



(REVIEW ARTICLE)



Non-pharmacological methods to reduce pain in preterm infants: A systematic review

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Abstract

Objective: To systematically review the literature to determine whether non-pharmacological interventions reduce preterm infants' pain during invasive procedures in the neonatal intensive care unit.

Methods: A systematic search was conducted according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for conducting and reporting systematic reviews. The search was performed in PubMed and Scopus from 2013 to 2023. Only studies in English were included.

Results: In total, forty-four studies were included. Kangaroo Mother Care, massage, Yakson Touch, Gentle Human Touch, music therapy, mother's voice, white noise, maternal heartbeat sounds, facilitated tucking, sucrose administration, olfactory stimulation, the use of "Calmer," environment modification, expressed breast milk, the mother scented simulated hand, and the combination of these methods proved to be effective in reducing pain in preterm infants undergoing various medical procedures.

Conclusion: Healthcare professionals should consider using non-pharmacological methods for pain relief during minor invasive procedures.

Keywords: Non-pharmacological methods; Pain; Preterm; Premature; Infants; Neonates; Neonatal intensive care unit

1. Introduction

Intubations and other painful procedures that penetrate the skin are frequently required for preterm infants undergoing critical intensive care. These interventions are suspected to influence normal brain maturation [1]. Indeed, Grunau et al. [2] observed that a higher count of skin-breaking procedures correlates with diminished cognitive and motor functions at 8 and 18 months corrected age (CCA). Similarly, Vinall et al. [3] reported that children born very preterm and subjected to repeated pain from numerous invasive procedures exhibited lower Fractional Anisotropy values in white matter at the age of 7. Furthermore, a significant correlation has been established between frequent invasive medical procedures, altered brain microstructure, and reduced Full-Scale Intelligence Quotient (FSIQ) scores in school-aged children who were born very prematurely. A retrospective observational study [4] highlighted that an increased number of painful invasive procedures was associated with lower cognitive scores at 6 months. This correlation was particularly evident in infants born at less than 28 weeks at 12 months, suggesting heightened vulnerability to the adverse effects of pain in very preterm infants. Additionally, a prospective case-control study [1] noted that preterm infants undergoing significant painful procedures during their hospitalization in a Neonatal Intensive Care Unit (NICU) exhibited reduced functional connectivity between the thalami and bilateral somatosensory

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cortex, as well as among the right insular cortex and the ipsilateral amygdala and hippocampal regions. These functional magnetic resonance imaging (fMRI) abnormalities were linked to motor outcomes at 24 months CCA.

Duerden and colleagues [5] demonstrated that early exposure to pain is associated with thalamic volume loss in the territory of the somatosensory thalamus, accompanied by abnormalities in thalamic metabolic growth and maturation of the thalamocortical pathways. These abnormalities were particularly pronounced in extremely preterm infants and associated with poorer cognitive and motor functions at 3 years of CCA. A prospective cohort study [6] further elucidated that recurrent neonatal pain is linked to reductions in white matter fractional anisotropy and decreased subcortical gray matter N-acetylaspartate (NAA) to choline ratios. Smith et al. [7] found a correlation between reduced brain size in the frontal and parietal regions and increased exposure to neonatal pain-related stress among preterm infants assessed at term equivalent age. Additionally, Ranger et al. [8] reported that premature infants exhibited a thinner cortex in multiple brain regions at school age, a consequence attributed to neonatal pain-related stress.

In his 1995 Presidential Address to the American Pain Society, Dr. James Campbell advocated for the assessment of pain as a vital sign, proposing it to be recognized as the fifth vital sign [9]. He posited that such recognition would ensure pain is appropriately assessed and managed. Since pain management is considered a human right, premature infants, who cannot verbally communicate their discomfort, are entitled to effective pain management and the minimization of unnecessary stress. Healthcare professionals have an ethical duty to act as advocates for these vulnerable patients [10]. Although premature infants cannot articulate their pain verbally, neonatal pain can be effectively assessed using behavioral indicators such as crying and the duration of specific facial expressions, alongside physiological responses including variations in heart rate, blood flow, respiratory rate, and oxygen saturation [11]. It is imperative that healthcare staff is vigilant in recognizing these signs to prevent premature infants from suffering in silence [10].

It has been documented that pharmacological approaches for managing infant pain can lead to significant adverse effects, including respiratory depression, apnea leading to bradycardia and desaturation, partial airway obstruction, and hypersalivation [12]. In light of these concerns, non-pharmacological techniques offer valuable alternatives for pain management during minimally invasive procedures. Such methods encompass a range of interventions, including kangaroo care, massage, human touch, music therapy, facilitated tucking, exposure to maternal voice, sucrose, non-nutritive sucking, and the reduction of environmental stimuli. These approaches provide effective pain relief without the risks associated with pharmacological treatments.

Considering the above evidence, the aim of our study was to systematically review non-pharmacological methods for reducing pain in preterm infants. This comprehensive analysis seeks to identify and evaluate the efficacy and safety of various non-drug interventions designed to alleviate discomfort in this vulnerable population.

2. Materials and Methods

A thorough literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. The databases used for this comprehensive search included major bibliographic sources (Pubmed and Scopus) tailored to the scope of the study, ensuring a systematic approach to the identification, selection, and synthesis of relevant research. This methodology provides a structured framework for enhancing the reliability and validity of the review findings. In addition to the electronic database search, manual searches were conducted to identify additional studies that may not have been indexed in the primary search. This dual approach maximized the scope of our review and ensured the inclusion of relevant literature.

The search strategy comprised the combination of Medical Subject Headings (MeSH) terms “preterm infants”, “preterm neonates”, “breast milk”, “white noise”, “facilitated tucking”, “non-nutritive sucking”, “sucrose”, “massage”, “mother's voice”, “maternal voice”, “non-pharmacological methods”, “music”, “maternal heart sounds”, “heartbeat sounds”, “kangaroo care”, “touch”, “positioning”, “less pain” “reduce pain”, “analgesic effect”, “procedural pain”, “pain”, “pain control”, “analgesia” and “NICU”. Studies involving animals were excluded. Restrictions limited the language of the papers included in the study to English only. The search spanned from 2013 – 2023.

