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Relief of Procedural Pain in Infants and Neonates

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Abstract

Procedural pain occurs in the hospital setting due to a variety of procedures and treatments conducted throughout a patient's stay. Pain is often assessed in infants and neonates but is not always treated consistently due to the multiple number of pain relief methods. The objective of this literature review is to identify the most effective interventions to relieve procedural pain in infants and neonates. Forty articles were analyzed and synthesized to determine the best pain relief methods to use when providing nursing care to infants and neonates. Based on the results of the literature review, nutritive sucking, positioning techniques, and combined interventions are recommended as first-line pain relief methods for infants and neonates. However, further research is needed to compare the effectiveness of these different methods.

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Relief of Procedural Pain in Infants and Neonates

Chapter I: Introduction

Pain relief is a topic commonly addressed in the care of adults, but it is a more challenging topic within the pediatric population due to the variety of pain relief methods available for infants and neonates. This research paper will review the available literature relating to pain relief for infants and neonates going through a procedure to determine what methods are being used in practice. As well, it will compare the methods to determine the most beneficial way to promote pain relief in infants and neonates. This project was conducted as a literature review, reviewing forty research articles found through searching the Wright State University Library databases. The articles were then evaluated and synthesized to summarize the present knowledge of pain relief methods available for the pediatric population.

The purpose of this project was to determine how to better care for infants and neonates in the clinical setting. This is relevant to nursing practice because it can be applied directly to the care of pediatric patients in the hospital. Evidence-based practice is crucial in the nursing field, requiring the literature to be routinely reviewed to identify the best methods available to provide care to patients.

The objectives of this project were to conduct a review of the available literature, synthesize and analyze the data, and identify the most effective way to treat procedural pain in infants and neonates. Following completion of the literature review, this project was disseminated at a research symposium at Wright State University. The research question for this project is: What is the most effective method for relieving procedural pain in infants and neonates?

Chapter II: Description of Project

For this project, procedural pain will be defined as pain associated with medical procedures, including venipuncture, heel lance, immunization, and other treatments occurring in the hospital setting. The population of interest for this review is infants and neonates, including those cared for in the Neonatal Intensive Care Unit (NICU).

A search was conducted through the Wright State University Library utilizing the Science Citation Index and Academic Search Complete databases yielding 260 results. Search terms used were pain relief or pain management or pain control or pain reduction, procedural pain, and neonates or infant or newborn. Inclusion criteria is as follows: English language, scholarly (peer reviewed) journals, and published between 2015 and 2020. After conducting the search, forty articles were selecting from the results to be included in the review by screening the article titles and abstracts for relevance to the topic. Each article was then evaluated using the Johns Hopkins research evidence appraisal tool, and the findings from these appraisals were summarized using the Johns Hopkins individual evidence summary tool.

The goal of this project is to contribute to the current state of knowledge regarding procedural pain relief by synthesizing current literature and determining the method that will most effectively minimize the pain experienced by infants and neonates during medical procedures. This information is applicable to the hospital setting and those working in pediatric units and NICUs. The information and conclusions from this project may be used to provide better patient care to infants and neonates based on evidence.

The results of this project were presented at Wright State University Symposium of Student Research, Scholarship, and Creative Activities. This allowed for the conclusions of the research project to be disseminated with the Wright State community.

Chapter III: Review of the Literature

After gathering the articles for inclusion, they were reviewed and critically appraised, looking at essential components of each article and the research conclusions. The included articles consist of 28 randomized controlled trials (RCT), 10 systematic reviews, and 2 quasi-experimental studies. This resulted in 32 articles classified as Level I evidence, and 8 articles classified as Level II evidence. Twenty studies conducted research in a NICU, 12 studies were performed in a nursery or post-partum unit, 4 studies were in a pediatric unit, 2 studies were in pediatric primary care offices, 1 study was in an immunization clinic, and 1 study was conducted in a pediatric emergency room. Interventions for pain relief included both non-pharmacologic methods and pharmacologic methods as well as a combination of interventions.

Non-Pharmacologic

Nutritive sucking. For this review, nutritive sucking will include breastfeeding and expressed breast milk. Of the forty articles included in this review, nine articles tested one or both of these interventions. Benoit, Martin-Misener, Latimer, and Campbell-Yeo (2017) compared the use of direct breast-feeding to expressed breast milk in infants and determined that direct breast-feeding is more effective for pain relief. This intervention is recommended due to its safety and simplicity.

Nutritive sucking is often researched in comparison to the use of oral sweet solutions. Gad, Dowling, Abusaad, Bassiouny, and Abd El Aziz (2019) and Gajbhiye, Rao, and Singh (2018) compared breastfeeding to oral sweet solution for pain relief during immunization, and both studies found better relief in the breastfeeding group. Vohra, Purani, Mehariya, and Shah (2017) compared expressed breast milk to oral sucrose and found that the expressed breast milk group experienced significantly less pain ($p < 0.001$). Hsieh et al. (2018) researched the use of

breast milk, 10% dextrose water, and distilled water on pain in neonates during heel stick. They found that both 10% dextrose and breast milk were effective and provided comparable pain relief. Shahid, Florez, and Mbuagbaw (2019) compared breast milk, oral sucrose, and EMLA cream on the reduction of venipuncture-associated pain in infants. It was found that breast milk and sucrose are both more effective than EMLA cream, but breast milk and sucrose provided similar efficacy of pain reduction.

