX0157; No. cstc2022ycjh-bgzxm0275).

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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. All data relevant to this study are available in the manuscript and its supplementary materials. Any more information can be requested from the corresponding author.

ORCID iD

Qiao Shen http://orcid.org/0000-0002-7864-5816

REFERENCES

1 Xu L, Ren HY, Cao XM. Epidemiology of painful procedures in premature and influencing factors in the intensive care unit. *Chin Pediatr Emerg Med* 2018;25:824–8.
2 Cong X, Wu J, Vittner D, *et al*. The impact of cumulative pain/stress on neurobehavioral development of preterm infants in the NICU. *Early Hum Dev* 2017;108:9–16.
3 Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med* 1987;317:1321–9.
4 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.
5 Walker SM. Long-term effects of neonatal pain. *Semin Fetal Neonatal Med* 2019;24:101005.
6 Waisel DB. Ethics of research for patients in pain. *Curr Opin Anaesthesiol* 2017;30:205–10.
7 Chen R, Yang Y, Shi Y. Expert consensus on neonatal pain assessment and analgesia management (2020 edition). *Chin J Contemp Pediatr* 2020;22:923–30.
8 Balice-Bourgois C, Zumstein-Shaha M, Vanoni F, *et al*. A systematic review of clinical practice guidelines for acute procedural pain on neonates. *Clin J Pain* 2020;36:390–8.
9 Bucsea O, Pillai Riddell R. Non-pharmacological pain management in the neonatal intensive care unit: managing neonatal pain without drugs. *Semin Fetal Neonatal Med* 2019;24:101017.
10 Walter-Nicolet E, Calvel L, Gazzo G, *et al*. Neonatal pain, still searching for the optimal approach. *Curr Pharm Des* 2017;23:5861–78.
11 Perry M, Tan Z, Chen J, *et al*. Neonatal pain: perceptions and current practice. *Crit Care Nurs Clin North Am* 2018;30:549–61.
12 Pillai Riddell RR, Racine NM, Gennis HG, *et al*. Non-pharmacological management of infant and young child procedural pain. *Cochrane Database Syst Rev* 2015;2015:CD006275.
13 Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008.
14 Smith V, Devane D, Begley CM, *et al*. Methodology in conducting a systematic review of systematic reviews of healthcare interventions. *BMC Med Res Methodol* 2011;11:15.
15 Higgins JPT, Thomas J, Chandler J, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.2*. Cochrane, 2021. www.training.cochrane.org/handbook
16 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
17 Smith HAB, Besunder JB, Betters KA, *et al*. 2022 Society of critical care medicine clinical practice guidelines on prevention and management of pain, agitation, neuromuscular blockade, and delirium in critically ill pediatric patients with consideration of the ICU environment and early mobility. *Pediatr Crit Care Med* 2022;23:e74–110.