Predetermined criteria as per the PICO (“Population,” “Intervention,” “Comparison,” “Outcomes,”) were applied as follows:

- Population: human preterm infants treated in neonatal intensive care units.
- Intervention: non-pharmacological methods to reduce pain
- Comparison: no methods to reduce pain

- Outcomes: pain levels measured by validated pain assessment scales

Initially, 151 records were identified from PubMed, Scopus, and our manual searches. After deduplication, we had 134 articles left. We excluded 73 of these because their titles indicated they were not related to the topic. Out of the 61 articles left, 1 was inaccessible. The remaining 60 articles were further assessed for their language, design, population, and outcomes. Of these, 1 article was retracted, 4 did not have appropriate study populations, 4 were systematic reviews, 1 was a meta-analysis, 6 were study protocols, and 1 could not be accessed. In the end, 44 articles satisfied our inclusion criteria and were considered for this systematic review. The Prisma flow chart is depicted in Figure 1.

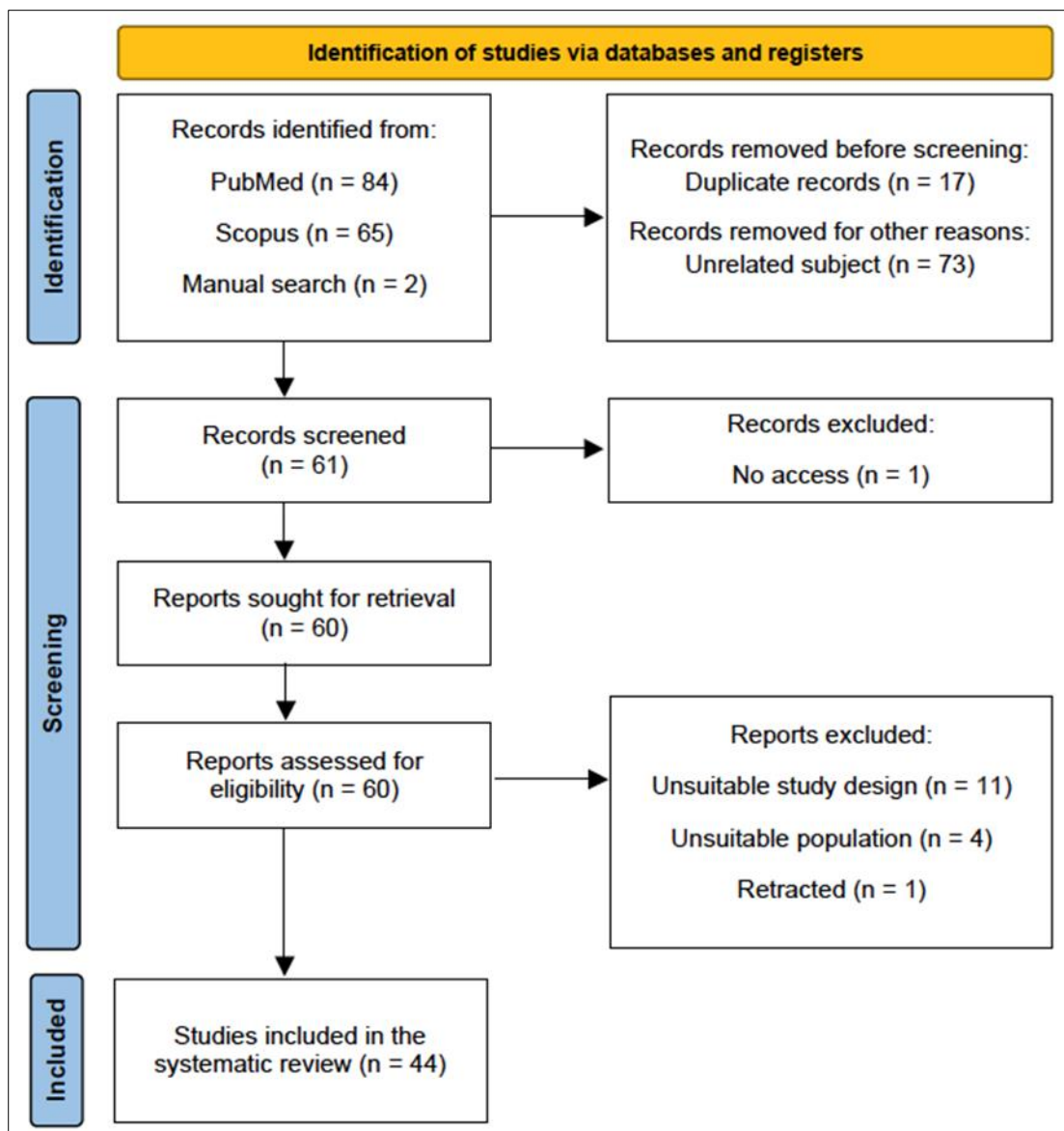


Figure 1 PRISMA flow chart

3. Results

3.1. Study Characteristics

Twenty-nine studies were conducted as randomized controlled trials, while 4 utilized a quasi-experimental design, 10 adopted a cross-over design, and 1 was a longitudinal observational study.

Two studies focused on the use of "calmer" as an analgesic technique. Three studies explored the pain-relieving effects of Yakson touch. Five studies assessed how music therapy could help alleviate pain. Two studies examined the pain-

relieving properties of maternal heartbeat sounds. Five studies looked at the impact of gentle human touch on pain. Seven studies evaluated the use of sucrose for pain relief. Five studies analyzed the benefits of kangaroo mother care in reducing pain. Seven studies investigated the efficacy of facilitated tucking as a pain relief method. One study assessed the pain-reducing effect of lavender oil scent during heel lancing. One study explored the impact of positioning infants in developmentally supportive postures for 20 minutes prior to venipuncture on pain reduction. One study evaluated the effects of white noise, recorded mother's voice, and ear protectors on pain and comfort in premature infants undergoing heel lance in neonatal intensive care units. One study determined the effectiveness of massage therapy in easing pain from umbilical vein catheter insertion in preterm infants. One study divided infants into three groups—experiencing intrauterine sounds, having covered eyes, and a control group—to study these methods' effectiveness in reducing pain during venipuncture. One study examined the impact of a modified developmental care bundle on reducing pain and stress in premature infants during retinopathy of prematurity examinations. One study investigated the effects of maternal voice on pain relief from heel stick procedures. Lastly, one study looked into how a hand-shaped device could enhance comfort and reduce pain during painful medical procedures.

