Is oral sucrose a safe and effective analgesic for premature neonates? An integrative literature review

By

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BSN, British Columbia Institute of Technology, 2006

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Abstract

Babies in neonatal intensive care units (NICU) endure many painful procedures on a daily basis including nasogastric tube and intravenous insertions, lumbar punctures, tape removals, and dressing changes. Although these babies experience painful procedures numerous times during their stay in the NICU, their pain is often undermanaged or it is not managed at all. There is mounting evidence suggesting that even a brief painful event in the early years of childhood can cause an altered response to pain lasting into teenage and adult years (Fitzgerald & Walker, 2009; Johnston, Fernandes & Campbell-Yeo, 2011; Hermann, Hohmeister, Demirakca, Zohsel & Herta, 2006). A joint statement from the American Academy of Pediatrics and the Canadian Pediatric Society recommends using nonpharmacological methods, such as oral sucrose, to reduce neonatal pain from minor but painful procedures (CPS, 2007). Sucrose "is a naturally occurring sweetener with analgesic effects in young infants" (Taddio, Shah, Atenafu & Katz, 2009, p. 43). An integrative review of the literature, based on the Whittemore and Knafl (2005) framework, was conducted to examine the effectiveness and safety of oral sucrose in premature neonates for procedural pain management. Eleven quantitative studies were critiqued. Overall, the evidence indicated that sucrose is a safe and effective analgesic for premature neonates. However, more research is needed to further explore clinicians' barriers to administering sucrose.

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Introduction

Babies endure many minor but painful procedures during their stay in the NICU. These procedures are necessary for monitoring and managing the care needs of these babies (Fitzgerald & Walker, 2009). Although there is mounting evidence that babies feel pain, it is often not managed adequately (Gibbins & Stevens, 2001; Johnston et al., 2011; Hatfield, Chang, Bittle, Deluca & Polomano, 2011; Fitzgerald, & Walker, 2009). Inadequate pain management in neonates can lead to long-term adverse consequences (Fitzgerald & Walker, 2009; Johnston et al., 2011; Hermann et al., 2006) some of which include development of low thresholds for pain and heightened responses to painful stimuli (Hermann et al., 2006; CPS, 2007). Therefore, it is important that neonatal pain is managed adequately through either pharmacological or non-pharmacological methods (CPS, 2007). One of the non-pharmacological methods recommended by the CPS (2007) is administering oral sucrose[1] before and during the procedures. However, in my area of practice, the concern is that sucrose may not be safe for premature neonates.

Therefore, for this project, I conducted an integrative literature review of peer-reviewed publications that explored the effectiveness and safety of oral sucrose as an analgesic in premature neonates for procedural pain management. The majority of the previous literature reviews included full-term and premature neonates whereas I included studies conducted in premature neonates only.

[1] Sucrose is administered orally through a syringe by placing the sucrose onto the anterior portion of the tongue.

Definitions

The Institute for Safe Medication Practices (ISMP) Canada (2007) defines medication safety as "freedom from preventable harm with medication use" (under definitions' heading). For the purpose of this project, safety is defined as being free of the adverse effects of sucrose including choking, coughing, vomiting, necrotizing enterocolitis (NEC), developmental delays, and hemoglobin desaturation (Hatfield et al., 2011; Mokhnach et al., 2010; & Stevens et al., 2005). Effectiveness is defined as the ability of sucrose to reduce or relieve pain in neonates undergoing commonly performed procedures (Hatfield et al., 2011; Mokhnach et al., 2010; Taddio et al., 2008).

Purpose of the Project

The purpose of this project is to explore the effectiveness and safety of oral sucrose in premature neonates for procedural pain management. It is hoped that the knowledge gained from this literature review will advance nursing knowledge on managing neonatal pain using oral sucrose and provide a basis for advance practice nurses in developing patient care guidelines on pain control using sucrose. Undertaking this integrative literature review will develop my skills of analyzing and synthesizing the literature, a core competency for advanced practice nursing.

Background

Looking into the history of neonatal pain, it was not uncommon 25 years ago for health care providers to believe that neonates did not feel pain (Schechter, 2006). The medical community accepted that neonates were incapable of experiencing pain due to the misconception that their central nervous system was underdeveloped and that they lacked pain receptors (Rouzan, 2001). Postoperative analgesia was not prescribed

especially for infants less than 3 months of age to avoid respiratory depression and a subsequent need for intubation and ventilation (Purcell-Jones, Dormon & Sumner, 1988).

I remember watching a circumcision being performed in the late 1980's, during my first year of nursing school, without any local analgesia. The baby clearly appeared to be in a lot of pain as he was crying non-stop for the duration of the procedure. When I asked the pediatrician about administering analgesic, he proceeded to tell me that young babies did not feel pain. However, all of these perceptions of neonatal pain slowly started to shift as a new body of knowledge emerged regarding neonatal pain and pain management. Anand, Hansen, and Hickey (1990) conducted a landmark study examining the impact of ductal ligation surgery with and without adequate anesthesia on both term and preterm infants. They found extreme hormonal and metabolic responses associated with increased mortality rates among these neonates who underwent these cardiac surgeries (Anand et al., 1990). There have been further studies conducted by Anand and colleagues showing that neonates not only experience pain, but that they also have a greater response to pain because their neurotransmitters, needed for descending inhibition of pain, are underdeveloped (Schechter, 2006; Menon, Anand & McIntosh, 1998; Gibbins & Stevens, 2001).

Evidence suggests that even a single painful event early in life can lead to an altered response to pain lasting into their teenage or even adult years (Fitzgerald & Walker, 2009; Johnston et al., 2010; Hermann et al., 2006; & CPS, 2007). It is important that neonatal pain is managed adequately not only to provide comfort but also to prevent long-term adverse consequences (CPS, 2007). The CPS (2007) recommends using non-pharmacological methods to reduce neonatal pain. One of these methods is the use of oral

sucrose. Although the analgesic mechanism of sucrose is not fully understood, it is thought to involve the activation of endogenous opioid system through taste (Taddio et al., 2008). The analgesic effects of oral sucrose are reversed by administering naloxone, which suggests that sucrose activates the endogenous opioid system (Blass, Fitzgerald, & Kehoe, 1987) thus has an analgesic effect.

Even though much is now known about neonatal pain, it is still under controlled or not controlled at all (Hatfield et al., 2011; Schechter, 2006). Some of the painful procedures that neonates go through during their stay in the NICU are intramuscular injection of vitamin K, venipuncture, lumbar puncture, suture removal, and heel lances (Taddio, et al., 2008; Pasek & Huber, 2012). Barker and Rutter (1995) conducted a survey in a NICU that documented the number of painful procedures endured by 54 neonates. This survey showed that these neonates were subjected to a total of 3283 painful procedures during their length of stay in the NICU and 74% of these procedures were performed in neonates who were less than 31 weeks gestation. The most common procedure of the total overall painful procedures was heel lance at 56% (Baker & Rutter, 1995). One 23-week gestational age neonate underwent 488 painful procedures during her stay in the NICU (Baker & Rutter, 1995). Another survey was done in 56 NICUs across the UK on the use of analgesics, which showed that less than 10% of the neonates received analgesic for intravenous insertion and venipuncture types of procedures (Sabrine & Sinha, 2000). A more recent survey done in the UK showed that staff in 35% of the NICUs reported administering analgesics for procedures such as venipunctures and central line insertions compared to only 5% in 2000 (Bellieni, & Buonocore, 2008). Although there was an increase in the use of analgesic over the last 8 years, there was still

a wide gap in what evidence suggested for neonatal pain management and what was actually being practiced.

Lastly, a survey was conducted in 14 NICUs across Canada to compare pain management practices over the last 12 years from 1997 to 2009 (Johnston, Barrington, Taddio, Carbajal, & Filion, 2011). During the 1997 study, analgesic was administered 4.9% of the times for heel stick, 14.3% for endotracheal intubation and for 14.3% lumbar puncture procedures. In 2009, an analgesic was administered 15.2% of the times for heel stick, 38.7% for endotracheal intubation, and 20% for lumbar puncture procedures (Johnston et al., 2011). Again, although there is an improvement in neonatal pain management compared to more than a decade ago, it falls short of what is recommended by the Canadian Pediatric Society, which states that analgesics must be administered for every painful procedure (CPS, 2007).

Up until recently, I also have witnessed many painful procedures being performed on neonates, including chest tube and intravenous insertions, eye exams, and lumbar punctures, without nurses assessing pain and administering any analgesics. In my experience, pain management depended on the culture of the unit; for example, in one of the units in which I worked, pain assessment and pain management was not a priority for the physicians or the nurses. In the other unit, although pain was not managed all the time, the physicians and the nurses were more proactive in pain management especially for such procedures as heel lances and endotracheal intubations.

Neonatal pain

The International Association for the Study of Pain (IASP, 2011) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential

tissue damage or described in terms of such damage" (Pain section, para. 4). Pain is a subjective experience that is understood through self-reporting (IASP, 2011). However, IASP (2011) states that just because an individual cannot communicate verbally, it does not mean that he or she is not in pain, or is not in need of appropriate pain relieving interventions. Because neonates are incapable of verbally self-reporting pain, other indicators such as physiologic, hormonal/biochemical, and behavioral responses to painful stimuli can be used as forms of self-reporting to infer neonates are experiencing pain (Gibbins & Stevens, 2001;Stevens, Johnston, & Grunau, 1995). Some of these physiologic indicators include increases in heart and respiratory rates and blood pressure and decreases in oxygen saturation (Gibbins & Stevens, 2001). The hormonal and biochemical indicators consist of increased stress hormones including catecholamine, corticosteroids, growth hormones, glucagon, epinephrine, and nonepinephrine (Gibbins & Stevens, 2001).

Lastly, the behavioral indicators include crying, body movement, and facial expressions, for example, brow bulge, eye squeeze, and nasolabial furrow (Gibbins & Stevens, 2001). Nasolabial furrow is manifested by the "the pulling upward and deepening of the nasolabial furrow (a line or wrinkle that begins adjacent to the nostril wings and runs downward and outward beyond the lip corners)" (Gardner, Hagedorn, & Dickey, 2006, p. 245). To assess neonatal pain, nurses rely on pain assessment tools for accurately assessing and interpreting neonatal pain from their behavioral, physiological, and contextual indicators (Taddio, Shah, Atenafu, & Katz, 2009). Utility of these pain scales is discussed later.

Assessing neonatal pain

Assessing pain is a crucial first step for pain management (Gibbins & Stevens, 2001). Because neonates cannot self-report pain, nurses need to accurately and consistently use pain assessment tools for assessing and interpreting neonatal pain. In the mid 1980s, around the same era as health care professionals were learning more about neonatal pain, various pain scale tools were being developed. Originally, these tools were utilized more in research than in clinical (Fitzgerald & Walker, 2009). Although more clinicians are now using these tools since they were developed, clinical utility of these tools still remains low according to the two European studies (Gradin & Eriksson, 2010; Lago, Guadagni, Merazzi, Ancora, Bellieni, & Cavazza, 2005). Swedish researchers conducted surveys in 1993, 1998, 2003 and 2008 to compare the trends in the use of assessment tools in 37 Sweden NICUs (Gradin & Eriksson, 2010; Lago et al., 2005). They found that the number of units that tried to assess pain increased from 64% in 1993 to 83% in 2008 (Gradin & Eriksson, 2010). Forty-four percent of these units used pain scales in 2003, compared to 3% in 1998 (Gradin & Eriksson, 2010). The Pain Study Group of the Italian Society of Neonatology also conducted a multicentre survey involving 102 NICUs in Italy (Lago et al., 2005). The main purpose of this study was to determine how pain was assessed and managed in these NICUs. They found that only 19% of the NICUs were using validated pain scale tools to assess pain (Lago et al., 2005). I could not find any data that described trends in the use of pain scale tools in the NICUs across Canada, US, or any other countries.

