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Addressing Pain in Neonatal Cancers: A Systematic Review

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ABSTRACT

Background: Neonatal cancers are a rarity, but this makes them all the more challenging, given the uniqueness of the physiological and developmental characteristics of neonates. Critical attention on effective pain management for this population is highly warranted, yet it often remains unaddressed. Objective: The aim of this systematic review is to summarize the existing literature on pain management strategies pertaining to neonatal cancers, investigate the quality of the current studies, highlight the knowledge gaps, and suggest orientations for future research.

Methods: A comprehensive literature search was carried out from PubMed, Scopus, and the Cochrane Library, using keywords relating to neonatal cancer and management of pain. The target population incorporated peer-reviewed research articles, clinical guidelines, and observational studies published between 2000-2023. Data were extracted by the PICO framework while methodological quality was assessed by GRADE criteria.

Results: The approaches of pain management revealed substantial heterogeneity without any consensus set on the best practice. Common standardized pain assessment tools included Neonatal Infant Pain Scale and Premature Infant Pain Profile, but their implementation varied from study to study. The pharmacological interventions (opioids and non-opioid analgesics) were supplemented with non-pharmacological therapies like skin-to-skin contact and sucrose analgesia. The barriers stated were lack of training among healthcare providers, misconceptions about neonates with respect to pain perception, and lastly, absence of clear guidelines. The non pharmacological therapies are more oriented towards addressing acute pain than chronic pain.

Conclusions: While effective pain management for neonatal cancers is warranted, lots of factors confound the process. Future research should look at standardizing pain traits, designing training for healthcare providers, and developing guidelines on evidence-based practice to improve care quality. Attention to these issues would greatly serve treatment outcomes and quality of life for neonates undergoing treatment for cancer. Non-pharmacological therapies, such as cognitive-behavioral techniques, physical interventions, and relaxation methods, can effectively alleviate neonatal cancer pain, minimizing drug side effects and enhancing overall patient comfort and well-being.

Keywords: *cancer, newborn, neonates, ,management, challenges*

1. INTRODUCTION

Neonatal cancers, though rare, pose unique and serious challenges, extending well beyond the basic diagnosis and treatment. They demand a certain management approach tied to the development and physiology of neonates, which very much differs from that of older pediatric patients and adults. The WHO reports that about 15,000 cases of cancer in children are diagnosed in developed countries each year. The non pharmacological therapies are more oriented towards addressing acute pain than chronic pain. [1]While it portrays a rather higher incidence of cancer in childhood, a small fraction of those cases belongs to the neonatal cohort, which is alarming in its own right. Pain management in neonatal cancers is a crucial aspect of patient care, but this is easily problematic. Neonates have an underdeveloped nervous system, which in turn changes their responses to pain; therefore, assessments of pain and the approach to treatment had better be individualized. Further complicating the picture is the debility in expressing pain, thus placing proper and cost-effective diagnostic tools and observation techniques in a primary priority context. Neonates presenting with benign or low-malignancy tumors include mature and immature teratomas, congenital mesoblastic nephromas, infantile fibrosarcomas, myofibromas, gangliogliomas, leukemias and plexiform neurofibromas.[2,3]

Some research indicates that unrelieved or inefficiently managed pain leads to not only acute tortured states but also long-term developmental disabilities, which require effective interventions.[4] Literature on pain management strategies for neonatal cancers outlines a mix of interventions and a radical error in the generality of treatments. Such divergence often contributes to an inconsistent pain management approach across the continuum of care, participating in care disparity. A systematic review will therefore aim to summarize the data on effective pain management strategies, assess the quality and rigor of the existing studies, highlight the knowledge gap of current literature, and plot the landscape of further research. By developing an all-encompassing understanding of pain control in this vulnerable group, clinicians will improve treatment outcomes, improve the quality of life among neonatal patients and potentially avert the long-term effects of pain from the treatment of cancer. [5,6]Clinical practice backed by evidence-based research will definitely aid in coming to terms with the special predicament faced in pain management.

