Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.64, No.1(2024). p.66-77 ; DOI: https://doi.org/10.14238/pi64.1.2024.66-77

Original Article

Effects of non-pharmacological methods on post-operative procedural pain management in neonates admitted in the neonatal intensive care unit: A systematic review

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Abstract

Background In the post-operative period during the NICU stay, neonates must undergo various painful procedures. Non-pharmacological methods may be beneficial in managing the harmful effects of procedural pain on the development of neonates in their early life.

Objectives To investigate the effect of non-pharmacological methods on post-operative procedural pain in neonates admitted to neonatal intensive care units.

Methods A search in electronic databases was done to identify randomized clinical trials published from 2010 to 2020 that encompassed neonates undergoing painful procedures in the NICU and followed PRISMA guidelines. Studies with non-human subjects, neonates with unstable vital signs, non-clinical studies, and incomplete methodology were excluded. *PubMed, Cochrane, and Physiotherapy Evidence Database* (PEDro) were evaluated respectively using *Medical Subject Headings* (MeSH) and *Health Sciences Descriptors* (DeCS).

Results Two reviewers examined articles independently and found 11 articles that met the study's inclusion criteria, with a total of 955 neonates with non-pharmacological methods of pain management in neonates. Non-pharmacological methods, such as massage therapy, oral sucrose, kangaroo mother care, and facilitated tucking showed significant reduction in pain scores among neonates who underwent painful procedures in NICU. Outcomes showed variability in effectiveness, emphasizing the need for tailored approaches.

Conclusions The findings indicated that non-pharmacological methods can effectively manage pain in neonates admitted to the NICU. Pain management improves the clinical condition of neonates and promotes parents-neonate bonding, with consequent reduction in length of stay in the hospital. **[Paediatr Indones. 2024;64:66-77; DOI: 10.14238/pi64.1.2024.66-77**].

Keywords: *: infant; neonates; newborns; NICU; procedural pain; pain management*

Pain is an unpleasant sensory and emotional experience associated with actual and potential tissue damage.[1] Neonates also experience pain similar to older children and adults. Neonates who go through various medical procedures experience acute pain. These procedures cause discomfort in the neonates, which may limit their capacity to adjust to their environment, cause stress, and disrupt their physiological balance. Therefore, it is crucial to avoid and reduce pain in neonates.[2] Evidence shows that pain control in the neonatal period helps improve behavioral, hormonal, and physiological outcomes.[3] By avoiding painful interventions, neonatal pain can be managed effectively. However, various therapeutic and diagnostic procedures are conducted in the NICU.[3]

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Submitted July 26, 2022. Accepted February 27, 2024.

In addition, disproportionate light and noise with the frequent handling of neonates increase the initial painful stimulus. Because of this, the clinical outcome is negatively affected.[4]

The inability to treat pain in neonates can lead to short-term complications and long-term physiological changes, which include hypoglycemia, an increase in the release of cortisol, aldosterone, and antidiuretic hormone, and protein catabolism increase.[5] There is an increase in the release of glutamate due to early exposure to procedural pain, as during early life, glutamate N-methyl-D-aspartate receptors are more active and involved in transmitting pain signals.[6] In the immature neonatal brain, the greater release of glutamate triggers the inflammatory process and causes stress.[7]

There are various non-pharmacological management approaches for pain reduction, such as kangaroo mother care (KMC), facilitated tucking, non-nutritive sucking, sucrose and other sweeteners, massage therapy, and acupressure.[8] These pain management methods have been shown to be effective in the NICU. Massage therapy decreases pain in infants in a similar way to skin-to-skin contact. Facilitated tucking has been reported to reduce infants' crying time.[9] Non-pharmacological management can be employed when there are contraindications or parents' unwillingness to the administration of pharmacological painkillers. Distraction techniques, both physical and psychological, are crucial in these situations.[10] Physical and psychological distraction techniques offer an added benefit in pain relief, even in patients who use analgesics.[11]

For these reasons, it is important to review the effects of non-pharmacological methods in managing post-operative procedural pain. This study aims to review the effects of non-pharmacological methods on post-operative procedural pain management in neonates.

