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ORIGINAL RESEARCH ARTICLE

Are Pharmacological Managements Effective than Non-Pharmacological Managements for Treating Pain in Neonates Admitted to NICU? A Systematic Review

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Abstract

Background: Neonates admitted to the Neonatal Intensive Care Unit (NICU) often undergo numerous painful procedures and interventions that, if inadequately managed, can lead to adverse neurodevelopmental outcomes and increased stress responses. Managing pain in neonates is thus essential, but the most effective approach remains unclear. While both pharmacological and non-pharmacological strategies are widely used, a systematic comparison is needed to determine which is more beneficial.

Objective: To evaluate and compare the effectiveness of pharmacological versus non-pharmacological pain management strategies in neonates admitted to the NICU.

Methods: A comprehensive search of PubMed, Cochrane Library, EMBASE, and CINAHL databases was conducted for studies published between January 2000 and October 2024. Studies were selected based on predefined inclusion criteria, including randomized controlled trials (RCTs) and observational studies that compared pharmacological with non-pharmacological pain management in neonates. Data extraction and quality assessment were independently performed by two reviewers using standardized tools.

Results: From 1200 articles only 25 studies met the inclusion criteria. Pharmacological interventions such as oral sucrose, paracetamol, and opioids were effective in reducing pain scores during acute painful procedures. Non-pharmacological strategies, including skin-to-skin contact, breastfeeding, and facilitated tucking, were equally effective and had the advantage of fewer adverse effects.

Conclusion: Both pharmacological and non-pharmacological approaches are effective in managing neonatal pain in the NICU setting. Given the non-invasive nature and low risk of side effects associated with non-pharmacological methods, they should be considered as the first line of treatment. Further studies are needed to establish standardized protocols for combining these methods to optimize pain management.

Keywords

Neonatal pain, Pharmacological management, Non-pharmacological management, NICU, Systematic review

Introduction

Neonates in the Neonatal Intensive Care Unit (NICU) are frequently subjected to painful medical procedures such as heel pricks, venipunctures, endotracheal intubations, and lumbar punctures. These interventions are necessary for the medical care and monitoring of critically ill neonates but often result in significant pain and stress. Unlike older children and adults, neonates have a lower threshold for pain and lack the ability to communicate discomfort verbally, making pain management a critical yet challenging component of neonatal care [1].

Untreated or poorly managed pain in neonates can lead to long-term negative consequences, including altered pain sensitivity, impaired cognitive and motor development, and increased risk of neurodevelopmental disorders [2]. Thus, the early and effective management of pain is not only necessary for alleviating immediate discomfort but also for promoting better long-term outcomes.

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Pharmacological interventions, such as oral sucrose, paracetamol, and opioids, are commonly used to manage pain in neonates. These agents act through physiological pathways to reduce pain perception, providing rapid and effective analgesia for procedural and post-surgical pain [3]. However, concerns about potential side effects and the risk of dependency, especially with prolonged use of opioids, have prompted the exploration of non-pharmacological alternatives [4].

Non-pharmacological interventions, including breastfeeding, skin-to-skin contact, swaddling, and facilitated tucking, have gained popularity as they provide comfort and support physiological stability without pharmacological side effects. Despite their widespread use, there is a lack of consensus on whether these methods are as effective as pharmacological interventions in managing acute pain [5].

Neonates admitted to the Neonatal Intensive Care Unit (NICU) often undergo various invasive procedures, exposing them to significant pain and stress. Pain in neonates, if left inadequately managed, can lead to short- and long-term negative outcomes, including altered neurodevelopment, heightened sensitivity to pain, and behavioral issues later in life. Managing neonatal pain is, therefore, a critical aspect of care in NICU settings. Traditionally, pharmacological methods such as opioid analgesics and sedatives have been the standard approach to pain management in neonates. However, concerns over potential side effects like respiratory depression, withdrawal symptoms, and developmental impact have raised questions about the exclusive reliance on these drugs [6].

In recent years, non-pharmacological pain management strategies, including skin-to-skin contact (kangaroo care), breastfeeding, non-nutritive sucking, and music therapy, have gained increasing attention. These methods, which are generally non-invasive and carry fewer risks, have shown promising results in reducing neonatal pain and stress responses [3,7]. However, despite the growing body of evidence supporting non-pharmacological approaches, many NICUs still prioritize pharmacological interventions, either as standalone treatments or in combination with non-pharmacological methods. The variability in pain management practices across NICUs reflects a gap in knowledge about the comparative effectiveness of these two strategies in addressing neonatal pain comprehensively.