3.2. Results of individual studies

3.2.1. Calmer

Two studies examined the impact of "calmer" on alleviating pain in preterm infants. Calmer is a mattress-shaped robot designed to mimic elements of skin-to-skin contact, including touch, rhythmic breathing movements, and soothing sounds. It features a skin-like surface and vertical movements that simulate breathing and heartbeat sounds, all intended to elicit physiological responses that reduce pain. In the first study [13], it was found that infants using Calmer displayed a significant 90% increase in parasympathetic activation immediately before a painful procedure began, suggesting lower stress levels. Additionally, during the procedure, there was an 82% increase in parasympathetic activation, and a 24% increase during the recovery phase, compared to infants not using Calmer. The second study [14] compared the effects of Calmer with facilitated tucking on regional cerebral hemodynamic activity, finding that infants in both the Calmer and facilitated tucking groups maintained normal levels of regional cerebral oxygen throughout the procedures.

3.2.2. Yakson touch

Yakson touch is a pain relief method derived from Korean tradition, involving a structured sequence of actions: initially, a five-minute period of hand resting, followed by five minutes of gentle caressing, and concluding with another five-minute hand rest. Three studies have assessed the effectiveness of Yakson touch in alleviating pain. The first study [15], which included three experimental groups and a control group (maternal voice group, Yakson touch group, maternal voice + Yakson touch group, and control group), found that during the nasal prong application, the average Neonatal Infant Pain Scale (NIPS) and Premature Infant Comfort Scale (PICS) scores of preterm infants in both the Yakson touch and the mother's voice + Yakson touch groups were significantly lower than those in the maternal voice alone and control group. These scores remained lower after the application, suggesting that Yakson touch was the most effective method for reducing pain, followed by the combined approach of maternal voice and Yakson touch, and then maternal voice alone. The second study [16], involving Yakson touch, gentle human touch (GHT), and a control group, noted reduced pain scores and heart rates during and after heel lancing in the Yakson and GHT groups compared to the control group. The third study [17] evaluated the effects of Yakson touch and oral glucose on alleviating pain from phlebotomy in preterm infants. It found that both experimental groups had significantly lower mean pain scores than the control group, though no significant difference was noted between the two experimental groups.

3.2.3. Music therapy

Five studies examined the role of music therapy in reducing pain. The first study [18], featuring a crossover design, tested an intervention that combined Brahms' lullaby with non-nutritive sucking, facilitated tucking, and holding, against standard care, which involved facilitated tucking and holding alone. Results showed a reduction in the mean Premature Infant Pain Profile (PIPP) scores and a lower incidence of abnormal heart rate occurrences during the intervention, indicating effective pain alleviation and maintenance of homeostasis during heel lance procedures. The second study [19], also with a crossover design, involved 42 infants, each serving as its own control. They were randomized into three groups: one listened to a recorded lullaby, another to music heard by their mothers during pregnancy, and a control group with no music. Pain scores were lowest when infants listened to their mothers' music, with no significant physiological differences noted across groups. Exposure to mothers' music also led to infants spending more time in a quiet alert state and a notable decrease in respiratory rates. The third study [20] divided premature infants into two groups for painful procedures, one with a music and touch intervention and the other without. The intervention used lullabies and nursery rhymes with a slower pitch and tempo, combined with gentle human touch. There were higher PIPP scores in the control group after two weeks, with no difference in cortisol levels

between the groups. However, serum β -endorphin levels were higher in the experimental group both at the start and after two weeks. The fourth study [21] compared the effects of Sonata K. 448, glucose, and no intervention during heel lancing, finding that both glucose and music were effective in reducing pain increases compared to the control, as measured by changes on the PIPP scale. The final study [22] randomized infants into a control group, an oral glucose group, and a lullaby group to assess pain relief during tracheal tube removal and reinsertion and oronasopharyngeal suctioning in infants on nasal continuous positive airway pressure. The results indicated that both oral glucose and lullabies were effective in providing pain relief during these procedures.

3.2.4. Maternal heart beat sounds

Two studies explored the pain-relieving effects of maternal heartbeat sounds. The first study [23] investigated whether prerecorded maternal heart sounds could reduce pain and increase comfort in preterm infants during endotracheal aspiration. Results showed that infants in the experimental group exhibited lower PIPP scores and improved comfort levels during the aspiration procedure compared to those in the control group. The second study [24] explored the effects of combining maternal heartbeat sounds with other interventions, rather than comparing them directly to a no-intervention group. This study involved four groups: one receiving breast milk odor or taste (BM-OT) alone, another with BM-OT plus heart beat sounds (BM-OT + HBs), a third combining BM-OT, HBs, and non-nutritive sucking (BM-OT+HBs+NNS), and a routine care control group. Measurements included crying duration from puncture to recovery, facial expressions, and body movements during various stages from baseline through recovery. Infants in the BM-OT+HBs and BM-OT+HBs+NNS groups showed significantly fewer facial actions and body movements, especially in the later stages. While BM-OT alone did not significantly reduce stress behaviors, the addition of NNS markedly reduced crying duration. Combining HBs and NNS with BM-OT proved most effective in reducing stress behaviors during recovery. The results indicated that integrating only HBs with BM-OT was less effective at alleviating stress compared to the more comprehensive approach of BM-OT+HBs+NNS in aiding pain recovery in infants.