18 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.
19 World Health Organization. *Who Handbook for Guideline development Ne*. Geneva: World Health Organization, 2014.
20 Shekelle PG, Ortiz E, Rhodes S, *et al*. Validity of the agency for healthcare research and quality clinical practice guidelines: how quickly do guidelines become outdated? *JAMA* 2001;286:1461–7.
21 Guyatt GH, Oxman AD, Vist GE, *et al*. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
22 Deng T, Wang Y, Wang YY. Methodology for clinical practice guidelines-application of GRADEpro GDT in evidence grading of systematic reviews of interventional trial. *Chin J Evid Based Cardiovasc Med* 2019;11:1–5.
23 Lian DM, Zhang DY, Sun J. The effectiveness of maternal voice on procedural pain reduction in neonates: a meta-analysis. *Chinese Nursing Management* 2021;21:380–7.
24 Rossi S, Buonocore G, Bellieni CV. Management of pain in newborn circumcision: a systematic review. *Eur J Pediatr* 2021;180:13–20.
25 Francisco ASPG, Montemezzo D, Ribeiro SNDS, *et al*. Positioning effects for procedural pain relief in NICU: systematic review. *Pain Manag Nurs* 2021;22:121–32.
26 Eissler AB, Zwakhalen S, Stoffel L, *et al*. Systematic review of the effectiveness of involving parents during painful interventions for their preterm infants. *J Obstet Gynecol Neonatal Nurs* 2022;51:6–15.
27 Cañadas DC, Perales AB, Martínez RG, *et al*. The impact of nonpharmacological interventions on cortisol during heel Lance procedures on preterm infants: a meta-analysis of RCTs. *Pain Manag Nurs* 2021;22:798–805.
28 Deng MQ, Xie XF, Liu S. Effectiveness of music therapy on relieving procedural pain in neonates: a systematic review. *Chinese Evidence-based Nursing* 2020;6:618–24.
29 Yasmeen I, Krewulak KD, Zhang C, *et al*. The effect of caregiver-facilitated pain management interventions in hospitalized patients on patient, caregiver, provider, and health system outcomes: a systematic review. *J Pain Symptom Manage* 2020;60:1034–+.
30 Sezavar M, Ahmadi R, Shojaei H. The effect of lavender oil for relief painful producer in children and infants: a systematic review. *International Journal of Pediatrics-Mashhad* 2020;8:11177–85.
31 Noroozíasl S, Nakhaei AA, Kalani-Moghaddam F. The effects of different strategies on the painful procedure management, and the physiological parameters in preterm infants: a systematic review. *International Journal of Pediatrics-Mashhad* 2020;8:11251–9.
32 Gomes Neto M, da Silva Lopes IA, Araujo ACCLM, *et al*. The effect of facilitated tucking position during painful procedure in pain management of preterm infants in neonatal intensive care unit: a systematic review and meta-analysis. *Eur J Pediatr* 2020;179:699–709.
33 Guo W, Liu X, Zhou X, *et al*. Efficacy and safety of combined nonpharmacological interventions for repeated procedural pain in preterm neonates: a systematic review of randomized controlled trials. *Int J Nurs Stud* 2020;102:103471.
34 De Clifford-Faugere G, Lavallée A, Khadra C, *et al*. Systematic review and meta-analysis of olfactive stimulation interventions to manage procedural pain in preterm and full-term neonates. *Int J Nurs Stud* 2020;110:103697.
35 Stadler J, Raith W, Mileder LP, *et al*. Invasive and non-invasive acupuncture techniques for pain management in neonates: a systematic review. *Acupunct Med* 2019;37:201–10.
36 Huang R-R, Xie R-H, Wen SW, *et al*. Sweet solutions for analgesia in neonates in China: a systematic review and meta-analysis. *Can J Nurs Res* 2019;51:116–27.
37 Hatfield LA, Murphy N, Karp K, *et al*. A systematic review of behavioral and environmental interventions for procedural pain management in preterm infants. *J Pediatr Nurs* 2019;44:22–30.
38 Zhang S, Su F, Li J, *et al*. The analgesic effects of maternal milk odor on newborns: a meta-analysis. *Breastfeed Med* 2018;13:327–34.
39 Disher T, Cameron C, Mitra S, *et al*. Pain-relieving interventions for retinopathy of prematurity: a meta-analysis. *Pediatrics* 2018;142:e20180401.
40 Lotto CR, Linhares MBM. "Skin-to-Skin" Contact in pain prevention in preterm infants: systematic review of literature. *Trends Psychol* 1715;2018:4.
41 Liu LX, BR M, Lei JF. Meta-analysis on the effect of kangaroo care in the alleviation of the pain caused by heel blood sampling of the newborns. *Nursing Practice and Research* 2017;14:7–11.