Methodology

Review of the literature

Review of the literature is defined as "an organized critique of the important scholarly literature that supports a study and is a key step in the research process" (p. 85, Krainovich-Miller & Cameron, 2009). There are various ways to conduct a review of the literature some of which include systematic reviews and integrative reviews (Krainovich-Miller & Cameron, 2009). For this project, I utilized an integrative review method. According to Whittemore and Knafl (2005), this method "summarizes past empirical or theoretical literature to provide a more comprehensive understanding of a particular phenomenon" (p. 546) and it "allows for the inclusion of diverse methodologies" (p. 547). This review method supported my learning needs as a novice researcher and the steps of this framework were straightforward and easy to follow. Whittemore and Knafl (2005) have developed a framework that includes five distinct stages to critique the rigour of research studies including problem identification, literature search, data evaluation, data analysis, and presentation.

Problem identification.

In the problem identification stage, the purpose of the review and clear problem identification provide the focus and boundaries for the integrative review process (Whittemore & Knafl, 2005). During this stage, the variables of interest such as target population and the problem are identified (Whittemore & Knafl, 2005). In this case, the specific research question I sought to answer was: Is oral sucrose a safe and effective analgesic for premature neonates? One of the concerns identified in my clinical area was the safety of sucrose on premature neonates. Therefore, the focus of this literature review

was specifically for premature neonates.

Literature search stage.

In the second step, "well-defined literature search strategies are critical for enhancing the rigour of any type of review" (Whittemore & Knafl, 2005, p. 548). These authors recommend using two to three search strategies. I conducted a literature search using four search strategies including The Cumulative Index to Nursing and Allied Health Literature (CINAHL), Medical Literature On-Line (MEDLINE), EBSCO, and Google Scholar. The key words to search literature included premature neonates, and/or infants, pain, analgesic, sucrose, effective* effectiveness*, safety, and side effects. I also used the Cochrane Reviews for neonates as these reviews are "of primary research in human health care and health policy, and are internationally recognized as the highest standard in evidence-based health care" (under Cochrane reviews heading). I also utilized the ancestry search approach to broaden my search of the topic. Ancestry search is referring to earlier studies cited in references of published articles (Polit & Beck, 2008). This search resulted in 61 articles; however, after reviewing these articles, only 11 met the inclusion criteria.

Inclusion/exclusion criteria.

One of the parameters of the search was to include only peer-reviewed research because the panel for peer-reviewed research uses scholarly criteria to judge the worthiness of publication similar to judging the strength and weakness of a study (Krainovich-Miller & Cameron, 2009). Other parameters included studies conducted and published in English between 2004-2012. Originally I was going to include studies conducted and published in Canada, United States, and England; however I had to

broaden my search to include other countries as I could only locate 4 articles from 2004 - 2011 conducted in United States, England, and Canada. Only primary research articles were included in this review. Krainovich-Miller & Cameron (2009) emphasize that "critical evaluation of mainly primary sources is essential to a thorough and relevant review of the literature" (p. 90). Primary sources are where the authors of the study conducted the research (Krainovich-Miller & Cameron, 2009). Lastly, studies conducted in premature neonates less than 37 weeks gestational age only were included.

The excluded articles were 4 previous literature reviews, 6 articles published prior to 2004, 2 articles on immunization as typically infants are immunized at 2 months of age, 10 articles on term neonates, 4 articles with studies conducted on oral glucose, and 24 articles, which were irrelevant to the research question. These inclusion/exclusion criteria produced total of 11 relevant studies. These studies are summarized in Appendix B according to the evaluation criteria.

Data evaluation.

The third stage involves data evaluation. Whittemore and Knafl (2005) suggest extracting specific methodological features to evaluate overall quality of the primary source research. They further recommend incorporating a quality score into the data analysis stage. The studies with high score indicate a high rigour whereas low score indicate a low rigour, suggesting that these studies contribute "less to the analytic process" (p. 549). However, they also suggest that studies with fewer scores should not be totally excluded because the scores are shown as a "variable in the data analysis stage" (p. 549). I developed evaluation criteria to serve as an evaluation guide based on Heerman, Craft, & Singh's (2009) quantitative appraisal tool (Appendix A). Using this

tool, I appraised the eleven studies and assigned each study a quality score out of 17 based on methodological elements in the appraisal tool criteria (see Appendix B). A score of less than 7 was used to indicate less rigour; however, based on the quality scores, no articles were excluded as all the studies scored 12 or greater. Therefore, all of these studies were considered high quality studies.

Data Analysis.

Whittemore and Knafl (2005) suggest that during data analysis stage, the data are extracted, ordered, categorized and summarized in a unified manner. I categorized and summarized the data in a table according to the following headings: a) citation, authors, and location where the study was conducted, b) research problem/statement, c) design, ethical considerations & data collection, d) sample, e) stimulus, f) intervention, g) instrument, h) results, and i) strengths/limitations (Appendix B). The next step to data analysis is to organize it in a way that is manageable.

Data Reduction.

Data reduction is a necessary process in an integrative review to simplify, focus, and organize data into a manageable framework (Whittemore & Knafl, 2005). The categories that I focused on are sample, data collection, instrument, stimuli, and intervention as these are the key elements to assess for myself as an advanced practice nurse who will be developing practice care guidelines on the use of oral sucrose.

Sample.

For quantitative studies, sample size and its characteristics are crucial elements in the analysis of data as they increase the rigour of the studies and enhance the generalizability of the findings (Haber & Singh, 2009). Sample sizes in the studies

reviewed ranged from 20-76 neonates. The total sample size included within the 11 studies was 475 neonates. Power analysis was done in 7 studies where the researchers reported that the sample sizes were adequate to carry out the studies. The other 4 studies did not report if power analysis was done or if the sample size was adequate. According to Haber and Singh (2009) if power analysis is not calculated, studies maybe based on samples that are too small, which may produce less accurate results and lead to unsupported hypotheses.

Ages for neonates in the study samples was based on gestational age and ranged from 24 weeks to 37 weeks. This age was appropriate for the purpose of this review as the results of these studies can be generalized to the patient population in my area of practice. Most of the sample selection was done based on each study's inclusion criteria, which was consistent for most of the studies. In the majority of the studies, one of the eligibility criteria included that neonates must no longer require mechanical ventilator and continuous positive airway pressure support as these devices obscure an accurate assessment of facial (behavioural) responses to pain. Also, the majority of the times these neonates are on other types of analgesic; therefore, sucrose is normally not administered. Other exclusion criteria in these studies included antenatal maternal sedation, neurologic sequelae, Apgar scores <5 at 1 and at 5 minutes of age, and cardiovascular disorders. These exclusion criteria are important as they all impact the neurological status of neonates; therefore, their response to sucrose would be inaccurate. These criteria were also consistent in the majority of the studies. These sample eligibility criteria are appropriate and relevant to my area of practice.

The sex of the sample was only reported in 3 studies (Biran et al., 2011; Okan et

al., 2007; & Gaspardo et. al., 2007) where overall 52.2% were male and 47.8% were female for all the three studies. The difference in response to pain among the sexes was not reported in any of the studies. It would have been interesting to see if males and females responded differently and had different requirements for sucrose.

In terms of protecting the rights of the subjects, a written consent was obtained in 10 of the studies. In one study, consent was not mentioned. Further ethics approval evaluation did not mention how they obtained the consent, who obtained it, if the study steps were explained, and if the parents were made aware of withdrawing from the study without any consequences. There was no evidence that parents were coerced to participate, for example, compensation for their time was not mentioned in any of the studies. In summary, the sample and its characteristics were appropriate for the studies and the findings of these studies can be generalized to my area of practice.

Data collection.

Data collection is another important element to assess for quantitative studies to add to the rigour of the study. Data can be collected in many ways depending on the design of the study (Whittemore, Grey, & Singh, 2009). Data collectors must be trained in the methods to be used for the study so that the data is collected in the same manner (Whittemore et al., 2009). In the reviewed studies, trained staff collected data in 9 of the 11 studies. These staff members were trained in how to use the pain scales, which were the instruments used to collect the data. They also had previous experience using the pain scales. Two of the studies did not identify if the data collectors were trained (Kristoffersen et al., 2011 & Elserafy et al., 2009). Physiological data (heart rate, blood pressure, and oxygen saturation) were collected using existing bedside cardiorespiratory

monitors in all of the studies. Behavioural response data was collected via video recordings in 8 of the studies; however, in the other 3 studies (Milazzo et al., 2011; Kristoffersen et al., 2011; & Elserafy et al., 2009) responses were observed and recorded by the data collectors according to the pain scales. In the studies where behavioural responses were video recorded, that data was then scored according to the pain scales. With the video recordings, the researcher had the ability to pause and go back to accurately score and confirm findings as opposed to one time direct observation. The data collection procedure was similar if not identical for all the subjects in each of the studies. All of the studies identified the instruments used to collect the data. These various instruments will be discussed next.

Instrument.

Rigour of the quantitative study is also determined by the reliability and validity of the instrument used to collect the data (LoBiondo-Wood, Haber, & Singh, 2009). Reliability refers to "the extent to which the instrument yields the same results on repeated measures" (LoBiondo-Wood et al., 2009, p. 298). An instrument is reliable if it produces the same results when behaviour is measured again using the same instrument (LoBiondo-Wood et al., 2009). According to LoBiondo-Wood et al. (2009), a tool is also considered reliable if reliability coefficient is at a level of 0.70 or higher. Validity is referring to whether an instrument is measuring what it is suppose to measure (LoBiondo-Wood et al., 2009). For the reviewed studies, various pain-measuring scales were used as instruments. The most common pain measuring tools included: NFCS (Neonatal Facial Coding System, NIPS (Neonatal Infant Pain Scale), and PIPP (Premature Infant Pain Profile). The other pain scales included DAN (Douleur Aigue du Nouveau-ne) and BPSN

(Bernese Pain Scale for Neonates). These two tools are used less commonly.

The PIPP is a multidimensional tool with established reliability and validity (Gibbins & Stevens, 2001), which was developed by Stevens, Johnston, Petryshen, and Taddio (1996). It has high interrater reliability of alpha = 0.95-0.97 and intrarater reliability of alpha = 0.89-0.91 (Stevens et al., 2005). It incorporates behavioral, physiological, and contextual indicators of pain that are scored on a scale of 0 to 3 for each of these indicators (Taddio, et al., 2009; Stevens et al., 1996). Total scores range from 0-18 (Taddio et al., 2009). Behavioral indicators of pain include eye squeezing, brow bulging, and naso-labial furrow; the physiological indicators include heart rate and oxygen saturation; and the contextual indicators include gestational age and infant states, for example, active, awake, asleep, and quiet (Taddio, et al., 2009; Gallo, 2003). The PIPP is the only tool that takes gestational age into account differentiating behavioral differences between full-term and preterm neonates (Gallo, 2003). This tool was used in more than half of the reviewed studies. Biran et al., (2011) used PIPP in conjunction with the DAN tool to measure the physiological response to pain and to measure the effectiveness of oral sucrose and EMLA cream after venipuncture. Researchers of five of the eleven studies used PIPP scales in their studies (Kristoffersen et al., 2011; Elserafy et al., 2009; Boyle et al., 2006; Stevens et al., 2005; & Mitchell et al., 2004).

The NIPS was developed by Lawrence, Alcock, McGrath, Kay, MacMurray, and Dulberg (1993). It includes six behavioral indicators of pain including facial expressions, cry, breathing patterns, arms, legs, and state of arousal (Gallo, 2003). These items are scored on either a 2-point (0-1) or a 3-point (0-2) scale (Lawrence et al., 1993). The total score can range from 0 to 7. It has a high interrater reliability (Pearson correlation .92 to

.97) and internal consistency (Cronbach's alphas of .95, .87, and .88 for before, during, and after procedure, respectively) (Stevens et al., 1996; Gallo, 2003). The construct and concurrent validity measured in Pearson correlations range from 0.53- 0.84 (Gallo, 2003). The study conducted by Milazzo et al., 2011 is the only study in this review that used NIPS.

NFCS is a one-dimensional pain-measuring tool that was developed by Grunau, and Craig (1987). This tool uses only neonatal facial expressions to measure pain. These include: brow bulge, eye squeeze, naso-labial furrow, open lips, vertical and horizontal stretches of the mouth, lip pursing, taut tongue, and chin quiver (Grunau & Craig, 1987). Inter and intrarater reliability has been reported to be above 0.85 measured in Cohen's Kappa (Stevens et al., 1996). Researchers of three of the studies used the NFSC scale in their studies (Gaspardo et al., 2007; McCullough et al., 2006; & Okan et al., 2006).