3.2.5. Gentle Human Touch

Five studies investigated the effectiveness of gentle human touch (GHT) in alleviating pain, employing a method that involves precise skin stimulation without massage or caress. The first study [25] demonstrated that GHT could lower both NIPS and COMFORT scale scores following heel lancing, in addition to reducing crying during the procedure. The second study [26], a crossover study, revealed that preterm infants receiving GHT did not show significant changes in respiration, heart rate, or cry duration during heel stick procedures compared to times without GHT. The third study [27], also utilizing a crossover design, found that most preterm infants experienced moderate to severe pain during endotracheal suctioning without GHT, while a significant number still experienced such pain even with GHT. The fourth study [28] indicated that infants receiving Gentle Human Touch exhibited lower pain levels during venipuncture and blood sampling, as reflected in their NIPS scores, compared to those in the control group. In the fifth study [29], referred to as Mother's Touch Therapy, three experimental groups were compared to a control group receiving routine care: one with Mother's Touch Therapy alone, another with just Mother's Voice Stimulus, and a third combining both interventions. Pain levels were assessed using the NIPS scale during preparation, therapy, and recovery phases. Results showed that Mother's Touch Therapy significantly reduced pain at 15-19 minutes and 25-29 minutes. Mother's Voice Stimulus lowered pain at 8, 19-23, and 27 minutes. The combined approach of both interventions led to reduced pain from 8 to 21 minutes.

3.2.6. Sucrose

Sucrose has been the focus of several studies investigating its analgesic properties. One study [30] compared the effects of sucrose, music, and their combination on pain reduction, revealing that both sucrose alone and in combination with music reduced pain during and 30 seconds after venipuncture, while music alone was effective only immediately post-procedure. Another study [31] assessed the effectiveness of oral melatonin versus 24% sucrose in managing pain during retinopathy of prematurity (ROP) screening, finding both treatments equally effective. A third study [32] evaluated the efficacy of repeated administrations of 0.12 ml of 24% sucrose before skin-breaking procedures, which consistently resulted in low PIPP-R scores, confirming its pain-relieving potential. Another research [33] compared expressed breast milk (EBM) and 24% oral sucrose for pain relief in preterm infants during venipuncture, showing similar analgesic effects from both, although sucrose provided lower pain scores in infants with a gestational age under 28 weeks. A comparison between 25% dextrose and 24% sucrose in another study [34] found both solutions equally effective in reducing pain during heel lancing. Another study [35] investigated the potential neurobehavioral side effects of using sucrose for repeated painful procedures, concluding there were no adverse outcomes at 40 weeks post-conceptual age. The last study [36] tested the efficacy of a single versus a double dose of sucrose administered before and after a heel prick. This study found no differences in pain perception between the two dosing strategies, as measured by the PIPP scale.

3.2.7. Kangaroo Mother Care

Kangaroo Mother Care (KMC) has been the subject of various studies assessing its effectiveness in pain reduction for preterm infants. One study using a crossover design compared pain scores during heel pricks between infants undergoing KMC and those without, finding significantly lower mean PIPP scores at 15 and 30 minutes post-procedure in the KMC group [37]. Another randomized controlled trial evaluated the efficacy of KMC across multiple painful procedures, noting that preterm infants in the KMC group exhibited lower heart rates and shorter durations of crying and facial grimacing from the blood collection phase through recovery [38]. A third study compared the effects of KMC and oral sucrose on reducing pain during heel lancing, with findings indicating that although sucrose decreased PIPP-R scores, KMC was more effective [39]. An additional study assessed how kangaroo care, neonatal positioning, and swaddling impact pain and comfort in preterm infants during peripheral vascular access. It concluded that positioning was the most effective, significantly reducing NIPS scores and enhancing comfort, followed by kangaroo care, with swaddling being the least effective [40]. Lastly, a study randomized infants into groups receiving KMC with music therapy, music therapy alone, KMC alone, or no additional intervention, while all groups received expressed breast milk. This study demonstrated that KMC, both with and without music therapy, significantly alleviated pain during heel-prick procedures compared to using expressed breast milk alone [41].

3.2.8. Facilitated tucking

Facilitated tucking, a method that gently positions an infant's arms and legs close to their trunk in a flexed, midline position, has been studied for its effectiveness in pain relief. Two semi-experimental studies [10,42] with control and interventional groups assessed this technique. Another study [43] randomized infants into six groups: control, swaddling, facilitated tucking, expressed breast milk, swaddling + expressed breast milk, and facilitated tucking + expressed breast milk, investigating pain reduction during orogastric tube insertion. A crossover study [44] examined the impact of facilitated tucking during endotracheal suctioning. Another study [45] compared facilitated tucking to oral dextrose for pain relief during heel sticks. One study [46] assessed the combination of facilitated tucking and non-nutritive sucking versus non-nutritive sucking alone during heel sticks. Finally, a study [47] involved three groups: control, sucking + breast milk, and sucking + breast milk + tucking, focusing on pain relief during heel stick procedures. The results from the first study [10] showed that facilitated tucking reduced pain associated with venipuncture, as indicated by PIPP scores. The second study [42] reported that infants in the facilitated tucking group cried less after blood sampling. The third study [43] found that swaddling, expressed breast milk, and facilitated tucking effectively reduced pain, with swaddling combined with expressed breast milk being the most effective. The fourth study [44] reported a decrease in severe pain during endotracheal suctioning from 38.2% to 8.8% with facilitated tucking. The fifth study [45] found that while both facilitated tucking and oral dextrose decreased pain during heel sticks, oral dextrose was more effective. The sixth study [46] observed that the combination of facilitated tucking and non-nutritive sucking sped up pain recovery, although it did not significantly reduce pain during the procedure. The final study [47] demonstrated that both interventions involving non-nutritive sucking, with and without facilitated tucking, were effective in alleviating pain, with facilitated tucking enhancing pain recovery.