The effectiveness of nutritive sucking may also be compared to other nonpharmacologic interventions. Aydin and Inal (2019) found that breastfeeding is more effective for pain reduction during heel lance when compared to heel warming ($p < 0.01$). In contrast, Zargham-Boroujeni, Elsagh, and Mohammadzadeh (2017) researched the use of breastfeeding and massage to relieve venipuncture pain in infants and found that massage produced lower pain scores than the breastfeeding group. Zhu et al. (2015) compared breastfeeding, music, and combined intervention and found that breastfeeding produced lower pain scores than music ($p < 0.001$). Breastfeeding and combined intervention produced comparable pain scores.

Non-nutritive sucking. Two articles researched the use of non-nutritive sucking and compared this intervention to the use of oral sweet solutions. Lima et al. (2017) utilized 25% glucose solution and non-nutritive sucking and found that non-nutritive sucking was not effective at reducing the newborns' pain scores. Gao et al. (2018) also compared these interventions to a combination method using both non-nutritive sucking and oral sucrose. Non-nutritive sucking did reduce pain, but it was more effective when used in combination with sucrose.

Devices. Devices included in this review are the Shot Blocker, Buzzy, and J-tip. Caglar, Buyukyilmaz, Coasansu, and Caglayan (2017) utilized the Shot Blocker, which uses blunt contact points to distract from injection pain, on a group of neonates receiving a hepatitis B

vaccine. It was found to significantly reduce pain during and after injection when compared to a control group ($p=0.000$). Kearl, Yanger, Montero, Morelos-Howard, and Claudius (2015) researched the use of the Buzzy device, which provides vibration as a distraction from pain, and the J-tip, which is a needless device that delivers lidocaine to the injection area. This study found that the use of the J-tip alone and the use of the J-tip plus Buzzy device reduced pain levels when compared to a control group. However, there was not a significant difference between the two groups ($p=0.121$). It was recommended that the J-tip be used alone as the Buzzy device did not increase the effectiveness of the intervention.

Music. Music was researched as an intervention in six of the forty articles. Of these, it was recommended in four studies. Kucukoglu et al. (2016) utilized music in the form of white noise to reduce pain during vaccination of infants. This significantly reduced pain when compared to a control group ($p<0.05$) and the intervention group also maintained lower heart rates and respiratory rates after vaccination. Uematsu and Sobue (2018) used music therapy in the form of Brahms lullaby which was compared to facilitated tucking. Music therapy significantly reduced pain scores during all times of measurement ($p<0.0001$ to $p=0.0039$). Ullsten, Eriksson, Klassbo, and Volgsten (2017) researched the use of music through live lullaby singing. It was found that the music reduced stress levels of the infants and stabilized their heart rate and respiratory rate. Beh, Hashim, Tan, and Latiff (2018) utilized music during venipuncture of infants and found that it was comparable to the effectiveness of EMLA cream. They recommend music as an intervention as it is simple and quick to implement.

While four articles recommended the use of music therapy, two studies found that it was less effective than other pain relief methods. Zhu et al. (2015) found that music therapy alone was less effective than breastfeeding and less effective than a combination of music and

breastfeeding. Shukla et al. (2018) tested music therapy, kangaroo care, and a combination of music and kangaroo care. Music therapy on its own was not found to be effective in reducing neonatal pain during heel stick.

Positioning. Methods of positioning may include kangaroo care, swaddling, and facilitated tucking. Uematsu and Sobue (2018) utilized facilitated tucking as a comparison to music therapy and found that facilitated tucking did not produce reduction of pain scores in the infants. However, Hartley, Miller, and Gephart (2015) found that facilitated tucking was able to reduce pain in newborns. Lopez et al. (2015) also found that facilitated tucking significantly reduced pain scores when compared to a control group ($p < 0.05$) with most newborns in the intervention group scoring in the category of no pain. Hatfield, Murphy, Karp, and Polomano (2019) found that facilitated tucking, kangaroo care, and oral sucrose are all able to reduce newborns' pain scores. They recommend the use of facilitated tucking or kangaroo care for pain relief. Shukla et al. (2018) utilized kangaroo care as well as kangaroo care in conjunction with music therapy. They found that kangaroo care produced lower pain scores ($p < 0.001$) as did the combination method ($p = 0.001$). As well, Johnston et al. (2017) found skin-to-skin care to be beneficial during painful procedures. Padhi et al. (2015) found that reverse kangaroo care, which is kangaroo care performed with the baby facing outward, led to less discomfort and less change in their respiratory rates than those in a control group ($p = 0.0037$). This intervention is simple and noninvasive which makes it appealing for use in the clinical setting. Dezhdar, Jahanpour, Bakht, and Ostovar (2016) researched the use of swaddling compared to kangaroo care to reduce venipuncture-associated pain in neonates. Both interventions reduced pain scores, though there was not a significant difference between the two groups. Pandita et al. (2018) also compared kangaroo care to swaddling. This study found that kangaroo care was more effective at reducing

pain ($p < 0.01$) and reducing crying time ($p < 0.01$) than swaddling. Ho, Ho, Leung, So, and Chan (2016) researched the use of swaddling with newborns. They found that swaddling was able to decrease pain scores and limit changes in heart rate and oxygen saturation in response to pain.