Methods

The systematic review is registered in *PROSPERO* (CRD42021267836) and follows the *PRISMA 2020* statement.[12] The following steps were used to find relevant studies: identifying the topic, developing the research question, and deciding the inclusion and exclusion criteria. The required information was extracted from the selected studies, which were thoroughly evaluated. Results are described in table format and the review was presented. The published literature of the last 10 years was searched using the databases *PubMed, Cochrane, Physiotherapy Evidence Database* (PEDro), and *EBSCO*.

Descriptors for Science and Health (DeCS) and *Medical Subject Headings* (MeSH) were used for the search strategy, using booleans such as 'AND' or 'OR.' Descriptors used for searching the articles are as follows: neonatal pain, kangaroo mother care, facilitated tucking, nest position, massage therapy, oral sucrose, acupressure, soft tissue therapy, and reflexology. The search strategy was defined as follows: neonatal surgeries AND pain, neonatal procedural pain AND Management, neonatal pain AND non-pharmacological methods, neonatal pain AND facilitated tucking, pain in neonates AND oral sucrose, neonatal pain AND kangaroo mother care AND facilitated tucking, neonatal pain AND NICU, neonatal pain management AND non-pharmacological methods.

We included randomized clinical trials published between 2010 and 2020. The subjects had to include neonates of both sexes, preterm, term, and post-term neonates who underwent various painful procedures in the NICU. Studies performed on non-human subjects, neonates with unstable vital signs, non-clinical studies, and studies with an incomplete description of the methods were excluded.

Investigators independently assessed the selected articles. The investigator (AS) first read the titles and abstracts of all identified studies to screen for relevance. A second reviewer (AC) resolved any discrepancies. The full-text versions of the articles selected in the first stage were read and again compared to the eligibility requirements in the second step. Any disagreements were settled by consensus, with the help of a third reviewer (NS), if necessary. When possible, we contacted authors of the studies for additional information.

The PEDro scale (http://www.pedro.fhs.usyd.edu.au) was used for quality assessment to determine the internal validity of the included studies. The PEDro scale is an 11-item scale assessing qualities such as allocation concealment, blinding, intention-to-treat analysis, and adequacy of follow-up. Each item was

given a score of 1 if the condition is met and 0 if it not met. The total score was calculated as the sum of all item scores. Each correct response was worth one point, except for the first item, which is distinct from the others because it is linked to the study's external validity.[12]

Microsoft Excel (*Microsoft*, Redmond, WA) was used for data collection and statistical analysis. *Review Manager (RevMan) 5.4* software (*The Nordic Cochrane Centre*, Copenhagen) was used to assess the risk of bias.[13]

Results

The flow of the selection of studies for review is shown in **Figure 1**. The included studies are summarized in the **Appendix**. Initially, 308 articles were identified in the searched databases. Out of these articles, 243 were excluded after applying filters (year of publication, involving human subjects, sex, and age). Of these, 20 were irrelevant to non-pharmacological management for neonates. After title and abstract screening, 30 articles were excluded. Fifteen articles were selected for review. Three more articles were subsequently excluded due to insufficient methodology, yielding 11 studies to be included in the review. The results of quality assessment of the studies are presented in **Table 1**.

When assessed for the risk of bias, almost all studies had a high risk of bias in allocation concealment and blinding of outcome. About half of the studies had a high or uncertain risk regarding the blinding of participants and professionals, incomplete outcomes, and other sources of bias. Only the item reporting incomplete outcome data and the selective outcome was the one with the lowest risk of bias since the study protocols and their primary outcomes were reported in detail (**Figure 2**. and the graph is shown in **Figure 3**.[25]