The DAN is a less commonly used pain scale developed by Carbajal, Hoenn, Lenclen, and Olivier-Martin (1997). It measures facial expressions, limb movement and vocal expressions. The score ranges from 0-10. Internal consistency is reported at 0.88 measured in Cronbach's coefficient Alpha. Interrater agreement measured in Krippendorff R test is 91.2 (Carbajal et al., 1997). Biran et al. (2011) are the only researchers who used DAN in this review.

The last scale is the BPSN, developed by NICU nurses and validated by Cignacco, Mueller, Hamers, and Gessler (2004). This scale contains 9 items: 3 physiological (heart rate, respiratory rate, and oxygen saturations), and 6 behavioural (grimacing, body movements, crying, skin colour, sleeping patterns, consolation). Each item is scored on a 3- point scale (0-3) with a possible score of 27. Interrater reliability

coefficient is reported at 0.98-0.99 and intrarater reliability coefficient is 0.86-0.97. Cignacco et al. (2012) used the BPSN scale in their study. Although there is no one tool that is considered gold standard, after reviewing these tools the PIPP scale was used more widely than any other tools in the reviewed studies. This scale is a multidimensional tool, which also takes gestational age into account as premature neonates respond to pain differently than term neonates (Johnston et al., 2011).

Intervention.

To make sure the results of the studies can be generalized to my area of practice, the intervention element is another key area to assess in these studies. All the studies evaluated for this literature review were randomized control trials. Randomized control trials "provide the strongest evidence in terms of whether an intervention or treatment impacts client outcomes" (Whittemore, Grey, & Singh, 2009, p. 227). In this case, the participants were randomized into various intervention groups some of which included facilitated tuck versus oral sucrose group, pacifier plus oral sucrose versus pacifier alone, and pacifier with water versus pacifier with oral sucrose or pacifier alone to measure the outcome of each intervention. Blinding of some of the interventions was not feasible due to the type of interventions such as the pacifiers and the facilitated tuck. Facilitated tuck is a technique where a caregiver holds the neonates by placing his/her hands over their hands and feet while positioning them in a flexed position in either side-lying, supine or prone position (Corff, Seideman, Venkataraman, Lutes, & Yates, 1995). This technique stabilizes behavioral and physiologic states during painful stimuli, thereby reducing the stress response of neonates to pain (Corff et al., 1995; Ward-Larson, Horn, & Gosnell, 2004; Huang, Tung, Kuo & Ying-Ju, 2004). Only one study used facilitated tuck as the

control group (Cignacco et al., 2012). The pacifiers were used in 4 studies (Kristoffersen et al, 2011; Elserafy et al., 2009; Stevens et al., 2005; & Mitchell et al., 2004).

In all of the reviewed studies, one of the main interventions was the administration of oral sucrose alone or in combination with other interventions. In all the studies, researchers were blinded to the sucrose and other placebo interventions such as water, glucose, and cream. Sucrose was administered orally in all of the interventions. The sucrose concentration and dose varied among all the studies. The concentration ranged from 20% to 33% and most commonly used concentration was 24% and 30%. The dose was either based on weight or a standard dose was used. The dose ranged either from 0.1mL-2mL for all participants in some studies to 0.2mL/kg for all the participants in one study. The most commonly used dose was 1mL-2mL in all the other studies. The dose range and concentrations are similar to guidelines in my area of practice, which is 24% sucrose ranging from 0.1mL-2mL depending on the gestational age.

Although there were inconsistencies for the dose amount and the concentration for these studies, most of the authors concluded that sucrose was effective in their studies. Even though the inconsistent doses and concentrations maybe confusing for the reviewer of the studies, this variety gives clinicians the flexibility of using the low concentration doses especially if the safety of sucrose is a concern for them. However, this wide range of doses and concentrations might put neonates at risks of either getting inadequate amounts or getting too much sucrose. Therefore, a weight specific dose would be a preferred choice.

Stimuli.

All of the stimulations used in the studies are similar to my area of practice. These included heel lance, venipunctures, eye exams, naso-gastric tube insertions, and arterial punctures. The effectiveness of oral sucrose with a wide variety of painful stimuli ensures that oral sucrose can be used in many different procedures. However, sucrose is used for short-term procedural pain, such as listed above, versus long-term pain because it has immediate response with short acting analgesic effect, which peaks at 2 minutes and lasts approximately 5 minutes (Harrison, Johnston, & Loughnan, 2003).

Presentation.

The last step of Whittemore and Knafl's framework on integrative review is the presentation of results. The remaining of this project focuses on the summaries of the findings of the studies, result, discussion, recommendations for clinical practice, and the conclusion.

Brief summary of the studies.

Cignacco et al. (2012). Oral sucrose and facilitated tucking for repeated pain relief in preterms: A randomized controlled trial.

Cignacco et al. (2012) conducted a RCT study investigating three interventions including facilitated tuck (FT) alone, oral sucrose 20% alone, and oral sucrose 20% with FT during heel lance procedure. The sample size was a total of 72 neonates but there was no power calculation done to determine if the sample size was adequate. The data were collected in three phases by trained and experienced nurses. Phase one was just prior to the procedure, phase 2 was during the procedure including skin preparation, heel stick, and homeostasis after blood was drawn, and phase 3 was during recovery 3 minutes after the heel stick. The Bernese Pain Scale for Neonates (BPSN) was utilized to measure the

data, which included physiological (P-BPSN) and behavioural (B-BPSN) responses to pain. Video recording was used to record facial expressions.

The data analysis was described well. Chi-square (X2) test and Kruskal-Eillis or Mann-Whitney U tests were used for comparing the demographic and medical characteristics of the neonates among the 3 intervention groups. Sample sizes for each group, sex, and delivery type (for example vaginal birth or cesarean section) were analyzed using the chi-square statistics. Kruskal-Ellis or Mann-Whitney U tests were used to compare the medical characteristics including mean gestational age, mean birth weight and mean number of painful procedures. A repeated measure analysis was utilized to test the hypothesis. The level of significance was reported at $p < 0.05$. During the heel stick phase, the FT group had significant higher behavioral B-BPSN scores ($p = .01$; .007) and physiologic P-BPSN scores ($p = .0002$; .003) than the sucrose and combination groups. During the recovery phase, there were significant differences in P-BPSN scores, but the combination group had statistically significant lower B-BPSN scores than both the other groups ($p = .006$; .008).

The results of this study showed that sucrose alone or in combination of FT are effective for pain control in neonates less than 32 weeks of gestational age. Although there was an added analgesic effect of facilitated tuck only during recovery phase, this technique was not recommended by the authors due to the added resources required for this procedure. They concluded that sucrose alone was just as effective as the combination of sucrose and FT during the heel lance phase. These authors did not mention the safety of sucrose.

Biran et al. (2011). Analgesic effects of EMLA cream and oral sucrose during venipuncture in preterm infants.

Biran et al. (2011) compared the analgesic effects of EMLA (Eutectic Mixture of Lidocaine and Prilocaine) cream and oral sucrose with that of oral sucrose alone during a venipuncture procedure. This was a prospective and double blind randomized control trial. Neonates of less than 37 weeks of gestational age were randomized to either EMLA plus sucrose group or to sucrose alone group. The total sample size was 76 neonates, which was calculated through power analysis to be a sufficient sample size. Trained staff collected the data in three phases including baseline, during venipuncture (from the time skin was punctured until needle was removed) and recovery (3 minutes after the heel stick). The Douleur Aigue Nouveau-ne (DAN) scale was used to measure the behavioural scores as a primary outcome and the Premature Infant Pain Profile (PIPP) scale was used to measure physiological scores as a secondary measure. Crying time was also measured. Facial expressions and body movement were video recorded.

For the data analysis, the demographic characteristics of the sample were summarized in a table using descriptive statistics. Pain scores over time and between treatments were compared using repeated-measures analysis of variance. Level of significance was reported at $p < 0.05$. Baseline DAN and PIPP were similar for both interventions. For the S+E group and S group, respectively, the mean baseline DAN score was 2.1 and 2.2 ($p = .843$) and mean baseline PIPP was 4.5 and 4.3 ($p = .645$). DAN pain scores were lower during venipuncture and post injection period in S+E group (6.4) compared with S group (7.7) reaching statistically significant treatment of $p = .018$. During the recovery period, DAN scores for S+E were 5.7 and for S were 7.1 reaching statistical significance of $p = .018$. PIPP scores were also lower in S+E group compared

with S group; however PIPP scores did not reach statistical significance. Crying time was also lower in the S+E group but did not reach statistical significance.

The researchers concluded that S+E was more effective than sucrose alone during venipuncture, but they were concerned about the safety of EMLA in neonates. The main concern they cited was the possibility of increased methemoglobin after EMLA application. The authors of this research study did not address this concern in their current study but it was mentioned from previous studies. Although the purpose of this project was to review studies that address safety of sucrose, it would have been useful for me if the authors had evaluated the concerned side effect of EMLA in their current study since EMLA had an added effect towards pain control. Otherwise, I am hesitant to recommend using the EMLA with sucrose. There were no other adverse effects observed such as choking, coughing, vomiting, tachycardia, and bradycardia. Oral sucrose was considered to be safe in the current study.

Milazzo et al. (2011). Oral sucrose to decease pain associated with arterial puncture in infants 30 to 36 weeks' gestation.

Milazzo et al. (2011) conducted a study on the effectiveness of sucrose during arterial punctures. Similarly to Biran et al. (2011) this was a double blind randomized controlled trial. Forty-seven neonates of 31 to 35 weeks gestational age were included in sucrose and no sucrose groups. This was an adequate sample size according to the power analysis calculation. Data were collected using NIPS pain scale and HR and oxygen saturation were also measured as a secondary outcome by trained RNs. There was no mention of video recording. Data were collected in three phases: baseline, immediately after the puncture, and at 1 minute after the puncture.

Data were summarized using descriptive statistics. Level of significance for all tests was reported at $p < 0.05$. Data were analyzed using chi-square statistics (for NIPS change scores) and analysis of variance and a Bonferroni multiple comparison test were utilized (for heart rate and saturations) to test the differences between the sucrose and no sucrose groups. Chi-square analysis of the changes in NIPS subscale and total scores found statistically significant lower subscale scores for changes in crying in the sucrose group compared to the no sucrose group at the time of the needle puncture and at 1 minute after completion of the puncture ($p = .0006$ and $p = 0.022$ respectively) suggesting that sucrose had an analgesic effect.

There were no differences in scores for facial expression, breathing pattern, arm and leg movement, and arousal between the two groups ($p > .05$). The authors contribute the lack of changes in arm and leg movement to the fact that neonates were bundled during the procedure obscuring observation of limb movement. Analysis of variance found no statistical differences for heart rate or oxygen saturation levels between the sucrose and no sucrose groups ($p > .05$). They contend that lack of changes to other subscales of NIPS could be due to low intensity of pain related to arterial puncture as compared to different types of needle sticks. Milazzo et al. (2011) cite a study by Lawrence et al. (1993), developers of the NIPS tool, where they found that during testing of the validity and reliability of NIPS, arterial puncture generated lower pain scores than venous and capillary puncture by 2 or more times. Nevertheless, the authors of the current study found that sucrose reduced crying time, which were statistically significant, immediately after the puncture. The safety of sucrose was not reported in this study. It would have been helpful to leave the neonates unbundled during the study period to

observe changes in limb movement, thereby, capturing more complete data and strengthening the findings.

Kristoffersen, Skogvoll, and Hafstrom (2011). Pain reduction on insertion of a feeding tube in preterm infants: A randomized controlled trial.

Kristoffersen et al. (2011) conducted a semi-blind randomized control trial to assess pain and to evaluate different pain measures for pain relief during naso-gastric tube (NGT) insertion. There were six intervention groups including no fluid and no pacifier, sterile water and no pacifier, sucrose and no pacifier, no fluid but had pacifier, pacifier and sterile water, and sucrose 30% and pacifier. Each neonate received all of the six interventions. Twenty-four preterm neonates of 28-32 weeks gestational ages were included in the study. The sample size was adequate according to power analysis, which only required 18 neonates. The neonates were observed by two experienced neonatal nurses. One nurse collected the data using the PIPP scale while the other nurse kept a track of the time. The facial expressions were not video-recorded. The data were collected during four phases: 15 seconds before NGT, within 30 seconds of NGT, 1 minute, and 5 minutes after NGT insertions.