Other non-pharmacologic. Non-pharmacologic methods of pain relief may also include massage, heat, covered eyes, and more. Squillaro et al. (2019) looked at the use of opioids in neonates compared to nonpharmacologic interventions. There was no recommendation about a specific intervention that is most effective for pain relief; however, it was recommended that nonpharmacologic interventions be used as first line for pain relief in neonates. Zargham-Boroujeni et al. (2017) found that massage led to significantly lower pain scores than breastfeeding ($p < 0.01$). Alemdar and Özdemir (2017) researched the use of covering infants' eyes during venipuncture. This intervention significantly reduced pain scores compared to a control group ($p < 0.05$). Chik, Ip, and Choi (2017) found that upper limb massage during venipuncture reduced newborns' pain compared to those receiving routine care. The intervention group demonstrated mild to moderate pain scores, while the control group experienced moderate to severe pain. Zahed Pasha, Ahmadpour-Kacho, Hajiahmadi, and Mirzaee (2017) utilized a radiant heater on newborns during injection. They found that the heater significantly reduced pain scores during injection ($p = 0.001$) and did not cause adverse effects from the heat application. Francis (2016) researched the use of nonpharmacologic interventions, topical anesthetics, exam techniques, and a combination of interventions during eye examinations of newborns. It was found that the nonpharmacologic interventions alone did not significantly reduce pain enough to allow for comfort of the newborns during examination.

Pharmacologic

Oral sweet solution. Oral sweet solutions include oral sucrose and oral dextrose in various dosages. Thirteen of the forty articles included tested oral sweet solution as an intervention, and it was recommended in eight of these studies. Chen, Zhang, Xie, Wen, and Harrison (2017) utilized oral sweet solutions, specifically 25% glucose and 24% sucrose, for pain relief in infants. They found that this reduced pain and did not negatively impact the infants' vital signs. Potana et al. (2015) found that neonates that received 24% sucrose solution had significantly lower pain scores than those in the control group ($p < 0.001$). Those in the control group experienced mild-moderate or severe pain while the intervention group experienced no pain or mild-moderate pain. Kassab, Almomani, Nuseir, and Alhouary (2020) studied the use of 50% sucrose solution in comparison to a control of sterile water for pain reduction in children receiving an immunization. The intervention group had lower pain scores for infants ($p = 0.038$) and young children ($p = 0.033$) as well as shorter crying times in infants ($p = 0.045$) and young children ($p = 0.013$). Kristoffersen et al. (2018) utilized oral sucrose in two different dosages. Neonates receiving 0.5 mL of sucrose had significantly lower pain scores during venipuncture than those receiving 0.2 mL ($p = 0.008$).

The use of oral sweet solutions is often compared to the use of nutritive sucking. Gad et al. (2019) and Gajbhiye et al. (2018) recommended breastfeeding over the use of oral sweet solutions, while Vohra et al. (2017) recommended breast milk over the use of oral sucrose. Hsieh et al. (2018) found that 10% dextrose water provided comparable pain relief to breast milk. Similarly, Shahid et al. (2019) recommended both oral sucrose and breast milk as they provided similar pain reduction in the infants they tested.

Oral sweet solutions may also be compared to non-nutritive sucking. Gao et al. (2018) compared oral sucrose to non-nutritive sucking and found that combining these two interventions was more effective than one of them alone. Lima et al. (2017) found that 25% glucose solution significantly reduced pain scores ($p < 0.001$) and crying time ($p < 0.001$) when compared to non-nutritive sucking.

As well, oral sweet solutions may be researched in comparison to non-pharmacologic methods. Hatfield et al. (2019) found that oral sucrose is effective at reducing pain scores similarly to positioning techniques. McGinnis, Murray, Cherven, McCracken, and Travers (2016) researched the effectiveness of oral sucrose as well as sucrose in combination with vibration. It was recommended to use a combination method as it produced lower pain scores than using sucrose alone.

Other pharmacologic. Pharmacologic methods may include the use of topical anesthetics such as EMLA cream or opioids. Shahid et al. (2019) tested EMLA cream for pain reduction in infants. They found that both breast milk and oral sucrose are more effective than the topical anesthetic. Beh et al. (2018) also tested EMLA cream and found that its' pain reduction was comparable to the use of music for intervention. Francis (2016) looked at the use of topical anesthetics for pain relief but found that this intervention alone was not effective at reducing newborns' pain response. Squillaro et al. (2019) determined that opioids can lead to poor neurodevelopment in neonates; therefore, the use of opioids should be avoided when possible. It is recommended to select a nonpharmacologic pain relief intervention as the first line therapy.

Combination of Interventions

At times, a combination of interventions may be more effective than a single intervention. Lago et al. (2017) recommended the use of combined intervention to most effectively reduce procedural pain. This includes combining pharmacologic and non-pharmacologic methods, such as using oral sucrose in conjunction with kangaroo care. Francis (2016) recommended the use of a combination of nonpharmacologic interventions or the use of a nonpharmacologic intervention with a topical anesthetic to achieve adequate pain control for newborns during eye examinations.

Oral sweet solution or breast milk was often combined with a non-pharmacologic intervention such as non-nutritive sucking or a positioning technique. Leng et al. (2016) researched the use of non-nutritive sucking with oral sucrose, swaddling with oral sucrose, and both non-nutritive sucking and swaddling with oral sucrose compared to a control group. The study found that the non-nutritive sucking plus sucrose and swaddling plus sucrose groups had lower pain scores than the other two groups ($p < 0.05$). The authors recommended that oral sucrose be used in conjunction with either non-nutritive sucking or swaddling to best manage procedural pain in newborns. Matsuda (2017) found that the use of oral sucrose in combination with non-nutritive sucking or with swaddling is more effective than using sucrose alone, and Gao et al. (2018) found that the use of oral sucrose with non-nutritive sucking was most effective to reduce neonatal pain when undergoing heel sticks when compared to the use of oral sucrose or non-nutritive sucking alone. McGinnis et al. (2016) recommended the use of oral sucrose in combination with vibration. This produced lower pain scores than sucrose alone ($p = 0.006$), and the neonates receiving a combination intervention had lower heart rate increases ($p = 0.002$). Peng et al. (2018) compared the use of non-nutritive sucking plus breast milk and non-nutritive

sucking plus breast milk and facilitated tucking to a control group. Both intervention groups had significantly lower pain scores than the control group ($p < 0.05$ for both groups). There was not a significant difference between the two intervention groups.