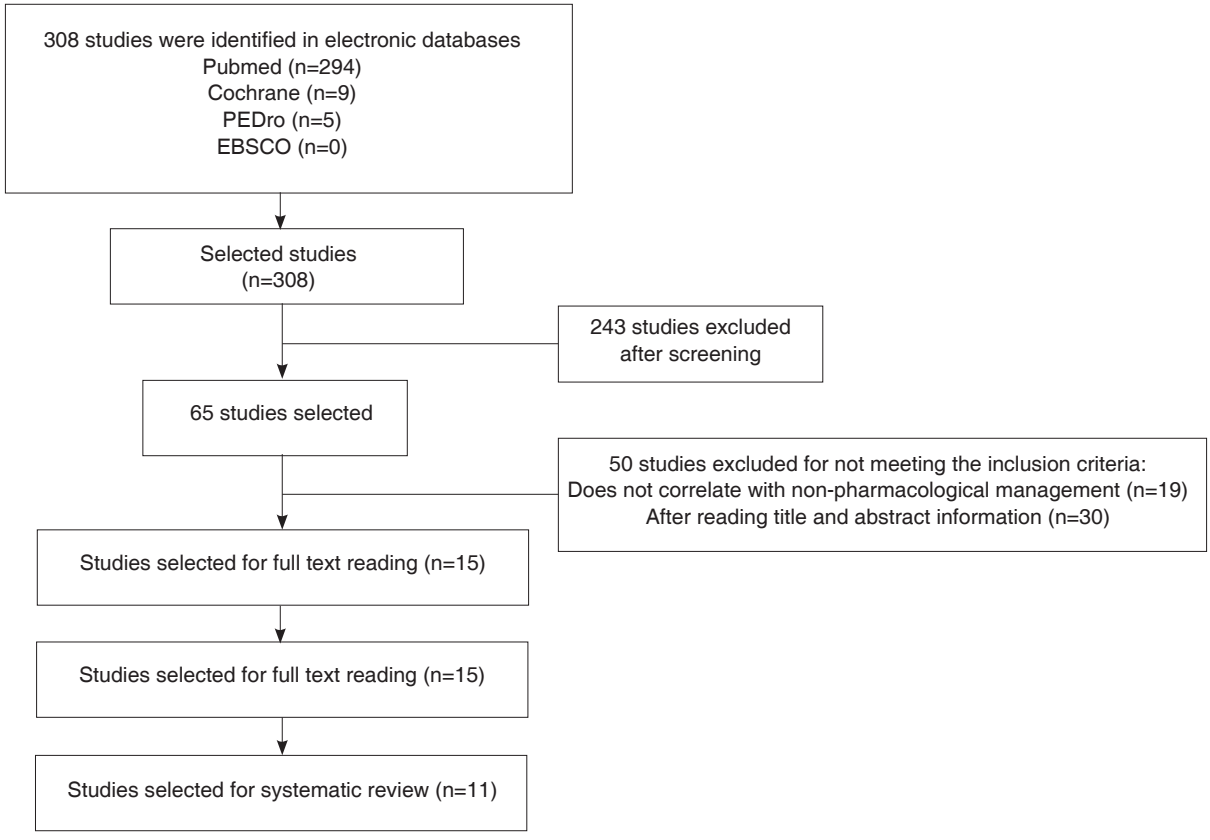

Figure 1. Flowchart of study selection

Table 1. Methodological quality assessment of included studies according to PEDro scale

Author/year	Criteria											
	1	2	3	4	5	6	7	8	9	10	11	Total score
Bayomi *et al.*[14] (2015)	1	-	-	-	1	-	-	1	1	-	1	5
Yin *et al.*[15] (2015)	1	1	-	1	-	1	1	-	1	1	1	8
Chik *et al.*[16] (2016)	1	1	1	1	1	1	-	-	1	1	1	9
Banga *et al.*[17] (2016)	1	1	1	1	1	-	1	-	1	1	1	9
Liaw *et al.*[18] (2011)	1	1	-	1	1	-	-	-	1	1	1	7
Stevens *et al.*[19] (2018)	1	1	1	1	-	1	-	-	1	1	1	8
Sundaram *et al.*[20] (2013)	1	1	1	1	-	-	1	-	1	1	1	8
Cong *et al.*[21] (2012)	1	1	1	1	-	1	1	-	1	1	1	9
Alinejad-Naeini *et al.*[22] (2014)	1	1	-	1	-	1	-	1	1	1	1	8
Mitchell *et al.*[23] (2013)	1	1	-	1	1	-	-	-	1	1	1	7
Gao *et al.*[24] (2015)	1	1	-	1	-	-	1	-	1	1	1	7