42 YB L, Xu M, Wang Y. Meta- analysis of oral sweet solution for pain relief during eye examinations for retinopathy of prematurity. *Anhui Medical and Pharmaceutical Journal* 2017;21:1662–6.
43 Pagni AM, Kellar S, Rood M. *Effects of kangaroo care on procedural pain in preterm infants: a systematic review*. Honors Research Projects, 2017.
44 Liu Y, Huang X, Luo B, *et al*. Effects of combined oral sucrose and nonnutritive sucking (NNS) on procedural pain of NICU newborns, 2001 to 2016: a PRISMA-compliant systematic review and meta-analysis. *Medicine* 2017;96:e6108.
45 Johnston C, Campbell-Yeo M, Disher T, *et al*. Skin-to-skin care for procedural pain in neonates. *Cochrane Database Syst Rev* 2017;2:CD008435.
46 Harrison D, Larocque C, Bueno M, *et al*. Sweet solutions to reduce procedural pain in neonates: a meta-analysis. *Pediatrics* 2017;139:35.
47 Chen S, Zhang Q, Xie R-H, *et al*. What is the best pain management during gastric tube insertion for infants aged 0–12 months: a systematic review. *J Pediatr Nurs* 2017;34:78–83.
48 Benoit B, Martin-Misener R, Latimer M, *et al*. Breast-feeding analgesia in infants: an update on the current state of evidence. *J Perinat Neonatal Nurs* 2017;31:145–59.
49 Stevens B, Yamada J, Ohlsson A, *et al*. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev* 2016;7:CD001069.
50 Gao H, Gao H, Xu G, *et al*. Efficacy and safety of repeated oral sucrose for repeated procedural pain in neonates: a systematic review. *Int J Nurs Stud* 2016;62:118–25.
51 Boundy EO, Dastjerdi R, Spiegelman D, *et al*. Kangaroo mother care and neonatal outcomes: a meta-analysis. *Pediatrics* 2016;137:e20152238.
52 Duerden EG, Grunau RE, Guo T, *et al*. Early procedural pain is associated with regionally-specific alterations in thalamic development in preterm neonates. *J Neurosci* 2018;38:878–86.
53 Corff KE, Seideman R, Venkataraman PS, *et al*. Facilitated tucking: a nonpharmacologic comfort measure for pain in preterm neonates. *J Obstet Gynecol Neonatal Nurs* 1995;24:143–7.
54 Avcin E, Kucukoglu S. The effect of breastfeeding, kangaroo care, and facilitated tucking positioning in reducing the pain during heel stick in neonates. *J Pediatr Nurs* 2021;61:410–6.
55 Gautheyrou L, Durand S, Jourdes E, *et al*. Facilitated tucking during early neonatologist-performed echocardiography in very preterm neonates. *Acta Paediatr* 2018;107:2079–85.
56 Ullsten A, Andreasson M, Eriksson M. State of the art in parent-delivered pain-relieving interventions in neonatal care: a scoping review. *Front Pediatr* 2021;9:651846.
57 Cristóbal Cañadas D, Bonillo Perales A, Galera Martínez R, *et al*. Effects of kangaroo mother care in the NICU on the physiological stress parameters of premature infants: a meta-analysis of RCTs. *Int J Environ Res Public Health* 2022;19:583.
58 Zhang Y, Deng Q, Zhu B, *et al*. Neonatal intensive care nurses' knowledge and beliefs regarding kangaroo care in China: a national survey. *BMJ Open* 2018;8:e021740.
59 McNair C, Campbell-Yeo M, Johnston C, *et al*. Nonpharmacologic management of pain during common needle puncture procedures in infants: current research evidence and practical considerations: an update. *Clin Perinatol* 2019;46:709–30.
60 Stevens B, Yamada J, Campbell-Yeo M, *et al*. The minimally effective dose of sucrose for procedural pain relief in neonates: a randomized controlled trial. *BMC Pediatr* 2018;18:85.
61 Küçük Alemdar D, Kardaş Özdemir F. Effects of having preterm infants smell amniotic fluid, mother's milk, and mother's odor during heel stick procedure on pain, physiological parameters, and crying duration. *Breastfeed Med* 2017;12:297–304.
62 Usta C, Tanyeri-Bayraktar B, Bayraktar S. Pain control with lavender oil in premature infants: a double-blind randomized controlled study. *J Altern Complement Med* 2021;27:136–41.
63 Fitri SYR, Wardhani V, Rakhmawati W, *et al*. Culturally based practice in neonatal procedural pain management: a mini review. *Front Pediatr* 2020;8:540–40.
64 COMMITTEE ON FETUS AND NEWBORN and SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE. Prevention and management of procedural pain in the neonate: an update. *Pediatrics* 2016;137:e20154271.
65 Wang YJ, Li Y, Sun J. Study of neonatal procedural pain in NICU. *J Nurs Sci* 2019;34:20–3.
66 van Ganzewinkel C-J, Andriessen P. We need to change how we deal with continuous pain in neonates. *Acta Paediatr* 2017;106:1212–4.