On the other hand, sometimes a combination of interventions does not provide greater pain relief than a single intervention. Zhu et al. (2015) researched a combination of breastfeeding and music therapy. They found it to be effective, however it was not more effective than breastfeeding alone. Shukla et al. (2018) utilized a combination of kangaroo care with music therapy which was effective at reducing pain scores but was not more effective than kangaroo care alone.

Chapter IV: Analysis of Data and Project Evaluation

Of the interventions utilized in the forty articles selected for review, oral sweet solution was the most commonly tested, and positioning techniques were the most frequently used non-pharmacologic method. Nutritive sucking, which includes breastfeeding and expressed breast milk, was recommended in 8 of the 9 studies it was tested in. Breastfeeding was found to be the most effective method in 5 out of 6 studies which researched it, while expressed breast milk was recommended in 3 of 4 studies. The only time expressed breast milk was not recommended was when compared to breastfeeding, which was found to be more effective. Music therapy was recommended in 4 of 6 studies it was tested in but was found to be less effective than kangaroo care and breastfeeding. Positioning techniques, including kangaroo care, facilitated tucking, and swaddling, were recommended in 9 out of 10 studies that utilized them. One study found that music therapy was more effective for pain reduction than facilitated tucking. Oral sweet solutions were researched in 13 articles, but this intervention was only recommended in 8 of these studies. Breastfeeding was found to be more effective in 2 of these studies, breast milk was

recommended in 1, and combination methods were recommended in 2 others. A combined intervention approach was recommended in 7 of 9 studies which utilized this method. In the 2 that did not recommend a combination method, kangaroo care was recommended in one and breastfeeding was recommended in the other.

Non-nutritive sucking, devices such as the Shot Blocker and Buzzy, pharmacologic methods such as EMLA cream and opioids, and non-pharmacologic methods such as covered eyes, heat, and massage do not have sufficient evidence to support their use based on this literature review.

Based on these findings, it should be recommended to utilize nutritive sucking through breastfeeding or expressed breast milk, positioning techniques, and combination methods as the first-line treatment for pain in infants and neonates. These methods are well researched and found to be effective in this patient population. However, due to the variety of available pain relief methods, future research should focus on comparing these methods to better determine what methods are more effective than others.

This project was intended to gather and analyze forty research articles in relation to procedural pain relief for infants and neonates. This was done through the use of evaluation tables, and information was synthesized in summary tables. The project was conducted as expected with no major changes except for the method of dissemination. Dissemination of the project was originally planned to occur at Wright State University's Symposium of Student Research, Scholarship, and Creative Activities. However, due to unexpected circumstances, this event was cancelled. Dissemination was instead completed through submission of a poster presentation to be available online through CORE Scholar for members of the Wright State University community to view.

Chapter V: Conclusions

Medical professionals must regularly assess pain in infants and neonates and implement interventions to help reduce pain when medical procedures are performed. Interventions such as positioning techniques are quick to implement and free to use. This review demonstrates how even methods as simple as these are able to provide comfort to the infants. As well, breastfeeding and the use of expressed breast milk are shown to be effective at reducing pain. Through the use of pain relief methods, nurses are able to decrease the emotional and physiological stress and pain that infants and neonates experience due to procedures performed in the medical setting.

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Table 1 – Evidence Summary Table

Article #	Author & Date	Evidence Type	Sample, Sample Size & Setting	Study findings that help answer the EBP question	Limitations	Evidence Level & Quality
1	Alemdar & Özdemir, 2017	RCT	94 preterm infants during venipuncture, NICU	There was a significant difference between the intervention of covered eyes and the control group NIPS score after venipuncture ($p < 0.05$). There was no significant difference of NIPS scores during venipuncture.	Blinding was not performed, potential for researcher bias	Level I, good quality
2	Aydin & Inal, 2019	RCT	150 newborns with heel stick, hospital nursery	It was found that procedural pain levels were lowest in the breastfeeding intervention group, followed by heel warming intervention, and then the control group. Both intervention groups had a shorter duration of crying time than the control group, but breastfeeding was more effective at reducing crying time ($p < 0.01$). Based on the findings, breastfeeding is recommended as a pain reduction intervention.	Pain level was only evaluated by one person	Level I, good quality
3	Beh et al., 2018	RCT	30 patients 2-24 months during venipuncture, general pediatric ward	EMLA cream and listening to music were both shown to reduce pain during venipuncture. There was not a statistically significant difference between these two interventions. The authors recommend music listening due to the simple, fast nature of the intervention that does not require medication. The authors concluded that listening to music is comparable to EMLA cream for pain relief.	Small sample size, does not cover all aspects of pain management and available techniques	Level I, low quality
4	Benoit et al., 2017	Systematic review	21 experimental or quasi-experimental studies of infants	This literature review examined the use of direct breast-feeding as a pain relief method for infants. When compared to the use of expressed breast milk, direct	Only one independent reviewer for the search of articles	Level II, high quality