Criteria: 1. eligibility criteria, 2. randomization, 3. concealed allocation, 4. baseline similarity of groups, 5. blinding of subjects, 6. blinding of therapist, 7. blinding of assessors, 8. less than 15% drop-out, 9. intention-to-treat analysis, 10. statistical comparison of between-group, 11. variability of data and point measures. Each point of PEDro met is scored 1. The maximum total score is 10.

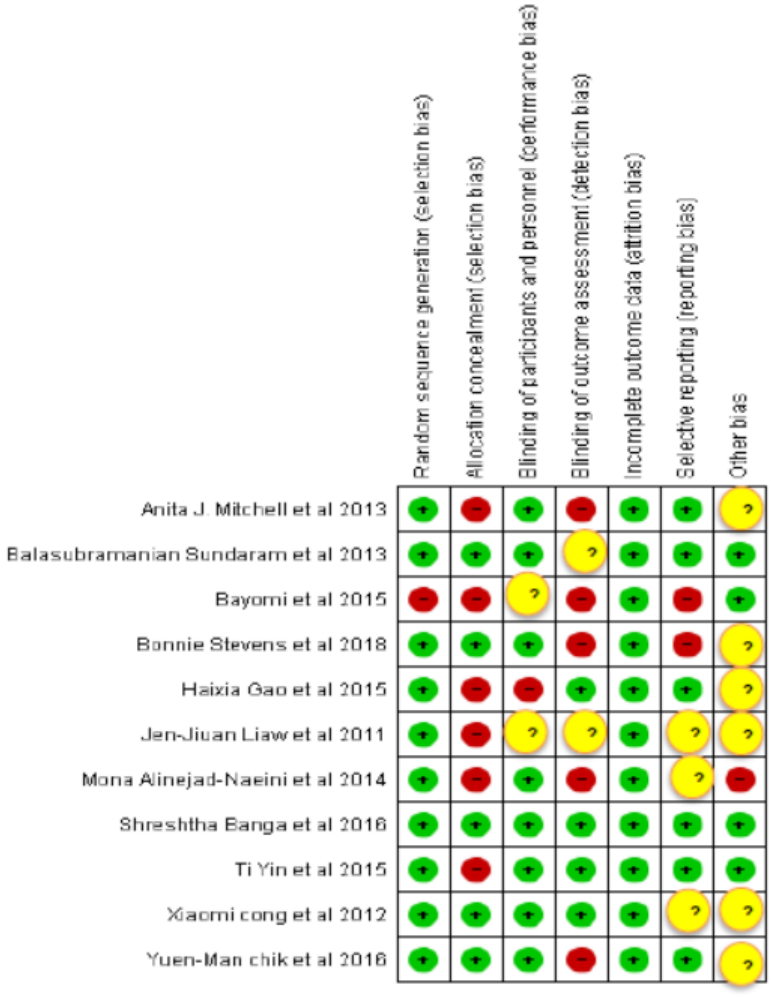

Figure 2. Risk of bias of individual studies

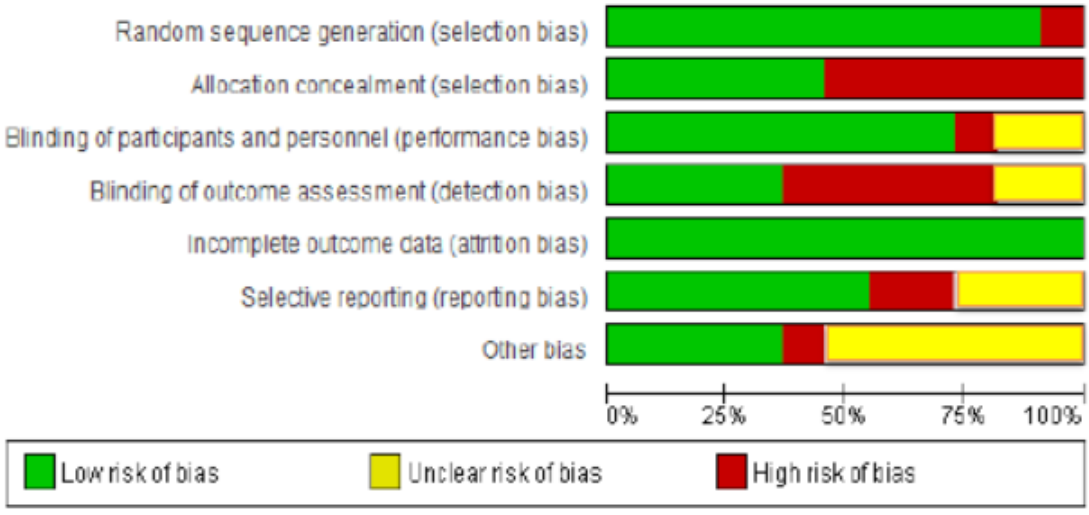

Figure 3. Risk of bias as percentages across all included studies

Discussion

In the present review, the effect of non-pharmacological methods on post-operative procedural pain was analyzed. This review mainly focuses on procedural pain due to various painful invasive procedures that a neonate must undergo during the post-operative period. Both the surgical procedure and ongoing post-operative procedures cause infants to feel discomfort during the recovery phase. Previously, it was stated that massage therapy application on neonates has resulted in weight gain, reduced stress levels, and a crying state.[26] The various ongoing procedures in the NICU may lead to an adverse neurodevelopmental outcome.[27]

Early exposure of neonates to painful stimuli has various adverse effects on the developing brain of neonates. Multiple changes in cerebral structures and pain may be a potential factor in somatosensory changes.[3] The massage therapy showed that applying various techniques on neonates can reduce the chances of neonatal pain, which, if not appropriately managed, can lead to severe alteration in neonates' behavioral and cognitive state. Various pharmacological measures used in the NICU for controlling and managing pain in neonates.[28] These measures help manage procedural pain and other types of pain, such as chronic pain.[29] The pharmacological measures have side effects, which can adversely affect the growth and development of neonates.