3.2.9. Other methods

Several studies have explored various methods for alleviating pain in neonatal care settings:

- *Lavender Oil*: One study [48] found that inhaling the scent of lavender oil during heel lancing resulted in lower PIPP-R scores during and after the procedure compared to a control group.
- *Developmental Supportive Positioning*: Another study [49] demonstrated that positioning infants in a developmentally supportive posture for 20 minutes before venipuncture significantly relieved pain.
- *White Noise and Mother's Voice*: A study [50] observed that using white noise, recorded mother's voice, and ear protectors (MiniMuffs) increased oxygen saturation levels and reduced heart rates, crying time, NIPS scores, and COMFORTneo scores compared to controls during heel lance procedures.
- *Massage Therapy*: Previous evidence [51] indicated that massage therapy reduced pain associated with umbilical vein catheter insertion in preterm infants.
- *Covered Eyes*: A study [55] found that covering the eyes of preterm infants during venipuncture improved pain scores post-procedure.
- *Modified Developmental Care Bundle*: Chuang et al. [52] revealed that a modified developmental care bundle, including dimmer lights, a quiet environment, gentle touching, and use of a pacifier, reduced pain, stress responses, and recovery time after examinations for retinopathy of prematurity.
- *Maternal Voice*: Yu et al. [53] reported that infants who listened to their mother's voice during procedures had lower heart rates and NIPS scores one minute post-procedure, suggesting maternal voice as a potential analgesic method.

- *Hand-Shaped Device*: Finally, Rashwan and Khamis [54] showed that a hand-shaped device scented with the mother's scent alleviated pain and enhanced comfort during painful procedures, according to the COMFORTneo scale.

These studies highlight a range of non-pharmacological interventions that can effectively reduce pain and discomfort in neonatal care settings.

Table 1 Characteristics of the included studies

Authors	Year of Publication	Study type	Analyzed population	Study outcomes
Belpinar et al.	2023	RCT	n=124	Yakson touch alone and the combination of mother's voice with Yakson touch were found to be effective in managing neonatal pain and promoting comfort during and after nasal CPAP application.
Sezer Efe et al.	2022	RCT	n=50	Preterm infants in the Gentle Human Touch group exhibited lower NIPS and COMFORT mean scores both during and after heel lancing compared to the control group, and they also had reduced crying time during the procedure.
Yu et al.	2022	RCT	n=64	One minute after the heel stick, the group exposed to a recording of the mother's voice exhibited significantly lower heart rates and Neonatal Infants Pain Scale scores compared to the control group.
Sasidharan et al.	2022	RCT	n=64	In preterm infants, 25% dextrose demonstrated similar results compared to 24% sucrose for providing analgesia during heel-lance procedures, as assessed by the PIPP score.
Behura et al.	2022	RCT	n=60	Oral melatonin demonstrated comparable efficacy to oral 24% sucrose in managing pain during ROP screening.
Çiftci et al.	2022	RCT	n=148	Swaddling, positioning, and kangaroo care were found to be helpful in reducing discomfort and increasing comfort in premature infants both during and after peripheral vascular access.
Ranger et al.	2021	RCT	n=28	Infants in both the Calmer and facilitated tucking groups maintained normal regional cerebral oxygen levels.
Efendi et al.	2021	RCT	n=63	The combination of Mother's Touch Therapy and Mother's Voice Stimulus was effective in reducing pain scores in infants undergoing invasive procedures.
Usta et al.	2021	RCT	n=61	Inhalation of lavender scent was effective in reducing pain in premature infants during and after heel lancing.
Sen et al.	2020	RCT	n=64	Kangaroo care proved superior to oral sucrose in alleviating pain during heel lancing in preterm infants.
Dur et al.	2020	RCT	n=90	During and after heel lance procedures, the group receiving Yakson touch and the group receiving Gentle Human Touch exhibited lower NIPS scores and heart rates compared to the control group.

Cirik et al.	2020	RCT	n=187	Infants who received a combination of swaddling and expressed breast milk demonstrated significantly lower pain profile scores during orogastric tube insertion compared to those receiving routine care, swaddling alone, facilitated tucking alone, expressed breast milk alone, or a combination of facilitated tucking and expressed breast milk.
Barandouzi et al.	2020	RCT	n=120	Pain scores during venipuncture were significantly lower in the sucrose group and the combination of sucrose and music group compared to the control group, but not in the music group alone. Thirty seconds after the venipuncture, pain scores in all three intervention groups (sucrose, music, and combination) were significantly lower than in the control group. However, ten minutes after the venipuncture, there were no significant differences in pain scores among the four groups.
Wu et al.	2020	RCT	n=140	Breast milk odor or taste, Breast milk odor or taste combined with heartbeat sounds and breast milk odor or taste combined with heartbeat sounds and non-nutritive sucking were effective in alleviating pain across venipuncture procedures. Among these interventions, the triple combination proved to be the most effective in reducing pain across all phases of the venipuncture procedure.
Lago et al.	2020	RCT	n=71	No difference in pain perception, as measured by the PIPP scale, was found between the group that received a single dose of sucrose and the group that received a double dose during the heel prick procedure.
Yazdanpanahi et al.	2020	RCT	n=54	The findings indicated a significant contrast in mean scores of facial expression alterations, heart rate, and neonatal blood oxygen saturation at two and five minutes post-needle removal between the intervention, which involved developmental supportive positioning of preterm neonates, and control groups. However, there was no notable difference in the mean respiratory rate of neonates at these time points between the intervention and control groups.
Kahraman et al.	2020	RCT	n=64	The average oxygen saturation levels were higher in the white noise, recorded mother's voice, and MiniMuffs (ear protectors) groups compared to the control group. Additionally, premature neonates in these groups showed significantly lower heart rates, crying time, mean NIPS scores, and COMFORTneo scores compared to those in the control group.
Bagheri et al.	2020	RCT	n=64	Massage was effective in reducing the pain caused by umbilical vein catheter insertion.
Williams et al.	2019	RCT	n=10	Calmer infants exhibited a 90% increase in parasympathetic activation 2 minutes before the start of the painful procedure, indicating reduced stress. Additionally, they showed an 82% increase in parasympathetic activation during the skin break and