			undergoing a painful procedure, hospital and clinics	breast-feeding was found to be more effective at relieving the infants' pain. Expressed breast milk compares similarly with the use of sucrose solutions. It is unclear if direct breast-feeding is more effective than sucrose solutions, but the researchers recommend direct breast-feeding as first line for pain relief.		
5	Caglar et al., 2017	RCT	100 neonates receiving hepatitis B vaccine, nursery	This study compares the use of the ShotBlocker to a control group while receiving hepatitis B immunization. Pain scores were significantly lower in the intervention group at injection and post-injection times ($p=0.000$). The ShotBlocker was effective at reducing pain in the neonates receiving the vaccine as well as their pain after injection was complete.	Not blinded, may not be generalizable due to giving vaccine within 15 minutes of birth which may not be possible in other nurseries	Level I, good quality
6	Chen et al., 2017	Systematic review	6 RCTs, 441 newborn infants undergoing OGT or NGT insertion, hospital	Oral administration of sweet solutions (25% glucose or 24% sucrose) effectively reduces pain of newborns during gastric tube insertion. The oral solutions were not shown to affect heart rate or oxygen saturation during the procedure, and adverse events were not different than the control group. This study recommends the use of small volumes of sucrose or glucose as pain relief during gastric tube insertion in newborns.	Small amount of studies included, limited ability to conduct meta-analysis, potential for bias in the individual studies	Level I, good quality
7	Chik et al., 2017	RCT	80 newborns undergoing venipuncture, NICU	Upper limb massage significantly reduced pain scores in infants during venipuncture compared to those receiving routine care during the procedure. No intervention scored in the	No strong basis of previous research for supporting massage as an	Level I, good quality

				moderate to severe pain range, while receiving massage showed minimal to moderate pain scores. This study demonstrated that massage can assist in reducing the pain that infants experience due to venipuncture.	intervention of pain reduction	
8	Dezhdar et al., 2016	RCT	82 premature neonates undergoing venous blood sampling, NICU	This study compared swaddling and kangaroo mother care as interventions to reduce pain scores of neonates during blood sampling. There was a reduction of pain in both the swaddling and kangaroo mother care groups compared to the control group. It was shown that these two interventions produced similar physiological changes in the neonates. There was not a statistically significant difference between the two interventions.	Some differences in demographics of neonates, limited use of current articles for literature review	Level I, good quality
9	Francis, 2016	Systematic review	14 studies regarding retinopathy eye exams in newborns, hospital units	The articles included in this review researched interventions to reduce pain during retinopathy eye exams in newborns. These interventions were divided into categories: nonpharmacological interventions, topical anesthetics, and eye examination techniques. It was found that most techniques were not enough to decrease pain alone, but a combination of techniques can reduce pain to a degree. It was concluded that there is not a clear answer of what method can best reduce pain associated with retinopathy eye exams.	Limited definitive conclusions from the articles included in the review, unable to draw strong conclusions or answer the research question	Level II, low quality
10	Gad et al., 2019	RCT	120 infants receiving routine immunizations,	Both the use of sucrose and breastfeeding reduced pain scores when compared to the control group. When sucrose and breastfeeding were compared to each	Lack of blinding, relied on gathering information from	Level I, high quality

			primary health center	other, it was found that breastfeeding was more effective at reducing pain in the infants during immunization. Based on the conclusions, breastfeeding is recommended as the more effective pain relief method.	the mothers which may lack accuracy	
11	Gajbhiye et al., 2018	RCT	150 full term newborns receiving their birth dose of hepatitis B vaccine, hospital post-partum unit	Pain scores were lower in both intervention groups (oral sucrose and breastfeeding) when compared to the control group. Breastfeeding intervention decreased pain more than oral sucrose ($p < 0.0001$). Increase in heart rate was lower in the intervention groups compared to the control, but the difference between the two interventions was not significant ($p = 0.0526$). Based on these findings, breastfeeding is more effective at reducing pain related to immunization of newborns.	Not blinded, did not study the mechanism of analgesic effect of the interventions	Level I, good quality
12	Gao et al., 2018	RCT	86 preterm newborns during heel stick, NICU	The use of sucrose alone, non-nutritive sucking alone, and a combination of sucrose and non-nutritive sucking were all found to reduce pain scores during heel stick. The combination group had significantly lower pain scores and the lowest amount of crying compared to the other groups. The use of sucrose with non-nutritive sucking was most effective to relief pain in newborns during heel stick.	Not fully blinded, cannot generalize to other severity of illness in newborns	Level I, good quality
13	Hartley et al., 2015	Systematic review	7 studies regarding newborns undergoing medical treatment	Facilitated tucking effectively reduced pain in premature newborns in the NICU. One included study showed the effectiveness of facilitated tucking combined with nonnutritive sucking. This intervention was found to be	Extensive exclusion criteria, possible observer bias during pain assessment	Level II, good quality

			and procedures, NICU	effective in procedures including heel stick, venipuncture, and endotracheal suctioning. The evidence supports the use of facilitated tucking and nonnutritive sucking in practice.		
14	Hatfield et al., 2019	Systematic review	14 RCTs addressing pain related to diagnostic and treatment procedures including heel lance, venipuncture, and suctioning, NICU	Facilitated tucking was the most frequently used intervention and has been shown to decrease pain response. Oral sucrose and kangaroo care are the other interventions included in the review that have been shown to be effective. This study identified a gap in research relating to comparison of pain methods, but it found that interventions are able to significantly decrease pain response of neonates.	Included articles had a lack of blinding and did not always provide consistent results	Level I, good quality
15	Ho et al., 2016	RCT	54 preterm newborns requiring heel stick, NICU	Swaddling was found to significantly decrease pain scores, limit the increase in heart rate related to pain, limit oxygen desaturation related to stress of the procedure, and minimize recovery time when compared to the control group when undergoing heel stick. This study found that swaddling is able to decrease both pain score and improve physiological data associated with the procedure. Swaddling can be used to help control minor procedural pain.	Potential assessor bias, unclear is positioning affects pain on own or in combination with swaddling	Level I, good quality
16	Hsieh et al., 2018	Quasi experimental	20 premature neonates requiring heel stick, NICU	This study looked at the use of breast milk, 10% dextrose water, and distilled water as potential pain relief methods during heel stick. Pain scores were assessed at six time intervals after heel stick was completed. It was found that dextrose and breast milk were effective at reducing pain when compared to the	Small sample size, referenced literature is not current	Level II, low quality