2. METHODOLOGY

Search Strategy

A systematic search was performed to seek out relevant research on pain in neonatal malignancies through multiple databases, viz., PubMed, Scopus, Embase, Google Scholar, Semantic Scholar, and the Cochrane Library. The search used a mix of words and phrases such as "neonatal cancer," "pain management," "neonatal pain," and "pediatric oncology." The wide spectrum of terms was selected to cast a wide net in covering literature on pain among neonates with cancer. Published studies between January 2000 and October 2023 alone were included to represent current practices and research advancement. Inclusion criteria included research articles that are peer-reviewed, clinical guidelines, and observational studies on pain management for cancer-bearing neonates in particular.

Data Extraction and PICO Framework

Systematic data extraction was conducted to identify important information from the studies included using the PICO (Population, Intervention, Comparison, Outcomes) approach. The Population was neonates with cancer, and the Intervention was the range of pain management strategies used in practice, both pharmacological and non-pharmacological. The Comparison could be other management strategies or standard care without particular pain interventions. The Outcomes of interest were pain assessment measures, levels of pain relief attained, and any adverse effects of the interventions. Data extraction was aimed at authors, year of publication, study design, sample size, methods of pain assessment, strategies used, outcomes in relation to pain relief, and future practice recommendations, for a complete understanding of the findings.

Quality Assessment

The methodological quality of the included studies was critically appraised using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) criteria. This evidence-based system assesses the methodological quality of studies and the strength of recommendations. Each study was classified into a quality level from one of four categories: high, moderate, low, or very low using several factors that included study design, risk of bias, consistency of findings, directness of evidence, and precision of estimate. This was necessary for gauging the reliability of findings and how they can be applied to clinical practice in managing pain in neonates with cancer. This comprehensive review further highlights the value of quality research in informing evidence-based methods of pain management in this high-risk patient group.