				a 24% increase during the recovery phase, compared to infants in the control group.
Tekgündüz et al.	2019	RCT	n=106	Administering oral glucose and playing lullabies provided pain relief during the removal and reinsertion of the tracheal tube, as well as during oronasopharyngeal suctioning in premature infants receiving nasal continuous positive airway pressure.
Alemdar et al.	2018	RCT	n=62	Listening to maternal heart sounds during aspiration proved to be an effective pain-reducing and comforting method for premature infants.
Perroteau et al.	2018	RCT	n=58	The combined use of facilitated tucking and non-nutritive sucking accelerated pain recovery following the heel-stick procedure.
Peng et al.	2018	RCT	n=109	The use of non-nutritive sucking with oral expressed breast milk and facilitated tucking, as well as non-nutritive sucking with oral expressed breast milk, effectively reduced mild and moderate-to-severe pain in preterm infants undergoing heel stick procedures. Adding facilitated tucking to clinical care helped infants recover faster from pain.
Shukla et al.	2018	RCT	n=200	Combining Kangaroo mother care with expressed breast milk, or with expressed breast milk and music therapy, showed significantly improved pain control compared to using expressed breast milk alone.
Alemdar et al.	2017	RCT	n=94	The practice of covering preterm infants' eyes during venipuncture reduced NIPS scores after venipuncture.
Banga et al.	2016	RCT	n=93	The administration of sucrose for managing pain during repeated procedures in preterm infants does not result in any notable difference in short-term neurobehavioral outcomes at 40 weeks post conceptional age.
Gao et al.	2015	RCT	n=75	Kangaroo Mother Care was associated with reductions in infants' heart rate, crying duration, and facial grimacing from the blood collection phase to the recovery phase during heel stick procedures.
Dehghani et al.	2019	RCT	n=99	Both Yakson touch and the oral administration of 1 cc of 50% glucose resulted in lower NIPS scores compared to the control group. There were no significant differences between these two experimental groups.
Bergomi et al.	2014	RCT	n=35	Both glucose administration and exposure to Mozart's music were found to be safe and effective methods for alleviating the increase in pain during heel lance procedures in preterm infants when compared to the standard procedure.
Fatollahzade et al.	2022	CT	n=34	During suctioning without GHT, 85.3% of neonates experienced moderate pain, while 8.8% experienced severe pain. In contrast, suctioning with GHT resulted in 64.7% experiencing moderate pain, with only 2.9% reporting severe pain.

Ranjbar et al.	2020	CT	n=60	During routine blood sampling, facilitated tucking was observed to be less effective than oral administration of 0.5 ml of 50% dextrose, yet more effective than routine care.
Uematsu et al.	2019	CT	n=25	Incorporating a recorded Brahms lullaby along with non-nutritive sucking, facilitated tucking and holding provided more effective pain relief and helped maintain homeostasis during heel lance procedures in preterm infants.
Chuang et al.	2019	CT	n=14	Environment modification, positioning and containment, oxygen supplement, interaction and approach, and cue-based and individual care notably alleviated pain and stress responses and expedited the infants' recovery to their physiological baseline following examinations for retinopathy of prematurity.
Collados-Gomez et al.	2018	CT	n=66	Both expressed breast milk and 24% sucrose provided similar pain relief during venipuncture for most preterm infants, although sucrose was more effective for extremely preterm infants.
Qiu et al.	2017	CT	n=42	The combination of recorded lullabies with GHT may reduce the pain response in preterm neonates by significantly enhancing β -endorphin concentration, although it does not affect blood cortisol concentration.
Badr et al.	2017	CT	N=42	When infants were exposed to recorded music previously listened to by their mothers during pregnancy during a heel stick procedure, they exhibited significantly lower pain scores compared to a silent control condition. However, these scores were not lower than those observed when a recorded lullaby was played.
Herrington et al.	2014	CT	n=11	Infants who did not receive Gentle Human Touch showed decreased respiration, increased heart rate, and prolonged crying during the heel stick procedure. On the other hand, infants who received GHT did not exhibit decreased respiration, elevated heart rates, or prolonged crying during the procedure.
Chidambaram et al.	2014	CT	n=100	In comparison to the control group, the KMC group's PIPP scores were lower at 15 and 30 minutes following the heel prick. The KMC group's mean PIPP differential from baseline to 30 minutes following heel prick was lower than that of the control group.
Alinejad-Naeini et al.	2014	CT	n=34	Facilitated tucking reduced pain in preterm infants during endotracheal suctioning.
Bahrami et al.	2023	quasi-experimental	n=52	Gentle touch alleviated infants' pain during venipuncture and blood sampling.
Rashwan et al.	2021	quasi-experimental	n=62	Mechanically ventilated neonates demonstrated significantly greater comfort levels when using "Mother scented simulated hand" compared to standard care both during and after endotracheal suctioning and heel breaking procedures. Additionally, neonates experienced significantly

				lower distress and pain scores when MSSH was used, during invasive procedures compared to standard care.
Lopez et al.	2015	quasi-experimental	n=42	Facilitated tucking resulted in lower PIPP scores in premature infants during venipuncture.
Reyhani et al.	2014	quasi-experimental	n=70	Facilitated tucking effectively reduced infant crying duration following blood sampling.
Bueno et al.	2023	longitudinal observational	n=172	Consistently low PIPP-R scores following a skin-breaking procedure indicated the analgesic effect of administering 0,12 ml 24% sucrose.

RCT: randomized controlled trial; CT: crossover trial

4. Discussion

Williams et al. [13] and Ranger et al. [14] investigated the use of "Calmer" in reducing preterm infants' pain. Calmer was developed to address the challenge of parental availability in the NICU environment, particularly when infants are not medically stable enough for extended holding periods. It is designed to complement, not replace, parental care. Both studies demonstrated that Calmer effectively reduces pain, underscoring its importance as a valuable device to fill the gap in care when human-based treatments are not feasible. Ranger et al.'s study, which utilized Near-Infrared Spectroscopy (NIRS) to assess cerebral response to pain, is significant due to previous findings that link decreased regional cerebral tissue oxygenation with cerebral injury and adverse neurodevelopmental outcomes [56, 57].