				control group who received nothing by mouth. Distilled water was tested as a placebo and results of this group were comparable to the control group. The researchers found that breast milk and dextrose were similar in their effectiveness. It was concluded that the act of feeding alone is not sufficient for pain reduction, but the solution must have a good taste in order to decrease pain scores.		
17	Johnston et al., 2017	Systematic review	25 studies regarding painful procedures including heel lance, venipuncture, and injections, hospital units	Skin-to-skin care was effective when compared to standard care, though the difference it makes may not be large. When skin-to-skin care was compared to sweet solution, skin-to-skin was found to be more effective in 2 of 3 studies, and the other study found that the best choice was to combine these two interventions. Skin-to-skin is recommended due to the simple and noninvasive technique.	Potential for researcher bias, unable to draw definitive conclusions due to limitations of included studies	Level II, good quality
18	Kassab et al., 2020	RCT	132 children receiving an immunization, immunization clinic	The intervention group received 2 mL of 50% sucrose solution and was compared to a control group who received 2 mL of sterile water. The intervention had statistically significantly lower pain scores than the control group for infants ($p=0.038$) and young children ($p=0.033$). Crying time was also shorter with intervention for infants ($p=0.045$) and young children ($p=0.013$). Sucrose is recommended to be used for relief of immunization pain.	Would need larger sample size to be able to generalize results	Level I, good quality
19	Kearl et al., 2015	Quasi experimental	356 infants requiring venipuncture,	This study looked at the use of the J-tip with lidocaine alone and then the J-tip used in combination with the Buzzy	Convenience sampling, no	Level II, good quality

			pediatric emergency department	device during venipuncture. The control group showed significantly higher pain scores than the J-tip intervention ($p=0.00$) and the combined J-tip and Buzzy intervention ($p=0.00$). however, there was not a significant difference between the two intervention groups ($p=0.121$). It was concluded that both interventions are effective at decreasing pain score in infants but the addition of the Buzzy device does not show a difference compared to use of the J-tip alone.	randomization, no blinding	
20	Kristoffersen et al., 2018	RCT	53 neonates requiring venipuncture, NICU	It was found that the use of oral sucrose decreased pain scores in neonates during venipuncture and that the administration of 0.5 mL was significantly more effective than the administration of 0.2 mL ($p=0.008$). The difference in pain after venipuncture between the two interventions was not significant ($p=0.291$). This study supports the use of oral sucrose with the most effective dose being 0.5 mL.	Unable to determine assessor reliability, did not account for number of previous painful procedures neonate previously experienced	Level I, good quality
21	Kucukoglu et al., 2016	RCT	75 infants undergoing vaccination, NICU	The PIPP scores of infants in the intervention (white noise) group were significantly lower than those of the control group ($p<0.05$). After vaccination, the peak heart rate and respiratory rate was lower in the intervention group and the oxygen saturation was higher. White noise was found to be effective at controlling procedural pain in premature infants. However, the researchers recommend	Results not generalizable, no blinding of observers	Level I, good quality

				using white noise in combination with a pharmacological method.		
22	Lago et al., 2017	Systematic review	232 RCT or quasi-randomized studies regarding needle-related procedures, hospital units	This systematic review supports a use of combined interventions to decrease pain in infants related to needle procedures. This includes a mixture of pharmacological and non-pharmacological methods. Methods may include the administration of oral glucose solutions, local analgesia, and the use of kangaroo care.	Does not discuss individual studies clearly, lacks clarity on specific conclusion drawn from the review, vague conclusions made	Level II, low quality
23	Leng et al., 2016	RCT	671 newborns undergoing heel stick, NICU and general pediatric units	Oral sucrose was used as routine care (control group) and the intervention groups were non-nutritive sucking with oral sucrose, swaddling with oral sucrose, and both non-nutritive sucking and swaddling with oral sucrose. Pain scores were significantly lower in the swaddling with sucrose and non-nutritive sucking with sucrose groups compared to the two other groups ($p < 0.05$). It was concluded that non-nutritive sucking and swaddling have increased effects on decreasing pain when combined with oral sucrose.	Potential for observer bias due to lack of blinding	Level I, high quality
24	Lima et al., 2017	RCT	78 newborns during immunization, maternity unit	Use of 25% glucose solution was compared to non-nutritive sucking. The glucose group had lower pain scores ($p < 0.001$) and shorter crying time ($p < 0.001$) when compared to non-nutritive sucking. Glucose solution is recommended for pain relief during immunization.	Partially blinded, all infants received comfort from mother during procedure	Level I, good quality
25	Lopez et al., 2015	RCT	42 neonates requiring	There was a significantly lower pain score in the infants receiving facilitated tucking compared to the control group	Not generalizable, may not be applicable to other	Level I, good quality