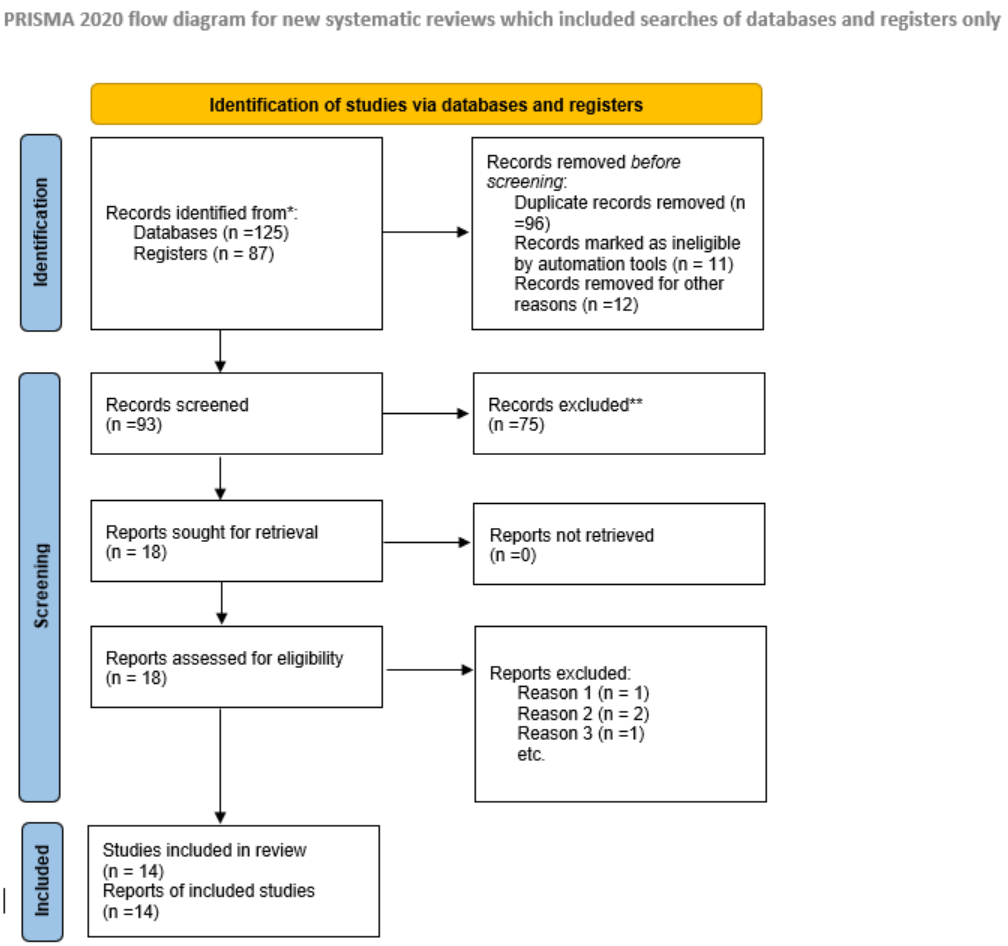

Figure 1 showing the PRISMA statement

3. RESULTS

A thorough literature search yielded 31 articles matching the inclusion criteria, shedding light on how pain in neonatal cancers is handled. Of these, there were clinical trials evaluating particular interventions, observational studies describing experiences and outcomes encountered in clinical settings. In among, consisted of reviews and clinical guidelines synthesizing existing knowledge and trends regarding neonatal pain management. The studies revealed heterogeneity in the approach to pain management, signalling a large vacuum of consensus on best practices in the field. The difference between approaches shows the absence of a general protocol used in pain management, which can lead to differences in treatment. The challenge in solving this problem lies in undertaking a reliable assessment of pain in neonates who are often unable to express their discomfort. The reviewed studies usually used standardized pain assessment tools such as the Neonatal Infant Pain Scale (NIPS) and the Premature Infant Pain Profile (PIPP), which are meant to assess indicators of pain in this susceptible population. However, great disparities in how the tools were applied were reported; some studies placed more emphasis on observational assessments, while others took into consideration physiological indicators, such as heart rate and oxygen saturation. [7,8]The current assessment methods based on behavioral cues, like facial expressions and cry sounds, raise further concern over their effectiveness. The absence of a universal pain assessment tool created for neonates further amplifies the grave need to accomplish standardized clinical practice. [9]The development of a comprehensive, widely accepted pain assessment tool for neonates will help in better pain management, improved treatment outcomes, and the ability to meet the varied requirements of this population.

Pain Management Strategies: The review studies suggest a multifaceted approach to cancer pain management in neonates, underlining the necessity of combined pharmacological and non-pharmacological modalities. The universal method takes care of the individual and complex needs of neonatal patients, who usually suffer from different types and intensities of pain. Pharmacological interventions constitute opioids, non-opioid analgesics, and adjuvant medications while other non-pharmacological therapies serve in addition to them to help in overall pain alleviation and patient comfort. The mingling of the said approaches embodies a commitment to tailored care of this sensitive population, where the complexity of efficient

pain relief comes from the effort of multidisciplinary teams. Pharmacological Interventions Opioids represented the linchpin of pharmacological management of pain for neonatal cancer patients. The studies have notified that the commonest opioid was *morphine* due to its effectiveness; however, titration to avoid side effects like respiratory depression, which might carry much more risk for this vulnerable population, should be observed. Continuous fentanyl infusion has been used in these vulnerable patients. Transdermal and intranasal fentanyl have gained a role in neonatal pain management. [11,12] Besides, non-opioid analgesics, like *acetaminophen* or NSAIDs, were often included. At times, these were also mixed with opioids in effective pain management and diminishment of reliance on their high doses, together with reducing side effects. The clinical patterns put across show a bias against the use of NSAIDS in babies, and these include ibuprofen, diclofenac, and indometacin. There have been proved efficacies on the indications such as fever and pediatric inflammatory rheumatic diseases; however in terms of safety and prolonged of use in malignancies, in most of the cases data available on infants are still scarce. Adverse reactions may be seen against renal, gastrointestinal, hematological, or immunologic systems. Beginning these medications at the lowest appropriate doses and monitoring infants for duration and adverse effects, in particular with chronic conditions, will increase safety. *Acetaminophen* is the most often prescribed drug to treat mild-to-moderate pain or fever in infants, including neonates, and can be administered by different routes (ie, oral, rectal, or intravenous). It has analgesic and antipyretic activity, but has only very modest peripheral anti-inflammatory properties [13-15]Also, *benzodiazepines*[16] were used as sedatives and anxiolytics to control anxiety and to induce sedation in babies during painful procedures. The problems would further come with the description of long-term use and a likely possibility of withdrawal syndrome and adverse effects on the neurological developing process. The sedation produced by these drugs may be unpredictable in neonates. This triggers the need for further investigations to equate the need for pain relief and the risk associated with these medications well stated in these researches dealing with the need for more ongoing basic research and piecing together in fine-tuning the cancer pain protocols for the neonates.