Thus, there is a critical need to systematically compare the effectiveness of pharmacological versus non-pharmacological pain management strategies in neonates admitted to NICUs. While both approaches aim to alleviate pain, their impacts on neonatal health outcomes, safety, and long-term neurodevelopmental consequences require further investigation. Such a comparison could provide much-needed clarity for healthcare providers, enabling them to make more informed decisions regarding the most effective and safest methods of managing neonatal pain. Addressing this gap in research could lead to improved guidelines and practices, ultimately enhancing the quality of care for neonates in critical care settings [8].

This systematic review aims to evaluate and compare the effectiveness of pharmacological and non-pharmacological pain management strategies in neonates admitted to the NICU. By synthesizing existing evidence, this review will provide insights into which approach is more effective and identify potential areas for future research.

The significance of this systematic review lies in its comprehensive evaluation of pharmacological and non-pharmacological interventions for managing pain in neonates admitted to the Neonatal Intensive Care Unit (NICU). Effective pain management in neonates is crucial because inadequate or poorly managed pain can have short- and long-term adverse effects on neurodevelopment and stress responses, potentially impacting the overall health and quality of life of these vulnerable infants. By comparing the efficacy of both pharmacological approaches, such as oral sucrose and opioids, and non-pharmacological methods, like skin-to-skin contact and breastfeeding, this review provides valuable insights for clinicians to make informed decisions on optimizing pain management strategies in NICUs.

Furthermore, highlighting the relative safety and effectiveness of non-pharmacological interventions reinforces their role as a first-line option, reducing the need for invasive pharmacological treatments and minimizing the risk of adverse effects. This review not only addresses a critical gap in the literature but also sets the stage for developing standardized, evidence-based guidelines that can be universally applied in neonatal pain management protocols, ultimately enhancing care outcomes and promoting better recovery and development in neonates.

Methods

Study design

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].

Eligibility criteria

Population: This review focused on studies that included neonates (both preterm and full-term) admitted to the NICU and who underwent painful procedures.

Interventions: Pharmacological pain management interventions included the use of sucrose, paracetamol,

and opioids. Non-pharmacological pain management strategies included breastfeeding, skin-to-skin contact, swaddling, and facilitated tucking.

Comparators: Studies that compared pharmacological with non-pharmacological pain management interventions, or a combination of both, were included.

Outcomes: The primary outcome was pain reduction, measured using validated pain scales such as the Neonatal Infant Pain Scale (NIPS) and the Premature Infant Pain Profile (PIPP). Secondary outcomes included physiological stability (e.g., heart rate, oxygen saturation) and adverse events.

Study design: Eligible studies included randomized controlled trials (RCTs), cohort studies, and observational studies.

Language: Only studies published in English were included in this review.

Information sources and search strategy

A comprehensive search was conducted in PubMed, Cochrane Library, EMBASE, and CINAHL databases for studies published between January 2000 and October 2024. The search strategy combined Medical Subject Headings (MeSH) terms and keywords such as "neonatal pain," "pharmacological management," "non-pharmacological management," "NICU". And a detail search was done by using terms like; ("Neonate*" OR "Newborn*" OR "Infant*" OR "Preterm*" OR "Premature*") AND ("Neonatal Intensive Care Unit" OR NICU OR "Intensive Care, Neonatal") AND ("Pharmacological" OR "Analgesia" OR "Opioids" OR "Morphine" OR "Fentanyl" OR "Acetaminophen" OR "Paracetamol" OR "NSAIDs") AND ("Non-pharmacological" OR "Kangaroo care" OR "Breastfeeding" OR "Non-nutritive sucking" OR "Music therapy" OR "Swaddling") AND (Pain OR "Pain management" OR "Pain response" OR "Acute pain" OR "Procedural pain"). Additionally, the reference lists of included studies were manually screened to identify any additional relevant articles.

Study selection and data extraction

All identified studies were imported into reference management software, and duplicates were removed. Two independent reviewers (G.T. and T.K.) screened the titles and abstracts for relevance. The full texts of studies deemed potentially eligible were reviewed to confirm their inclusion. Any disagreements were resolved through discussion or by consulting a third reviewer. Data extraction was conducted using a standardized form, capturing details on study characteristics, population, interventions, comparators, outcomes, and key findings.