Descriptive statistics were used to summarize the results. The level of significance was reported at $p < .05$. The maximum PIPP score for each intervention for neonates in this study was 19 or 20 depending on the gestational age and weight of the neonates. The median PIPP score for no intervention was 9, water group 11, 30% sucrose only 8, pacifier only 10, pacifier and sterile water 9, and pacifier and 30% sucrose 7. The combination of sucrose and pacifier during nasogastric tube insertion provided the most effective pain reduction ($p < .001$) versus no treatment. Sterile water alone had the highest pain scores among all the groups. The authors concluded that if pacifiers were not

available or suitable then sucrose alone was a good alternative. No safety outcomes were reported in this study. Overall, this study was rigorously conducted except that the data was collected within 30 seconds of the procedure, which is a very short window of opportunity to insert a NGT and capture complete data manually, especially facial expressions.

Elserafy, Alsaedi, Louwrens, Sadiq, and Mersal (2009). Oral sucrose and a pacifier for pain relief during simple procedures in preterm infants: A randomized controlled trial.

Elserafy et al. (2009) conducted a randomized double-blinded control trial to assess the analgesic effect of sucrose versus other interventions prior to venipuncture procedure. Similar to Kristoffersen et al. (2011) the neonates in this study were assigned to 6 intervention groups including sterile water with pacifier, sterile water without pacifier, sucrose 24% with pacifier, 24% sucrose without pacifier, pacifier alone, and standard care or no treatment. There were 36 neonates less than 37 weeks gestational age included in this study, however, there was no power analysis done to determine if this was an adequate sample. Since every neonate in the study received each of the six regimens, I believe this sample size was adequate. The data were collected in six phases including immediately prior to the procedure, during the procedure, and at 1, 3, 5, and 10 minutes after the procedure using the PIPP scale. There is no mention of video recording and who collected the data. Crying time and blood glucose was also measured.

Repeated measures analysis of variance was used for the statistical analysis. The level of significance is reported at $p < 0.05$. Pain score comparisons between different treatments were summarized using mixed between-within ANOVA. There were no significant differences between treatment groups in heart rate, blood pressure, oxygen

saturation, and glucose measurements, but there were significant differences in crying time and pain score (P= .001). Pain scores were significantly reduced in infants who received 0.5 mL (0.12g) of 24% oral sucrose with mean pain score of 0.9 reaching level of significance p= 0.05. The combination of pacifier and oral sucrose were more effective and reduced crying time reaching statistical significance of p=.001. The use of sterile water alone (mean score 1.4) or pacifier alone (mean score 1.4) or the combination of sterile water (mean score 1.5) and pacifier (mean score 1.8) were not statistically different in terms of pain control compared with control group that received standard care (no treatment).

These authors concluded that oral sucrose is a safe and effective analgesic for minor procedures. Pain scores were reduced significantly in neonates receiving sucrose only; however, the combination of pacifier and sucrose were more effective and reduced crying time. The highest pain score occurred at one minute after painful stimuli with the entire treatment group, but the maximum pain was experienced by the control group and with the use of the pacifier alone group. There were no adverse effects reported in this study, which included bradycardia (HR <80 beats/minute), tachycardia (HR >160 beats/minute), and hypoxia (oxygen saturation below 88%), concluding that sucrose is safe and effective analgesic for painful procedures.

Gaspardo, Miyase, Chimello, Martinez, and Linhares (2008). Is pain relief equally efficacious and free of side effects with repeated doses of oral sucrose in preterm neonates?

Gaspardo et al. (2008) conducted a randomized double blind placebo controlled trial to assess the effectiveness of repeated doses of sucrose in all painful procedures. Specifically, these procedures were venipuncture, arterial puncture, heel-lance,

intravenous and endotracheal tube insertions, endotracheal tube suctioning, gavage insertion for feeding, and removal of electrode leads or tape. There were 33 neonates included in the study of less than 37 weeks gestational age. These neonates were assigned to either a sucrose group receiving 24% sucrose of 0.5mL/kg or a control group receiving water. There was no power analysis done to calculate the sample size. There were 16 neonates in the control group and 17 neonates in the sucrose group. The data was collected between 0700-0900 in five phases over 4 days, unlike the other studies where data was normally collected in 3 phases. Each day was referred to as either assessment 1 meaning no intervention or assessments 2, 3, and 4, which included administering of either sucrose or water. The five phases were Baseline (BL), Antisepsis (A) handling the neonate for antisepsis prior to puncture, Puncture (P), Dressing (D) handling the neonate for dressing until positioned to rest, and Recovery (R). Two trained staff collected the data. Facial activities were videotaped and the NFCS pain-measuring tool was used with a score of 3 as a cut of value. Heart rate, behavioural state, and crying state were also measured.

Descriptive statistical analysis was used to analyze the data. The level of significance was reported at $p < 0.05$. On the first assessment day, there were no statistically significant differences between groups. Both groups showed a high percentage (>50%) of neonates with NFCS scores of 3 or greater in the puncture phase. On the second assessment, there was a statistical significant between the groups in regards to NFCS scores of 3 or greater during the Puncture phase (SG= 23%, CG= 56%, p=.05. On the third assessment day, there was a statistically significant difference between groups in terms of percentage of neonates with NFCS scores of 3 or greater in the Antisepsis phase

(SG= 0%, CG= 31%, p= .02). On the fourth assessment day, there was also a statistical significant difference between groups for NFCS 3 or greater during the Puncture (SG= 26%, CG 56%, p=.08) and Dressing (SG= 13%, CG= 31%, p=.09) phases. For behavioral state measurements (during the second and fourth assessments), statistically significant differences between groups were found in the Puncture phase. The percentage of SG neonates with activated behavioral state was lower than the CG (p=.05 for second assessment and p=.02 for fourth assessment).

For crying measurements, on the second assessment, crying was significantly greater in CG group than SG (p= .0009) during Antisepsis and Puncture phases. On the third assessment, the difference was during Dressing phase (p=.04). On the fourth assessment, a difference was detected in the Puncture phase (p=.03). For heart rate measurements for a heart rate of >160, there were no differences in all groups for all four assessments during all the phases. There were no short-term negative side effects, such as necrotizing entero-colitis, from repeated doses of sucrose.

Both the safety and effectiveness of repeated doses of sucrose were reported. On average, infants received approximately six doses of 25% oral sucrose per day during the study period (one neonate received 14 doses). There were no adverse effects reported that were associated with repeated doses especially when the authors had a concern of neonates developing necrotizing entero-colitis. Sucrose was found to be an effective analgesic for minor painful procedures. Although this study addressed both the effectiveness and safety of the sucrose, the methodology was unclear for the reader especially the assessments representing the number of days. The other lack of clarity was

how the data was collected in phases instead of in minutes, while most of the other researchers had done in the other studies.

Boyle et al. (2006). Sucrose and non-nutritive sucking for the relief of pain in screening for retinopathy of prematurity: A randomized controlled trial.

The study by Boyle et al. (2006) evaluated the use of oral sucrose and pacifier for reducing pain responses during eye examinations. In this randomized controlled trial 40 neonates were assigned into one of the four groups. This was an adequate sample size according to power analysis, which indicated that only 7 neonates per group were required. Group 1 received sterile water (1mL), group two had 1mL sucrose 33%, group 3 received 1mL sterile water plus pacifier and group four had 1mL sucrose 33% plus pacifier. Data was collected using the PIPP scale and facial expressions were video recorded, both of which were collected and analyzed by the experienced staff. The neonates in the sample were less than 32 weeks gestational age or weighed less than1500 grams. Also, neonates on continuous positive airway pressure (CPAP) via nasal prongs were included.

One-way analysis of variance showed no significant difference in PIPP scores between those neonates who received oral sucrose (14.3) versus those who received water orally (15.3, $p= 0.321$). The PIPP scores were significantly lower ($p= 0.003$) in infants receiving a pacifier (12.3 group 3 and 12.1 group 4) than those without a pacifier (15.3 group 1 and 14.3 group 2), suggesting that non-nutritive sucking and oral sucrose has a pain relieving effect. This is in contrast to Kristoffersen et al. (2011) study, which concluded that pacifier was not an effective intervention for pain control. There was a

trend of lowest scores in the sucrose plus pacifier group (12.1), but this did not reach statistical significance. There were no adverse effects associated with a single dose of sucrose in this study. The authors concluded that given the uncertainty of long-term effects of sucrose, a pacifier alone is effective for providing pain control during neonatal eye examination.

They also suggested that sucrose can be utilized for breastfed neonates whose parents prefer that their babies not have a pacifier. Eye examination is a stressful and painful procedure. A single dose of sucrose was administered for this procedure in this study. It may be that repeated doses of sucrose are necessary for it to be effective for this particular procedure. In contrast to the other studies, this study included neonates who were on CPAP, which would have obscured some of the facial expressions, possibly affecting the accuracy of facial assessment. The number of neonates on CPAP included in the study was not reported.

McCullough, Halton, Mowbray, and Macfarlane (2006). Lingual sucrose reduces the pain response to nasogastric tube insertion: A randomized clinical trial.

McCullough et al. (2006) conducted a randomized placebo controlled trial to determine if lingual [2]sucrose reduces the pain response to NG insertion preterm neonates. Twenty neonates were included in the study and a total of 51 naso-gastric insertion episodes were evaluated. Subjects were assigned to either sucrose 24% or placebo (water) groups. Power analysis was not done to determine if sample was adequate. However, neonates in this study were allowed to be randomized more than once into either group as long as they were eligible and required naso-gastric tube insertion, therefore, I believe

[2] Lingual sucrose in this study referred to administering oral sucrose by placing it onto the anterior portion of the tongue, the same way as other studies had administered.

this was an adequate sample size. Twelve hours had to be lapsed between the interventions to avoid any carry over effect that could have biased the findings. The NFCS pain-measuring tool was used to collect the data; however, video recording was not used. Heart rate and oxygen saturations were recorded as a secondary outcome. The presence and absence of cry was also recorded. Data was collected in three phases instead of minutes, which included baseline, during the procedure, and at the end of the procedure. The nurse who collected the data was not present during administering of the solutions.

Descriptive statistics were used to analyze the data. The sucrose group had a statistically significant lower median NFCS score (1, range 0-4, p= 0.004) during NGT insertion than the placebo group (3, range 0-4). Fewer neonates in the sucrose group cried (8/26) compared with the placebo group (14/25), reaching statistical significance of p= 0.069. Neonates in the sucrose group had a higher mean pretreatment baseline heart rate (170 beats per minute) than the placebo group (158 beats per minute), but there was no change in heart rate during NGT insertion. In contrast, in the placebo group, the heart rate increased by 11 beats per minute reaching statistical significance p= .055 compared to the sucrose group. There were no significant differences between the two groups with regards to the number of adverse events during NGT insertion (p= 0.53). Brief apnea or self-limiting bradycardia was seen in handful of neonates. The authors concluded that sucrose was a safe and effective analgesic in preterm neonates for brief procedural pain.

Okan, Coban, Ince, Yapici, and Can (2006). Analgesia in preterm newborns: The comparative effects of sucrose and glucose.

Okan et al. (2006) conducted a prospective randomized double blind control trial evaluating and comparing the analgesic effects of oral sucrose and oral glucose for heel

lancing in 31 neonates less than 37 weeks of gestational age. Power analysis was done, determining that this was an adequate sample size. Neonates were randomized into one of the three groups including sucrose 20% (2mL), glucose 20% (2mL), and sterile water (2mL). The NFCS measuring tool was used to score behavioural responses. Heart rate, respiratory rate, oxygen saturations, and crying time were recorded. Facial reactions were video recorded. The data was recorded at baseline (heel prick) and at 1, 2, 3, 4, and 5 minutes after heel prick. Two trained staff collected and analyzed the data.