[30] Morphine is the drug of choice for managing pain in neonates, but it has a major side effect of hypotension and alters the pulmonary mechanics, leading to bronchospasm.[31] To avoid these side effects, non-pharmacological measures in managing the procedural pain in neonates are needed.[32]

Apart from morphine, fentanyl is considered a more potent drug in managing pain in neonates but has the major side effect of bradycardia and can lead to chest wall rigidity, compromising ventilation.[33] Massage therapy also provides tactile stimulation for neonates.[34] It is considered that neonates who have received the moderate pressure massage had increased weight gain, increased activation of the natural killer cell, and reduced hospitalization stay.[35,36] Various non-pharmacological methods can prevent pharmacological side effects and are frequently used in NICU. The KMC is the potential method for reducing autonomic pain responses in neonates admitted to ICU.[21]

KMC is a very effective technique for neonates 30 minutes before the heel stick procedure. In their study, they have divided two groups of neonates, and neonates who received KMC before repeated heel stick procedures showing reduced pain responses. There was a significant reduction in the grimacing and crying of neonates who received KMC before the painful heel stick procedure.[13] However, in a previous study, KMC did not show any effect during the suctioning procedure, which indicated that pain

management is required during the endotracheal suctioning procedure.[23] Facilitated tucking is an effective non-pharmacological measure in reducing pain among neonates during suctioning. The neonates who received suctioning with facilitated tucking have shown reduced pain scores.[9] Another study concluded that facilitated tucking is an effective non-pharmacological technique that can be used in NICU.[20]