Quality assessment

The quality of RCTs was evaluated using the Cochrane Risk of Bias Tool, assessing factors like random sequence generation, allocation concealment, blinding, and outcome reporting. Observational studies were evaluated using the Newcastle-Ottawa Scale, which examines selection, comparability, and outcome domains. Based on these assessments, studies were classified as having low, moderate, or high risk of bias.

Results

Study selection

The initial search resulted in 1,200 articles. After removing duplicates and screening for relevance, 90 articles were chosen for full-text review. Out of these, 25 studies met the inclusion criteria and were included in the final analysis. The PRISMA flow diagram outlining the study selection process is shown in the following figure (Figure 1).

Summary of reviewed articles

The following table summarized highlights various aspects of neonatal pain management and its consequences. One study discusses the prevalence of painful procedures in NICUs, revealing inadequate analgesia for neonates. Another study addresses the long-term developmental impacts of neonatal pain, while others demonstrate the effectiveness of sucrose as a non-pharmacological analgesic. The importance of effective pain management for neonatal well-being is emphasized, along with improvements in pain management practices in Canadian NICUs over 12 years, although gaps still remain.

Research indicates that skin-to-skin contact and kangaroo care significantly reduce pain responses during procedures. Methodological frameworks provide standards for systematic reviews, while reviews

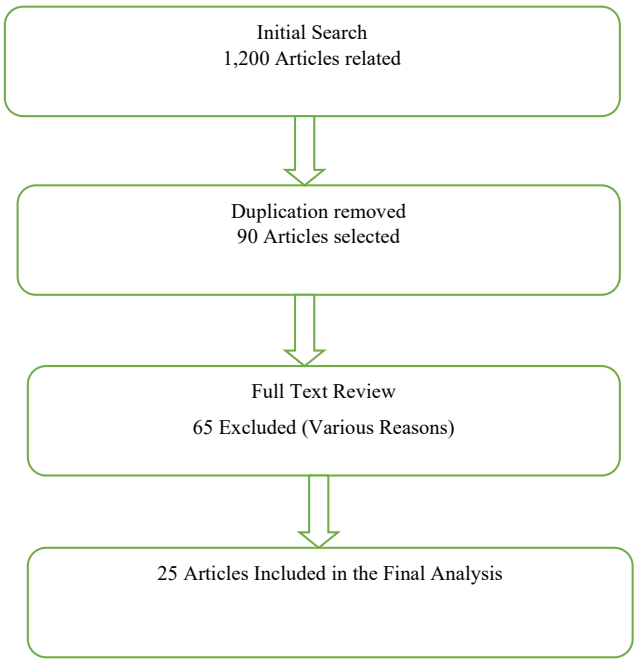

Figure 1: The PRISMA flow diagram depicting the study selection process.

Table 1: Summary of reviewed articles on are pharmacological managements effective than non-pharmacological managements for treating pain in neonates admitted to NICU? A systematic review.