REFERENCE	SUMMARY
Kart T et al. (1997)	This literature review recommends morphine usage in neonates, infants, and children for effective pain management based on clinical cases.
Ahmed H. Othman et al. (2016)	Examines the use of transdermal fentanyl in managing cancer-related pain in opioid-naive pediatric patients, emphasizing its efficacy and safety.
Michael S. Harlos et al. (2013)	Highlights the application of intranasal fentanyl in palliative care for newborns, offering a non-invasive approach to pain management.
Puia-Dumitrescu et al. (2021)	Assesses neurodevelopmental outcomes in extremely preterm infants receiving opioids and benzodiazepines, indicating the need for careful monitoring of these medications.
Anand KJS et al. (2001)	A consensus statement outlining the prevention and management of pain in newborns, emphasizing the role of opioids in comprehensive pain management strategies.

Figure 2 showing the table for the use of opioids in neonatal pain management

Non-Pharmacological Therapies

A number of research studies have emphasized the importance of non-pharmacological treatments to augment pain care in neonates, especially if they are integrated with pharmacotherapy. [17]The non-pharmacological treatments not only seek to diminish pain but are also designed to foster comfort, emotional attachment, and developmental assistance for the child. By integrating non-pharmacological methods, healthcare providers can address multiple dimensions of pain management, providing a more holistic approach to care that suits the unique needs of neonates undergoing treatment for cancer. The non pharmacological therapies are more oriented towards addressing acute pain than chronic pain. The explored non-pharmacological strategies include skin-to-skin contact (Kangaroo Care), swaddling and positioning techniques, sucrose analgesia, and the innovative application of music therapy.

Skin-to-Skin Contact (Kangaroo Care)

One of the most effective non-pharmacological interventions determined is skin-to-skin contact, or Kangaroo Care. Studies have established that this method has the ability to lessen significantly neonates' perception of pain during painful procedures, such as venipunctures or other invasive treatments. Skin-to-skin contact has to do with holding the baby in direct contact against a parent's or caregiver's bare chest, supplying warmth, comfort, and security. This method not only has been linked to reduced pain reaction but also encourages positive effects on physiological stability, such as heart rate, oxygen saturation, and temperature control. The emotional connection developed through Kangaroo Care is the other crucial factor; it encourages maternal and paternal attachment, strengthening the parental-infant relationship, that can contribute towards

better initiation and continuation of breastfeeding. In addition, this method can result in reduced stress hormone levels and establish a soothing environment for the newborn. [18,19]With its myriad of advantages, Kangaroo Care is an easy yet effective pain management and infant care strategy in clinical practice, providing important assistance during difficult times in the treatment process of a neonate.

Swaddling and Positioning

Another useful non-pharmacological treatment is swaddling and ergonomic positioning of the neonate. Correct positioning and swaddling can successfully limit discomfort and also give a secure feeling to newborns, most particularly in relation to medical examinations. Swaddling is defined as tightly dressing the baby within a soft wrap, which is not only representative of the confines of the womb but also temperature regulation and limiting startle reactions commonly caused by abrupt movement or noise. Research has shown that swaddling can increase comfort by providing the neonate with a calming environment, thus decreasing stress and anxiety levels. Supportive positioning techniques, including having the infant in a side-lying or fetal position, can also increase comfort. [19,20]This is done to achieve improved respiratory mechanics and decrease body strain during painful procedures. Combined, these practices enhance the hospital experience for neonates as a whole, leading to improved health outcomes and recovery through a reduction in pain-related physiological stress responses.