The data were analyzed using analysis of variance with a repeated measures method. Physiological variables and pain scores were expressed as mean and the total crying time and the duration of the first cry were given as median and interquartile range. A p value < 0.05 was considered significant. Heart rates of neonates in the placebo group were significantly higher than sucrose and glucose groups (P=0.007). No significant differences were noted between sucrose and glucose. There was a slight increase in respiratory rate and slight decrease in oxygen saturation for all three groups; however, there were no statistically significant differences between all three groups for respiratory rate and O2 saturation. NFCS scores were the highest at the heel prick phase for all three groups. The NFCS was significantly higher in the placebo group compared with the sucrose and glucose groups at the 4^{th} and 5^{th} minute (P=0.009 and P=0.046, respectively). No significant differences were noted in NFCS scores between sucrose and glucose groups. The total crying time and the duration of the first cry was shortest in the sucrose group and statistically significant longer in the placebo group compared with the sucrose and glucose groups (P=0.005 and P=0.007 respectively). No statistically significant differences were observed between the sucrose and glucose groups. Both sucrose and

glucose administered orally before a heel prick reduced the pain response in preterm neonates. The authors concluded that both sucrose and glucose reduced pain associated with heel prick. These authors did not study the adverse effects of sucrose in this study.

Stevens et al. (2005). Consistent management of repeated procedural pain with sucrose in preterm neonates: Is it effective and safe for repeated use over time?

Stevens et al. (2005) conducted a randomized control trial to determine if consistent management of procedural pain with sucrose from repeated painful procedures in preterm neonates is safe and effective throughout the neonatal period. The second aim was to explore the impact of repeated painful procedures on clinical outcomes and neurobiological risk status. Sixty-six neonates were recruited for the study and were assigned to three intervention groups. There was no power analysis done but I believe this sample size is adequate as in some of the previous studies sample sizes were smaller but yet adequate according to the power calculation. These groups consisted of standard care involving no intervention, water 0.1mL plus pacifier, and 0.1mL of sucrose 24% plus pacifier.

The PIPP tool was used to measure pain response and the Neurobiologic Risk Score (NBRS) was used to measure the impact of repeated painful procedure on neuro-biological risk status and clinical outcomes. According to Stevens et al. (2005), NBRS is a "7-item scale scored at NICU discharge to assess the degree of hypoxemia, ischemia, metabolic aberration, and brain injury occurring during the course of the infant's hospitalization" (p. 545). For each of the aims, the data was collected from different painful stimuli. To assess the effectiveness and safety of the sucrose, the data was collected from a heel lance in five phases. These phases included baseline, warming of the heel prior to heel stick, heel stick, heel squeeze, and return to baseline at 5 minutes.

The facial expressions were video recorded and physiological data was obtained from a pulse oximeter by a trained coder who was blinded to the pacifier study groups. The data for the second aim was collected on the total number of painful procedures performed on the neonates over the first 28 days of life.

Chi-square and post hoc analysis methods were used to analyze the data. A significance level of 0.05 was used for the primary outcome and 0.01 of the secondary outcomes. For primary aim, post hoc analysis indicated significant differences of PIPP scores between the sucrose plus pacifier and the standard care group (P = .01). Differences between the water plus pacifier group and the standard care group-approached significance (P = .051). PIPP scores were highest in the standard care group over time. Chi-square analysis was used to compare the incidence of immediate and long-term events. There were no statistically significant differences between the three groups for the number of immediate adverse events and long-term adverse events. Short term adverse included heart rate <100 and >240, O2 desaturation <85%, apnea >15 seconds, and choking at each of the follow-up session (P> .05). Long-term adverse included hyperglycemia >10.0 mmol, oral infection, NEC, IVH grades 3 or 4, and death (P> .05).

For the secondary aim of the study, there were no statistically significant differences between the three groups in terms of days on ventilator, CPAP, days until no apnea bradycardia, and desaturation, days to full enteral feeds, and days until discharge home. The neurobiological risk scores were similar in all groups (water + pacifier, sucrose + pacifier, and standard care, 3.76, 3.33, 3.20 respectively, p= 0.77). The authors of this study concluded that sucrose is not only an effective analgesia but is also safe. There were no adverse effects reported up to 28 days of neonatal life.

Mitchell et al. (2004). Analgesic effects of oral sucrose and pacifier during eye examinations for retinopathy of prematurity.

Mitchell et al. (2004) conducted a randomized control trial investigating the effects of sucrose on pain during an eye examination. Thirty preterm neonates were allocated to two groups. This was an adequate sample size according to the power analysis. One group received local anesthetic eye drops plus pacifier and 3 doses of 0.1mL sterile water and the second group received local anesthetic eye drop plus pacifier and three doses of 0.1mL 24% sucrose. This was a double blind randomized controlled trial. The PIPP tool was used to measure pain scores. Facial expressions were video recorded by a research assistant who was blinded to the study. Physiological data was collected from the bedside monitors. The data was recorded in four phases consisting of baseline (phase A), receiving a pacifier and the first drop of sucrose or water orally (phase B), eye drop administration (phase C), and second drop of sucrose and or water and placement of speculum [3](phase D). Unlike Boyle et al. (2006) study, neonates on CPAP were excluded in this study.

Demographic was reported using frequencies and analyzed using chi square statistic. A repeated measures analysis of variance was used to analyze PIPP scores. The level of significance was reported at $p < 0.05$. PIPP scores during phase C (instillation of eye drops) were not statistically significant between the two groups. PIPP scores during phase D (eye examination) were significantly different between water group and sucrose group (11.4 and 8.8 respectively, $p = .0077$) indicating a statistically significant greater pain score in the water group.

[3] Speculum is an instrument used to retract the eyelids during an eye examination procedure (Mitchell et al., 2004).

In contrast to Boyle et al. (2006) study, Mitchell et al. (2004) concluded that oral sucrose is effective for eye examination. The difference between these two studies was that in the current study, the neonates received two doses of oral sucrose instead of one in Mitchell et al. (2004) However, the concentration of sucrose in Boyle et al. (2006) was 33% and the amount was 10 times higher compared to the current study.

Limitations

This integrative review included total of 11 quantitative studies. I appraised these studies using an appraisal tool (Appendix A) and identified several limitations, which posed threats to external validity in three of the studies, particularly the study conditions and type of observations (LoBiondo-Wood & Singh, 2009). The first external threat was Boyle et al. (2006) using only single dose of sucrose to test its effectiveness for eye examination procedure, a very painful procedure, when Mitchell et al. (2004) had used a minimum of 2 doses for the same procedure. This could be a possible explanation why sucrose was ineffective for this procedure. Secondly, these researchers included neonates on CPAP in their study, which would have obscured the visibility of facial expressions. The third threat to external validity was that neonates in the Milazzo et al. (2011) study were bundled during the arterial line insertion when the researchers were observing body movement indicators as response to pain. Bundling the neonates would limit the researchers' ability to observe body movement; therefore posing a threat to external validity specifically to the type of observations. Lastly, Kristofersen et al. (2011) collected data manually within 30 seconds of NGT insertion, which is a very short time to perform the procedure and to collect the data. In this study, the study conditions were a threat to external validity.

Despite these limitations, I believe each of these articles contributed to nursing body of knowledge and advancement of nursing practice. I considered them to be rigourous enough for inclusion in this integrative review as all the researchers of the articles maintained ethical integrity, all the articles scored high on the quality score (ranged from 12 to 17), all were peer reviewed, and all but one had the same conclusions (Boyle et al, 1995).

Results

The main purpose of the project was to explore the effectiveness and safety of oral sucrose for management of procedural pain in preterm neonates. Therefore, the results of the review are discussed in this context.

Effectiveness

The effectiveness of oral sucrose was measured by comparing the pain scores including physiological and behavioural responses to pain with various other interventions. The majority of the investigators of the studies reported that oral sucrose was effective as pain scores were lower among sucrose groups than those among placebo groups. The oral sucrose intervention also reduced crying time and duration of crying, and the heart rate either did not increase or if it did, it stabilized faster than those neonates who did not receive sucrose for painful stimuli. Boyle et al. (2006) are the only investigators who found that oral sucrose was not effective for an eye examination procedure. However, as discussed earlier, the limitation of their study was that they only administered one dose of sucrose for this very painful procedure compared to the Mitchell et al. (2004) study where they administered a minimum of two doses for the same procedure and found sucrose to be effective.

Safety

Five of the reviewed studies did not report adverse effects (Cignacco et al., 2012; Milazzo et al., 2011; Kristoffersen et al., 2011; Okan et al., 2006; Mitchell et al., 2004). It is unclear whether or not these investigators monitored the adverse effects. The other six studies reported the presence or absence of adverse effects (Biran et al., 2011; Elserafy et al., 2009; Gaspardo et al., 2008; Boyle et al., 2006; McCullough et al., 2008; Stevens et al., 2005). There were no short-term adverse effects associated with sucrose including chocking, vomiting, hyperglycemia, bradycardia, tachycardia, and desaturations in all of the studies except for the McCullough et al. (2008) study. These investigators reported brief apnea and bradycardia in few neonates where no clinical interventions were required for recovery. These authors did not quantify how many neonates had apnea and bradycardia. There were also no long-term adverse effects reported. The long-term effects included necrotizing entero-colitis, intraventicular hemorrhage, and neurobiological risks. Johnston et al. (2002) found that repeated doses of sucrose were a predictive of high NBRS scores at 2 weeks postnatal age. They also reported that neonates who received repeated doses of sucrose showed low motor development and low vigor at 40 weeks of age, although, this study has not been replicated. Stevens et al. (2005), however, found NBRS scores were similar among all the study groups including the group who received repeated doses of sucrose. They concluded that there were no neurological adverse effects associated with repeated doses of sucrose.

Discussion

This integrative literature review focused on some key areas that assessed the

effectiveness and safety of oral sucrose as a non-pharmacological analgesic for minor procedures. The review has answered my question for this project, which shows that sucrose is both safe and effective as a pain management intervention for preterm neonates. The findings from this review also highlight the inadequacy of our current standards of practice in managing procedural pain in neonates (Schechter, 2006; Sabrine & Sinha, 2000) even though there is overwhelming evidence that noxious stimuli in the early days of neonates' life can have negative effects lasting into adulthood (Fitzgerald & Walker, 2009; Johnston et al., 2010; Hermann et al., 2006). Although much more is now known about neonatal pain and the importance of treating pain, there has not been much advancement in assessing and managing the pain partly because this research has not been mobilized into clinical practice (Gradin & Eriksson, 2010; Lango et al, 2005). It would be useful to conduct a qualitative research where researchers can focus on finding what knowledge the clinicians have about the use of sucrose for management of neonatal pain and what hinders them from applying this evidence.

Recommendations

After reviewing the studies and based on my previous experience working within the context of an NICU, I am presenting recommendations for all health professionals and for advanced practice nurses, in order to improve neonatal pain management to prevent long-term consequences of untreated pain. I am recommending that all health professionals involved in neonatal care:

- Learn more about neonatal pain and its short term and long term effects; how to assess and manage it;
- Monitor pain routinely and before, during, and post procedures;

- Manage procedural pain using oral sucrose as per guidelines; and
- Involve parents in comforting their babies during procedures.

Additional recommendations for advanced practice nurses (APNs) are to:

- Develop patient care guidelines on the use of oral sucrose that highlight doses, concentrations, neonatal age, and frequency of dosing;
- Focus on mobilizing evidence-based research on oral sucrose into practice in order to close the gap between theory and practice. For example, APNs may hold pain education days and educate nurses on neonatal pain including the importance of treating pain and the consequences of undermanaged pain on neonates. Education needs to be continuous and reinforced in order to change the culture of the unit;
- Select and implement a validated pain measuring instrument for their units;
- Evaluate the use of this instrument;
- Evaluate the use of the guidelines/how sucrose is used, for example, is it being used inappropriately such as for more long term pain;
- Teach nurses how to assess pain using this validated instrument;
- Develop parent-teaching resources on neonatal pain (such as pamphlets or DVDs) for parents and encourage them to comfort their children during the painful procedures.