Belpinar et al. [15], Dur et al. [16] and Dehghani et al. [17] explored the effects of Yakson touch in alleviating pain in premature infants. These studies demonstrated that Yakson touch significantly reduces pain scores and physiological indicators of pain during various procedures, including nasal prong application, heel lancing, and phlebotomy. Yakson touch showed comparable outcomes to gentle human touch and oral glucose in terms of pain relief during these invasive procedures. Although it did not prove superior to the other two methods, the consistent significant reductions in pain scores and physiological distress highlight its potential as a valuable addition to pain management for premature infants. Importantly, Yakson touch does not require special equipment, making it an easily accessible option in clinical settings.

Previous scientific teams [18-21] have studied the analgesic effects of music on preterm infants. These studies revealed that music is a safe and effective method for pain relief, showing promising results compared to standard care. Whether it was Brahms lullabies, Mozart's compositions, nursery rhymes, or melodies sung by mothers, the use of music consistently led to lower pain scores and improved physiological responses. Benefits observed from music interventions, such as increased time spent in quiet alert states and reduced respiratory rates, further highlight its value in promoting comfort and well-being during medical procedures. These results suggest that incorporating music into neonatal care protocols could be highly beneficial. In understanding Qiu et al.'s results [20], it is important to note that pain triggers an endocrine response that increases cortisol levels. β -Endorphin, an endogenous opioid released in response to pain, can block pain signals. The researchers believe that the intervention combining music and touch might have alleviated the pain response in preterm infants by significantly improving β -endorphin concentration.

Alemdar et al. [23] provided evidence supporting the effectiveness of maternal heartbeat sounds (HBs) in reducing pain compared to a control group. However, Wu et al. [24] found that adding mother's HBs to breast milk odor therapy (BM-OT) alone was less effective in reducing pain compared to the combined intervention of BM-OT, HBs, and non-nutritive sucking (NNS). Nonetheless, it is noteworthy that when NNS is not suitable for preterm infants, such as in cases involving the prevention of nipple confusion, oral surgery, or oral endotracheal tube insertion, the integration of BM-OT and HBs can still offer a valuable approach for relieving stress and enhancing comfort during medical procedures. Thus, incorporating prerecorded maternal heart sounds into care routines, especially when complemented with additional techniques like NNS, can serve as a promising strategy for alleviating pain and enhancing comfort among preterm infants undergoing medical interventions.

Gentle human touch (GHT) has been proven to be an effective non-pharmacological intervention for promoting comfort and minimizing pain in neonatal care settings, according to Herrington et al. [26], Bahrami et al. [28], Fatollahzade et al. [27], Sezer Efe et al. [25], and Efendi et al. [29]. Infants who received GHT, either alone or in combination with other

interventions, exhibited notable improvements, including stabilized respiratory rates, heart rates, and reduced crying during procedures such as heel lancing, venipuncture, blood sampling, and suctioning.

Previous evidence [30-34] suggests that sucrose is an effective analgesic method for various painful procedures in premature infants. Specifically, sucrose, either alone or in combination with music, demonstrated analgesic effects during and after venipuncture. Consistently low PIPP-R scores following skin-breaking procedures indicated the analgesic effect of administering 0.12 ml of 24% sucrose. Furthermore, sucrose exhibited comparable effectiveness to dextrose, oral melatonin, and expressed breast milk (EBM) in alleviating pain during different procedures. However, in extremely preterm infants, sucrose was found to be more effective than EBM. These findings highlight sucrose as an effective analgesic option for premature infants undergoing painful procedures. Furthermore, Bueno et al. conducted a randomized trial involving preterm neonates who were assigned to receive either sucrose or distilled water orally for every potentially painful procedure within the initial 7 days after enrollment. Neurodevelopmental status was assessed at 40 weeks post conceptional age using the domains of the Neurobehavioral Assessment of Preterm Infants scale, finding that sucrose did not lead to adverse neurodevelopmental outcomes, thus making it a safe method of analgesia. However, Johnston et al.'s study [58], published in 2002, found that administering higher doses of sucrose (>10 doses per day) was linked to lower scores in motor development, vigor, alertness, and orientation at 36 and 40 weeks gestation. Therefore, they could not recommend the routine use of sucrose analgesia for every painful event in infants <32 weeks' post conceptional age, despite substantial evidence of its immediate beneficial effects. A systematic review published in 2010 expressed concerns about the potential impact on neurodevelopmental outcomes associated with the repeated administration of oral sucrose for pain relief [59]. Lago et al. [36] found no differences in pain perception between infants that received a single standard dose of sucrose before heel prick and those that received a double dose of sucrose 2 minutes before and 30 seconds after heel prick. Therefore, they do not recommend repeating doses during this procedure. Another noteworthy study is Slater et al.'s [60] research, which concluded that oral sucrose lacks a significant effect on nociceptive circuits in the neonatal brain or spinal cord, suggesting that it may not be an effective pain-relieving method. Therefore, the observed reduction in clinical observational scores following painful events in newborn infants should not be equated with pain relief.

Studies investigating the effect of Kangaroo Mother Care (KMC) as an analgesic method have highlighted its valuable role in alleviating pain among preterm infants undergoing various medical procedures. Notably, KMC outperformed sucrose administration, which has been associated with adverse effects in the literature [39]. Additionally, the combination of KMC with complementary approaches can offer enhanced pain relief benefits for preterm infants undergoing medical interventions [41].

According to the findings of the included studies [10, 42–47] on facilitated tucking, this method was found to be effective for pain relief in premature infants undergoing various medical procedures. Facilitated tucking demonstrated a reduction in pain across different procedures such as venipuncture, blood sampling, and endotracheal suctioning. Although it was less efficacious than oral dextrose and the combination of swaddling with expressed milk in some instances, facilitated tucking was still superior to routine care in reducing pain. Additionally, the inclusion of facilitated tucking was shown to enhance the recovery phase following painful procedures, suggesting its potential value in promoting post-procedural comfort for premature infants.