Sucrose Analgesia

One other notable non-pharmacologic approach is oral sucrose administration, which has been found to offer effective analgesic properties during acute, painful procedures among neonates. Studies have shown that sucrose is able to stimulate the body's own pain relief system, triggering the release of endogenous opioids that reduce pain. Its use before invasive procedures, including blood sampling or lumbar puncture, has been shown to significantly reduce pain reactions, enabling the neonate to tolerate required procedures more comfortably. Administration of sucrose is widely safe, inexpensive, and readily available, so it is an appealing choice for clinicians looking to improve pain management options in a neonatal patient population. [22,23]Nevertheless, despite numerous studies attesting to its effectiveness, additional research on optimal dosing, timing of administration, and long-term impact on development is needed to ensure that sucrose analgesia continues to be a valuable part of pain management strategies in neonatal care.

Music Therapy

More recently, the creative application of music therapy has become a fascinating non-pharmacological option. Other research has investigated the music's therapeutic role in neonates, proposing that music is effective in distracting and calming infants in the face of medically stressful situations. The soft melodies and rhythmical sounds have been linked with decreased pain scores, lower heart rates, and overall better mood in infants. Music therapy could also be beneficial in developing a more soothing environment in the clinical setting, and this could further lead to improved outcomes with painful procedures. Although the preliminary findings are encouraging, more research needs to be done to confirm the effectiveness of music therapy as an established intervention within the neonatal population. Knowledge of how varying forms of music, sound level, and timing of sessions are able to customize interventions will be essential to help maximize its potential in pain management. In general, music therapy [25,26]is an innovative area for the promotion of pain management techniques, providing a distinct combination of emotional and physiological support that will be particularly helpful to neonates being treated for cancer.

The significant findings are given in figure 3

REFERENCE	SUMMARY
Thrane SE et al. (2016)	This paper presents non-pharmacologic treatment strategies for procedural pain in children from infancy to school age.
Sharma H, Ruikar M (2022)	A meta-analysis confirming the effectiveness of Kangaroo Mother Care for pain management in infants during procedures.
Wang F et al. (2022)	A meta-analysis showing significant pain relief in premature infants through the application of Kangaroo Care.
Haug S et al. (2020)	Discusses the need for appropriate end-of-life pain management in neonates, highlighting relevant distressing symptoms.
Erkut Z, Yildiz S (2017)	Explores how swaddling can reduce pain and distress during painful procedures in newborns.
Stevens B et al. (2016)	Reviews the efficacy of sucrose as an analgesic for neonates undergoing painful procedures.

Figure 3 showing the studies – nonpharmacological methods

INTERVENTION TYPE	COMMON AGENTS	KEY FINDINGS
Opioids	Morphine, Fentanyl	Effective for managing severe pain; requires careful monitoring due to potential side effects.
NSAIDs	Ibuprofen, Ketorolac	Safe and effective for mild to moderate pain; monitored for gastrointestinal and renal side effects.
Acetaminophen	Acetaminophen	Proven as a reliable analgesic and antipyretic for mild pain relief in neonates.
Non-Pharmacologic Methods	Sucrose, Music Therapy	Sucrose shown to significantly reduce procedural pain; music therapy provides calming effects.