			venipuncture, NICU	($p < 0.05$). It was found that the control group scored in the category of mild pain, while the facilitated tucking group score in the category of no pain. The researchers concluded that this is a helpful technique but may not be applicable to every situation in the NICU.	painful procedures that the infants undergo in the NICU	
26	Matsuda, 2017	Systematic review	74 RCTs including neonates undergoing painful procedures including venipuncture, heel lance, and circumcision, NICU	The use of oral sucrose for pain control was compared to a variety of other methods including breastfeeding, positioning, and facilitated tucking. Sucrose of 20-30% showed a decrease in pain scores and physiologic pain reactions in newborns during heel lance while 24-30% sucrose was effective during venipuncture. It was found that sucrose used in combination with nonnutritive sucking and swaddling was more effective in pain reduction than sucrose alone.	Not enough evidence to make conclusions on some of the procedures, did not address long-term outcomes	Level I, low quality
27	McGinnis et al., 2016	RCT	56 neonates requiring heel lance, NICU	The increase in pain of the intervention group receiving sucrose and vibration was significantly lower than the control group receiving only sucrose ($p = 0.006$). The intervention group also had a lower increase in heart rate compared to the control group ($p = 0.002$). It was concluded that vibration is a useful adjunct to oral sucrose in relieving pain for infants during heel lance.	No blinding, sample size does not meet calculated statistical power of 60	Level I, good quality
28	Padhi et al., 2015	RCT	20 neonates undergoing retinopathy of prematurity screening,	Reverse kangaroo mother care (infant facing outwards) was utilized and compared to a control group. Change in heart rate and oxygen saturation were not significant with $p = 0.9108$ and $p = 0.3965$	Small sample size, limited prior evidence base	Level I, low quality

			hospital neonatal unit	respectively. The change in respiratory rate was significantly lower in the intervention group ($p=0.0037$). Based on behavioral changes, it was concluded that only two neonates in the intervention group experienced moderate-to-severe discomfort during the procedure. It was concluded that the neonates in reverse kangaroo mother care were comfortable or had mild discomfort during the exam.		
29	Pandita et al., 2018	RCT	61 infants undergoing vaccination, department of neonatology at a physician office	This study found that kangaroo mother care (KMC) was effective at reducing pain during vaccination when compared to swaddling. Pain scores were significantly lower in the KMC group ($p<0.01$) and duration of crying was also lower in this group ($p<0.01$). There were no significant differences in heart rate and oxygen saturation between the two groups.	Lack of blinding, did not calculate statistical power to determine sample size	Level I, good quality
30	Peng et al., 2018	RCT	109 neonates requiring heel stick, NICU and neonatal special care unit	This study measured pain scores at eight phases during the heel stick procedure. The group that received non-nutritive sucking and breast milk had significantly lower pain scores than the control group at 6 of 8 phases ($p<0.05$). Similarly, the group that received non-nutritive sucking, breast milk, and facilitated tucking had significantly lower pain scores than the control group at 7 of 8 phases ($p<0.05$). There was not a significant difference between the two intervention groups. It was concluded that breast milk is effective when used in combination with other non-pharmacologic methods of pain relief and	Limited to one procedure, cannot generalize to other procedures, only measured pain score and no physiological measures	Level I, good quality

				can be used as an alternative to oral sucrose.		
31	Potana et al., 2015	RCT	76 neonates requiring echocardiography, NICU	Pain scores in the intervention group receiving 24% sucrose solution were significantly lower than the control group ($p < 0.001$). Neonates in the control group experienced mild-moderate or severe pain while most of the neonates in the intervention group had no pain or mild-moderate pain. None of the neonates receiving intervention experienced severe pain. Oral sucrose was effective at reducing or eliminating pain for the neonates during echocardiography.	Limited basis of previous evidence related to this procedure	Level I, good quality
32	Shahid et al., 2019	Systematic review with meta-analysis	10 RCTs including infants under 3 months undergoing venipuncture, hospital pediatric units	EMLA was compared to nonpharmacological interventions including sucrose and breast milk. It was found that while EMLA can reduce pain in infants during venipuncture, it is less effective than the other interventions of sucrose and breast milk. As well, EMLA comes with more risks including skin irritation and toxicity. The researchers concluded that EMLA cream is not the most effective choice of pain relief for infants during venipuncture.	Researched only infants under 3 months of age, EMLA may not be compared to other interventions not stated in this systematic review	Level I, high quality
33	Shukla et al., 2018	RCT	200 neonates requiring heel stick procedure, NICU	Kangaroo care (KMC) with music therapy, KMC, and music therapy were compared to a control group. KMC and KMC with music therapy had significantly lower pain scores than the control group ($p < 0.001$ and $p = 0.001$). There was not a significant difference between the music therapy and control groups ($p = 0.18$). It was found that KMC with or without music therapy is	Only tested one form of music therapy, different gestational ages may react differently to interventions	Level I, good quality

				effective at reducing pain during heel stick. KMC is the recommended method from this research study.		
34	Squillaro et al., 2019	Systematic review	Over 90 studies regarding procedural pain in neonates, NICUs and pediatric units	This review examined various opioids as well as alternatives to opioids for pain relief. It was concluded that using more alternatives and avoiding the use of opioids is useful in reducing poor neurodevelopment in neonates. Nonopioid pharmacologic agents and nonpharmacologic interventions should be used as the first line for pain relief in neonates.	Does not provide evidence in statistical form to show quality of research, vague descriptions of studies utilized, not reproducible search strategy due to lack of information given	Level II, low quality
35	Uematsu & Sobue, 2018	RCT	25 infants requiring heel lance, NICU	This study compared an intervention of playing Brahms lullaby and using a pacifier to a control group of facilitated tucking. The intervention group had lower pain scores at all 10 times of measurement excluding baseline (p value ranging from <0.0001 to 0.0039). It was concluded that the addition of Brahms lullaby to the already established use of non-nutritive sucking through a pacifier is an effective way to reduce pain levels in infants during heel lance.	Not blinded, small sample size	Level I, good quality
36	Ullsten et al., 2017	RCT	38 infants undergoing venipuncture, special care nursery	It was found that the intervention of live lullaby singing led to infants having more consistent reactions over the venipuncture process. This was shown by the changes in heart rate and respiratory rate of the infants. It was concluded that the lullaby singing decreased stress of the infants and facilitated a faster recovery after venipuncture was completed.	Microanalysis of two infants, small sample size, lacks statistical analysis of data	Level I, low quality