Conclusion

In this integrative review, I critiqued eleven primarily randomized control trial studies that examined the effectiveness and safety of oral sucrose for treating procedural pain in premature neonates. This review highlighted the importance of evaluating

neonatal pain and managing it adequately to avoid the long-term negative effects of pain in premature neonates. The studies in this review support oral sucrose administration in premature neonates and suggest that it is not only effective but it is also safe for minor but painful procedures. Therefore, it is crucial that health care providers implement strategies to assess pain regularly and manage it adequately. These strategies will help improve pain and alleviate long-term consequences of under managed pain in premature neonates. APNs play a critical role in generating research, interpreting data from the research, synthesizing evidence to improve patient care, developing strategies such as clinical guidelines to translate evidence into practice, and evaluating practice. It is important that APNs educate all the health care providers about neonatal pain, develop and implement patient care guidelines for neonatal pain and its management, and evaluate practice.

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Appendix A

Methodology elements	Critique questions	Scores
Problem statement and purpose	1. What is the problem or the purpose of the research study? 2. Does the problem statement or the purpose specify the nature of the population being studied?	2
Research design	1. What type of design is used in the study? 2. What is the rationale for the design classification?	2
Sampling	1. How was the sample selected? 2. What type of sampling method is used in the study? 3. Does the sample reflect the population as identified in the problem or the purpose statement?	3
Procedures and data collection	1. Who collected the data? 2. What data collection methods were used? 3. What type of instrument was used? 4. What type of reliability was reported for each instrument? 5. What type of validity was reported for each instrument?	5
Data analysis	1. Were the statistical tests detailed (test and p-value)? 2. Does the author report the level of significance set for the study?	2

Ethical issues	1. Did the study discuss informed consent of the subjects was received?	1
Relevance to nursing	1. How and under what circumstances are the findings applicable to nursing practice? 2. What recommendations are stated or implied for future research?	2
Total score		**17**

Adapted from Heermann, Craft & Singh (2009). Total scores are 17. High = 13-17 Medium 7-12 Low 1-6

Heermann, J., Craft, B. & Singh, M., H. (2009). Chapter 19: Critiquing quantitative research. In C. Cameron & M. Sing (Eds.).

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Appendix B

Authors, citation, and location of study 1.	Research problem/statement	Design, Ethical considerations & data collection	Sample	Stimulus	Intervention	Instrument	Results	Strengths/ Limitations of the study	Scores
Cignacco, E. et al., (2012). Oral sucrose and "facilitated tucking" (FT) for repeated pain relief in preterms: A randomized controlled trial. 3 NICUs: 2 in Basel and 1 in Bern, Switzerland	To test the comparative effectiveness of 2 non-pharmacologic pain-relieving interventions administered alone or in combination across time for repeated heel sticks in preterm infants.	• A multicenter Randomized Controlled Trial (RCT) in 3 NICUs. • The local ethical boards approved the study. • Parents consented to participate in the research. • Data was collected in three phases: 1. during baseline (before any manipulation), 2. Heel stick (skin preparation, heel stick, and hemostasis after blood was drawn), and 3. Recovery (3 minutes after the heel stick). • Phases were videotaped	• n= 72 infants for three intervention groups, n=24/group • Power analysis was done to calculate adequate sample size of 24 for each intervention group. • **Inclusion criteria**: Gestational age 24-32 weeks, requiring 5 routine capillary blood samples within 2 weeks after birth. • **Exclusion**	Heel lance	Facilitated Tuck (FT) alone, sucrose 20%, 0.2mL/kg alone, and Sucrose 20%, 0.2mL/kg with FT	• Bernese Pain Scale for Neonates (BPSN) was used to measure pain with an intrarater and interrater reliability correlation coefficients of r= 0.98 to 0.99 and r= 0.86 to 0.97 respective-ly. • Good construct validity with differenti-ation between painful and non-painful procedure	• Level of significance is reported at $p < 0.05$. • X2 test and Kruskal-Eillis or Mann-Whitney U tests were used for comparison among the 3 intervention groups. • During the heel stick phase, the FT group had significant higher behavioral B-BPSN scores (p= .01; .007) and physiologic P-BPSN scores (p= .0002; .003) than the sucrose and	**Strengths**: • Enhanced internal validity of the results. • Trained and experienced nurses to perform pain assessment. • Randomiza-tion of the sequences to blind the rater to the phase of the procedure. **Limitations:** • The rater could only be blinded partially to the FT procedure	**16**

		(using panasonic high-definition camcorder) for at least 3 minutes by a trained study nurse.	**criteria:** neonates with severe intraventricular hemorrhage (Gr. III and IV), had life-threatening malformations or disorders affecting brain and the cardiovascular system, had a surgical procedure, pH< 7 or had any problem that could impair pain expression.			(F= 41.27 P ≤ .0001	combination groups. • During the recovery phase, there were significant differences in P-BPSN scores, but the combination group had significantly lower B-BPSN scores than both the other groups (p= .006; .008). • FT alone is not as effective and cannot be recommend-ed as a non-pharmacolo-gic pain relieving intervention. • Sucrose alone or sucrose with FT is effective during heel sticks in <32 weeks		

							gestational infants. There is an additive analgesic effect with combination of sucrose and FT during the recovery period. As FT is time-consuming intervention, the challenges of this specific intervention need to be taken into account especially when resources are constrained.		
Authors, citation, and location of study 2.	Research problem/statement	Design, Ethical considerations & data collection	Sample	Stimulus	Intervention	Instrument	Results	Strengths/ Limitations of the study	Scores
Biran, V. et al., (2011). Analgesic effects of EMLA	To compare the analgesic effect of sucrose with that of the combination of sucrose and the	• Prospective, controlled randomizeda nd double-blind study. • Neonates	• 76 neonates. • Group 1 n= 37 or group 2 n=	Veni-puncture	Group S: 30% sucrose 0.5mL with placebo cream Group S + E:	Douleur Aigue Nouveau-ne (DAN) scale for the primary outcome measure, PIPP	• Level of significance is reported at p <0.05. • DAN pain scores were	**Strengths:** • Steps for how data were collected and analyzed were well	**13**

cream and oral sucrose during veni-puncture in preterm infants. 2 NICUs: Hospital France Arman of Trousseau, Paris and Centre Hospitalier de Meaux, Meaux, France.	local anesthetic cream EMLA during venipuncture in preterm neonates.	were allocated to two groups. • Written informed consent was obtained from parents. • Local ethics committee approved the study. • Data were collected in three phases: baseline, during venipuncture (the time from skin puncture until removal of the needle) and the recovery period (30 seconds after the removal of the needle). • Data were collected using a videotape with a color digital	39. • Power analysis was done to calculate adequate sample size of 37 neonates/ group. • **Inclusion criteria:** Neonates <37 weeks, last feeding within last 30 minutes or having continuous enteral feeding. • **Exclusion criteria:** Mechanical ventilation, or continuous positive airway pressure, abnormal neurologic clinical examination, administration of sulfonamides, metoclopra-mide, sedatives, or analgesia within 24hrs		30% sucrose 0.5mL with EMLA cream.	for the secondary outcome measure and crying time. DAN scale is a behavioral scale developed to rate acute pain and scores range from 0 (no pain) to 10 (maximum pain). This scale evaluates 3 items: facial expressions, limb movements and vocal expression. PIPP scale is based on gestational age, behavioral state, heart rate, oxygen saturation and 3 facial reactions (brow bulge, eye squeeze, and nasolabial furrow. Scores range from 0 (no pain) to 21 (maximum pain). Validity of these tools	lower during venipuncture and post injection period in S+E group (6.4) compared with S group (7.7) reaching statistically significant treatment effect (P= .018) during the venipucture period. During the recovery period, DAN scores for S+E were 5.7 and for S were 7.1 reaching statistical significant of p=. 018. • PIPP scores (secondary outcome) were also lower in S+E group compared with S group; however	documented, which add to the rigor of the study. **Limitations:** • Random assignment was not computerized (opaque sealed envelopes for treatment assignment were used). This had potential risk of treatment identification by study participants. • Secondly, there was no placebo group to determine the absolute effectiveness for each analgesic intervention.	

		camera. • Facial actions, body movements, physiologic parameters, behavioral state and crying time were captured on the camera, which included real-time counter. • Two specifically trained observer nurses assessed the recordings according to the DAN and PIPP scales. • These observer nurses were not members of the unit staff and were unaware of the design or treatment assignments or the objective of	before inclusion, known allergy to local anesthetics, porphyria, clinical instability, methemoglob-iemia, Apgar scores of <7 at 1 minute or 5 minutes and parents who did not understand French.			was not reported	PIPP scores did not reach statistical significance. • Crying time was also lower in S+E group but did not reach statistical significance. • Although EMLA was effective, authors warn about a concern of EMLA's safety in neonates. Of the main concern they cite is the possibility of increased methemoglob in concentration after EMLA application. This was not reported in this study but the concern was mentioned from		

		the study. • Each observer conducted an independent assessment and then the two observers reevaluated all the procedures where scores had not been identical in the first assessment.					previous studies. • No adverse effects occurred in this study except for a temporary blanching of the skin in 28 of 39 neonates. Blanching disappeared within few minutes. • No adverse effects were observed after administration of sucrose. • Adverse effects include chocking, coughing, vomiting, skin reactions (post EMLA application), sustained tachycardia (HR > 200), bradycardia (HR < 80), sustained		

							tachypnea (respiratory rate <20 breaths per minute), and oxygen desaturation (<80% for >15 seconds after sucrose administration).		
Authors, citation, and location of study. 3.	Research problem/statement	Design, Ethical considerations & data collection	Sample	Stimulus	Intervention	Instrument	Results	Strengths/ Limitations of the study	Scores
Milazzo, W. et al., (2011). Oral sucrose to decrease pain associated with arterial puncture in infants 30 to 36 weeks' gestation. Saint Lukes Hospital, Kansas City, Missouri.	To determine the effect of oral sucrose solution on pain responses of neonates to arterial puncture compared with neonates who did not receive a sucrose solution.	• Double blind randomized controlled trial convenience sampling. • Random assignment to groups was done through computer randomi-zation. • Study approval was obtained from the institution's investiga-tional review	• 47 neonates. • n= 24 for sucrose group and n= 23 for no sucrose group. • Power analysis determined a minimum sample of 39 neonates for the study. • **Inclusion**	Arterial puncture	Sucrose 24%, 1mL and no sucrose (comfort measures only)	• Neonatal Infant Pain Scale (NIPS) for primary outcome. • HR and oxygen saturation were recorded, for secondary outcome, using IntelliVue cardiac monitors • Validity and	• Level of significance for all tests is reported at p <0.05. • Data were summarized using descriptive statistics. Data were analyzed with chi-square analysis (NIPS change scores) and analysis of variance and a Bonferroni multiple	**Strengths:** • Double blind RCT. • Power analysis calculation for sample size. **Limitations:** • No written consent is mentioned. • Some of the other subscale of NIPS (eg. breathing pattern, arm and leg	**15**

		board. • Informed consent is not mentioned. • HR and O2 saturations were recorded from digital display on the bedside cardiac monitor. • Investigators (trained RNs with extensive use of NIPS) collected NIPS score, HR, and O2 data at baseline, immediately after puncture, and again 1 minute after puncture.	**criteria:** 31-35 weeks gestational age, nothing by mouth status, 48hours of age. • **Exclusion criteria:** Intubation, narcotic analgesia administered since admission, and/or fetal exposure to maternal opioids.			reliability of this scale is reported to be Cronbach alpha= 0.88-0.95; Pearson r= 0.92-0.97	comparison test (heart rate, O2 saturations). • Chi-square analyses of the change in NIPS subscale and total scores found significantly lower subscale scores for changes in crying in the sucrose group compared to the no sucrose group at the time of the needle puncture and at 1 minute after completion of the puncture (p= .0006 and p= 0.022 respectively). • None of the other NIPS subscale or NIPS total	movement were studied due to swaddling of the neonates during and after the procedure.	