Massage therapy as a non-pharmacological intervention has shown its effects on the physical, physiological, and behavioral patterns of neonates admitted to NICU. Massage therapy has positively impact them, and there is a significant reduction in pain scores in neonates.[14] Similarly, massage therapy on the upper limb among neonates who will have painful venepuncture concluded that massage therapy had reduced the pain scores in neonates when applied 2 minutes before treatment.[16] In a previous study, the effects of sucrose analgesia on short-term neurobehavioral outcomes in preterm neonates for repeated painful procedures were analyzed. They divided neonates into two groups and administered a 24% sterile solution of sucrose orally and another group with distilled water 2 minutes before any painful routine care procedure for 7 days. They concluded that sucrose solution and distilled water have no effect in controlling pain in neonates.[17]

A "spinal gating mechanism" in the dorsal horn of the spinal cord controls the transmission of painful impulses and is controlled by activity in the large-diameter nerve fibers.[7] The activity of large-diameter nerve fibers affects the gating mechanism; stimulation of these fibers 'closes the gate' and prevents the transmission of pain along ascending fibers.[37] Massage may change other natural painkillers like serotonin and substance P, as well as descending endogenous opioid and non-opioid pathways to decrease nociceptive transmission and lessen pain. It is also possible that massage causes a soothing sensation.[38]

Liaw et al. studied the effect of three non-pharmacological methods on pain in neonates during hepatitis B vaccination. They divided neonates into three interventional groups: the non-nutritive sucking group, the oral sucrose group, and the routine care group. They found that both non-nutritive sucking and orally administered sucrose are effective in managing pain in neonates when given 1 minute before vaccination.[18] The minimum effective dose of sucrose in neonates undergoing heel stick procedures in NICU was also studied, but there is no significant difference in pain scores among neonates. They found that the effective dose of 20% sucrose was 0.1 mL.[19] On comparison of three non-pharmacological methods, which included non-nutritive sucking, oral sucrose, and facilitated tucking in neonates before, during, and after the painful heel stick procedure. These methods have shown a reduction in the withdrawal behavior of neonates and there is a reduction in grimace and crying among them.[39]

Neonatal perceptions of pain are affected by birth weight, gestational week, postpartum age, gender, and the type of birth. Infants that cannot speak use crying as a form of communication. Crying is accepted as an important behavioral indicator for the assessment of pain in infants.[33] Given the effects of short-term and long-term pain on various aspects of neonatal development and well-being, prevention and treatment of pain in neonates are of utmost importance. Despite the wide range of procedures that result in pain in newborns, the amount of pain management done by medical personnel for these patients is still limited.

Additional randomized clinical trials are required to assess whether combining two or more approaches to comparing merely one technique to pharmaceutical and adjuvant therapies. The latter reduces procedure discomfort more effectively. There is a lack of development of proper non-pharmacological methods protocol, which includes adequate positioning of neonates, time duration, and application of techniques. Therefore, there is a requirement for more randomized controlled trials and blind studies that can elucidate a proper way of technique application.

In this study, all the non-pharmacological methods are included and have shown their effects among neonates who underwent a painful procedure, which is performed to check their prognosis. Newborns frequently undergo painful, invasive procedures such as heel sticks because they are required for treatment. Neonatal pain may have long-lasting impacts later in life since neonates are just as susceptible to painful stimuli as adults. As a result, managing and mitigating newborn pain is a crucial aspect of neonatal healthcare. Non-pharmacological methods, either alone or in combination with pacifier usage, are

beneficial in lowering pain responses in newborns, and these low-tech pain-relieving measures should be considered.

Conflicts of interest

None declared.