Figure 4 showing metanalyses of data

4. CHALLENGES AND BARRIERS

Despite the increasing wealth of information that has been made available on neonatal cancers with regard to pain management, still, there exist many barriers towards the effectiveness of administered care. The first most critical issue would be the deficiency in education and training among the healthcare providers. Many clinicians, including nurses and physicians, receive inadequate exposure to specialized training pertaining to pain management in neonates. This deficiency affects their confidence and competence in assessing and addressing pain appropriately, which may lead to under-treatment in this vulnerable population. The lack of comprehensive educational programs focused on neonatal pain management within medical and nursing curricula perpetuates this gap. As a result, providers may rely on outdated practices or default to adult-centered pain management strategies that do not align with the unique physiological and emotional needs of neonates. Providing specialized training and materials to healthcare practitioners on the finer points of managing neonatal pain is critical for enhancing outcomes and encouraging evidence-based practice in acute care environments.

A related major obstacle is the widespread misunderstanding that neonates do not experience pain to the same degree as older children and adults. It has been continued for decades while mounting evidence suggests that infants do have the neurobiological equipment to feel pain. The medical providers may underestimate the urgency or need for intervention owing to the misunderstanding of the severity and implications of neonatal pain and result in poor pain management practices. It can also affect parents' perceptions and expectations about pain management, potentially discouraging them from requesting a more effective treatment option. The variability in clinical approaches to pain management is also compounded by the glaring absence of clear guidelines that outline best practices for neonatal oncology. In this case, a lack of standardized recommendations can lead to inconsistencies in care, creating disparities between facilities and individual providers. [27,28]Developing and disseminating evidence-based guidelines for clinical practice among the unique issues in pain management in neonates is a very important factor in establishing a unified approach that will improve the quality of care and general outcomes in patients with this sensitive population.

Future Research Directions

Some of the top recommendations regarding future research while considering the note on pain management for neonates diagnosed with cancer would include. First and foremost, is the immediate need for the standardization of pain assessment tools. There is huge variety among present methods to assess pain in neonates, and there is no consensus in terms of a proper evaluation approach; this fact directly influences all evaluations from center to center in a healthcare setting. Larger multicenter studies for developing and validating a universal pain assessment tool for neonates will get rid of uncertainties regarding pain assessments and will directly lead to improved treatment outcomes. Second, education programs and training of healthcare providers in issues surrounding neonatal pain management will provide the knowledge and skills needed to eradicate common misconceptions that neonates experience pain in a lesser degree than do older patients, therefore greatly improving the quality of care. Longitudinal studies will then engage in assessing the long-term impact of which pain management option for neonates with cancer works best. These should involve psychological and developmental assessments into how pain during infancy can affect well-being throughout and even past childhood. And lastly, clear and evidence-based guidelines for the management of pain in neonatal oncology must be developed; this could serve as a framework for all caregivers throughout and help meet the intention of standardizing practices by allowing its constituents to develop a cohesive approach to the entire process of pain management.[29-31] By attending to these areas, researchers can accentuate practical means of addressing pain relief in neonates to meet their uniqueness, which can vastly improve their health outcomes during cancer treatment and even thereafter.

5. CONCLUSION

Effective pain management for neonatal cancers is a complex but critical element of pediatric care. It requires an exhaustive and intricate understanding of the specific physiological characteristics inherent within this susceptible population. Clinicians could greatly improve upon the management of pain by tackling the various existing barriers that include insufficient training, misconceptions about neonatal pain, and lack of standard guidelines. Future research directions, including the standardization of pain assessment tools, development of training programs, and evidence-based guideline establishment, are needed so that

neonates are treated most effectively. Improved pain management strategies will benefit the treatment outcomes and quality of life of the infant with cancer.

REFERENCES

[1] Alfaar A.S., Hassan W.M., Bakry M.S., Qaddoumi I. Neonates with Cancer and Causes of Death; Lessons from 615 Cases in the SEER Databases. Cancer Med. 2017;6:1817–1826. doi: 10.1002/cam4.1122.

[2] De Ioris MA, Fabozzi F, Lodi M, Vitali G, De Pasquale MD, Del Baldo G, Abbas R, Agolini E, Crocoli A, Iacusso C, Milano GM, Serra A, Mastronuzzi A. The Fight Just Born-Neonatal Cancer: Rare Occurrence with a Favorable Outcome but Challenging Management. Cancers (Basel). 2022 Apr 29;14(9):2244. doi: 10.3390/cancers14092244.