							scores were found to be significantly different between the 2 groups (all P values > .05). • Analysis of variance found no statistical difference for heart rate or O2 saturation levels between the sucrose and no sucrose groups (P> .05).		
Authors, citation, and location of study 4.	Research problem/statement	Design, Ethical considerations & data collection	Sample	Stimulus	Intervention	Instrument	Results	Strengths/ Limitations of the study	Scores
Kristoffersen et al., (2011). Pain reduction on insertion of a feeding tube in preterm infants: A	To investigate the use of pacifier, water, sucrose, and their combination for pain relief during and immediately after insertion of a feeding tube in preterm infants.	• Randomized semi- blind control trial. Pacifier use could not be blinded. • Randomization was done through computerized method to six	• 24 preterm infants. • Power analysis required minimum of 18 neonates per sample size.	Nasogastric tube insertion	No fluid and no pacifier, Sterile water (0.2mL) and no pacifier Sucrose (0.2 mL) and no pacifier,	Premature Infant Pain Profile (PIPP) score scale.	• Level of significance is reported at p <0.05. • Descriptive analysis and graphs were used to summarize the results. • Maximum	**Strength:** • Randomized, placebo-controlled design. **Limitations:** • Observers could only be semi-blinded due to	**14**

randomized controlled trial. St. Olav University Hospital, Tronheim, Norway.		different groups. • The regional committee for medical research ethics approved the study. • Informed written consent was obtained from parents. • Data was collected 15 seconds before NGT insertion, within 30 seconds of NGT insertion, 1 minute later, and at 5 minutes after the insertion. • Nasogastric tube was changed twice/week, which was inserted by 2 alternated experienced nurses. • Two	• **Inclusion criteria:** 28-32 weeks gestational age, stable condition, and at low risk for neurologic sequelae. • **Exclusion criteria:** Neonates on ventilator or continuous positive pressure, or on opioids treatment. Neonates with serious infections and those requiring oral feeding tube.		No fluid but had pacifier, Pacifier and sterile water (0.2mL), Sucrose 30% (0.2mL) and pacifier		PIPP score for each intervention for neonates in this study was 19 or 20 depending on the gestational age and weight of the neonates. • Median PIPP score for no intervention was 9, water group 11, sucrose 8, pacifier only 10, pacifier and sterile water 9, and pacifier and 30% sucrose 7. • The combination of sucrose and pacifier during tube insertion provided the most effective pain reduction (P< .001) versus no treatment.	visibility of pacifier. • Data were not video-recorded; therefore, inability to go back and confirm assessment/ evaluation. • Only one observer observed and collected data.	

		experienced nurses observed the neonates during the study. One nurse collected the data and the other was a timekeeper during the entire procedure. These observers were asked to turn away for a brief period to avoid seeing if anything was given orally.					Sterile water alone had the highest pain scores among all the groups.		
Authors, citation and location of study 5.	Research problem/statement	Design, Ethical considerations & data collection	Sample	Stimulus	Intervention	Instrument	Results	Strengths/ Limitations of the study	Scores
Elserafy F. et al., (2009). Oral sucrose and a pacifier for pain relief during	To assess the analgesic effect of sucrose versus sterile water alone or with a pacifier in relieving pain in preterm infants prior to painful procedures.	• Randomized, prospective, double-blinded control trial. • Written parental consent was obtained.	• 36 neonates. • Each sample received each of six different regimens	Veni-puncture	0.5 mL sterile water with pacifier, 0.5 mL sterile water without pacifier, 0.5 mL	PIPP score tool. Reliability and validity of the instrument not reported.	• Level of significance is reported at $p < 0.05$. • Repeated measures analysis of variance was used for the	**Strengths:** • RCT, placebo groups. **Limitations:** • Procedure section not described well,	**13**

simple procedures in preterm infants: a randomized controlled trial. King Faisal Specialist Hospital Jeddah, Saudi Arabia.	Another aim was to determine whether there is a synergistic effect with oral sucrose when combined with non-pharmacologic interventions to relieve pain during painful procedures in preterm infants.	• The study was approved by the hospital institutional review board. • For each assignment, a paper was randomly picked so that assignments were random and double blinded for the sucrose and water solutions. • Document-ation of the identity of the solution was kept in a closed cabinet, which was opened only at the time of analyzing the results. • The nurse opened a consecutive-ly numbered envelope. All envelopes were	their during stay. • **Inclusion criteria:** <37 weeks gestational age • **Exclusion criteria:** Exposure to maternal sedation antenatally, occurrence of any procedure performed within 24hrs of neonates' age, major neurologic abnormalities, Apgar scores < 5 at 5 minutes, necrotizing intestinal colitis, nothing by mouth status and hyperglycemi		sucrose 24% with pacifier 0.5mL sucrose 24% without pacifier, pacifier alone, standard care or no treatment (control group)		statistical analysis. • Pain score comparisons between different treatments were summarized using mixed between-within ANOVA. There were no significant differences between treatment groups in HR, BP, O2 saturation and glucose measurements, but there were significant differences in crying time and pain score (P= .001). • Pain scores were significantly reduced in infants who received 0.5	specifically the stimulus. • Under the patients and methods section authors discuss the stimulus as veni-puncture; however, under the results section, they discuss that sucrose decreased the behavioral pain indicators and composite pain scores in neonates undergoing heel stick and/or venipuncture. • The reader is left wondering which procedure the authors evaluated?	

		previously prepared with codes for the six treatment regimens each in a folded paper. • Data were collected immediately prior to the procedure, during procedure, 1, 3, 5, and 10 minutes after the procedure. • Data collected included: physiological (HR and O2 saturations from pulse oximeter) and behavioral pain parameters, crying time, and glucose measure-ments.					mL (0.12g) of 24% sucrose with mean pain score of 0.9 reaching 0.05 level of significance. • The combination of pacifier and sucrose were more effective and reduced crying time reaching statistical significance of p=.001. • The use of sterile water alone (mean score 1.4) or pacifier alone (mean score 1.4) or the combination of sterile water (mean score 1.5) and pacifier (mean score 1.8) were not statistically different in terms of pain		

							control compared with control group that received standard care (no treatment). • Sucrose is safe and effective analgesic for minor procedures.		
Authors, citation and location of study 6.	Research problem/statement	Design, Ethical considerations & data collection	Sample	Stimulus	Intervention	Instrument	Results	Strengths/ Limitations of the study	Scores
Gaspardo, C., et al., (2008). Is pain relief equally efficacious and free of side effects with repeated doses of oral sucrose in preterm neonates? Hospital of Clinics,	The aim of the present study was to assess the efficacy of giving repeated doses of oral sucrose to neonates for pain relief during painful procedures and to determine whether there are any negative side effects.	• Randomized, double blind, placebo-controlled trial. • The study was approved by the Clinical Research Ethics Board of the hospital. • Informed consent was obtained from parents. • Neonates	• 33 neonates. • Sucrose group n= 17 Control group N= 16 • **Inclusion criteria:** <37 weeks GA, wt. <1500 g • **Exclusion criteria**: Major congenital anomalies,	All painful procedures	Sucrose 25% 0.5mL/kg (Sucrose Group= SG) and placebo (Control Group= CG).	Neonatal Facial Coding System (NFCS). Reliability and validity of the instrument not reported.	• Level of significance is reported at $p < 0.05$. • The descriptive statistical analysis was used. • On the first assessment day, there were no statistically significant differences	**Strengths:** • Along with baseline, puncture, and recovery phases, this study also included the phases involving nurses' contact with neonates during antisepsis and dressing demonstratin g that such	**14**

School of Medicine, University of Sao Paulo, Brazil.		were randomly allocated to two groups according to a computer-generated randomiz-ation list. • Data were collected between 0700-0900 in 5 phases (Baseline, Anitsepsis, covering the period of handling the neonate for antisepsis prior to puncture, Puncture, Dressing covering the period from handling the neonate for dressing until positioning to rest, and Recovery) The data was collected over four days as per	intraventricular hemorrhage (gr. III/IV) and hypoglycemia, hyperblycemia, or who were on opioid or sedative medications and umbilical catheter in the first or second weeks of life. Ventilated neonates were included.				between groups. Both groups showed a high percentage (>50%) of neonates with NFCS scores of 3 or greater in the puncture phase. • On the second assess-ment, there was a statistical significant between the groups in regards to NFCS scores of 3 or greater during the Puncture phase	minor procedures can provoke facial activity and behavioral state where these behaviors can act as an anticipatory distress for painful stimulus. **Limitations:** Ventilated neonates were included in the study questioning the facial visualization of facial expression and how well these were evaluated?	

		below: Assessment 1 (no intervention), assessments 2,3, and 4 (administra-tion of sucrose or sterile water). • Pain responses (facial actions) were recorded using a digital video camera. Each facial action was scored by observing the videotape for the first 20 s of each phase (baseline, antisepsis, puncture, dressing, and recovery). Each 20s recording was divided into ten 2s segments to be analyzed independ-					(SG= 23%, CG= 56%, p=.05. • On the third assessment day, there was a statistically significant difference between groups in terms of percentage of neonates with NFCS scores of 3 or greater in the Antisepsis phase (SG= 0%, CG= 31%, p= .02). • On the fourth assessment day, there was also a statistical		

		ently by two coders as 1 or 0 (occurred, or did not occur). • Coders were blinded regarding the assessment phases, medical information, and the characterist-ics of neonates. • The reliability coding between two trained and independent coders was carried out on 10% of the study sample, with a reliability coefficient of 93%. • HR was measured with a Philips monitor.					significant difference between groups for NFCS 3 or greater during the Puncture (SG= 26%, CG 56%, p=.08) and Dressing (SG= 13%, CG= 31%, p=.09) phases. • For behavior state measure-ments: during second and fourth assessments, statistically significant differences between groups were found in the Puncture phase. • The percentage of SG neonates		

							with activated behavioral state was lower than the CG (p=.05 second assessment and p=.02 fourth assessment). • For crying measurements, on the second assessment, crying was significantly greater in CG group than SG (p= .0009) during Antisepsis and Puncture phases. • On the third assessment, the difference was during Dressing phase (p=.04). • On the fourth assessment, a difference was detected		

							in the Puncture phase (p=.03). • For heart rate measurements for a heart rate of >160, there were no differences in all groups for all four assessments during all the phases. • There were no short-term negative side effects, such as necrotizing entero-colitis, of repeated doses of sucrose. • In this study, repeated sucrose meant administering sucrose repeatedly in every painful procedure over consecutive days.		

							• On average, infants received around six doses of 25% sucrose a day during the study period (one neonate received 14 doses). • Sucrose was found to be effective and had no short-term side effects on the neonatal health.		
Authors, citation and the location of study. 7.	Research problem/statement	Design, Ethical considerations & data collection	Sample	Stimulus	Intervention	Instrument	Results	Strengths/ Limitations of the study	Scores
Boyle, E. et al., (2006). Sucrose and non-nutritive sucking for the relief of pain screening for retinopathy of	To evaluate the use of oral sucrose and/or pacifier for reducing pain responses during eye examinations.	• Prospective randomized controlled trial. • The study was approved by two local research ethics committees. • Written	• 40 neonates. • Power analysis indicated that a sample size of seven per group would be required.	Eye examinatio n	Group 1: 1mL sterile water (single dose). Group 2: 1mL sucrose 33% (single dose). Group 3: 1mL sterile water plus	PIPP. Reliability and validity of the instrument not reported.	• Level of significance is reported at $p < 0.05$. • One way analysis of variance showed a significantly lower scores in infants	**Strengths:** • Study design and a placebo group. **Limitation:** • Steps for eye examination procedure and timing of the	**12**

prematurity: a randomized controlled trial. Location of the study not mentioned.		parental was also obtained. • Neonates were randomized into one of four groups using sealed opaque envelopes. • Data were evaluated for single eye only due to the nature of the procedure. • Data were video recorded during the examination and until two minutes after completions of the examination. • Baseline physiological data were collected prior to the examination including maximum heart rate and minimum	• There were 10 neonates/ water and sucrose alone group and 10 neonates/ water plus pacifier and 11 neonates/ sucrose plus pacifier groups. • **Inclusion Criteria:** <32 weeks gestational age, or <1500g birth weight. Neonates on continuous positive pressure airways via nasal prongs. • **Exclusion criteria:**		pacifier (single dose). Group 4: 1 mL sucrose 33% (single dose) plus pacifier.		receiving a pacifier (p= 0.003) than those without a pacifier. • There was no significant difference between those neonates who received sucrose versus those who received water. • Scores of neonates receiving pacifiers were lower than those who did not, suggesting that non-nutritive sucking is effective as sucrose.	interventions were not described. • Although data were videotaped, there is no mention of which part of the data were analyzed and included in the results. Only single dose of intervention was administered for this long procedure. • Would repeated doses of sucrose have been more effective than single dose for this very painful procedure?	