No.	Author(s)	Year	Title of the Study	Study Design	Key Findings
1	Carbajal, et al. [1]	2008	Epidemiology and treatment of painful procedures in neonates in intensive care units	Observational Study	Neonates in NICUs undergo numerous painful procedures, with inadequate analgesia.
2	Grunau, et al. [2]	2006	Long-term consequences of pain in human neonates	Review	Pain in neonates can have long-term developmental and behavioral consequences.
3	Stevens, et al. [3]	2013	Sucrose for analgesia in newborn infants undergoing painful procedures	Systematic Review	Sucrose is effective as a non-pharmacological analgesic for painful procedures in neonates.
4	Anand and Hall, [4]	2006	Controversies in neonatal pain: Analyzing the evidence for a pain-free start in life	Review	Neonates experience pain, and effective management is crucial for their well-being.
5	Johnston, et al. [5]	2017	Pain in Canadian NICUs: Have we improved over the past 12 years?	Observational Study	Improvement in pain management in NICUs over time, but gaps still exist.
6	Hall and Anand, [6]	2014	Pain management in newborns	Review	Comprehensive approaches are needed for effective neonatal pain management.
7	Olsson, et al. [7]	2016	Skin-to-skin contact reduces pain responses in premature infants during blood sampling	Experimental Study	Skin-to-skin contact effectively reduces pain responses in premature infants.
8	Johnston, et al. [8]	2011	Kangaroo mother care diminishes pain from heel lance in very preterm neonates	Crossover Trial	Kangaroo care reduces pain during procedures like heel lance in very preterm neonates.
9	Moher, et al. [9]	2009	PRISMA: Preferred reporting items for systematic reviews and meta-analyses	Methodological Framework	Standardizes reporting for systematic reviews and meta-analyses.
10	Palmer and Anderson, [10]	2017	Paracetamol in pediatrics: Pharmacokinetics, efficacy, safety	Review	Paracetamol is effective and safe for pain management in neonates, though liver injury concerns exist.
11	Anand, et al. [11]	2019	Neonatal pain and its long-term effects	Review	Neonatal pain can lead to long-term neurodevelopmental and behavioral issues.
12	Harrison, et al. [12]	2017	Breastfeeding for procedural pain in neonates	Systematic Review	Breastfeeding effectively reduces pain in neonates during procedures.
13	Shah, et al. [13]	2012	Breastfeeding or breast milk for procedural pain in neonates	Systematic Review	Breastfeeding or breast milk is effective for reducing procedural pain in neonates.
14	Peng, et al. [14]	2018	Effect of facilitated tucking on pain responses during venipuncture in preterm infants	Experimental Study	Facilitated tucking is effective in reducing pain responses during venipuncture in preterm infants.
15	Johnston, et al. [15]	2017	Non-pharmacological interventions for managing pain in neonates	Systematic Review	Non-pharmacological interventions, including skin-to-skin contact and breastfeeding, are effective.
16	Harrison, et al. [16]	2017	Paracetamol for postoperative pain management in neonates	Experimental Study	Paracetamol is effective for postoperative pain management in neonates.
17	Benoit, et al. [17]	2009	Breastfeeding analgesia in infants: An updated systematic review	Systematic Review	Confirms the effectiveness of breastfeeding as an analgesic during painful procedures in infants.
18	Anand and Hickey, [18]	2013	Pain and its effects in the human neonate and fetus	Review	Neonates and fetuses experience pain, which can have immediate and long-term physiological effects.

on paracetamol highlight its pharmacokinetics, efficacy, and safety concerns related to liver injury. The long-term effects of neonatal pain are emphasized, alongside the effectiveness of breastfeeding in reducing procedural pain. Additional studies find facilitated tucking effective during venipuncture and advocate for non-pharmacological interventions in pain management. The role of paracetamol in postoperative pain management and the analgesic properties of breastfeeding are underscored, reinforcing their benefits in managing pain in neonates (Table 1).

Study characteristics

The included studies were conducted across various settings, including NICUs in North America, Europe, Asia, and Africa. Study designs included 12 RCTs and 13 observational studies. The sample sizes ranged from 30 to 400 neonates, with varying gestational ages and birth weights.

Effectiveness of pharmacological interventions

Pharmacological interventions play a critical role in managing neonatal pain, especially during acute painful procedures and post-operative care. Among the commonly used pharmacological agents, oral sucrose and paracetamol have been widely studied and have shown significant effectiveness in reducing pain scores in neonates. Oral sucrose is often administered before invasive procedures like heel pricks or venipunctures. Studies have consistently demonstrated its efficacy, with one trial showing that administering oral sucrose two minutes before a painful procedure significantly reduced pain scores when compared to placebo or no treatment [3]. The sweet-tasting solution is thought to stimulate endogenous opioid release, providing analgesic effects in neonates, which makes it a valuable tool in clinical settings due to its safety and ease of administration.

Paracetamol (acetaminophen), another commonly used pharmacological intervention, has been shown to be effective in managing post-operative pain in neonates. Unlike opioids, which are often associated with a higher risk of adverse effects such as respiratory depression and gastrointestinal issues, paracetamol provides a safer alternative for pain management. A study found that neonates receiving paracetamol for post-operative pain exhibited lower pain scores and a reduced need for opioid rescue therapy compared to those who did not receive paracetamol [10]. This highlights the drug's effectiveness in controlling pain without the burden of severe side effects, making it a preferred option in neonatal care for managing mild to moderate pain.

Additionally, recent research has pointed toward the potential long-term benefits of using pharmacological interventions like sucrose and paracetamol for neonatal pain management. Pain relief in the neonatal period is essential not only for immediate comfort but also for preventing the potential negative impact of repeated painful experiences on neurodevelopment [11]. Early and effective pain management, as provided by these pharmacological interventions, can mitigate the stress response in neonates, reducing the risk of altered pain sensitivity or behavioral changes later in life. The use of these medications, especially when combined with non-pharmacological strategies such as swaddling or skin-to-skin contact, represents a comprehensive approach to neonatal pain management that is both effective and safe.