[3] Perry M, Tan Z, Chen J, Weidig T, Xu W, Cong XS. Neonatal Pain: Perceptions and Current Practice. Crit Care Nurs Clin North Am. 2018 Dec;30(4):549-561. doi: 10.1016/j.cnc.2018.07.013.

[4] Hall RW, Anand KJ. Pain management in newborns. Clin Perinatol. 2014 Dec;41(4):895-924. doi: 10.1016/j.clp.2014.08.010.

[5] Stevens B. Pain assessment and management in infants with cancer. Pediatr Blood Cancer. 2007 Dec;49(7 Suppl):1097-101. doi: 10.1002/pbc.21347.

[6] Parthasarathy S, Arthi PR, Preya R, Varman M, Balachandar S, et al. Systematic review: Exploring the impact of nutrition on acute pain including cancer pain. Oncol Radiother. 2024;18:1-5.

[7] Sposito NPB, Rossato LM, Bueno M, Kimura AF, Costa T, Guedes DMB. Assessment and management of pain in newborns hospitalized in a neonatal intensive care unit: a cross-sectional study. Rev Lat Am Enfermagem. 2017;25:e2931. 3. Chen M, Shi X, Chen Y, et al. A prospective study of pain experience in a neonatal intensive care unit of China. Clin J Pain. 2012;28:700–704

[8] Llerena A, Tran K, Choudhary D, Hausmann J, Goldgof D, Sun Y, Prescott SM. Neonatal pain assessment: Do we have the right tools? Front Pediatr. 2023 Feb 2;10:1022751. doi: 10.3389/fped.2022.1022751.

[9] Faye PM, De Jonckheere J, Logier R, Kuissi E, Jeanne M, Rakza T, Storme L. Newborn infant pain assessment using heart rate variability analysis. Clin J Pain. 2010 Nov-Dec;26(9):777-82. doi: 10.1097/ajp.0b013e3181ed1058

[10] Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review: Part 2--Clinical use. Paediatr Anaesth. 1997;7(2):93-101. doi: 10.1111/j.1460-9592.1997.tb00488.x.

[11] Ahmed H. Othman, Mohamad Farouk Mohamad, Heba Abdel-Razik Sayed, Transdermal Fentanyl for Cancer Pain Management in Opioid-Naive Pediatric Cancer Patients, *Pain Medicine*, Volume 17, Issue 7, July 2016, Pages 1329–1336, https://doi.org/10.1093/pm/pnw004

[12] Michael S. Harlos, Simone Stenekes, David Lambert, Chris Hohl, Harvey Max Chochinov, Intranasal Fentanyl in the Palliative Care of Newborns and Infants, Journal of Pain and Symptom Management, Volume 46, Issue 2,2013,265-274. https://doi.org/10.1016/j.jpainsymman.2012.07.009.

[13] Titchen T, Cranswick N, Beggs S. Adverse drug reactions to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital. Br J Clin Pharmacol. 2005;59(6):718–23.

[14] Kiskaddon AL, Stock AC, Fierstein JL, Miller A, Quintessenza JA, Goldenberg N. Ketorolac in neonates and infants following congenital heart surgery: a retrospective review. Cardiol Young. 2024 Jun;34(6):1199-1205. doi: 10.1017/S1047951123004262.

[15] Cooper TE, Heathcote LC, Anderson B, Grégoire MC, Ljungman G, Eccleston C. Non-steroidal anti-inflammatory drugs (NSAIDs) for cancer-related pain in children and adolescents. Cochrane Database Syst Rev. 2017 Jul 24;7(7):CD012563. doi: 10.1002/14651858.

[16] Puia-Dumitrescu, M., Comstock, B. A., Li, S., Heagerty, P. J., Perez, K. M., Law, J. B., et al. PENUT Consortium (2021). Assessment of 2-year neurodevelopmental outcomes in extremely preterm infants receiving opioids and benzodiazepines. *JAMA Netw. Open* 4 (7), e2115998. doi:10.1001/jamanetworkopen.2021.15998.