		oxygen saturation. • Two experienced observers with the PIPP score analyzed the videotapes. • Inter-observer reliability was >90%.	Neonates on mechanical ventilation, neonates receiving nothing by mouth, and neonates receiving other analgesics.						
Authors, citation and the location of study. 8.	Research problem/statement	Design, Ethical considerations & data collection	Sample	Stimulus	Intervention	Instrument	Results	Strengths/ Limitations of the study	Scores
McCullough, S., et al. (2006). Lingual sucrose reduces the pain response to nasogastric tube insertion: a randomized clinical trial. Rotherham General	To determine whether lingual sucrose modifies the pain response to nasogastric tube insertion in preterm infants.	• Randomized, placebo controlled clinical trial. • Written parental consent was obtained. • Randomiza-tion was performed by the pharmacy department using a computer-generated	• 20 stable preterm neonates. • Mean gestation age was 30.7 weeks. • Power analysis was not calculated. • Authors had planned to evaluate total of 50 NG	Nasogastri c tube (NGT) insertion	Sucrose 24% or water placebo 2 mL of either solution was administer-ed for neonates weighing > 2kg and 1.5mL for neonates weighing <1.5kg	Neonatal Facial Coding Score (NFCS) for primary outcome measure and Nellcor pulse oximeter for secondary outcome measure. Reliability and validity of the instrument not reported.	• Level of significance is not reported. • Descriptive analysis was used to analyze and summarize data. • The sucrose group had a statistically significant (p= 0.004) lower median	**Strengths:** • Randomized control design. **Limitations:** • Power analysis not calculated to ensure adequate sampling. • Data not collected using a video	**13**

Hospital, Rotherham, South Yorkshire, UK.		random number. • Enrolled neonates could be randomized more than once as long as they remained eligible but 12hr must have lapsed before they could be randomized again to avoid any possibility of carry over effect. • Data was collected in three phases: baseline- prior to the procedure, during the procedure, and at the end of the procedure. • One nurse administered solution and inserted NG tube. Second	insertions, 25 for sucrose and 25 for water group. • Total of 51 insertions were evaluated. • **Inclusion criteria:** Neonates requiring nasogastric tube insertion for feeding. • **Exclusion criteria:** Neonates requiring ventilatory support or supplemental oxygen, had any facial congenital anomalies or neurological impairment, were receiving opiates or were infants of opiate-using mothers.				NFCS score during NGT insertion than the placebo group. • There was non-significant difference in crying between both the groups. • Neonates in sucrose group had higher mean pretreatment baseline heart rate than the placebo group, but showed no change in heart rate during NGT insertion. • In contrast, in the placebo group, heart rate increased. • There were no significant differences between the two groups with regard to	recording and not validated between two independent observers.	

		nurse, who had not witnessed administra-tion of solution recorded NFCS scores. • Maximum/ minimum heart rate and lowest O2 saturations were recorded. • HR and O2 saturations were measured using Nellcor pulse oximeter.					the number of adverse events. • Brief apnea or self-limiting bradycardia was seen in handful of neonates. • Sucrose is an effective analgesic in neonates for brief procedural pain.		
Authors, citation and the location of study. 9.	Research problem/statement	Design, Ethical considerations & data collection	Sample	Stimulus	Intervention	Instrument	Results	Strengths/ Limitations of the study	Scores
Okan, F. et al., (2006). Analgesia in preterm newborns: the comparative effects of sucrose and	To evaluate and compare the analgesic and soothing effects of various carbohydrates solutions (sucrose and glucose) given orally in healthy preterm	• Prospective, randomized, double blind, placebo-controlled, crossover trial. • The study was approved by the	• 31 neonates. • Power analysis was done to calculate sample size needed was 30 neonates.	Heel lance	Sucrose 20%, (2mL), glucose 20%, (2mL), and 2mL sterile water.	NFCS score for behavioral response. Validity and reliability of the instrument not reported.	• Physiological variables and pain scores are expressed as mean and the total crying time and the duration of the first cry	**Strengths:** • Double blind placebo controlled trial. • Data evaluated by two independent trained	**14**

glucose. No location of the study is mentioned. Authors are from Istanbul, Turkey.	infants subjected to heel prick.	hospital Ethical Committee. • Parental informed consent was also approved. • The neonates were tested three times in a crossover manner (sucrose, glucose, and sterile water). • There was 24-48hr differences between testing. • Solutions were put into identical containers coded by a nurse who did not take part in the study. This code was revealed at the end of the study. • The data were (HR, respiratory	• **Inclusion criteria:** <37 weeks gestation age, clinical stability, no oxygen treatment, no administration of sedative medicines with the last 7 days, no intolerance of enteral feedings, no use of drugs other than vitamins and iron, free of perinatal asphyxia, congenital malformations, and intra-ventricular hemorrhage, and the requirement of blood sample collection by heel prick.				are given as median and interquartile range. • HR of the placebo group was significantly higher than sucrose and glucose groups (P=0.007). • No significant differences were noted between sucrose and glucose. • There was a slight increase in respiratory rate and slight decrease in oxygen saturation for all three groups; however, there were no statistical significants between all three groups	observers.	

		rate and O2 saturations) collected prior to the procedure using beside monitor. • First cry and total cry were recorded. • The facial reaction was videotaped using a Sony DR10E Handycam with a real-time counter. • The recordings were analyzed by two observers independent-ly and they were blinded to the solutions. These observers were trained with the NFCS scores and interobserver reliability was 95%.					for respiratory rate and O2 saturation. • NFCS scores were the highest at the heel prick phase for all three groups. • The NFCS was significantly higher in the placebo group compared with the sucrose and glucose groups at the 4^{th} and 5^{th} minute (P=0.009 and P=0.046, respectively). • No significant differences were noted in NFCS scores between sucrose and glucose groups. • The total crying time		

							and the duration of the first cry was shortest in the sucrose group and significantly longer in the placebo group compared with the sucrose and glucose groups (P=0.005 and P=0.007 respectively). • No significant differences were observed between the sucrose and glucose groups. • Both sucrose and glucose administered orally before a heel prick reduce the pain response in preterm neontaes.		
Authors,	Research	Design, Ethical	Sample	Stimulus	Intervention	Instrument	Results	Strengths/	Scores

citation and the location of study. 10.	problem/statement	considerations & data collection						Limitations of the study	
Stevens, B. et, al., (2005). Consistent management of repeated procedural pain with sucrose in preterm neonates: is it effective and safe for repeated use over time? Tertiary NICU in Canada.	First aim of this study was to determine if consistent management of procedural pain with sucrose from repeated painful procedures in preterm newborns in the NICU is effective and safe throughout the neonatal period. Second aim was to explore the impact of repeated painful procedures on clinical outcomes and neurobiological risk status.	• A prospective RCT design, a convenience sampling was used including all infants who met the inclusion criteria. • The Research Ethics Board approved the study. • Parental consents were obtained. • Infants were randomized into three groups: two intervention groups and one control group by determining a priori from a computer-generated table of random	• 66 preterm neonates. • Standard care (n= 21), sterile water plus pacifier (n=23), or 24% sucrose plus pacifier (n=22). • There was no power calculation done to estimate adequate sample size. • **Inclusion criteria**: >26 and <30 weeks gestational age. • **Exclusion criteria**: Neonates who had major congenital	Heel lance	Standard Care group (no interven-tion). Water plus pacifier group, and Sucrose 24% plus pacifier group	PIPP tool was used to measure pain response. Has high interrater (alpha= 0.95-0.97) and intrarater reliability (alpha= 0.89-0.91) and construct validity.	• A significance level of 0.05 was used for the primary outcome and 0.01 of the secondary outcomes. • Chi-square analyses were used to compare the incidence of immediate and long-term events. • Post hoc analysis indicated significant differences of PIPP scores between the sucrose plus pacifier and the standard care group [t (60)= -2.54, P = .01]. • Differences between the water plus	**Strengths**: • Randomiza-tion and strategies used to reduce threats to internal validity. • Trained coders were used to evaluate facial actions of the infants. • Sucrose was only provided to study patients. • The same research nurse interacted with the staff nurses on a daily basis. **Limitations:** • The use of pacifiers in the water plus and sucrose plus pacifier groups	**16**

		numbers and recorded on a master sheet that was only available to the neonatal pharmacist. • Group assignment was also done using allocation concealment. • Data were collected by trained staff during the heel lance procedure including base line, warming, heel stick, heel squeeze, and return to baseline. • Behavioral and physiological data were collected using videotaping and computerized data collection	anomalies requiring correction during the first week of life or who had undergone major stressful procedures during the first 72 hours of life.				pacifier group and the standard care group-approached significance [t (60)= -1.99, P = .051]. • PIPP scores were higher in the standard care group. • There were no statistically significant differences between the groups for the number of immediate adverse events and long-term adverse events. • Short term adverse included heart rate <100 and >240, O2 desaturation <85%, apnea >15 seconds,	precluded double blinding. However, the caregivers who delivered the interventions were not involved in measuring the research outcome. • Individuals who entered and analyzed the data were blind to group assignment. • No power calculation was done for sample size.	

		system.					and choking at each of the follow-up session (P> .05). • Long-term adverse included hyperglycemia >10.0 mmol, oral infection, NEC, IVH grades 3 or 4, and death (P> .05). • Sucrose plus pacifier was effective and safe for preterm neonates during their stay in the NICU. Further research is needed to investigate long term developmental effects on infants		
Authors, citation and the location	Research problem/statement	Design, Ethical considerations & data collection	Sample	Stimulus	Intervention	Instrument	Results	Strengths/ Limitations of the study	Scores

of study. 11.									
Mitchell, A., et al., (2004). Analgesic effects of oral sucrose and pacifier during eye examinations for retinopathy of prematurity. NICU at the University of Mississippi Medical Center.	To determine the effectiveness of local anesthetic eye drops and a pacifier, plus repeated doses of 24% sucrose, to relieve pain associated with eye examination for retinopathy of prematurity.	• Double- • Blind randomized controlled trial. • Neonates were randomly assigned to one of the two treatments using a priori computer-generated randomization. • Parental consent was obtained. • Data were collected before, during, and following an examination of the left eye. • The same ophthalmologist performed all the eye	• 30 preterm neonates. • **Inclusion criteria:** Neonates requiring examinations of the retina, weighing between 1500-2000gms at birth and required oxygen more 72hrs. • **Exclusion criteria:** History of cardiopulmonary resuscitation, surgery, 1 and 5 minute Apgar socres at birth <6 or an interraventricular hemorrhage greater than grade 2, neonates who received opiod analgesics or sedatives over the past 24 hours, on	Eye Examination	Local anesthetic eye drops, a pacifier and 3 doses of 0.1mL of sterile water OR local anesthetic eye drops, a pacifier, and three doses of 24% sucrose 0.1mL.	PIPP	• Level of significance is reported at $p < 0.05$. • PIPP scores during phase C (instillation of eye drops) were not statistically significant between the two groups. • PIPP scores during phase D (eye examination) were significantly different between water group and sucrose group ($p = .0077$) indicating a statistically significant greater pain score in the water group. • Authors also noted PIPP scores are higher for eye	**Strengths**: • Study design **Limitations:** • Due to the nature of eye examination procedure, only one eye could be used to evaluate facial expressions. • It is not known if pain response and the effectiveness of sucrose for the second eye examination would be the same as the first eye examination.	**14**

		exams. • A trained research assistant who was blinded to the treatment groups videotaped facial expressions. • The nurse who administered the treatment according to the instructions in the sealed envelope did not evaluate the outcomes and did not communicate with any health care providers who performed the procedure. • Two independent observers analyzed the videos away from the	continuous positive airway pressure and intubation.				examination as compared to heel lance evaluated in other studies. • Sucrose plus pacifier is effective analgesic for eye examination. Authors recommend this treatment be implemented in practice as a evidenced based practice.		

		clinical setting and were blinded to the group allocation. • Physiologic data were collected off the bedside monitors. • Data were recorded in 4 phases: Phase A baseline, phase B neonate receiving treatment, phase C during eye drop administration, and phase D, second drop of sucrose/ water and placement of speculum.							