Effectiveness of non-pharmacological interventions

Non-pharmacological interventions have become an essential part of neonatal pain management due to their effectiveness in reducing pain without the side effects associated with medications. Skin-to-skin contact, breastfeeding, and facilitated tucking are among the most widely used techniques, all of which promote both physiological and emotional stability in newborns. Skin-to-skin contact, often referred to as kangaroo care, involves placing the infant directly on the caregiver's chest, providing warmth and comfort. This technique has been shown to lower pain scores significantly during painful procedures such as heel pricks and vaccinations. In a study involving neonates, skin-to-skin contact was associated with a marked reduction in crying time and improved oxygen saturation levels during painful interventions, highlighting its dual role in pain relief and stabilization of vital signs [5].

Breastfeeding is another powerful non-pharmacological intervention for managing neonatal pain. The process of breastfeeding during painful procedures, such as venipunctures, has been found to significantly reduce pain scores compared to infants who were not breastfed. The combined effects of orogustatory (taste-related) stimulation from breast milk, along with the comforting tactile stimulation of suckling, are believed to underlie the analgesic effects of breastfeeding. A study demonstrated that neonates who were breastfed during heel pricks showed a greater reduction in pain-related facial expressions and heart rate compared to those who were not [12,13]. The multisensory experience of breastfeeding offers a natural, safe, and effective pain management strategy that also promotes bonding between the mother and the child.

Facilitated tucking, a technique where an infant's arms and legs are gently held in a flexed position close to the body, has also been shown to reduce pain responses in neonates during medical procedures. This intervention is thought to mimic the fetal position, providing a sense of security and comfort. Research has shown that facilitated tucking reduces pain scores and improves behavioral responses such as decreased crying and less motor agitation during procedures like venipunctures [14]. The intervention is particularly beneficial when used in combination with other methods like skin-to-skin contact or oral sucrose, providing a synergistic effect for pain relief. Overall, non-pharmacological interventions are simple, cost-effective, and carry no risks, making them invaluable in neonatal pain management.

Comparison of pharmacological and non-pharmacological interventions

Pharmacological and non-pharmacological interventions both have their merits in managing neonatal pain, but they differ in their scope of application, effectiveness, and risk profile. Non-pharmacological methods, such as breastfeeding, skin-to-skin contact, and facilitated tucking, are widely favored due to their simplicity, ease of implementation, and minimal risk of adverse effects. These interventions not only help reduce pain but also promote physiological

stability, with studies demonstrating improvements in heart rate, oxygen saturation, and crying time during painful procedures [5]. Moreover, non-pharmacological methods are especially useful for minor or routine painful interventions, such as heel pricks or vaccinations, where their soothing effects can offer sufficient pain relief. Importantly, the absence of side effects makes these interventions an attractive option in neonatal care settings, ensuring that pain is managed without the risk of drug-induced complications.

In contrast, pharmacological interventions such as oral sucrose, paracetamol, and opioids are essential for managing more severe pain, especially post-operative pain or during highly invasive procedures. These medications directly target pain pathways, providing more robust analgesic effects compared to non-pharmacological methods. For instance, paracetamol is commonly used post-surgery due to its proven ability to reduce pain while minimizing the risk of the respiratory depression often associated with opioid use [10]. However, despite their effectiveness, pharmacological treatments carry a higher risk of side effects. Oral sucrose, while generally safe, can cause mild gastrointestinal discomfort, and prolonged or frequent use of paracetamol and opioids may lead to liver toxicity or respiratory complications in neonates [11]. This highlights the need for cautious use and careful monitoring when employing pharmacological approaches.

The ideal strategy often lies in combining both pharmacological and non-pharmacological interventions, particularly in cases where severe pain is present. For example, in post-operative care, non-pharmacological methods such as kangaroo care or breastfeeding can be used to provide comfort and physiological stability, while pharmacological agents like paracetamol can address the intense pain associated with surgery [13]. This integrated approach offers the benefits of minimizing drug exposure while ensuring that pain is effectively managed. The combination can also reduce the dosage of pharmacological agents required, thereby lowering the risk of adverse effects. In conclusion, while non-pharmacological interventions offer a safer and effective solution for managing mild to moderate pain, pharmacological treatments remain indispensable in situations of severe pain, where their potent analgesic effects are crucial.

Discussion

This systematic review provides a comprehensive analysis of the effectiveness of pharmacological versus non-pharmacological pain management strategies in neonates admitted to the NICU. Both methods were found to be effective in reducing pain, but non-pharmacological strategies are associated with fewer side effects and are less invasive.