Funding acknowledgment

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

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Appendix

Characteristics of studies included in the systematic review

Authors and years	Study objectives	N	Interventions	Outcome measures	Results	Conclusion	Study type
Bayomi *et al.*[14] (2015)	Effect of applying massage on premature neonates and their behavioral, physical, and physiological aspects.	64	Massage therapy was given to neonates for approximately one hour which consists of 5 minutes of tactile stimulation, 5 minutes of kinesthetic stimulation by stroking, and concluded with another 5 minutes of tactile stimulation (total of 15 minutes)	1. Premature neonates massage observation sheet 2. Neonatal infant pain scale (NIPS)	Neonates with mild, moderate, and severe pain showed reduction in pain level after massage therapy.	Applying massage during NICU stay has a positive impact on physical, behavioral, and physiological aspects of neonates, reduction in pain scores with reduced length of stay in hospital.	Quasi-experimental study
Yin *et al.*[15] (2015)	Effect of three non-pharmacological interventions (non-nutritive sucking, facilitated tucking, and oral sucrose) on the behavior of neonates before, during, and after heel stick procedure.	110	Neonates were assigned to five combinations of nonpharmacological methods: (1) routine care, (2) non-nutritive sucking + facilitated tucking, (3) oral sucrose + facilitated tucking, (4) non-nutritive sucking + oral sucrose, and (5) non-nutritive sucking + oral sucrose + facilitated tucking.	1. Neonatal Facial Coding System (NFCS) 2. Physiological paramaters such as heart rate (HR) and respiratory rate (RR)	Withdrawal behaviors of neonates were significantly reduced in the intervention groups; the frequency of grimaces decreased to 32.2%, 30.6%, 19.7%, and 13.8% in the 2nd, 3rd, 4th, and 5th group, respectively.	The combined effect of non-pharmacological methods has shown the reduction in withdrawal behaviors of neonates during the prognostic procedures performed.	Prospective, randomized controlled trial.
Chik *et al.*[16] (2016)	Effects of massage on an upper limb among neonates going for venipuncture	80	Neonates were divided into 2 groups each group consisting of n=40 neonates. The “massage first” group received massage for 2 minutes before venipuncture on the first occasion and the second group received routine care for 24 to 48 hours followed by massage.	1. Premature infant pain profile (PIPP)	Mean pain scores were significantly reduced in the massage group.	Massage therapy is an effective way in managing pain from venipuncture in the upper limb.	Crossover study
Banga *et al.*[17] (2016)	The effects of sucrose analgesia on preterm neonates' short-term neurobehavioral outcomes for repeated painful procedures.	93	The neonates recruited in the study were administered orally either with 24% sucrose sterile solution or with double distilled water 2 minutes before each painful procedure for a 7-days period.	1. Score of motor development and vigor (MDV) 2. Neurobehavioral Assessment of Preterm Infants (NAPI)	Sucrose analgesia did not produce any significant difference in results from distilled water.	Oral sucrose in comparison with distilled water as a placebo did not lead to a poor neurobehavioral outcome in neonates. Provision of oral glucose for procedural pain in neonates for 7 days is free of any adverse effects.	Randomized controlled trial

Appendix

Characteristics of studies included in the systematic review (continued)

Authors and years	Study objectives	N	Interventions	Outcome measures	Results	Conclusion	Study type
Liaw *et al.*[18] (2011)	Effects of three different non-pharmacological methods of pain relief strategies among neonates pain, cry duration, and physiological parameters before, during, and after hepatitis B injection intramuscularly (IM).	165	The neonates received IM injections and	1. NFCS 2. Physiological parameters such as HR and RR	Pain was significantly reduced among neonates in the non-nutritive sucking group (baseline-11.27, P<0.001) and sucrose (baseline-11.75, P<0.001) groups than that in controls.	Non-nutritive sucking and oral sucrose are proved to be an effective measure in reducing pain among neonates and need to be given at least one minute before. Orally administered sucrose can reduce the pain in neonates when given 2 minutes before injection when compared to non-nutritive sucking.	A prospective randomized controlled trial.
Stevens *et al.*[19] (2018)	The minimal effective dose of sucrose among neonates who are undergoing heel lancing procedures in NICU	245	Neonates were randomized into three groups to receive one of three doses of 24% sucrose, and non-nutritive sucking, 2 min before heel lance: 0.1 mL (group 1; n=81), 0.5 mL (group 2; n=81), and 1.0 mL (group 3; n=83). The primary outcome was pain intensity measured at 30 and 60 s following the heel lance.	1. PIPP-Revised 2. Physiological parameters such as HR, RR, Oxygen saturation	No significant difference was observed in mean pain intensity between treatment groups at 30 seconds (P=0.97) and 60 seconds (P=0.93)	For treatment of pain resulting from a single heel lancing procedure, an effective dose of sucrose 24% was 0.1 mL.	A prospective multi-centered single-blind randomized
Sundaram *et al.*[20] (2013)	To analyze the effect of facilitated tucking on pain among preterm neonates in NICU.	20	The first group received the heel stick procedure with facilitated tucking in the morning and without facilitated tucking in the evening. After an adequate washout period of 12 hours, the remaining neonates received the heel stick procedure without facilitated tucking in the morning and with facilitated tucking in the evening.	1. PIPP 2. HR 3. Oxygen saturation	The result showed a significant lowering of pain score at 30,60 and 120 seconds when heel prick was done with facilitated tucking when compared with without tucking.	Facilitated tucking is an effective non-pharmacological pain management technique in preterm neonates in NICU	Randomized controlled crossover pilot study