[17] Thrane SE, Wanless S, Cohen SM, Danford CA. The Assessment and Non-Pharmacologic Treatment of Procedural Pain From Infancy to School Age Through a Developmental Lens: A Synthesis of Evidence With Recommendations. J Pediatr Nurs. 2016 Jan-Feb;31(1):e23-32. doi: 10.1016/j.pedn.2015.09.002.

[18] Sharma H, Ruikar M. Kangaroo mother care (KMC) for procedural pain in infants: A meta-analysis from the current evidence of randomized control trials and cross-over trials. J Family Med Prim Care. 2022 Apr;11(4):1250-1256. doi: 10.4103/jfmpc.jfmpc_1383_21.

[19] Wang F, Zhang Q, Ni ZH, Lv HT. Effects of kangaroo care on pain relief in premature infants during painful procedures: A meta-analysis. J Spec Pediatr Nurs. 2022 Oct;27(4):e12390. doi: 10.1111/jspn.12390.

[20] Haug S, Dye A, Durrani S. End-of-Life Care for Neonates: Assessing and Addressing Pain and Distressing Symptoms. Front Pediatr. 2020 Sep 24;8:574180. doi: 10.3389/fped.2020.574180.

[21] Erkut Z, Yildiz S. The Effect of Swaddling on Pain, Vital Signs, and Crying Duration during Heel Lance in Newborns. Pain Manag Nurs. 2017 Oct;18(5):328-336. doi: 10.1016/j.pmn.2017.05.007.

[22] Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database Syst Rev. 2016 Jul 16;7(7):CD001069. doi: 10.1002/14651858.CD001069.

[23] Yamada J, Bueno M, Santos L, Haliburton S, Campbell-Yeo M, Stevens B. Sucrose analgesia for heel-lance procedures in neonates. Cochrane Database of Systematic Reviews 2023, Issue 8. Art. No.: CD014806. DOI: 10.1002/14651858.CD014806.

[24] Imseytoglu et al. . Music therapy in neonatal intensive care units. Istanbul Univers Flor Nightin Nurs J, 2012;20:160-165.

[25] Sasikala T, Kamala S. Therapeutic effects of music therapy on preterm neonates-pilot study report. Int J Nurs Edu Res, 2016;4: 42-44.

[26] Sharara-Chami R, El-Hout Y, Lakissian Z, Hafez B, Abi-Gerges C, et al. Music as an adjunct to combination analgesia for neonatal circumcision: A randomized controlled trial. J Pedia Urol 2022;18: 184.e1-184.e6.

[27] Neshat H, Hassankhani H, Jabraeili M, Negarandeh R. Organisational challenges of pain management in neonatal intensive care unit: a qualitative study. BMJ Open. 2023 Sep 5;13(9):e072695. doi: 10.1136/bmjopen-2023-072695.

[28] Al-Qarni, F. K. A., Alkhathami, A. M., Al-Qahtani, M. M. A., Alharbi, A. A., Alhawit, M. E., Albushi, A. et.al (2024). Barriers to effective pain management in oncology units: Insights into nursing and health administration. International Journal of Health Sciences, 8(S1), 1812–1827. https://doi.org/10.53730/ijhs.v8nS1.15399.

[29] Anand KJS, and the International Evidence-Based Group for Neonatal Pain. Consensus Statement for the Prevention and Management of Pain in the Newborn. *Arch Pediatr Adolesc Med.* 2001;155(2):173–180. doi:10.1001/archpedi.155.2.173

[30] Neshat H, Hassankhani H, Jabraeili M, Negarandeh R. Organisational challenges of pain management in neonatal intensive care unit: a qualitative study. BMJ Open. 2023 Sep 5;13(9):e072695. doi: 10.1136/bmjopen-2023-072695.

[31] Brummelte S, Grunau RE, Chau V, et al. Procedural pain and brain development in premature newborns. *Ann Neurol*. 2012; **71**(3): 385-396.