Usta et al. [48] found that the inhalation of lavender scent was an effective method of pain control in premature infants. Aromatherapy begins when aroma molecules are absorbed through the nasal mucosa. These molecules are then transformed into nervous signals in the olfactory bulb, amygdala, and the limbic system, triggering the release of neurotransmitters like enkephalin, endorphins, and serotonin, which produce therapeutic effects. This method is easily used and does not interfere with medical care.

Yazdanpanahi et al. (49) investigated the efficacy of developmental supportive positioning in relieving pain caused by venipuncture. This method involved placing each infant on their side or stomach inside a nest for 20 minutes, with their arms bent and positioned near their face, and their legs bent towards their abdomen. Their shoulders and pelvis were gently rounded to maintain a fetal-like position. The findings revealed significant differences between the intervention and control groups in mean scores of facial expression changes, heart rate, and neonatal blood oxygen saturation at two and five minutes following needle removal. However, there was no notable difference in the mean respiratory rate of neonates at these time points. Notably, the initial respiratory rate was significantly lower in the intervention group compared to the control group, indicating a calmer state immediately after needle insertion, possibly due to the prior administration of developmental supportive care.

Kahraman et al. [50] investigated the effects of white noise (intrauterine sounds), recorded mother's voice, and ear protectors on pain reduction during heel lance. Previous studies have found that fetuses begin to detect and react to

auditory stimuli as early as 24–25 weeks gestation [61]. In the womb, the fetus is exposed to sounds such as the mother's voice, bowel sounds, and heartbeat, which help safeguard the fetus and aid in transitioning to life outside the womb [62]. This study found that sound stimulation, mostly white noise, was more effective in alleviating pain than reducing environmental sounds. Given the ability of auditory interventions to distract infants during invasive procedures, the authors suggest that in situations where the mother's voice is unavailable or she is absent, medical staff can use white noise. Additionally, recording the mothers' voices for infants to listen to can facilitate pain management when maternal involvement is not feasible.

Bagheri et al. [51] tested whether massage therapy is an effective method of reducing pain caused by umbilical vein catheter insertion. Following umbilical vein catheter insertion, infants in the massage therapy group and the control group experienced an increase in heart rate, with a more pronounced increase in the control group. During insertion, arterial oxygen saturation decreased in both groups, with a greater decline seen in the control group. The mean PIPP score change was approximately three and a half times higher in the control group than in the experimental group. Moreover, the majority of infants in the experimental group restored their initial heart rate in less than 30 seconds, while it took over 120 seconds for most infants in the control group. Similarly, most infants in the experimental group regained their initial oxygen saturation level in less than 30 seconds, whereas it took over 120 seconds for the majority of infants in the control group. These results indicate that massage therapy was effective in alleviating pain.

Chuang et al. [52] found that environmental modification, positioning and containment, oxygen supplementation, interaction and approach, and cue-based and individual care effectively reduced pain and stress responses. These interventions also shortened the recovery time needed for infants to regain their physiological status following examinations for retinopathy of prematurity.

Mother Scented Simulated Hand (MSSH) is a specially designed supportive pillow that mimics the touch of a human hand. It replicates the shape, weight, warmth, and comforting touch of a real hand, providing a sensation similar to being hugged. The MSSH is infused with the mother's body odor, known to promote relaxation and calmness. It is used by placing one hand of the MSSH on the infant's head and the other on their lower body and extremities, combining tactile and olfactory stimulation. Tactile stimulation activates pressure receptors, which then stimulate the vagal nerve, increasing its activity and creating a calm and relaxed response. Maternal scent can decrease stress-related behaviors in newborns through olfactory stimulation. Rashwan et al. [54] used MSSH in their study to investigate its effects on enhancing comfort among mechanically ventilated preterm infants during invasive procedures. The study revealed that infants wrapped with MSSH had lower NRS-distress and NRS-pain scores during endotracheal suctioning and heel prick procedures, indicating a higher level of comfort compared to infants in the control group. Moreover, the mean SpO₂ levels of neonates in the MSSH group were significantly higher than those in the standard care group during both endotracheal suctioning and the heel prick procedure. Additionally, applying MSSH resulted in an increase in mean SpO₂ levels after suctioning compared to baseline. Overall, MSSH was found to be an effective method of reducing pain, especially in instances where the infants' mothers are unavailable in the NICU.

It is worth noting though that Holsti et al. [63] encourage clinicians to use sucrose with caution and explore alternative non-pharmacological comfort strategies. However, additional research is needed to validate this theory. Moreover, using a combination of two or more non-pharmacological interventions may be more effective than relying on a single method for pain reduction [64]. The effectiveness of this approach lies in its basis in sensorial saturation, meaning that tactile, gustatory, auditory, and visual stimulation could deliver more effective pain management [65].

Limitations

One limitation of this systematic review is the inclusion of various types of studies, such as randomized controlled trials, observational studies, and quasi-experimental studies. Due to the heterogeneous nature of these study designs, we did not conduct a comprehensive methodological assessment. This variability in study design might affect the consistency and comparability of the findings, potentially influencing the overall conclusions drawn from the review. Additionally, the lack of methodological assessment means that potential biases and differences in study quality were not formally evaluated, which could impact the reliability of the synthesized evidence.

5. Conclusions

Kangaroo mother care, massage, Yakson touch, gentle human touch, music therapy, mother's voice, white noise, maternal heartbeat sounds, facilitated tucking, sucrose administration, olfactory stimulation, the use of "calmer," environment modification, expressed breast milk, the mother scented simulated hand and combinations of these methods have proven effective in reducing pain in preterm infants undergoing various medical procedures.

Nevertheless, conducting large-scale, multicenter randomized controlled trials to establish stronger evidence for the efficacy and safety of various non-pharmacological interventions as well as comparative effectiveness research to determine the most beneficial combinations of interventions is imperative. The field of neonatology and neonatal care can advance by the development of standardized protocols and guidelines for the use of non-pharmacological interventions in NICUs along with policy changes that support the integration of them in neonatal care settings.

Compliance with ethical standards

Disclosure of conflict of interest

All authors declare that they have no conflicts of interest.

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