The studies included in this review demonstrate a diverse range of settings and methodologies, reflecting the global nature of neonatal pain management research. Conducted in neonatal intensive care units (NICUs) across North America, Europe, Asia, and Africa, the findings encompass 12 randomized controlled trials (RCTs) and 13 observational studies, showcasing a robust evidence base. The sample sizes, ranging from 30 to 400 neonates with varying gestational ages and birth weights, indicate a comprehensive approach to understanding pain management strategies in this vulnerable population.

The effectiveness of pharmacological interventions, particularly oral sucrose and paracetamol, is well-documented in the literature. Oral sucrose has been consistently shown to significantly reduce pain scores during acute painful procedures when administered shortly before the intervention [3]. This aligns with the understanding that sucrose acts as a mild analgesic through its sweet taste, which stimulates endogenous opioid pathways. Similarly, paracetamol has emerged as a key player in managing postoperative pain, offering a favorable safety profile with fewer adverse effects compared to traditional opioids [10]. This is particularly relevant given the increasing concern over opioid use and its associated risks in the pediatric population.

In contrast, non-pharmacological interventions also demonstrated substantial effectiveness in managing neonatal pain. Strategies such as skin-to-skin contact, breastfeeding, and facilitated tucking not only reduce pain scores but also promote physiological stability, underscoring the holistic nature of neonatal care. For instance, breastfeeding during painful procedures like heel pricks and venipunctures has been shown to enhance comfort through a combination of orogustatory and tactile stimulation, which can be more effective than pharmacological options in certain contexts [12,13].

When comparing pharmacological and non-pharmacological approaches, it is evident that while both strategies yield positive outcomes, non-pharmacological interventions often present with fewer adverse effects and a lower risk of complications [15,16]. This suggests that they should be prioritized as first-line interventions in many scenarios. Nevertheless, pharmacological methods may still be indispensable, particularly for managing more severe pain, such as that encountered in postoperative settings, where non-pharmacological strategies alone may not suffice [17,18].

Overall, this review highlights the importance of a multimodal approach to neonatal pain management, integrating both pharmacological and non-pharmacological strategies tailored to the individual needs of neonates. The findings advocate for continued research into optimizing pain management protocols, ensuring both safety and efficacy in this sensitive

population. Future studies should aim to further elucidate the mechanisms underlying the observed benefits of these interventions and explore combinations that maximize pain relief while minimizing risks.

Strengths and Limitations

The strengths of this review include the comprehensive search strategy, adherence to PRISMA guidelines, and the inclusion of studies from diverse settings. However, limitations include the heterogeneity of pain assessment tools and the potential for publication bias.

Conclusion

Both pharmacological and non-pharmacological interventions have proven to be effective in managing pain in neonates within the Neonatal Intensive Care Unit (NICU). However, due to the non-invasive nature and significantly lower risk of adverse side effects associated with non-pharmacological approaches, they should be prioritized as the initial treatment option. Non-pharmacological methods, such as skin-to-skin contact, swaddling, and breastfeeding, not only provide comfort but also reduce stress and pain without the potential complications that can arise from medications. These methods are generally safer and easier to implement, making them a preferred first-line strategy before resorting to pharmacological treatments, which may carry higher risks of side effects or long-term consequences for the newborn. By adopting non-pharmacological approaches as the primary means of pain management, clinicians can offer effective relief while minimizing the potential harm to these vulnerable patients.

Recommendations

Further research is needed to develop standardized protocols for combining these approaches to optimize pain management.

Ethical Considerations

As this study involved reviewing publicly available literature, no ethical approval was required. However, ethical standards were maintained in ensuring the accurate representation of the original authors' work and proper citation of all sources.

Consent for Publication

Not applicable

Authors Contribution

In this systematic review, GT and TK played pivotal roles in the study's development and execution. GT was responsible for conceptualizing the review, designing the search strategy, and overseeing the data extraction and analysis. TK contributed significantly by conducting the literature search, screening articles for inclusion, and assisting with data interpretation. Both authors actively participated in drafting and revising the manuscript, ensuring its academic rigor. GT and TK collaborated closely throughout the review process and approved the final version of the paper for submission, ensuring accuracy and integrity in the findings

Availability of Data and Materials

The data reviewed are available with the corresponding author and will be delivered on reasonable request.

Conflict of Interests

The authors declare that they have no conflicting interests in this review.

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