37	Vohra et al., 2017	RCT	500 newborns receiving Hepatitis B vaccination, postpartum unit	The use of expressed breast milk (EBM) was compared to sucrose solution (SS) for pain relief during vaccination. The pain score in the EBM group was significantly lower than the SS group ($p < 0.001$). There was a significant change in maximum heart rate and minimum oxygen saturation between the groups that favors the use of EBM. Crying time was shorter in the EBM group but it was not statistically significant. It was concluded that EBM is more effective than SS and is cost-effective, easily available, and safe.	Referenced literature is not most current	Level I, high quality
38	Zahed Pasha et al., 2017	RCT	40 neonates receiving vitamin K injection, nursery	This study examined the use of a radiant heater for the use of pain relief during intramuscular injection of vitamin K. Intervention included two minutes in control mode and two minutes at 100% while control received four minutes in control mode. The pain score of the intervention group during injection was significantly lower than the control group ($p = 0.001$). There was not a significant difference in skin temperature of the groups. Heat application can be effective at reducing pain in newborns.	Lack of current literature for references, needs further research	Level I, good quality
39	Zargham-Boroujeni et al., 2017	RCT	75 infants undergoing venipuncture, NICU	This study used massage and breastfeeding as interventions compared to a control group. The average pain scores in the groups were 0.92 (massage), 4.84 (breastfeeding), and 6.16 (control). This reveals a significant difference in the pain scores of the groups ($p < 0.01$). Both interventions were	Does not provide actual data for evaluation by reader, only provides overall pain scores per group	Level I, good quality

				effective compared to the control with massage being the most effective.		
40	Zhu et al., 2015	RCT	250 neonates undergoing heel lance, postpartum unit	This study compared breast feeding (BF), music therapy (MT), combined intervention (BF+MT), and a control (no intervention) group. The BF group had a significantly lower pain score than MT ($p < 0.001$) and no intervention ($p < 0.001$). The BF+MT group had a significantly lower pain score than MT ($p = 0.003$) and no intervention ($p = 0.001$). There was not a significant difference between the BF and BF+MT groups. It was concluded that breast feeding is effective to reduce pain during heel lance and music therapy does not increase the effectiveness of intervention.	Not blinded, interventions should be researched for other procedures	Level I, good quality

Table 2 – Results Summary Table

Article	Breastfeeding	Breast Milk	Combination Method	Device	Music	Non-Nutritive Sucking	Oral Sweet Solution	Pharmacologic	Positioning	Other Nonpharmacologic
1	-	-	-	-	-	-	-	-	-	R (covered eyes)
2	R	-	-	-	-	-	-	-	-	T (heel warming)
3	-	-	-	-	R	-	-	R (EMLA cream)	-	-
4	R	T	-	-	-	-	-	-	-	-
5	-	-	-	R (Shot Blocker)	-	-	-	-	-	-
6	-	-	-	-	-	-	R	-	-	-
7	-	-	-	-	-	-	-	-	-	R (massage)
8	-	-	-	-	-	-	-	-	R (swaddle, Kangaroo)	-
9	-	-	R	-	-	-	-	T	-	T
10	R	-	-	-	-	-	T	-	-	-
11	R	-	-	-	-	-	T	-	-	-
12	-	-	R (sucrose with NNS)	-	-	T	T	-	-	-
13	-	-	-	-	-	-	-	-	R (facilitated tucking)	-
14	-	-	-	-	-	-	R	-	R (facilitated tucking, Kangaroo)	-
15	-	-	-	-	-	-	-	-	R (swaddle)	-
16	-	R	-	-	-	-	R	-	-	T (water)
17	-	-	-	-	-	-	-	-	R (skin to skin)	-
18	-	-	-	-	-	-	R	-	-	-
19	-	-	-	T (Buzzy); R (J-tip)	-	-	-	-	-	-
20	-	-	-	-	-	-	R	-	-	-
21	-	-	-	-	R	-	-	-	-	-
22	-	-	R (sucrose with Kangaroo)	-	-	-	-	-	-	-

23	-	-	R (sucrose with NNS or swaddle)	-	-	-	-	-	-	-
24	-	-	-	-	-	T	R	-	-	-
25	-	-	-	-	-	-	-	-	R (facilitated tucking)	-
26	-	-	R (sucrose with NNS or swaddle)	-	-	-	-	-	-	-
27	-	-	R (sucrose with vibration)	-	-	-	T	-	-	-
28	-	-	-	-	-	-	-	-	R (Kangaroo)	-
29	-	-	-	-	-	-	-	-	T (swaddle), R (Kangaroo)	-
30	-	-	R (NNS with milk)	-	-	-	-	-	-	-
31	-	-	-	-	-	-	R	-	-	-
32	-	R	-	-	-	-	R	T (EMLA cream)	-	-
33	-	-	T (Kangaroo with music)	-	T	-	-	-	R (Kangaroo)	-
34	-	-	-	-	-	-	-	T (opioids)	-	R
35	-	-	-	-	R	-	-	-	T (facilitated tucking)	-
36	-	-	-	-	R	-	-	-	-	-
37	-	R	-	-	-	-	T	-	-	-
38	-	-	-	-	-	-	-	-	-	R (heat)
39	T	-	-	-	-	-	-	-	-	R (massage)
40	R	-	T (BF with music)	-	T	-	-	-	-	-

T, tested; R, recommended method; -, not tested