Appendix

Characteristics of studies included in the systematic review (continued)

Authors and years	Study objectives	N	Interventions	Outcome measures	Results	Conclusion	Study type
Cong *et al.*[21] (2012)	Analyze the response of autonomic pain responses, in preterm neonates, for shorter and longer effects of KMC before, during, and after heel prick procedure.	26	Neonates were randomized to receive one of 3 different sequences of KMC for 30 minutes (KC30), KMC for 15 minutes (KC 15), and incubator care (IC) before and throughout a heel prick procedure. A sequence of KC30-KC15-IC, KC15-IC-KC30, and IC-KC30-KC15 were compared.	1. Anderson Behavioral State Scoring System (ABSS) 2. Heart rate variability (HRV)	The study showed that both longer and shorter duration of KC before and throughout the heel stick procedure can stabilize Heart rate response in preterm neonates and longer duration KC significantly affected neonates' sympathetic and parasympathetic responses during heel stick procedure.	KMC had significantly reduced the effect of autonomic pain responses in preterm neonates and KMC is a safe and effective technique for pain reduction in NICU.	Randomized cross-over study
Alinejad-Naeini *et al.*[22] (2014)	Effect of facilitated tucking on behavioral pain in premature neonates during the suctioning procedure	34	The neonates were divided into two equal groups. The first group received suctioning without intervention followed by suctioning with intervention. The second group received suctioning with intervention followed by suctioning without intervention.	1. PIPP	The results showed that there are substantially significant differences in decrease in pain scores between intervention and non-intervention groups.	Facilitated tucking is used as a safe non-pharmacological intervention in managing procedural pain.	Crossover study
Mitchell *et al.*[23] (2013)	To assess the effect of KMC in providing relief from pain beyond the skin-to-skin holding period.	38	The neonates were randomized into two groups. The first group is received KMC and the second group received standard care. Neonates in the KMC group received KMC for 2 hours daily from the 5th to the 9th day of life and the second group received incubator care.	1. PIPP 2. Salivary cortisol	The study's PIPP scores were elevated after suctioning procedure which indicated mild to moderate pain, After suctioning, average PIPP scores were 7.64 (SD 0.40) (KC group) and 7.89 (SD 0.21) SE (SC group, P=0.59). There were no significant changes in scores.	KMC did not show any change in PIPP scores after suctioning in preterm. PIPP scores after suctioning were high enough to indicate that infants may need pain relief during suctioning.	Randomized controlled trial

Appendix

Characteristics of studies included in the systematic review (continued)

Authors and years	Study objectives	N	Interventions	Outcome measures	Results	Conclusion	Study type
Gao *et al.*[24] (2015)	To analyze the efficacy of repeated KMC on repeated heel prick pain in preterm neonates.	80	The neonates were randomized into the KMC group and incubator group. During the first heel prick, both groups did not receive any intervention. During the next three heel prick procedures, the KMC group received the intervention 30 minutes before the prick and the incubator group received the routine care in the incubator.	1. Videotaping the procedure 2. HR	Within-group analyses revealed that there was a significant difference in the duration of crying and grimacing both between the baseline and recovery phases for the incubator group ($P< 0.0001$; $P<0.0001$) and the KMC group ($P=0.008$; $P=0.003$)	The study concludes that 30-minute KMC remains effective in reducing heel stick procedure pain across at least three heel stick procedures.	Randomized controlled trial